MEDICAL GENETICS

UpToDate
CLINICAL GENETICS

2015

Index

2

Derleme
Dr. Yavuz ŞAHİN

Genetic and environmental causes of birth defects

Author
Harry Ostrer, MD

Section Editor
Louise Wilkins-Haug, MD, PhD

Deputy Editor
Vanessa A Barss, MD, FACOG

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Jan 20, 2015.

INTRODUCTION — A major birth defect is one of medical, surgical or cosmetic significance. The prevalence of these defects is 2 to 4 percent among live born infants and does not vary among ethnic groups (table 1). Birth defects may be isolated or multiple and can affect one or more organ systems. Both genetic and environmental factors play a role in their pathogenesis. As an example, parents with a birth defect, a previously affected child, or a family history of birth defects are at higher risk of having a baby with the same, or a different, anomaly. Other risk factors include maternal age, illness, drug use, exposure to infectious or environmental agents, and the physical features of the intrauterine environment.

The relative contribution of various etiologies to the overall frequency of birth defects is estimated to be [1]:

- Unknown cause, including suspected polygenic and multifactorial causes (65 to 75 percent)
- Genetic: single gene disorders (15 to 20 percent), chromosomal abnormalities (5 percent)
- Environmental exposures (eg, maternal medical conditions, substance abuse, infection, drugs, chemicals, radiation, hyperthermia; mechanical constraints on fetal development) (10 percent)

COMMON FEATURES OF CHROMOSOMAL DISORDERS — There are certain common characteristics of the syndromes that are produced by constitutional chromosomal abnormalities:

- Greater than 90 percent of embryos/fetuses with constitutional chromosomal abnormalities do not survive to term. In trisomy 21, as an example, 40 percent of fetuses are lost after 12 weeks of gestation. Even higher embryonic and fetal loss rates are found with monosomy X.
- Multiple organ systems tend to be involved, especially the central nervous system. Intellectual disability, in particular, is a common abnormality in viable infants.
- The longevity and fertility of individuals with these conditions tend to be reduced. As an example, the risk of malignancy is increased for certain chromosomal disorders, such as trisomy 21, deletions of the long arm of chromosome 13; deletions of the short arm of chromosome 11, and 46,XY gonadal dysgenesis.

STRUCTURAL CHROMOSOMAL ABNORMALITIES — Chromosomal abnormalities affect approximately 1 in 200 newborn infants [2,3]. These defects may be either sporadic or heritable and are due to a number of different etiologies. (See "Basic principles of genetic counseling for the obstetrical provider" and "Basic principles of genetic disease".)

Nondisjunction — The most common sporadic chromosomal abnormalities result from loss or gain of a chromosome, usually from nondisjunction. Nondisjunction refers to the process whereby paired chromosomes fail to separate during cell division so that both chromosomes go to one daughter cell and none to the other. Thus, after fertilization, one daughter cell inherits three chromosomes of the affected chromosome and becomes trisomic (eg, trisomy 21 or Down syndrome), while the other daughter cell inherits only one chromosome resulting in monosomy (figure 1 and figure 2). Cytogenetic surveys of spontaneous abortions during the first trimester of pregnancy demonstrated that approximately one-half

were associated with trisomic or monosomic abortuses [4,5]. (See "Congenital cytogenetic abnormalities".)

Trisomic embryos have been described for almost all of the autosomes. Some trisomies (eg, trisomy 13, 18, 21, and those involving the sex chromosomes) can result in live births [6], while others (eg, trisomy 16) are detected only in abortuses. The risk of trisomy of the autosomal and sex chromosomes increases with maternal age, but the magnitude of this risk varies somewhat depending on the chromosome (table 2) [7-9]. The incidence of monosomy X (Turner syndrome) does not increase with maternal age.

The extra chromosome of a trisomic group is maternal in origin in the vast majority of cases. This suggests a defect in chromosome segregation during oogenesis, rather than defective spermatogenesis. Prolonged retention of oocytes or sperm in the reproductive tract before fertilization does not seem to be a cause of nondisjunction leading to Down syndrome or of major birth defects [10], but altered recombination appears to have a role [11,12]. In this model, age-related perturbations in the meiotic machinery cause homologues with susceptible crossover configurations to segregate incorrectly. Distal crossovers may be unable to lock homologues together, allowing them to move independently and possibly drift together to the same spindle pole; pericentromeric crossovers may lock homologues too tightly, so they are unable to separate from one another and thus migrate together to the same spindle pole.

Nonallelic homologous recombination — Other sporadic chromosomal defects occur through abnormalities in recombination, which refers to the natural process of breaking and rejoining DNA strands during meiosis to produce new combinations of genes and, thus, generate genetic variation.

Nonallelic homologous recombination (NAHR) typically involves the exchange of unequal amounts of genetic material during pairing between homologous chromosomes. Thus, the gene copy number is altered or hybrid genes are formed with novel properties. Single-gene phenotypes (ie, a trait or series of traits that can be attributed to mutation in a single gene), are produced that may be transmitted in a Mendelian fashion. For the X and Y chromosomes, the frequency of new unequal recombinational events is approximately 1:30,000 [13]. Structural variation of chromosomes can increase the frequency of unequal recombination.

Unequal recombination may delete or disrupt one or more genes; in the latter case, two or more Mendelian phenotypes can be produced. This condition is called a "contiguous gene syndrome" [14]. (See "Congenital cytogenetic abnormalities".)

Inversions — Chromosome inversions are the result of abnormal recombinational events. There are two types of inversion (figure 3):

- Paracentric, involving both sides of the centromere.
- Pericentric, involving only one side [15,16].

Paracentric chromosomes form inversion loops to pair with their normal chromosome partners. If crossing over occurs outside the inversion loop, then no abnormal products are formed. If the breakage and recombination occur within the loop, the products have both duplicated and deleted segments, a phenomenon that is referred to as "recombination aneusomy" [17]. The phenotype may be abnormal if the duplicated and deleted regions in the offspring are large in size. The sites of recombination may vary from one gamete to another, so that each offspring may appear to be a sporadic case with a novel phenotype.

Deletions and duplications — Deletions are missing portions of a chromosome, while duplications involve an extra copy of a portion of the chromosome. Deletion carriers are effectively monosomic for the genes in the missing segment, whereas duplication carriers are trisomic for the duplicated genes.

Deletions and duplications are generally described by their location (eg, duplication 4p) or by the two chromosomal break points defining the defective area (4p15.2,16.1). If the deletion is a common one, it may be defined by an eponym (5 p minus is known as Cri du Chat syndrome).

Larger deletions and duplications can be identified cytogenetically because these banding patterns are unique to each chromosome. However, microdeletions and microduplications may be too small to be detected by traditional cytogenetic techniques and may require molecular techniques. Common microdeletions/duplications can be identified by fluorescence in situ hybridization (FISH) using a probe for the deleted or duplicated genes or by array genomic hybridization using microarrays (DNA chips).

Some deletions occur more frequently than would be expected by chance alone and cause several specific contiguous gene deletion syndromes. DiGeorge syndrome, as an example, usually results from a microdeletion of the long arm of chromosome 22 (22q11.2) and is associated with phenotypic abnormalities due to defects of the fourth branchial arch and adjacent structures (ie, a developmental field defect). Clinical manifestations include: thymic and parathyroid hypoplasia or aplasia, aortic arch malformations, short palpebral fissures, micrognathia with a short philtrum, and ear anomalies. Another common contiguous gene deletion syndrome is terminal deletion of the short arms of the 4th chromosome (4 p minus, or Wolf-Hirschhorn syndrome). (See "Congenital cytogenetic abnormalities".)

Translocations — Translocations are rearrangements that occur as a result of breaks in each of two different chromosomes with subsequent joining of the non-contiguous ends. In a number of cases in which the breakpoints of the translocated chromosomes have been identified, the sites of recombination were shown to involve both homologous and non-homologous DNA sequences [18,19]. These occur via NAHR or non-homologous end-joining. If the chromosomal constitution is such that there has been no net loss or gain of information, then the translocation is considered to be balanced.

By comparison, if the net genetic information has changed, then the translocation is unbalanced (figure 4). Unbalanced translocations produce variant phenotypes by changing the gene copy number through deletion or duplication, and by interrupting genes and putting them under the control of new regulatory elements. This may be recognizable as a Mendelian condition, such as Duchenne muscular dystrophy or neurofibromatosis I [20,21]. However, physical rearrangement of chromosomes, including translocations, may cause the chromosomes to be transmitted in a non-Mendelian, but predictable, pattern [6].

Both the duplicated and deleted chromosomal regions may contribute to the phenotype, although one may be overriding. As an example, the deletion of one of the short arms of chromosome 17 may produce isolated lissencephaly (smooth brain) despite the fact that there may be a duplicated segment on another chromosome [22]. This suggests that no genes are present in these duplicate regions or that dosage alterations of genes in these regions do not affect the phenotype in ways that have been recognized.

SINGLE GENE DISORDERS

Patterns of inheritance — Infants are at increased risk for having birth defects if their parents are carriers of genetic mutations. Three traditional patterns of single gene transmission are recognized in humans, although distinctions among them have become increasingly blurred as more sensitive biochemical markers of phenotype expression become available. (See "Basic principles of genetic disease".)

Autosomal dominant — Autosomal dominant traits are generally expressed in the heterozygous state (figure 5). The likelihood of transmitting a dominant trait from parent to child is usually 50 percent. Generally, these traits are expressed equally in male and female offspring. For some dominant traits, such as familial hypercholesterolemia and factor V Leiden, the phenotype may be more severe in the homozygous than the heterozygous state. For other traits, including blood groups and hemoglobin variants, expression of the allele from each of the parents can be demonstrated, a phenomenon that is

referred to as co-dominance.

The phenotype of an individual carrying a gene with an autosomal dominant mutation may vary based upon the penetrance and expressivity of the mutation.

- Penetrance indicates whether or not the mutant gene is expressed as a specific phenotype. If a dominant mutation produces a characteristic abnormal phenotype expression in all affected individuals, it has complete penetrance, whereas a dominant mutation whose characteristic phenotype is not present in all affected individuals has incomplete penetrance.
- Expressivity is the extent to which an autosomal dominant mutation that is penetrant produces characteristic phenotypic features. If all individuals carrying the affected gene do not share very similar phenotypes, the mutation has variable expressivity. Such a gene can produce a range of phenotypic features, from mild to severe. Neurofibromatosis is an example of a disease with variable expressivity. (See "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis".)

Autosomal recessive — Autosomal recessive traits are generally expressed in homozygotes, but not in heterozygotes (figure 6). The usual likelihood that carrier parents will have affected offspring is 25 percent. Proof of this pattern of inheritance requires demonstrating that both parents are heterozygotes. This can be readily accomplished if each of the parental alleles can be identified. As an example, electrophoretic analysis of affected individuals with sickle cell anemia will reveal primarily the S form of the hemoglobin beta chain, while carriers will demonstrate both S and A forms.

Double heterozygotes carry two different mutated versions of a given gene, with pathological consequences. As an example, in hemoglobin SC disease an affected individual has inherited both an S and a C beta hemoglobin chain mutated gene from his or her parents. Currently, many heterozygote detection tests are performed by direct analysis of DNA. (See "Laboratory diagnosis of the hemoglobinopathies".)

Consanguinity — Autosomal recessive conditions are found more commonly in ethnic groups who marry within the group or in consanguineous relationships, because recessive genes are relatively rare. Consanguineous marriages occur in most populations. It is a customary practice in the Middle East, in parts of South Asia and Southeast Asia, and among many tribes in sub-Saharan Africa people who have migrated from these parts of the world to other countries may still practice consanguineous marriages. On a global basis, it is estimated that at least 20 percent of people live in communities with a preference for consanguineous marriage and that ≥8.5 percent of children have consanguineous parents [23]. The birth prevalence of congenital and genetic disorders among offspring of consanguineous couples is about double that compared to non-consanguineous couples (7.9 versus 4.3 percent in the Birmingham Birth Study [24]; 6.1 versus 2.5 percent in the Born in Bradford study [25]; 6.1 versus 2.8 percent in a multiethnic population in Berlin [26]). These percentages vary somewhat depending on the degree of consanguinity (eg, in the Berlin study: first cousin 8.5 percent, beyond first cousin 3.9 percent [26]).

X-linked conditions — These disorders are more commonly manifested in males than females. Males transmit their Y rather than their X chromosome to their sons, thus X linkage is characterized by the absence of male-to-male transmission (figure 7). By comparison, all of the daughters of affected males inherit the gene for the disorder. X-linked dominant conditions are those for which the presence of a single allele is sufficient to result in expression in females, whereas X-linked recessive conditions require two alleles for expression in females. Relatively few X-linked dominant conditions have been identified. These conditions (eg, hypophosphatemic rickets and adrenomyeloneuropathy [27]) are generally milder in females than they are in males. Some X-linked dominant conditions, such as incontinentia pigmenti and Rett syndrome, are rarely observed in males and are presumed to be lethal to

the affected male embryo since it has only one X chromosome [28,29].

Manifestations — The catalog for clinical phenotypes is Mendelian Inheritance in Man, originally published by Victor McKusick in 1964, and now updated on a continuous basis by him and others in an online version (www.ncbi.nlm.nih.gov/omim) [30]. The catalog lists over 7000 conditions, which represent distinct phenotypes or allelic forms of a disorder.

The frequency of single gene disorders in North America was tracked by the British Columbia Birth Defects Registry [31]. The overall frequency was estimated to be 1 percent, with 0.7 percent as dominant conditions, 0.25 percent as recessive conditions, and 0.04 percent as X-linked conditions [32].

The impact of disadaptive Mendelian phenotypes in humans has been examined using Mendelian Inheritance in Man as a guide [33]. Twenty-five percent of these phenotypes are apparent at birth, and over 90 percent by the end of puberty. Conditions with decreased reproductive fitness are generally manifested earlier in life.

Disadaptive Mendelian phenotypes typically require that some cumulative damage occur before they become apparent. Over one-half of the phenotypes involve more than one anatomic or functional system. Lifespan is reduced in 57 percent of these disorders, more commonly in autosomal recessive and X-linked diseases; reproductive capacity is reduced in 69 percent; and the nervous system is affected in over 30 percent. The age of appearance tends to be more variable for autosomal dominant compared to autosomal recessive or X-linked conditions. However, studies of frequency, morbidity, and fitness of single-gene conditions were based upon known human disorders. Therefore, these figures may represent an underestimate because the Mendelian basis for fetal and adult-onset disorders may not have been recognized when the studies were performed.

NON-MENDELIAN PATTERNS OF INHERITANCE

Unstable DNA and fragile X syndrome — Certain genes have been found to be inherently unstable triplet repeat regions, with the number of triplet repeats (usually cytosine-guanine-guanine (CGG)n) varying during both meiosis and mitosis. If the number of triplet repeats reaches a critical level, the affected gene can become methylated and, thus inactivated. This can result in phenotypic abnormalities.

Some triplet regions expand only during female meiosis, while others can expand when transmitted by either parent. As an example, fragile X syndrome is due to the fragile X mutation, which is a region of unstable CGG triplet repeats on the X chromosome at the position, Xq27. This region is inactivated by methylation when it reaches a critical size: individuals carrying 2 to 49 repeats are phenotypically normal; those carrying 50 to 199 repeats are also asymptomatic, although they are said to have a premutation which can expand if it is passed on to an offspring; and those with more than 200 repeats have the full mutation and, if methylation occurs, are usually affected. Phenotypic variability is caused by lyonization in affected females and mosaicism due to selective mitotic expansion and/or variable degrees of methylation in both males and females. Therefore, it is exceedingly difficult to precisely predict an offspring's degree of neurologic abnormality.

Fragile X syndrome is the most common form of familial intellectual disability in males. Affected individuals have mild to severe intellectual disability, attention deficit-hyperactivity disorder, speech and language problems, narrow face with large jaw, long prominent ears, macroorchidism (in postpubertal males), and, occasionally, seizures. The incidence of the full fragile X syndrome is generally quoted as 1/1000 males and 1/2000 females.

Fragile X syndrome was originally diagnosed by culturing cells in a folate deficient medium and then assessing the cultures for X-chromosome breakage by cytogenetic analysis of the long arm of the X chromosome (Xq27-28). This technique proved unreliable for both diagnosis and carrier testing. The fragile X abnormality is now directly determined by analysis of the number of CGG repeats and their

methylation status using restriction endonuclease digestion and Southern blot analysis.

Other autosomal dominant neurologic disorders caused by triplet repeat expansion include myotonic dystrophy, Huntington chorea, Friedreich ataxia, X-linked spinal, bulbar muscular atrophy (Kennedy's disease), and spinocerebellar ataxia.

Imprinting — Imprinting refers to the differential expression of genetic material depending upon whether it was inherited from the male or female parent. Thus, the same genetic information transmitted from a mother or a father can result in a different phenotype because the alleles are reversibly modified in the parental gametes such that in the offspring the two alleles are expressed in functionally different ways. Imprinted genes are inactivated by methylation of their promoter region; this chemical modification of the gene allele can be used to identify maternal or paternal origin of chromosome. The extent of the imprinting is determined by the gender of the transmitting parent. Gene function is dependent upon the active gene inherited from the other parent.

Imprinted genes can cause genetic disease if the nonimprinted, active gene is mutated or deleted. As an example, two distinct genetic diseases with very different phenotypes result from the same chromosomal deletion at 15q11-13 depending upon the parental source of both the imprinted and deleted gene. If the paternally-derived chromosome 15 is deleted, the result is Prader-Willi syndrome, which is characterized by obesity; hyperphagia; short stature; small hands, feet, and external genitalia; and mild intellectual disability. In contrast, if the maternally-derived chromosome 15 is deleted, the affected individual will have Angelman syndrome, which is characterized by normal stature and weight, severe intellectual disability, absent speech, seizures, ataxia and jerky arm movements, and paroxysms of inappropriate laughter. A deletion is not absolutely required to produce the phenotype. If an individual has two normal intact copies of chromosome 15, but both came from the father (ie, uniparental disomy), the phenotype is Angelman syndrome. Conversely, uniparental disomy (figure 8) resulting in two maternal copies of chromosome 15 produces Prader-Willi syndrome. The risk of the imprinting disorders, Angelman syndrome and Beckwith-Wiedeman syndrome, appears to be increased among children conceived by intracytoplasmic sperm injection (ICSI) [34]. It is unclear whether this association is related to ICSI, in vitro fertilization, or subfertility. (See "Pregnancy outcome after assisted reproductive technology" and "Beckwith-Wiedemann syndrome".)

Mitochondrial inheritance — Mitochondria have a small amount of their own DNA (mtDNA), which is a relatively small portion of total body DNA. This DNA is also subject to deletion or point mutation and several diseases associated with mutations in mtDNA have been found. The inheritance patterns of these disorders are unique since an individual inherits virtually all of his mtDNA from his mother, not from his father. This occurs because the relatively large ovum has many copies of mitochondrial DNA while the sperm has very few, and these are lost during fertilization. The inheritance pattern of mitochondrial DNA disorders is:

- Children of affected males will not inherit the disease.
- Approximately 4 percent (95% CI 0.86-11.54) of children of females affected with a mitochondrial deletion disorder will inherit it [35]. Children of women with a mitochondrial point mutation will inherit the mutation, but the risk of developing the disease, such as Leber hereditary optic neuropathy, is about 50 percent for males and about 10 percent for females [36]. The reason for this gender discordance is not known.

Mitochondrial deletion disorders include Kearns–Sayre syndrome, chronic progressive external ophthalmoplegia, and Pearson bone-marrow pancreas syndrome. Mitochondrial point mutation disorders include Leber hereditary optic neuropathy, myoclonic epilepsy with ragged red fibers (MERRF), and Leigh syndrome (ataxia, hypotonia, spasticity, and optic abnormalities).

Germline or gonadal mosaicism — Mitotic errors occurring in embryonic cells destined to become the

gonad can cause gonadal mosaicism. This entity may explain the occurrence of autosomal dominant mutations causing disease in the absence of a family history. Some examples are achondroplasia or osteogenesis imperfecta or X-linked diseases, such as Duchenne muscular dystrophy. Gonadal mosaicism may account for 6 percent of cases of new autosomal dominant or X-linked recessive mutations.

Multifactorial and polygenic traits — Most inherited traits (eg, height and intelligence) are multifactorial or polygenic: they result from the combined effects of multiple genes interacting with environmental factors. Birth defects caused by this mechanism recur at a far lower rate than those inherited by a Mendelian inheritance pattern. The recurrence risk for first-degree relatives is generally about 2 or 3 percent (eg, neural tube defects). (See "Prenatal screening and diagnosis of neural tube defects".)

Some multifactorial/polygenic disorders have a predilection for one gender. When a family includes an affected member who is of the less frequently affected gender, it indicates that a greater number of abnormal genes or environmental influences are present and, thus, the recurrence risk is higher. As an example, pyloric stenosis is more common in males, therefore when an infant girl is affected, the recurrence risk for her siblings or for her future children is higher than expected. Her male siblings or offspring will have the highest risk of the disease because they are the most susceptible sex; they will also inherit more than the usual number of predisposing genes. (See "Infantile hypertrophic pyloric stenosis".)

The recurrence risk of multifactorial/polygenic disorders is also higher if the defect is more severe, since severity is another indication of a greater burden of abnormal genes and/or environmental influences. As an example, the recurrence risk after the birth of an infant with bilateral cleft lip and palate is twice as high as that after birth of a child with unilateral cleft lip without cleft palate (8 versus 4 percent).

TERATOGENS — A teratogen is an agent that can cause abnormalities in growth, form, or function of a developing fetus. It acts by producing cell death, altering normal growth of tissues, or interfering with normal cellular differentiation or other morphologic processes. The consequences of these actions can be fetal loss, fetal growth restriction, birth defects, or impaired neurologic performance. The following criteria by Shepard have been derived from Koch's postulates and can be used to establish the teratogenicity of an agent [37]:

1 - Exposure to the agent at critical time(s) in prenatal development

2 - Consistent dysmorphic findings reported by high quality epidemiologic studies

3 - Careful delineation of the clinical cases, ideally with a specific defect or syndrome

4 - The presence of a rare environmental exposure associated with a rare defect

5 - Teratogenicity observed in experimental animal studies

6 - The observed association between the agent and the defect is biologically plausible

7 - The agent acts in an unaltered state

Items 1 to 3 or 1, 3, and 4 are essential; 5 to 7 are helpful, but not essential.

Approximately 10 percent of birth defects are caused by exposure to teratogens in the environment. These include maternal illnesses, infectious agents, physical agents, and drugs and chemical agents. Timing is a critical factor:

- The all-or-none rule is thought to apply during the first two weeks after conception. If only a few cells are damaged, then their roles may be compensated by other totipotent cells. If too many cells

are damaged, then the early embryo will not implant or will be spontaneously aborted.

- The embryo is most vulnerable to teratogenic insults since organogenesis is occurring during the embryonic period of development (figure 9). The embryonic period in humans can be defined as from fertilization until the end of the 10th week of gestation (8th week postconception).
- During the fetal period (figure 9), teratogens can cause cell death, retardation of cell growth, or inhibition of normal differentiation. This may result in fetal growth restriction or disorders of the central nervous system that may not be apparent at birth. The eyes, genitalia, central nervous system, and hematopoietic systems continue to develop during the fetal period and remain susceptible to teratogenic insults.

Response to the teratogenic agent is highly individual, influenced not only by timing and dose, but also by the genetic make-up of the mother and the fetus (host susceptibility).

Maternal illness — Several maternal illnesses are associated with birth defects. In each of these conditions, a metabolite or antibody diffuses across the placenta and is toxic to the fetus.

- Pregestational diabetes mellitus is associated with a two to three-fold increase in risk of congenital anomalies, including congenital heart disease and spina bifida, and, less commonly, caudal regression and focal femoral hypoplasia (see "Pregestational diabetes: Preconception counseling, evaluation, and management"). Infants of diabetic mothers are at increased risk for abnormal growth and for hypoglycemia in the newborn period. (See "Infant of a diabetic mother".) All of these risks can be diminished by strict control of the maternal glucose concentration from the time of conception to the time of delivery (figure 10) [38].
- Phenylketonuria is associated with microcephaly, intellectual disability, and congenital heart disease. These abnormalities are thought to result from diffusion of toxic amounts of phenylalanine and its metabolites across the placenta. The risk can be minimized by maternal dietary control of the disease starting from conception and continuing throughout the pregnancy [39,40].
- Androgen producing tumors of the adrenal glands or ovaries can produce virilization of female fetuses.
- Systemic lupus erythematosus is associated with fetal, but not maternal, heart block. (See "Pregnancy in women with systemic lupus erythematosus".)

Obesity — Maternal obesity has been associated with an increased risk of certain types of birth defects. (See "The impact of obesity on female fertility and pregnancy", section on 'Congenital anomalies'.)

Infection — Exposure to infectious agents can result in a variety of problems in the fetus and neonate, including malformations, congenital infection, short and long-term disability, and death. In some instances, the infection may be asymptomatic in the mother [41]. The pathogenesis of the fetal defects is usually direct invasion of fetal tissues leading to damage from inflammation and cell death.

Agents known to be toxic to the fetus or embryo are toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis (the so-called TORCH infections), as well as varicella, parvovirus B19, and lymphocytic choriomeningitis virus (LCMV) [42-47]. Prior immunization is an effective means for preventing rubella and varicella infections during pregnancy. Maternal treatment of syphilis during pregnancy can improve the outcome for both mother and fetus. Influenza may also cause birth defects [48]. (See "Syphilis in pregnancy" and "Varicella-zoster virus infection in pregnancy" and "Parvovirus B19 infection during pregnancy" and "Rubella in pregnancy" and "Prenatal evaluation and intrapartum management of the HIV-infected patient in resource-rich settings" and "Viral meningitis: Clinical features and diagnosis in children", section on 'Other viruses' and "Influenza and pregnancy".)

Nonspecific sonographic signs suggestive of fetal infection include:

- Microcephaly
- Cerebral or hepatic calcifications
- Intrauterine growth restriction
- Hepatosplenomegaly
- Cardiac malformations, limb hypoplasia, hydrocephalus
- Hydrops

Neonates with birth defects associated with disorders of movement and muscle tone, chorioretinitis or cataracts, hearing impairment, hepatosplenomegaly, skin rash, thrombocytopenia, jaundice, or low birth weight are suspects for congenital infection.

Fever associated with infection also can be teratogenic. (See 'Fever/hyperthermia' below.)

Drugs — Maternal drug ingestion, both medical and recreational, is common in pregnancy [49] and can cause adverse fetal and neonatal outcomes. Nonpregnant women are sometimes prescribed medications that are contraindicated in pregnancy because of evidence that the risk of birth defects outweighs any potential benefits of the medication (ie, US Food and Drug Administration category X). These women should be counseled about the adverse effects of these medications and the importance of consistent use of effective contraception. Despite these measures, one study found that 40 percent of women who were prescribed category X medications and oral contraception had refill patterns suggesting suboptimal adherence to the oral contraceptive [50]. This pattern of contraceptive use highlights the difficulty in preventing embryo/fetal exposure to these medications and the desirability of using equivalent but safer medications or other forms of therapy, if available, in women of childbearing potential.

Some common teratogenic medications include:

- Angiotensin converting enzyme inhibitors. (See "Angiotensin converting enzyme inhibitors and receptor blockers in pregnancy".)
- Anticonvulsant agents. (See "Risks associated with epilepsy and pregnancy".)
- Antineoplastic agents. (See "Gestational breast cancer: Epidemiology and diagnosis" and "Management of classical Hodgkin lymphoma during pregnancy".)
- Thalidomide, retinoic acid, methylene blue, misoprostol, penicillamine, fluconazole, lithium, isotretinoin, and acitretin [51-62].

A partial list of additional known teratogens is provided in the table (table 3):

- Retinoic acid is highly teratogenic in the first trimester of pregnancy, leading to spontaneous abortions and fetal malformations, including microcephaly and cardiac anomalies [63]. At doses of only several times the RDA [64], many animal models as well as human studies have shown high incidence of birth defects in mothers who ingested therapeutic doses of retinoic acid for dermatological uses [63]. A safe upper limit for vitamin A intake has been recognized at about 800 to 10,000 IU/day [65]. Acitretin should not be used by women who want to become pregnant as conception is **contraindicated for at least three years after discontinuation**.
- Androgenic agents, such as testosterone or danazol, do not cause malformation, but can virilize a female fetus. Cocaine induced vasoconstriction of uterine vessels is one mechanism for fetal damage from this substance [66]. Infants whose mothers consume alcohol during pregnancy can have fetal alcohol effects (FAE), alcohol-related birth defects (ARBD), fetal alcohol syndrome, or they may be normal [67]. (See "Alcohol intake and pregnancy".)

- Folic acid antagonists (eg, trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbital, primidone, methotrexate) increase the risk of neural-tube defects and possibly cardiovascular defects, oral clefts, and urinary tract defects [68] and placenta-mediated adverse pregnancy outcomes, including preeclampsia, placental abruption, fetal growth restriction, and fetal death [69].

Specific information on the fetal and neonatal risks of maternal drug ingestion during pregnancy and lactation are available from several resources, including:

- www.perinatology.com/exposures/druglist.htm
- www.reprotox.org
- www.OTISpregnancy.org
- http://depts.washington.edu/terisweb/teris/ (requires subscription)
- www.motherisk.org/women/drugs.jsp
- UpToDate drug information database

Physical and environmental agents — A wide variety of physical agents and environmental chemicals have been implicated in the pathogenesis of birth defects. It is impossible to generate a complete list and discussion of environmental teratogens here, but numerous resources are available (eg, http://toxnet.nlm.nih.gov/ and www.OTISpregnancy.org).

Lead — High plasma lead levels are associated with adverse neurobehavioral effects in infants and children; intrauterine exposure may have similar consequences [70]. Studies of potential associations between parental lead exposure and congenital malformations in offspring have not demonstrated a consistent increase in risk or pattern of defects, but often lack biological indices of exposure at developmentally significant times [71]. (See "Occupational and environmental risks to reproduction in females", section on 'Lead'.)

Ionizing radiation — The effects of ionizing radiation on the embryo/fetus are discussed in detail separately. (See "Diagnostic imaging procedures during pregnancy".)

Fever/hyperthermia — Elevation of maternal core temperature from a febrile illness or other source (eg, hot tub) in the first trimester of pregnancy may be associated with an increased risk of congenital anomalies, especially neural tube defects, or miscarriage [72,73]. In a 2014 systematic review and meta-analysis of 46 case-control and cohort studies of the effect of antepartum maternal fever on offspring, maternal fever was associated with increased risks of neural tube defects (OR 2.90, 95% CI 2.22-3.79; nine studies), congenital heart disease (OR 1.54, 95% CI 1.37-1.74; seven studies), and oral clefts (1.94, 95% CI 1.35-2.79; five studies) [74]. Miscarriage rates were not increased. The authors hypothesized that recruitment of patients too late to identify those with early pregnancy losses may explain this finding since animal studies and individual studies support an association [73,75]. The findings from this review underscore the need for carefully performed prospective studies as the available data had several limitations. For example, fever was ascertained by maternal self-report in all but one study and included episodes of fever from up to three months before conception through the prepartum period. In addition, the degree and duration of fever were not consistently reported or accurately determined and it is known from animal studies that the consequences of hyperthermia depend on the extent of temperature elevation, its duration, and the stage of development when it occurs [73,76]. Importantly, fever usually occurs as a response to infection, which necessitates distinguishing the effects of fever from those of an underlying infection and its treatment.

Antipyretic use seems to attenuate the risks associated with fever exposure [74]. As an example, the National Birth Defects Prevention Study (NBDPS) observed that, among women with infection-related fever, single agent use of acetaminophen was not associated with an increase in the overall risk of birth defects, and was associated with a statistically significant reduction in neural tube defects, as well as cleft lip/palate and gastroschisis [77]. These data support the safety of acetaminophen for relief of fever

and pain; however, the reduction in birth defects should be confirmed in other studies before acetaminophen is recommended to febrile women for this purpose.

Fish consumption — Methylmercury exposure, primarily through ingestion of contaminated fish, can cause severe central nervous system damage [78], as well as milder intellectual, motor, and psychosocial impairment [79-81]. Some limitations on fish intake during pregnancy are recommended. (See "Nutrition in pregnancy", section on 'Counseling women about common dietary issues' and "Fish consumption during pregnancy".)

DEFORMATIONS — Deformations are abnormalities that are mechanically produced by alterations of the normal fetal environment. These alterations may be physical constraints or related to vascular accidents. Amniotic bands, as an example, can constrict a developing body part and compromise its blood supply leading to amputation involving the limb, cranium, or body wall. Oligohydramnios may compress the fetus, sometimes causing a flattened facial appearance (ie, Potter's facies). In addition, alterations of normal amniotic fluid pressure and egress of lung fluid may result in pulmonary hypoplasia. The position of the fetus in the uterus (eg, breech) can influence its development by altering head shape or neck positioning in the absence of external influences. Intrauterine leiomyoma or other uterine structural anomalies rarely may cause fetal deformation. (See "Amniotic band sequence".)

SUMMARY AND RECOMMENDATIONS

- Chromosomal abnormalities affect approximately 1 in 200 newborn infants. These defects may be either sporadic or heritable and are due to different etiologies, such as nondisjunction, recombination, inversion, deletion, duplication, and translocation. (See 'Structural chromosomal abnormalities' above.)
- The frequency of single gene disorders is estimated to be 1 percent, with 0.7 percent as dominant conditions, 0.25 percent as recessive conditions and 0.04 percent as X-linked conditions. Twenty-five percent of these phenotypes are apparent at birth, and over 90 percent are apparent by the end of puberty. (See 'Single gene disorders' above.)
- Nonmendelian patterns of inheritance may involve unstable triplet repeat regions, imprinting, mitochondrial inheritance, germline mosaicism, and multifactorial inheritance. (See 'Non-Mendelian patterns of inheritance' above.)
- A teratogen is an agent that can cause abnormalities in form or function of a developing fetus. Maternal exposure to drugs, medical disorders, infection, and environmental agents can be teratogenic. A partial list of additional known teratogens is provided in the table (table 3). (See 'Teratogens' above.)
- Deformations are abnormalities that are mechanically produced by alterations of the normal fetal environment, such as amniotic bands or oligohydramnios. (See 'Deformations' above.)

REFERENCES

1. Brent RL. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and postconception environmental radiation exposures. Teratology 1999; 59:182.
2. Jacobs PA, Melville M, Ratcliffe S, et al. A cytogenetic survey of 11,680 newborn infants. Ann Hum Genet 1974; 37:359.
3. Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. Clin Genet 1975; 8:223.

4. Boué A, Boué J. Chromosome abnormalities and abortion. Basic Life Sci 1974; 4:317.
5. Burgoyne PS, Holland K, Stephens R. Incidence of numerical chromosome anomalies in human pregnancy estimation from induced and spontaneous abortion data. Hum Reprod 1991; 6:555.
6. Sutherland, GRJM. Chromosome Abnormalities and Genetic Counseling, Oxford University Press, New York, 1996.
7. Thomas NS, Ennis S, Sharp AJ, et al. Maternal sex chromosome non-disjunction: evidence for X chromosome-specific risk factors. Hum Mol Genet 2001; 10:243.
8. Risch N, Stein Z, Kline J, Warburton D. The relationship between maternal age and chromosome size in autosomal trisomy. Am J Hum Genet 1986; 39:68.
9. Hassold T, Warburton D, Kline J, Stein Z. The relationship of maternal age and trisomy among trisomic spontaneous abortions. Am J Hum Genet 1984; 36:1349.
10. Simpson JL, Gray R, Perez A, et al. Fertilisation involving ageing gametes, major birth defects, and Down's syndrome. Lancet 2002; 359:1670.
11. Lamb, NE, Hassold, TJ. Nondisjunction — A view from ringside. N Engl J Med 2004; 19:1931.
12. Lamb NE, Sherman SL, Hassold TJ. Effect of meiotic recombination on the production of aneuploid gametes in humans. Cytogenet Genome Res 2005; 111:250.
13. de la Chapelle A. Analytic review: nature and origin of males with XX sex chromosomes. Am J Hum Genet 1972; 24:71.
14. Schmickel RD. Contiguous gene syndromes: a component of recognizable syndromes. J Pediatr 1986; 109:231.
15. Madan K. Paracentric inversions: a review. Hum Genet 1995; 96:503.
16. Pericentric inversions in man. A French collaborative study. Groupe de Cytogeneticiens Francais. Annales Genet 1986; 29:129.
17. Schroeder HW Jr, Forbes S, Mack L, et al. Recombination aneusomy of chromosome 5 associated with multiple severe congenital malformations. Clin Genet 1986; 30:285.
18. van Bakel I, Holt S, Craig I, Boyd Y. Sequence analysis of the breakpoint regions of an X;5 translocation in a female with Duchenne muscular dystrophy. Am J Hum Genet 1995; 57:329.
19. Petit C, de la Chapelle A, Levilliers J, et al. An abnormal terminal X-Y interchange accounts for most but not all cases of human XX maleness. Cell 1987; 49:595.
20. Monaco AP, Kunkel LM. Cloning of the Duchenne/Becker muscular dystrophy locus. Adv Hum Genet 1988; 17:61.
21. Ledbetter DH, Rich DC, O'Connell P, et al. Precise localization of NF1 to 17q11.2 by balanced translocation. Am J Hum Genet 1989; 44:20.
22. Dobyns WB, Truwit CL. Lissencephaly and other malformations of cortical development: 1995 update. Neuropediatrics 1995; 26:132.
23. Modell B, Darr A. Science and society: genetic counselling and customary consanguineous marriage. Nat Rev Genet 2002; 3:225.
24. Bundey S, Alam H. A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. Eur J Hum Genet 1993; 1:206.
25. Sheridan E, Wright J, Small N, et al. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet 2013; 382:1350.
26. Becker R, Keller T, Wegner RD, et al. Consanguinity and pregnancy outcomes in a multi-ethnic, metropolitan European population. Prenat Diagn 2015; 35:81.
27. Moser HW, Moser AE, Singh I, O'Neill BP. Adrenoleukodystrophy: survey of 303 cases: biochemistry, diagnosis, and therapy. Ann Neurol 1984; 16:628.

28. LENZ W. [On the genetics of incontinentia pigmenti]. Ann Paediatr 1961; 196:149.
29. Comings DE. The genetics of Rett syndrome: the consequences of a disorder where every case is a new mutation. Am J Med Genet Suppl 1986; 1:383.
30. McKusick, VA. "Mendelian Inheritance in Man", Johns Hopkins University Press, Baltimore, 1998.
31. Baird PA, Anderson TW, Newcombe HB, Lowry RB. Genetic disorders in children and young adults: a population study. Am J Hum Genet 1988; 42:677.
32. Baird PA. Measuring birth defects and handicapping disorders in the population: the British Columbia Health Surveillance Registry. CMAJ 1987; 136:109.
33. Costa T, Scriver CR, Childs B. The effect of Mendelian disease on human health: a measurement. Am J Med Genet 1985; 21:231.
34. Allen C, Reardon W. Assisted reproduction technology and defects of genomic imprinting. BJOG 2005; 112:1589.
35. Chinnery PF, DiMauro S, Shanske S, et al. Risk of developing a mitochondrial DNA deletion disorder. Lancet 2004; 364:592.
36. Man PY, Turnbull DM, Chinnery PF. Leber hereditary optic neuropathy. J Med Genet 2002; 39:162.
37. Shepard TH. "Proof" of human teratogenicity. Teratology 1994; 50:97.
38. Garner P. Type I diabetes mellitus and pregnancy. Lancet 1995; 346:157.
39. Waisbren SE, Hanley W, Levy HL, et al. Outcome at age 4 years in offspring of women with maternal phenylketonuria: the Maternal PKU Collaborative Study. JAMA 2000; 283:756.
40. Levy HL, Ghavami M. Maternal phenylketonuria: a metabolic teratogen. Teratology 1996; 53:176.
41. Klein, JO, Baker, CJ, Remington, JS, Wilson, CB. Current concepts of infections of the fetus and newborn infant. In: Infectious Diseases of the Fetus and Newborn Infant, 6th ed, Remington, JS, Klein, JO, Wilson, CB, Baker, CJ (Eds), Elsevier Saunders, Philadelphia 2006. p.3.
42. Webster WS. Teratogen update: congenital rubella. Teratology 1998; 58:13.
43. Lynfield R, Eaton RB. Teratogen update: congenital toxoplasmosis. Teratology 1995; 52:176.
44. Demmler GJ. Congenital cytomegalovirus infection and disease. Adv Pediatr Infect Dis 1996; 11:135.
45. Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. Br J Obstet Gynaecol 1998; 105:836.
46. Jordan EK, Sever JL. Fetal damage caused by parvoviral infections. Reprod Toxicol 1994; 8:161.
47. Bonthius DJ, Perlman S. Congenital viral infections of the brain: lessons learned from lymphocytic choriomeningitis virus in the neonatal rat. PLoS Pathog 2007; 3:e149.
48. Luteijn JM, Brown MJ, Dolk H. Influenza and congenital anomalies: a systematic review and meta-analysis. Hum Reprod 2014; 29:809.
49. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open 2014; 4:e004365.
50. Steinkellner A, Chen W, Denison SE. Adherence to oral contraception in women on Category X medications. Am J Med 2010; 123:929.
51. Barr M Jr. Teratogen update: angiotensin-converting enzyme inhibitors. Teratology 1994; 50:399.
52. Hanson JW. Teratogen update: fetal hydantoin effects. Teratology 1986; 33:349.
53. Lammer EJ, Sever LE, Oakley GP Jr. Teratogen update: valproic acid. Teratology 1987; 35:465.
54. Cragan JD. Teratogen update: methylene blue. Teratology 1999; 60:42.
55. Miller MT, Strömland K. Teratogen update: thalidomide: a review, with a focus on ocular findings

and new potential uses. Teratology 1999; 60:306.

56. Rosa FW, Wilk AL, Kelsey FO. Teratogen update: vitamin A congeners. Teratology 1986; 33:355.
57. Rosa FW. Teratogen update: penicillamine. Teratology 1986; 33:127.
58. Warkany J. Teratogen update: lithium. Teratology 1988; 38:593.
59. Gonzalez CH, Marques-Dias MJ, Kim CA, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. Lancet 1998; 351:1624.
60. Pursley TJ, Blomquist IK, Abraham J, et al. Fluconazole-induced congenital anomalies in three infants. Clin Infect Dis 1996; 22:336.
61. Eller DP, Patterson CA, Webb GW. Maternal and fetal implications of anticonvulsive therapy during pregnancy. Obstet Gynecol Clin North Am 1997; 24:523.
62. Mulvihill JJ, McKeen EA, Rosner F, Zarrabi MH. Pregnancy outcome in cancer patients. Experience in a large cooperative group. Cancer 1987; 60:1143.
63. Soprano DR, Soprano KJ. Retinoids as teratogens. Annu Rev Nutr 1995; 15:111.
64. Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high vitamin A intake. N Engl J Med 1995; 333:1369.
65. Biesalski HK, Hemmes C, El Hanafy M, et al. Long-term administration of high dose vitamin A to rats does not cause fetal malformations: macroscopic, skeletal and physicochemical findings. J Nutr 1996; 126:973.
66. Landry SH, Whitney JA. The impact of prenatal cocaine exposure: studies of the developing infant. Semin Perinatol 1996; 20:99.
67. Gladstone J, Nulman I, Koren G. Reproductive risks of binge drinking during pregnancy. Reprod Toxicol 1996; 10:3.
68. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000; 343:1608.
69. Wen SW, Zhou J, Yang Q, et al. Maternal exposure to folic acid antagonists and placenta-mediated adverse pregnancy outcomes. CMAJ 2008; 179:1263.
70. Gomaa A, Hu H, Bellinger D, et al. Maternal bone lead as an independent risk factor for fetal neurotoxicity: a prospective study. Pediatrics 2002; 110:110.
71. Rischitelli G, Nygren P, Bougatsos C, et al. Screening for elevated lead levels in childhood and pregnancy: an updated summary of evidence for the US Preventive Services Task Force. Pediatrics 2006; 118:e1867.
72. Li DK, Janevic T, Odouli R, Liu L. Hot tub use during pregnancy and the risk of miscarriage. Am J Epidemiol 2003; 158:931.
73. Edwards MJ. Review: Hyperthermia and fever during pregnancy. Birth Defects Res A Clin Mol Teratol 2006; 76:507.
74. Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. Pediatrics 2014; 133:e674.
75. Edwards MJ. Hyperthermia as a teratogen: a review of experimental studies and their clinical significance. Teratog Carcinog Mutagen 1986; 6:563.
76. Graham JM Jr, Edwards MJ, Edwards MJ. Teratogen update: gestational effects of maternal hyperthermia due to febrile illnesses and resultant patterns of defects in humans. Teratology 1998; 58:209.
77. Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects: findings from the National Birth Defects Prevention Study. Obstet Gynecol 2010; 115:109.
78. Harada M. Congenital Minamata disease: intrauterine methylmercury poisoning. Teratology 1978;

18:285.

79. Crump KS, Kjellström T, Shipp AM, et al. Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. Risk Anal 1998; 18:701.
80. Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 1997; 19:417.
81. Kjellstrom T, Kennedy P, Wallis S, et al. Physical and mental development of children with prenatal exposure to mercury from fish. Stage 1 and stage 2 results at ages 4 and six. National Swedish Envirnomental Board Reports #3080 (1980) and 3642 (1986).

Topic 6829 Version 17.0

GRAPHICS

Leading categories of birth defects

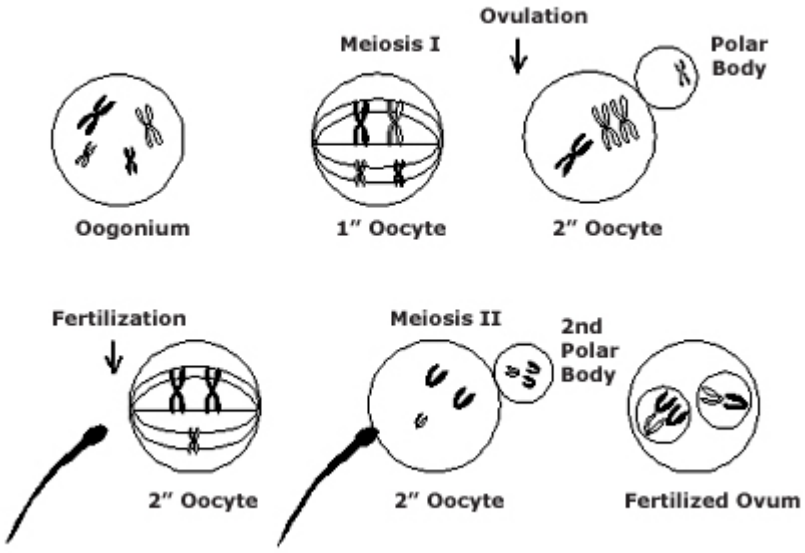
Birth defects	Estimated incidence
Structural/metabolic	
Heart and circulation	1 in 115 births
Muscles and skeleton	1 in 130 births
Club foot	1 in 735 births
Cleft lip/palate	1 in 930 births
Genital and urinary tract	1 in 135 births
Nervous system and eye	1 in 235 births
Anencephaly	1 in 8,000 births
Spina bifida	1 in 2,000 births
Chromosomal syndromes	1 in 600 births
Down syndrome (trisomy 21)	1 in 900 births
Respiratory tract	1 in 900 births
Metabolic disorders	1 in 3,500 births
PKU	1 in 12,000 births
Congenital infections	
Congenital syphilis	1 in 2,000 births
Congenital HIV infection	1 in 2,700 births
Congenital rubella syndrome	1 in 100,000 births
Other	
Rh disease	1 in 1,400 births
Fetal alcohol syndrome	1 in 1,000 births

Note: all numbers are based on the best available estimates, which underestimate the incidence of many birth defects.

Unpublished review of the literature and information from various state and regional birth defects surveillance systems (California, Iowa, Metropolitan Atlanta, New York, and Texas). http://www. marchofdimes.com/aboutus/680_2164.asp Copyright © 2000 March of Dimes Perinatal Data Center. Used by permission.

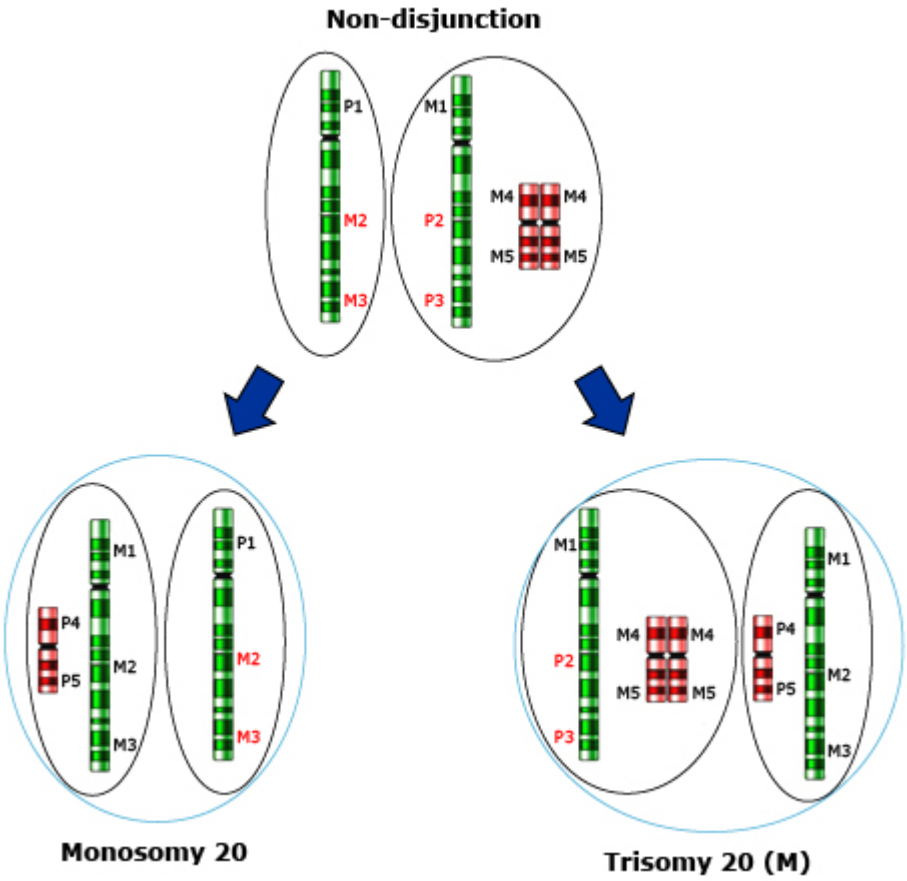
Graphic 79937 Version 1.0

Chromosomal nondisjunction in meiosis I resulting in trisomy



Graphic 51363 Version 1.0

Non-disjunction



Consequence of non-disjunction of chromosome 20, with two copies of chr20 in one gamete, and none in the other. Either monosomy (left) or trisomy (right) can result, depending on which of the two abnormal gametes contributes to embryo formation.

Graphic 81597 Version 1.0

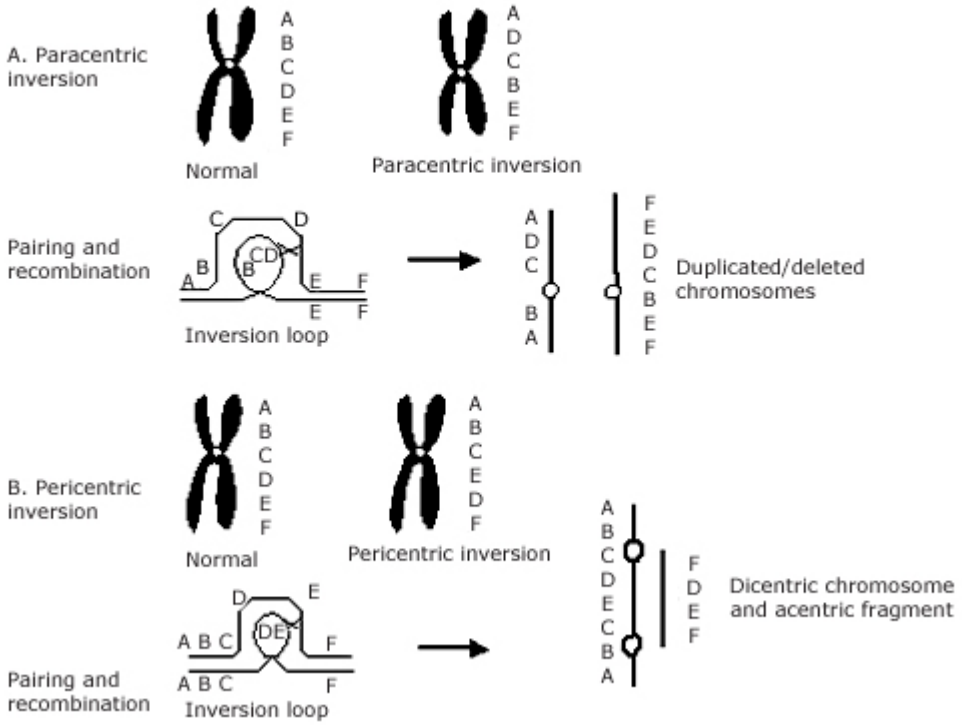
Maternal age-related Down syndrome risk at three gestational ages

Maternal age (completed years)	Down syndrome risk (1:n) at:		
	Term*	16 weeks	10 weeks
20	1477	1211	1152
21	1461	1184	1125
22	1441	1168	1110
23	1415	1147	1090
24	1382	1120	1064
25	1340	1085	1032
26	1287	1029	978
27	1221	977	928
28	1141	901	856
29	1047	827	775
30	939	733	686
31	821	632	591
32	696	536	494
33	572	435	401
34	456	346	315
35	353	265	240
36	267	197	179
37	199	147	131
38	148	108	96
39	111	80	71
40	85	60	53
41	67	47	41
42	54	38	32
43	45	31	27
44	39	26	22
45	35	23	19

* Based on Risk = $1/((1 + \exp^{(7.330-4.211)}/(1 + \exp^{(-0.282x(age-37.23))}))$ from Morris JK, et al. J Med Screen 2002; 9:2.

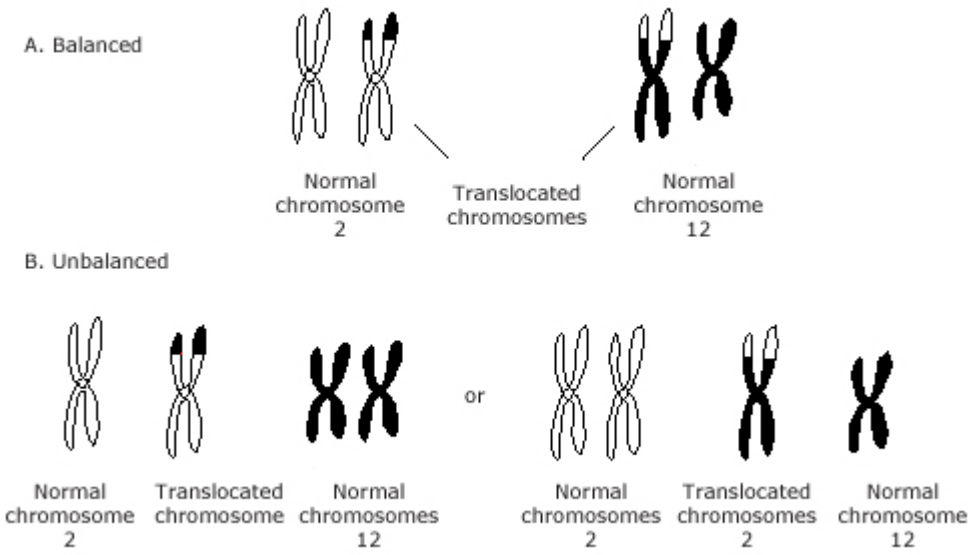
Graphic 75423 Version 6.0

Effects of chromosomal inversions on recombination



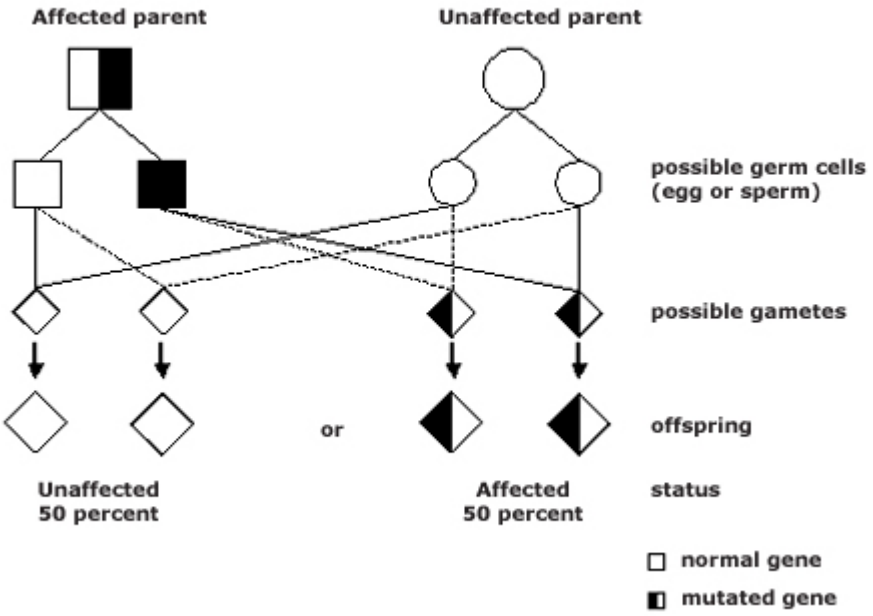
Graphic 65339 Version 1.0

Chromosomal translocations



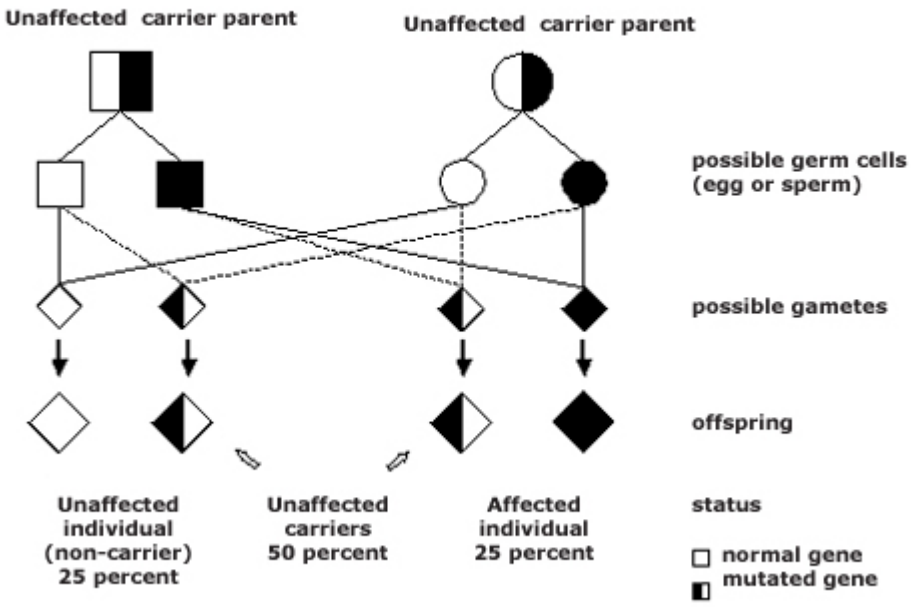
Graphic 71519 Version 1.0

Dominant inheritance



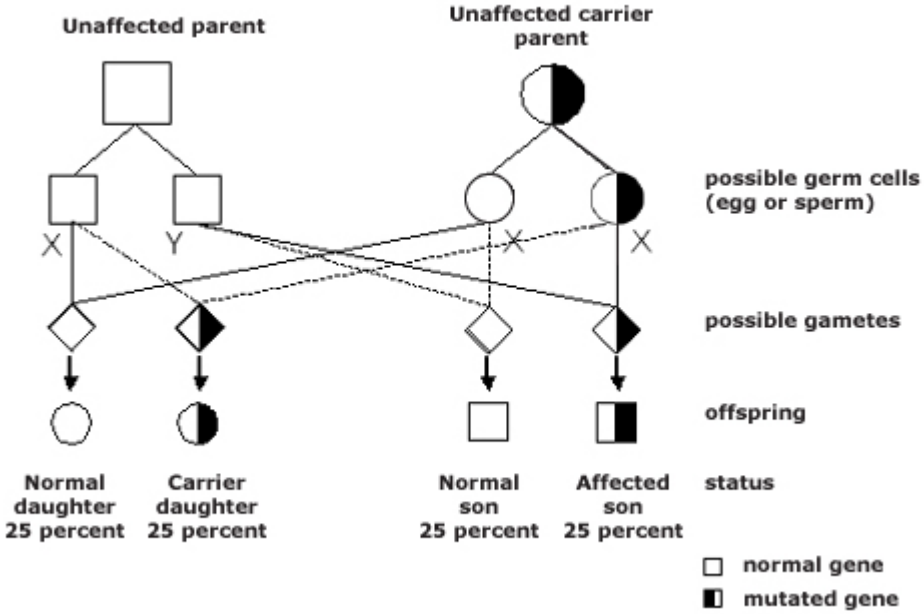
Graphic 71414 Version 1.0

Recessive inheritance



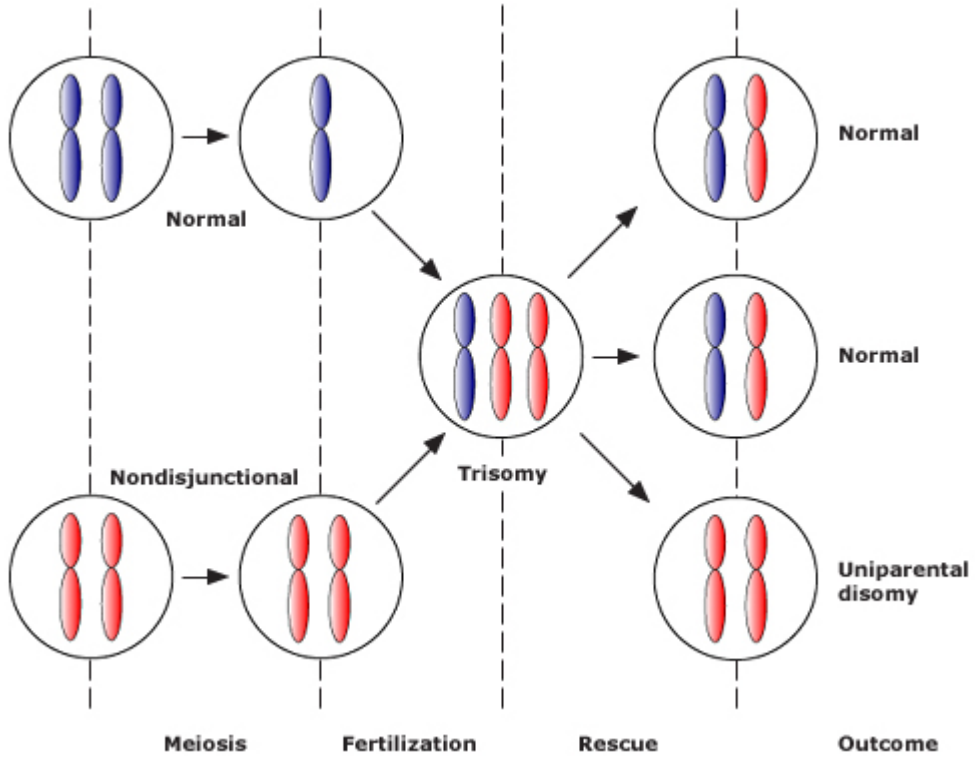
Graphic 50436 Version 1.0

X linked inheritance



Graphic 53159 Version 1.0

Postulated mechanism of uniparental disomy

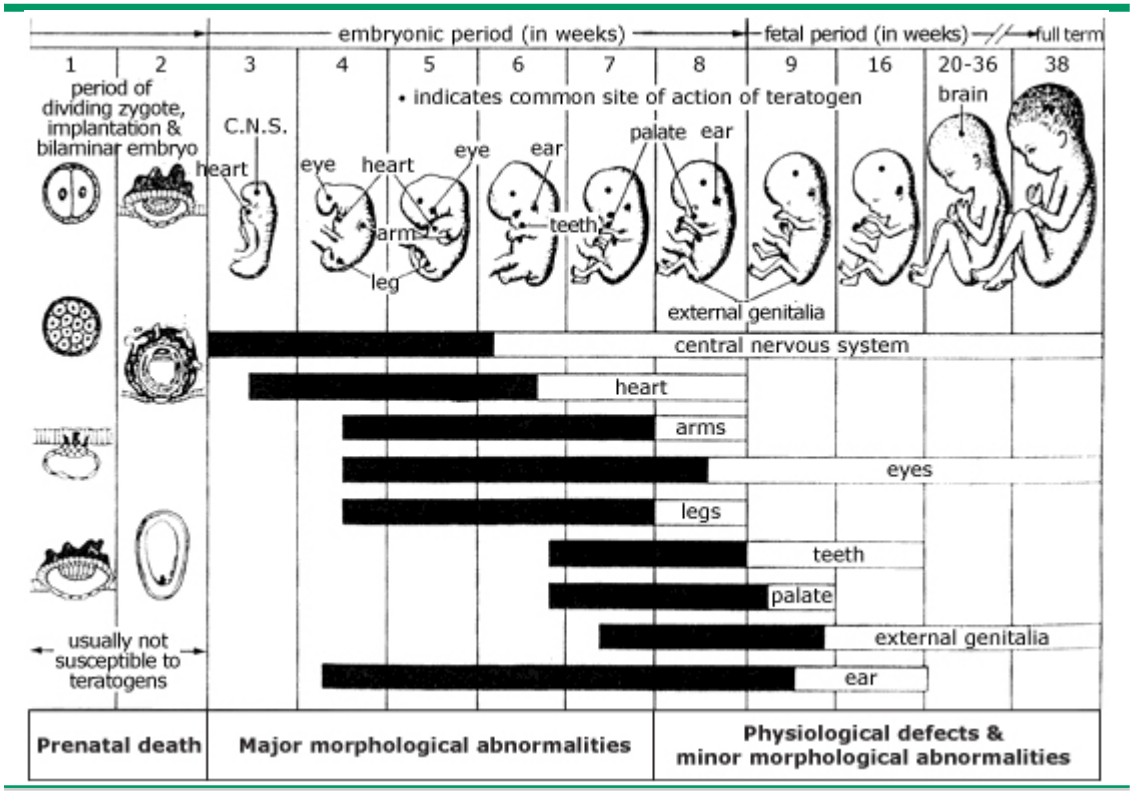


Chromosomal nondisjunction during meiosis leads, after fertilization, to trisomy. Subsequent loss of one chromosome (rescue) could lead to the formation of cells with a chromosome from each parent or cells in which both chromosomes were from the disomic gamete.

Reprinted from Preece, MA, Moore, GE. Genomic Imprinting, Uniparental Disomy and Fetal Growth. Trends in Endocrinology and Metabolism 2000; 11:270. Copyright 2000, with permission from Elsevier Science.

Graphic 72197 Version 1.0

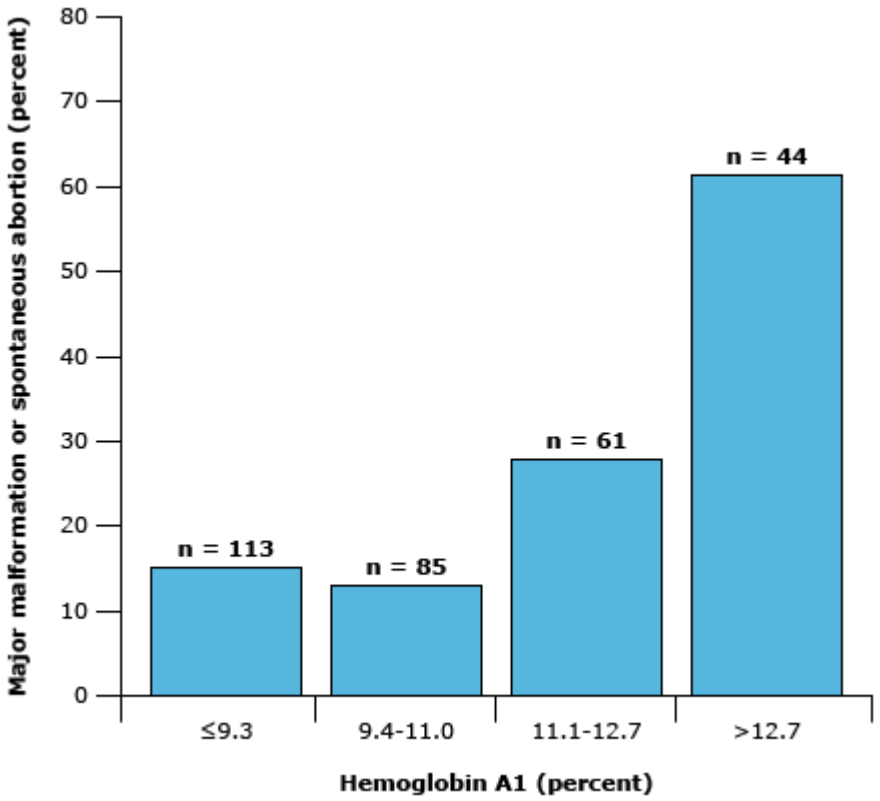
The developing fetus



Reproduced with permission from: Moore, K. The developing human: Clinically oriented embryology, WB Saunders, Philadelphia 1982. Copyright ©1982 Elsevier.

Graphic 56642 Version 1.0

Deleterious effect of poor glycemic control on fetal outcome



Combined incidence of major malformation and spontaneous abortion according to the hemoglobin A1 (HbA1) value during the first trimester of pregnancy in 303 women with type 1 diabetes. The risk rose markedly at HbA1 values above 11 percent (approximately equivalent to an AIC value of 8.5 percent). Other studies have found an increase in risk at A1C values above 9.5 percent.

Data from: Greene MF, Hare JW, Cloherty JP, et al, Teratology 1989; 39:225.

Graphic 67498 Version 4.0

Selected agents with potential adverse fetal effects

Reproductive toxin	Alleged effects
Aminopterin, methotrexate	Growth retardation, microcephaly, meningomyelocele, mental retardation, hydrocephalus, and cleft palate
Androgens	Masculinization of the developing female fetus can occur from androgens and high doses of some male-derived progestins.
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	Fetal hypotension syndrome in second and third trimester resulting in fetal kidney hypoperfusion and anuria, oligohydramnios, pulmonary hypoplasia, and cranial bone hypoplasia. Heart defects from 1st trimester exposure.
Antidepressants	Recent publications have implicated some of the SSRIs administered in the last trimester with postnatal neurobehavioral effects that are transient and whose long-term effects have not been determined. First-trimester exposures to some SSRIs have been
Tetracycline	This drug produces bone and teeth staining, it does not increase the risk of any other malformations.
Thalidomide	This drug results in an increased incidence of deafness, anotia, preaxial limb-reduction defects, phocomelia, ventricular septal defects, and gastrointestinal atresias. The susceptible period is from the twenty-second to the thirty-sixth day after conception.
Trimethoprim	This drug was used frequently to treat urinary tract infections and has been linked to an increased incidence of neural tube defects. The risk is not high, but it is biologically plausible because of the drug's effect on lowering folic acid levels, which has resulted in neurologic symptoms in adults taking this drug.
Vitamin A	The malformations reported with the retinoids have been reported with very high doses of vitamin A (retinol). Dosages

	reported to increase the risk of some congenital malformations, predominantly congenital heart disease. The results have not been consistent, but warnings have been issued.
Antituberculous therapy	Isoniazid and paraaminosalicylic acid have an increased risk for some CNS abnormalities.
Caffeine	Moderate caffeine exposure is not associated with birth defects; high exposures are associated with an increased risk of abortion but the data are inconsistent.
Cobalt in hematemic multivitamins	Fetal goiter
Cocaine	Vascular disruptive type malformations in very low incidence; pregnancy loss.
Corticosteroids	High exposures administered systemically have a low risk for cleft palate in some studies, but the epidemiologic studies are not consistent.
Cyclophosphamide and other chemotherapeutic agents and immunosuppressive	Many chemotherapeutic agents used to treat cancer have a theoretical risk for
	to produce birth defects would have to be in excess of 25,000 to 50,000 units/d.
Warfarin and warfarin derivatives	Early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth restriction. Central nervous system malformations can occur in late pregnancy exposure because of bleeding.
Anticonvulsants	
Phenytoin	Increases risk of fetal hydantoin syndrome, consisting of facial dysmorphology, cleft palate, ventricular septal defect, and growth and mental retardation.
Trimethadione and paramethadione	Increases the risk of characteristic facial dysmorphology, mental retardation, V-shaped eyebrows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, and severe developmental delay.
Valproic acid	Increases the risk of spina bifida, facial dysmorphology, autism, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis.

agents (eg, cyclosporine, leflunomide)	producing malformations in the fetus when administered to pregnant women, especially because most of these drugs are teratogenic in animals, but the clinical data are not consistent. Many of these drugs have not been shown to be teratogenic, but the numbers of cases in the studies are small. Caution is the byword.
Diethylstilbestrol	Administration during pregnancy produces genital abnormalities, adenosis, and clear cell adenocarcinoma of vagina in adolescents. The last has a risk of 1:1000 to 1:10,000, but the other effects, such as adenosis, can be quite high.
Ethyl alcohol	Fetal alcohol syndrome consists of microcephaly, mental retardation, growth retardation, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures.
Ionizing radiation	Radiation exposure above a threshold of 20 rad (0.2 Gy) can increase the
Carbamazepine	Increases the risk facial dysmorphology, neural tube defects, cardiovascular defects, and urinary tract defects.
Chemicals	
Carbon monoxide poisoning	Central nervous system damage has been reported with very high exposures, but the risk seems to be low*.
Lead	Very high exposures can cause pregnancy loss; intrauterine teratogenesis is not established at very low exposures below 20 microgram/percent in the serum of pregnant mothers.
Gasoline addiction embryopathy	Facial dysmorphology, mental retardation
Methyl mercury	Minamata disease consists of cerebral palsy, microcephaly, mental retardation, blindness, and cerebellum hypoplasia. Other epidemics have occurred from adulteration of wheat with mercurycontaining chemicals that are used to prevent grain spoilage. Present environmental levels of mercury are unlikely to represent a teratogenic risk, but reducing or limiting the consumption of

	risk for some fetal effects such as microcephaly or growth retardation, but the threshold for mental retardation is higher.
Insulin shock therapy	Insulin shock therapy, when administered to pregnant women, resulted in microcephaly, mental retardation.
Lithium therapy	Chronic usage for the treatment of manic depressive illness has an increased risk for Ebstein's anomaly and other malformations, but the risk seems to be very low.
Minoxidil	This drug's promotion of hair growth was discovered because administration during pregnancy resulted in hirsutism in newborns.
Methimazole	Aplasia cutis has been reported to be increased in mothers administered this drug during pregnancy*.
Methylene blue intra-amniotic instillation	Fetal intestinal atresia, hemolytic anemia, and jaundice in neonatal period. This procedure is no longer used to identify one twin.
	carnivorous fish has been suggested to avoid exceeding the maximum permissible exposure recommended by the Environmental Protection Agency, an exposure level far below the level at which the toxic effects of mercury are seen.
Polychlorinated biphenyls	Poisoning has occurred from adulteration of food products ("Cola-colored babies," CNS effects, pigmentation of gums, nails, teeth, and groin; hypoplastic deformed nails; intrauterine growth retardation; abnormal skull calcification). The threshold exposure has not been determined, but it is unlikely to be teratogenic at the present environmental exposures.
Toluene addiction embryopathy	Facial dysmorphology, mental retardation
Embryonic and fetal infections	
Cytomegalovirus infection	Retinopathy, CNS calcification, microcephaly, mental retardation
Rubella	Deafness, congenital heart disease, microcephaly, cataracts, mental retardation
Herpes simplex	Fetal infection, liver disease, death

Misoprostol	A low incidence of vascular disruptive phenomenon, such as limb-reduction defects and Mobius syndrome, has been reported in pregnancies in which this drug was used to induce an abortion.
Mycophenolate mofetil	1st trimester exposure associated with miscarriage, abnormalities of the ear, distal limbs, heart, esophagus, kidney, and cleft lip/palate.
Penicillamine (D-penicillamine)	This drug results in the physical effects referred to as "lathyrism," the results of poisoning by the seeds of the genus *Lathyrus*. It causes collagen disruption, cutis laxa, and hyperflexibility of joints. The condition seems to be reversible, and the risk is low.
Progestin therapy	Very high doses of androgen hormone-derived progestins can produce masculinization. Many drugs with progestational activity do not have masculinizing potential. None of these drugs have the potential for producing nongenital
HIV	Perinatal HIV infection
Parvovirus infection, B19	Stillbirth, hydrops
Syphilis	Maculopapular rash, hepatosplenomegaly, deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis
Toxoplasmosis	Hydrocephaly, microphthalmia, chorioretinitis, mental retardation
Varicella zoster	Skin and muscle defects; intrauterine growth retardation; limb reduction defects, CNS damage (very low increased risk)
Venezuelan equine encephalitis	Hydranencephaly; microphthalmia; destructive CNS lesions; luxation of hip
Maternal disease states	
Corticosteroid-secreting endocrinopathy	Mothers who have Cushing's disease can have infants with hyperadrenocortism, but anatomic malformations do not seem to be increased.
Iodine deficiency	Can result in embryonic goiter and mental retardation.
Intrauterine problems of constraint and vascular disruption	These defects are more common in multiple-birth pregnancies, pregnancies with anatomic defects of

	malformations.
Propylthiouracil	This drug and other antithyroid medications administered during pregnancy can result in an infant born with a goiter.
Radioactive isotopes	Tissue- and organ-specific damage depends on the radioisotope element and distribution (ie, high doses of Iodine-131 administered to a pregnant woman can cause fetal thyroid hypoplasia after the eighth week of development).
Retinoids	Systemic retinoic acid, isotretinoin, and etretinate can cause increased risk of CNS, cardioaortic, ear, and clefting defects such as microtia, anotia, thymic aplasia, other branchial arch and aortic arch abnormalities, and certain congenital heart malformations.
Retinoids, topical	Topical administration is very unlikely to have teratogenic potential, because teratogenic serum levels cannot be attained by topical exposure to retinoids.

	the uterus, placental emboli, or amniotic bands. Possible birth defects include club feet, limb-reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, midline closure defects, cleft palate and muscle aplasia, cleft lip, omphalocele, and encephalocele).
Maternal androgen endocrinopathy (adrenal tumors)	Masculinization of female fetuses
Maternal diabetes with poor glycemic control	Increases the risk of a wide variety of congenital anomalies; cardiac abnormalites are most common.
Maternal folic acid in reduced amounts	An increased incidence of neural tube defects.
Maternal phenylketonuria	Abortion, microcephaly, and mental retardation; very high risk in untreated patients.
Maternal starvation	Intrauterine growth restriction, abortion, neural tube defects (Dutch famine experience)
Tobacco smoking	Abortion, intrauterine growth restriction, stillbirth
Zinc deficiency*	Neural tube defects*

Streptomycin	Streptomycin and a group of ototoxic drugs can affect the eighth nerve and interfere with hearing; it is a relatively low-risk phenomenon. Children are less sensitive than adults to the ototoxic effects of these drugs.
Sulfa drugs and vitamin K	These drugs can produce hemolysis in some subpopulations of fetuses.

CNS: central nervous system.
* Controversial.

Updated July 15, 2010 Gerald Briggs, B.Pharm.

Graphic 73369 Version 11.0

Disclosures

Disclosures: **Harry Ostrer, MD** Nothing to disclose. **Louise Wilkins-Haug, MD, PhD** Nothing to disclose. **Vanessa A Barss, MD, FACOG** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Macrocephaly in infants and children: Etiology and evaluation

Author
Julie A Boom, MD

Section Editors
Jan E Drutz, MD
Marc C Patterson, MD, FRACP
Helen V Firth, DM, FRCP, DCH

Deputy Editor
Mary M Torchia, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Mar 13, 2014.

INTRODUCTION — The measurement of head circumference (also called occipitofrontal circumference, OFC), a direct reflection of head growth, is an important step in the evaluation of childhood growth and development. Deviations from normal head growth may be the first indication of an underlying congenital, genetic, or acquired problem (eg, congenital infection, genetic syndrome, hydrocephalus, intracranial hemorrhage, storage disease, or neoplasm) [1-4]. Many genetic conditions are associated with an abnormal pattern of head growth; the earlier these conditions are detected, the earlier appropriate treatment, services, and genetic counseling can be provided [5].

The etiology and evaluation of macrocephaly in infants and children will be discussed here. The etiology and evaluation of microcephaly are discussed separately. (See "Microcephaly in infants and children: Etiology and evaluation".)

NORMAL HEAD GROWTH — Head growth is affected by growth and alterations in the contents of the cranium (eg, brain, blood, cerebrospinal fluid [CSF], and bone) and the timing of these changes in relation to closure of the fontanelles and sutures. Changes in the volume of any component before the closure of the fontanelles and sutures may alter the OFC. In contrast, changes in volume that occur after closure of the fontanelles and sutures bring about compensatory changes in the other components. (See "The pediatric physical examination: HEENT", section on 'Anterior and posterior fontanelles'.)

General guidelines regarding changes in OFC during infancy and childhood in term infants are presented separately. (See "Normal growth patterns in infants and prepubertal children", section on 'Head growth'.)

Measurement — OFC should be measured at health maintenance visits between birth and three years of age. OFC should also be measured at each visit in children with neurologic complaints.

The measuring tape should encircle the head and include an area 1 to 2 cm above the glabella anteriorly and the most prominent portion of the occiput posteriorly (picture 1). Measurement of OFC in the newborn may be unreliable until the third or fourth day of life since it may be affected by caput succedaneum, cephalohematoma, or molding [6]. In older infants, the accuracy of the measurement may be affected by thick hair and deformation or hypertrophy of the cranial bones.

Monitoring — OFC measurements are most informative when plotted over time [7]. Normal infants may experience a slow genetic shifting in OFC percentiles. Standards have been determined for head growth in healthy children between 0 and 18 years of age [8-11]. Most clinicians use the standard growth curves to monitor the head growth of premature infants, with an adjustment for prematurity (ie, corrected age), until approximately 12 to 24 months of age [12,13]. (See "Growth management in preterm infants", section on 'Monitoring of growth'.)

Head circumference charts — Several standardized charts are available for monitoring head circumference. These include:

- The Centers for Disease Control and Prevention (CDC) National Center for Health Statistics head circumference charts for children 0 to 36 months of age (CDC growth charts) (figure 1A-B) (calculator 1). These charts are based on a nationally representative demographic sample.
- The World Health Organization (WHO) head circumference charts for children zero to five years of age (WHO growth standards). These charts are based on data from the Multicentre Growth Reference Study of breastfed children living under optimal environmental conditions.
- The Nellhaus head circumference charts for children 0 to 18 years of age. These charts are based on a 1968 international meta-analysis [8]. They are available in the full text of reference [8].
- The Fels head circumference charts for children 0 to 18 years. These charts are based on data from the Fels Longitudinal Study of 888 white children from the United States [9]. They are available in the full text of reference [9].
- The United States Head Circumference Growth Reference charts for children 0 to 21 years of age. These charts combine growth reference data from the CDC, Nellhaus, the Fels Longitudinal Study, and others [10]. They are available in the full text of reference [10].
- The Bushby charts for adults. These charts are based on data from 354 white adults (median age 40 years, range 17 to 83 years) in two British centers; OFC percentiles are related to height [14]. Bushby charts are available in the full text of reference [14].

In September 2010, the CDC recommended that the WHO growth charts be used for children zero to two years (figure 2A-B) (calculator 2), and the CDC growth charts for children older than two years [11]. The clinical consequences of using the WHO standards for children younger than two years of age and a different standard for older children will need to be monitored over time [11]. The particular chart that is chosen for young children may affect the categorization of head size, particularly at the higher percentiles [15,16]. In a retrospective cohort study of 75,412 children in a primary care network, the proportion of children with OFC >95th percentile was 8.6 percent with the CDC curve and 14 percent with the WHO curve [15]. The proportion of subjects with OFC <5th percentile was 2.9 percent using the CDC curves and 2.3 percent using the WHO curve. Another potential problem is that changing from one curve to another after age two years may change the way a particular child's head growth is classified. The United States Head Circumference Growth Reference charts, published in 2010, address this problem but require additional validation before their use can be widely adopted [10].

It may be inappropriate to use a single head circumference standard for children in all countries or ethnic groups. A study that compared mean head circumference from a variety of studies including >11,000,000 children from economically advantaged populations (1988 to 2013) with the WHO reference standards found that the mean head circumferences in certain national or ethnic groups were sufficiently different from the WHO means to affect diagnosis of microcephaly or macrocephaly [17].

The standard growth curves are not appropriate for monitoring the head size of children with certain medical conditions associated with macrocephaly (eg, achondroplasia, neurofibromatosis). Growth curves for children with achondroplasia are available through the American Academy of Pediatrics. Growth curves for children with neurofibromatosis also are available. (See "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis".)

DEFINITIONS

- Macrocephaly is defined as an OFC greater than two standard deviations (SD) above the mean for a given age, sex, and gestation (ie, ≥97th percentile) [5,18,19].
- Megalencephaly (also called macrencephaly) is enlargement of the brain parenchyma [20].

ETIOLOGY — Macrocephaly is caused by an increase in size of any of the components of the cranium

(brain, CSF, blood, or bone) or can be attributable to increased intracranial pressure (table 1) [5,7,21].

Increased brain — Megalencephaly is classified as anatomic or metabolic [22].

Anatomic megalencephaly — Anatomic megalencephaly is caused by an increase in the size or number of brain cells in the absence of metabolic disease or acute encephalopathy [5,7,22]. Anatomic megalencephaly is usually present at birth [21]. Postnatally, the OFC continues to be large, continuing to progress along a trajectory parallel to the upper growth curve percentiles.

- Familial megalencephaly – The most common type of anatomic megalencephaly is benign familial megalencephaly (also called genetic megalencephaly) [23]. Children with this condition are born with large heads and normal body size. During infancy, OFC increases to greater than the 90th percentile, typically 2 to 4 cm above, but parallel to, the 98th percentile [5,7]. The OFC may increase by 0.6 to 1 cm per week (compared with the normal 0.4 cm/week) [22,24]. Head growth velocity slows to a normal rate by approximately six months of age [5].

  In children with a normal neurologic examination, normal development, no clinical features suggestive of a specific syndrome, and no family history of abnormal neurologic or developmental problems, familial megalencephaly can be confirmed by measuring the patient's parents' head circumferences and by using Weaver curves [5,25]. If the child's OFC falls within the normal ranges as estimated using the Weaver curves, radiologic evaluation is not necessary. (See 'Parental OFC' below.)

- Other causes of anatomic megalencephaly – Other disorders associated with anatomic megalencephaly include (table 1) [7,18,21]:

  - Neurocutaneous disorders (eg, neurofibromatosis, tuberous sclerosis complex, linear sebaceous nevus syndrome, and hypomelanosis of Ito) (table 2). (See "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis" and "Tuberous sclerosis complex: Genetics, clinical features, and diagnosis".)

  - Autism spectrum disorder. Macrocephaly, accelerated head growth during the first year of life, and megalencephaly may be associated with autism spectrum disorders (ASD). Children with ASD have associated impairments in socialization, communication, and behavior. (See "Autism spectrum disorder: Clinical features", section on 'Macrocephaly'.)

    Some children with ASD and macrocephaly may have germline *PTEN* mutations (See "PTEN hamartoma tumor syndrome, including Cowden syndrome", section on 'Autism spectrum disorders and macrocephaly'.).

  - Achondroplasia. Achondroplasia is the most frequent form of short-limbed dwarfism (picture 2A-B). In addition to megalencephaly, children with achondroplasia also may develop hydrocephalus.

  - Cerebral gigantism (Sotos syndrome). Cerebral gigantism is an overgrowth syndrome with prenatal onset. In addition to megalencephaly, children with cerebral gigantism also may develop hydrocephalus [26]. (See "The child with tall stature and/or abnormally rapid growth", section on 'Cerebral gigantism'.)

  - Fragile X syndrome. Fragile X syndrome is the most common form of familial intellectual disability (mental retardation) in boys. The OFC usually is large compared with weight and length, but may not be more than 2 SD above the mean. Characteristic features (which typically are mild or absent before puberty) include a long face, large ears, prominent jaw, and macroorchidism. (See "Fragile X syndrome: Clinical features and diagnosis in children and

adolescents".)

- Cowden syndrome. Cowden syndrome is an autosomal dominant cancer predisposition syndrome that is caused by mutations in the *PTEN* gene. Affected individuals have an increased risk for thyroid malignancy, and females have a risk for early breast cancer. (See "PTEN hamartoma tumor syndrome, including Cowden syndrome", section on 'Cowden syndrome'.)
- Nevoid basal cell carcinoma syndrome (also called Gorlin syndrome). Nevoid basal cell carcinoma syndrome is an autosomal dominant syndrome that predisposes to basal cell carcinoma (BCC's) during adolescence and young adulthood. Affected individuals have a large OFC, “coarse” facial features (eg, prominent forehead, hypertelorism, widened nasal bridge, and mandibular prognathism), jaw cysts, and palmar/plantar pits. It is caused by mutations in the *PTCH1* gene. (See "Nevoid basal cell carcinoma syndrome".)

Metabolic megalencephaly — The deposition of metabolic products in the brain tissue causes metabolic megalencephaly [5,22,27]. The OFC of children with metabolic megalencephaly is usually within the normal range at the time of birth but increases during the neonatal period [7,21].

Examples of diseases that cause metabolic megalencephaly include leukodystrophies (Alexander disease, Canavan disease, megalencephalic leukoencephalopathy), and lysosomal storage disorders (Tay-Sachs, mucopolysaccharidosis, and gangliosidosis) (table 1) [5,7,20]. (See appropriate topic reviews).

Increased CSF

Hydrocephalus — Hydrocephalus is a disorder in which the cerebral ventricular system contains an excessive amount of CSF, resulting in increased pressure and dilatation. Hydrocephalus may be caused by increased production, decreased absorption, or obstruction to CSF flow. Hydrocephalus is discussed separately. (See "Hydrocephalus".)

Increased OFC is frequently the presenting sign of hydrocephalus (figure 3). In a retrospective cohort of 298 children <5 years of age who were hospitalized for intracranial expansion, 216 had hydrocephalus [28]. Approximately three-fourths were referred for increasing OFC; other signs and symptoms included nausea/vomiting, irritability, delayed development, and aberrant head shape [28].

Benign enlargement of the subarachnoid space — Benign enlargement of the subarachnoid space (also called benign extra-axial fluid, idiopathic external hydrocephalus, extraventricular hydrocephalus, and benign subdural effusion) is another cause of macrocephaly [29-31].

Benign enlargement of the subarachnoid space is relatively common, occurring in approximately 16 percent of infants [5]. It is more common in boys than in girls and frequently has occurred or occurs in other family members [5,29]. Macrocephaly may or may not be present at birth; if it is not present at birth, the OFC rapidly increases to greater than the 95th percentile and then tends to parallel the curve [7,29,32,33]. The head growth velocity typically slows to normal by the time the child reaches six months of age [5].

Imaging is necessary to make the diagnosis. Head ultrasonography or computed tomography (CT) scan demonstrates enlargement of the subarachnoid space in the frontal or frontoparietal areas with a prominent interhemispheric fissure and normal ventricles [7,29]. The anterior location of the fluid collection distinguishes benign enlargement of the subarachnoid space from cerebral atrophy, in which the fluid collection is distributed anteriorly and posteriorly [31].

Children who were born at term and have enlargement of the subarachnoid space typically have normal development and normal neurologic examinations, though there are exceptions [29,32-39]. These

children should be observed closely for developmental or neurologic problems. OFC measurements should be plotted monthly for six months to be certain that head growth slows to a normal rate and begins to parallel the normal curve [5]. Repeat imaging is unnecessary unless head growth deviates from the normal curve, the neurologic examination is abnormal, or the development is delayed [7]. (See 'Neuroimaging' below.)

Children with benign enlargement of the subarachnoid space usually do not require surgical intervention. However, they may be at increased risk for subdural hematoma with minimal or no trauma [40,41]. (See "Intracranial subdural hematoma in children: Epidemiology, anatomy, and pathophysiology" and "Intracranial subdural hematoma in children: Clinical features, evaluation, and management".)

"Benign" enlargement of the subarachnoid space should be distinguished from extra-axial fluid collections that occur in survivors of the neonatal intensive care unit and/or extracorporeal membrane oxygenation. Macrocephaly and extra-axial fluid in these children are associated with adverse neurologic and developmental outcomes [42-44]. The relative contributions of the extra-axial fluid, medical problems, and/or complications of therapy to the adverse outcome are not clear.

Increased blood — Increased intracranial blood volume may be caused by hemorrhage (intraventricular, subdural, epidural) or arteriovenous malformation (AVM). (See "Intracranial subdural hematoma in children: Epidemiology, anatomy, and pathophysiology" and "Intracranial subdural hematoma in children: Clinical features, evaluation, and management".)

Increased OFC is rarely the sole manifestation of intracranial hemorrhage. In a retrospective cohort of 298 children <5 years of age who were hospitalized for intracranial expansion, 58 had intracranial bleeding [28]. Increased OFC was the presenting sign in only two; more common presentations included irritability, seizures, nausea/vomiting, fatigue/drowsiness, and paresis.

Increased bone — Bone thickening, a rare cause of macrocephaly, can occur from bone marrow expansion, as seen in thalassemia major, or primary bone disorders (eg, skeletal and cranial dysplasias) (table 1).

Increased ICP — Increased intracranial pressure may be idiopathic (ie, pseudotumor cerebri) or caused by increased volume of the intracranial contents (eg, brain, CSF, blood, mass lesions), infection, inflammation, and various toxic or metabolic abnormalities (eg, lead poisoning, vitamin A deficiency or excess, galactosemia). (See "Elevated intracranial pressure (ICP) in children" and "Idiopathic intracranial hypertension (pseudotumor cerebri): Clinical features and diagnosis".)

Mass lesions — Intracranial mass lesions include intracranial cysts, tumors, or abscesses [18]. Increased OFC is rarely the sole manifestation of intracranial tumor. In a retrospective cohort of 298 children <5 years of age who were hospitalized for intracranial expansion, 120 had tumors [28]. Increased OFC was the presenting sign in only three; more common presentations included nausea/vomiting, unsteadiness, headache, fatigue, torticollis, and irritability. In the same cohort, 36 children had intracranial cyst; increased OFC was the most frequent presenting sign (in nine patients); other symptoms included seizures, headache, and nausea/vomiting. (See "Clinical manifestations and diagnosis of central nervous system tumors in children".)

EVALUATION

Postnatal macrocephaly

Overview of approach — Evaluation for macrocephaly should be initiated when a single OFC measurement is abnormal, when serial measurements reveal progressive enlargement (ie, crossing of one or more major percentile lines [eg, 10th, 25th, 50th, 75th, 90th] between health supervision visits), or when there is an increase in OFC of >2 cm/month (for infants aged zero to six months) [27,32,45]. It is important to verify the measurement; isolated deviant measurements often are due to technical error.

The evaluation of macrocephaly includes a thorough history and physical examination of the child and parents (in consideration of familial variation in head size). Additional evaluation, which is directed by clinical findings from the history and examination, may include neuroimaging and other tests. (See 'Other tests' below and 'Neuroimaging' below.)

Factors that determine the urgency and extent of the imaging and laboratory evaluation include [20,32]:

- Age at onset (table 3)
- History of central nervous system trauma or infection
- Associated symptoms (eg, headache, ataxia), neurodevelopmental abnormalities, or syndromic features
- Family history of neurologic or cutaneous abnormalities

Elevated ICP — If there are symptoms or signs of increased ICP, CNS trauma, or CNS infection, urgent evaluation is necessary. (See "Elevated intracranial pressure (ICP) in children".)

Syndromic features — If syndromic features are present (table 2), consultation with, or referral to, a clinical geneticist should be initiated to determine the appropriate diagnostic evaluation. (See 'Other tests' below.)

Developmental delay — If syndromic features are absent and the child has developmental delay, neuroimaging (usually with magnetic resonance imaging [MRI] or CT) is warranted. Neuroimaging may reveal abnormalities consistent with a particular etiology (eg, hydrocephalus, leukodystrophy, gangliocytoma in PTEN hamartoma syndrome) [20]. (See 'Neuroimaging' below.)

If neuroimaging is normal in a child with delayed development, referral to a developmental pediatrician, clinical geneticist, or pediatric neurologist, and the initiation of diagnostic testing, may be indicated. The differential diagnosis includes autism, metabolic disorders, microduplication syndromes, and microdeletion syndromes [20]. (See 'Other tests' below.)

Normal development — If syndromic features are absent, the degree of macrocephaly is modest, and development is normal, the OFC of first-degree relatives (parents, siblings) should be measured to assess for familial macrocephaly [20]. Ultrasonography of the head may be undertaken in infants with an open fontanelle. (See 'Parental OFC' below and 'Neuroimaging' below.)

History — Important aspects of the history include [46]:

- Birth weight, length, and OFC and growth trajectory (table 3) (see 'Physical examination' below)
- Rate of attainment and/or loss of milestones
- History of seizures
- History of predisposing factors for hydrocephalus (eg, meningitis, prematurity with intraventricular hemorrhage)
- Family history of consanguinity, large OFC, neurocutaneous disorders, metabolic disorders, and malignancies (the PTEN syndromes [eg, Bannayan-Riley-Ruvalcaba/Cowden syndrome, Proteus syndrome] are associated with breast and thyroid cancers). The family history should include three generations to detect recessive disorders, which may skip a generation. (See "PTEN hamartoma tumor syndrome, including Cowden syndrome".)

Physical examination — Important aspects of the physical examination of a child with macrocephaly include [18,21,32,46]:

- General appearance – Dysmorphic features may suggest a particular syndrome (table 2). A large cranial vault may be associated with a prominent forehead and a long occipitofrontal diameter

(dolichocephaly or scaphocephaly) [20]. Increased width at the cranial base may be associated with mild hypertelorism, down-slanting palpebral fissures, and a relatively small facial area (giving the face a triangular appearance).

- OFC – The OFC should be measured and plotted on a standard curve. (See 'Head circumference charts' above.) Spurious causes of increased OFC should be excluded (eg, caput succedaneum, cephalohematoma, hair arrangements, abnormal head shape) [18].

  The OFC should be compared with any previous plotted measurements to help determine the onset and progression of increased OFC (table 3). Children with anatomic megalencephaly often are macrocephalic at birth, whereas children with metabolic megalencephaly usually are normocephalic at birth and become macrocephalic in the neonatal period [7].

- Weight and stature trajectories – The child's weight and length (or height) should also be measured and plotted on standard curves. They should be compared to previous plotted points to assess the growth trajectory. Several macrocephaly syndromes are associated with short or tall stature (overgrowth) (table 2) [20,21].

- Head – In addition to measuring the OFC, examination of the head should include assessment of the fontanelles and auscultation for intracranial bruits (suggestive of AVM). Transillumination of the skull may be performed in infants younger than one year.

  The size and timing of closure of the fontanelles should be noted. Palpation or shining a light tangentially across the anterior fontanelle should reveal a slightly concave contour when the child is relaxed and in the upright position. Increased intracranial pressure (ICP) may manifest as an enlarged, convex fontanelle or separation of the suture lines. The anterior fontanelle usually closes by 24 months. Persistent enlargement of the anterior fontanelle in children with macrocephaly may be due to hydrocephalus, achondroplasia, cleidocranial dysplasia, rickets, and osteogenesis imperfecta [32]. (See appropriate topic reviews).

  Transillumination of the skull may be performed in children younger than one year of age. Transillumination of the skull requires a flashlight that has a narrow, opaque, sponge-rubber cuff around the light [45]. An alternative is a "cold" fiberoptic halogen light source. The light is applied to the infant's scalp in a darkened room. Translucency that extends beyond 2 to 2.5 cm in the frontal area and beyond 2 cm in the occipital region may be abnormal and indicative of subdural effusion, subdural hematoma, hydrocephalus, hydranencephaly, porencephaly, or increased ICP. Transillumination is hampered by cephalohematoma, caput succedaneum, scalp edema, thick black hair, or bony cortex thicker than 1 cm.

- Eyes – The eyes should be examined for papilledema (suggestive of increased ICP, but may be absent in infants), cataracts, and retinal abnormalities (suggestive of metabolic disease and/or syndromic macrocephaly). (See "Cataract in children", section on 'Clinical features'.)

- Skin – Examination of the skin for hypopigmented or hyperpigmented macules, angiomas, shagreen patches, telangiectasia, subcutaneous nodules, lipomas, papillomata (table 2).

- Cardiovascular system – Signs of congenital heart disease or heart failure (suggestive of a neuro-cardio-facio-cutaneous syndrome) (table 2).

- Abdomen – Hepatosplenomegaly (suggestive of a metabolic or storage disorder).

- Musculoskeletal system – Evidence of skeletal dysplasia (eg, short limbs, absent or hypoplastic clavicles) (table 1).

- Neurologic assessment – Abnormal tone or deep tendon reflexes. Hypotonia is a common feature of overgrowth syndromes (table 2); spasticity may be a feature of leukodystrophy (eg, Canavan disease, Alexander disease). (See "Alexander disease".)

Parental OFC — The parents' OFC measurements should be obtained if possible. These measurements can be used to calculate a standard score for use with the Weaver curves to determine the genetic contribution to macrocephaly [25].

Weaver curve — The Weaver curve helps to determine whether genetic influences contribute to a child's macrocephaly [25]. A standard score is calculated for the child and each of the parents using the following formula:

Standard score (SS) = (OFC - mean value)/SD

The mean values and SD for age and sex are listed in the table (table 4). In calculating the parents' standard scores, the mean value and standard deviation for an 18-year-old should be used.

The average of the parents' SS and the child's SS are plotted on the Weaver curve (figure 4). A genetic contribution to macrocephaly is suggested if the child's standard score is within the range determined by the average parental score, thus permitting the evaluation to be tailored appropriately [25].

Neuroimaging — Neuroimaging should be obtained in children in whom an expanding lesion is suspected [45]. Among other children, neuroimaging is most helpful (in terms of determining an etiology) for those who have developmental delay but lack features suggestive of a particular syndrome [46]. Among children who have features suggestive of a particular syndrome, other laboratory tests (eg, genetic tests) are more helpful in confirming the diagnosis. (See 'Other tests' below.)

Overview — Radiologic evaluation of macrocephaly may involve plain radiographs, ultrasonography, CT, or MRI of the head. The optimal imaging strategy permits the detection of significant intracranial pathology and minimizes the potential hazards of radiation and/or sedation [47]. (See "Approach to neuroimaging in children".)

The approach to imaging in children with macrocephaly depends upon the age of onset and associated symptoms. Normal infants may experience genetic shifting in OFC percentiles. Thus, a slow shift across one or two major percentile lines (eg, 10th, 25th, 50th, 75th, 90th) in a developmentally normal child warrants careful clinical observation. If the child's OFC remains within the predicted ranges based on Weaver curves, imaging is not necessary. However, if a child has a dramatic increase in OFC across several major percentile lines or exhibits worrisome neurologic or developmental symptoms, neuroimaging should be undertaken.

The timing of closure of the anterior fontanelle is an important factor when considering clinical observation versus imaging. Head ultrasonography, which is noninvasive and does not require sedation, can only be performed in infants with an open fontanelle. Once the anterior fontanelle closes, neuroimaging options include head CT or MRI, each of which may require sedation.

Plain radiographs — Plain radiographs may provide evidence of primary skeletal dysplasia or increased ICP. Findings associated with increased ICP include widening of sutures, prominent convolutional markings on the inner table of the skull ("beaten silver skull"), and erosion of the sella turcica [18].

Ultrasonography — Head ultrasonography is a reasonable initial study in infants with macrocephaly, normal neurodevelopmental examination, no evidence of increased ICP, and an open anterior fontanelle [47]. It may identify ventricular or subarachnoid space enlargement. If head ultrasonography is normal, the infant's OFC and neurodevelopmental status should be monitored closely. (See 'Management' below.)

MRI and CT — Infants with neurologic abnormalities, progressively enlarging OFC, or increased ICP and a closed anterior fontanelle should be evaluated with MRI or CT. The choice between these studies depends upon a number of factors, including the suspected etiology, acuity of symptoms, need for sedation, and availability. The lack of radiation exposure is a major advantage of MRI over CT. Consultation with a pediatric neurologist and/or neuroradiologist can be helpful in determining the best study for a particular child. (See "Approach to neuroimaging in children".)

- MRI – MRI can delineate the size and position of the ventricles; determine the width of the subarachnoid space; distinguish communicating from noncommunicating hydrocephalus; and identify white matter changes, mass lesions, vascular malformations, subdural fluid collections, and porencephalic cysts [32,46]. MRI with contrast or angiography may be performed to evaluate vascular abnormalities.

- CT – CT is used primarily in the acute setting for the evaluation of obstructive hydrocephalus. CT also may be used to identify intracranial calcification (which may be present in basal cell nevus syndrome, infection, hypoparathyroidism, or parasitic cysts) [32]. In addition, CT can identify tubers in tuberous sclerosis complex or asymmetry of the cerebral hemispheres in children with linear sebaceous nevus syndrome. (See "Tuberous sclerosis complex: Management", section on 'Brain imaging'.)

Other tests — Additional diagnostic evaluation is directed by the history and physical examination. Consultation with, or referral to, a clinical geneticist can be helpful in determining the appropriate studies.

- Children with syndromic macrocephaly may need evaluation for associated abnormalities (eg, echocardiogram, ophthalmologic examination, abdominal ultrasonography, long bone radiographs) [21].

- Children with loss of milestones, degenerative conditions, autism spectrum disorder, or intellectual disability/developmental delay may need metabolic evaluation (eg, urine organic acids and mucopolysaccharidosis screen), genetic studies (eg, for duplications, fragile X syndrome, or *PTEN* mutation analysis), or electroencephalogram. (See "Inborn errors of metabolism: Metabolic emergencies", section on 'Initial evaluation' and "Inborn errors of metabolism: Identifying the specific disorder", section on 'Laboratory evaluation' and "PTEN hamartoma tumor syndrome, including Cowden syndrome", section on 'Diagnostic criteria'.)

- Children with suspected primary skeletal disturbance may need plain radiographs of the long bones to evaluate cortical thickness.

- A skeletal survey is warranted in young children in whom physical abuse is suspected (eg, those with subdural hematoma). (See "Intracranial subdural hematoma in children: Clinical features, evaluation, and management" and "Orthopedic aspects of child abuse", section on 'Skeletal survey'.)

Referral indications — Indications for referral depend upon clinical features and the results of the initial evaluation.

- Referral to a clinical geneticist may be helpful in directing additional evaluation in children with syndromic features or suspected metabolic disease.

- Children with seizures or abnormal MRI features should be referred to a pediatric neurologist [46].

- Children with hydrocephalus or mass lesions may require referral to a neurosurgeon.

- Children with developmental problems may benefit from referral to a child development team.

Prenatal macrocephaly — Prenatally, macrocephaly is diagnosed by ultrasound examination and is

defined as head circumference >2 standard deviations above the mean or above the 98th percentile for gestational age (as assessed by last menstrual period or femur length). The diagnosis is complicated by limitations in accuracy of head circumference measurements and inconsistency between prenatal and postnatal head circumference growth curves [48]. Although there are reference values for fetal head circumference [49], standards have not been developed for specific populations (eg, based on sex, race/ethnicity).

The approach to evaluation of prenatal macrocephaly depends upon the presence of associated ultrasonographic anomalies, appropriateness of other fetal biometric parameters (eg, length of bones, abdominal circumference) in relation to gestational age, historical features (eg, consanguinity, familial macrocephaly), and head circumference measurements of parents and siblings [48]. Associated ultrasonographic anomalies (eg, callosal dysgenesis, malformations of cortical development, hypertelorism, enlarged kidneys, polydactyly, hypoplastic long bones) may indicate syndromic macrocephaly (table 2) [48]. Head circumference, abdominal circumference, and long-bone length that are greater than expected for gestational age may indicate an overgrowth syndrome (eg, Sotos syndrome, Weaver syndrome). Fetal head circumference between 2 and 2.5 SD above the mean for gestational age and family members with macrocephaly but no stigmata of autosomal dominant conditions that include macrocephaly (table 2) may indicate familial macrocephaly, although it is unusual for this to present prenatally. (See 'Anatomic megalencephaly' above.)

Additional evaluation (eg, karyotype, fetal brain MRI) may be obtained if a specific diagnosis is desired to help with pregnancy management. Indications for these evaluations may include [48]:

- Parental consanguinity
- Family members with macrocephaly and stigmata of autosomal dominant conditions that include macrocephaly (table 2)
- Otherwise unexplained fetal macrocephaly (eg, family members with normal head circumference and fetal biometric parameters other than head circumference appropriate for gestational age)

The developmental outcome of prenatal macrocephaly depends upon the underlying etiology and associated abnormalities [50].

Cesarean delivery is indicated in cases in which the head circumference is increased and vaginal delivery is thought not to be possible. The cut-off for determining when a cesarean delivery is indicated will vary with gestational age at delivery, the absolute and relative head circumference, and the size of the maternal pelvis. When the head circumference exceeds 40 cm, abdominal delivery should be considered.

MANAGEMENT — The management of macrocephaly depends upon the etiology.

- Children who have asymptomatic familial megalencephaly do not require treatment.
- Children who have hydrocephalus may require neurosurgical intervention (eg, placement of a ventriculoperitoneal shunt) to reduce CSF volume. (See "Hydrocephalus", section on 'Management'.)
- Infants and children who have benign enlargement of the subarachnoid space do not usually require intervention. They should be followed closely for developmental or neurologic problems. OFC measurements should be plotted monthly for six months to be certain that the growth is paralleling the normal curve. Repeat imaging is not necessary unless head growth deviates from the curve, the neurologic examination is abnormal, or the development is delayed [7]. (See 'Benign enlargement of the subarachnoid space' above and "Developmental-behavioral surveillance and screening in primary care", section on 'When to perform developmental-behavioral screening'.)

SUMMARY AND RECOMMENDATIONS

- Head circumference (occipitofrontal circumference, OFC) should be measured at health maintenance visits between birth and three years of age. OFC measurements are most informative when plotted over time. (See 'Measurement' above and 'Monitoring' above.)
- Macrocephaly is an OFC greater than two standard deviations (SD) above the mean for a given age, sex, and gestation (ie, ≥97th percentile). Megalencephaly is enlargement of the brain parenchyma (see 'Definitions' above).
- Macrocephaly is caused by an increase in size of any of the components of the cranium (brain, CSF, blood, or bone), or increased intracranial pressure (table 1). (See 'Etiology' above.)
- Evaluation for macrocephaly should be initiated when a single OFC measurement is abnormal (after confirmation that it was accurately measured), when serial measurements reveal progressive enlargement, or when there is an increase in OFC of >2 cm/month (for infants aged zero to six months). (See 'Overview of approach' above.)
- Factors that determine the urgency and extent of the evaluation of the child with macrocephaly include age at onset (table 3); history of central nervous system trauma or infection; associated symptoms, neurodevelopmental abnormalities, or syndromic features (table 2); and family history. (See 'Overview of approach' above.)
- Neuroimaging should be obtained in children suspected of having an expanding lesion. Among other children, neuroimaging is most helpful (in terms of determining an etiology) for those who have developmental delay but lack features suggestive of a particular syndrome. The optimal imaging strategy permits the detection of significant intracranial pathology and minimizes the potential hazards of radiation and/or sedation. (See 'Neuroimaging' above.)
- Additional diagnostic evaluation is directed by the history and physical examination. Consultation with, or referral to, a clinical geneticist can be helpful in determining the appropriate studies. (See 'Other tests' above.)

REFERENCES

1. Stoll C. Problems in the diagnosis of fragile X syndrome in young children are still present. Am J Med Genet 2001; 100:110.
2. Zvulunov A, Weitz R, Metzker A. Neurofibromatosis type 1 in childhood: evaluation of clinical and epidemiologic features as predictive factors for severity. Clin Pediatr (Phila) 1998; 37:295.
3. Furuta T, Tabuchi A, Adachi Y, et al. Primary brain tumors in children under age 3 years. Brain Tumor Pathol 1998; 15:7.
4. Tomita T, McLone DG. Brain tumors during the first twenty-four months of life. Neurosurgery 1985; 17:913.
5. Nard JA. Abnormal head size and shape. In: Common & Chronic Symptoms in Pediatrics, Gartner JC, Zitelli BJ (Eds), Mosby, St. Louis 1997.
6. Rios A. Microcephaly. Pediatr Rev 1996; 17:386.
7. Fenichel GM. Disorders of cranial volume and shape. In: Clinical Pediatric Neurology: A Signs and Symptoms Approach, 5th, Elsevier Saunders, Philadelphia 2005. p.353.
8. Nellhaus G. Head circumference from birth to eighteen years. Practical composite international

and interracial graphs. Pediatrics 1968; 41:106.

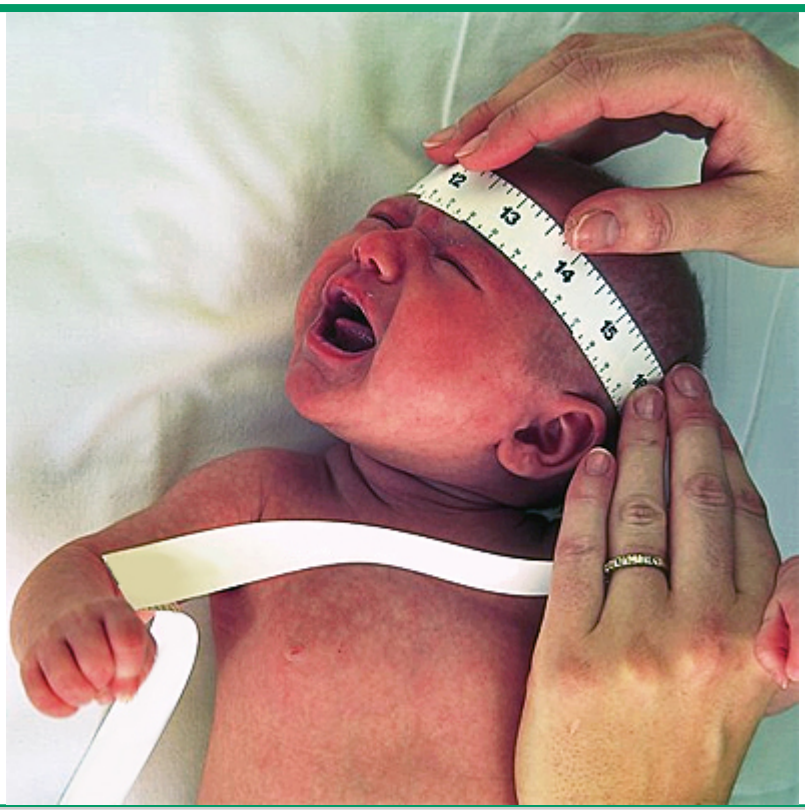
9. Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: birth to 18 years. Pediatrics 1987; 79:706.
10. Rollins JD, Collins JS, Holden KR. United States head circumference growth reference charts: birth to 21 years. J Pediatr 2010; 156:907.
11. Grummer-Strawn LM, Reinold C, Krebs NF, Centers for Disease Control and Prevention (CDC). Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States. MMWR Recomm Rep 2010; 59:1.
12. American Academy of Pediatrics Committee on Nutrition. Failure to thrive. In: Pediatric Nutrition, 7th, Kleinman RE, Greer FR. (Eds), American Academy of Pediatrics, Elk Grove Village, IL 2014. p.663.
13. Wright CM, Williams AF, Elliman D, et al. Using the new UK-WHO growth charts. BMJ 2010; 340:c1140.
14. Bushby KM, Cole T, Matthews JN, Goodship JA. Centiles for adult head circumference. Arch Dis Child 1992; 67:1286.
15. Daymont C, Hwang WT, Feudtner C, Rubin D. Head-circumference distribution in a large primary care network differs from CDC and WHO curves. Pediatrics 2010; 126:e836.
16. Wright CM, Inskip HM, Godfrey K, et al. Monitoring head size and growth using the new UK-WHO growth standard. Arch Dis Child 2011; 96:386.
17. Natale V, Rajagopalan A. Worldwide variation in human growth and the World Health Organization growth standards: a systematic review. BMJ Open 2014; 4:e003735.
18. Varma R, William, SD, Wessel HB. Neurology. In: Atlas of Pediatric Physical Diagnosis, 5th, Zitelli BJ, Davis HW (Eds), Mosby Elsevier, Philadelphia 2007. p.563.
19. Opitz JM, Holt MC. Microcephaly: general considerations and aids to nosology. J Craniofac Genet Dev Biol 1990; 10:175.
20. Williams CA, Dagli A, Battaglia A. Genetic disorders associated with macrocephaly. Am J Med Genet A 2008; 146A:2023.
21. Olney AH. Macrocephaly syndromes. Semin Pediatr Neurol 2007; 14:128.
22. DeMyer W. Megalencephaly: types, clinical syndromes, and management. Pediatr Neurol 1986; 2:321.
23. Day RE, Schutt WH. Normal children with large heads--benign familial megalencephaly. Arch Dis Child 1979; 54:512.
24. Lorber J, Priestley BL. Children with large heads: a practical approach to diagnosis in 557 children, with special reference to 109 children with megalencephaly. Dev Med Child Neurol 1981; 23:494.
25. Weaver DD, Christian JC. Familial variation of head size and adjustment for parental head circumference. J Pediatr 1980; 96:990.
26. Aoki N, Oikawa A, Sakai T. Serial neuroimaging studies in Sotos syndrome (cerebral gigantism syndrome). Neurol Res 1998; 20:149.
27. Gleeson JG, Dobyns WB, Plawner L, Ashwal S. Congenital structural defects. In: Pediatric Neurology Principles and Practice, 4th ed, Swaiman KF, Ashwal S, Ferriero DM (Eds), Mosby Elsevier, Philadelphia 2006. p.399.
28. Zahl SM, Wester K. Routine measurement of head circumference as a tool for detecting intracranial expansion in infants: what is the gain? A nationwide survey. Pediatrics 2008; 121:e416.
29. Alvarez LA, Maytal J, Shinnar S. Idiopathic external hydrocephalus: natural history and relationship to benign familial macrocephaly. Pediatrics 1986; 77:901.

30. Ment LR, Duncan CC, Geehr R. Benign enlargement of the subarachnoid spaces in the infant. J Neurosurg 1981; 54:504.
31. Kumar R. External hydrocephalus in small children. Childs Nerv Syst 2006; 22:1237.
32. Menkes JH, Sarnat HB, Flores-Sarnat L. Malformations of the central nervous system. In: Child Neurology, 7th, Menkes JH, Sarnat HB, Maria BL (Eds), Lippincott Williams & Wilkins, Philadelphia 2006. p.284.
33. Hellbusch LC. Benign extracerebral fluid collections in infancy: clinical presentation and long-term follow-up. J Neurosurg 2007; 107:119.
34. Andersson H, Elfverson J, Svendsen P. External hydrocephalus in infants. Childs Brain 1984; 11:398.
35. Gherpelli JL, Scaramuzzi V, Manreza ML, Diament AJ. Follow-up study of macrocephalic children with enlargement of the subarachnoid space. Arq Neuropsiquiatr 1992; 50:156.
36. Pettit RE, Kilroy AW, Allen JH. Macrocephaly with head growth parallel to normal growth pattern: neurological, developmental, and computerized tomography findings in full-term infants. Arch Neurol 1980; 37:518.
37. Hamza M, Bodensteiner JB, Noorani PA, Barnes PD. Benign extracerebral fluid collections: a cause of macrocrania in infancy. Pediatr Neurol 1987; 3:218.
38. Nickel RE, Gallenstein JS. Developmental prognosis for infants with benign enlargement of the subarachnoid spaces. Dev Med Child Neurol 1987; 29:181.
39. Bosnjak V, Besenski N, Marusić-Della Marina B, Kogler A. Cranial ultrasonography in the evaluation of macrocrania in infancy. Dev Med Child Neurol 1989; 31:66.
40. Ravid S, Maytal J. External hydrocephalus: a probable cause for subdural hematoma in infancy. Pediatr Neurol 2003; 28:139.
41. Ghosh PS, Ghosh D. Subdural hematoma in infants without accidental or nonaccidental injury: benign external hydrocephalus, a risk factor. Clin Pediatr (Phila) 2011; 50:897.
42. Lago P, Rebsamen S, Clancy RR, et al. MRI, MRA, and neurodevelopmental outcome following neonatal ECMO. Pediatr Neurol 1995; 12:294.
43. Canady AI, Fessler RD, Klein MD. Ultrasound abnormalities in term infants on ECMO. Pediatr Neurosurg 1993; 19:202.
44. Lorch SA, D'Agostino JA, Zimmerman R, Bernbaum J. "Benign" extra-axial fluid in survivors of neonatal intensive care. Arch Pediatr Adolesc Med 2004; 158:178.
45. The head. In: Pediatric Diagnosis Interpretation of Symptoms and Signs in Children and Adolescents, 6th, Green MG (Ed), WB Saunders, Philadelphia 1998. p.4.
46. Firth HV, Hurst JA, Hall JG. Macrocephaly. In: Oxford Desk Reference: Clinical Genetics, 1st, Oxford University Press, Oxford 2005. p.162.
47. Smith R, Leonidas JC, Maytal J. The value of head ultrasound in infants with macrocephaly. Pediatr Radiol 1998; 28:143.
48. Malinger G, Lev D, Ben-Sira L, et al. Can syndromic macrocephaly be diagnosed in utero? Ultrasound Obstet Gynecol 2011; 37:72.
49. Kurmanavicius J, Wright EM, Royston P, et al. Fetal ultrasound biometry: 1. Head reference values. Br J Obstet Gynaecol 1999; 106:126.
50. Biran-Gol Y, Malinger G, Cohen H, et al. Developmental outcome of isolated fetal macrocephaly. Ultrasound Obstet Gynecol 2010; 36:147.

Topic 2849 Version 19.0

GRAPHICS

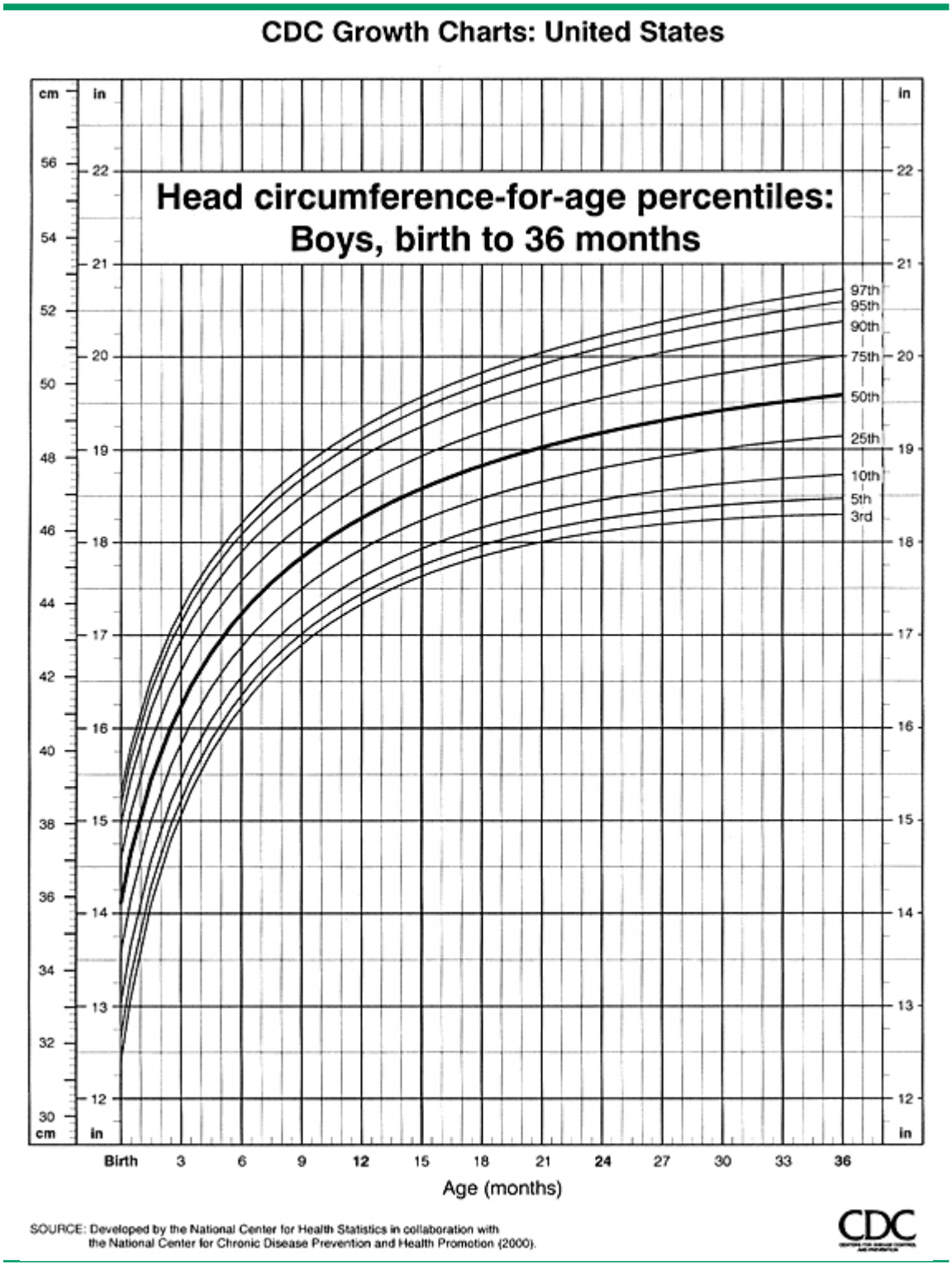
Measurement of head circumference



Measuring head circumference. The measuring tape passes just above the eyebrows and around the prominent posterior aspect of the head.

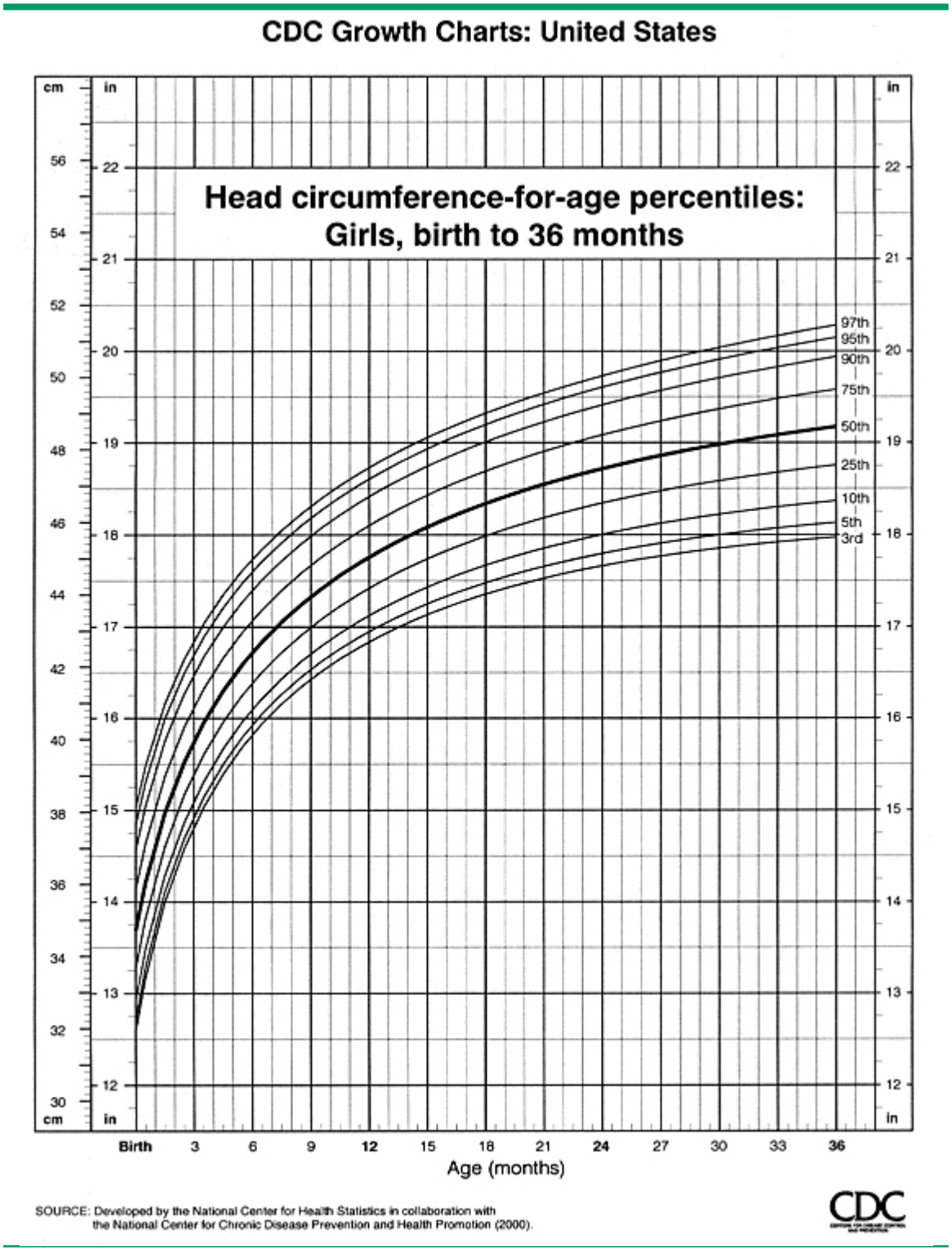
Graphic 70799 Version 2.0

Head circumference-for-age percentiles, boys birth to 36 months, CDC growth charts



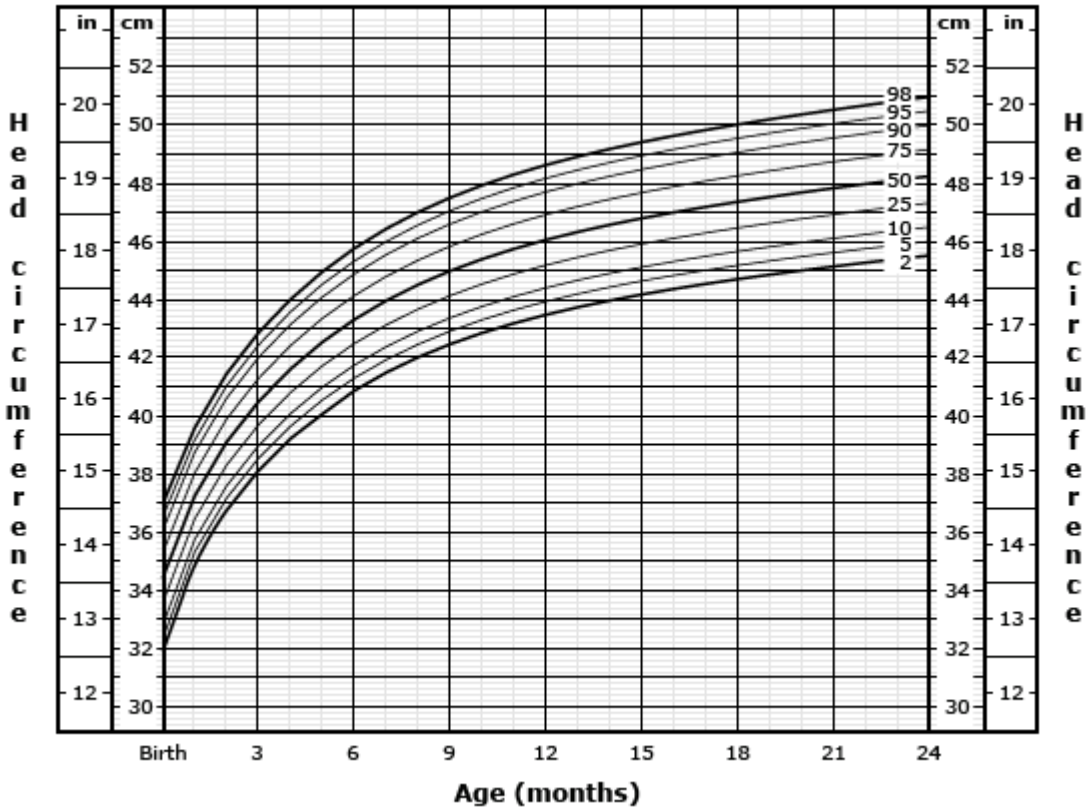
Graphic 80863 Version 3.0

Head circumference-for-age percentiles, girls 0 to 36 months, CDC growth charts



Graphic 59076 Version 3.0

Head circumference-for-age percentiles, boys 0 to 24 months, WHO growth standards

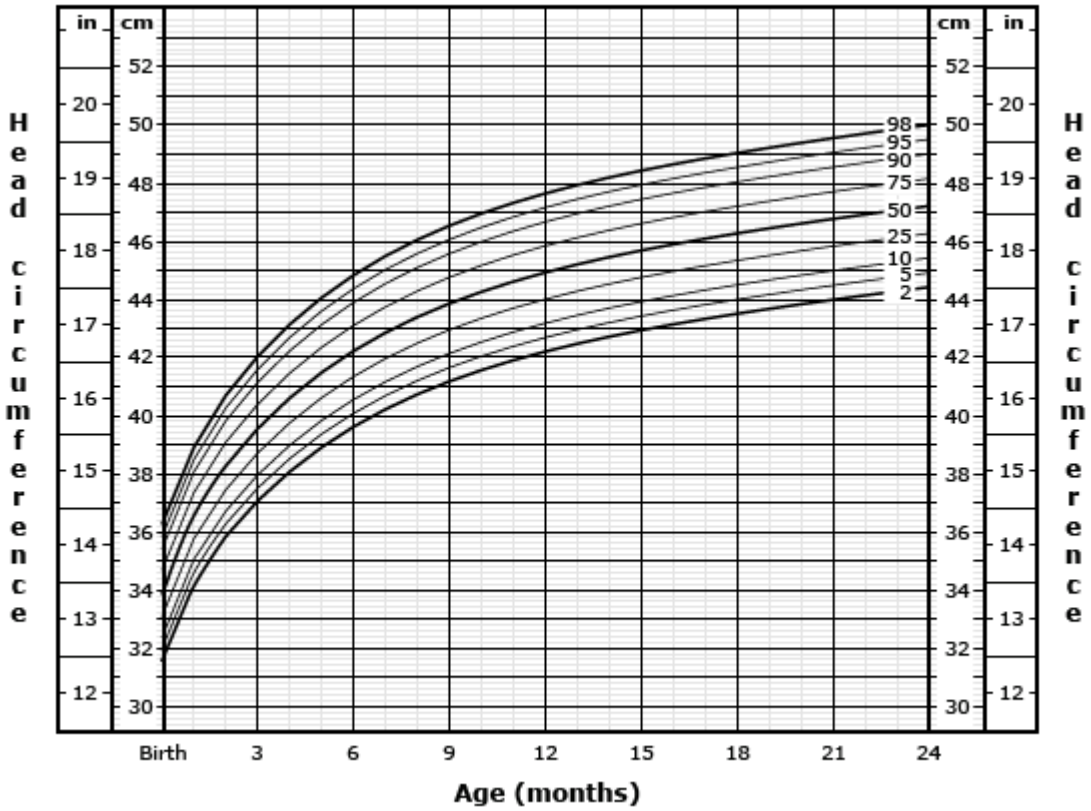


WHO: World Health Organization.

Reproduced from: Centers for Disease Control and Prevention based on data from the WHO Child Growth Standards.

Graphic 58632 Version 3.0

Head circumference-for-age percentiles, girls 0 to 24 months, WHO growth standards



WHO: World Health Organization.

Reproduced from: Centers for Disease Control and Prevention based on data from the WHO Child Growth Standards.

Graphic 74503 Version 3.0

Selected causes of macrocephaly

Increased brain (megalencephaly)
Anatomic
Familial megalencephaly
Neurocutaneous disorders (eg, neurofibromatosis, tuberous scleorsis, linear sebaceous nevus syndrome, Sturge-Weber syndrome, Klippel-Trenaunay-Weber syndrome, nevoid basal call carcinoma syndrome [Gorlin syndrome])
Autism spectrum disorder
Achondroplasia
Cerebral gigantism (Sotos syndrome)
Fragile X syndrome
PTEN hamartoma syndromes (eg, Cowden syndrome, Bannayan-Riley-Ruvalcaba)
Metabolic
Leukodystrophies (eg, Alexander, Canavan, megalencephalic leukoencephalopathy)
Lysosomal storage disorders (eg, Tay-Sachs, mucopolysaccharidosis, gangliosidosis)
Increased cerebrospinal fluid
Hydrocephalus*
Benign enlargement of the subarachnoid space
Hydranencephaly
Choroid plexus papilloma

Increased blood
Hemorrhage (intraventricular, subdural, epidural, subarachnoid)
Arteriovenous malformation
Increased bone
Bone marrow expansion (eg, thalassemia major)
Primary bone disorders (eg, skeletal and cranial dysplasias such as achondroplasia, osteogenesis imperfecta, cleidocranial dysostosis, metaphyseal dysplasia, osteopetrosis, hyperphosphatasia)
Increased intracranial pressure
Idiopathic (pseudotumor cerebri)
Infection or inflammation (eg, meningitis)
Toxins (eg, lead)
Metabolic abnormalities (eg, vitamin A deficiency or excess, galactosemia)
Mass lesions
Intracranial cyst
Intracranial tumor
Intracranial abscess

* Please see the topic review on hydrocephalus.

Graphic 65812 Version 4.0

Clinical features of selected syndromes associated with macrocephaly

Syndrome	Clinical features (in addition to macrocephaly)
Predominantly cutaneous syndromes	
Tuberous sclerosis* OMIM 191100	Facial angiofibromas, shagreen patch, hypopigmented macules, periungual fibromas, gingival fibromas
Neurofibromatosis type 1* OMIM 162200	Café-au-lait spots, axillary freckling, dermal neurofibroma, short stature, Lisch nodules
Linear epidermal nevus syndrome OMIM 163200	Asymmetric overgrowth, coloboma (eyelids, iris, choroid), linear nevus sebaceous; associated with basal cell carcinoma
Klippel-Trenaunay-Weber OMIM 149000	Large cutaneous hemangioma with hypertrophy of related bones and soft tissues; syndactyly; polydactyly
Proteus OMIM 176920	Asymmetric, disproportionate overgrowth of body parts, epidermal nevi, hypertrophy of skin of soles, hemangioma (thorax, upper abdomen)
Macrocephaly cutis marmorata telangiectatica congenita OMIM 602501	Vascular mottling of the skin; congenital telangiectasias, syndactyly of second and third toes; polydactyly; asymmetry of the head, face, or body; nevus flameus of the lip and/or philtrum; overgrowth with prenatal onset
Nevoid basal cell carcinoma syndrome* (Gorlin syndrome) OMIM 109400	Frontoparietal bossing, broad nasal bridge, coarse facial features, highly arched eyebrows, pouting lower lip; odontogenic keratocysts of the mandible and maxilla; increased risk of basal cell carcinoma
PTEN hamartoma tumor syndromes	
Bannayan-Riley Ruvalcaba* OMIM 153480	Lipomas, hemangiomas, pigmented macules; congenital macrosomia (birth weight usually >4 kg) followed by postnatal growth deceleration and normal adult height; down-slanting palpebral fissures; increased risk of certain malignancies
Cowden* and Lhermitte-Duclos* OMIM 158350	Birdlike facies; hypoplastic mandible and maxilla; cataract; microstomia; high-arched palate; pectus excavatum; genitourinary anomalies; skin tags; lipomas
Predominantly overgrowth syndromes	
Sotos OMIM 117550	High-prominent forehead, down-slanting palpebral fissures, long pointed chin, high-arched palate; tall stature and advanced bone age; normal adult height

Weaver* OMIM 277590	Accelerated growth with prenatal onset, advanced bone age, broad forehead, flat occiput, long philtrum, camptodactyly, broad thumbs, loose skin, deep-set nails; deep palmar and plantar creases
Simpson-Golabi OMIM 312870	Accelerated growth with prenatal onset (weight more affected than height), coarse facial features, down-slanting palpebral fissures, thickened lips, wide mouth, large tongue, high-arched palate, prominent jaw, short neck, supernumary nipples, hepatomegaly
Beckwith-Wiedemann* OMIM 130650	Omphalocele (or other umbilical abnormalities), hemihypertrophy, coarse facial features, macroglossia, neonatal macrosomia, neonatal hypoglycemia, increased risk of certain tumors (eg, Wilms tumor, hepatoblastoma)
Neuro-cardio-facio-cutaneous syndromes•	
Noonan* OMIM 163950	Short stature (postnatal onset), congenital heart defects (atrial septal defect, ventricular septal defect, pulmonic stenosis), webbed neck, abnormal chest, hypertelorism, down-slanting palpebral fissures, epicanthal folds, deafness (sensorineural); deeply grooved philtrum
LEOPARD* OMIM 151100	Lentigenes, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, deafness (sensorineural)
Costello* OMIM 218040	Failure to thrive, short stature, developmental delay, coarse facial features, deep palmar and plantar creases, papillomata, cardiac abnormalities, risk for tumors
Cardiofaciocutaneous OMIM 115150	Cardiac abnormalities (atrial septal defect, pulmonic stenosis, hypertrophic cardiomyopathy), cutaneous abnormalities (ichthyosis, hyperkeratosis, hemangioma), postnatal short stature, prominent forehead, bitemporal narrowing, coarse facial features, prominent philtrum, down-slanting palpebral fissures, short upturned nose

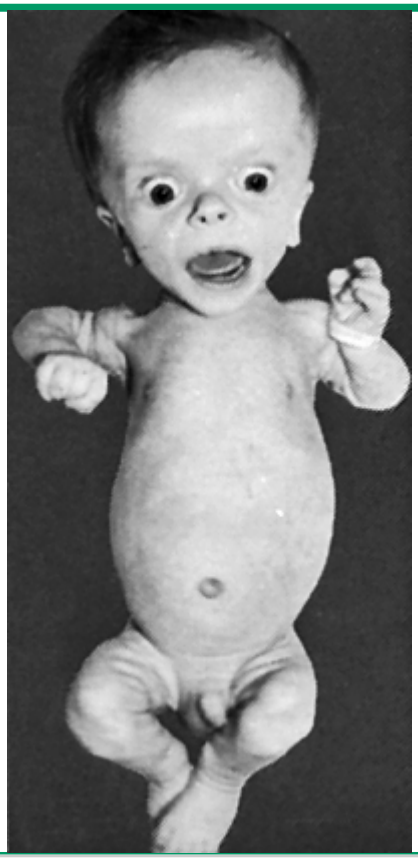
PTEN: phosphate and tensin homolog deleted on chromosome gene.
* Autosomal dominant inheritance.
• Associated with mutations in the RAS/MAP kinase signaling pathway genes.

Data from:

1. *Williams CA, Dagli A, Battaglia A. Genetic disorders associated with macrocephaly. Am J Med Genet A 2008; 146A:2023.*
2. *Olney AH. Macrocephaly syndromes. Semin Pediatr Neurol 2007; 14:128.*
3. *Firth HV, Hurst JA, Hall JG. Macrocephaly. In: Oxford Desk Reference: Clinical Genetics, 1st ed. Oxford University Press, Oxford 2005. p.162.*

Graphic 75193 Version 7.0

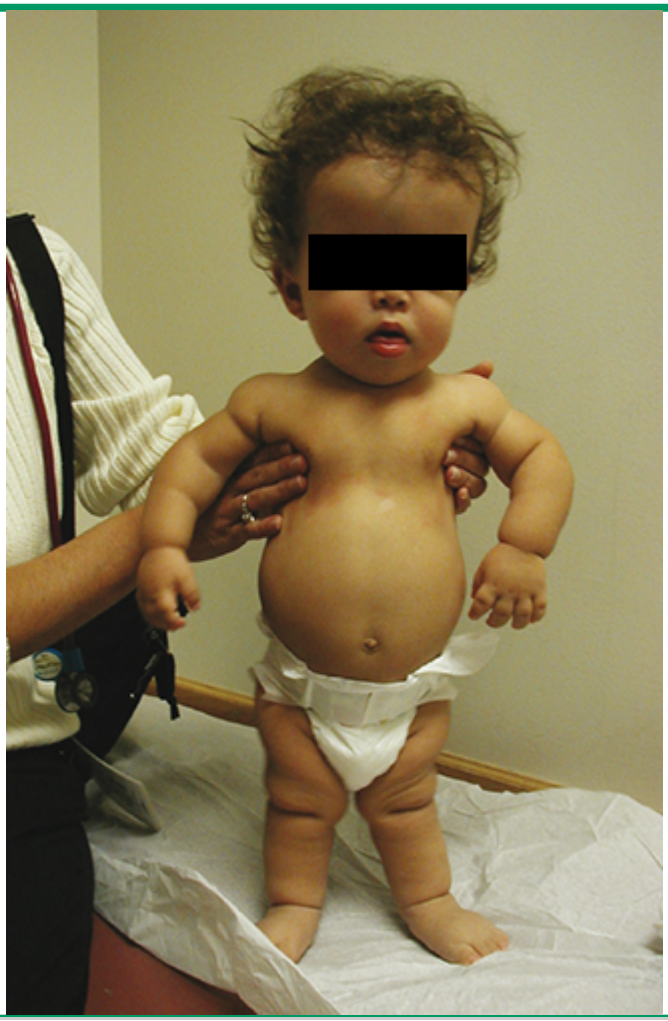
Achondroplasia



Three-month-old infant with achondroplasia. Note the large head, short extremities, and protruding abdomen.

Graphic 80450 Version 1.0

Achondroplasia

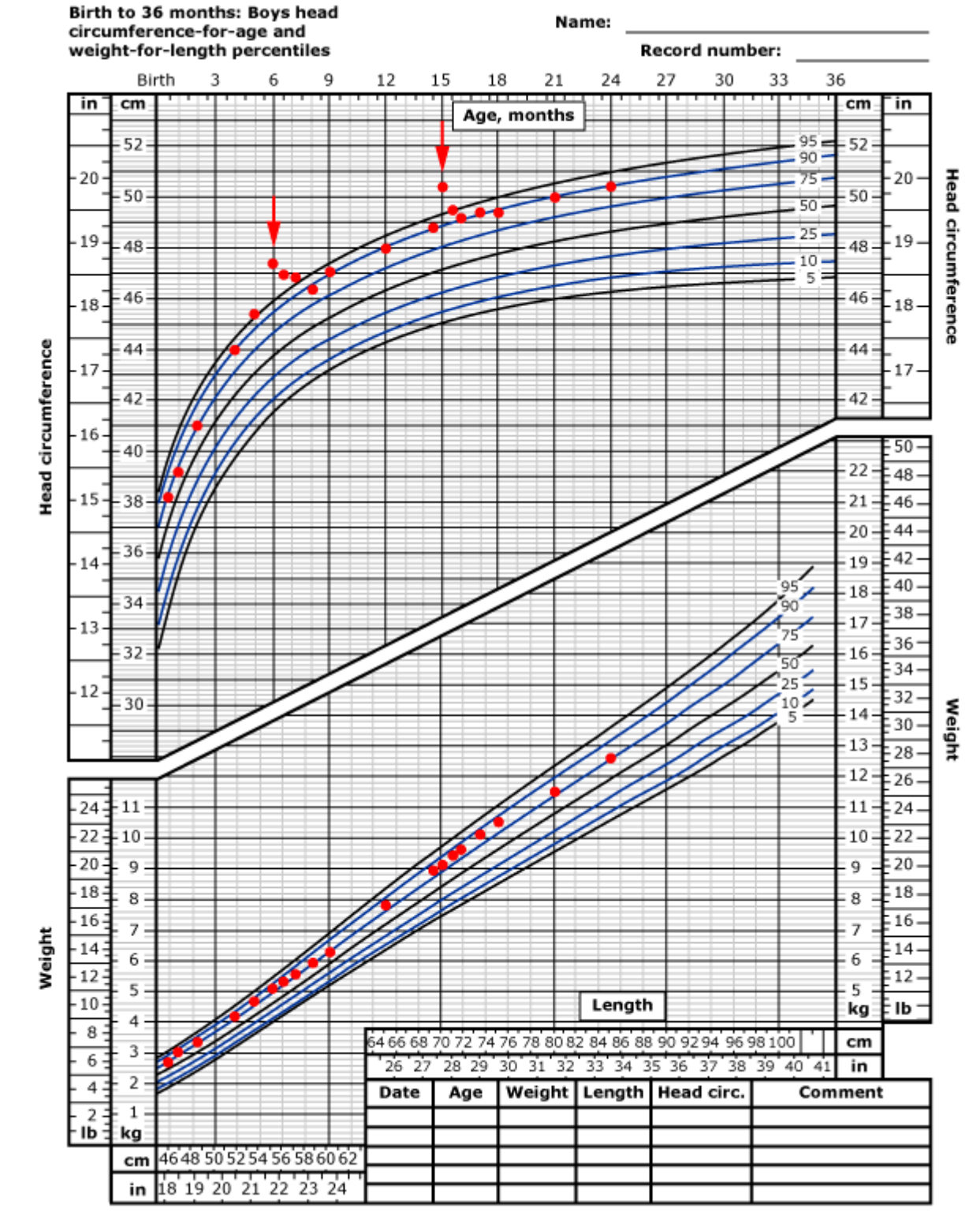


This infant with achondroplasia has tibial bowing, frontal bossing, rhizomelia (the proximal limb segment, is shorter than the distal segment), and brachydactyly (short fingers).

Photo courtesy of Paul S Matz, MD. Reproduced from: Chung EK, Boom JA, Datto GA, Matz PS (Eds). Visual Diagnosis in Pediatrics. Philadelphia: Lippincott Williams & Wilkins, 2006. Copyright © 2006.

Graphic 66831 Version 1.0

Head circumference in a child with communicating hydrocephalus



Head circumference of a child with communicating hydrocephalus. A ventriculo-peritoneal shunt was placed at 6 months of age; it became nonfunctional at 15 months and was revised.

Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). http://www.cdc.gov/growthcarts.

Graphic 82118 Version 1.0

Common causes of macrocephaly in children according to time of clinical presentation

Early infantile (birth to 6 mo of age)	Hydrocephalus (progressive or "arrested")	
	Induction disorders	Spina bifida cystica, cranium bifidum, Chiari malformations (types I, II, and III), aqueductal stenosis, holoprosencephaly
	Mass lesions	Neoplasms, atrioventricular malformations, congenital cysts
	Intrauterine infections	Toxoplasmosis, cytomegalic inclusion disease, syphilis, rubella
	Perinatal or postnatal infections	Bacterial, granulomatous, parasitic
	Perinatal or postnatal hemorrhage	Hypoxia, vascular malformation, trauma
	Hydranencephaly	
	Subdural effusion	
	Hemorrhagic, infectious, cystic hygroma	
	Normal variant (often familial)	
Late infantile (6 mo to 2 yr of age)	Hydrocephalus (progressive or "arrested")	
	Space-occupying lesions	Tumors, cysts, abscess
	Postbacterial or granulomatous meningitis	
	Posthemorrhagic	Trauma or vascular malformation
	Dandy-Walker syndrome	
	Subdural effusion	
	Increased intracranial pressure syndrome	
	Pseudotumor cerebri	Lead, tetracycline, hypoparathyroidism, corticosteroids, excess or deficiency of vitamin A, cyanotic congenital heart disease
	Primary skeletal cranial dysplasias (thickened or enlarged skull)	
	Osteogenesis imperfecta, hyperphosphatemia, osteopetrosis, rickets	
	Megalencephaly (increase in brain substance)	
	Metabolic central nervous system diseases	Leukodystrophies (eg, Canavan, Alexander), lipidoses (Tay-Sachs), histiocytosis, mucopolysaccharidoses
	Proliferative neurocutaneous syndromes	von Recklinghausen tuberous sclerosis, hemangiomatosis, Sturge-Weber
	Cerebral gigantism	Sotos syndrome
	Achondroplasia	

	Primary megalencephaly	May be familial and unassociated with abnormalities of cellular architecture, or associated with abnormalities of cellular architecture
Early to late childhood (older than 2 yr of age)	Hydrocephalus (progressive or "arrested")	
	Space-occupying lesions	
	Preexisting induction disorder	Aqueductal stenosis
	Postinfectious	
	Hemorrhagic	
	Chiari type I malformation	
	Megalencephaly	
	Proliferative neurocutaneous syndromes	
	Familial	
	Pseudotumor cerebri	
	Normal variant	

Reproduced with permission from: Child Neurology, 7th ed, Menkes JH, Sarnat HB, Maria BL (Eds), Lippincott Williams & Wilkins, New York 2005. Copyright © 2005 Lippincott Williams & Wilkins. www.lww.com.

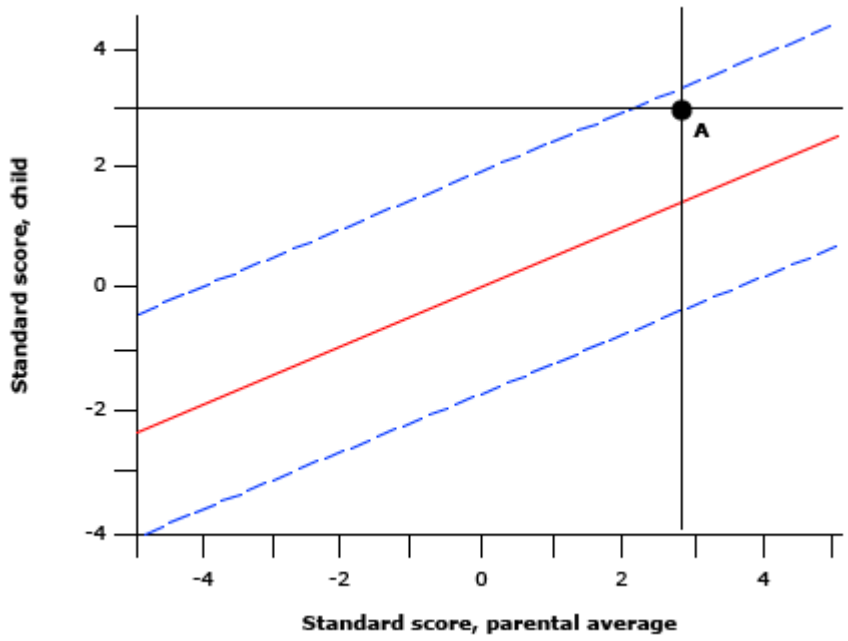
Graphic 74157 Version 14.0

Head circumference data of Nellhaus

Age	Males		Females	
	Mean (cm)	1 SD	Mean (cm)	1 SD
Birth	34.74	1.33	34.02	1.22
1 mo	37.30	1.30	36.43	1.22
3 mo	40.62	1.23	39.71	1.20
6 mo	43.76	1.29	42.68	1.38
9 mo	45.75	1.28	44.69	1.30
12 mo	47.00	1.31	45.81	1.29
18 mo	48.31	1.36	47.27	1.36
2 yr	49.19	1.39	48.02	1.29
3 yr	50.63	1.38	49.25	1.36
4 yr	50.91	1.39	50.10	1.37
5 yr	51.41	1.37	50.55	1.32
6 yr	51.40	1.41	50.52	1.31
7 vr	52.24	1.52	51.46	1.35
8 yr	52.35	1.40	51.64	1.44
9 yr	52.58	1.44	51.87	1.33
10 yr	53.16	1.41	52.15	1.50
11 yr	53.25	1.53	52.64	1.39
12 vr	53.71	1.52	53.01	1.50
13 yr	54.14	1.57	53.70	1.37
14 yr	54.59	1.30	54.04	1.39
15 yr	54.95	1.51	54.39	1.34
16 yr	55.37	1.11	54.64	1.16
17 yr	55.77	1.32	54.78	1.35
18 yrs and older	55.95	1.34	54.94	1.40

Graphic 61299 Version 4.0

Weaver curve



Plotted above is an example of the use of the Weaver curve. The child's OFC was 49.5 cm at the age of 9 months, placing him well above the 97th percentile on Nellhaus's head circumference chart. His standard score (SS) was calculated to be +2.93. The father had an OFC of 59.5 cm, and the mother's was 59.0 cm with SS of +2.65 and +2.90, respectively. Their average parental SS was +2.78. When plotted, the intercept (A) of lines from the SS falls below the +2 SD regression line. Thus, the child's head size in relationship to that of his parents is judged to be normal.

Graphic 80059 Version 5.0

Disclosures

Disclosures: **Julie A Boom, MD** Nothing to disclose. **Jan E Drutz, MD** Nothing to disclose. **Marc C Patterson, MD, FRACP** Grant/Research/Clinical Trial Support: Actelion [Lysosomal diseases (Miglustat)]. Consultant/Advisory Boards: Amicus; Agios; Cydan; Genzyme; Orphazyme; Shire HGT [Lysosomal diseases (Arimoclomol, cyclodextrin, glucocerebrosidase)]; Stem Cells, Inc; Vtesse [Lysosomal diseases (Human embryonic stem cells)]. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Mary M Torchia, MD** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Sex chromosome abnormalities

Author Carlos A Bacino, MD, FACMG
Section Editor Helen V Firth, DM, FRCP, DCH
Deputy Editor Elizabeth TePas, MD, MS

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Feb 02, 2015.

INTRODUCTION — Sex chromosome abnormalities are due to numeric abnormalities (eg, aneuploidies such as monosomy X) or structural defects (eg, isochromosome Xq leading to Turner syndrome). Congenital sex chromosome abnormalities occur in at least 1 in 448 births [1]. (See "Glossary of genetic terms" and "Genomic disorders: An overview".)

Other congenital cytogenetic abnormalities are discussed in detail separately. (See "Congenital cytogenetic abnormalities" and "Microdeletion syndromes (chromosomes 1 to 11)" and "Microdeletion syndromes (chromosomes 12 to 22)" and "Microduplication syndromes".)

NUMERIC ABNORMALITIES (ANEUPLOIDIES) — The most common sex chromosome aneuploidies are 45,X (Turner syndrome); 47,XXY (Klinefelter syndrome); 47,XYY; and 47,XXX, which have birth frequencies of approximately 1 in 2500, 1 in 500 to 1 in 1000, 1 in 900 to 1 in 1500, and 1 in 1000, respectively [2-7]. Sex chromosome mosaicism involving a normal cell line is not unusual. The two most common forms of sex chromosome mosaicism are 45,X/46,XX and 45,X/46,XY [8,9]. The severity of the phenotype in patients with mosaicism is related to the percentage of abnormal cells among critical tissues [10,11].

Monosomy X (45,X or Turner syndrome) — Most patients with Turner syndrome have monosomy for the X chromosome with a 45,X karyotype. Other forms of Turner include mosaicism for X chromosome monosomy (eg, 45,X/46,XX) or 45,X/46,XY mosaic with or without a partial deletion of the Y chromosome. The remaining patients have a structural abnormality of the second X chromosome (eg, an isochromosome of the long arm of X or a deletion involving the short arm of one X). Deletions involving the distal portion of the short arm of the Y chromosome are associated with the Turner phenotype because these individuals are missing the so-called "anti-Turner" genes (*SHOX*, *RPSY4*, and *ZFY*). Deletions of the short arm of the X chromosome are also associated with a Turner phenotype [12]. Most cases represent sporadic events. (See '45,X/46,XX mosaicism' below and '45,X/46,XY mosaicism' below and 'Isochromosome Xq' below and 'Xp22 SHOX deletions' below.)

Turner syndrome is characterized by short stature. Dysmorphic features are common and include low and posteriorly rotated ears, webbing of the neck, shield-like chest (broad chest with wide-spaced nipples), cubitus valgus, short fourth metacarpals, and hypoplastic nails. Other frequent findings include lymphedema, pigmented nevi, and congenital heart defects. Lymphedema in the dorsum of hands and feet may be the only clinical features seen in newborns. The heart defects typically involve the left outflow tract and coarctation of the aorta is a common finding. In addition, Turner patients develop streak gonads with ovarian failure and pubertal delay. Renal anomalies can also occur (horseshoe kidneys). Individuals with Turner syndrome that carry Y chromosome material (as is seen in some patients with mosaicism) are at increased risk of developing gonadoblastoma. Turner syndrome is discussed in detail separately. (See "Clinical manifestations and diagnosis of Turner syndrome (gonadal dysgenesis)" and "Management of Turner syndrome (gonadal dysgenesis)".)

47,XXY Klinefelter syndrome — Klinefelter syndrome is the most common sex chromosome abnormality causing primary hypogonadism. The 47,XXY karyotype results from nondisjunction of the sex chromosomes and can be maternal or paternal in origin. Most cases are detected postnatally and

are diagnosed during evaluation for infertility or gynecomastia.

Male newborns with the 47,XXY karyotype are phenotypically normal, with normal male external genitalia and no dysmorphic features. The major clinical manifestations of Klinefelter syndrome include tall stature, small testes, and infertility (azoospermia) that become noticeable after puberty. Patients with Klinefelter syndrome are at increased risk for psychiatric disorders, autism spectrum disorders, and social problems. Patients diagnosed with Klinefelter syndrome should have a neurodevelopmental evaluation and should be referred to an endocrinologist. Klinefelter syndrome is discussed in greater detail separately. (See "Causes of primary hypogonadism in males", section on 'Klinefelter's syndrome' and "The child with tall stature and/or abnormally rapid growth", section on 'Klinefelter syndrome' and "Causes of male infertility", section on 'Klinefelter's syndrome'.)

47,XYY — Individuals with 47,XYY have tall stature and may have mild delay in motor and language development. A significant proportion of XYY males require special educational intervention, but are generally educated in mainstream school [13]. They have normal pubertal development and most are fertile [14] (see "The child with tall stature and/or abnormally rapid growth"). Due to the subtlety of the phenotype and lack of associated health problems, many individuals with 47,XYY remain undiagnosed throughout their lifespan.

In an early report, 47,XYY males were thought to have increased aggressive behavior [15]. However, a subsequent large collaborative study by European and United States geneticists concluded that the increased rate of antisocial behavior in XYY males was related to a lack of judgment and lower socioeconomic status due to a lower mean intelligence quotient (IQ) score (by 10 points), which led them into difficulties with the law and involvement in minor crimes [16-18]. Higher rates of attention-deficit hyperactivity disorder and autism spectrum disorders are reported in 47,XYY [19]. A neurodevelopmental evaluation is recommended in patients diagnosed with 47,XYY, given the high prevalence of learning disabilities and behavioral problems.

47,XXX — 47,XXX (also called triple X) is the most common sex chromosome abnormality in females [5]. Most individuals with 47,XXX are diagnosed incidentally on prenatal genetic screening [20]. These women do not appear to be at increased risk of having chromosomally abnormal offspring [21].

A review of 155 females with 47,XXX karyotype found that 62 percent of these individuals were physically normal [22]. Thus, it is estimated that most individuals with 47,XXX are never diagnosed [5]. 47,XXX females have a tendency to be tall, with many reaching the 80th percentile in height by adolescence, but with an average head circumference between the 25th to 35th percentile [16]. Puberty and fertility are generally the normal range, but premature ovarian failure can occur [5,16]. Another prospective study of 11 47,XXX females identified in a newborn survey at birth reported that their verbal and performance IQ scores were 15 to 20 points lower than those of their siblings [23]. Thus, monitoring for developmental delays and psychologic problems is recommended.

Other — Over 100 cases of 49,XXXXY [24], at least 20 cases of 49,XXXXX [25], and a few cases of 49,XYYYY [26], have been reported. There appears to be a direct relationship between the number of additional sex chromosomes and the severity of the phenotype. In addition, a review of tetrasomy and pentasomy of sex chromosomes concluded that polysomy of the X chromosome results in a more deleterious effect than polysomy of the Y chromosome [1]. Studies have shown that the IQ is reduced by 10 points for every extra X chromosome beyond the normal number [27].

49,XXXXY — The characteristic clinical features of the XXXXY karyotype are low nasal bridge with a wide or up-turned tip, wide-set eyes, epicanthal folds, skeletal anomalies (especially radioulnar synostosis), congenital heart disease, endocrine disorders, and severe hypogonadism and hypogenitalism [24,28,29]. Severe intellectual disability and moderately short stature are usual. Although individuals with this karyotype are often labeled as Klinefelter variant, the characteristic features of

XXXXY all point to a distinct phenotype [24,30].

49,XXXXX — Intellectual disability is always present in females with 49,XXXXX (also called pentasomy X) [25]. Other findings, such as craniofacial, cardiovascular, and skeletal abnormalities are quite variable. Patients with pentasomy X may have clinical features resembling those seen in Down syndrome. Radioulnar synostosis is also commonly seen in patients with multiple X chromosomes. Some patients have mosaicism of 48,XXXX and 49,XXXXX [31,32]. (See "Down syndrome: Clinical features and diagnosis".)

45,X/46,XX mosaicism — This is the most common sex chromosome mosaicism diagnosed by amniocentesis and prenatal karyotyping [8,9]. Individuals with this type of mosaicism have milder clinical features of Turner syndrome [9,33-35]. Many women undergo spontaneous puberty and have reproduced. (See 'Monosomy X (45,X or Turner syndrome)' above and "Clinical manifestations and diagnosis of Turner syndrome (gonadal dysgenesis)" and "Management of Turner syndrome (gonadal dysgenesis)".)

A review of 156 prenatally diagnosed cases of 45,X/46,XX with available outcome information found that 14 percent had an abnormal outcome [36]. There were two stillbirths and 20 cases with an abnormal phenotype (12 had some features of Turner syndrome and 8 showed anomalies possibly not related to Turner syndrome). Over 85 percent of cases appeared to result in phenotypically normal females either at birth or at termination. However, the major features of Turner syndrome (eg, short stature and lack of secondary sex characteristics) are only manifested later in childhood or adolescence and would not be detected among infants. 45,X/46,XX mosaicism is reported in some women with premature ovarian failure who are otherwise phenotypically normal [37,38].

45,X/46,XY mosaicism — Mosaicism involving 45,X/46,XY has a wide phenotypic spectrum [39,40]. In a retrospective series of 151 postnatally diagnosed cases of 45,X/46,XY mosaicism, for example, 42 percent of patients were phenotypic females with typical or atypical Turner syndrome, 42 percent had ambiguous external genitalia and asymmetrical gonads (ie, mixed gonadal dysgenesis), and 15 percent had a male phenotype with incomplete masculinization [40]. Thus, all postnatally diagnosed cases were phenotypically abnormal. However, this can be explained by the fact that children or adults with mosaicism and a normal phenotype are not likely to seek medical attention (ascertainment bias). In contrast, among 80 prenatally diagnosed cases of 45,X/46,XY mosaicism, 74 (92.5 percent) were grossly normal males [36]. (See 'Monosomy X (45,X or Turner syndrome)' above and "Clinical manifestations and diagnosis of Turner syndrome (gonadal dysgenesis)".)

A high resolution ultrasound exam of the fetus with special emphasis on the external genitalia is recommended when a diagnosis of 45,X/46,XY is made prenatally. Visualization of male genitalia can be more reassuring to parents than a quantitative estimate of risk of phenotypic abnormality. However, it is not known whether linear growth and fertility may be influenced by the 45,X cell line in phenotypically normal male infants.

STRUCTURAL ABNORMALITIES — Structural abnormalities primarily consist of isochromosomes, deletions, duplications, ring chromosomes, and translocations. (See "Genomic disorders: An overview" and "Chromosomal translocations, deletions, and inversions".)

Isochromosome Xq — Isochromosome for the long arm of the X chromosome, isoXq or i(Xq), in which the short arm (p) is deleted and replaced with an exact copy of the long arm (q), is one of the most common structural sex chromosome abnormalities [16,41].

It is not associated with increased parental age [42]. 46,X,i(Xq) can occur as a nonmosaic or as a mosaic with a normal 46,XX cell line, 45,X cell line, or both. Isochromosomes Xq and Yq are associated with Turner syndrome, probably because the major anti-Turner syndrome gene, *SHOX* (short stature homeobox-containing gene on the X chromosome), is located at the distal portion of the short arms of

the X and Y chromosomes (at the pseudoautosomal pairing regions) [40,43]. The Xq isochromosome is also seen in patients with a variant of Klinefelter syndrome, 47,X,i(Xq),Y [44-48]. (See "Clinical manifestations and diagnosis of Turner syndrome (gonadal dysgenesis)" and "Causes of primary hypogonadism in males", section on 'Klinefelter's syndrome'.)

X-chromosome deletions

Xp11.22 deletions — Deletions of the Xp11.22 region including the *PHF8* (plant homeo domain [PHD] finger protein 8) gene have been reported in association with intellectual disability, cleft lip/palate, and autistic spectrum disorders [49]. Truncating mutations of the *PHF8* gene are associated with the X-linked mental retardation (XLMR) Siderius-Hamel syndrome (MIM #300263).

Xp22.11 deletion — A deletion in Xp22.11 involving *PTCHD1* (patched domain-containing protein 1) gene was reported in several families with autism spectrum disorder and in three families with intellectual disability [50]. *PTCHD1* is a candidate gene for X-linked intellectual disability with or without autism [51]. The function and role of this gene is unknown.

Xp22.3 deletion — Deletion of this region is often associated with microphthalmia and linear skin defects (MLS) syndrome, an X-linked dominant disorder that is lethal in males and therefore only seen in females [52]. A gene in this region encoding mitochondrial holocytochrome c-type synthetase (*HCCS*) was found mutated in patients with MLS who did not have the deletion [53-56]. The clinical presentation of MLS consists of microphthalmia and anophthalmia (unilateral or bilateral) and linear skin defects, mostly in the face and neck that heal with time. Structural brain abnormalities, developmental delay, and seizures are part of the clinical spectrum. Heart defects (such as hypertrophic cardiomyopathy and arrhythmias), short stature, diaphragmatic hernia, nail dystrophy, preauricular pits and hearing loss, and genitourinary malformations, are also common clinical findings.

Screening evaluations include ophthalmologic evaluation (consider prosthesis), developmental and dermatology evaluations, echocardiogram, brain magnetic resonance imaging (MRI), and electroencephalogram (EEG). Patient may benefit from physical, occupation, and speech therapy (PT, OT and ST).

Xp22 SHOX deletions — Deletions of Xp22 encompassing the short stature homeobox-containing (*SHOX*) gene is causative for idiopathic short stature [43,57,58]. The *SHOX* gene is found in the pseudoautosomal region 1 (PAR1) of the X and Y chromosomes. This gene is considered a major player in the short stature of Turner syndrome and haploinsufficiency of this gene causes Leri-Weill dyschondrosteosis (LWD) [43,59]. LWD is characterized by short stature, more severe in females, and Madelung deformities (focal dysplasia of the distal radial physis). Homozygous deletions of SHOX cause Langer dysplasia, a more severe form of metaphyseal dysplasia [60]. SHOX deletions can also be seen in patients with short stature and no other specific skeletal signs. More than 60 percent of the SHOX rearrangements are gene deletions, therefore array comparative genomic hybridization (array CGH) should be considered in the work-up of idiopathic short stature, followed by sequencing to ascertain point mutations if no deletions are found. (See "Clinical manifestations and diagnosis of Turner syndrome (gonadal dysgenesis)", section on 'Pathogenesis' and "Causes of chronic wrist pain in children and adolescents", section on 'Madelung deformity' and "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Array comparative genomic hybridization' and "Genomic disorders: An overview", section on 'Array comparative genomic hybridization' and "Causes of short stature", section on 'Idiopathic short stature'.)

X chromosome duplications

Xp22.31 duplication — Duplications in Xp22.31 have been extensively reported in the literature. There has been much debate about whether this duplication is pathogenic or a benign finding, underscoring the difficulties in determining the consequences of copy number variations (CNVs) [61,62].

This duplication involves the *STS* (steroid sulfatase) gene. Deletions of this gene are associated with X-linked ichthyosis in males. This duplication has been reported in patients with intellectual disabilities. However, it has also been seen in the patients' normal relatives as well as in the general population. While duplications of this gene may have no phenotypic consequences, triplications are consistently associated with intellectual disabilities [63]. Fluorescent in situ hybridization (FISH) studies can ultimately aid in distinguishing duplications from triplications or multiple copy number gains. (See "Overview of genetic variation", section on 'Copy number variations (CNVs)' and "Genomic disorders: An overview", section on 'Copy number variations'.)

Xp26.3 microduplication — Microduplications in the Xp26.3 region that include the *GPR101* (G protein-coupled receptor 101) gene are associated with gigantism due to an excess of growth hormone, termed X-linked acrogigantism (X-LAG) [64]. All patients identified with this microduplication had disease-onset before five years of age. The G protein-coupled receptor was overexpressed in the patients' pituitary lesions. A recurrent mutation in *GPR101* is found in some adults with acromegaly. (See "Pituitary gigantism" and "Causes and clinical manifestations of acromegaly", section on 'Causes'.)

MECP2 duplication syndrome — Mutations in the gene encoding methyl-CpG binding protein 2 (*MECP2*) located in Xq28 are responsible for Rett syndrome. Duplications of this region have little or no phenotypic significance in females, who are most likely normal due to X inactivation of the abnormal X chromosome. Males with this duplication are severely impaired (MIM #300260). The clinical presentation includes early hypotonia, severe to profound intellectual disability, speech delay, feeding difficulties, frequent respiratory infections, and seizures (ranging from tonic-clonic type to absence seizures) that are sometimes refractory to treatment [65-68]. Many patients with this duplication have been diagnosed with autism or autism spectrum disorder [69]. Similarly to what is seen in Rett syndrome, patients with *MECP2* duplication experience developmental regression. In addition, they develop ataxia, progressive lower limbs spasticity, and often lose their ability to ambulate. Gastrointestinal problems and severe constipation have been reported. The prognosis is guarded and most males with this duplication die in their mid-20s secondary to respiratory infections. The gene for interleukin-1 receptor-associated kinase 1 (*IRAK1*) is often involved in the duplication and may play a role in the immune abnormalities seen in this group of patients [69]. Triplication of this region produces an even more severe phenotype in males.

Screening studies for these patients include an EEG, swallowing studies, and assessment of humoral and cellular immunity. Treatment may include management of hypotonia (PT and OT) and spasticity, speech therapy, gastrostomy tube (g-tube or g-button) for feeding difficulties, and management of respiratory infections.

SUMMARY

- Sex chromosome abnormalities can be due to numeric abnormalities (aneuploidies) or structural defects. (See 'Introduction' above.)
- The most common sex chromosome aneuploidies are 45,X (Turner syndrome); 47,XXY (Klinefelter syndrome); 47,XYY; and 47,XXX. Sex chromosome mosaicism involving a normal cell line is not unusual. The two most common sex chromosome mosaicisms are 45,X/46,XX and 45,X/46,XY. The severity of the phenotype in patients with mosaicism is related to the percentage of abnormal cells. (See 'Numeric abnormalities (aneuploidies)' above.)
- Structural abnormalities of the X and Y chromosomes primarily consist of isochromosomes, deletions, duplications, ring chromosomes, and translocations. One example of a genomic disorder is duplication of methyl-CpG binding protein 2 *(MECP2)* in males, which is associated with hypotonia, severe to profound intellectual disability, speech delay, feeding difficulties, frequent respiratory infections, and seizures. (See 'Structural abnormalities' above.)

REFERENCES

1. Nielsen J, Wohlert M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Birth Defects Orig Artic Ser 1990; 26:209.
2. Stochholm K, Juul S, Juel K, et al. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab 2006; 91:3897.
3. Herlihy AS, Halliday JL, Cock ML, McLachlan RI. The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison. Med J Aust 2011; 194:24.
4. Stochholm K, Juul S, Gravholt CH. Diagnosis and mortality in 47,XYY persons: a registry study. Orphanet J Rare Dis 2010; 5:15.
5. Tartaglia NR, Howell S, Sutherland A, et al. A review of trisomy X (47,XXX). Orphanet J Rare Dis 2010; 5:8.
6. Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 1991; 87:81.
7. Maeda T, Ohno M, Matsunobu A, et al. A cytogenetic survey of 14,835 consecutive liveborns. Jinrui Idengaku Zasshi 1991; 36:117.
8. Wilson MG, Lin MS, Fujimoto A, et al. Chromosome mosaicism in 6,000 amniocenteses. Am J Med Genet 1989; 32:506.
9. Koeberl DD, McGillivray B, Sybert VP. Prenatal diagnosis of 45,X/46,XX mosaicism and 45,X: implications for postnatal outcome. Am J Hum Genet 1995; 57:661.
10. Sarkar R, Marimuthu KM. Association between the degree of mosaicism and the severity of syndrome in Turner mosaics and Klinefelter mosaics. Clin Genet 1983; 24:420.
11. Homer L, Le Martelot MT, Morel F, et al. 45,X/46,XX mosaicism below 30% of aneuploidy: clinical implications in adult women from a reproductive medicine unit. Eur J Endocrinol 2010; 162:617.
12. Ogata T, Muroya K, Matsuo N, et al. Turner syndrome and Xp deletions: clinical and molecular studies in 47 patients. J Clin Endocrinol Metab 2001; 86:5498.
13. Jones KL. Smith's recognizable patterns of human malformation, 6th ed, Elsevier Saunders, Philadelphia 2006.
14. Abdel-Razic MM, Abdel-Hamid IA, ElSobky ES. Nonmosaic 47,XYY syndrome presenting with male infertility: case series. Andrologia 2012; 44:200.
15. Jacobs PA, Brunton M, Melville MM, et al. Aggressive behavior, mental sub-normality and the XYY male. Nature 1965; 208:1351.
16. Robinson A, Linden MG, Bender BG, et al. Prenatal diagnosis of sex chromosome abnormalities. In: Genetic disorders and the fetus, 4th ed, Milunsky A (Ed), The Johns Hopkins University Press, Baltimore 1998. p.249.
17. Witkin HA, Mednick SA, Schulsinger F, et al. Criminality in XYY and XXY men. Science 1976; 193:547.
18. Stochholm K, Bojesen A, Jensen AS, et al. Criminality in men with Klinefelter's syndrome and XYY syndrome: a cohort study. BMJ Open 2012; 2:e000650.
19. Ross JL, Roeltgen DP, Kushner H, et al. Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome. Pediatrics 2012; 129:769.
20. Lalatta F, Quagliarini D, Folliero E, et al. Triple X syndrome: characteristics of 42 Italian girls and parental emotional response to prenatal diagnosis. Eur J Pediatr 2010; 169:1255.

21. Gardner RJM, Sutherland GR. Chromosome abnormalities and genetic counseling, 3rd ed, Oxford University Press, 2003.
22. Barr ML, Sergovich FR, Carr DH, Saver EL. The triplo-X female: an appraisal based on a study of 12 cases and a review of the literature. Can Med Assoc J 1969; 101:247.
23. Robinson A, Bender BG, Linden MG, Salbenblatt JA. Sex chromosome aneuploidy: the Denver Prospective Study. Birth Defects Orig Artic Ser 1990; 26:59.
24. Peet J, Weaver DD, Vance GH. 49,XXXXY: a distinct phenotype. Three new cases and review. J Med Genet 1998; 35:420.
25. Kassai R, Hamada I, Furuta H, et al. Penta X syndrome: a case report with review of the literature. Am J Med Genet 1991; 40:51.
26. Shanske A, Sachmechi I, Patel DK, et al. An adult with 49,XYYYY karyotype: case report and endocrine studies. Am J Med Genet 1998; 80:103.
27. Rovet J, Netley C, Bailey J, et al. Intelligence and achievement in children with extra X aneuploidy: a longitudinal perspective. Am J Med Genet 1995; 60:356.
28. Patacchiola F, Sciarra A, Di Fonso A, et al. 49, XXXXY syndrome: an Italian child. J Pediatr Endocrinol Metab 2012; 25:165.
29. Gropman AL, Rogol A, Fennoy I, et al. Clinical variability and novel neurodevelopmental findings in 49, XXXXY syndrome. Am J Med Genet A 2010; 152A:1523.
30. Tartaglia N, Ayari N, Howell S, et al. 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klinefelter syndrome. Acta Paediatr 2011; 100:851.
31. Ricci N, Dallapiccola B, Ventimiglia B, et al. 48,XXXX-49,XXXXX mosaic: asynchronies among the late-replicating X chromosomes. Cytogenetics 1968; 7:249.
32. Wood A, Kleis L, Toriello H, Cemeroglu AP. Mosaic pentasomy X/tetrasomy X syndrome and premature ovarian failure. Indian Pediatr 2011; 48:402.
33. Suri M, Kabra M, Jain U, et al. A clinical and cytogenetic study of Turner syndrome. Indian Pediatr 1995; 32:433.
34. Hsu LY. Prenatal diagnosis of 45,X/46,XX. Am J Hum Genet 1996; 58:634.
35. Gunther DF, Eugster E, Zagar AJ, et al. Ascertainment bias in Turner syndrome: new insights from girls who were diagnosed incidentally in prenatal life. Pediatrics 2004; 114:640.
36. Hsu LYF. Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In: Genetic disorders and the fetus, 4th ed, Milansky A (Ed), The Johns Hopkins University Press, Baltimore 1998. p.179.
37. Devi AS, Metzger DA, Luciano AA, Benn PA. 45,X/46,XX mosaicism in patients with idiopathic premature ovarian failure. Fertil Steril 1998; 70:89.
38. Devi A, Benn PA. X-chromosome abnormalities in women with premature ovarian failure. J Reprod Med 1999; 44:321.
39. El Moussaif N, Haddad NE, Iraqi N, Gaouzi A. 45,X/46,XY mosaicisme: report of five cases and clinical review. Ann Endocrinol (Paris) 2011; 72:239.
40. Hsu LY. Phenotype/karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases. Am J Med Genet 1994; 53:108.
41. Scott SA, Cohen N, Brandt T, et al. Large inverted repeats within Xp11.2 are present at the breakpoints of isodicentric X chromosomes in Turner syndrome. Hum Mol Genet 2010; 19:3383.
42. James RS, Dalton P, Gustashaw K, et al. Molecular characterization of isochromosomes of Xq. Ann Hum Genet 1997; 61:485.
43. Rao E, Weiss B, Fukami M, et al. Pseudoautosomal deletions encompassing a novel homeobox

gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet 1997; 16:54.

44. Kalousek D, Biddle CJ, Rudner M, et al. 47,X,i(Xq),Y karyotype in Klinefelter's syndrome. Hum Genet 1978; 43:107.
45. Donlan MA, Dolan CR, Metcalf MJ, et al. Trisomy Xq in a male: the isochromosome X Klinefelter syndrome. Am J Med Genet 1987; 27:189.
46. Fryns JP, Kleczkowska A, Steeno O. Isochromosome Xq in Klinefelter syndrome. Am J Med Genet 1990; 36:365.
47. Arps S, Koske-Westphal T, Meinecke P, et al. Isochromosome Xq in Klinefelter syndrome: report of 7 new cases. Am J Med Genet 1996; 64:580.
48. Demirhan O, Pazarbaşi A, Tanriverdi N, et al. The clinical effects of isochromosome Xq in Klinefelter syndrome: report of a case and review of literature. Genet Couns 2009; 20:235.
49. Qiao Y, Liu X, Harvard C, et al. Autism-associated familial microdeletion of Xp11.22. Clin Genet 2008; 74:134.
50. Filges I, Röthlisberger B, Blattner A, et al. Deletion in Xp22.11: PTCHD1 is a candidate gene for X-linked intellectual disability with or without autism. Clin Genet 2011; 79:79.
51. Noor A, Whibley A, Marshall CR, et al. Disruption at the PTCHD1 Locus on Xp22.11 in Autism spectrum disorder and intellectual disability. Sci Transl Med 2010; 2:49ra68.
52. al-Gazali LI, Mueller RF, Caine A, et al. Two 46,XX,t(X;Y) females with linear skin defects and congenital microphthalmia: a new syndrome at Xp22.3. J Med Genet 1990; 27:59.
53. Schaefer L, Ballabio A, Zoghbi HY. Cloning and characterization of a putative human holocytochrome c-type synthetase gene (HCCS) isolated from the critical region for microphthalmia with linear skin defects (MLS). Genomics 1996; 34:166.
54. Wimplinger I, Morleo M, Rosenberger G, et al. Mutations of the mitochondrial holocytochrome c-type synthase in X-linked dominant microphthalmia with linear skin defects syndrome. Am J Hum Genet 2006; 79:878.
55. Sharma VM, Ruiz de Luzuriaga AM, Waggoner D, et al. Microphthalmia with linear skin defects: a case report and review. Pediatr Dermatol 2008; 25:548.
56. Wimplinger I, Rauch A, Orth U, et al. Mother and daughter with a terminal Xp deletion: implication of chromosomal mosaicism and X-inactivation in the high clinical variability of the microphthalmia with linear skin defects (MLS) syndrome. Eur J Med Genet 2007; 50:421.
57. Huber C, Rosilio M, Munnich A, et al. High incidence of SHOX anomalies in individuals with short stature. J Med Genet 2006; 43:735.
58. Morizio E, Stuppia L, Gatta V, et al. Deletion of the SHOX gene in patients with short stature of unknown cause. Am J Med Genet A 2003; 119A:293.
59. Cormier-Daire V, Belin V, Cusin V, et al. SHOX gene mutations and deletions in dyschondrosteosis or Leri-Weill syndrome. Acta Paediatr Suppl 1999; 88:55.
60. Robertson SP, Shears DJ, Oei P, et al. Homozygous deletion of SHOX in a mentally retarded male with Langer mesomelic dysplasia. J Med Genet 2000; 37:959.
61. Furrow A, Theisen A, Velsher L, et al. Duplication of the STS region in males is a benign copy-number variant. Am J Med Genet A 2011; 155A:1972.
62. Li F, Shen Y, Köhler U, et al. Interstitial microduplication of Xp22.31: Causative of intellectual disability or benign copy number variant? Eur J Med Genet 2010; 53:93.
63. Liu P, Erez A, Nagamani SC, et al. Copy number gain at Xp22.31 includes complex duplication rearrangements and recurrent triplications. Hum Mol Genet 2011; 20:1975.
64. Trivellin G, Daly AF, Faucz FR, et al. Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. N Engl J Med 2014; 371:2363.

65. del Gaudio D, Fang P, Scaglia F, et al. Increased MECP2 gene copy number as the result of genomic duplication in neurodevelopmentally delayed males. Genet Med 2006; 8:784.
66. Meins M, Lehmann J, Gerresheim F, et al. Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. J Med Genet 2005; 42:e12.
67. Ramocki MB, Tavyev YJ, Peters SU. The MECP2 duplication syndrome. Am J Med Genet A 2010; 152A:1079.
68. Van Esch H, Bauters M, Ignatius J, et al. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet 2005; 77:442.
69. Ramocki MB, Peters SU, Tavyev YJ, et al. Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome. Ann Neurol 2009; 66:771.

Topic 16974 Version 5.0

Disclosures

Disclosures: **Carlos A Bacino, MD, FACMG** Nothing to disclose. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Elizabeth TePas, MD, MS** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Pulmonic stenosis (PS) in neonates, infants, and children

Authors
Lynn F Peng, MD
Stanton Perry, MD

Section Editor
David R Fulton, MD

Deputy Editor
Carrie Armsby, MD, MPH

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Jul 22, 2014.

INTRODUCTION — Pulmonic stenosis (PS) is a common congenital heart defect, characterized by obstruction to flow from the right ventricle (RV) to the pulmonary arteries (PAs). PS can occur in isolation or be associated with other types of cardiac defects.

The pathophysiology, clinical features, diagnosis, and management of PS in children will be presented here. The clinical manifestations, evaluation, and management of PS in adults are discussed separately. (See "Clinical manifestations and diagnosis of pulmonic stenosis in adults" and "Natural history and treatment of pulmonic stenosis in adults" and "Echocardiographic evaluation of the pulmonic valve and pulmonary artery".)

ANATOMY AND EMBRYOLOGY

Anatomy — PS is defined as obstruction to right ventricle (RV) outflow at the level of the pulmonary valve. The obstruction can occur at several different locations, as follows:

- Valvar stenosis is the most common type of PS, and is typically characterized by fused or absent commissures with thickened leaflets of the pulmonary valve. In most patients, the valve is a dome-shaped structure with a small orifice (movie 1) [1].
  - Severe PS is associated with right ventricular hypertrophy and infundibular muscle hypertrophy, which can cause further dynamic obstruction below the pulmonary valve during RV contraction.
  - Critical PS is the most severe case of valvar PS resulting in an inadequate antegrade pulmonary blood flow. As a result, survival for affected infants is dependent upon maintaining a patent ductus arteriosus (PDA) for pulmonary blood flow (image 1).
  - Dysplastic pulmonary valves are another form of valvar PS and are less common. These valves are often irregular with prominent leaflet thickening leading to a small (hypoplastic) valve annulus and reduced mobility [2]. This anatomic variant is associated with Noonan syndrome. (See 'Associated conditions' below.)
- Subvalvar PS is uncommon and is caused by primary fibromuscular narrowing below the pulmonary valve. It is often associated with other congenital cardiac conditions including double-chambered right ventricle and tetralogy of Fallot (TOF) [3]. The obstruction may be dynamic in nature with further restriction of blood flow with right ventricular contraction. Occasionally, subvalvar PS can be due to a ridge or ring located just below the pulmonary valve.
- Supravalvar PS is defined as a discrete narrowing of the main pulmonary artery, located just above the pulmonary valve.
- Peripheral PS (PPS) refers to discrete areas of narrowing in the pulmonary arteries that can be unilateral, bilateral, or at several locations, including at pulmonary artery (PA) branch take-offs.

Associated conditions — PS commonly occurs with other congenital heart defects, including double-outlet right ventricle, tricuspid atresia, tetralogy of Fallot, and both D- and L-transposition of the great arteries. (See "Tricuspid valve (TV) atresia", section on 'Associated cardiac lesions' and "Pathophysiology, clinical features, and diagnosis of tetralogy of Fallot", section on 'Right ventricular outflow obstruction' and "Pathophysiology, clinical manifestations, and diagnosis of D-transposition of the great arteries", section on 'Other cardiac anomalies' and "L-transposition of the great arteries", section on 'Associated cardiac abnormalities'.)

Several syndromes are associated with PS, including the following:

- Valvar PS with dysplastic pulmonary valves is associated with Noonan syndrome [4,5]. (See "Causes of short stature", section on 'Noonan syndrome'.)
- PPS is associated with Alagille and congenital rubella syndromes. In patients with Williams-Beuren syndrome, PPS is the second most common congenital heart defect following supraaortic valvar stenosis [6]. (See "Inherited disorders associated with conjugated hyperbilirubinemia", section on 'Alagille syndrome' and "Congenital rubella syndrome: Clinical features and diagnosis", section on 'In infants and children' and "Williams-Beuren syndrome", section on 'Clinical diagnosis'.)

PATHOGENESIS — The underlying pathogenesis of PS is unknown.

Embryology — During the fifth week of gestation, the conotruncus (also refereed to as the bulbus cordis) separates into the ascending aorta and the main pulmonary artery. At the end of the fifth week of gestation, the pulmonary valve develops from a section of the conotruncus and begins moving from a position that is posterior of the aortic valve to one that is anterior and leftward of the aortic valve. It has been postulated that valvar PS is due to a maldevelopment of the distal portion of the conotruncus, but there are no data to support this theory.

Genetics — In most cases, PS is sporadic and is not caused by a known genetic defect. However, support for a genetic predisposition includes reports of familial occurrence [7,8] and the association of PS with syndromes due to underlying genetic defects. These include:

- Noonan syndrome – PTPN11 gene mutation, mapped to chromosome 12q24.1, which encodes the nonreceptor protein tyrosine phosphatase SHP2 (see "Causes of short stature", section on 'Noonan syndrome')
- Alagille syndrome – JAG-1 mutation, mapped to chromosome 20p12 (see "Inherited disorders associated with conjugated hyperbilirubinemia", section on 'Alagille syndrome')
- Williams-Beuren syndrome – Elastin gene mutation, mapped to chromosome 7q.11.23 (see "Williams-Beuren syndrome", section on 'Clinical diagnosis')

EPIDEMIOLOGY — Valvar pulmonic stenosis is a common congenital heart defect and occurs in 0.6 to 0.8 per 1000 live births [9,10]. However, the incidence may be an underestimation as mild PS may be considered a trivial lesion and not be referred to a pediatric cardiology center, and therefore not be counted in studies that rely on data from cardiac referral centers [9].

PATHOPHYSIOLOGY — Pulmonic stenosis (PS) obstructs blood flow from the right ventricle (RV) to the pulmonary arteries (PAs). As a result, the RV needs to generate enough pressure to overcome the obstruction. The greater the obstruction, the higher the RV pressure needed to overcome the obstruction to blood flow, which leads to an increasing pressure gradient across the pulmonary valve. The need to generate this elevated amount of pressure causes RV hypertrophy and a less compliant RV.

Severity of PS is determined by the pressure gradient across the pulmonary valve, which is typically determined by echocardiography and, in some cases, cardiac catheterization.

- Mild – <40 mmHg

- Moderate – 40 to 60 mmHg
- Severe – >60 mmHg

Clinical manifestations, the natural course, and management decisions vary depending on the severity of PS. (See 'Clinical manifestations' below and 'Management' below.)

CLINICAL MANIFESTATIONS

Antenatal presentation — Antenatal presentation is uncommon, as routine ultrasonography does not detect mild or moderate pulmonic stenosis because of the relative lack of pulmonary blood flow, and these fetuses grow and develop normally. An antenatal diagnosis usually occurs only in cases with significant right ventricular outflow tract (RVOT) obstruction, such as in severe PS or pulmonary atresia with an intact ventricular septum. (See "Pulmonary atresia with intact ventricular septum (PA/IVS)", section on 'Fetal presentation'.)

In one series of 7477 fetal echocardiographic examinations from two fetal cardiology units, 12 cases of PS were diagnosed including 7 cases of severe PS [11]. In these fetuses, echocardiographic findings included dilated right atrium (n = 10), right ventricular wall hypertrophy (n = 7), and regurgitation through the atrioventricular valve (n = 6). Reasons for referral included an abnormal routine four-chamber antenatal ultrasound (n = 7), a positive family history of congenital heart disease (n = 3), and one case each of fetal arrhythmia and intrauterine growth restriction.

Postnatal presentation — The timing of postnatal presentation of PS is dependent on the severity of PS and whether or not it is associated with other cardiac lesions or syndromes.

Neonate or infancy

Severe and critical PS — Soon after delivery, neonates with severe PS and elevated right ventricle (RV) pressure due to RVOT obstruction may present with cyanosis due to significant right-to-left shunting through a patent foramen ovale (PFO). In some cases, the severity of the RVOT obstruction is life-threatening (ie, critical PS) because of inadequate antegrade pulmonary blood flow (image 1), and survival is dependent on maintaining patency of the ductus arteriosus by the administration of prostaglandin E1 (alprostadil) therapy [12]. Infants with severe cases of PS may be identified by screening with pulse oximetry, which detects oxygen desaturation before it is clinically evident (ie, cyanosis). (See "Diagnosis and initial management of cyanotic heart disease in the newborn", section on 'Prostaglandin E1' and "Congenital heart disease (CHD) in the newborn: Presentation and screening for critical CHD", section on 'Pulse oximetry screening'.)

Mild or moderate PS — PS may be identified by an astute clinician who detects the characteristic cardiac findings during the routine newborn physical examination. (See "Congenital heart disease (CHD) in the newborn: Presentation and screening for critical CHD", section on 'Physical examination'.)

Other congenital anomalies — As noted above, pulmonic stenosis is often seen in patients with other cardiac conditions, which may present as critical cyanotic congenital heart disease defined as heart defects that require surgery or catheter-based intervention in the first year of life. These conditions may be detected by newborn pulse oximetry screening and include tricuspid atresia, D-transposition of the great arteries, and tetralogy of Fallot. (See "Tricuspid valve (TV) atresia", section on 'Associated cardiac lesions' and "Pathophysiology, clinical manifestations, and diagnosis of D-transposition of the great arteries", section on 'Other cardiac anomalies' and "Pathophysiology, clinical features, and diagnosis of tetralogy of Fallot", section on 'Right ventricular outflow obstruction' and "Congenital heart disease (CHD) in the newborn: Presentation and screening for critical CHD", section on 'Pulse oximetry screening'.)

Pulmonic stenosis may also be a component of the following syndromes, which usually present during

infancy with characteristic clinical features.

- Noonan syndrome – Dysmorphic facial features (hypertelorism, downward eye slant, and low-set ears), short webbed neck, pectus excavatum, cryptorchidism, and poor growth. (See "Causes of short stature", section on 'Noonan syndrome'.)
- Alagille syndrome – Dysmorphic facial features (broad nasal bridge, triangular facies, and deep-set eyes), jaundice, and failure to thrive. (See "Inherited disorders associated with conjugated hyperbilirubinemia", section on 'Alagille syndrome'.)
- Congenital rubella syndrome – Intrauterine growth restriction, ophthalmologic abnormalities (cloudy cornea, cataract, and glaucoma), hepatosplenomegaly with jaundice, petechiae and purpura ("blueberry lesion"), adenopathy, hemolytic anemia, and thrombocytopenia. (See "Congenital rubella syndrome: Clinical features and diagnosis", section on 'In neonates'.)
- Williams-Beuren syndrome – Dysmorphic facial features described as elfin or pixie-like (broad forehead, medial eyebrow flare, strabismus, flat nasal bridge, malar flattening, a short nose with a long philtrum, full lips, and a wide mouth), supravalvar aortic stenosis, and hypertension. (See "Williams-Beuren syndrome".)

Childhood — Because most children with isolated PS are asymptomatic, most postnatal presentations occur in childhood during a routine healthcare visit when a cardiac murmur is detected incidentally on physical examination. With increasing RVOT obstruction, some patients may become symptomatic (cyanosis, and dyspnea and fatigue with exertion).

Physical exam — Most patients with PS are asymptomatic and typically do not have any noncardiac physical findings. Cyanosis may be seen in infants with a significant right-to-left shunt due to RVOT obstruction.

Cardiac findings — Although there is some variability in the cardiac findings based on the severity of the defect, the following characteristic features are distinctive for valvar PS [13].

- The first heart sound is normal. In patients with mild or moderate PS, it is typically followed by an audible click. The closer the click to the first heart sound, the more severe the PS, until it merges with the first heart sound [14]. The click corresponds to the time when the doming pulmonary valve reaches its open position.
- The split between the second heart sounds is dependent on the severity of the obstruction. As the severity increases, the longer it takes the right ventricle to empty and the wider is the splitting. The second component (pulmonary) is also decreased, and proportionally lower as the pressure in the pulmonary artery decreases in more severe PS.
- The characteristic murmur of valvar PS is a systolic ejection murmur heard at the 2nd left intercostal space. In general, the intensity of the murmur increases with the severity of the obstruction. Of note, in neonates with severe PS, the murmur may be very soft as a result of the decreased flow through the pulmonary valve.
- In more severe cases, a thrill is palpable at the 2nd and 3rd intercostal space.

In the setting of supravalvar and subvalvar PS, a systolic ejection murmur is also noted at the 2nd left intercostal space, whereas in patients with peripheral PS, there is a systolic ejection murmur, which can be heard in the back. If the obstruction is bilateral, the murmur can be found equally loud over the chest and back.

Initial testing — Most patients will undergo initial testing that includes electrocardiography and chest radiography. However, the diagnosis is generally confirmed by echocardiography.

Electrocardiogram — The baseline electrocardiogram is often normal in cases of mild pulmonic stenosis, and in others there may be a slight right axis deviation. In patients with moderate or severe disease, there is almost always a right axis deviation and findings of right ventricular hypertrophy (eg, larger R waves in the right chest leads) in proportion to the severity of RVOT obstruction (waveform 1). In infants older than 24 hours of age, upright T waves in the right chest leads may be observed.

Chest radiography — Radiographic features also vary depending on the severity of the obstruction. Chest radiographs in PS may demonstrate an enlarged cardiac silhouette, most commonly in severe cases, and occasionally dilated pulmonary arteries can also be seen (image 2).

DIAGNOSIS — The diagnosis of PS is usually suspected based on a cardiac examination that identifies the distinctive characteristics of PS (normal first sound accompanied by an audible click, a split second sound, and a systolic ejection murmur at the 2nd left intercostal space). However, the diagnosis is confirmed by echocardiography, as even experienced pediatric cardiologists may miss making a diagnosis of PS based on clinical examination alone [15]. (See 'Cardiac findings' above.)

Echocardiography — Two-dimensional echocardiogram is the test of choice for the diagnosis of valvar PS as it provides excellent visualization of the anatomy of the pulmonary valve annulus, easy localization of the stenosis, and evaluation of right ventricular size and function (movie 2 and movie 3). In patients with critical PS, usually only a tiny jet of blood flow can be seen crossing the pulmonary valve (image 3).

Continuous wave Doppler echocardiography can assess the severity of stenosis by estimation of the pressure gradient over the pulmonary valve based on conversion of peak flow velocity using the simplified Bernoulli equation (image 4). There is good correlation between the Doppler-derived gradient and that obtained by direct catheterization measurements. However, the maximum instantaneous gradient measured by Doppler echocardiography can overestimate the catheter gradient by 20 to 30 mmHg, whereas the mean gradient may be an underestimation of the peak to peak gradient obtained from catheterization.

Echocardiography is also the test of choice to diagnose cases of subvalvar and supravalvar PS, and those of peripheral PS that involve the major pulmonary arteries. However, echocardiography may have more difficulty detecting distal branch pulmonary artery (PA) stenosis. In these patients, other imaging modalities may be necessary to confirm the diagnosis.

Other imaging modalities — Because of the refinement in echocardiography, other imaging modalities are usually not necessary for diagnosis. However, in some cases in which the diagnosis remains uncertain, such as in patients with peripheral PS that involves distal branch arteries, magnetic resonance and computed tomographic angiography are useful, noninvasive imaging studies that provide excellent visualization of the pulmonary artery architecture [16]. With the availability of these excellent imaging modalities and echocardiography, cardiac catheterization has become primarily a therapeutic intervention rather than a diagnostic procedure. (See 'Percutaneous balloon valvuloplasty' below.)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of isolated PS includes other cardiac conditions that present as an incidental finding of a cardiac murmur in asymptomatic children. Although the cardiac examination (eg, click after a normal heart sound) is suggestive, echocardiography conclusively distinguishes these conditions from PS [15].

- Ventricular septal defect (see "Pathophysiology and clinical features of isolated ventricular septal defects in infants and children")
- Innocent or functional murmurs (see "Suspected heart disease in infants and children: Criteria for referral", section on 'Murmurs')
- Atrial septal defects (see "Classification of atrial septal defects (ASDs), and clinical features and

diagnosis of isolated ASDs in children")

- Aortic stenosis
- Cases of tetralogy of Fallot without significant right ventricular outflow tract (RVOT) obstruction, and balanced pulmonary and systemic flow (see "Pathophysiology, clinical features, and diagnosis of tetralogy of Fallot", section on 'Clinical presentation')

In patients with cyanotic heart disease, echocardiography differentiates severe/critical isolated PS from other cyanotic heart diseases, some of which may include RVOT obstruction, such as tetralogy of Fallot and pulmonary atresia with an intact ventricular septum.

NATURAL HISTORY

Valvar pulmonic stenosis — The natural course of patients with valvar PS varies with the severity of the defect and the age at initial presentation.

- Mild (pressure gradient of <40 mmHg) – Mild valvar PS is generally benign, and in patients greater than one or two years of age, PS is unlikely to progress to more serious disease [17,18].
    - This was illustrated in a retrospective single-center study of 146 patients with mild valvar PS diagnosed by echocardiography (median age at diagnosis 3.9 months) that reported progression of disease in only two patients after a mean follow-up of four years [17]. Both patients with progressive disease were diagnosed as young infants [17]. Of the remaining patients at follow-up, 103 had very mild disease with a pressure gradient ≤25 mmHg, and 16 had a pressure gradient between 25 mmHg and <40 mmHg.
    - In another study of 147 patients, increases in pressure gradients were noted in a significant number of affected infants [18]. In this cohort, progression from mild to moderate or severe PS occurred in 11 of 40 neonates, and in 10 of 68 patients over one month of age. In contrast, no patient initially evaluated over the age of two years who had a gradient <50 mmHg progressed to severe obstruction.
    - Additional evidence supporting a benign course for mild PS includes an older natural history study (the First Natural History Study of Congenital Heart Defects) that reported only 3 of 261 patients with mild stenosis who were treated medically developed severe PS (pressure gradient >60 mmHg) over a four- to eight-year period [19]. Other data from the subsequent Second Natural History of Congenital Heart Defects Study showed that only 5 percent of children with very mild PS (pressure gradient <25 mmHg) underwent valvotomy, and no older patients with very mild disease went on to have valvotomy [20].
- Moderate (pressure gradient between 40 and 60 mmHg) – The natural course of moderate valvar PS varies. Data from two natural history studies suggest that patients with moderate PS may develop more progressive right ventricular outflow tract (RVOT) obstruction [19,21]. In the second Natural History Study, after the second decade of life, some patients with uncorrected moderate disease had decreased cardiac output and elevated right ventricle (RV) end-diastolic pressure, particularly with exercise [20]. In addition, in this cohort, a significant number of patients with moderate PS underwent surgical correction, presumably because of progressive symptoms or right ventricular dysfunction.
- Severe (pressure gradient >60 mmHg) – Severe valvar disease does not appear to remit and may progress during childhood [19]. These patients already have evidence of increased RV end diastolic pressure, and in some patients RV hypertrophy, which if untreated results in irreversible RV dysfunction [22-24].

Peripheral pulmonic stenosis — Peripheral PS, in the setting of a normal electrocardiogram, is mild,

does not progress, and often regresses [5,25]. In patients with Alagille or Williams-Beuren syndrome, peripheral PS is typically more severe and requires intervention.

Indications for intervention include:

- Right ventricular pressure that is equal to or greater than one-half of systemic pressure
- Lung perfusion scan that demonstrates less than 20 percent flow to one lung

MANAGEMENT

General considerations — The following issues need to be considered in the management of PS:

- Identifying neonates with critical PS who require emergent intervention.
- In more stable patients with PS, deciding who requires valvotomy and who can be conservatively managed with ongoing monitoring.
- When valvotomy is indicated, balloon valvuloplasty is currently the intervention of choice. However, in some cases, surgical correction may be a more reasonable option.

Critical pulmonic stenosis — As noted above, critical pulmonic stenosis is a life-threatening condition in the neonate because of inadequate antegrade pulmonary flow through the right ventricular outflow tract. Survival is dependent on maintaining patency of the ductus arteriosus by the administration of prostaglandin E1 (alprostadil) therapy, thereby providing adequate pulmonary blood flow [12]. Once the neonate is medically stable, definite valvotomy should be performed. Currently, balloon valvuloplasty is the procedure of choice, as it is as effective as surgical correction and is less invasive [26]. However, if balloon valvulotomy fails, urgent surgical intervention is required.

Indications for valvotomy — Based on the natural course of PS, the indications for valvotomy are based on the severity of the pressure gradient across the pulmonary valve. (See 'Natural history' above.)

- Mild (gradient <40 mmHg) – Given the benign natural history of patients with mild PS, these patients do not require intervention.
- Moderate PS (gradient 40 to 60 mmHg) – After the second decade of life, uncorrected patients can have decreased cardiac output and elevated right ventricle (RV) end-diastolic pressure, particularly with exercise [20]. Because of the excellent success rate of balloon valvuloplasty with minimal risk, valvotomy is suggested for patients who continue to have gradients approaching 60 mmHg because of the long-term consequences of unrepaired lesions. (See "Natural history and treatment of pulmonic stenosis in adults", section on 'Moderate stenosis'.)
- Severe PS (gradient >60 mmHg) patients have abnormal cardiac output, RV hypertrophy, and increased RV end-diastolic pressure at rest or with exercise. These pathophysiological changes may be irreversible if not corrected. These patients are typically symptomatic and present with cyanosis, and dyspnea and fatigue with exertion. Intervention is recommended for these patients to improve symptoms and prevent irreversible cardiac injury. As a result, valvotomy is recommended for patients with severe PS, including neonates with critical PS.
- Intervention for peripheral PS (PPS) lesions is based on a marked decrease in flow to the affected lung segment demonstrated by radionuclide scans, significant pressure gradient across the area of stenosis resulting in elevated right ventricle pressure that approaches or is greater than systemic pressure, and clinical symptoms of fatigue or decrease in exercise tolerance [27-29].

Valvotomy procedures

Percutaneous balloon valvuloplasty — In this procedure, a catheter and wire are introduced after

the femoral vein is accessed, and advanced across the pulmonary valve. A balloon 120 to 140 percent the size of the pulmonary valve annulus is used to dilate the pulmonary valve (image 5).

Valvar PS — Balloon valvuloplasty is the first line treatment for the typical dome-shaped valvar PS, as it is an effective intervention with rare complications [30-35]. More than 90 percent of patients with this type of PS who undergo balloon valvuloplasty are left with gradients <20 mmHg (image 4) [36,37].

Balloon valvuloplasty is also the preferred treatment in neonatal patients with critical PS (image 5 and movie 4 and image 6) [38,39]. In these patients, although prostaglandin therapy can be discontinued following dilation, infants may remain cyanotic over weeks with residual right-to-left shunting through a patent foramen ovale because of persistent RV noncompliance, which resolves over time. In some cases, additional pulmonary blood flow with a surgically placed aortic-to-pulmonary artery shunt (modified Blalock-Taussig shunt or central shunt) may be required.

Other PS variants — Balloon valvuloplasty is also used to treat PPS [27-29,40-44]. A balloon two to four times the diameter of the narrowed segment is required to dilate the peripheral stenosis. Vessels resistant to pulmonary angioplasty can be addressed with high pressure balloons, cutting balloons, or stents.

Balloon valvotomy may be successful in select patients with dysplastic pulmonary valves; however, surgical correction is generally needed in patients with either a hypoplastic annulus or main pulmonary artery, and in those who fail balloon valvuloplasty.

Balloon valvuloplasty is not an effective intervention in cases of supravalvar PS due to the close proximity of the stenotic area of the pulmonary artery to the pulmonary valve. In addition, catheterization treatment is not effective in patients with subvalvar PS. In these cases, surgical repair is necessary.

Complications — Overall, complications for balloon valvuloplasty for PS are extremely rare [34]. They include perforation of the pulmonary valve or right ventricle with oversized balloon use, and tricuspid valve injury resulting in regurgitation. Femoral vein occlusion is another complication, seen most commonly in small infants [26].

Following balloon valvuloplasty, most patients develop some degree of pulmonary regurgitation [35]. Careful selection of balloon size should reduce the degree of pulmonary insufficiency (PI) [26]. However, balloon dilations performed when the procedure was initially devised have resulted in moderate to severe PI and RV dilation [38,45]. There is no consensus regarding timing for pulmonary valve replacement in the setting of severe PI after valvar PS intervention.

Surgery — Surgical valvotomy may be performed as an open procedure requiring cardiopulmonary bypass or through a closed transventricular approach. Access is through a median sternotomy for both operations.

Surgery is not usually needed to treat typical valvar PS. However, surgery is often needed in patients with dysplastic pulmonary valves and a hypoplastic annulus or main pulmonary artery [34,46]. In these patients, surgical repair is required to excise thickened and obstructive valve leaflets and place a transannular patch.

Surgery is also the intervention of choice for patients with subvalvar PS, as the muscular nature of this lesion is not amenable to balloon dilation, and requires muscular resection. It is also the preferred procedure in patients with supravalvar PS because the stenotic area of the pulmonary artery is in close proximity of the pulmonary valve, and requires patch placement.

Surgery is also used to correct moderate and severe PPS in patients with Williams-Beuren and Alagille syndromes [47].

Our approach — Our management approach for infants and children with PS is dependent on the severity of RV outflow tract obstruction as follows:

- Neonates with critical PS are treated initially with intravenous prostaglandin therapy (also known as alprostadil) to maintain ductal patency and pulmonary flow. When medically stable, percutaneous balloon valvuloplasty is performed.
- Patients with mild PS (gradient <40 mmHg) do not require intervention. Although most mild PS will not progress, we continue to monitor patients with echocardiography. Initially, testing should be done every six months.
    - If the gradient regresses so that it is less than 25 mmHg, follow-up can be done at five-year intervals.
    - If the gradient remains between 25 and 40 mmHg after one year, the frequency of follow-up can be decreased with follow-up at one year following the second echocardiography, and then subsequent follow-up every three years.
    - Of note, women with mild PS can develop more severe disease during pregnancy. Hence, it is important to continue to monitor these patients through adulthood. (See "Natural history and treatment of pulmonic stenosis in adults", section on 'Pregnancy'.)
- Patients with moderate PS (gradient 40 to 60 mmHg) have a risk for developing more severe PS or becoming symptomatic later in life due to RV dysfunction. We monitor these patients on an annual basis. We consider intervention in patients with moderate PS who have gradients approaching 60 mmHg or who become symptomatic (eg, school-aged children who become exercise intolerant).
- Valvotomy is indicated in patients with severe PS (gradient >60 mmHg). Percutaneous balloon valvuloplasty is the preferred procedure in patients with typical valvular dome-shaped PS. Surgery is generally reserved for patients with dysplastic pulmonary valves and hypoplastic annulus or main pulmonary artery, or for those with supravalvar or subvalvar PS.

LONG-TERM OUTCOME

Uncorrected PS — As discussed above, the long-term prognosis of uncorrected PS is dependent on the severity of the obstruction. (See 'Natural history' above.)

- Mild stenosis with a pressure gradient <40 mmHg is typically associated with right ventricular pressure that is less than half of the systemic pressure. The long-term course of these patients is benign [21]. In the first and second Natural History Studies, patients with mild disease were unlikely to progress to more severe obstruction, especially in patients older than two years of age. These patients have normal hemodynamic response to exercise and do not require any restriction in activity.
- In patients with moderate disease (gradient 40 to 60 mmHg), 20-year survival is excellent whether or not the care is conservative, or interventional therapy is provided [19]. However, there are data that suggest patients with long-standing moderate stenosis may have an impaired cardiac response to formal exercise testing manifested by increased right ventricular end-diastolic pressure [22].
- As noted above, uncorrected patients with severe PS (gradient >60 mmHg) are at risk for irreversible right ventricular injury.

Surgical outcome — The long-term results of patients treated with surgical valvotomy are excellent, with reported survival rates of 93 percent at a mean follow-up period of 25 years [48]. In the Second Natural History Study, 96 percent of surgically treated patients remained free of reoperation at 10 years

after the initial intervention [20]. However, one study of 53 patients (mean age of surgery was 10 years) reported that about half of the cohort had reoperation for pulmonary insufficiency, primarily pulmonary valve replacement, at a mean follow-up time period of 33 years [49]. It is thought that with advances in surgical technique, the severity of subsequent pulmonary insufficiency should be reduced.

Balloon valvuloplasty outcome — Long-term data are limited to mean follow-up of 12 years based on a single tertiary center study of 150 pediatric patients, in whom the freedom from reintervention was 90, 83, and 77 percent at 1, 10 and 15 years follow-up, respectively [35]. In another pediatric series of 85 patients, restenosis defined as a gradient >50 mmHg was observed in nine patients over the 3- to 10-year follow-up period, and the freedom from reintervention was 94, 88, and 84 percent at 1, 5, and 10 years, respectively [37].

HEALTHCARE MAINTENANCE

Follow-up care — The need and timing for long-term cardiac follow-up varies with the degree of obstruction and whether the patient has undergone valvotomy.

At each visit, a focused cardiac history that includes exercise tolerance, a physical examination, and testing that includes electrocardiography and echocardiography are performed. In our center, we use the following approach:

- Patients with mild stenosis (pressure gradient <40 mmHg) are initially followed at six-month intervals until they reach one or two years of age.
    - If the pressure gradient is <25 mmHg, cardiac follow-up is performed at five years of age, and subsequently at five-year intervals.
    - If the pressure gradient is between 25 and 40 mmHg, the patient is followed until he/she is two years of age, after which follow-up visits are performed at three- to five-year intervals.
- For patients with pressure gradients between 40 and 60 mmHg, ongoing monitoring is conducted every one to two years.
- Valvotomy is recommended if the pressure remains consistently above 55 to 60 mmHg. After valvotomy, if the post-intervention gradient remains mild, follow-up visits are conducted every year initially for the first two years and subsequent visits are performed every three to five years; the frequency depends on the individual patient's clinical status. Reintervention is considered if there is evidence of restenosis, which has a pressure gradient that reaches the criterion used for initial dilation. In addition, other factors used to consider reintervention include increased right ventricular (RV) outflow tract obstruction, RV hypertrophy, or RV dysfunction. In addition, patients need to be monitored for evidence of significant pulmonary insufficiency. In these patients, cardiac magnetic resonance imaging (MRI) is useful in determining the degree of pulmonary insufficiency and RV size and function.

Activity — Most patients with PS do not require any restriction on exercise or physical activity. Although the 36th Bethesda Conference guidelines suggest restriction for patients with moderate or severe PS (gradient >40 mmHg) or for those with residual pulmonic regurgitation to class 1A and 1B (figure 1), there is no evidence to support these recommendations and these consensus guidelines based on the opinions of the participants [50].

Most pediatric cardiologists, including the authors, do not restrict activity in patients with mild or moderate PS (gradient <60 mmHg), mild residual pulmonic regurgitation, or in most patients with moderate pulmonic regurgitation.

Physical activity and exercise in patients with congenital heart disease are discussed separately. (See "Physical activity and exercise in patients with congenital heart disease (CHD)".)

Antibiotic prophylaxis — Patients with PS do not require antibiotic prophylaxis for the prevention of endocarditis. (See "Antimicrobial prophylaxis for bacterial endocarditis", section on 'Clinical approach'.)

SUMMARY AND RECOMMENDATIONS — Pulmonic stenosis (PS) is a common congenital heart defect, with an incidence of 0.6 to 0.8 per 1000 live births, that is characterized by obstruction to flow from the right ventricle (RV) to the pulmonary arteries (PAs) at the level of the pulmonary valve.

- There are several different levels at which obstruction can occur. (See 'Anatomy' above.)
    - Valvar PS is the most common variant, in which stenosis occurs at the level of the pulmonary valve, which typically is characterized by a dome-shaped valve (movie 1). Dysplastic pulmonary valves are a less common form of valvar PS, which is often seen in patients with Noonan syndrome.
    - Subvalvar PS is uncommon and is usually caused by primary fibromuscular narrowing below the pulmonary valve.
    - Supravalvar PS is caused by a discrete narrowing of the main pulmonary artery, located just above the pulmonary valve.
    - Peripheral PS is caused by peripheral discrete areas of narrowing in the pulmonary arteries.
- PS can be isolated or be associated with other cardiac lesions including double-outlet right ventricle, tricuspid atresia, tetralogy of Fallot, and both D- and L-transposition of the great arteries. In addition, several syndromes are associated with PS including Noonan, Alagille, Williams-Beuren, and congenital rubella syndrome. (See 'Associated conditions' above.)
- Because PS results in RV outflow tract (RVOT) obstruction, the RV pressure needed to overcome the obstruction rises as the severity of the obstruction increases, resulting in a higher pressure gradient across the pulmonary valve, which is usually determined by echocardiography. The pressure gradient defines the severity of obstruction and is used to make management decisions. (See 'Pathophysiology' above.)
    - Mild – <40 mmHg
    - Moderate – 40 to 60 mmHg
    - Severe – >60 mmHg
- Antenatal presentation of isolated PS is uncommon, as routine ultrasonography typically does not detect mild or moderate pulmonic stenosis. (See 'Antenatal presentation' above.)
- The timing of postnatal presentation of PS is dependent on the severity of the PS and whether or not it is associated with other cardiac lesions or syndromes. (See 'Postnatal presentation' above.)
    - Soon after delivery, neonates with severe PS may present with cyanosis due to significant right-to-left shunting through a patent foramen ovale.
    - Isolated moderate or mild PS is identified as an incidental finding during routine physical examination.
    - PS may also present with other congenital heart diseases or as a component of a defined syndrome (eg, Noonan).
- The characteristic cardiac findings of valvar PS include a normal first heart sound followed by an audible click, systolic ejection murmur at the 2nd left intercostal space, and a split second heart sound. (See 'Cardiac findings' above.)

- The clinical diagnosis of PS is generally confirmed by echocardiography, which provides excellent visualization of the pulmonary valve annulus, easy localization of the stenosis, and evaluation of the RV size and function. (See 'Diagnosis' above.)
- Echocardiography distinguishes other cardiac conditions that are in the differential diagnosis of PS. (See 'Differential diagnosis' above.)
- The management approach of PS is dependent on the severity of the PS. (See 'Management' above and 'Natural history' above.)
    - Critical PS – Emergent care is needed in neonates with critical PS as they have a life-threatening condition due to inadequate pulmonary flow through the RVOT. We recommend the administration of prostaglandin E1 (alprostadil) therapy to maintain patency of the ductus arteriosus (**Grade 1A**). After medical stabilization, we recommend correction of PS by percutaneous balloon valvuloplasty (**Grade 1B**).
    - Mild PS is a benign condition. We recommend conservative management without further intervention (**Grade 1B**). However, ongoing monitoring is needed, especially during the first two years of life, as more severe obstruction may develop in a small number of patients with mild disease.
    - Severe PS – Because uncorrected severe PS results in irreversible RV injury, we recommend valvotomy in patients with severe PS (**Grade 1B**).
    - Moderate PS – Because the natural course of moderate PS varies, the criteria for intervention remains uncertain. In our practice, we intervene with balloon valvotomy if the gradient approaches 60 mmHg or if older patients (ie, school-aged children) begin to have clinical symptoms (eg, exercise intolerance).
- In patients with valvar PS, percutaneous balloon valvuloplasty is the preferred procedure for valvotomy, as it is as equally effective and safe as surgical repair, but less invasive. Surgical intervention is required for patients with supravalvar and subvalvar PS, and in some patients with dysplastic pulmonary valves and a hypoplastic annulus or main pulmonary artery. (See 'Valvotomy procedures' above.)
- Based on the above management approach, the long-term outcome is excellent in pediatric patients with PS. (See 'Long-term outcome' above.)
- The level of cardiac follow-up is dependent on the degree of obstruction and whether or not the patient has undergone valvotomy. At each visit, a focused cardiac history and physical examination, and testing that includes electrocardiography and echocardiography are performed. (See 'Follow-up care' above.)

REFERENCES

1. Edwards JE. Congenital malformations of the heart and great vessels. In: Pathology of the Heart, Gould SE (Ed), Charles C. Thomas Publisher, Springfield, IL 1953.
2. Beçu L, Somerville J, Gallo A. 'Isolated' pulmonary valve stenosis as part of more widespread cardiovascular disease. Br Heart J 1976; 38:472.
3. Cabrera A, Martinez P, Rumoroso JR, et al. Double-chambered right ventricle. Eur Heart J 1995; 16:682.

4. Noonan JA, Ehmke DA. Associated non-cardiac malformations in children with congenital heart disease. J Pediatr 1963; 63:468.
5. Colquitt JL, Noonan JA. Cardiac findings in Noonan syndrome on long-term follow-up. Congenit Heart Dis 2014; 9:144.
6. Collins RT 2nd, Kaplan P, Somes GW, Rome JJ. Long-term outcomes of patients with cardiovascular abnormalities and williams syndrome. Am J Cardiol 2010; 105:874.
7. CAMPBELL M. Factors in the aetiology of pulmonary stenosis. Br Heart J 1962; 24:625.
8. Driscoll DJ, Michels VV, Gersony WM, et al. Occurrence risk for congenital heart defects in relatives of patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. Circulation 1993; 87:I114.
9. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002; 39:1890.
10. Reller MD, Strickland MJ, Riehle-Colarusso T, et al. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. J Pediatr 2008; 153:807.
11. Todros T, Paladini D, Chiappa E, et al. Pulmonary stenosis and atresia with intact ventricular septum during prenatal life. Ultrasound Obstet Gynecol 2003; 21:228.
12. Freed MD, Rosenthal A, Bernhard WF, et al. Critical pulmonary stenosis with a diminutive right ventricle in neonates. Circulation 1973; 48:875.
13. Vogelpoel L, Schrire V. Auscultatory and phonocardiographic assessment of pulmonary stenosis with intact ventricular septum. Circulation 1960; 22:55.
14. Sholler GF, Colan SD, Sanders SP. Effect of isolated right ventricular outflow obstruction on left ventricular function in infants. Am J Cardiol 1988; 62:778.
15. Danford DA, Salaymeh KJ, Martin AB, et al. Pulmonary stenosis: defect-specific diagnostic accuracy of heart murmurs in children. J Pediatr 1999; 134:76.
16. Geva T, Greil GF, Marshall AC, et al. Gadolinium-enhanced 3-dimensional magnetic resonance angiography of pulmonary blood supply in patients with complex pulmonary stenosis or atresia: comparison with x-ray angiography. Circulation 2002; 106:473.
17. Drossner DM, Mahle WT. A management strategy for mild valvar pulmonary stenosis. Pediatr Cardiol 2008; 29:649.
18. Rowland DG, Hammill WW, Allen HD, Gutgesell HP. Natural course of isolated pulmonary valve stenosis in infants and children utilizing Doppler echocardiography. Am J Cardiol 1997; 79:344.
19. Nugent EW, Freedom RM, Nora JJ, et al. Clinical course in pulmonary stenosis. Circulation 1977; 56:I38.
20. Hayes CJ, Gersony WM, Driscoll DJ, et al. Second natural history study of congenital heart defects. Results of treatment of patients with pulmonary valvar stenosis. Circulation 1993; 87:I28.
21. Levine OR, Blumenthal S. Pulmonic stenosis. Circulation 1965; 32:III33.
22. Krabill KA, Wang Y, Einzig S, Moller JH. Rest and exercise hemodynamics in pulmonary stenosis: comparison of children and adults. Am J Cardiol 1985; 56:360.
23. JOHNSON AM. Impaired exercise response and other residua of pulmonary stenosis after valvotomy. Br Heart J 1962; 24:375.
24. Stone FM, Bessinger FB Jr, Lucas RV Jr, Moller JH. Pre- and postoperative rest and exercise hemodynamics in children with pulmonary stenosis. Circulation 1974; 49:1102.
25. Nomura Y, Nakamura M, Kono Y, et al. Risk factors for persistence of pulmonary arterial branch stenosis in neonates and young infants. Pediatr Int 2001; 43:36.
26. Rao PS. Percutaneous balloon pulmonary valvuloplasty: state of the art. Catheter Cardiovasc Interv 2007; 69:747.

27. Sugiyama H, Veldtman GR, Norgard G, et al. Bladed balloon angioplasty for peripheral pulmonary artery stenosis. Catheter Cardiovasc Interv 2004; 62:71.
28. Bergersen L, Jenkins KJ, Gauvreau K, Lock JE. Follow-up results of Cutting Balloon angioplasty used to relieve stenoses in small pulmonary arteries. Cardiol Young 2005; 15:605.
29. Kannan BR, Qureshi SA. Catheterisation laboratory is the place for rehabilitating the pulmonary arteries. Ann Pediatr Cardiol 2008; 1:107.
30. Kan JS, White RI Jr, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary-valve stenosis. N Engl J Med 1982; 307:540.
31. Radtke W, Keane JF, Fellows KE, et al. Percutaneous balloon valvotomy of congenital pulmonary stenosis using oversized balloons. J Am Coll Cardiol 1986; 8:909.
32. Chen CR, Cheng TO, Huang T, et al. Percutaneous balloon valvuloplasty for pulmonic stenosis in adolescents and adults. N Engl J Med 1996; 335:21.
33. Gournay V, Piéchaud JF, Delogu A, et al. Balloon valvotomy for critical stenosis or atresia of pulmonary valve in newborns. J Am Coll Cardiol 1995; 26:1725.
34. Stanger P, Cassidy SC, Girod DA, et al. Balloon pulmonary valvuloplasty: results of the Valvuloplasty and Angioplasty of Congenital Anomalies Registry. Am J Cardiol 1990; 65:775.
35. Garty Y, Veldtman G, Lee K, Benson L. Late outcomes after pulmonary valve balloon dilatation in neonates, infants and children. J Invasive Cardiol 2005; 17:318.
36. Tabatabaei H, Boutin C, Nykanen DG, et al. Morphologic and hemodynamic consequences after percutaneous balloon valvotomy for neonatal pulmonary stenosis: medium-term follow-up. J Am Coll Cardiol 1996; 27:473.
37. Rao PS, Galal O, Patnana M, et al. Results of three to 10 year follow up of balloon dilatation of the pulmonary valve. Heart 1998; 80:591.
38. Poon LK, Menahem S. Pulmonary regurgitation after percutaneous balloon valvoplasty for isolated pulmonary valvar stenosis in childhood. Cardiol Young 2003; 13:444.
39. Weber HS. Initial and late results after catheter intervention for neonatal critical pulmonary valve stenosis and atresia with intact ventricular septum: a technique in continual evolution. Catheter Cardiovasc Interv 2002; 56:394.
40. Gentles TL, Lock JE, Perry SB. High pressure balloon angioplasty for branch pulmonary artery stenosis: early experience. J Am Coll Cardiol 1993; 22:867.
41. Fogelman R, Nykanen D, Smallhorn JF, et al. Endovascular stents in the pulmonary circulation. Clinical impact on management and medium-term follow-up. Circulation 1995; 92:881.
42. Rosales AM, Lock JE, Perry SB, Geggel RL. Interventional catheterization management of perioperative peripheral pulmonary stenosis: balloon angioplasty or endovascular stenting. Catheter Cardiovasc Interv 2002; 56:272.
43. Bergersen LJ, Perry SB, Lock JE. Effect of cutting balloon angioplasty on resistant pulmonary artery stenosis. Am J Cardiol 2003; 91:185.
44. Cunningham JW, McElhinney DB, Gauvreau K, et al. Outcomes after primary transcatheter therapy in infants and young children with severe bilateral peripheral pulmonary artery stenosis. Circ Cardiovasc Interv 2013; 6:460.
45. Berman W Jr, Fripp RR, Raisher BD, Yabek SM. Significant pulmonary valve incompetence following oversize balloon pulmonary valveplasty in small infants: A long-term follow-up study. Catheter Cardiovasc Interv 1999; 48:61.
46. DiSessa TG, Alpert BS, Chase NA, et al. Balloon valvuloplasty in children with dysplastic pulmonary valves. Am J Cardiol 1987; 60:405.
47. Monge MC, Mainwaring RD, Sheikh AY, et al. Surgical reconstruction of peripheral pulmonary

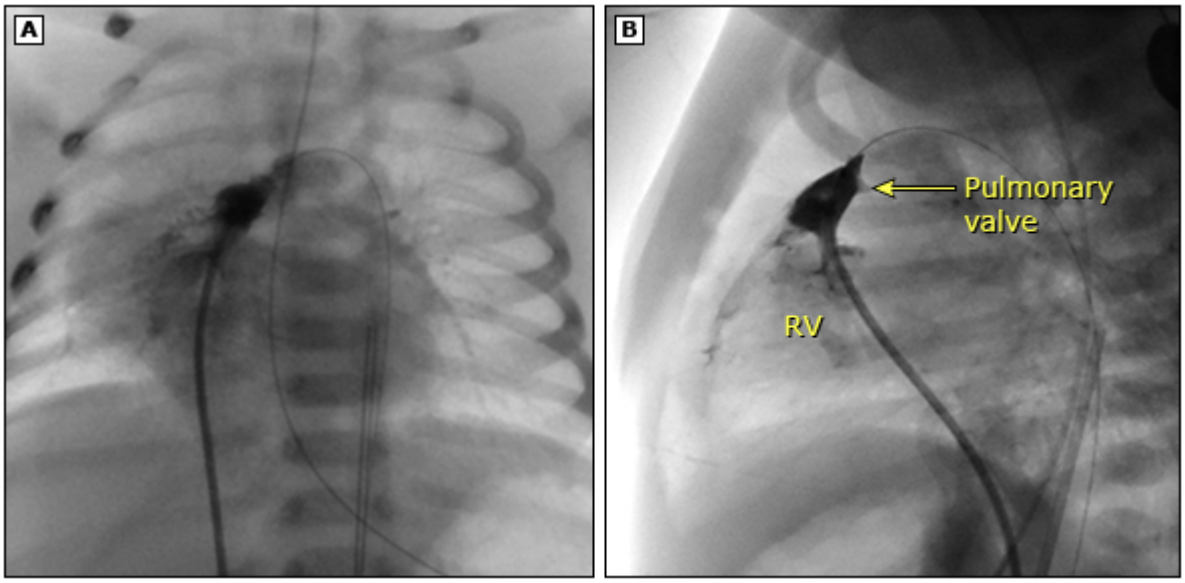
artery stenosis in Williams and Alagille syndromes. J Thorac Cardiovasc Surg 2013; 145:476.

48. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years). Eur Heart J 2006; 27:482.
49. Earing MG, Connolly HM, Dearani JA, et al. Long-term follow-up of patients after surgical treatment for isolated pulmonary valve stenosis. Mayo Clin Proc 2005; 80:871.
50. Graham TP Jr, Driscoll DJ, Gersony WM, et al. Task Force 2: congenital heart disease. J Am Coll Cardiol 2005; 45:1326.

Topic 14578 Version 3.0

GRAPHICS

Angiogram of critical pulmonic stenosis

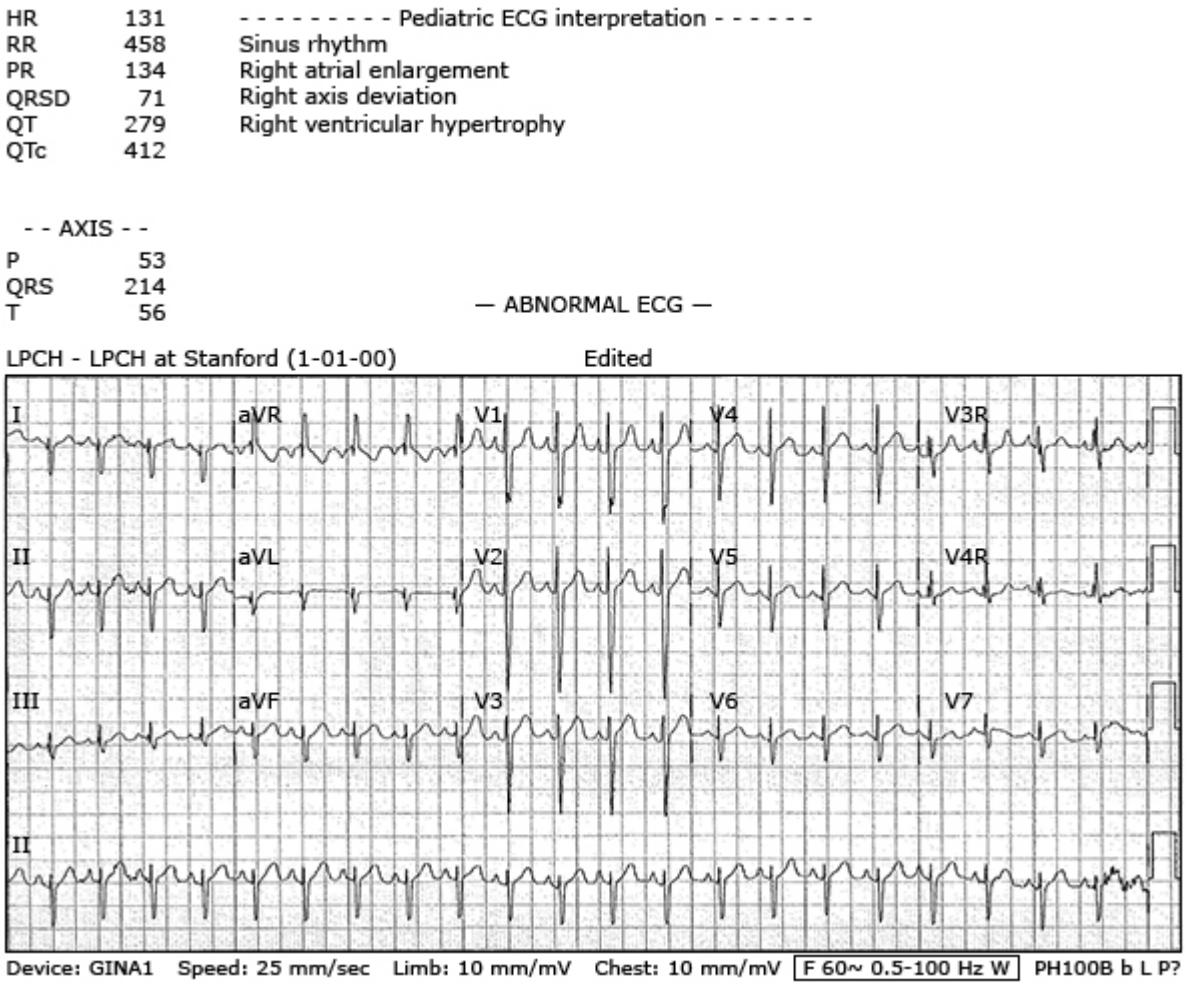


Angiogram in a neonate with critical pulmonic stenosis that shows minimal contrast passing from the right ventricle through the pulmonary valve into the main pulmonary artery. A wire is seen crossing through the pulmonary valve. Panel (A) is a frontal image, and panel (B) is a lateral image at higher magnification.

RV: right ventricle.

Graphic 91424 Version 1.0

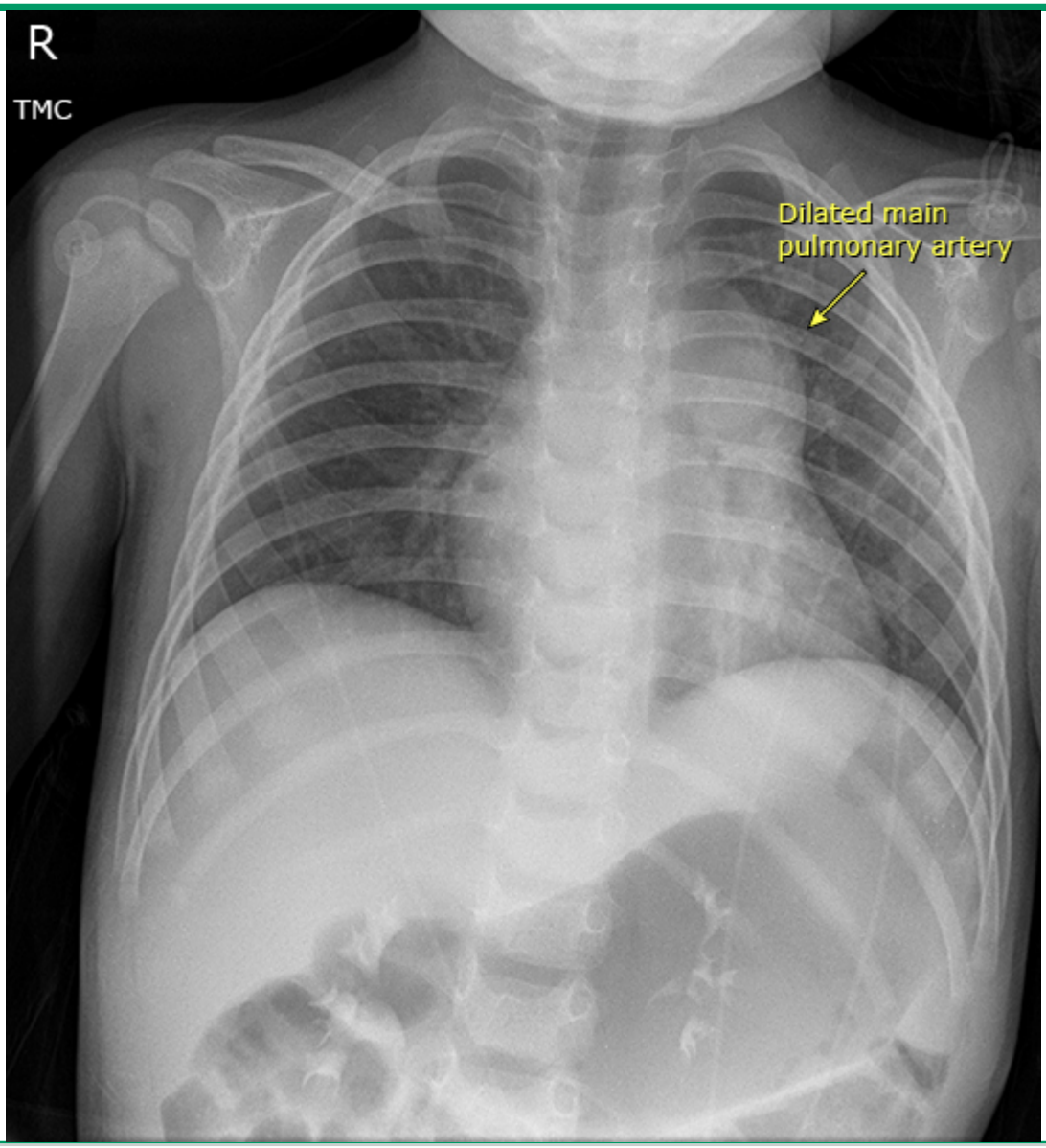
Electrocardiogram of a patient with pulmonic stenosis



Electrocardiogram (ECG) of a one-month-old child with pulmonic stenosis demonstrating right axis deviation, right atrial enlargement (increased magnitude of P waves in lead II), and right ventricular hypertrophy (increased QRS waves in the right precordial leads V1, V2, and V3).

Graphic 91514 Version 1.0

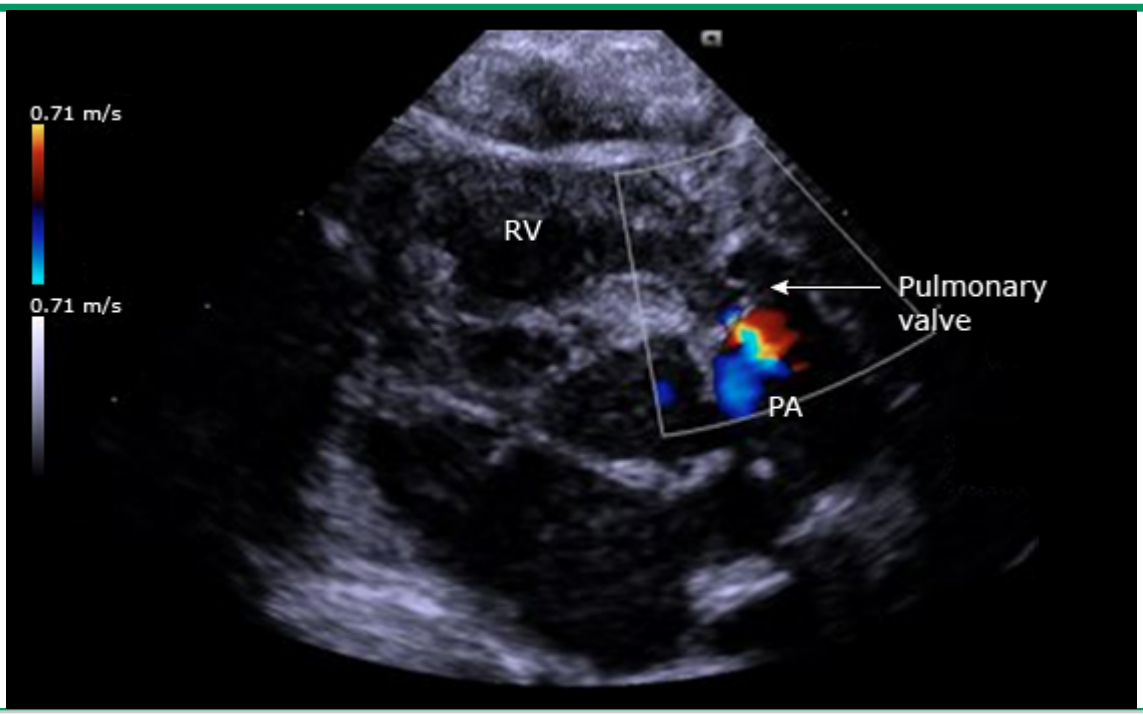
Chest radiograph of a patient with pulmonic stenosis



Chest radiograph of a three-year-old child with pulmonic stenosis demonstrating enlarged heart and dilation of the main pulmonary artery (arrow).

Graphic 91513 Version 1.0

Echocardiographic image of critical pulmonic stenosis

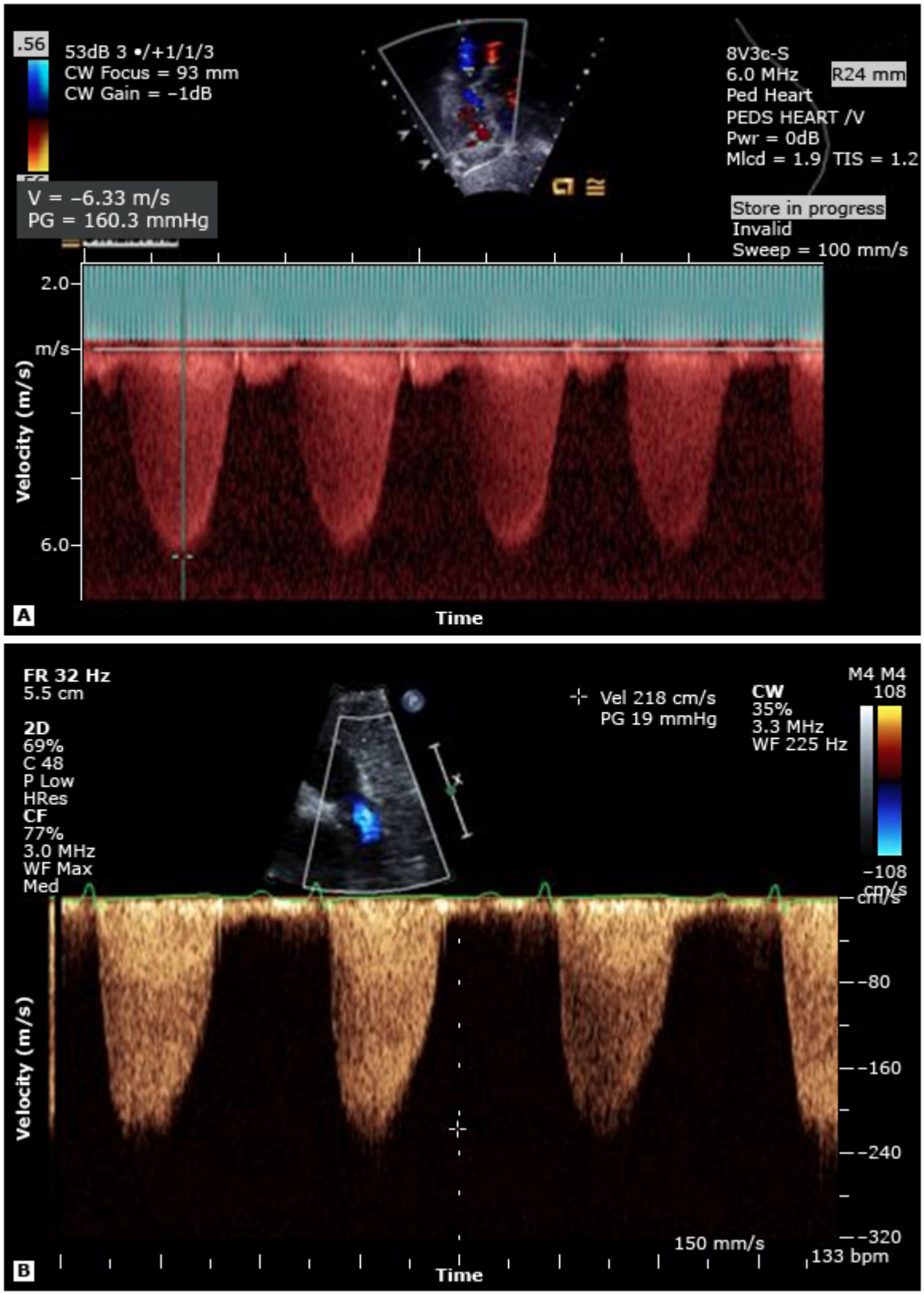


Echocardiographic image of a patient with critical pulmonic stenosis that shows virtually no antegrade flow from the right ventricle through the pulmonary valve into the main pulmonary artery.

RV: right ventricle; PA: pulmonary artery.

Graphic 91430 Version 1.0

Echocardiogram Doppler of pulmonic stenosis pre- and post-balloon dilation



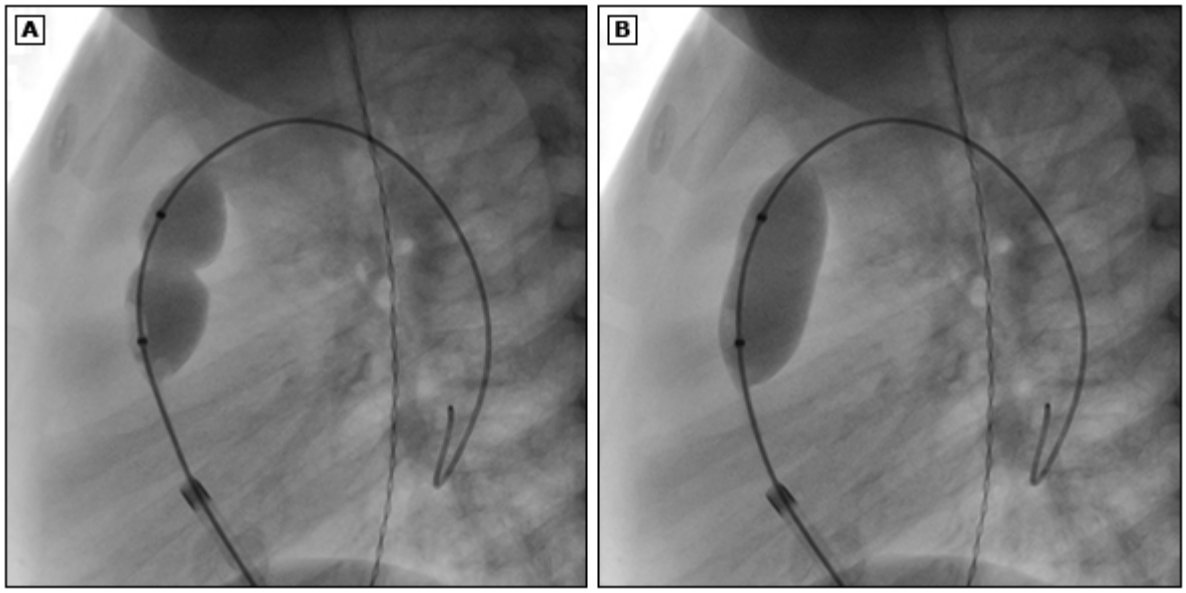
Note the different scales used to measure velocity on the y-axis. In panel (A): m/s on the y-axis on the left; panel (B): cm/s on the y-axis on the right.

(A) Pre-balloon dilation; this demonstrates the velocity across the pulmonary valve of 6.33

m/s, which correlates to a peak gradient of 160 mmHg across the pulmonary valve. (B) Post-balloon dilation; this demonstrates the velocity across the pulmonary valve of 2.2 m/s, which correlates to a peak gradient of 19 mmHg across the pulmonary valve.

Graphic 91427 Version 2.0

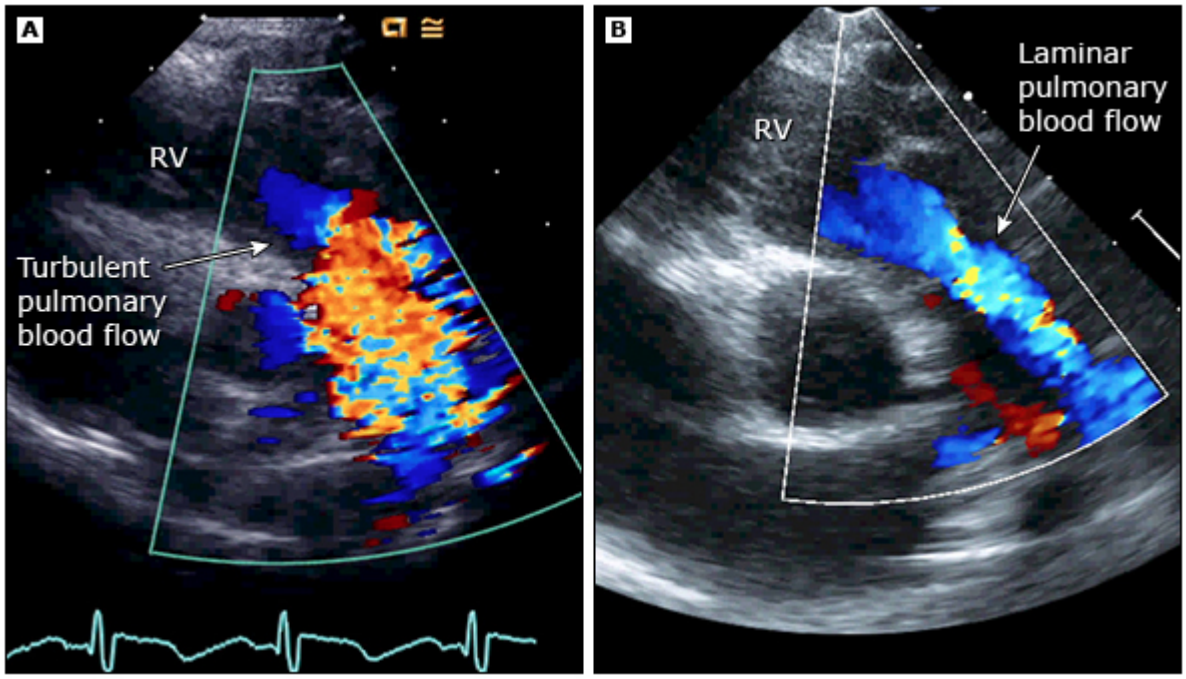
Percutaneous balloon valvuloplasty in pulmonic stenosis



Angiographic images of percutaneous balloon valvuloplasty.
(A) Demonstrates the waist of the balloon at the pulmonary valve.
(B) Shows the inflation of the balloon at the pulmonary valve.

Graphic 91426 Version 1.0

Echocardiogram of valvar pulmonic stenosis pre- and post-balloon dilation

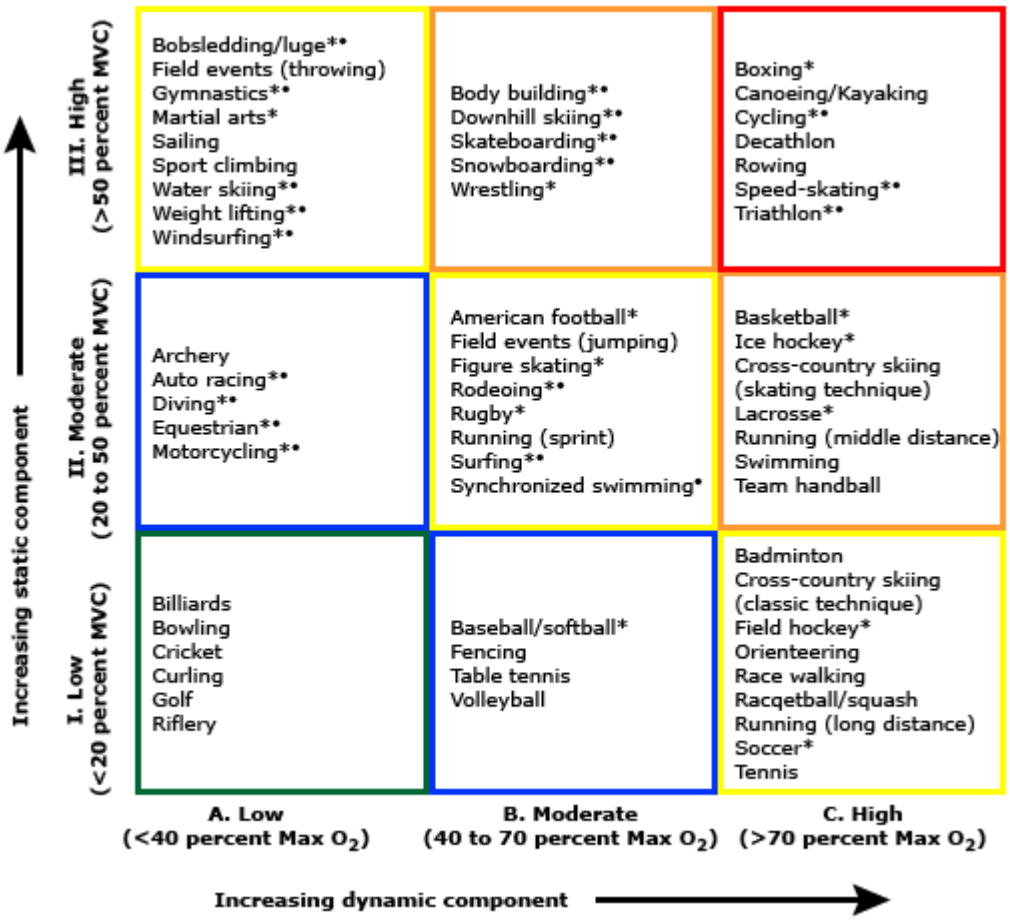


Ultrasound of a patient with valvar pulmonic stenosis pre- and post-balloon dilation, with color.
(A) Shows turbulent pulmonary blood flow across a pulmonary valve with severe stenosis.
(B) Shows unobstructed color flow across the pulmonary valve after dilation.

RV: right ventricle.

Graphic 91433 Version 2.0

Classification of sports



This classification is based on peak static and dynamic components achieved during competition. It should be noted, however, that higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percent of maximal oxygen uptake ($MaxO_2$) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percent of maximal voluntary contraction (MVC) reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in green and the highest in red. Blue, yellow, and orange depict low moderate, moderate, and high moderate total cardiovascular demands.

* Danger of bodily collision.
• Increased risk if syncope occurs.

Reproduced with permission from: Mitchell JH, Haskell W, Snell P, Van Camp SP. Task Force 8: classification of sports. J Am Coll Cardiol 2005; 45:1364. Copyright © 2005 American College of Cardiology Foundation.

Graphic 64493 Version 5.0

Disclosures

Disclosures: **Lynn F Peng, MD** Nothing to disclose. **Stanton Perry, MD** Nothing to disclose. **David R Fulton, MD** Nothing to disclose. **Carrie Armsby, MD, MPH** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Evaluation of male infertility

Authors
Ronald S Swerdloff, MD
Christina Wang, MD

Section Editors
Peter J Snyder, MD
Alvin M Matsumoto, MD

Deputy Editor
Kathryn A Martin, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Apr 09, 2014.

INTRODUCTION — Infertility in a couple is defined as the inability to achieve conception despite one year of frequent unprotected intercourse. Use of this time period, while arbitrary, was based upon a study of 5574 English and American women engaging in unprotected coitus who ultimately conceived between 1946 and 1956 [1]. Among these women, 50 percent conceived within three months, 72 percent within six months, and 85 percent within 12 months.

One population-based study found the following distribution of causes when evaluating infertile couples [2] (see "Causes of male infertility"):

- Male factor – 23 percent
- Ovulatory dysfunction – 18 percent
- Tubal damage – 14 percent
- Endometriosis – 9 percent
- Coital problems – 5 percent
- Cervical factor – 3 percent
- Unexplained – 28 percent

The causes of male infertility can be divided into four main areas (table 1):

- Hypothalamic pituitary disease (secondary hypogonadism) – 1 to 2 percent
- Primary hypogonadism – 10 to 15 percent
- Post-testicular defects (disorders of sperm transport) – 10 to 20 percent
- Seminiferous tubule dysfunction – 60 to 80 percent including microdeletions of the Y chromosome

The noted frequencies represent an estimate of the approximate proportion of men in each category presenting to a tertiary referral center with capabilities to diagnose subtle defects of Y chromosome microdeletion [3]. (See "Causes of male infertility".)

The assessment of the male partner of a childless couple is frustrating for both the patient and clinician, because a specific etiology or treatment can be found in only a few of them (see "Causes of male infertility"). The disorders in most men are characterized primarily by descriptions of observed abnormalities, such as decreased sperm number, movement, or egg penetrating and fusion capabilities. Even testicular biopsies have provided little insight; they simply indicated the extent of impaired germ cell maturation. Use of molecular biology techniques has allowed definition of gene deletions and mutations in male infertility [4,5].

The components of the evaluation of the man include:

- History
- Physical examination
- Semen analyses
- Genetic tests

- Endocrine testing

The profile created by the results permits a systematic assessment of the male partner (algorithm 1 and algorithm 2).

HISTORY — The evaluation of an infertile man should begin with a detailed history that focuses on potential causes of infertility. A detailed history of the female partner should also be obtained, including history of previous fertility (or infertility), and any prior evaluation or treatment. In the male, the clinician should inquire about:

- Developmental history, including testicular descent, pubertal development, loss of body hair, or decrease in shaving frequency
- Chronic medical illness
- Infections, such as mumps orchitis, sinopulmonary symptoms, sexually transmitted infections, and genitourinary tract infections including prostatitis
- Surgical procedures involving the inguinal and scrotal areas such as vasectomy, orchiectomy, and herniorrhaphy
- Drugs and environmental exposures, including alcohol, radiation therapy, anabolic steroids, cytotoxic chemotherapy, drugs that cause hyperprolactinemia, and exposure to toxic chemicals (eg, pesticides, hormonal disrupters)
- Sexual history, including libido, frequency of intercourse, and previous fertility assessments of the man and his partner
- School performance, to determine if he has a history of learning disabilities suggestive of Klinefelter's syndrome

PHYSICAL EXAMINATION — The physical examination should include a general medical examination with a focus on finding evidence of androgen deficiency, which may accompany decreased fertility. The clinical manifestations of androgen deficiency depend upon the age of onset. Androgen deficiency during early gestation presents as ambiguous genitalia; in late gestation as micropenis; in childhood as delayed pubertal development; and in adulthood as decreased sexual function, infertility, and eventually, loss of secondary sex characteristics. The examination of the man should include the following components.

General appearance — Eunuchoidal proportions (upper/lower body ratio <1 with an arm span 5 cm >standing height) suggest androgen deficiency antedating puberty. On the other hand, increased body fat and decreased muscle mass suggest current androgen deficiency.

Skin — Loss of pubic, axillary, and facial hair, decreased oiliness of the skin, and fine facial wrinkling suggest long-standing androgen deficiency.

External genitalia — Several abnormalities that can affect fertility can be recognized by examination of the external genitalia:

- Incomplete sexual development can be recognized by examining the phallus and testes and finding a Tanner stage other than 5 (table 2). (See "Normal puberty".)
- Diseases that affect sperm maturation and transport can be detected by examination of the scrotum for absence of the vas, epididymal thickening, varicocele, and hernia. The presence of a varicocele should be confirmed with the man standing and performing a Valsalva maneuver.
- Decreased volume of the seminiferous tubules can be detected by measuring testicular size by Prader orchidometer or calipers. The Prader orchidometer consists of a series of plastic ellipsoids

with a volume from 1 to 35 mL. In an adult man, testicular volume below 15 mL and testicular length below 3.6 cm are considered small.

The Prader orchidometer has been reported to estimate greater testicular volumes than those by ultrasound, but not all ultrasound instruments use the same formula to calculate volume [6-8]. The difference between the two methods is greater for smaller than larger volumes, eg, about 5 mL difference for testicular volumes 5 to 15 mL but only 1 to 3 mL for volumes 20 to 25 mL [6].

Breasts — Gynecomastia suggests a decreased androgen to estrogen ratio. (See "Epidemiology, pathophysiology, and causes of gynecomastia".)

STANDARD SEMEN ANALYSIS — The semen analysis is the cornerstone of the assessment of the male partner of an infertile couple. In addition to the standard analysis, specialized analyses can be performed in some laboratories [9]. The standard semen analysis consists of the following:

- Measurement of semen volume and pH
- Microscopy for debris and agglutination
- Assessment of sperm concentration, motility, and morphology
- Sperm leukocyte count
- Search for immature germ cells

The semen sample should be collected after two to seven days of sexual abstinence, preferably at the doctor's office by masturbation [10]. If this is not possible, then the samples can be collected with condoms without chemical additives and delivered to the laboratory within an hour of collection.

Because of the marked inherent variability of semen analyses, at least two samples should be collected one to two weeks apart. The semen analysis should be performed using standardized methods, preferably those described in the World Health Organization (WHO) Laboratory Manual for Human Semen and Sperm Cervical Mucus Interaction [10]. In addition, the laboratory should employ internal quality control measures and participate in external quality control programs available from national andrology, clinical chemistry, and pathology societies [10-13].

WHO lower reference limits — The WHO has published revised lower reference limits for semen analyses [14]. The following parameters represent the generally accepted 5th percentile (lower reference limits and 95% confidence intervals in parentheses), derived from a study of over 1900 men whose partners had a time-to-pregnancy of ≤12 months [14].

- Volume – 1.5 mL (95% CI 1.4-1.7)
- Sperm concentration – 15 million spermatozoa/mL (95% CI 12-16)
- Total sperm number – 39 million spermatozoa per ejaculate (95% CI 33-46)
- Morphology – 4 percent normal forms (95% CI 3-4), using "strict" Tygerberg method [10]
- Vitality – 58 percent live (95% CI 55-63)
- Progressive motility – 32 percent (95% CI 31-34)
- Total (progressive + nonprogressive motility) – 40 percent (95% CI 38-42)

Semen volume — The mean semen volume in the WHO study was 3.7 mL; the lower reference limit was 1.5 mL [14]. A low volume in the presence of azoospermia (no sperm) or severe oligozoospermia (severely subnormal sperm concentration) suggests genital tract obstruction (eg, congenital absence of the vas deferens and seminal vesicles or ejaculatory duct obstruction). Congenital absence of vas deferens is diagnosed by physical examination and low semen pH, whereas ejaculatory duct obstruction is diagnosed by the finding of dilated seminal vesicles on transrectal ultrasonography.

Low semen volume with normal sperm concentration is most likely due to semen collection problems (loss of a portion of the ejaculate) and partial retrograde ejaculation. Androgen deficiency is also associated with low semen volume and low sperm concentration. The patient should be asked to return for a carefully collected repeat semen sample after emptying the bladder; post-ejaculation urine can be collected to assess whether there is retrograde ejaculation [14]. Endocrine assessment of possible androgen deficiency is reviewed below. (See 'Endocrine tests' below.)

Sperm concentration — The lower reference limit for sperm concentration is 15 million/mL (95% CI 12-16) [14]. However, some men with sperm counts considered to be low can be fertile, while others above the lower limit of normal can be subfertile [15-19] and, for the purposes of fertilization in vitro, 10 million/mL or even less can be satisfactory [10].

If only a few spermatozoa per high power field are observed, the sensitivity of detecting spermatozoa can be increased by labeling the spermatozoa with a fluorescent nuclei stain and then counting the spermatozoa using a deep chamber. The sensitivity is reduced to 2000 spermatozoa per mL ejaculate [20]. If no spermatozoa are seen, the semen should be centrifuged and the whole pellet should be smeared on a slide and examined for the presence of spermatozoa before the diagnosis of azoospermia is given [14]. The presence of adequate motile sperm in the pellet will allow intracytoplasmic sperm injection (ICSI) to be performed with ejaculated spermatozoa. Identifying even a few spermatozoa in the ejaculate is useful because it indicates that the patient may have spermatogenesis in a few seminiferous tubules even in atrophic testis, and microdissection testicular sperm extraction (TESE) could/should be attempted by experienced urologists and the testicular spermatozoa used for ICSI [21]. (See "Treatment of male infertility".)

Round cells observed in the semen smear may be leukocytes, immature germ cells or degenerating epithelial cells [10]. Presence of immature germ cells in the semen usually indicated disorders of spermatogenesis. Leukocytes can also be seen microscopically and counted with the hemocytometer. Agglutination suggests autoimmunity, which should be confirmed by tests for sperm surface antibodies.

Sperm motility — Sperm motility is assessed microscopically and is classified as progressive motility, non-progressive motility, and immotile spermatozoa. At least 40 percent of spermatozoa should be motile and at least 32 percent should have progressive motility. If sperm motility is poor, sperm vitality should be assessed by supravital stains or the hypoosmotic swelling test to determine whether the majority of immotile spermatozoa are dead [10]. The distinction between living, non-moving sperm, and dead sperm influences the type of assisted reproductive treatment that can be used for the induction of pregnancy. (See "Treatment of male infertility".)

Sperm morphology — The criteria for normal morphology were previously based mainly on shape, as observed microscopically. They now also include length, width, width ratio, area occupied by the acrosome, and neck and tail defects [14,22,23]. These criteria are called “strict” criteria and have good predictive value in terms of fertilization in vitro and pregnancy rates after in vitro fertilization (IVF) [22-25]. Based upon these correlations between "strict criteria" sperm morphology and IVF pregnancy rate, the lower limit of normal sperm morphology was estimated to be about 4 percent of spermatozoa [14,17,18,24,25].

Leukocytes — White blood cells, mainly polymorphonuclear leukocytes, are frequently present in the seminal fluid. Assessment of white blood cells is usually performed by using the peroxidase stain. The peroxidase positive cells are counted using the hemocytometer [14]. Presence of increased white blood cells in the ejaculate may be a marker of genital infection/inflammation and may be associated with poor semen quality because of the release of reactive oxygen species from the leukocytes. The suggested cut-off for the diagnosis of a possible infection is one million leukocytes/mL of ejaculate. However, this cut-off is not evidence-based [26].

Hyperviscosity — Hyperviscosity may interfere with the semen analysis, in particular, evaluation of sperm motility. Hyperviscous samples should be treated in the laboratory to reduce viscosity by passing the sample via a large gauge needle, diluting with a physiological solution or use of enzyme digestion before testing for sperm parameters in the laboratory. Although the cause of hyperviscosity is unclear, it is thought to be due to inflammation of the genitourinary tract [27].

Prediction of fertility — The standard semen analysis provides descriptive data, which do not always distinguish fertile from infertile men. In one prospective data of 430 couples, among those with a sperm concentration ≥40x10(6)/mL, 65 percent achieved pregnancy, compared with 51 percent of those with lower sperm concentrations [16]. In a study of male partners in 765 infertile couples in which the female partners who had normal infertility workup and in 696 control fertile couples recruited from prenatal classes [19]:

- There was extensive overlap between fertile and infertile men in sperm concentration, motility, and morphology.
- The subfertile ranges were a concentration less than 13.5 million/mL, less than 32 percent motility, and less than 9 percent normal morphology using "strict criteria."
- The fertile ranges included sperm concentration greater than 48 million/mL, greater than 63 percent motility, and greater than 12 percent normal morphology.
- Values in between these ranges were not useful in discriminating fertile from infertile couples (termed intermediate by the authors). The likelihood of infertility generally increased with decreases in any of the three parameters.
- The percentage of sperm with normal morphology had the greatest discriminatory power. It should be noted that none of the semen parameters was a powerful discriminator although each of these helped to distinguish between fertile and infertile men.

Lack of sperm in the ejaculate does not indicate the absence of testicular sperm production; these patients should be evaluated for retrograde ejaculation, congenital absence of the vas deferens, and other causes of obstructive azoospermia. (See 'Summary and recommendations' below and "Causes of male infertility".)

At-home test — An over the counter at-home test for evaluating sperm quality is commercially available (Fertell). The test provides an estimate of the total motile sperm using a "swim-up" technique followed by reaction with a monoclonal antibody against a sperm surface antigen. Data on the reliability of this test or its ability to predict fertility are very limited [28]. A second "dip stick" test that requires dilution of the semen (Sperm Check) has been used to monitor the sperm concentration after vasectomy [29]. However, as these tests do not assess sperm motility and morphology, we do not recommend them in the evaluation of male infertility.

SPECIALIZED SEMEN ANALYSIS — More specialized semen tests are not routinely performed, but can be used to help determine the cause of male infertility under certain circumstances (table 3).

Sperm autoantibodies — Sperm autoantibodies are present in about 4 to 8 percent of subfertile men. The presence of agglutination in the initial semen analysis suggests sperm autoimmunity; this should be confirmed by the mixed antiglobulin reaction or the immunobead test [10], both of which detect sperm surface antibodies. Antibodies are considered clinically important when over 50 percent of the spermatozoa are coated with them and when the spermatozoa fail to penetrate preovulatory human cervical mucus or demonstrate impaired fertilizing capacity. Studies suggest use of new proteomic analyses to assess such antibodies may provide a greater understanding of this disorder [30].

Semen biochemistry — Sperm biochemistry is frequently described in semen analyses, but is rarely

useful in clinical practice. The most commonly ordered test is fructose, which is a marker of seminal vesicle function. Low or non-detectable semen fructose is associated with congenital absence of the vas deferens and seminal vesicles or with ejaculatory duct obstruction; in comparison, obstruction of the epididymis is associated with normal semen fructose. The diagnosis of ejaculatory duct obstruction can be confirmed by transrectal ultrasonography, which will demonstrate dilated seminal vesicles [31].

Semen culture — Semen culture is frequently performed in men whose semen samples contain inflammatory cells, but the results are usually not diagnostic. If semen culture is performed, precautions must be taken by the man during sample collection to prevent skin contamination. The yield of semen culture may be improved by performing a prostatic massage before sample collection.

Sperm-cervical mucus interaction — Sperm-cervical mucus interaction identifies whether the problem is in the sperm or in the cervical mucus and is assessed in vivo by the postcoital test and in vitro by the slide or capillary tube tests [10].

- The postcoital test should be done in the doctor's office or laboratory when the female partner is in the preovulatory phase of the cycle. The number and motility of sperm in the cervical mucus is assessed 9 to 24 hours after vaginal intercourse.
- The in vitro tests, such as the slide or the capillary tests, can be performed on sperm and cervical mucus from the infertile couple together with donor semen and cervical mucus. These so-called "crossed tests" identify whether the problem is in the sperm or cervical mucus.

The inability of spermatozoa to penetrate the cervical mucus is correlated with poor sperm motility and the presence of sperm antibodies, and failure of sperm to penetrate zona-free hamster eggs is correlated with failure of in vitro fertilization (IVF) [32,33], and in vivo conception [34]. If the sperm-cervical mucus interaction tests are incorporated into the evaluation of an infertile couple, failure of sperm to penetrate a good sample of cervical mucus may suggest that the couple should proceed with assisted reproductive technologies more expeditiously. Thus, sperm-cervical mucus penetration test can be used as a sperm function test. (See "In vitro fertilization".)

Sperm function tests — Screening male partners of infertile couples with the following advanced andrology diagnostic tests is impractical and costly, but selective use may be justified when the standard semen analysis is normal or near normal (table 3) [35].

Computer-aided sperm analysis — Quantitative measurement of sperm motion characteristics (sperm kinematics) is useful in identifying men with unexplained infertility, predicting in vivo and in vitro fertilizing capacity, and in toxicology studies. Commercially available CASA systems measure sperm kinematics, such as sperm velocity (curvilinear, straight line, average path), amplitude of lateral displacement, and other derived functions [36-38]. The predictive value of CASA-derived sperm motility characteristics for in vivo [39-41] and in vitro fertility [42,43] has been demonstrated. The accuracy of this technique, however, is highly dependent upon the technology, analytic conditions, and technical training of the operators. When conditions are optimized, this technique can be used to assess sperm concentration, motility, and morphology.

Acrosome reaction — The acrosome reaction involves the fusion of the acrosome and the plasma membrane, leading to release of the acrosomal enzymes and exposure of the sperm head. This reaction must be precisely timed to occur after sperm binding to the zona pellucida. Premature loss of the acrosome leads to loss of zona pellucida recognition sites from the sperm and compromises sperm binding to the zona [44]. The acrosome reaction can be assessed in human sperm by fluorescein-labeled pea or peanut agglutinins and specific monoclonal antibodies [10] before and after stimulation by calcium ionophore challenge [45].

The occurrence of acrosome reaction abnormalities as a principal cause of male infertility is probably

uncommon, thus acrosome reaction tests should be reserved for couples in whom a specialized procedure such as intracytoplasmic sperm injection (ICSI) and or IVF are contemplated.

Zona-free hamster oocyte penetration test — Since its introduction in the 1970s, the hamster oocyte penetration test (HOPT) has been used in clinical andrology laboratories as a predictor of success for in vitro and in vivo fertilization [35,46]. This test is based upon the observation that hamster oocytes denuded of zona pellucida can be penetrated by the spermatozoa of several mammalian species, including humans. The HOPT can assess the ability of the spermatozoa to capacitate, undergo acrosome reaction, penetrate the oocyte membrane, and fuse with the oocyte. False positive and false negative rates are high. The test is technically demanding and should be performed only in a specialized laboratory with proven record of good assay repeatability.

Human zona pellucida binding test — Two zona binding tests have been used to predict the success of IVF: the hemizona assay [47] and a competitive zona binding assay [48]. In the hemizona assay, human zona pellucida from an oocyte not previously exposed to spermatozoa is bisected; one-half zona is incubated with the test sample, the other half with control spermatozoa. In the competitive binding assay, the test and control spermatozoa are labeled with different fluorochromes [39].

In both tests, the number of spermatozoa bound to the zona from the test sample is compared with a control sample. These tests are technically demanding and are not often used for evaluation of male infertility because of the difficulty in obtaining human oocytes.

Sperm biochemistry — Generation of reactive oxygen species may be a cause of sperm dysfunction and a predictor of fertilization in vitro [49]. Reactive oxygen species lead to lipid peroxidation of the sperm membrane and are also deleterious to sperm motility. This is still regarded as a research test and is not often used for diagnosis of a specific sperm defect.

Sperm chromatin and DNA assays — A flow cytometric assay of sperm chromatin structure after low pH-induced denaturation has been developed to measure sperm chromatin integrity and sperm function [50,51]. Similarly, DNA fragmentation (a measure of sperm apoptosis) has also been utilized as a measure of sperm nuclear integrity [52,53]. Flow cytometry to evaluate DNA of sperm can distinguish the mature haploid and the abnormal diploid mature spermatozoa, cellular fragments and immature germ cells [54]. These tests of sperm nuclear chromatin or DNA structure may provide information to semen analysis in male infertility assessment and reproductive toxicology studies, and may have predictive values for assisted reproduction outcome [55-59].

The usefulness of tests of DNA integrity for prediction of fertility remains controversial. A meta-analysis reported that DNA integrity was not predictive of pregnancy outcomes in assisted reproduction. However, it is possible that subgroups of infertile men may benefit from assessment of sperm chromatin structure assays or assessment of DNA fragments [60].

GENETIC TESTS — The introduction of ICSI has made it possible for men with severe oligozoospermia and azoospermia to father children, but the genetic risks of this highly invasive technique must be considered. These include the risks of transferring the cystic fibrosis conductance regulator (CFTR) gene, somatic and sex chromosome abnormalities, and microdeletions of the Y chromosome [61-64].

CFTR gene — Men with CFTR gene mutations present with obstructive azoospermia, normal testicular volume, no vas deferens on palpation of the external genitalia, and normal serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone concentrations. In this setting, a family history of cystic fibrosis should be obtained, and both the male and female partner should be tested for CFTR gene mutations.

The likelihood of transfer of a mutant CFTR gene was illustrated in a study of 102 men with congenital

absence of the vas deferens [62]:

- 19 had mutations in both copies of the CFTR gene, although none had the 5T allele.
- 54 had a mutation in one copy of the CFTR gene, and 34 of these had the 5T allele in the other CFTR gene.

The 5T allele mutation may result in clinical presentations such as moderate cystic fibrosis and congenital bilateral absence of vas [62]. (See "Cystic fibrosis: Genetics and pathogenesis".)

Sex chromosome and somatic mutations — Approximately 10 to 18 percent of infertile men, previously classified as having idiopathic oligozoospermia, have microdeletions of the Y chromosome. Complete deletions of the AZFa or AFZb regions lead to azoospermia and Sertoli cell only syndrome. Partial deletions of these regions or complete deletion of the AFZc regions result in a variable phenotype varying from hypospermatogenesis to Sertoli cell only syndrome and present with severe oligozoospermia or azoospermia. (See "Causes of male infertility", section on 'Y chromosome and related defects'.)

A substantial number of men with known causes of infertility also have Y chromosome microdeletions [65], but such deletions are rare in men with sperm concentrations over 5 million/mL [66]. Using sufficient number of markers (primers) allows the detection of over 95 percent of clinically relevant deletions [67,68]. Genetic diagnosis is important because ISCI with testicular derived spermatozoa would not be possible in men with complete deletions of the AZFa or AZFb regions. (See "Causes of male infertility", section on 'Y chromosome and related defects'.)

These Y chromosome deletions may be transmitted from father to son by ICSI [69]. In addition, low-level sex chromosome mosaicism has been reported in infertile couples [70]. Most recently, a gr/gr deletion at the AFZc region of the Y chromosome was associated with male infertility in epidemiological studies with a possible increase in risk of testicular germ cell tumor [71]. The results have not been confirmed. Other gene polymorphisms have been reported to be associated with male infertility but the assessment can only be done in qualified laboratories [68,72].

Therefore, genetic counseling and chromosome and other molecular genetic tests are undertaken before ICSI is undertaken [65,73]. Routine karyotyping is recommended for infertile men with spermatogenic failure and a sperm concentration less than 10 million/mL [74]. In Europe and many infertility centers in the United States, tests for Y chromosome deletions are offered to the infertile couple when the male partner has severe oligospermia or azoospermia. These men usually have small testicular volumes. Some may have elevated serum FSH concentrations but normal serum LH and testosterone levels. In some infertility centers, all men with “idiopathic” oligozoospermia are screened for Y chromosome microdeletions. In other centers, these tests are only done in men with severe oligozoospermia and azoospermia.

Androgen receptor — There is renewed interest in the androgen receptor (AR) transcriptional activity with male infertility. The trinucleotide (CAG) repeats in exon 1 of the AR regulates the functional activity of the AR. In some reports, long CAG repeats are associated with lower AR activity and azoospermia in infertile men [75-77] and may have implications for selection of patients for ICSI.

ENDOCRINE TESTS — The endocrine assessment of an infertile man includes measurements of serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and perhaps other tests [78]:

Serum testosterone — Measurement of a morning serum total testosterone is usually sufficient. In men with borderline values, the measurement should be repeated and measurement of serum free testosterone may be helpful. (See "Clinical features and diagnosis of male hypogonadism", section on 'Serum total testosterone'.)

Serum LH and FSH — When the serum testosterone concentration is low, high serum FSH and LH concentrations indicate primary hypogonadism and values that are low or normal indicate secondary hypogonadism. (See "Clinical features and diagnosis of male hypogonadism".)

Men with low sperm counts and low serum LH concentrations who are well-androgenized should be suspected of exogenous anabolic or androgenic steroid abuse. (See "Use of androgens and other hormones by athletes".)

Other — Serum prolactin should be measured in any man with a low serum testosterone concentration and normal to low serum LH concentration. Although inhibin assays are not widely available outside of research laboratories, low serum inhibin concentrations may be an even more sensitive test of primary testicular dysfunction than high serum FSH concentrations, provided the assay is specific for inhibin B [79-82].

OBSTRUCTIVE AZOOSPERMIA — If a patient has normal testicular volumes, normal serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) and testosterone and azoospermia, the likely diagnosis is obstructive azoospermia (algorithm 2). Bilateral congenital absence of the vas can be detected on physical examination and confirmed by a low fructose level in the semen. Ejaculatory duct obstruction can be diagnosed by a transrectal ultrasound showing dilated seminal vesicles [83,84]. Patients with obstructive azoospermia should be referred to a urologist specialized in infertility for further evaluation and treatment. (See "Treatment of male infertility", section on 'Obstructive azoospermia'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient information: Infertility in men (The Basics)")
- Beyond the Basics topics (see "Patient information: Treatment of male infertility (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS — The diagnosis of an infertile man can be approached algorithmically (algorithm 1 and algorithm 2). The infertile couple should be evaluated together in an infertility center, if possible. (See "Overview of infertility".)

- Semen analysis is the fundamental investigation for the infertile man and directs the subsequent evaluation. (See 'Standard semen analysis' above.)
    - If the semen analysis is normal, the female partner should be thoroughly investigated. If investigation of the woman is normal, then specialized tests of sperm function may be helpful.
    - If routine semen analysis is abnormal, it should be repeated. If repeated semen analyses demonstrate severe oligozoospermia (less than 5 million spermatozoa/mL) or azoospermia, basal serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone should be measured.
- If serum concentrations of FSH, LH, and testosterone are normal and the man has azoospermia, a post-ejaculatory urine sample to examine for spermatozoa will provide evidence about retrograde

ejaculation if sperm are seen in the urine. If spermatozoa are not present in the postejaculatory urine, the man has obstructive azoospermia or impaired spermatogenesis.

- Absence of the vas deferens on physical examination, together with low seminal fluid volume and acidic pH, suggest congenital absence of vas deferens. Low or absent semen fructose will help to confirm the diagnosis of this condition, because the seminal vesicles are usually also absent. These patients should be tested for the cystic fibrosis conductance regulator (CFTR) gene mutations and, if positive in either the man or the female partner, genetic counseling is necessary before in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). (See 'CFTR gene' above.)
- If semen fructose is present in a man with azoospermia, normal-sized testes, and normal serum LH, FSH, and testosterone concentrations, epididymal obstruction is likely. In this situation, fine needle aspiration or open biopsy of the testis should be considered to demonstrate the presence of normal testicular histology. Microsurgical aspiration of spermatozoa from a dilated proximal epididymis for ICSI should then be considered. In many men with either normal or high serum FSH concentrations, obstruction of the outflow system will not be demonstrated and a testicular fine needle or open biopsy should be considered to determine if sperm are present and to aspirate them for ICSI. (See "Treatment of male infertility", section on 'Obstructive azoospermia'.)
- In men with oligozoospermia and normal serum hormone concentrations, the presence of varicocele, reproductive tract infection, and sperm antibodies should be assessed by physical examination and laboratory tests before the diagnosis of idiopathic male infertility is made. If these men have sperm counts of more than 10 million/mL, specialized sperm function tests may help to define the abnormality. (See 'Sperm function tests' above.)
- Genetic assessment for Y chromosomal disorders can be performed in specialized centers for men with “idiopathic” non-obstructive severe oligozoospermia and azoospermia. If a chromosomal abnormality is found, genetic counseling is recommended before ICSI is undertaken. (See 'Genetic tests' above.)
- At present, the evaluation of male infertility is more art than science. The available treatments are limited to gonadotropin replacement for hypothalamic or pituitary deficiency, dopamine agonists for hyperprolactinemia, ligation for varicocele, surgical correction of obstruction, and assisted reproductive techniques to provide subfertile sperm directly to or within the collected egg. (See "Treatment of male infertility".)

REFERENCES

1. GUTTMACHER AF. Factors affecting normal expectancy of conception. J Am Med Assoc 1956; 161:855.
2. Hull MG, Glazener CM, Kelly NJ, et al. Population study of causes, treatment, and outcome of infertility. Br Med J (Clin Res Ed) 1985; 291:1693.
3. de Kretser DM. Male infertility. Lancet 1997; 349:787.
4. Brugh VM 3rd, Lipshultz LI. Male factor infertility: evaluation and management. Med Clin North Am 2004; 88:367.
5. Vogt PH. Azoospermia factor (AZF) in Yq11: towards a molecular understanding of its function for human male fertility and spermatogenesis. Reprod Biomed Online 2005; 10:81.
6. Sakamoto H, Saito K, Oohta M, et al. Testicular volume measurement: comparison of

ultrasonography, orchidometry, and water displacement. Urology 2007; 69:152.

7. Rivkees SA, Hall DA, Boepple PA, Crawford JD. Accuracy and reproducibility of clinical measures of testicular volume. J Pediatr 1987; 110:914.
8. Diamond DA, Paltiel HJ, DiCanzio J, et al. Comparative assessment of pediatric testicular volume: orchidometer versus ultrasound. J Urol 2000; 164:1111.
9. Sigman M, Baazeem A, Zini A. Semen analysis and sperm function assays: what do they mean? Semin Reprod Med 2009; 27:115.
10. World Health Organization Department of Reproductive Health and Research. World Health Organization Laboratory Manual for the Examination and Processing of Human Semen, 5th ed, World Health Organization, Geneva, Switzerland 2010.
11. Cooper TG, Neuwinger J, Bahrs S, Nieschlag E. Internal quality control of semen analysis. Fertil Steril 1992; 58:172.
12. Dunphy BC, Kay R, Barratt CL, Cooke ID. Quality control during the conventional analysis of semen, an essential exercise. J Androl 1989; 10:378.
13. McLachlan RI, Baker HW, Clarke GN, et al. Semen analysis: its place in modern reproductive medical practice. Pathology 2003; 35:25.
14. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010; 16:231.
15. MACLEOD J, GOLD RZ. The male factor in fertility and infertility. II. Spermatozoon counts in 1000 men of known fertility and in 1000 cases of infertile marriage. J Urol 1951; 66:436.
16. Bonde JP, Ernst E, Jensen TK, et al. Relation between semen quality and fertility: a population-based study of 430 first-pregnancy planners. Lancet 1998; 352:1172.
17. Jørgensen N, Andersen AG, Eustache F, et al. Regional differences in semen quality in Europe. Hum Reprod 2001; 16:1012.
18. Swan SH, Brazil C, Drobnis EZ, et al. Geographic differences in semen quality of fertile U.S. males. Environ Health Perspect 2003; 111:414.
19. Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001; 345:1388.
20. Cooper TG, Hellenkemper B, Jonckheere J, et al. Azoospermia: virtual reality or possible to quantify? J Androl 2006; 27:483.
21. Bryson CF, Ramasamy R, Sheehan M, et al. Severe testicular atrophy does not affect the success of microdissection testicular sperm extraction. J Urol 2014; 191:175.
22. Menkveld R, Stander FS, Kotze TJ, et al. The evaluation of morphological characteristics of human spermatozoa according to stricter criteria. Hum Reprod 1990; 5:586.
23. Kruger TF, du Toit TC, Franken DR, et al. Sperm morphology: assessing the agreement between the manual method (strict criteria) and the sperm morphology analyzer IVOS. Fertil Steril 1995; 63:134.
24. Kruger TF, Menkveld R, Stander FS, et al. Sperm morphologic features as a prognostic factor in in vitro fertilization. Fertil Steril 1986; 46:1118.
25. Kruger TF, Acosta AA, Simmons KF, et al. Predictive value of abnormal sperm morphology in in vitro fertilization. Fertil Steril 1988; 49:112.
26. Wolff H. The biologic significance of white blood cells in semen. Fertil Steril 1995; 63:1143.
27. Elia J, Delfino M, Imbrogno N, et al. Human semen hyperviscosity: prevalence, pathogenesis and therapeutic aspects. Asian J Androl 2009; 11:609.
28. Björndahl L, Kirkman-Brown J, Hart G, et al. Development of a novel home sperm test. Hum

Reprod 2006; 21:145.

29. Klotz KL, Coppola MA, Labrecque M, et al. Clinical and consumer trial performance of a sensitive immunodiagnostic home test that qualitatively detects low concentrations of sperm following vasectomy. J Urol 2008; 180:2569.
30. Bohring C, Krause W. Immune infertility: towards a better understanding of sperm (auto)-immunity. The value of proteomic analysis. Hum Reprod 2003; 18:915.
31. Dieudonné O, Godin PA, Van-Langendonckt A, et al. Biochemical analysis of the sperm and infertility. Clin Chem Lab Med 2001; 39:455.
32. Berberoglugil P, Englert Y, Van den Bergh M, et al. Abnormal sperm-mucus penetration test predicts low in vitro fertilization ability of apparently normal semen. Fertil Steril 1993; 59:1228.
33. Barratt CL, Osborn JC, Harrison PE, et al. The hypo-osmotic swelling test and the sperm mucus penetration test in determining fertilization of the human oocyte. Hum Reprod 1989; 4:430.
34. Eggert-Kruse W, Leinhos G, Gerhard I, et al. Prognostic value of in vitro sperm penetration into hormonally standardized human cervical mucus. Fertil Steril 1989; 51:317.
35. Consensus workshop on advanced diagnostic andrology techniques. ESHRE (European Society of Human Reproduction and Embryology) Andrology Special Interest Group. Hum Reprod 1996; 11:1463.
36. Davis RO, Katz DF. Computer-aided sperm analysis: technology at a crossroads. Fertil Steril 1993; 59:953.
37. Mortimer D, Aitken RJ, Mortimer ST, Pacey AA. Workshop report: clinical CASA--the quest for consensus. Reprod Fertil Dev 1995; 7:951.
38. Farrell PB, Foote RH, Zinaman MJ. Motility and other characteristics of human sperm can be measured by computer-assisted sperm analysis of samples stained with Hoechst 33342. Fertil Steril 1996; 66:446.
39. Barratt CL, Tomlinson MJ, Cooke ID. Prognostic significance of computerized motility analysis for in vivo fertility. Fertil Steril 1993; 60:520.
40. Macleod IC, Irvine DS. The predictive value of computer-assisted semen analysis in the context of a donor insemination programme. Hum Reprod 1995; 10:580.
41. Krause W. Computer-assisted semen analysis systems: comparison with routine evaluation and prognostic value in male fertility and assisted reproduction. Hum Reprod 1995; 10 Suppl 1:60.
42. Liu DY, Clarke GN, Baker HW. Relationship between sperm motility assessed with the Hamilton-Thorn motility analyzer and fertilization rates in vitro. J Androl 1991; 12:231.
43. Chan SY, Wang C, Ng M, et al. Evaluation of computerized analysis of sperm movement characteristics and differential sperm tail swelling patterns in predicting human sperm in vitro fertilizing capacity. J Androl 1989; 10:133.
44. Liu DY, Baker HW. Tests of human sperm function and fertilization in vitro. Fertil Steril 1992; 58:465.
45. Cummins JM, Pember SM, Jequier AM, et al. A test of the human sperm acrosome reaction following ionophore challenge. Relationship to fertility and other seminal parameters. J Androl 1991; 12:98.
46. Aitken J. On the future of the hamster oocyte penetration assay. Fertil Steril 1994; 62:17.
47. Oehninger S, Coddington CC, Scott R, et al. Hemizona assay: assessment of sperm dysfunction and prediction of in vitro fertilization outcome. Fertil Steril 1989; 51:665.
48. Liu DY, Clarke GN, Lopata A, et al. A sperm-zona pellucida binding test and in vitro fertilization. Fertil Steril 1989; 52:281.
49. Aitken RJ, Clarkson JS, Fishel S. Generation of reactive oxygen species, lipid peroxidation, and

human sperm function. Biol Reprod 1989; 41:183.

50. Larson KL, DeJonge CJ, Barnes AM, et al. Sperm chromatin structure assay parameters as predictors of failed pregnancy following assisted reproductive techniques. Hum Reprod 2000; 15:1717.
51. Evenson DP, Jost LK, Corzett M, Balhorn R. Characteristics of human sperm chromatin structure following an episode of influenza and high fever: a case study. J Androl 2000; 21:739.
52. Donnelly ET, O'Connell M, McClure N, Lewis SE. Differences in nuclear DNA fragmentation and mitochondrial integrity of semen and prepared human spermatozoa. Hum Reprod 2000; 15:1552.
53. Chohan KR, Griffin JT, Lafromboise M, et al. Comparison of chromatin assays for DNA fragmentation evaluation in human sperm. J Androl 2006; 27:53.
54. Hacker-Klom UB, Göhde W, Nieschlag E, Behre HM. DNA flow cytometry of human semen. Hum Reprod 1999; 14:2506.
55. Bungum M, Humaidan P, Spano M, et al. The predictive value of sperm chromatin structure assay (SCSA) parameters for the outcome of intrauterine insemination, IVF and ICSI. Hum Reprod 2004; 19:1401.
56. Alvarez JG. The predictive value of sperm chromatin structure assay. Hum Reprod 2005; 20:2365.
57. O'Brien J, Zini A. Sperm DNA integrity and male infertility. Urology 2005; 65:16.
58. Spano M, Seli E, Bizzaro D, et al. The significance of sperm nuclear DNA strand breaks on reproductive outcome. Curr Opin Obstet Gynecol 2005; 17:255.
59. Benchaib M, Lornage J, Mazoyer C, et al. Sperm deoxyribonucleic acid fragmentation as a prognostic indicator of assisted reproductive technology outcome. Fertil Steril 2007; 87:93.
60. Collins JA, Barnhart KT, Schlegel PN. Do sperm DNA integrity tests predict pregnancy with in vitro fertilization? Fertil Steril 2008; 89:823.
61. Bhasin S, Ma K, de Kretser DM. Y-chromosome microdeletions and male infertility. Ann Med 1997; 29:261.
62. Chillón M, Casals T, Mercier B, et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. N Engl J Med 1995; 332:1475.
63. Testart J, Gautier E, Brami C, et al. Intracytoplasmic sperm injection in infertile patients with structural chromosome abnormalities. Hum Reprod 1996; 11:2609.
64. Palermo GD, Schlegel PN, Sills ES, et al. Births after intracytoplasmic injection of sperm obtained by testicular extraction from men with nonmosaic Klinefelter's syndrome. N Engl J Med 1998; 338:588.
65. Krausz C, Quintana-Murci L, Barbaux S, et al. A high frequency of Y chromosome deletions in males with nonidiopathic infertility. J Clin Endocrinol Metab 1999; 84:3606.
66. De Kretser DM, Baker HW. Infertility in men: recent advances and continuing controversies. J Clin Endocrinol Metab 1999; 84:3443.
67. Krausz C, Forti G, McElreavey K. The Y chromosome and male fertility and infertility. Int J Androl 2003; 26:70.
68. Simoni M, Bakker E, Krausz C. EAA/EMQN best practice guidelines for molecular diagnosis of y-chromosomal microdeletions. State of the art 2004. Int J Androl 2004; 27:240.
69. Page DC, Silber S, Brown LG. Men with infertility caused by AZFc deletion can produce sons by intracytoplasmic sperm injection, but are likely to transmit the deletion and infertility. Hum Reprod 1999; 14:1722.
70. Mau UA, Bäckert IT, Kaiser P, Kiesel L. Chromosomal findings in 150 couples referred for genetic counselling prior to intracytoplasmic sperm injection. Hum Reprod 1997; 12:930.

71. Nathanson KL, Kanetsky PA, Hawes R, et al. The Y deletion gr/gr and susceptibility to testicular germ cell tumor. Am J Hum Genet 2005; 77:1034.
72. Krausz C, Giachini C, Xue Y, et al. Phenotypic variation within European carriers of the Y-chromosomal gr/gr deletion is independent of Y-chromosomal background. J Med Genet 2009; 46:21.
73. McLachlan RI, Aitken RJ, Cram D, et al. Need for standardization and confirmation of STS deletions on the Y chromosome. Fertil Steril 2008; 90:463.
74. McLachlan RI, O'Bryan MK. Clinical Review#: State of the art for genetic testing of infertile men. J Clin Endocrinol Metab 2010; 95:1013.
75. Yong EL, Loy CJ, Sim KS. Androgen receptor gene and male infertility. Hum Reprod Update 2003; 9:1.
76. Mengual L, Oriola J, Ascaso C, et al. An increased CAG repeat length in the androgen receptor gene in azoospermic ICSI candidates. J Androl 2003; 24:279.
77. Asatiani K, von Eckardstein S, Simoni M, et al. CAG repeat length in the androgen receptor gene affects the risk of male infertility. Int J Androl 2003; 26:255.
78. Sokol RZ. Endocrinology of male infertility: evaluation and treatment. Semin Reprod Med 2009; 27:149.
79. Anawalt BD, Bebb RA, Matsumoto AM, et al. Serum inhibin B levels reflect Sertoli cell function in normal men and men with testicular dysfunction. J Clin Endocrinol Metab 1996; 81:3341.
80. Pierik FH, Vreeburg JT, Stijnen T, et al. Serum inhibin B as a marker of spermatogenesis. J Clin Endocrinol Metab 1998; 83:3110.
81. Andersson AM. Inhibin B in the assessment of seminiferous tubular function. Baillieres Best Pract Res Clin Endocrinol Metab 2000; 14:389.
82. Mabeck LM, Jensen MS, Toft G, et al. Fecundability according to male serum inhibin B--a prospective study among first pregnancy planners. Hum Reprod 2005; 20:2909.
83. Meacham RB, Hellerstein DK, Lipshultz LI. Evaluation and treatment of ejaculatory duct obstruction in the infertile male. Fertil Steril 1993; 59:393.
84. Jarow JP. Transrectal ultrasonography in the diagnosis and management of ejaculatory duct obstruction. J Androl 1996; 17:467.

Topic 7453 Version 11.0

GRAPHICS

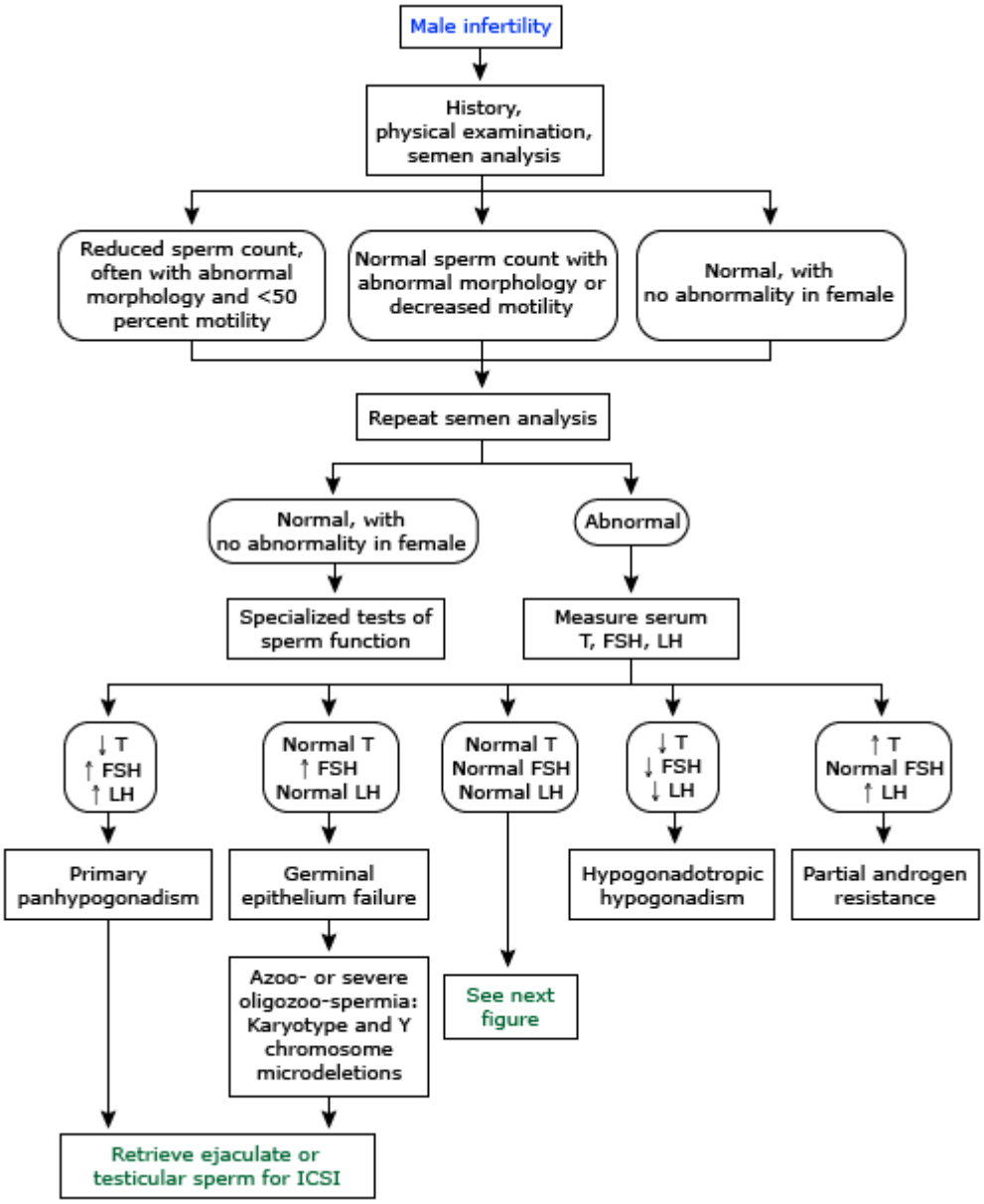
Causes of male infertility

Hypothalamic-pituitary disorders (GnRH; LH and FSH deficiency)
Congenital disorders
Congenital GnRH deficiency (Kallmann syndrome)
Hemochromatosis
Multiorgan genetic disorders (Prader-Willi syndrome, Laurence-Moon-Beidl syndrome, familial cerebellar ataxia)
Acquired disorders
Pituitary and hypothalamic tumors (macroadenoma, craniopharyngioma)
Infiltrative disorders (sarcoidosis, histiocytosis, tuberculosis, fungal infections)
Trauma, postsurgery, postirradiation
Vascular (infarction, aneurysm)
Hormonal (hyperprolactinemia, androgen excess, estrogen excess, cortisol excess)
Drugs (opioids and psychotropic drugs, GnRH agonists or antagonists)
Systemic disorders
Chronic illnesses
Nutritional deficiencies
Obesity
Primary gonadal disorders
Congenital disorders
Klinefelter's syndrome (XXY) and its variants (XXY/XY; XXXY)
Cryptorchidism
Myotonic dystrophy
Functional prepubertal castrate syndrome (congenital anorchia)
Varicocele
Androgen insensitivity syndromes
5-alpha-reductase deficiency
Y chromosome deletions
Acquired disorders
Viral orchitis (mumps, echovirus, arbovirus)
Granulomatous orchitis (leprosy, tuberculosis)
Epididymo-orchitis (gonorrhea, chlamydia)
Drugs (eg, alkylating agents, alcohol, marijuana, antiandrogens, ketoconazole, spironolactone, histamine2 receptor antagonists)

Ionizing radiation
Environmental toxins (eg, dibromochloropropane, carbon disulfide, cadmium, lead, mercury, environmental estrogens and phytoestrogens)
Hyperthermia
Immunologic disorders, including polyglandular autoimmune disease
Trauma
Torsion
Castration
Systemic illness (eg renal failure, hepatic cirrhosis, cancer, sickle cell disease, amyloidosis, vasculitis, celiac disease)
Disorders of sperm transport
Epididymal dysfunction (drugs, infection)
Abnormalities of the vas deferens (congenital absence, Young's syndrome, infection, vasectomy)
Ejaculatory dysfunction (spinal cord disease, autonomic dysfunction, premature ejaculation)
Unexplained male factor infertility

Graphic 54356 Version 1.0

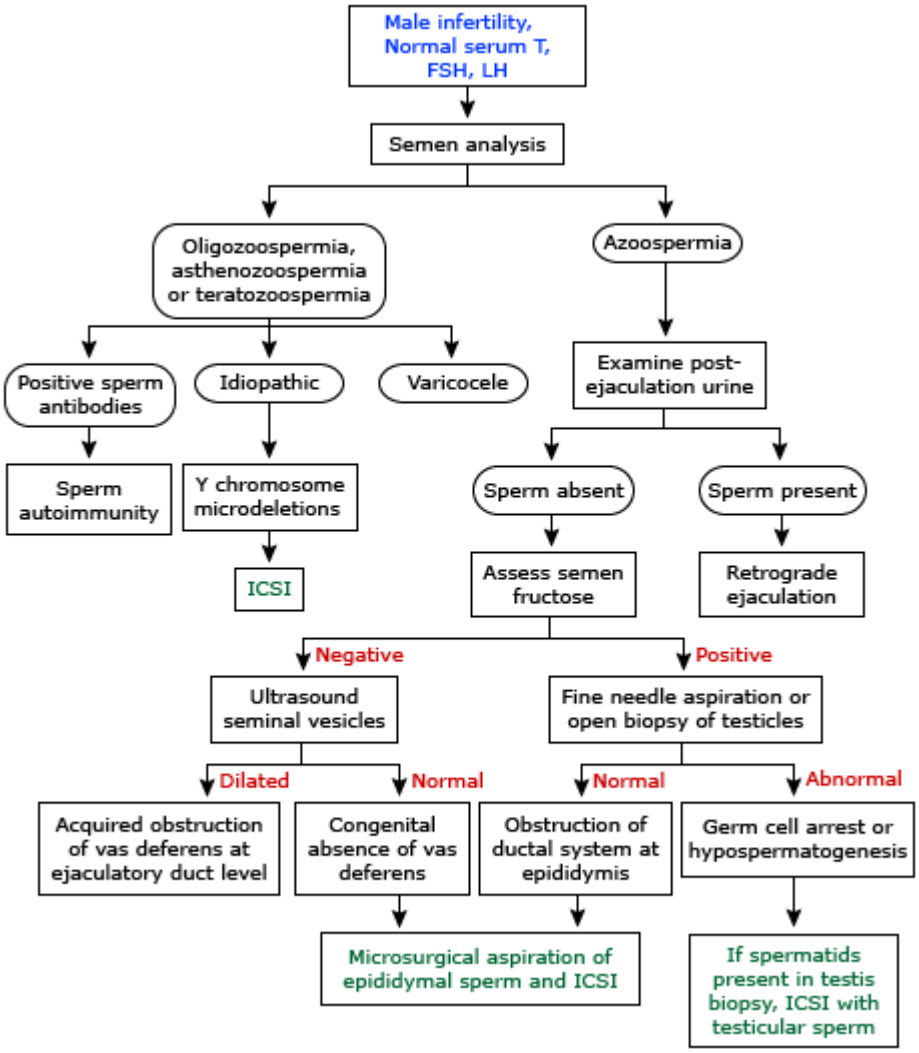
Approach to diagnosis of male infertility



T: testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ICSI: intracytoplasmic sperm injection.

Graphic 79044 Version 3.0

Approach to diagnosis of male infertility in patients with normal serum hormone concentrations



T: testosterone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ICSI: intracytoplasmic sperm injection.

Graphic 60940 Version 3.0

Tanner stages of puberty in normal adolescent boys

Stage of puberty	Age (mean ± SD)	Genitalia	Serum testosterone (ng/dL)
1		Prepubertal	87
2	11.6 ± 1.1	Beginning enlargement of scrotum and testes; change in texture and reddening of scrotal skin	251
3	12.9 ± 1.0	Beginning growth of the penis, mainly in length; further growth of testes and scrotum	336
4	13.8 ± 1.0	Further growth of penis in length and breadth; further darkening of scrotal skin	525
5	14.9 ± 1.1	Adult size genitalia	571

Description of genitalia from: Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970; 45:13; serum testosterone concentrations from Lee PA, Jaffe RB, Midgely AR Jr. Serum gonadotropin, testosterone and prolactin concentrations throughout puberty in boys: a longitudinal study. J Clin Endocrinol Metab 1974; 39:664.

Graphic 76165 Version 3.0

Specialized tests for semen analysis

Sperm autoantibodies
Semen biochemistry (semen fructose)
Semen culture
Sperm-cervical mucus interaction tests
Sperm function tests
Computer-aided sperm analysis
Acrosome reaction
Zona free hamster oocyte penetration test
Human zona pellucida binding test
Sperm reactive oxygen species generation
Sperm chromatin/DNA assays

Graphic 51745 Version 1.0

Disclosures

Disclosures: **Ronald S Swerdloff, MD** Nothing to disclose. **Christina Wang, MD** Nothing to disclose. **Peter J Snyder, MD** Grant/Research/Clinical Trial Support: AbbVie [hypogonadism (Testosterone gel 1% and 1.62%)]; Novo Nordisk [GH deficiency (norditropin)]; Ipsen [Acromegaly (Lanreotide)]. Consultant/Advisory Boards: Novartis [Cushing's syndrome (Pasireotide)]; Pfizer [Acromegaly (Pegvisomant)]. **Alvin M Matsumoto, MD** Grant/Research/Clinical Trial Support: AbbVie (testosterone [AndroGel]); GSK (BPH [Dutasteride]). Consultant/Advisory Boards: Endo Pharmaceuticals (testosterone [Delatestryl, Fortesta, AVEED]); AbbVie (testosterone [AndroGel]) Lilly (testosterone [Axiron]); Clarus (testosterone [Rextoro]). **Kathryn A Martin, MD** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Microdeletion syndromes (chromosomes 1 to 11)

Author Carlos A Bacino, MD, FACMG
Section Editor Helen V Firth, DM, FRCP, DCH
Deputy Editor Elizabeth TePas, MD, MS

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Oct 14, 2014.

INTRODUCTION — Chromosome deletions that span at least five megabases (Mb) are usually microscopically visible on chromosome banded karyotypes. Microdeletions, or submicroscopic deletions, are chromosomal deletions that are too small to be detected by light microscopy using conventional cytogenetic methods. Specialized testing is needed to identify these deletions. Microdeletions are typically one to three Mb long and involve several contiguous genes. The exact size and location of a microdeletion that causes a syndrome may vary, but a specific "critical region" is consistently involved. Most phenotypic effects of these microdeletions are due to haploinsufficiency of a few critical genes or in some cases a single gene.

This topic reviews microdeletion syndromes involving chromosomes 1 through 11. Microdeletion syndromes involving chromosomes 12 through 22 are discussed separately, as are microduplication syndromes, and congenital abnormalities of the sex chromosomes. Other congenital chromosomal abnormalities, such as trisomies, are also reviewed in detail elsewhere. (See "Microdeletion syndromes (chromosomes 12 to 22)" and "Microduplication syndromes" and "Sex chromosome abnormalities" and "Congenital cytogenetic abnormalities".)

OVERVIEW OF GENOMIC DISORDERS — Genomic disorders are diseases that result from the loss or gain of chromosomal/DNA material. The most common and better delineated genomic disorders are divided in two main categories, those resulting from copy number losses (deletion syndromes) and copy number gains (duplication syndromes). (See "Genomic disorders: An overview".)

Copy number variations (CNVs) are submicroscopic genomic differences in the number of copies of one or more sections of DNA that result in DNA gains or losses (figure 1). Some CNVs are pathogenic and cause syndromic disorders with consistent phenotypic features, as are discussed here. Other CNVs are associated with disease susceptibility or resistance and the same CNVs can be associated with several diverse disorders. Still other CNVs are part of normal genetic variation and have no recognized disease association. Contiguous gene syndromes can occur when CNVs affect several adjacent genes. (See "Overview of genetic variation", section on 'Copy number variations (CNVs)' and "Basic principles of genetic disease", section on 'Copy number variation'.)

The main mechanism that leads to disease in genomic disorders secondary to deletions and duplications is a change in the copy number of a dose-sensitive gene or genes. Other disease mechanisms include interference with imprinted genes and with regulatory elements outside genes. (See "Genomic disorders: An overview", section on 'Disease mechanisms'.)

Genomic disorders are typically detected by array comparative genomic hybridization (CGH) (figure 2). Most laboratories confirm gains or losses detected on an array with an independent method, such as fluorescent in situ hybridization (FISH), multiple ligation-dependent probe amplification (MLPA), or quantitative polymerase chain reaction (Q-PCR). (See "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Array comparative genomic hybridization' and "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Fluorescence in situ hybridization'.)

1p36 DELETION SYNDROME — This syndrome (MIM #607872), caused by a deletion with variable

breakpoints at the distal tip of the short arm of chromosome 1, is one of the most common deletion syndromes. It is characterized by moderate to severe intellectual disabilities and craniofacial dysmorphisms, including microcephaly, brachycephaly, large and persistently open anterior fontanelle, deep-set eyes, straight eyebrows, posteriorly-rotated and low-set ears, midface hypoplasia, flat nasal bridge, and pointy chin [1-7]. Orofacial clefting can be seen in this deletion. In addition, these patients have hypotonia, congenital heart disease (some may develop noncompaction cardiomyopathy), renal anomalies, ophthalmologic abnormalities, skeletal anomalies, hearing loss, feeding difficulties, and hypothyroidism. Fifty percent develop seizures. Brain abnormalities are prevalent.

Screening and monitoring studies include electroencephalogram (EEG) to check for seizures if suspected or as a baseline around one year of age, renal ultrasound upon diagnosis to evaluate for structural anomalies, annual thyroid function tests, echocardiogram (ECG) upon diagnosis and subsequently every two to three years, swallowing evaluations, and auditory brainstem response (ABR) hearing screening. Therapies essential to help with muscle tone and delays include physical, occupational, and speech therapies. Noncompaction cardiomyopathies respond well to conservative treatment [1].

1q21.1 DELETION SYNDROME — This 1.35 megabases (Mb) deletion is recurrent in size due to flanking segments that mediate these rearrangements. It is associated with microcephaly, intellectual disabilities (speech delay, learning disabilities), and mild dysmorphic facial features (MIM #612474) [8-10]. However, the presentation is variable given incomplete penetrance and variable expressivity, and the microdeletion is seen in unaffected carriers. Other findings can include more severe intellectual disabilities, seizures, cardiac abnormalities, and cataracts. Autism, attention deficit hyperactivity disorder (ADHD), schizophrenia, and other psychiatric abnormalities have been reported.

HYDIN is the key gene implicated in this disorder, since homozygous mutations in the paralog mouse gene cause hydrocephalus. *GJA5* and *GJA8* are the hypothesized genes responsible for the heart phenotype.

Patients may require physical, occupational, and/or speech therapy.

DISTAL 1q21 DELETION SYNDROME (THROMBOCYTOPENIA-ABSENT RADIUS SYNDROME) — Thrombocytopenia-absent radius syndrome (TAR syndrome, MIM #274000) is characterized by hypomegakaryocytic thrombocytopenia and bilateral absent radii in the presence of thumbs [11]. The thrombocytopenia improves with age and normally disappears by school age. Other skeletal abnormalities, as well as heart and genitourinary anomalies, may occur. Non IgE-mediated cow milk's allergy with gastrointestinal symptoms is observed in some of these children and may exacerbate thrombocytopenia [12]. (See "Causes of neonatal thrombocytopenia", section on 'Thrombocytopenia-absent radius syndrome'.)

The etiology and inheritance is complex, although the syndrome is associated with a 1q21.1 deletion [13,14]. This deletion extends approximately 200 kilobases (kb) containing 11 genes and is adjacent but distal (telomeric) to the deletion previously described on 1q21. The gene for RNA-binding motif protein 8A (*RBM8A*) encodes the Y14 subunit of exon-junction complex that carries out crucial RNA processing tasks. *RBM8A* is located on 1q21.1 within the minimal deleted region in 1q21.1. Patients with TAR syndrome have been identified to have changes in this gene in addition to the 1q21.1 deletion [15]. This second change consists of a low-frequency single nucleotide polymorphism (SNP) in the 5' untranslated region (5'UTR) of *RBM8A* or a novel SNP in the first intron of the same gene. These changes were found in 53 of 55 cases of patients with TAR syndrome in one series, with 51 also having the 1q21.1 deletion. This SNP appears to have regulatory properties and ultimately leads to a hypomorphic allele.

Screening and monitoring studies include an echocardiogram (ECG) to evaluate for congenital heart disease and close monitoring of platelet counts, particularly in the first weeks to months of life.

2p15-16.1 DELETION SYNDROME — Deletions of this region extend between 4 to 6 megabases (Mb). Clinical features include severe intellectual disability, autism/autistic features, microcephaly, cortical dysplasia/pachygyria on brain magnetic resonance imaging (MRI), renal abnormalities (multicystic kidneys, hydronephrosis), and camptodactyly [16,17]. Craniofacial features are characteristic and include progressive microcephaly, flat occiput, small palpebral fissures, telecanthus, broad and high nasal root, long philtrum, rounded upper vermillion border, and everted lower lips. Two genes have been identified in the area as candidates for the autism component: exportin 1 (*XPO1*) and orthodenticle homolog 1 (*OTX1*).

Screening for these patients includes a neurodevelopmental and autism evaluation, brain imaging studies, and a renal ultrasound.

2q23.1 DELETION SYNDROME — Deletions of 2q23.1 have been seen in association with severe intellectual disability, seizures, autism spectrum disorder, short stature, and microcephaly [18,19]. The severity of the seizures and the phenotype often leads to initial diagnoses of Rett, Angelman, or Smith-Magenis syndrome. *MBD5*, a gene involved in the deleted region, belongs to the methyl CpG-binding protein domain family that also includes the *MECP2* gene mutated in Rett syndrome. *MBD5* has also been implicated in autism. Other clinical findings include coarse facial features, abnormal sleep patterns, and behavioral problems.

Screening for these patients include neurodevelopmental and autism evaluations, neurology evaluations with brain imaging studies, and electroencephalograms (EEGs). Treatment includes management of seizures and specific therapies for autism. (See "Overview of the treatment of seizures and epileptic syndromes in children" and "Autism spectrum disorder in children and adolescents: Overview of management".)

2q37 DELETION SYNDROME — This deletion (MIM #600430) is often referred to as Albright hereditary osteodystrophy-like syndrome. This is due to the fact that patients with distal 2q deletions present with mild to moderate intellectual disabilities, hypotonia, obesity, short stature, and brachydactyly with short phalanges (especially the third to fifth phalanges [brachydactyly type E]), as seen in patients with Albright syndrome [20]. Dysmorphic features include thin, highly-arched eyebrows, prominent forehead, depressed nasal bridge, full cheeks, hypoplastic alae nasi, prominent nasal septum, thin upper lip, and ear anomalies [21,22]. Autism is commonly reported in this deletion. Less common features include congenital heart disease (septal defects, aortic coarctation), gastrointestinal anomalies (pyloric stenosis, duodenal atresia), and central nervous system (CNS) anomalies.

The main candidate gene for the brachymetaphalangism seen in this deletion syndrome is histone deacetylase 4 *(HDAC4)*. Mice with deletions of the homologous gene Hdac4(-/-) have severe bone malformations resulting from premature ossification of developing bones [23,24]. The obesity and intellectual disabilities may involve glypican 1 (*GPC1*), G protein-coupled receptor 35 (*GPR35*), and serine/threonine protein kinase 25 (*STK25*). The proposed genes for autism are gamma-2 centaurin (*CENTG2*) and serotonin receptor 2B (*HTR2B*). Mutations in the C-natriuretic peptide gene (*NPPC*) that maps to the region are a possible cause of the skeletal dysplasia seen in these patients [25].

Screening studies include neurodevelopmental and autism evaluations, skeletal survey, endocrine evaluation, and an echocardiogram (ECG). Patients usually require physical, occupational, and speech therapy.

3p DELETION SYNDROME — Deletion of the distal short arm of chromosome 3 (MIM #613792) is characterized by low birth weight, growth deficiency, intellectual disability, microcephaly, ptosis, telecanthus, downslanting palpebral fissures, micrognathia, postaxial polydactyly, and renal anomalies [26-28]. Congenital heart defects (typically atrioventricular [AV] canal) occur in one-third of patients. Sensorineural hearing loss is frequently reported. The critical region for the deletion is located at 3p25 to

3p26. The deletion develops de novo in almost all cases. Haploinsufficiency of *CNTN4* (contactin 4), a brain expressed gene, may play a key role in these patients' intellectual disability and autistic characteristics [29,30].

Screening of these patients includes echocardiogram (ECG) at the time of diagnosis, renal ultrasound, and hearing, neurodevelopmental, and autism evaluations.

3q29 DELETION SYNDROME — Patients with this recurrent deletion (MIM #609425) have variable clinical findings despite the fact that the size of the deletion is almost identical (approximately 1.5 to 1.6 megabases [Mb]) [31,32]. The deletion encompasses 22 genes, although *PAK2* (p21 protein-activated kinase 2) and *DLG1* (discs large, drosophila, homolog of, 1) are candidates for the critical genes responsible for the phenotype. These genes are homologues of known X-linked genes associated with intellectual disabilities. The clinical features include mild to moderate intellectual disability, microcephaly (50 percent of cases), and mild dysmorphisms including a narrow face, large ears, short philtrum, and a high nasal bridge. Patients with this deletion may have autism and ataxia. A higher prevalence of psychiatric disorders, such as bipolar disorder, depression, and schizophrenia, are seen in these patients [33-38]. Less frequent features include chest wall deformities, cleft lip/palate, long tapered fingers, ligamentous joint laity, horseshoe kidneys, and hypospadias.

Screening studies include brain imaging studies, renal ultrasound, and neurodevelopmental and autism evaluations. Patients may require physical, occupational, and/or speech therapy.

4p DELETION SYNDROME (WOLF-HIRSCHHORN SYNDROME) — This syndrome (MIM #194190) is due to partial deletion of the short arm of chromosome 4 at 4p16.3. The deletion occurs de novo in approximately 87 percent of cases (about 80 percent involve the paternal chromosome), and in the remainder of the cases is due to a balanced translocation in one of the parents (most involve the maternal chromosome) [39-41]. The critical region for this syndrome has been narrowed to an approximately 200 kilobase (kb) region that includes the *WHSCR1* and *WHSCR2* genes [42]. Wolf-Hirschhorn syndrome candidate 1 (*WHSC1*) gene is deleted in all known cases of WHS. This gene encodes an H3K36me3-specific histone methyltransferase (HMTase) that plays a role in transcriptional regulation. One of the factors that WHSC1 modulates is Nkx2-5, a central transcriptional regulator of cardiac development. The interaction of WHSC1 with multiple different transcription factors may account for the variability in clinical phenotype [43]. In addition, haploinsufficiency of the leucine zipper/EF hand-containing transmembrane protein gene (*LETM1*), which is also located in the critical region, is implicated in the seizures, motor delay, and growth restriction seen in patients with WHS [44,45]. This gene encodes a mitochondrial inner membrane protein involved in ion transport. Some patients have larger deletions that can be visually identified in karyotypes, while others have microdeletions. There is some correlation between deletion size and clinical severity [46].

The common clinical manifestations include pre- and postnatal growth restriction, microcephaly, congenital heart disease (atrial septal defect [ASD], ventricular septal defect [VSD], pulmonic stenosis [PS]), distinctive facial features with a "Greek warrior helmet" appearance of the nose due to high forehead, prominence of the glabella, hypertelorism, high and arched eyebrows, epicanthal folds, and downturned corners of the mouth. All of these patients have significant intellectual disabilities.

Patients have frequent episodes of respiratory infections, due in part to recurrent aspiration. Antibody deficiencies are also common. In one series of 190 patients with WHS, immune defects occurred in about 4 percent of patients and included common variable immunodeficiency, immunoglobulin A (IgA) and immunoglobulin G2 (IgG2) subclass deficiency, and impaired polysaccharide responsiveness [47]. T cell immunity is normal. Immunodeficiency does not appear to correlate with deletion size. (See "Syndromic immunodeficiencies", section on 'Partial deletions of chromosome 4p (Wolf-Hirschhorn syndrome)'.)

Screening studies include neurodevelopmental evaluation and appropriate interventions. Feeding difficulties are common, therefore swallow studies are warranted. In some instances, the placement of a gastrostomy tube may be required [48]. Cardiac evaluations should be done by echocardiography. Screening of immunoglobulin subclasses in serum is recommended to assess for humoral deficiency.

5q35 DELETION SYNDROME (SOTOS SYNDROME) — Sotos syndrome (MIM #117550), also known as cerebral gigantism, is caused by haploinsufficiency of the *NSD1* gene located at 5q35 [49]. NSD1 is a histone methyltransferase that is involved in histone modification and chromatin remodeling. Deletions in the chromosomal region containing *NSD1* are the most common cause of Sotos syndrome in the Japanese population [50], whereas point mutations of the *NSD1* gene are the most common cause in Caucasian populations [51]. There is some overlap between this condition and Weaver syndrome that is associated with mutations in *EZH2*, a gene that plays a role in methylation of H3 histones [52]. Patients with Weaver syndrome have overgrowth and camptodactyly.

Clinically, Sotos syndrome is characterized by overgrowth that is evident at birth with an increase in head circumference [53-55]. Hypotonia and delayed gross and fine motor milestones are typical. Often times, these children are considered "clumsy." They have mild intellectual disabilities. Patients with Sotos syndrome have characteristic facial features, with a bossed forehead, receding hairline, hypertelorism, downslanting palpebral fissures, large ears, high-arched palate, and pointy chin. Premature teeth eruption is commonly seen. Skeletal features include scoliosis and large hands and feet. Advanced bone age is commonly seen. Brain imaging may show dilated ventricles, increased extra-axial cerebrospinal fluid (CSF), cortical atrophy spaces, and abnormalities of the corpus callosum. Cardiac anomalies, including patent ductus arteriosus (PDA) and atrial septal defect (ASD), are frequent in patients with 5q35 deletion. Renal anomalies may include hypoplastic kidneys and hydronephrosis. (See "The child with tall stature and/or abnormally rapid growth", section on 'Cerebral gigantism'.)

The *NKX2.5* gene is also located in this deletion region. This gene is associated with congenital heart disease and atrioventricular (AV) conduction defects.

Array comparative genomic hybridization (CGH) is the first line of testing if the diagnosis is suspected, followed by mutation studies if negative. Screening and monitoring studies include brain imaging, renal ultrasound, echocardiogram (ECG), and bone age. Therapy is supportive and includes referral to physical and occupational therapy.

6p25 DELETION SYNDROME — Microdeletion of distal 6p (MIM #612582) is associated with a distinctive clinical phenotype including eye abnormalities (anterior chamber dysgenesis), hearing loss, congenital heart disease, dental anomalies, developmental delay, and a characteristic facial appearance [56-58].

The facial features include a prominent forehead with turricephalic appearance, midface hypoplasia, downslanting palpebral fissures, hypertelorism, epicanthal folds, ptosis, proptosis, ear anomalies, flat nasal bridge, short and/or smooth philtrum, and high palate [59]. Central nervous system (CNS) malformations are common, including hydrocephalus (ventriculomegaly), hypoplasia of the cerebellum (Dandy-Walker malformation), and brainstem and corpus callosum anomalies. Mild to moderate developmental delay is part of the syndrome. Other white matter abnormalities have been seen as part of this deletion [60]. Lastly, heart defects (ventricular septal defect [VSD]/atrial septal defect [ASD], patent foramen ovale [PFO], and patent ductus arteriosus [PDA]) have been reported.

The eye malformations seen are known as the Axenfeld–Rieger malformation and include corneal opacities, iris coloboma, and hypoplasia of the iris with adherent iris strands to the peripheral cornea. The patient is considered to have Rieger anomaly if the iris demonstrates stromal hypoplasia, the pupils are distorted, or there are extra holes in the iris [61]. The iris is normal in patients who only have the Axenfeld anomaly.

Posterior embryotoxon is a term used to describe a prominent and anteriorly-displaced Schwalbe line (the anatomic line demarcating the outer limit of the corneal endothelium layer) that is seen in patients with the Axenfeld-Rieger malformation. Half of the patients with posterior embryotoxon will go on to develop glaucoma. Mutations in the human homologue of FoxC1 (mice), known as the forkhead transcription factor gene, *FKHL7,* cause an autosomal dominant form of glaucoma and are probably responsible for the glaucoma phenotype seen in this deletion syndrome [62,63]. *FOXC1*, *FOXF2,* and *FOXQ1,* which are part of the forkhead family of genes, are involved in the deletion and also appear to play a significant role in this disorder.

Careful ophthalmologic evaluations are needed, especially for patients with posterior embryotoxon given their increased risk for glaucoma. Other screening and monitoring studies include an echocardiogram (ECG), brain imaging studies, audiology evaluations including auditory brainstem response (ABR) testing and neurodevelopmental evaluation. Patients typically benefit from physical, occupational, and speech therapy.

7q11.23 DELETION SYNDROME (WILLIAMS SYNDROME) — This syndrome, also known as Williams-Beuren syndrome (WBS, MIM #194050), results from a heterozygous deletion of approximately 1.6 megabases (Mb) at 7q11.23 [64,65]. The deletion includes the elastin gene *ELN* [66]. Cardiovascular abnormalities are frequent and are related to elastin haploinsufficiency. These abnormalities include supravalvular aortic stenosis (in 70 percent of cases), pulmonic valve stenosis, and renal artery stenosis. Renal abnormalities are also seen. (See "Williams-Beuren syndrome".)

Other clinical features include constipation, which is often significant and is associated with an increased risk for diverticulosis and diverticulitis, failure to thrive, and sensorineural or conductive hearing loss [64,65,67,68]. Classical facial features include periorbital fullness of subcutaneous tissues, hypertelorism, stellate pattern of the iris, long philtrum, thick vermillion border of the lips, wide mouth, and small jaw (often referred to as elfin facies) [64,65]. Idiopathic hypercalcemia is observed and is frequently transient.

Mild to moderate intellectual disability is common, with uneven cognitive disabilities. Verbal and memory performance is less impaired than visual-spatial perception [69]. Young patients with WBS tend to be very social, gregarious, and often overly friendly with strangers. Haploinsufficiency of the *GTF2I* gene appears to lead to the increased social interactions seen in patients with WBS [70]. Behavioral abnormalities include anxiety and attention deficit disorder [71].

Screening of these patients should include echocardiography, renal ultrasound with special attention to the renal artery, serum calcium, neurodevelopmental evaluations, and audiology evaluations including auditory brainstem response (ABR) testing.

8q22.1 DELETION SYNDROME (NABLUS MASK-LIKE FACIAL SYNDROME) — Deletions in the 8q21.3-q22.1 region that include a 2.79 megabase (Mb) region at 8q22.1 are associated with the Nablus mask-like facial syndrome (MIM #608156) [72,73]. This rare condition has a striking phenotype that is characterized by severe blepharophimosis (bilateral ptosis with reduced lid size); glistening, tight-appearing facial skin; sparse and unruly hair; a flat and broad nose; and ears that are small and triangular in shape with prominent antihelices and unfolded helices [74]. Other anomalies include acquired microcephaly and submucous cleft palate. Hand anomalies include contractures and interdigital webbing. Developmental delay is also reported.

A smaller deletion (1.6 Mb) in the 8q22.1 region was associated with speech delay and autism spectrum disorder, but not the other features noted with the larger deletion [75].

Patients will need ophthalmologic and plastic surgery evaluations for the surgical correction of blepharophimosis. In addition, patients with speech and/or swallowing abnormalities should be evaluated for submucous cleft palate. Developmental evaluations and referral for physical, occupational, and/or

speech therapy may also be required.

8q24.11 DELETION SYNDROME (LANGER-GIEDION SYNDROME OR TRICHORHINOPHALANGEAL SYNDROME TYPE II) — Patients with this syndrome (MIM #105230) present with multiple dysmorphic facial features including large, laterally protruding ears, a bulbous nose, and an elongated upper lip [76-79]. Additional clinical features include sparse scalp hair, winged scapulae, multiple cartilaginous exostoses, redundant skin, and intellectual disabilities. Skeletal findings also include cone epiphyses that are easily detected by hand radiographs. Tibial hemimelia has also been reported [80].

The 8q24.11 deletion involves *EXT1* (multiple exostoses type I gene, MIM #133700), the gene responsible for the exostoses.

Trichorhinophalangeal syndrome type I (TRPS type I) is an autosomal dominant disorder with similar findings to TRPS type II, including the facial and skeletal findings (cone epiphyses) [81]. However, patients with type I do not have intellectual disabilities or exostoses. TRPS type I is caused by mutations in *TRPS1* gene located in the 8q24.1 region. Therefore, haploinsufficiency of TRPS is directly related to most of the clinical features seen in this disorder.

Skeletal surveys are performed to assess for exostoses and bone deformities. Patients may require developmental evaluations and referral to physical, occupational, and/or speech therapy.

9p22 DELETION SYNDROME — The clinical manifestations of this syndrome consist of intellectual disability, trigonocephaly, midface hypoplasia, upward-slanting palpebral fissures, short nose with depressed nasal bridge, long philtrum, and micrognathia [82-84].

Most of these cases are due to a de novo deletion of the distal portion of the short arm of chromosome 9 [82,84]. The deletion occurs with similar frequency among chromosomes of paternal and maternal origin. Therefore, genomic imprinting does not seem to play a role [84]. The critical region for the 9p deletion syndrome maps to a 4 to 6 megabase (Mb) region in 9p22-9p23.

Screening for these patients should include neurodevelopmental evaluations, echocardiogram (ECG) to assess structural heart defects, and referral to a craniofacial surgeon to address trigonocephaly when present [85].

9q34.3 DELETION SYNDROME OR 9q SUBTELOMERE DELETION SYNDROME — This syndrome, also called Kleefstra syndrome (MIM #610253), is characterized by moderate to severe intellectual disability, microcephaly and/or brachycephaly, hypertelorism, synophrys (joined eyebrows) and/or arched eyebrows, midface hypoplasia, a short nose with upturned nares, a protruding tongue with everted lower lip, and downturned corners of the mouth [86,87].

Patients with this deletion often have congenital heart defects (primarily atrial septal defect [ASD] or ventricular septal defect [VSD], tetralogy of Fallot, aortic coarctation, bicuspid aortic valve, and pulmonic stenosis). About half of patients have seizures (tonic-clonic, absence, complex partial seizures, and generalized seizure with focal onset). Behavioral abnormalities include maladaptive behaviors (aggression, hyperactivity, self mutilation) and autistic spectrum features [88]. Sleep disturbances are reported and can be severe. Other features include major and minor eye, ear, genital, and limb anomalies [89].

The 9q34.3 deletion syndrome is caused by haploinsufficiency of the *EHMT1* gene [90]. The product of this gene is a histone H3 Lys 9 (H3-K9) methyltransferase involved in histone methylation. Most patients with Kleefstra syndrome have this microdeletion, but some have mutations of the *EHMT1* gene [91]. The loss of other genes in the same region may cause additional clinical manifestations. The deletion of the distal long arm of chromosome 9 can be detected with subtelomeric fluorescent in situ hybridization (FISH) or array comparative genomic hybridization (CGH).

Screening studies include developmental/autism evaluations, ophthalmologic evaluations, echocardiogram (ECG), and electroencephalogram (EEG). Patients require physical, occupational, and/or speech therapy.

10p14-p13 DELETION (DiGEORGE SYNDROME TYPE II) — A second locus for DiGeorge syndrome was recognized in patients with 10p deletions that presented with conotruncal heart defects, hypoparathyroidism, and T cell immunodeficiency (MIM #146255) [92-96]. These patients also have sensorineural hearing loss, which is not typically present in patients with DiGeorge syndrome type I (22q11.2 deletion). *GATA3*, the critical gene for this disorder, is essential for development of the parathyroid gland, auditory system, and kidneys [97]. (See "DiGeorge syndrome: Epidemiology and pathogenesis", section on 'Other defects'.)

Patients with this deletion should have hearing evaluations and renal ultrasound, in addition to the usual screening studies in patients with DiGeorge syndrome. (See "DiGeorge syndrome: Management and prognosis".)

11p13 DELETION SYNDROME (WAGR SYNDROME) — WAGR is an acronym that defines a group of abnormalities that include **W**ilms tumor, **A**niridia, **G**enitourinary anomalies, and mental **R**etardation (MIM #194072). Ophthalmologic findings include aniridia, cataracts, glaucoma, and nystagmus. The most common abnormalities of the genitourinary tract are cryptorchidism in males and streak ovaries and bicornuate uterus in females. Ambiguous genitalia have been reported in males and females. WAGR syndrome and Wilms tumor are reviewed in greater detail separately. (See "Presentation, diagnosis, and staging of Wilms tumor", section on 'WAGR syndrome'.)

WAGR syndrome is a contiguous gene deletion syndrome. Deletions of *WT1* are responsible for Wilms tumor, while *PAX6* deletions are responsible for aniridia. *PAX6* and *WT1* are proximally located within 11p13. There is a different entity known as Denys-Drash syndrome (renal nephropathy, gonadal anomaly, predisposition to Wilms tumor) that is associated with *WT1* mutations. In addition, there are reports of larger deletions combining WAGR and Potocki-Shaffer syndrome [98].

Patients with WAGR require aggressive renal surveillance, with renal ultrasounds every three months. The risk for Wilms tumor in patients with WT1 deletions is up to 50 percent and up to 40 percent of survivors with Wilms tumors will progress to end-stage renal disease (ESRD) [99].

11p11.2 DELETION SYNDROME (POTOCKI-SHAFFER SYNDROME) — This is a contiguous gene deletion syndrome characterized by the presence of parietal foramina, abnormal craniofacial features, moderate to severe developmental delay, and exostoses (MIM #601224) [98,100,101]. The parietal foramina appear related to deletions in *ALX4* and the exostoses are secondary to deletions of *EXT2* (exostosis type II) gene [102,103]. Studies of translocations in this region suggest that the intellectual disability and craniofacial anomalies seen in this syndrome are due to haploinsufficiency of *PHF21A*, a protein involved in histone methylation that mediates repression of neuron-specific genes [104].

Screening studies include a skeletal survey, magnetic resonance imaging (MRI) of the brain, renal ultrasound, and laboratory studies including a complete blood count, comprehensive metabolic panel, thyroid studies, and urinalysis [105].

11q24.1 DELETION SYNDROME (JACOBSEN SYNDROME) — Distal deletions of the long arm of chromosome 11 are associated with a condition known as Jacobsen syndrome (MIM #147791). More than 90 percent of these patients have Paris-Trousseau syndrome characterized by thrombocytopenia and platelet dysfunction that typically normalizes over time [106,107]. More than half have serious congenital heart defects, including hypoplastic left heart syndrome, coarctation of the aorta, type B truncus arteriosus, and double outlet right ventricle. Recurrent infections of the upper respiratory system are common. Short stature and insulin-like growth factor 1 (IGF-1) deficiency are also frequently seen. (See "Hypoplastic left heart syndrome".)

These patients have dysmorphic craniofacial features, including hypertelorism, downslanting palpebral fissures, ptosis, sparse eyebrows, broad nasal bridge with short nose and anteverted nares, thin upper lip, V-shaped mouth, and high-arched palate. Other abnormalities include structural renal defects (duplicated ureters, single kidney, and hydronephrosis), genitourinary anomalies (undescended testes, hypospadias), and gastrointestinal anomalies (pyloric stenosis, constipation). Limb anomalies include syndactyly of hands and feet, fifth digit clinodactyly, and toe anomalies.

Cognitive function ranges from normal intelligence to moderate intellectual disability. Nearly half of the patients have mild mental retardation with a characteristic neuropsychiatric profile demonstrating near normal receptive language ability, but mild to moderate impairment in expressive language.

This syndrome can sometimes be diagnosed with conventional cytogenetic studies. Use of array comparative genomic hybridization (CGH) has redefined the phenotype and narrowed the critical region. Deletion of at least three out of the four platelet function critical genes that reside in the area, *ETS-1, FLI-1, NFRKB*, and *JAM3*, are apparently needed to develop thrombocytopenia, and deletions of *KCNJ1* and *ADAMTS15* may contribute to the renal anomalies [108]. The heart genes are not yet identified.

Screening studies include an echocardiogram (ECG), renal ultrasound, neurodevelopmental evaluations, and monitoring of platelet and coagulation function.

SUMMARY

- Microdeletions, or submicroscopic deletions, are chromosomal deletions that are too small to be detected by light microscopy using conventional cytogenetics methods. (See 'Introduction' above.)
- Genomic disorders are diseases that result from the loss or gain of chromosomal/DNA material. The most common and better delineated genomic disorders are divided in two main categories, those resulting from copy number losses (deletion syndromes) and copy number gains (duplication syndromes). (See 'Overview of genomic disorders' above.)
- 1p36 deletion syndrome (MIM #607872) is one of the most common microdeletion syndromes. It is characterized by moderate to severe intellectual disabilities and craniofacial dysmorphisms. In addition, these patients have hypotonia, congenital heart disease, renal and skeletal anomalies, ophthalmologic abnormalities, hearing loss, feeding difficulties, and hypothyroidism. Brain abnormalities and seizures may also occur. (See '1p36 deletion syndrome' above.)
- 4p deletion syndrome (Wolf-Hirschhorn syndrome, MIM #194190) is characterized by pre- and postnatal growth restriction, microcephaly, congenital heart disease, significant intellectual disabilities, and distinctive facial features with a "Greek warrior helmet" appearance. (See '4p deletion syndrome (Wolf-Hirschhorn syndrome)' above.)
- The common clinical features of 7q11.23 deletion syndrome (Williams or Williams-Beuren syndrome, MIM #194050) include cardiovascular and renal abnormalities, failure to thrive, sensorineural hearing loss, constipation, and classical facial features often referred to as "elfin facies." (See '7q11.23 deletion syndrome (Williams syndrome)' above.)

REFERENCES

1. Battaglia A, Hoyme HE, Dallapiccola B, et al. Further delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics 2008; 121:404.

2. Gajecka M, Mackay KL, Shaffer LG. Monosomy 1p36 deletion syndrome. Am J Med Genet C Semin Med Genet 2007; 145C:346.
3. Heilstedt HA, Ballif BC, Howard LA, et al. Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. Am J Hum Genet 2003; 72:1200.
4. Shapira SK, McCaskill C, Northrup H, et al. Chromosome 1p36 deletions: the clinical phenotype and molecular characterization of a common newly delineated syndrome. Am J Hum Genet 1997; 61:642.
5. GeneReviews: 1p36 Deletion Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK1191/.
6. Genetics Home Reference: 1p36 deletion syndrome. http://ghr.nlm.nih.gov/condition/1p36-deletion-syndrome (Accessed on December 21, 2011).
7. Buck A, du Souich C, Boerkoel CF. Minimal genotype--phenotype correlation for small deletions within distal 1p36. Am J Med Genet A 2011; 155A:3164.
8. Brunetti-Pierri N, Berg JS, Scaglia F, et al. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet 2008; 40:1466.
9. Mefford HC, Sharp AJ, Baker C, et al. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. N Engl J Med 2008; 359:1685.
10. GeneReviews: 1q21.1 Microdeletion. http://www.ncbi.nlm.nih.gov/books/NBK52787/ (Accessed on December 29, 2011).
11. GeneReviews: Thrombocytopenia Absent Radius syndrome http://www.ncbi.nlm.nih.gov/books/NBK23758/ (Accessed on December 29, 2011).
12. Gounder DS, Pullon HW, Ockelford PA, Nicol RO. Clinical manifestations of the thrombocytopenia and absent radii (TAR) syndrome. Aust N Z J Med 1989; 19:479.
13. Klopocki E, Schulze H, Strauss G, et al. Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. Am J Hum Genet 2007; 80:232.
14. Ward RE, Bixler D, Provisor AJ, Bader P. Parent to child transmission of the thrombocytopenia absent radius (TAR) syndrome. Am J Med Genet Suppl 1986; 2:207.
15. Albers CA, Paul DS, Schulze H, et al. Compound inheritance of a low-frequency regulatory SNP and a rare null mutation in exon-junction complex subunit RBM8A causes TAR syndrome. Nat Genet 2012; 44:435.
16. Rajcan-Separovic E, Harvard C, Liu X, et al. Clinical and molecular cytogenetic characterisation of a newly recognised microdeletion syndrome involving 2p15-16.1. J Med Genet 2007; 44:269.
17. Liu X, Malenfant P, Reesor C, et al. 2p15-p16.1 microdeletion syndrome: molecular characterization and association of the OTX1 and XPO1 genes with autism spectrum disorders. Eur J Hum Genet 2011; 19:1264.
18. van Bon BW, Koolen DA, Brueton L, et al. The 2q23.1 microdeletion syndrome: clinical and behavioural phenotype. Eur J Hum Genet 2010; 18:163.
19. Talkowski ME, Mullegama SV, Rosenfeld JA, et al. Assessment of 2q23.1 microdeletion syndrome implicates MBD5 as a single causal locus of intellectual disability, epilepsy, and autism spectrum disorder. Am J Hum Genet 2011; 89:551.
20. GeneReviews: 2q37 Deletion Syndrome http://www.ncbi.nlm.nih.gov/books/NBK1158/ (Accessed on December 31, 2011).
21. Falk RE, Casas KA. Chromosome 2q37 deletion: clinical and molecular aspects. Am J Med Genet C Semin Med Genet 2007; 145C:357.
22. Galasso C, Lo-Castro A, Lalli C, et al. Deletion 2q37: an identifiable clinical syndrome with mental

retardation and autism. J Child Neurol 2008; 23:802.

23. Shrimpton AE, Braddock BR, Thomson LL, et al. Molecular delineation of deletions on 2q37.3 in three cases with an Albright hereditary osteodystrophy-like phenotype. Clin Genet 2004; 66:537.
24. Williams SR, Aldred MA, Der Kaloustian VM, et al. Haploinsufficiency of HDAC4 causes brachydactyly mental retardation syndrome, with brachydactyly type E, developmental delays, and behavioral problems. Am J Hum Genet 2010; 87:219.
25. Tassano E, Buttgereit J, Bader M, et al. Genotype-Phenotype Correlation of 2q37 Deletions Including NPPC Gene Associated with Skeletal Malformations. PLoS One 2013; 8:e66048.
26. Tazelaar J, Roberson J, Van Dyke DL, et al. Mother and son with deletion of 3p25-pter. Am J Med Genet 1991; 39:130.
27. Nienhaus H, Mau U, Zang KD. Infant with del(3) (p25-pter): karyotype-phenotype correlation and review of previously reported cases. Am J Med Genet 1992; 44:573.
28. Drumheller T, McGillivray BC, Behrner D, et al. Precise localisation of 3p25 breakpoints in four patients with the 3p-syndrome. J Med Genet 1996; 33:842.
29. Shuib S, McMullan D, Rattenberry E, et al. Microarray based analysis of 3p25-p26 deletions (3p-syndrome). Am J Med Genet A 2009; 149A:2099.
30. Fernandez TV, García-González IJ, Mason CE, et al. Molecular characterization of a patient with 3p deletion syndrome and a review of the literature. Am J Med Genet A 2008; 146A:2746.
31. Ballif BC, Theisen A, Coppinger J, et al. Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. Mol Cytogenet 2008; 1:8.
32. Willatt L, Cox J, Barber J, et al. 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome. Am J Hum Genet 2005; 77:154.
33. Levinson DF, Duan J, Oh S, et al. Copy number variants in schizophrenia: confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. Am J Psychiatry 2011; 168:302.
34. Città S, Buono S, Greco D, et al. 3q29 microdeletion syndrome: Cognitive and behavioral phenotype in four patients. Am J Med Genet A 2013; 161A:3018.
35. Sagar A, Bishop JR, Tessman DC, et al. Co-occurrence of autism, childhood psychosis, and intellectual disability associated with a de novo 3q29 microdeletion. Am J Med Genet A 2013; 161A:845.
36. Stewart LR, Hall AL, Kang SH, et al. High frequency of known copy number abnormalities and maternal duplication 15q11-q13 in patients with combined schizophrenia and epilepsy. BMC Med Genet 2011; 12:154.
37. Quintero-Rivera F, Sharifi-Hannauer P, Martinez-Agosto JA. Autistic and psychiatric findings associated with the 3q29 microdeletion syndrome: case report and review. Am J Med Genet A 2010; 152A:2459.
38. Clayton-Smith J, Giblin C, Smith RA, et al. Familial 3q29 microdeletion syndrome providing further evidence of involvement of the 3q29 region in bipolar disorder. Clin Dysmorphol 2010; 19:128.
39. Estabrooks LL, Rao KW, Driscoll DA, et al. Preliminary phenotypic map of chromosome 4p16 based on 4p deletions. Am J Med Genet 1995; 57:581.
40. Wright TJ, Ricke DO, Denison K, et al. A transcript map of the newly defined 165 kb Wolf-Hirschhorn syndrome critical region. Hum Mol Genet 1997; 6:317.
41. Dallapiccola B, Mandich P, Bellone E, et al. Parental origin of chromosome 4p deletion in Wolf-Hirschhorn syndrome. Am J Med Genet 1993; 47:921.
42. Battaglia A, Filippi T, Carey JC. Update on the clinical features and natural history of

Wolf-Hirschhorn (4p-) syndrome: experience with 87 patients and recommendations for routine health supervision. Am J Med Genet C Semin Med Genet 2008; 148C:246.

43. Nimura K, Ura K, Shiratori H, et al. A histone H3 lysine 36 trimethyltransferase links Nkx2-5 to Wolf-Hirschhorn syndrome. Nature 2009; 460:287.
44. Hart L, Rauch A, Carr AM, et al. LETM1 haploinsufficiency causes mitochondrial defects in cells from humans with Wolf-Hirschhorn syndrome: implications for dissecting the underlying pathomechanisms in this condition. Dis Model Mech 2014; 7:535.
45. Andersen EF, Carey JC, Earl DL, et al. Deletions involving genes WHSC1 and LETM1 may be necessary, but are not sufficient to cause Wolf-Hirschhorn Syndrome. Eur J Hum Genet 2014; 22:464.
46. Zollino M, Murdolo M, Marangi G, et al. On the nosology and pathogenesis of Wolf-Hirschhorn syndrome: genotype-phenotype correlation analysis of 80 patients and literature review. Am J Med Genet C Semin Med Genet 2008; 148C:257.
47. Hanley-Lopez J, Estabrooks LL, Stiehm R. Antibody deficiency in Wolf-Hirschhorn syndrome. J Pediatr 1998; 133:141.
48. Battaglia A, Carey JC, Cederholm P, et al. Natural history of Wolf-Hirschhorn syndrome: experience with 15 cases. Pediatrics 1999; 103:830.
49. Kurotaki N, Imaizumi K, Harada N, et al. Haploinsufficiency of NSD1 causes Sotos syndrome. Nat Genet 2002; 30:365.
50. Kurotaki N, Stankiewicz P, Wakui K, et al. Sotos syndrome common deletion is mediated by directly oriented subunits within inverted Sos-REP low-copy repeats. Hum Mol Genet 2005; 14:535.
51. Nagai T, Matsumoto N, Kurotaki N, et al. Sotos syndrome and haploinsufficiency of NSD1: clinical features of intragenic mutations and submicroscopic deletions. J Med Genet 2003; 40:285.
52. Tatton-Brown K, Rahman N. The NSD1 and EZH2 overgrowth genes, similarities and differences. Am J Med Genet C Semin Med Genet 2013; 163C:86.
53. Faravelli F. NSD1 mutations in Sotos syndrome. Am J Med Genet C Semin Med Genet 2005; 137C:24.
54. Genetics Home Reference: Sotos syndrome. http://ghr.nlm.nih.gov/condition/sotos-syndrome (Accessed on December 21, 2011).
55. GeneReviews: Sotos Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK1479/ (Accessed on December 21, 2011).
56. Le Caignec C, De Mas P, Vincent MC, et al. Subtelomeric 6p deletion: clinical, FISH, and array CGH characterization of two cases. Am J Med Genet A 2005; 132A:175.
57. Maclean K, Smith J, St Heaps L, et al. Axenfeld-Rieger malformation and distinctive facial features: Clues to a recognizable 6p25 microdeletion syndrome. Am J Med Genet A 2005; 132A:381.
58. Tonoki H, Harada N, Shimokawa O, et al. Axenfeld-Rieger anomaly and Axenfeld-Rieger syndrome: clinical, molecular-cytogenetic, and DNA array analyses of three patients with chromosomal defects at 6p25. Am J Med Genet A 2011; 155A:2925.
59. DeScipio C. The 6p subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet 2007; 145C:377.
60. van der Knaap MS, Kriek M, Overweg-Plandsoen WC, et al. Cerebral white matter abnormalities in 6p25 deletion syndrome. AJNR Am J Neuroradiol 2006; 27:586.
61. Alward WL. Axenfeld-Rieger syndrome in the age of molecular genetics. Am J Ophthalmol 2000; 130:107.
62. Nishimura DY, Swiderski RE, Alward WL, et al. The forkhead transcription factor gene FKHL7 is

responsible for glaucoma phenotypes which map to 6p25. Nat Genet 1998; 19:140.

63. Smith RS, Zabaleta A, Kume T, et al. Haploinsufficiency of the transcription factors FOXC1 and FOXC2 results in aberrant ocular development. Hum Mol Genet 2000; 9:1021.
64. Morris CA. Introduction: Williams syndrome. Am J Med Genet C Semin Med Genet 2010; 154C:203.
65. GeneReviews: Williams Syndrome. http://www.ncbi.nlm.nih.gov.ezp-prod1.hul.harvard.edu/books/NBK1249/ (Accessed on February 15, 2012).
66. Francke U. Williams-Beuren syndrome: genes and mechanisms. Hum Mol Genet 1999; 8:1947.
67. Marler JA, Sitcovsky JL, Mervis CB, et al. Auditory function and hearing loss in children and adults with Williams syndrome: cochlear impairment in individuals with otherwise normal hearing. Am J Med Genet C Semin Med Genet 2010; 154C:249.
68. Barozzi S, Soi D, Comiotto E, et al. Audiological findings in Williams syndrome: a study of 69 patients. Am J Med Genet A 2012; 158A:759.
69. Pober BR. Williams-Beuren syndrome. N Engl J Med 2010; 362:239.
70. Sakurai T, Dorr NP, Takahashi N, et al. Haploinsufficiency of Gtf2i, a gene deleted in Williams Syndrome, leads to increases in social interactions. Autism Res 2011; 4:28.
71. Mervis CB, John AE. Cognitive and behavioral characteristics of children with Williams syndrome: implications for intervention approaches. Am J Med Genet C Semin Med Genet 2010; 154C:229.
72. Teebi AS. Nablus mask-like facial syndrome. Am J Med Genet 2000; 95:407.
73. Raas-Rothschild A, Dijkhuizen T, Sikkema-Raddatz B, et al. The 8q22.1 microdeletion syndrome or Nablus mask-like facial syndrome: report on two patients and review of the literature. Eur J Med Genet 2009; 52:140.
74. Shieh JT, Aradhya S, Novelli A, et al. Nablus mask-like facial syndrome is caused by a microdeletion of 8q detected by array-based comparative genomic hybridization. Am J Med Genet A 2006; 140:1267.
75. Jain S, Yang P, Farrell SA. A case of 8q22.1 microdeletion without the Nablus mask-like facial syndrome phenotype. Eur J Med Genet 2010; 53:108.
76. Hall BD, Langer LO, Giedion A, et al. Langer-Giedion syndrome. Birth Defects Orig Artic Ser 1974; 10:147.
77. Bowen P, Biederman B, Hoo JJ. The critical segment for the Langer-Giedion syndrome: 8q24.11----q24.12. Ann Genet 1985; 28:224.
78. Parrish JE, Wagner MJ, Hecht JT, et al. Molecular analysis of overlapping chromosomal deletions in patients with Langer-Giedion syndrome. Genomics 1991; 11:54.
79. Wilson WG, Herrington RT, Aylsworth AS. The Langer-Giedion syndrome: report of a 22-year old woman. Pediatrics 1979; 64:542.
80. Carvalho DR, Santos SC, Oliveira MD, Speck-Martins CE. Tibial hemimelia in Langer-Giedion syndrome with 8q23.1-q24.12 interstitial deletion. Am J Med Genet A 2011; 155A:2784.
81. Momeni P, Glöckner G, Schmidt O, et al. Mutations in a new gene, encoding a zinc-finger protein, cause tricho-rhino-phalangeal syndrome type I. Nat Genet 2000; 24:71.
82. Jones KL. Smith's recognizable patterns of human malformation, 6th ed, Elsevier Saunders, Philadelphia 2006.
83. Alfi O, Donnell GN, Crandall BF, et al. Deletion of the short arm of chromosome no.9 (46,9p-): a new deletion syndrome. Ann Genet 1973; 16:17.
84. Christ LA, Crowe CA, Micale MA, et al. Chromosome breakage hotspots and delineation of the critical region for the 9p-deletion syndrome. Am J Hum Genet 1999; 65:1387.

85. Swinkels ME, Simons A, Smeets DF, et al. Clinical and cytogenetic characterization of 13 Dutch patients with deletion 9p syndrome: Delineation of the critical region for a consensus phenotype. Am J Med Genet A 2008; 146A:1430.
86. Harada N, Visser R, Dawson A, et al. A 1-Mb critical region in six patients with 9q34.3 terminal deletion syndrome. J Hum Genet 2004; 49:440.
87. Stewart DR, Huang A, Faravelli F, et al. Subtelomeric deletions of chromosome 9q: a novel microdeletion syndrome. Am J Med Genet A 2004; 128A:340.
88. Verhoeven WM, Egger JI, Vermeulen K, et al. Kleefstra syndrome in three adult patients: further delineation of the behavioral and neurological phenotype shows aspects of a neurodegenerative course. Am J Med Genet A 2011; 155A:2409.
89. Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet 2007; 145C:383.
90. Kleefstra T, van Zelst-Stams WA, Nillesen WM, et al. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. J Med Genet 2009; 46:598.
91. Genetics Home Reference: Kleefstra syndrome. http://ghr.nlm.nih.gov/condition/kleefstra-syndrome (Accessed on January 03, 2012).
92. Greenberg F, Valdes C, Rosenblatt HM, et al. Hypoparathyroidism and T cell immune defect in a patient with 10p deletion syndrome. J Pediatr 1986; 109:489.
93. Monaco G, Pignata C, Rossi E, et al. DiGeorge anomaly associated with 10p deletion. Am J Med Genet 1991; 39:215.
94. Obregon MG, Mingarelli R, Giannotti A, et al. Partial deletion 10p syndrome. Report of two patients. Ann Genet 1992; 35:101.
95. Schuffenhauer S, Seidel H, Oechsler H, et al. DiGeorge syndrome and partial monosomy 10p: case report and review. Ann Genet 1995; 38:162.
96. Shapira M, Borochowitz Z, Bar-El H, et al. Deletion of the short arm of chromosome 10 (10p13): report of a patient and review. Am J Med Genet 1994; 52:34.
97. Van Esch H, Groenen P, Nesbit MA, et al. GATA3 haplo-insufficiency causes human HDR syndrome. Nature 2000; 406:419.
98. Brémond-Gignac D, Crolla JA, Copin H, et al. Combination of WAGR and Potocki-Shaffer contiguous deletion syndromes in a patient with an 11p11.2-p14 deletion. Eur J Hum Genet 2005; 13:409.
99. GeneReviews: Wilms Tumor Overview. http://www-ncbi-nlm-nih-gov.ezp-prod1.hul.harvard.edu/books/NBK1294/ (Accessed on April 08, 2014).
100. Chien WH, Sue WC, Kuo PL, et al. Potocki-Shaffer syndrome: report of one case. Acta Paediatr Taiwan 2003; 44:242.
101. Romeike BF, Wuyts W. Proximal chromosome 11p contiguous gene deletion syndrome phenotype: case report and review of the literature. Clin Neuropathol 2007; 26:1.
102. Hall CR, Wu Y, Shaffer LG, Hecht JT. Familial case of Potocki-Shaffer syndrome associated with microdeletion of EXT2 and ALX4. Clin Genet 2001; 60:356.
103. Wu YQ, Badano JL, McCaskill C, et al. Haploinsufficiency of ALX4 as a potential cause of parietal foramina in the 11p11.2 contiguous gene-deletion syndrome. Am J Hum Genet 2000; 67:1327.
104. Kim HG, Kim HT, Leach NT, et al. Translocations disrupting PHF21A in the Potocki-Shaffer-syndrome region are associated with intellectual disability and craniofacial anomalies. Am J Hum Genet 2012; 91:56.
105. Swarr DT, Bloom D, Lewis RA, et al. Potocki-Shaffer syndrome: comprehensive clinical

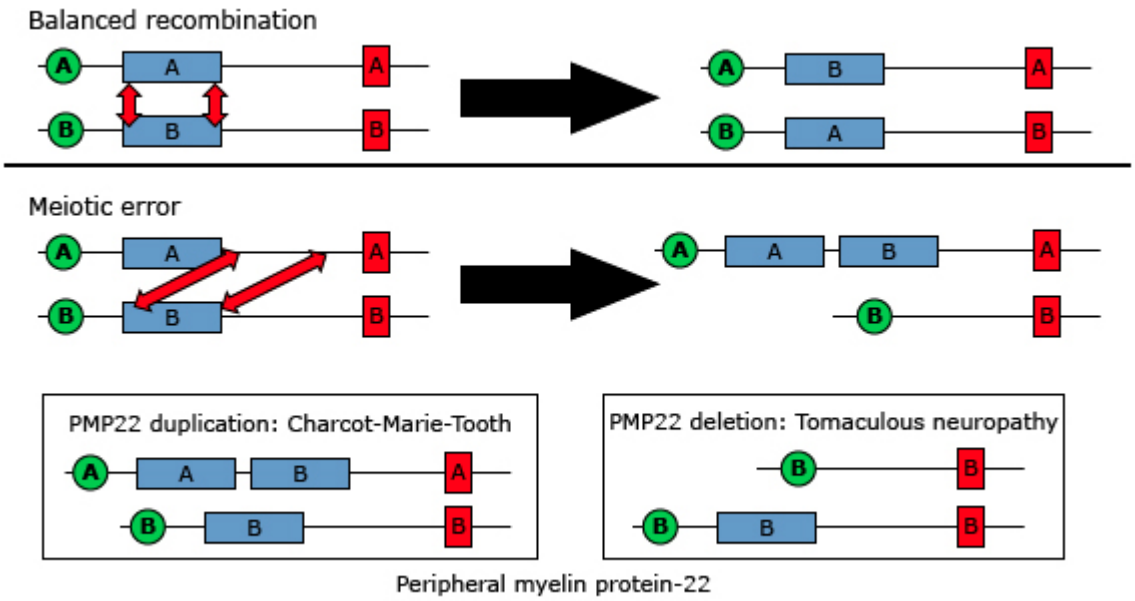
assessment, review of the literature, and proposals for medical management. Am J Med Genet A 2010; 152A:565.

106. Favier R, Jondeau K, Boutard P, et al. Paris-Trousseau syndrome : clinical, hematological, molecular data of ten new cases. Thromb Haemost 2003; 90:893.
107. Grossfeld PD, Mattina T, Lai Z, et al. The 11q terminal deletion disorder: a prospective study of 110 cases. Am J Med Genet A 2004; 129A:51.
108. Tyson C, Qiao Y, Harvard C, et al. Submicroscopic deletions of 11q24-25 in individuals without Jacobsen syndrome: re-examination of the critical region by high-resolution array-CGH. Mol Cytogenet 2008; 1:23.

Topic 16660 Version 3.0

GRAPHICS

Nonhomologous recombination resulting in copy number variation

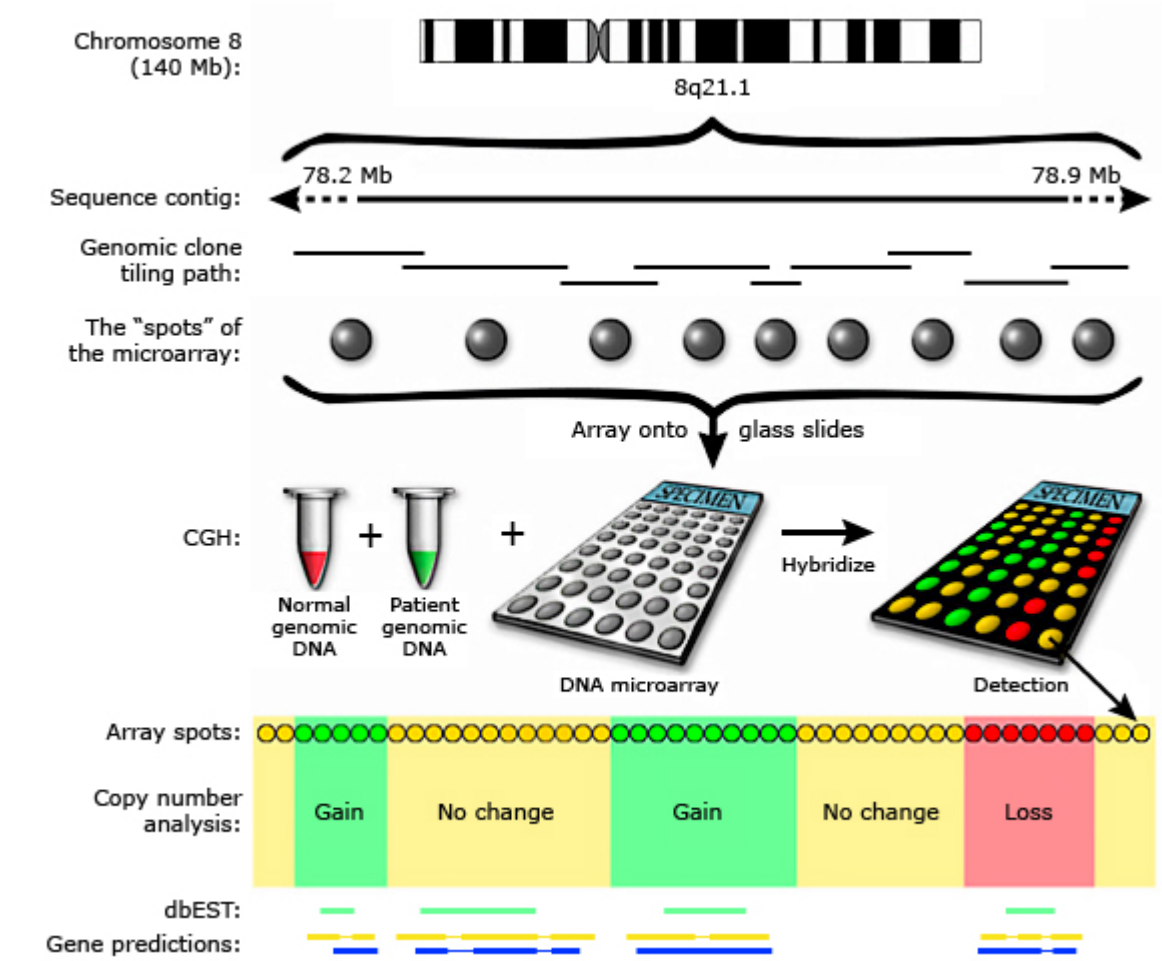


(Upper panel) Normal recombination of homologous region.
(Lower panel) Aberrant recombination, resulting in imbalanced swap of DNA between chromosomes.

PMP22: peripheral myelin protein 22.

Graphic 67644 Version 3.0

Schematic CGH for microarray setup



Schematic representation of the array CGH technique for a focused analysis of copy number imbalances along a region of interest (eg, 8q21.1). A tiling path of genomic clones (eg, BACs, PACs, PIs, cosmids) is generated to cover the region. After extraction and purification, these genomic DNA targets are arrayed onto glass slides.
Array CGH is performed by hybridizing labeled normal (Cy3) and tumor (Cy5) genomic DNA into the microarray and detected using a microarray scanner.
Each array spot, realigned *in silico* as a single contiguous map to correspond with the tiling path, can be analyzed by fluorescence ratio to identify the regions of copy number changes. These results may be correlated with *in silico* techniques to identify candidate genes of interest.

CGH: comparative genomic hybridization; BAC: bacterial artificial chromosome; PAC: P1 bacteriophage artificial chromosome; P1: P1 bacteriophage; Cy3: cyanine dye with green fluorescence; Cy5: cyanine dye with red fluorescence.

Graphic 58888 Version 10.0

Disclosures

Disclosures: **Carlos A Bacino, MD, FACMG** Nothing to disclose. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Elizabeth TePas, MD, MS** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Microdeletion syndromes (chromosomes 12 to 22)

Author Carlos A Bacino, MD, FACMG
Section Editor Helen V Firth, DM, FRCP, DCH
Deputy Editor Elizabeth TePas, MD, MS

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Apr 21, 2014.

INTRODUCTION — Chromosome deletions that span at least 5 megabases (Mb) are usually microscopically visible on chromosome banded karyotypes. Microdeletions, or submicroscopic deletions, are chromosomal deletions that are too small to be detected by light microscopy using conventional cytogenetic methods. Specialized testing is needed to identify these deletions. Microdeletions are typically 1 to 3 Mb long and involve several contiguous genes. The exact size and location of a microdeletion that causes a syndrome may vary, but a specific "critical region" is consistently involved. Most phenotypic effects of these microdeletions are due to haploinsufficiency of a few critical genes or in some cases a single gene.

This topic reviews microdeletion syndromes involving chromosomes 12 through 22. Microdeletion syndromes involving chromosomes 1 through 11 are discussed separately, as are microduplication syndromes and congenital abnormalities of the sex chromosomes. Other congenital chromosomal abnormalities, such as trisomies, are also reviewed in detail elsewhere. (See "Microdeletion syndromes (chromosomes 1 to 11)" and "Microduplication syndromes" and "Sex chromosome abnormalities" and "Congenital cytogenetic abnormalities".)

OVERVIEW OF GENOMIC DISORDERS — Genomic disorders are diseases that result from the loss or gain of chromosomal/DNA material. The most common and better delineated genomic disorders are divided in two main categories, those resulting from copy number losses (deletion syndromes) and copy number gains (duplication syndromes). (See "Genomic disorders: An overview".)

Copy number variations (CNVs) are submicroscopic genomic differences in the number of copies of one or more sections of DNA that result in DNA gains or losses (figure 1). Some CNVs are pathogenic and cause syndromic disorders with consistent phenotypic features, as are discussed here. Other CNVs are associated with disease susceptibility or resistance and the same CNV can be associated with several diverse disorders. Still other CNVs are part of normal genetic variation and have no recognized disease association. Contiguous gene syndromes can occur when CNVs affect several adjacent genes. (See "Overview of genetic variation", section on 'Copy number variations (CNVs)' and "Basic principles of genetic disease", section on 'Copy number variation'.)

The main mechanism that leads to disease in genomic disorders secondary to deletions and duplications is a change in the copy number of a dose-sensitive gene or genes. Other disease mechanisms include interference with imprinted genes and with regulatory elements outside genes. (See "Genomic disorders: An overview", section on 'Disease mechanisms'.)

Genomic disorders are typically detected by array comparative genomic hybridization (array CGH) (figure 2). Most laboratories confirm gains or losses detected on an array with an independent method, such as fluorescent in situ hybridization (FISH), multiple ligation dependent probe amplification (MLPA), or quantitative polymerase chain reaction (Q-PCR). (See "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Array comparative genomic hybridization' and "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Fluorescence in situ hybridization'.)

13q14 DELETION SYNDROME (RETINOBLASTOMA SYNDROME) — Children with microdeletions of

13q14.11 have an increased risk of developing retinoblastomas (MIM #613884). Intellectual disability and facial dysmorphic features also may occur and depend upon the size of the deletion [1]. Retinoblastoma is caused by mutational inactivation of both alleles of the retinoblastoma (RB1) gene that encodes a tumor suppressor. Children with an *RB1* germline mutation or with deletions of *RB1*, as is seen in patients with 13q deletion, need to have an eye examination under anesthesia every three to four weeks until age six months to evaluate for retinoblastoma. After that, examinations are typically performed every three to six months until age seven years. The frequency is then tapered to yearly and eventually to every two years for a lifetime [2]. (See "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Retinoblastoma gene' and "Overview of retinoblastoma", section on 'Epidemiology'.)

15q11.2 DELETION SYNDROME (BP1-BP2) — The region proximal (more centromeric) to the Prader-Willi syndrome (PWS)/Angelman syndrome (AS) region in chromosome 15 has significant variability in the general population. The deletions and duplications of the region between breakpoints 1 and 2 (BP1-BP2) were considered benign and probably familial variations. However, several reports indicate that deletions in this region are associated with developmental delay and behavioral abnormalities in some individuals [3-6]. Many people who carry these deletions are asymptomatic, which can be attributed to nonpenetrance or the need of additional modifiers (genetic and environmental factors). There are four highly conserved genes in this region: *NIPA1*, *NIPA2*, *CYFIP1*, and *GCP5*. These genes are not imprinted and patients with this deletion have normal methylation studies for the 15q11-q13 region.

15q11-13 MATERNAL DELETION SYNDROME (ANGELMAN SYNDROME) — A small interstitial deletion between 15q11 and 15q13 can result in two completely different clinical syndromes depending upon the parental origin of the chromosome. A paternally-derived chromosome 15 with this deletion results in Prader-Willi syndrome (PWS), whereas a maternally-derived chromosome 15 with a similar deletion is associated with Angelman syndrome (AS). (See '15q11-13 paternal deletion syndrome (Prader-Willi syndrome)' below.)

AS (MIM #105830) is a neurodevelopmental disorder characterized by severe to profound intellectual disability, postnatal microcephaly, and a movement or balance disorder, usually in the form of gait ataxia and/or tremulous movement of limbs [7-9]. AS patients may have any combination of the following behavior characteristics: frequent laughter or smiling; apparent happy demeanor; an easily excitable personality, often with hand flapping movements; hypermotoric behavior; fascination with water; mouthing behaviors; and a short attention span. More than 80 percent of individuals with AS have seizures, and abnormal electroencephalograms (EEGs) with large amplitude slow-spike waves are seen even in the absence of seizures. Sleep is often compromised with frequent waking and altered sleep cycles.

AS is caused by absence of the maternally inherited copy of the *UBE3A* gene. *UBE3A* maps to chromosome 15q11-q13 and encodes E6 associated protein ubiquitin protein ligase 3A [10,11]. *UBE3A* is subject to genomic imprinting (the differential expression of genetic information depending upon whether the information is inherited from the father or the mother). The maternally-inherited copy of the *UBE3A* gene is functional and the paternally-inherited copy is inactive or silenced. In the normal situation, a functional copy of *UBE3A* from the maternal chromosome prevents AS. (See "Basic principles of genetic disease" and "Basic principles of genetic disease", section on 'Imprinting'.)

There are four known molecular defects of *UBE3A* that result in AS:

- Large (approximately 4 megabases [Mb]) deletions of maternal chromosome 15q11-q13 [12,13].
- Paternal uniparental disomy (UPD) [14], where both copies of chromosome 15 are inherited from the father, and no chromosome 15 is inherited from the mother.

- Imprinting center defects, causing the maternal chromosome to have the methylation and gene expression pattern of a paternal chromosome [15,16].
- Point mutations in *UBE3A,* which produce no functional gene product [17].

Deletions account for over 70 percent of cases of AS. There are a number of breakpoints (BP, chromosome regions prone to breakage) in the 15q11-q13 region known as BP1 to BP3. Deletions in this region can be subclassified into class I and class II deletions based upon these BPs. Class I deletions are larger and extend from BP1 to BP3, while class II deletions extend from BP2 to BP3 [12]. Patients with class I deletions tend to have greater disease severity when compared with class II patients, with greater difficulties in expressive language, need for more seizure medications, and higher incidence of autism spectrum disorders [18].

If AS is suspected, the workup should include methylation studies and chromosome microarray (array comparative genomic hybridization [array CGH]). If methylation studies are positive, the next step is to determine by microarray if the patient has a class I or class II deletion. If the array is negative, consider UPD studies to determine if the patient has paternal UPD using microsatellite DNA markers, or if available, single nucleotide polymorphisms (SNP) array. If UPD studies are negative, imprinting center studies are warranted. Imprinting center abnormalities can be a result of deletions that are familial and inherited. They can also be the result of epimutations (heritable changes in gene expression that do not alter the DNA sequence) that are sporadic and have a low recurrence risk. Sometimes epimutations are postzygotic, resulting in mosaicism [15,18-20]. If the methylation studies are negative and suspicion for AS remains, sequencing studies for *UBE3A* should be obtained.

Screening and monitoring studies include developmental evaluations and EEG to check for seizures. The EEG is often abnormal, therefore the author suggests obtaining an EEG after one year of age in all children with AS. Patients should also be evaluated for feeding problems and gastroesophageal reflux. Referrals to physical, occupational, and speech therapy are recommended. Augmentative communication methods may be beneficial. Consider melatonin and/or clonidine to alleviate severe sleep disturbances. (See "Developmental and behavioral screening tests in primary care" and "Clinical and laboratory diagnosis of seizures in infants and children" and "Overview of the treatment of seizures and epileptic syndromes in children" and "Physiology and available preparations of melatonin".)

15q11-13 PATERNAL DELETION SYNDROME (PRADER-WILLI SYNDROME) — This deletion is associated with Prader-Willi syndrome (PWS, MIM #176270), which is characterized by hypotonia; poor feeding in infancy with failure to thrive, but increased appetite and obesity in children and adults; genital hypoplasia; small hands and feet; and distinctive facial features (eg, almond-shaped eyes, narrowed bifrontal diameter, thin upper lip). Mild intellectual disability occurs in two-thirds of cases. Although the exact gene(s) responsible for PWS are still unknown, two reports have identified possible causes. Truncating mutations in the *MAGEL2* gene that encodes an ubiquitin ligase enhancer involved in endosomal protein recycling were identified in patients with PWS and autism [21]. In addition, deletions of the small nucleolar RNA (snoRNA) HBII-85 cluster are associated with PWS [22]. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome" and "Epidemiology and genetics of Prader-Willi syndrome".)

15q13.3 DELETION SYNDROME — This 1.5 megabases (Mb) microdeletion (MIM #612001) has a variable phenotype and extends between breakpoints 4 and 5 (BP4 and BP5), which are adjacent and distal to breakpoints 1 and 3 (BP1 to BP3) involved in Prader-Willi syndrome (PWS) and Angelman syndrome (AS) deletions [23-26]. The clinical manifestations range from mild to severe intellectual disabilities, seizures, behavioral abnormalities, autism, and schizophrenia. This deletion may also predispose to epilepsy. The region contains six genes, but *CHRNA7*, a cholinergic receptor gene, appears linked to seizures and the clinical phenotype. Some authors hypothesize that this deletion alone is not sufficient to cause disease and that other abnormalities or modifiers are needed. Several patients

whose deletion involves *KLF13*, a gene located in the critical region, have congenital heart defects.

Screening and monitoring studies include formal developmental and psychologic evaluations and electroencephalogram (EEG). Echocardiography should also be considered. Patients may benefit from physical, occupational, and speech therapies.

15q15.3 DELETION SYNDROME — This is an uncommon contiguous gene deletion syndrome (MIM #611102). The main clinical features associated with this syndrome are sensorineural hearing loss and male infertility due to sperm dysmotility [27]. The disease is autosomal recessive and is caused by haploinsufficiency of *CATSPER2* and *STRC*, two genes included in the deleted region that are expressed in the sperm and inner ear, respectively. Males who inherit two *CATSPER2-STRC* deletions are infertile and deaf [28]. Females who inherit two *CATSPER2-STRC* deletions are deaf.

Hearing evaluations should be performed in patients with this deletion. Males should also be tested for infertility.

15q24 DELETION SYNDROME

This rare deletion disorder ranges from 1.7 to 3.9 megabases (Mb) in size. The core cognitive features of the 15q24 microdeletion syndrome, including developmental delays and severe speech problems, are largely due to deletion of genes in a 1.1 Mb critical region [29].

The majority of breakpoints lie within segmental duplication (SD) blocks. The region is surrounded by multiple locus control regions (LCRs) that control chromatin structure and amplify expression of linked genes.

The syndrome is characterized by mild to moderate intellectual disability, growth retardation, microcephaly, digital abnormalities, hypospadias, and connective tissue abnormalities (loose joints) (MIM #613406) [30-32]. Patients have distinctive dysmorphic features including a receding hairline, hypertelorism, epicanthal folds, broad inner aspect of the eyebrows, downslanting palpebral fissures, broad nasal bridge, long smooth philtrum, thin upper lip, and a full lower lip. Skeletal findings include delayed bone age, brachydactyly, and broad phalanges with distal hypoplasia. Genital anomalies include hypospadias, micropenis, and a small scrotum. Congenital diaphragmatic hernia has been frequently reported in this deletion [33].

CYP11A1 maps to the region and encodes cytochrome P450 side-chain cleavage enzyme (P450scc) that converts progesterone to pregnenolone. Deletion of this gene may be responsible for the genital abnormalities in males (complete absence of this gene causes sex reversal in males and congenital adrenal insufficiency). Other deleted genes include a number of enzymes involved in glycosylation (loss of both copies is usually required to exhibit symptoms; thus, this deletion may uncover recessive phenotypes). Other genes potentially responsible for this phenotype includes *CPLX3*, a regulator of neurotransmitter release that is expressed in the brain and eye, and *SEMA7A*, a gene that mediates peripheral and central axon growth required during neuronal development [34].

Screening and monitoring studies include formal developmental evaluation and skeletal survey to uncover skeletal anomalies. Males may need endocrine evaluations and other imaging studies should be considered to evaluate for diaphragmatic hernias. Patients may benefit from physical, occupational, and speech therapies.

16p13.3 DELETION SYNDROME (RUBINSTEIN-TAYBI SYNDROME) — A submicroscopic deletion that includes the cAMP response element-binding protein (CREB)-binding protein gene, *CREBBP* or *CBP*, located on chromosome 16 at p13.3, has been identified in approximately 10 percent of individuals with Rubinstein-Taybi syndrome (RTS, MIM #180849) [35,36]. This clinical entity is characterized by prenatal and postnatal growth restriction, microcephaly, dysmorphic features, broad thumbs and toes, and intellectual disability [37-40]. Facial features include highly-arched eyebrows, long eyelashes,

beaked nose with prominent septum extending below nares, downslanting palpebral fissures, high-arched palate, and micrognathia. The thumbs are broad and radially deviated, and the toes are also quite broad and internally deviated. The incisors may have talon cusps. Hirsutism is commonly seen. Congenital heart disease is seen in one-third of patients. Eye abnormalities may include glaucoma, cataracts, and strabismus.

Mutation of the *CBP* gene has been detected in about 40 percent of affected individuals with RTS. Mutations in another gene, *EP300*, account for a small number of cases [41,42]. Other yet unknown genes may also be responsible for this disorder, because approximately 50 percent of individuals with clinical features consistent with RTS do not have a detectable deletion or mutation in *CBP* or *EP300*.

Screening and monitoring studies include developmental and ophthalmologic evaluations. An echocardiogram should be performed to evaluate for congenital heart disease.

16p13.11 DELETION SYNDROME — A recurrent 1.65 megabases (Mb) deletion of this region is associated with intellectual disabilities and multiple congenital anomalies. Clinical findings include developmental delay (motor, speech, and language delays), as well as behavioral/psychiatric problems. Patients with this deletion also have microcephaly, short stature, and epilepsy [43-45]. Mild dysmorphic features are present, but without a specific pattern. Polymicrogyria was reported in one patient. This deletion is reported as one of the most prevalent deletions predisposing patients to idiopathic epilepsy [44,46].

Screening studies include formal developmental evaluations, electroencephalogram (EEG), and brain magnetic resonance imaging (MRI) studies (to look for central nervous system (CNS) anomalies, such as polymicrogyria and other neuronal migration defects) in the presence of microcephaly.

16p11.2 DELETION SYNDROME — This deletion in 16p11.2 spans almost 600 kb at position 29.5 to 30.1 megabases (Mb) [47]. It is recurrent in size due to flanking segments that mediate these rearrangements. Clinical findings include variable levels of intellectual disability with a high incidence of language delay, expressive more so than receptive [33,48-52]. This chromosomal abnormality is considered one of the most common recurrent genomic disorders associated with autism spectrum disorders [51]. Some studies have shown that up to 55 percent of patients with this deletion met criteria for autism or autism spectrum disorders, and the frequency of this microdeletion is around 0.6 percent in patients with autism [53,54].

Other data indicate that this deletion may contribute to psychiatric disorders including attention deficit hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, and panic disorder [53,55]. Some patients with this deletion have been diagnosed with cervicothoracic syringomyelia [56] and are also at higher than average risk for seizures and/or electroencephalogram (EEG) abnormalities. There are several reported patients with a smaller deletion, approximately 200 kb, distal to the classical deletion (coordinates 29.7 to 29.9 Mb) who present with morbid obesity [57,58]. Thus, obesity can be part of this deletion phenotype.

Formal developmental, neuropsychiatric, and autism evaluations may be required. Spine MRIs should be considered, since syringomyelia may be asymptomatic. Other screening and monitoring studies include speech and hearing evaluation, EEG, and monitoring of weight gain and overall growth. (See "Autism spectrum disorder: Diagnosis" and "Autism spectrum disorder: Screening tools" and "Developmental and behavioral screening tests in primary care".)

17p13.3 DELETION SYNDROMES — There are several deletions in the 17p13.3 region and the clinical manifestations depend upon the size and genes involved. Larger deletions of the distal short arm of chromosome 17 are responsible for Miller-Dieker syndrome (MDS). These deletions involve *PAFAH1B1* (the lissencephaly gene formerly known as *LIS1*). There are more distal deletions that encompass *YWHAE* (and do not involve *PAFAH1B1)* that have a distinct clinical phenotype [59].

17p13.3 deletion including PAFAH1B1 (Miller-Dieker syndrome) — Miller-Dieker syndrome (MDS, MIM #247200) is a contiguous gene deletion syndrome that is characterized by lissencephaly, growth restriction, and dysmorphic features [60-64]. Haploinsufficiency of *LIS1* (now called *PAFAH1B1*) due to point mutations or deletions is causative of lissencephaly, a generalized agyria-pachygyria brain malformation that results from an arrest of neuronal migration at 9 to 13 weeks gestation [65,66]. (See "Microcephaly in infants and children: Etiology and evaluation", section on 'Neuroanatomic abnormalities'.)

The craniofacial clinical features seen in MDS include a prominent forehead, bitemporal hollowing, short nose with upturned nares, protuberant upper lip, thin vermilion border, and small jaw [67]. The clinical course of these patients is marked by failure to thrive, severe psychomotor retardation, opisthotonos, seizures, and death early in life with very few children reaching 10 years of age. (See "Etiology and pathogenesis of infantile spasms", section on 'CNS malformations' and "Prenatal diagnosis of CNS anomalies other than neural tube defects and ventriculomegaly", section on 'Lissencephaly'.)

Some patients have smaller deletions or mutations involving *PAFAH1B1* that are associated with isolated lissencephaly (LIS type 1 or classic lissencephaly, MIM #607432) [68,69].

Patients should undergo formal developmental evaluation. Brain magnetic resonance imaging (MRI) studies are recommended to delineate the degree of lissencephaly and structural central nervous system (CNS) abnormalities. Neurology evaluation and electroencephalogram (EEG) is recommended for evaluation and management of seizures. Swallowing evaluations are usually necessary, and patients may need an intragastric or transpyloric feeding tube. (See "Overview of the classification, etiology, and clinical features of pediatric seizures and epilepsy", section on 'Neurodevelopmental lesions' and "Overview of the treatment of seizures and epileptic syndromes in children" and "Enteral nutrition in infants and children" and "Enteral feeding: Gastric versus post-pyloric".)

17p13.3 deletion including YWHAE — A series of patients with deletions including *YWHAE,* but not *PAFAH1B1,* presented with significant growth restriction, cognitive impairment, shared craniofacial features, and variable structural abnormalities of the brain, but no lissencephaly [70]. One patient in this group did not have growth restriction. *CRK* appears to be the gene responsible for growth restriction [71]. *YWHAE,* a gene involved in the region that encodes tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon, is believed responsible for the brain findings.

Features of this microdeletion syndrome include prenatal and postnatal growth retardation, macrocephaly, and dysmorphic features including prominent forehead, downslanting palpebral fissures, epicanthal folds, broad nasal root, low-set ears, cleft palate, and eye abnormalities. Seizures have been reported. MRI studies show microcysts in the white matter and corpus callosum, ventricular dilatation, enlargement of subarachnoid spaces, and Chiari type I malformation [59,67,71].

Patients should undergo formal developmental evaluation. Brain MRI studies are recommended to determine the presence of structural CNS abnormalities. Neurology evaluation with EEG and ophthalmologic evaluation are also recommended.

17p11.2 DELETION SYNDROME (HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSY) — Hereditary neuropathy with liability to pressure palsy (HNPP, MIM #162500) is an autosomal entity characterized by recurrent mononeuropathy, typically associated with minor compression or trauma [72]. It is associated with deletions in 17p11.2 involving the peripheral myelin protein 22 *(PMP22)* gene. Use of protective gear when practicing sports, protective pads at pressure points, and avoidance of repetitive movements or activities may prevent nerve trauma. (See "Overview of hereditary neuropathies", section on 'Hereditary neuropathy with liability to pressure palsy'.)

17p11.2 DELETION SYNDROME (SMITH-MAGENIS SYNDROME) — This deletion of chromosome 17p11.2 (image 1) involves the retinoic acid-induced 1 *(RAI1)* gene that is suspected to be a

transcriptional regulator. Both microdeletions and mutations of *RAI1* can cause Smith-Magenis syndrome (SMS, MIM #182290) [73-78]. The circadian defect seen in this disorder is due to disruption of transcription of the circadian locomotor output cycles kaput (*CLOCK*) gene [79].

The syndrome is characterized by brachycephaly, midface hypoplasia, prognathism, hoarse voice, speech delay with or without hearing loss, psychomotor and growth retardation, and behavior problems [80-82]. Feeding problems are seen in infants, along with hypotonia and sometimes lethargy. Patients have mild to moderate intellectual disability and autism spectrum disorder. Sleep problems are often significant and include difficulty falling asleep, shortened sleep cycles, frequent and prolonged nocturnal awakenings (altered rapid eye movement [REM] sleep), excessive daytime sleepiness, daytime napping, snoring, and bedwetting [83]. Behavioral abnormalities include head banging, hand and wrist biting, onychotillomania (pulling own nails), excessive nose picking, and polyembolokoilomania (inserting objects in body orifices) [81]. Self hugging is also a typical behavior. Electroencephalograms (EEGs) are frequently abnormal, but are not associated with overt seizures.

Some patients display neurologic signs, such as decreased or absent deep tendon reflexes, pes planus or pes cavus, decreased sensitivity to pain, and decreased leg muscle mass suggestive of peripheral neuropathy [84]. The deletion in these patients involves the peripheral myelin protein 22 *(PMP22)* gene. Other common problems include hearing loss and, in some cases, hyperacusis, short stature, scoliosis, velopharyngeal insufficiency, and ocular abnormalities (iris anomalies, microcornea). (See '17p11.2 deletion syndrome (Hereditary neuropathy with liability to pressure palsy)' above.)

Elevated cholesterol and triglycerides is common. Hypothyroidism is reported in up to half of these patients [85].

Screening laboratory studies include thyroid function tests and lipid panel. Patients should undergo a formal developmental evaluation. Swallowing evaluation is indicated in infants with feeding problems. Ophthalmologic evaluations are important, as well as hearing evaluations. Cardiac evaluations including echocardiography are recommended to rule out structural anomalies. Neuroimaging, sleep, and EEG studies are strongly recommended. In patients with large deletions, nerve conduction velocity studies are recommended to evaluate for hereditary neuropathy with liability to pressure palsy (HNPP). Patients may benefit from occupational, physical, and speech therapies. Management of sleep and behavioral abnormalities may require psychotropic medications. (See "Assessment of sleep disorders in children".)

17q12 DELETION SYNDROME — This deletion is recurrent in size due to flanking segments that mediate these rearrangements and spans approximately 1.5 megabases (Mb) [86,87]. The critical gene in this region is hepatocyte nuclear factor-1-beta *(HNF1B)*, which is also called transcription factor 2 *(TCF2)*. Clinical findings include congenital renal anomalies (multicystic kidney disease) and maturity-onset diabetes of the young type 5 (MODY5) (MIM #137920). Cognitive impairment and central nervous system (CNS) abnormalities may be part of the clinical spectrum [87]. This deletion confers a higher risk for autism and schizophrenia [88]. (See "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'Hepatocyte nuclear factor-1-alpha' and "Renal cystic diseases in children".)

The reciprocal duplication appears to be associated with an increased risk for epilepsy, but the extent of the clinical consequences is not yet clear.

Screening studies include renal ultrasound and brain magnetic resonance imaging (MRI). Referral to an endocrinologist is recommended for management of diabetes. (See "Management of type 2 diabetes mellitus in children and adolescents".)

17q21.31 DELETION SYNDROME — This deletion involves the gene encoding microtubule associated protein tau (MAPT) and is associated with a common inversion polymorphism, known as the H2 inversion, in at least one of the parents. This inversion appears to mediate aberrant recombination

events leading to the deletion. It was originally thought that the *MAPT* gene encoding microtubule associated protein tau was the gene causative for this disorder [89,90]. However, it was subsequently determined that this disorder is due to haploinsufficiency of the *KANSL1* gene instead [91,92]. KANSL1 (KAT8 regulatory nonspecific lethal [NSL] complex subunit 1) is a regulator of a chromatin modifier, KAT8, that effects gene expression. As such, this condition is now known as *KANSL1*-related intellectual disability syndrome [93]. (See "Genetic and environmental causes of birth defects", section on 'Nonallelic homologous recombination'.)

Clinically, this microdeletion is associated with mild to severe intellectual disability, hypotonia, and characteristic facies [89,90,94-97]. The hypotonia is also associated with poor sucking and feeding difficulties early on in infancy. Craniofacial features in these patients include a long face, large ears, and tubular or pear-shaped nose with a bulbous nasal tip. Other features include seizures in over half of cases, cardiac defects (septal defects), cryptorchidism in almost 80 percent of males, and skeletal anomalies (slender lower limbs, hip dislocation, feet deformities, and scoliosis). Patients typically have a friendly disposition, sometimes with frequent laughing that is reminiscent of Angelman syndrome (AS). Attention span problems and hyperactivity are also reported.

Management of these patients includes developmental evaluations, an echocardiogram to examine for cardiac defects, brain magnetic resonance imaging (MRI), and referral to neurology for electroencephalogram (EEG) and management of seizures if present. Physical, occupational, and speech therapies are helpful, particularly for issues with hypotonia and feeding. Patients may also benefit from augmentative communication methods.

18p DELETION SYNDROME — This is one of the most common deletion syndromes after cri-du-chat syndrome. The estimated frequency of 18p deletion syndrome is 1 in 50,000 liveborn infants, with more females than males affected [98]. Deletions can range in size from the whole short arm of chromosome 18 to microdeletions. The terminal deletion occurs de novo in about two-thirds of cases. The remaining cases are due to a de novo unbalanced translocation with loss of the 18p or malsegregation of parental chromosome rearrangement (balanced translocation or inversion) or a ring chromosome 18 [99]. Familial transmission of the del(18p) syndrome has been reported. The 18p deletion can usually be diagnosed by conventional cytogenetic analysis, but is now often detected by array comparative genomic hybridization (array CGH) testing.

The phenotype is variable, depending upon the size and location of the deleted region. Major clinical features may include hypotonia, short stature, microcephaly and brachycephaly, round face with short philtrum, palpebral ptosis, large ears with detached pinnae, downturned corners of the mouth, and mild to moderate cognitive impairment with speech delay [98,100,101]. Approximately, 10 to 15 percent of cases present with holoprosencephaly (HP) [98,102]. Some patients with HP may present with bilateral cleft lip and palate, while others may display a single maxillary central incisor, a subtle manifestation of HP. Mutations in the *TGIF* gene that is located in 18p11.3 are associated with HP, but not all patients with deletion of *TGIF* have HP, indicating a more complex interaction. About 10 percent of cases may present with congenital heart defects [103]. Severe keratosis pilaris and ulerythema ophryogenes [104], autoimmune disease [101,105], and antibody deficiencies [106] have also been reported.

Patients with this deletion should have a brain magnetic resonance imaging (MRI) to assess for HP and other central nervous system (CNS) abnormalities. An echocardiogram should be considered if clinically indicated. Other recommended clinical interventions include physical therapy for hypotonia and speech therapy.

20p11 DELETION SYNDROME (ALAGILLE SYNDROME) — Alagille syndrome (MIM #118450) is mostly due to mutations in Jagged-1 *(JAG1)*, but some patients have a microdeletion that includes this entire gene [107]. This syndrome is characterized by paucity of interlobular bile ducts, chronic cholestasis, cardiac anomalies, butterfly vertebrae, posterior embryotoxon of the eye, and dysmorphic

facies. Alagille syndrome is covered in greater detail separately. (See "Inherited disorders associated with conjugated hyperbilirubinemia", section on 'Alagille syndrome'.)

22q11.2 DELETION SYNDROMES (DiGEORGE SYNDROME/VELOCARDIOFACIAL SYNDROME) — This region in chromosome 22 is surrounded by low-copy repeats known as LCR22-1 through 6. The classic velocardiofacial syndrome (VCFS)/DiGeorge deletion is approximately 3 megabases (Mb) and includes the *TBX1* gene between LCR22-1 and LCR22-3 [108].

Approximately 80 to 90 percent of patients with DiGeorge syndrome (MIM #188400) have microdeletions involving chromosome 22q11 (ie, 22q11.21-q11.23). This syndrome is characterized by abnormalities in the development of the third and fourth branchial arches, resulting in hypoplasia of the thymus and/or parathyroid gland, conotruncal cardiac defects, and facial dysmorphism. Clinical manifestations may include neonatal hypocalcemia and susceptibility to infection, as well as a predisposition to autoimmune diseases later in life. Mild to moderate learning difficulties are common.

VCFS has some overlapping features with DiGeorge syndrome, such as conotruncal cardiac defects and facial abnormalities, and is also caused by interstitial deletions of 22q11. Molecular deletions are detected in 90 percent of individuals, while cytogenetically visible deletions are observed in approximately 15 to 30 percent of cases.

The clinical manifestations, diagnosis, and treatment of this disorder are discussed separately. (See "DiGeorge syndrome: Epidemiology and pathogenesis" and "DiGeorge syndrome: Management and prognosis".)

22q11.2 DISTAL DELETION SYNDROME — A number of deletions occur distally to the classic velocardiofacial syndrome (VCFS)/DiGeorge 22q11.2 deletion (MIM #611867) [109-111], including one between LCR22-4 and LCR22-6 of approximately 2.1 megabases (Mb) and another one between LCR22-5 and LCR22-6 spanning 1.4 Mb. All patients with these deletions presented with characteristic dysmorphic features, history of prematurity, prenatal and postnatal growth restriction that may correct in childhood, developmental delay/learning disabilities, and mild skeletal abnormalities. The craniofacial features include arched eyebrows, deep-set eyes, a smooth philtrum, a thin upper lip, hypoplastic alae nasi, and a small, pointed chin. A few patients have cardiovascular malformations (truncus arteriosus, bicuspid aortic valve).

Management of these patients includes developmental evaluations, an echocardiogram to examine for cardiac defects, and occupational and speech therapies.

22q13.3 DELETION SYNDROME (PHELAN-MCDERMID SYNDROME) — Deletions of distal 22q13.3 (MIM #606232) are associated with generalized hypotonia, global developmental delay, severe speech delay, and normal to advanced growth [112-116]. The deletion encompasses the SH3 and multiple ankyrin repeat domains 3 *(SHANK3)* gene that is responsible for the neurologic findings [117-119]. This deletion is also associated with severe expressive language delays and autism.

Formal developmental and autism evaluations are recommended. Management includes occupational and speech therapies. Patients may benefit from augmentative communication methods. (See "Autism spectrum disorder: Diagnosis" and "Autism spectrum disorder: Screening tools" and "Developmental and behavioral screening tests in primary care".)

SUMMARY

- Microdeletions, or submicroscopic deletions, are chromosomal deletions that are too small to be detected by light microscopy using conventional cytogenetics methods. (See 'Introduction' above.)
- Genomic disorders are diseases that result from the loss or gain of chromosomal/DNA material. The most common and better delineated genomic disorders are divided in two main categories,

those resulting from copy number losses (deletion syndromes) and copy number gains (duplication syndromes). (See 'Overview of genomic disorders' above.)

- 15q11-13 deletion syndromes are some of the most common microdeletions. A paternally-derived chromosome 15 with this deletion results in Prader-Willi syndrome (PWS, MIM #176270), whereas a maternally-derived chromosome 15 with a similar deletion is associated with Angelman syndrome (AS, MIM #105830). PWS is characterized by hypotonia; poor feeding in infancy with failure to thrive, but increased appetite and obesity in children and adults; genital hypoplasia; small hands and feet; and distinctive facial features. AS is a neurodevelopmental disorder characterized by severe to profound intellectual disability, postnatal microcephaly, and a movement or balance disorder, usually in the form of gait ataxia and/or tremulous movement of limbs. Patients also often have seizures and characteristic behaviors. (See '15q11-13 maternal deletion syndrome (Angelman syndrome)' above and '15q11-13 paternal deletion syndrome (Prader-Willi syndrome)' above.)
- 16p11.2 deletion syndrome is one of the most common recurrent genomic disorders associated with autism spectrum disorders. Clinical findings include variable levels of intellectual disability with a high incidence of language delay, expressive more so than receptive. (See '16p11.2 deletion syndrome' above.)
- Approximately 80 to 90 percent of patients with DiGeorge syndrome (MIM #188400) have microdeletions involving chromosome 22q11.2. This syndrome is characterized by abnormalities in the development of the third and fourth branchial arches, resulting in hypoplasia of the thymus and/or parathyroid gland, conotruncal cardiac defects, and facial dysmorphism. Clinical manifestations may include neonatal hypocalcemia, susceptibility to infection, mild to moderate learning difficulties, as well as a predisposition to autoimmune diseases later in life. Velocardiofacial syndrome (VCFS) has some overlapping features with DiGeorge syndrome, such as conotruncal cardiac defects and facial abnormalities, and is also caused by interstitial deletions of 22q11. (See '22q11.2 deletion syndromes (DiGeorge syndrome/velocardiofacial syndrome)' above.)

REFERENCES

1. Mitter D, Ullmann R, Muradyan A, et al. Genotype-phenotype correlations in patients with retinoblastoma and interstitial 13q deletions. Eur J Hum Genet 2011; 19:947.
2. GeneReviews: Retinoblastoma. http://www-ncbi-nlm-nih-gov.ezp-prod1.hul.harvard.edu/books/NBK1452/ (Accessed on April 21, 2014).
3. Burnside RD, Pasion R, Mikhail FM, et al. Microdeletion/microduplication of proximal 15q11.2 between BP1 and BP2: a susceptibility region for neurological dysfunction including developmental and language delay. Hum Genet 2011; 130:517.
4. Doornbos M, Sikkema-Raddatz B, Ruijvenkamp CA, et al. Nine patients with a microdeletion 15q11.2 between breakpoints 1 and 2 of the Prader-Willi critical region, possibly associated with behavioural disturbances. Eur J Med Genet 2009; 52:108.
5. Murthy SK, Nygren AO, El Shakankiry HM, et al. Detection of a novel familial deletion of four genes between BP1 and BP2 of the Prader-Willi/Angelman syndrome critical region by oligo-array CGH in a child with neurological disorder and speech impairment. Cytogenet Genome Res 2007; 116:135.
6. Sempere Pérez A, Manchón Trives I, Palazón Azorín I, et al. [15Q11.2 (BP1-BP2) microdeletion, a new syndrome with variable expressivity]. An Pediatr (Barc) 2011; 75:58.
7. Williams CA, Angelman H, Clayton-Smith J, et al. Angelman syndrome: consensus for diagnostic

criteria. Angelman Syndrome Foundation. Am J Med Genet 1995; 56:237.

8. Williams CA, Beaudet AL, Clayton-Smith J, et al. Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet A 2006; 140:413.
9. GeneReviews: Angelman Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK1144/ (Accessed on January 18, 2012).
10. Kishino T, Lalande M, Wagstaff J. UBE3A/E6-AP mutations cause Angelman syndrome. Nat Genet 1997; 15:70.
11. Matsuura T, Sutcliffe JS, Fang P, et al. De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. Nat Genet 1997; 15:74.
12. Sahoo T, Peters SU, Madduri NS, et al. Microarray based comparative genomic hybridization testing in deletion bearing patients with Angelman syndrome: genotype-phenotype correlations. J Med Genet 2006; 43:512.
13. Saitoh S, Buiting K, Cassidy SB, et al. Clinical spectrum and molecular diagnosis of Angelman and Prader-Willi syndrome patients with an imprinting mutation. Am J Med Genet 1997; 68:195.
14. Malcolm S, Clayton-Smith J, Nichols M, et al. Uniparental paternal disomy in Angelman's syndrome. Lancet 1991; 337:694.
15. Buiting K, Gross S, Lich C, et al. Epimutations in Prader-Willi and Angelman syndromes: a molecular study of 136 patients with an imprinting defect. Am J Hum Genet 2003; 72:571.
16. Buiting K, Lich C, Cottrell S, et al. A 5-kb imprinting center deletion in a family with Angelman syndrome reduces the shortest region of deletion overlap to 880 bp. Hum Genet 1999; 105:665.
17. Abaied L, Trabelsi M, Chaabouni M, et al. A novel UBE3A truncating mutation in large Tunisian Angelman syndrome pedigree. Am J Med Genet A 2010; 152A:141.
18. Peters SU, Beaudet AL, Madduri N, Bacino CA. Autism in Angelman syndrome: implications for autism research. Clin Genet 2004; 66:530.
19. Horsthemke B, Buiting K. Imprinting defects on human chromosome 15. Cytogenet Genome Res 2006; 113:292.
20. Horsthemke B, Dittrich B, Buiting K. Imprinting mutations on human chromosome 15. Hum Mutat 1997; 10:329.
21. Schaaf CP, Gonzalez-Garay ML, Xia F, et al. Truncating mutations of MAGEL2 cause Prader-Willi phenotypes and autism. Nat Genet 2013; 45:1405.
22. Sahoo T, del Gaudio D, German JR, et al. Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster. Nat Genet 2008; 40:719.
23. Miller DT, Shen Y, Weiss LA, et al. Microdeletion/duplication at 15q13.2q13.3 among individuals with features of autism and other neuropsychiatric disorders. J Med Genet 2009; 46:242.
24. Sharp AJ, Mefford HC, Li K, et al. A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. Nat Genet 2008; 40:322.
25. van Bon BW, Mefford HC, Menten B, et al. Further delineation of the 15q13 microdeletion and duplication syndromes: a clinical spectrum varying from non-pathogenic to a severe outcome. J Med Genet 2009; 46:511.
26. GeneReviews: 15q13.3 Microdeletion. http://www.ncbi.nlm.nih.gov/books/NBK50780/ (Accessed on January 18, 2012).
27. Hildebrand MS, Avenarius MR, Smith RJH. CATSPER-related male infertility. In: GeneReviews, Pagon RA, Bird TD, Dolan CR, Stephens K (Eds), Seattle (WA), University of Washington, Seattle; 1993-2009 Dec 03. PMID: 20301780.
28. GeneReviews: CATSPER-Related Male Infertility. http://www.ncbi.nlm.nih.gov/books/NBK22925/ (Accessed on January 18, 2012).

29. Mefford HC, Rosenfeld JA, Shur N, et al. Further clinical and molecular delineation of the 15q24 microdeletion syndrome. J Med Genet 2012; 49:110.
30. Klopocki E, Graul-Neumann LM, Grieben U, et al. A further case of the recurrent 15q24 microdeletion syndrome, detected by array CGH. Eur J Pediatr 2008; 167:903.
31. McInnes LA, Nakamine A, Pilorge M, et al. A large-scale survey of the novel 15q24 microdeletion syndrome in autism spectrum disorders identifies an atypical deletion that narrows the critical region. Mol Autism 2010; 1:5.
32. Sharp AJ, Selzer RR, Veltman JA, et al. Characterization of a recurrent 15q24 microdeletion syndrome. Hum Mol Genet 2007; 16:567.
33. Van Esch H, Backx L, Pijkels E, Fryns JP. Congenital diaphragmatic hernia is part of the new 15q24 microdeletion syndrome. Eur J Med Genet 2009; 52:153.
34. GeneReviews: 15q24 Microdeletion Syndrome http://www-ncbi-nlm-nih-gov.ezp-prod1.hul.harvard.edu/books/NBK84258/ (Accessed on April 08, 2014).
35. Punnett HH, Zakai EH. Old syndromes and new cytogenetics. Dev Med Child Neurol 1990; 32:824.
36. Breuning MH, Dauwerse HG, Fugazza G, et al. Rubinstein-Taybi syndrome caused by submicroscopic deletions within 16p13.3. Am J Hum Genet 1993; 52:249.
37. RUBINSTEIN JH, TAYBI H. Broad thumbs and toes and facial abnormalities. A possible mental retardation syndrome. Am J Dis Child 1963; 105:588.
38. Hennekam RC. Rubinstein-Taybi syndrome. Eur J Hum Genet 2006; 14:981.
39. Hennekam RC, Lommen EJ, Strengers JL, et al. Rubinstein-Taybi syndrome in a mother and son. Eur J Pediatr 1989; 148:439.
40. GeneReviews: Rubinstein-Taybi Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK1526/ (Accessed on January 18, 2012).
41. Roelfsema JH, White SJ, Ariyürek Y, et al. Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. Am J Hum Genet 2005; 76:572.
42. Tsai AC, Dossett CJ, Walton CS, et al. Exon deletions of the EP300 and CREBBP genes in two children with Rubinstein-Taybi syndrome detected by aCGH. Eur J Hum Genet 2011; 19:43.
43. Hannes FD, Sharp AJ, Mefford HC, et al. Recurrent reciprocal deletions and duplications of 16p13.11: the deletion is a risk factor for MR/MCA while the duplication may be a rare benign variant. J Med Genet 2009; 46:223.
44. Heinzen EL, Radtke RA, Urban TJ, et al. Rare deletions at 16p13.11 predispose to a diverse spectrum of sporadic epilepsy syndromes. Am J Hum Genet 2010; 86:707.
45. Nagamani SC, Erez A, Bader P, et al. Phenotypic manifestations of copy number variation in chromosome 16p13.11. Eur J Hum Genet 2011; 19:280.
46. de Kovel CG, Trucks H, Helbig I, et al. Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. Brain 2010; 133:23.
47. Human Genome Browser (HG18). http://genome.ucsc.edu/cgi-bin/hgGateway?db=hg18 (Accessed on April 09, 2014).
48. Ballif BC, Hornor SA, Jenkins E, et al. Discovery of a previously unrecognized microdeletion syndrome of 16p11.2-p12.2. Nat Genet 2007; 39:1071.
49. Fernandez BA, Roberts W, Chung B, et al. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11.2 in individuals ascertained for diagnosis of autism spectrum disorder. J Med Genet 2010; 47:195.
50. Hanson E, Nasir RH, Fong A, et al. Cognitive and behavioral characterization of 16p11.2 deletion syndrome. J Dev Behav Pediatr 2010; 31:649.

51. Kumar RA, KaraMohamed S, Sudi J, et al. Recurrent 16p11.2 microdeletions in autism. Hum Mol Genet 2008; 17:628.
52. GeneReviews: 16p11.2 Microdeletion. http://www.ncbi.nlm.nih.gov/books/NBK11167/ (Accessed on January 18, 2012).
53. Weiss LA, Shen Y, Korn JM, et al. Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med 2008; 358:667.
54. Kumar RA, Marshall CR, Badner JA, et al. Association and mutation analyses of 16p11.2 autism candidate genes. PLoS One 2009; 4:e4582.
55. Guha S, Rees E, Darvasi A, et al. Implication of a rare deletion at distal 16p11.2 in schizophrenia. JAMA Psychiatry 2013; 70:253.
56. Schaaf CP, Goin-Kochel RP, Nowell KP, et al. Expanding the clinical spectrum of the 16p11.2 chromosomal rearrangements: three patients with syringomyelia. Eur J Hum Genet 2011; 19:152.
57. Bochukova EG, Huang N, Keogh J, et al. Large, rare chromosomal deletions associated with severe early-onset obesity. Nature 2010; 463:666.
58. Walters RG, Jacquemont S, Valsesia A, et al. A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. Nature 2010; 463:671.
59. Bruno DL, Anderlid BM, Lindstrand A, et al. Further molecular and clinical delineation of co-locating 17p13.3 microdeletions and microduplications that show distinctive phenotypes. J Med Genet 2010; 47:299.
60. Jones KL, Gilbert EF, Kaveggia EG, Opitz JM. The MIller-Dieker syndrome. Pediatrics 1980; 66:277.
61. Stratton RF, Dobyns WB, Airhart SD, Ledbetter DH. New chromosomal syndrome: Miller-Dieker syndrome and monosomy 17p13. Hum Genet 1984; 67:193.
62. Dobyns WB, Stratton RF, Parke JT, et al. Miller-Dieker syndrome: lissencephaly and monosomy 17p. J Pediatr 1983; 102:552.
63. Greenberg F, Stratton RF, Lockhart LH, et al. Familial Miller-Dieker syndrome associated with pericentric inversion of chromosome 17. Am J Med Genet 1986; 23:853.
64. vanTuinen P, Dobyns WB, Rich DC, et al. Molecular detection of microscopic and submicroscopic deletions associated with Miller-Dieker syndrome. Am J Hum Genet 1988; 43:587.
65. Dhellemmes C, Girard S, Dulac O, et al. Agyria--pachygyria and Miller-Dieker syndrome: clinical, genetic and chromosome studies. Hum Genet 1988; 79:163.
66. Oostra BA, de Rijk-van Andel JF, Eussen HJ, et al. DNA analysis in patients with lissencephaly type I and other cortical dysplasias. Am J Med Genet 1991; 40:383.
67. Nagamani SC, Zhang F, Shchelochkov OA, et al. Microdeletions including YWHAE in the Miller-Dieker syndrome region on chromosome 17p13.3 result in facial dysmorphisms, growth restriction, and cognitive impairment. J Med Genet 2009; 46:825.
68. Pilz DT, Macha ME, Precht KS, et al. Fluorescence in situ hybridization analysis with LIS1 specific probes reveals a high deletion mutation rate in isolated lissencephaly sequence. Genet Med 1998; 1:29.
69. De Rijk-van Andel JF, Catsman-Berrevoets CE, Halley DJ, et al. Isolated lissencephaly sequence associated with a microdeletion at chromosome 17p13. Hum Genet 1991; 87:509.
70. Schiff M, Delahaye A, Andrieux J, et al. Further delineation of the 17p13.3 microdeletion involving YWHAE but distal to PAFAH1B1: four additional patients. Eur J Med Genet 2010; 53:303.
71. Tenney JR, Hopkin RJ, Schapiro MB. Deletion of 14-3-3{varepsilon} and CRK: a clinical syndrome with macrocephaly, developmental delay, and generalized epilepsy. J Child Neurol 2011; 26:223.
72. GeneReviews: Hereditary Neuropathy with Liability to Pressure Palsies.

http://www.ncbi.nlm.nih.gov/books/NBK1392/ (Accessed on January 25, 2012).

73. Carmona-Mora P, Walz K. Retinoic Acid Induced 1, RAI1: A Dosage Sensitive Gene Related to Neurobehavioral Alterations Including Autistic Behavior. Curr Genomics 2010; 11:607.
74. Greenberg F, Guzzetta V, Montes de Oca-Luna R, et al. Molecular analysis of the Smith-Magenis syndrome: a possible contiguous-gene syndrome associated with del(17)(p11.2). Am J Hum Genet 1991; 49:1207.
75. Seranski P, Hoff C, Radelof U, et al. RAI1 is a novel polyglutamine encoding gene that is deleted in Smith-Magenis syndrome patients. Gene 2001; 270:69.
76. Slager RE, Newton TL, Vlangos CN, et al. Mutations in RAI1 associated with Smith-Magenis syndrome. Nat Genet 2003; 33:466.
77. Williams SR, Girirajan S, Tegay D, et al. Array comparative genomic hybridisation of 52 subjects with a Smith-Magenis-like phenotype: identification of dosage sensitive loci also associated with schizophrenia, autism, and developmental delay. J Med Genet 2010; 47:223.
78. Girirajan S, Elsas LJ 2nd, Devriendt K, Elsea SH. RAI1 variations in Smith-Magenis syndrome patients without 17p11.2 deletions. J Med Genet 2005; 42:820.
79. Williams SR, Zies D, Mullegama SV, et al. Smith-Magenis syndrome results in disruption of CLOCK gene transcription and reveals an integral role for RAI1 in the maintenance of circadian rhythmicity. Am J Hum Genet 2012; 90:941.
80. Colley AF, Leversha MA, Voullaire LE, Rogers JG. Five cases demonstrating the distinctive behavioural features of chromosome deletion 17(p11.2 p11.2) (Smith-Magenis syndrome). J Paediatr Child Health 1990; 26:17.
81. Smith AC, Dykens E, Greenberg F. Behavioral phenotype of Smith-Magenis syndrome (del 17p11.2). Am J Med Genet 1998; 81:179.
82. GeneReviews: Smith-Magenis Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK1310/ (Accessed on January 25, 2012).
83. Smith AC, Dykens E, Greenberg F. Sleep disturbance in Smith-Magenis syndrome (del 17 p11.2). Am J Med Genet 1998; 81:186.
84. Gropman AL, Duncan WC, Smith AC. Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2). Pediatr Neurol 2006; 34:337.
85. Potocki L, Shaw CJ, Stankiewicz P, Lupski JR. Variability in clinical phenotype despite common chromosomal deletion in Smith-Magenis syndrome [del(17)(p11.2p11.2)]. Genet Med 2003; 5:430.
86. Mefford HC, Clauin S, Sharp AJ, et al. Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes, and epilepsy. Am J Hum Genet 2007; 81:1057.
87. Nagamani SC, Erez A, Shen J, et al. Clinical spectrum associated with recurrent genomic rearrangements in chromosome 17q12. Eur J Hum Genet 2010; 18:278.
88. Moreno-De-Luca D, SGENE Consortium, Mulle JG, et al. Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. Am J Hum Genet 2010; 87:618.
89. Koolen DA, Vissers LE, Pfundt R, et al. A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. Nat Genet 2006; 38:999.
90. Sharp AJ, Hansen S, Selzer RR, et al. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. Nat Genet 2006; 38:1038.
91. Koolen DA, Kramer JM, Neveling K, et al. Mutations in the chromatin modifier gene KANSL1 cause the 17q21.31 microdeletion syndrome. Nat Genet 2012; 44:639.
92. Zollino M, Orteschi D, Murdolo M, et al. Mutations in KANSL1 cause the 17q21.31 microdeletion syndrome phenotype. Nat Genet 2012; 44:636.
93. GeneReviews: KANSL1-Related Intellectual Disability Syndrome. http://www.ncbi.nlm.nih.gov

/books/NBK24676/ (Accessed on April 09, 2014).

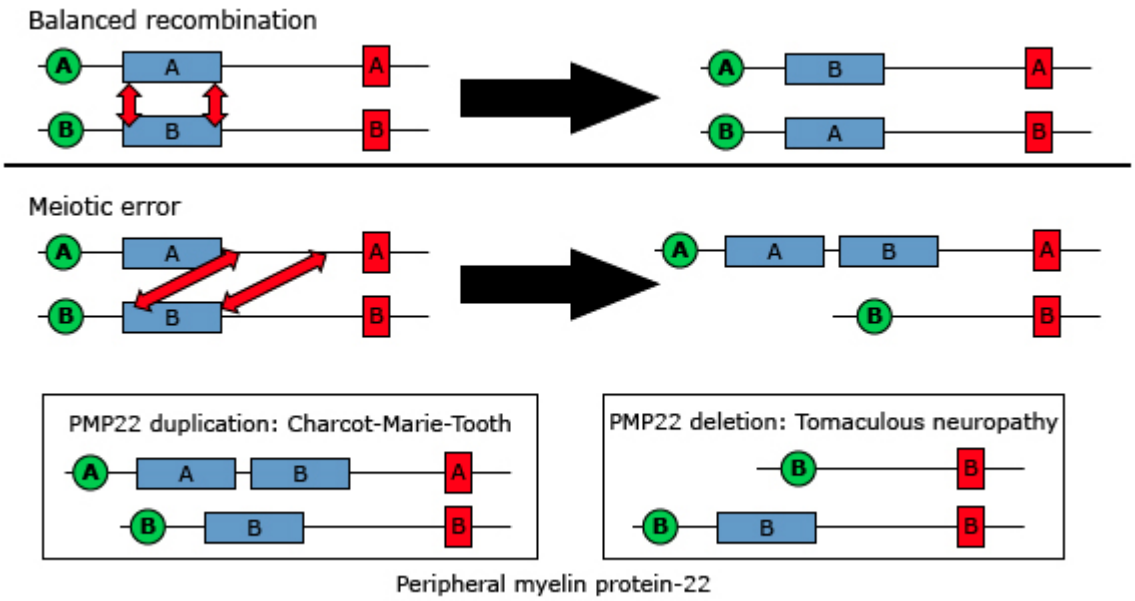
94. Koolen DA, Sharp AJ, Hurst JA, et al. Clinical and molecular delineation of the 17q21.31 microdeletion syndrome. J Med Genet 2008; 45:710.
95. Sharkey FH, Morrison N, Murray R, et al. 17q21.31 microdeletion syndrome: further expanding the clinical phenotype. Cytogenet Genome Res 2009; 127:61.
96. Shaw-Smith C, Pittman AM, Willatt L, et al. Microdeletion encompassing MAPT at chromosome 17q21.3 is associated with developmental delay and learning disability. Nat Genet 2006; 38:1032.
97. GeneReviews: 17q21.31 Microdeletion Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK24676/ (Accessed on January 25, 2012).
98. Turleau C. Monosomy 18p. Orphanet J Rare Dis 2008; 3:4.
99. Koshy B, Mandal K, Srivastava VM, et al. Familial 18p deletion syndrome and 18p partial trisomy inherited from a mother with balanced translocation. Clin Dysmorphol 2011; 20:148.
100. Margarit E, Morales C, Rodríguez-Revenga L, et al. Familial 4.8 MB deletion on 18q23 associated with growth hormone insufficiency and phenotypic variability. Am J Med Genet A 2012; 158A:611.
101. McGoey RR, Gedalia A, Marble M. Monosomy 18p and immunologic dysfunction: review of the literature and a new case report with thyroiditis, IgA deficiency, and systemic lupus erythematosus. Clin Dysmorphol 2011; 20:127.
102. Portnoï MF, Gruchy N, Marlin S, et al. Midline defects in deletion 18p syndrome: clinical and molecular characterization of three patients. Clin Dysmorphol 2007; 16:247.
103. Xie CH, Yang JB, Gong FQ, Zhao ZY. Patent ductus arteriosus and pulmonary valve stenosis in a patient with 18p deletion syndrome. Yonsei Med J 2008; 49:500.
104. Carvalho CA, Carvalho AV, Kiss A, et al. Keratosis pilaris and ulerythema ophryogenes in a woman with monosomy of the short arm of chromosome 18. An Bras Dermatol 2011; 86:S42.
105. Jain N, Reitnauer PJ, Rao KW, et al. Autoimmune polyendocrinopathy associated with ring chromosome 18. J Pediatr Endocrinol Metab 2011; 24:847.
106. Browning MJ. Specific polysaccharide antibody deficiency in chromosome 18p deletion syndrome and immunoglobulin A deficiency. J Investig Allergol Clin Immunol 2010; 20:263.
107. GeneReviews: Alagille Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK1273/ (Accessed on January 25, 2012).
108. GeneReviews: 22q11.2 Deletion Syndrome. http://www.ncbi.nlm.nih.gov/books/NBK1523/ (Accessed on January 25, 2012).
109. Ben-Shachar S, Ou Z, Shaw CA, et al. 22q11.2 distal deletion: a recurrent genomic disorder distinct from DiGeorge syndrome and velocardiofacial syndrome. Am J Hum Genet 2008; 82:214.
110. Nogueira SI, Hacker AM, Bellucco FT, et al. Atypical 22q11.2 deletion in a patient with DGS/VCFS spectrum. Eur J Med Genet 2008; 51:226.
111. Rødningen OK, Prescott T, Eriksson AS, Røsby O. 1.4Mb recurrent 22q11.2 distal deletion syndrome, two new cases expand the phenotype. Eur J Med Genet 2008; 51:646.
112. Phelan MC, Rogers RC, Saul RA, et al. 22q13 deletion syndrome. Am J Med Genet 2001; 101:91.
113. Manning MA, Cassidy SB, Clericuzio C, et al. Terminal 22q deletion syndrome: a newly recognized cause of speech and language disability in the autism spectrum. Pediatrics 2004; 114:451.
114. Okamoto N, Kubota T, Nakamura Y, et al. 22q13 Microduplication in two patients with common clinical manifestations: a recognizable syndrome? Am J Med Genet A 2007; 143A:2804.
115. Peeters H, Vermeesch J, Fryns JP. A cryptic duplication 22q13.31 to qter leads to a distinct phenotype with mental retardation, microcephaly and mild facial dysmorphism. Genet Couns 2008; 19:365.

116. Prasad C, Prasad AN, Chodirker BN, et al. Genetic evaluation of pervasive developmental disorders: the terminal 22q13 deletion syndrome may represent a recognizable phenotype. Clin Genet 2000; 57:103.
117. Bonaglia MC, Giorda R, Mani E, et al. Identification of a recurrent breakpoint within the SHANK3 gene in the 22q13.3 deletion syndrome. J Med Genet 2006; 43:822.
118. Dhar SU, del Gaudio D, German JR, et al. 22q13.3 deletion syndrome: clinical and molecular analysis using array CGH. Am J Med Genet A 2010; 152A:573.
119. Wilson HL, Wong AC, Shaw SR, et al. Molecular characterisation of the 22q13 deletion syndrome supports the role of haploinsufficiency of SHANK3/PROSAP2 in the major neurological symptoms. J Med Genet 2003; 40:575.

Topic 16648 Version 3.0

GRAPHICS

Nonhomologous recombination resulting in copy number variation

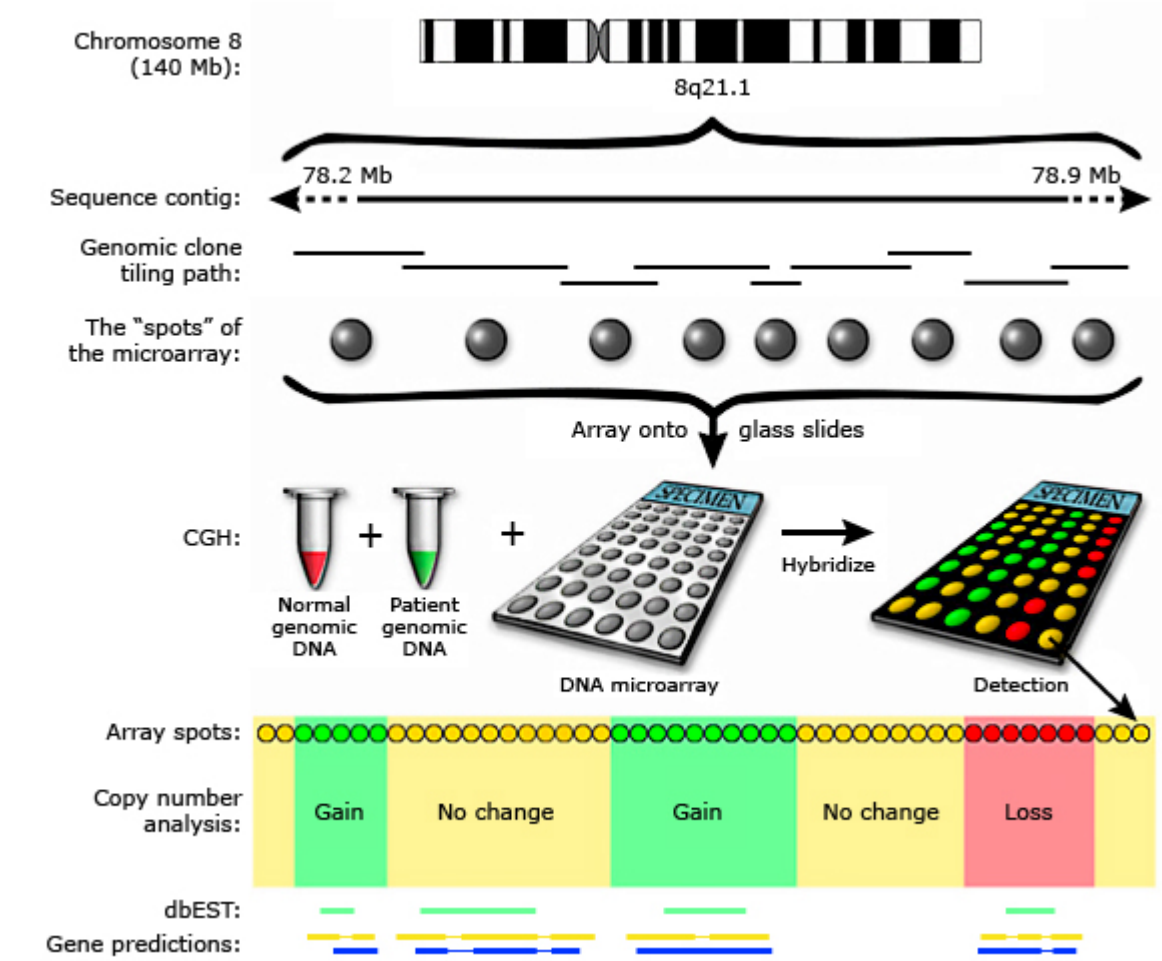


(Upper panel) Normal recombination of homologous region.
(Lower panel) Aberrant recombination, resulting in imbalanced swap of DNA between chromosomes.

PMP22: peripheral myelin protein 22.

Graphic 67644 Version 3.0

Schematic CGH for microarray setup

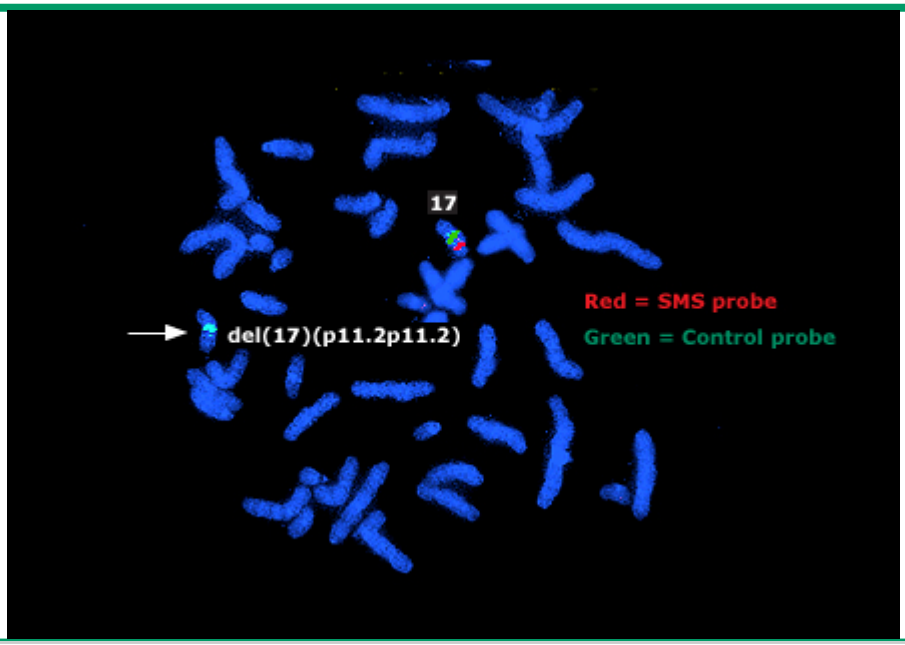


Schematic representation of the array CGH technique for a focused analysis of copy number imbalances along a region of interest (eg, 8q21.1). A tiling path of genomic clones (eg, BACs, PACs, PIs, cosmids) is generated to cover the region. After extraction and purification, these genomic DNA targets are arrayed onto glass slides.
Array CGH is performed by hybridizing labeled normal (Cy3) and tumor (Cy5) genomic DNA into the microarray and detected using a microarray scanner.
Each array spot, realigned *in silico* as a single contiguous map to correspond with the tiling path, can be analyzed by fluorescence ratio to identify the regions of copy number changes. These results may be correlated with *in silico* techniques to identify candidate genes of interest.

CGH: comparative genomic hybridization; BAC: bacterial artificial chromosome; PAC: P1 bacteriophage artificial chromosome; P1: P1 bacteriophage; Cy3: cyanine dye with green fluorescence; Cy5: cyanine dye with red fluorescence.

Graphic 58888 Version 10.0

Smith-Magenis syndrome



Smith-Magenis syndrome (SMS) is typified by a microdeletion of chromosome band 17p11.2. Fluorescence in situ hybridization (FISH) analysis of a patient's chromsomes is shown. The green control probe shows that an unrelated region of chromosome 17 is present in both chromosomes 17. The red probe, which detects the 17p11.2 region commonly deleted in SMS, only fluoresces on a single chromosome. This finding strongly supports the diagnosis of SMS.

Courtesy of Athena Cherry, Stanford Hospital and Clinics.

Graphic 67417 Version 3.0

Disclosures

Disclosures: **Carlos A Bacino, MD, FACMG** Nothing to disclose. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Elizabeth TePas, MD, MS** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Microduplication syndromes

Author Carlos A Bacino, MD, FACMG
Section Editor Helen V Firth, DM, FRCP, DCH
Deputy Editor Elizabeth TePas, MD, MS

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Oct 14, 2014.

INTRODUCTION — Microduplications, or submicroscopic duplications, are chromosomal duplications that are too small to be detected by light microscopy using conventional cytogenetics methods. Specialized testing is needed to identify these duplications. Microduplications are typically one to three megabases (Mb) long and involve several contiguous genes. The exact size and location of a microduplication that causes a syndrome may vary, but a specific "critical region" is consistently involved. Most of the phenotypic effects of these microduplications are due to changes in a few critical dose-sensitive genes, or in some cases, a single gene.

The phenotype of microduplication syndromes is often less clear and less well defined than for the corresponding microdeletion syndrome. In addition, some microduplication syndromes may be inherited from apparently normal parents raising important issues regarding incomplete penetrance and ascertainment bias in these newly described clinical entities.

This topic reviews microduplication syndromes of chromosomes 1 to 22. Microdeletion syndromes, congenital abnormalities of the sex chromosomes, and other congenital chromosomal abnormalities, such as trisomies, are reviewed in detail elsewhere. (See "Microdeletion syndromes (chromosomes 1 to 11)" and "Microdeletion syndromes (chromosomes 12 to 22)" and "Sex chromosome abnormalities" and "Congenital cytogenetic abnormalities".)

OVERVIEW OF GENOMIC DISORDERS — Genomic disorders are diseases that result from the loss or gain of chromosomal/DNA material. The most common and better delineated genomic disorders are divided in two main categories: those resulting from copy number losses (deletion syndromes) and those resulting from copy number gains (duplication syndromes). (See "Genomic disorders: An overview".)

Copy number variations (CNVs) are submicroscopic genomic differences in the number of copies of one or more sections of DNA that result in DNA gains or losses (figure 1). Some CNVs are pathogenic and cause syndromic disorders with consistent phenotypic features, as are discussed here. Other CNVs are associated with disease susceptibility or resistance, and the same CNV can be associated with several diverse disorders. Still, other CNVs are part of normal genetic variation and have no recognized disease association. Contiguous gene syndromes can occur when CNVs affect several adjacent genes. (See "Overview of genetic variation", section on 'Copy number variations (CNVs)' and "Basic principles of genetic disease", section on 'Copy number variation'.)

The main mechanism that leads to disease in genomic disorders secondary to deletions and duplications is a change in the copy number of a dose-sensitive gene or genes. Other disease mechanisms include interference with imprinted genes and with regulatory elements outside genes. (See "Genomic disorders: An overview", section on 'Disease mechanisms'.)

Genomic disorders are typically detected by array comparative genomic hybridization (array CGH) (figure 2). Most laboratories confirm gains or losses detected on an array with an independent method, such as fluorescent in situ hybridization (FISH), multiple ligation-dependent probe amplification (MLPA), or quantitative polymerase chain reaction (Q-PCR). (See "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Array comparative genomic hybridization' and "Tools for genetics

and genomics: Cytogenetics and molecular genetics", section on 'Fluorescence in situ hybridization'.)

1q21.1 DUPLICATION SYNDROME — Recurrent duplications in this region encompassing approximately 1.35 megabases (Mb) are associated with macrocephaly and mild intellectual disabilities (speech delay, learning disabilities) (MIM #612475) [1,2]. Psychiatric conditions, such as schizophrenia in adult patients [3], and attention-deficit hyperactivity disorder (ADHD) have also been reported. *HYDIN* (hydrocephalus-inducing, mouse, homolog of) is the gene implicated in this disorder. The presentation is variable, due to incomplete penetrance and variable expressivity. Thus, this microduplication is also seen in asymptomatic individuals. (See "Microdeletion syndromes (chromosomes 1 to 11)", section on '1q21.1 deletion syndrome'.)

Neurodevelopmental evaluation is recommended. Older patients should be assessed for later onset psychiatric conditions such as schizophrenia. Patients may benefit from physical, occupational, and speech therapies.

3q29 DUPLICATION SYNDROME — This recurrent duplication has variable clinical findings and is the reciprocal rearrangement of the deletion. *PAK2* (p21 protein-activated kinase 2) and *DLG1* (discs large, drosophila, homolog of, 1) are the critical gene candidates. Clinical findings include microcephaly; low set, simple ears; downturned corners of the mouth; long, bushy eyebrows; long eyelashes; high nasal bridge; eye abnormalities (microphthalmia, cataracts, irides colobomas); cleft palate; and renal and cardiac anomalies (MIM #611936) [4-6]. Mild to moderate intellectual disabilities are common and patients may have speech delay. However, this duplication has been seen in apparently unaffected individuals. (See "Microdeletion syndromes (chromosomes 1 to 11)", section on '3q29 deletion syndrome'.)

Brain imaging studies are recommended in the presence of microcephaly. Other screening studies include renal ultrasound, echocardiogram, and fundoscopic eye exam. Patients may benefit from physical, occupational, and speech therapies.

5q35 MICRODUPLICATION SYNDROME — 5q35 is the Sotos syndrome critical region that contains the Sotos syndrome gene, *NSD1* (nuclear receptor-binding Su-var, enhancer of zeste, and trithorax domain protein 1). The 5q35 microduplication syndrome is basically a reverse of the Sotos syndrome (overgrowth) phenotype [7,8]. Patients with duplications involving *NSD1* present with microcephaly, global developmental delay, short stature, growth retardation, and delayed bone age. Seizures have been reported in some patients. (See "Microdeletion syndromes (chromosomes 1 to 11)", section on '5q35 deletion syndrome (Sotos syndrome)'.)

Recommended screening studies include brain magnetic resonance imaging (MRI) and electroencephalogram (EEG). Growth should be monitored.

7q11.23 DUPLICATION SYNDROME (WILLIAMS-BEUREN REGION DUPLICATION SYNDROME) — Deletions in this region are associated with Williams syndrome (MIM #609757). The reciprocal duplication causes a different clinical phenotype characterized by hypotonia and global developmental delay, with speech delay that can range from moderate to severe. Many of these patients have been diagnosed with autism spectrum disorders [9,10]. Dysmorphic features are mild and without a clear characteristic pattern. Brain abnormalities have been observed and seizures reported [11]. The genes responsible for the phenotype are not yet known.

Hearing evaluations are recommended to rule out other causes of speech delay. Other screening studies include speech evaluation, brain magnetic resonance imaging (MRI), and electroencephalogram (EEG). Referral to speech therapy is recommended.

11p15 DUPLICATIONS IN BECKWITH-WIEDEMANN SYNDROME — Beckwith-Wiedemann syndrome (BWS, MIM #130650) can be caused by microduplication of the 11p15 region of paternal origin. The

major clinical features of this syndrome are macrosomia, macroglossia, omphalocele, prominent eyes, ear creases, large kidneys, hyperplasia of pancreas, and hemihypertrophy. BWS is discussed in greater detail separately. (See "Beckwith-Wiedemann syndrome".)

15q11-13 DUPLICATION SYNDROME — Deletion of this imprinted region causes Angelman/Prader-Willi syndromes. Gains and duplications of this region are seen in some patients with autism (MIM #608636) [12-14]. In most of the cases, the diagnosis of autism is associated with duplication of the maternally inherited allele [15,16]. These patients may also present with hypotonia, global developmental delay, attention-deficit hyperactivity disorder (ADHD), ataxia, and seizures. The Angelman syndrome gene, *UBE3A* (ubiquitin-protein ligase E3A), is the gene potentially responsible for the autism. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '15q11-13 maternal deletion syndrome (Angelman syndrome)' and "Microdeletion syndromes (chromosomes 12 to 22)", section on '15q11-13 paternal deletion syndrome (Prader-Willi syndrome)'.)

Formal developmental and autism evaluations are recommended. Assessment of seizures includes an electroencephalogram (EEG). (See "Autism spectrum disorder: Diagnosis" and "Autism spectrum disorder: Screening tools" and "Developmental and behavioral screening tests in primary care".)

15q13.3 DUPLICATION SYNDROME — This 1.5 megabase (Mb) microduplication is reciprocal to the 15q13.3 deletion and extends between breakpoints BP4 and BP5. One-half of individuals ascertained with this duplication have a range of neuropsychiatric disorders [17]. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '15q13.3 deletion syndrome'.)

15q24 DUPLICATION SYNDROME — This is the reciprocal duplication of the 15q24 deletion (MIM #613406). The cases described share similar clinical features with the deletion syndrome, including mild intellectual disability, receding anterior hairline, broad medial eyebrows, hypertelorism, epicanthal folds, downslanting palpebral fissures, broad nasal base and high nasal bridge, full lower lip, joint laxity, and in some cases, contractures, as well as hypospadias and genital anomalies in males [18,19]. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '15q24 deletion syndrome'.)

Formal developmental evaluation is recommended. Endocrine and urology evaluation is performed in males if needed. Patients may benefit from physical, occupational, and speech therapies.

16p13.3 DUPLICATION SYNDROME — This duplication involves the Rubinstein-Taybi critical region and includes the *CREBBP* (cyclic adenosine monophosphate [cAMP]–response element-binding protein [CREB]-binding protein) gene. Clinical features include normal growth, mild to moderate developmental delay, small and proximally implanted thumbs, long fingers, and mild arthrogryposis (multiple joint contractures) with camptodactyly (flexion deformities of the proximal interphalangeal joints). Dysmorphic features include deep set eyes, narrow palpebral fissures, wide nasal bridge, long philtrum, and thin upper lip. This duplication is occasionally associated with heart defects (atrial septal defect [ASD], tetralogy of Fallot [TOF]), submucous cleft palate anomalies, and eye anomalies (strabismus, blepharophimosis, and ptosis). The penetrance of this duplication is variable, since it has been found in normal transmitting parents [20,21].

16p13.11 DUPLICATION SYNDROME — Clinical findings for this duplication that spans approximately 1.65 megabases (Mb) include behavioral abnormalities, cognitive impairment, autism, congenital heart defects, and skeletal manifestations, such as hypermobility, craniosynostosis, and polydactyly [22,23].

16p11.2 DUPLICATION SYNDROME — This recurrent rearrangement is the reciprocal event of the deletion in 16p11.2 that spans almost 600 kb. There is significant variability in the clinical manifestations, ranging from normal in the majority of cases to developmental delay and autistic spectrum disorders [24-27]. A number of other neurodevelopmental and behavioral disorders have been observed as well [28]. This duplication is associated with an increased risk for seizure disorders such as infantile spasms [29] and Rolandic epilepsy [30]. Other clinical findings seen in patients with this duplication include

thoracolumbar syringomyelia [31]. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '16p11.2 deletion syndrome'.)

Formal developmental and autism evaluations are recommended in affected patients. Electroencephalography (EEG) evaluation is indication in patients with clinically suspected seizures. A spine magnetic resonance image (MRI) should be considered, since syringomyelia may be asymptomatic.

17p13.3 DUPLICATION SYNDROME — While deletions in the distal short arm of chromosome 17 cause Miller-Dieker lissencephaly syndrome, duplications in this region are associated with developmental delay, central nervous system (CNS) anomalies, and autism spectrum disorder (MIM #613215) [32]. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '17p13.3 deletion syndromes'.)

There are two duplication types: class I and class II. The critical region for class I spans 258 kb and includes six genes: exons 2 to 3 of *TUSC5* (tumor suppressor candidate 5), *YWHAE* (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon isoform), *CRK* (v-crk avian sarcoma virus CT10 oncogene homolog), *MYO1C* (myosin IC), *SKIP* (sphingosine kinase 1 [SPHK1]-interacting protein), and exons 1 to 4 of *PITPNA* (phosphatidylinositol transfer protein, alpha). It appears that *YWHAE* plays the main role in the CNS anomalies and autism phenotype, while *CRK* seems to be the gene responsible for growth restriction. The class II duplication additionally includes *PAFAH1B1/LIS1* (platelet-activating factor acetylhydrolase, isoform 1B, alpha subunit), the lissencephaly gene responsible for lissencephaly type I.

Clinical findings for class I duplications include autistic features, behavioral problems, speech and motor delays, mild dysmorphic features (or none), hand and feet malformations (large hands, small distal phalanges), and overgrowth (a rare feature for a chromosomal/genomic disorder). Class II duplications show a range from normal intellect to severe intellectual disability, hypotonia that can be severe, autism, attention-deficit hyperactivity disorder (ADHD), microcephaly, dysmorphic features, and severe growth restriction. There are no migration abnormalities in the brain even though *LIS1* is involved. However, corpus callosum dysgenesis and cerebellar volume loss have been reported. *LIS1* overexpression appears to lead to smaller brains based upon animal studies [33]. Other abnormalities for class II duplications include craniosynostosis, intestinal malrotation, scoliosis, cardiovascular anomalies, and other skeletal anomalies.

Formal developmental and autism evaluations are recommended. A brain magnetic resonance image (MRI) is also recommended in patients with class II duplications. Patients may benefit from physical, occupational, and speech therapies.

17p11.2 DUPLICATION SYNDROME (CHARCOT-MARIE-TOOTH TYPE 1A DISEASE) — Recurrent 1.5 megabases (Mb) duplications in 17p11.2 involving the *PMP22* (peripheral myelin protein 22) gene are responsible for Charcot-Marie-Tooth type 1A (CMT1A) disease (MIM #118220). *PMP22* is a dose-sensitive gene that causes CMT1A when overexpressed and hereditary neuropathy with liability to pressure palsy (HNPP) when underexpressed. CMT1A is a demyelinating motor-sensory neuropathy clinically characterized by progressive distal neuromuscular weakness. These patients present with foot and ankle problems including pain, weakness, deformity, and paresthesias. Foot drop and bilateral pes cavus are common. The muscles are wasted distally and conserved proximally. CMT1A is discussed in greater detail separately. (See "Hereditary primary motor sensory neuropathies, including Charcot-Marie-Tooth disease" and "Microdeletion syndromes (chromosomes 12 to 22)", section on '17p11.2 deletion syndrome (Hereditary neuropathy with liability to pressure palsy)'.)

17p11.2 DUPLICATION SYNDROME (POTOCKI-LUPSKI SYNDROME) — This duplication, also known as Potocki-Lupski syndrome (PLS, MIM #610883), is reciprocal to the deletion on chromosome 17 that is

responsible for Smith-Magenis syndrome [34-36]. The common duplication spans 3.7 megabases (Mb), but the critical region spans 1.3 Mb and includes the *RAI1* (retinoic acid receptor 1) gene, a dose-sensitive gene presumably involved in the neurobehavioral and autism phenotype seen in these patients [37]. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '17p11.2 deletion syndrome (Smith-Magenis syndrome)'.)

The clinical findings include infantile hypotonia, failure to thrive, intellectual disability, poor feeding, oropharyngeal dysplasia, and sleep apnea (obstructive and central sleep apnea with hypercarbia) [34,35,38]. Speech development is significantly impaired, with delays, absent speech, delayed echolalia, and verbal apraxia. Autistic spectrum disorders are seen. Structural cardiovascular abnormalities (septal defects) are part of the spectrum and can be rather severe, including hypoplastic left heart [36,39].

Formal developmental and autism evaluation are recommended. Other screening studies include a brain magnetic resonance image (MRI), echocardiogram, swallowing evaluations, and sleep studies. Referral to physical, occupational, and speech therapies is recommended.

17q21.31 DUPLICATION SYNDROME — This duplication involves the *MAPT* (microtubule-associated protein Tau) and *CRHR1* (corticotropin-releasing hormone receptor 1) genes (MIM #613533) and is similarly mediated by the inversion repeats flanking the *MAPT* gene as seen in the deletion. In the few reports of this duplication, it is associated with variable clinical features that range from normal cognition to severe intellectual disability, hypotonia, and joint laxity [40]. Further reports are required to determine the clinical range of this duplication. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '17q21.31 deletion syndrome'.)

22q11.2 DUPLICATION SYNDROME — Duplications of the 22q11.2 region are reciprocal to the velocardiofacial syndrome (VCFS)/DiGeorge syndrome (DGS) recurrent deletions. The size of the duplications ranges from 1.5 to 3 megabases (Mb), depending upon the low copy repeats (LCRs) involved in the rearrangement. The LCRs surrounding the region are known as LCR22A to LCR22D. The common duplication is 3 Mb long and encompasses LCR22A to LCR22B. The common duplication includes *TBX1* (T-box 1), the putative gene for the congenital heart defects seen in this condition. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '22q11.2 deletion syndromes (DiGeorge syndrome/velocardiofacial syndrome)'.)

The clinical features share some similarities with VCFS/DGS, including mild to severe intellectual disability (deficits of memory performance, perceptual organization, and verbal comprehension; attention-deficit hyperactivity disorder [ADHD]; and speech impairment), growth restriction, velopharyngeal incompetence, heart defects, and palatal abnormalities. Heart defects reported share similarities with the deletion and include defects affecting the outflow ventricular tracts and other conotruncal abnormalities [41-43]. Other clinical findings reported include visual and hearing impairment, seizures, microcephaly, ptosis, and urogenital abnormalities. Many of these duplications are inherited, some of them from unaffected parents, therefore caution should be applied in interpreting genetic testing results and counseling families appropriately given the interfamilial and intrafamilial clinical variability seen with this duplication [44,45].

Screening studies include formal developmental evaluation, echocardiogram, and swallowing evaluations. Patients may benefit from physical, occupational, and speech therapies.

22q13 DUPLICATIONS — Duplications of the 22q13 region have been reported in a few children with infantile hypotonia, mild to moderate developmental delay, microcephaly, autism spectrum disorder, growth deficiency, and mild dysmorphic facial features [46]. This region includes several genes associated with mitochondrial function, and one patient with 22q13 duplication has been reported with mitochondrial disease [47]. The critical region includes the *SHANK3* (Src homology 3 and multiple ankyrin repeat domains 3) gene. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on

'22q13.3 deletion syndrome (Phelan-McDermid syndrome)'.)

SUMMARY

- Genomic disorders are diseases that result from the loss or gain of chromosomal/DNA material. The most common and better delineated genomic disorders are divided in two main categories: those resulting from copy number losses (deletion syndromes) and those resulting from copy number gains (duplication syndromes). (See 'Overview of genomic disorders' above.)
- Microduplications, or submicroscopic duplications, are chromosomal duplications that are too small to be detected by light microscopy using conventional cytogenetics methods. (See 'Introduction' above.)
- Deletions in the 7q11.23 region are associated with Williams syndrome (MIM #609757). The reciprocal duplication causes a different clinical phenotype characterized by hypotonia and global developmental delay, with speech delay that can range from moderate to severe. (See '7q11.23 duplication syndrome (Williams-Beuren region duplication syndrome)' above.)
- Gains and duplications of the 15q11-13 region are seen in some patients with autism (MIM #608636). These patients may also present with hypotonia, global developmental delay, attention-deficit hyperactivity disorder (ADHD), ataxia, and seizures. (See '15q11-13 duplication syndrome' above.)
- Recurrent 1.5 megabase (Mb) duplications in 17p11.2 involving the *PMP22* (peripheral myelin protein 22) gene are responsible for Charcot-Marie-Tooth type 1A (CMT1A) disease (MIM #118220). CMT1A is a demyelinating motor-sensory neuropathy clinically characterized by progressive distal neuromuscular weakness. (See '17p11.2 duplication syndrome (Charcot-Marie-Tooth type 1A disease)' above.)
- Duplications of the 22q11.2 region are reciprocal to the velocardiofacial syndrome (VCFS)/DiGeorge syndrome (DGS) recurrent deletions. The clinical features share some similarities with VCFS/DGS, including mild to severe intellectual disability (deficits of memory performance, perceptual organization, and verbal comprehension; ADHD; and speech impairment), growth restriction, velopharyngeal incompetence, heart defects, and palatal abnormalities. Other clinical findings reported include visual and hearing impairment, seizures, microcephaly, ptosis, and urogenital abnormalities. (See '22q11.2 duplication syndrome' above.)

REFERENCES

1. Brunetti-Pierri N, Berg JS, Scaglia F, et al. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet 2008; 40:1466.
2. Mefford HC, Sharp AJ, Baker C, et al. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. N Engl J Med 2008; 359:1685.
3. Dolcetti A, Silversides CK, Marshall CR, et al. 1q21.1 Microduplication expression in adults. Genet Med 2013; 15:282.
4. Ballif BC, Theisen A, Coppinger J, et al. Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. Mol Cytogenet 2008; 1:8.
5. Goobie S, Knijnenburg J, Fitzpatrick D, et al. Molecular and clinical characterization of de novo and

familial cases with microduplication 3q29: guidelines for copy number variation case reporting. Cytogenet Genome Res 2008; 123:65.

6. Lisi EC, Hamosh A, Doheny KF, et al. 3q29 interstitial microduplication: a new syndrome in a three-generation family. Am J Med Genet A 2008; 146A:601.
7. Franco LM, de Ravel T, Graham BH, et al. A syndrome of short stature, microcephaly and speech delay is associated with duplications reciprocal to the common Sotos syndrome deletion. Eur J Hum Genet 2010; 18:258.
8. Zhang H, Lu X, Beasley J, et al. Reversed clinical phenotype due to a microduplication of Sotos syndrome region detected by array CGH: microcephaly, developmental delay and delayed bone age. Am J Med Genet A 2011; 155A:1374.
9. Sanders SJ, Ercan-Sencicek AG, Hus V, et al. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. Neuron 2011; 70:863.
10. Berg JS, Brunetti-Pierri N, Peters SU, et al. Speech delay and autism spectrum behaviors are frequently associated with duplication of the 7q11.23 Williams-Beuren syndrome region. Genet Med 2007; 9:427.
11. Torniero C, Dalla Bernardina B, Novara F, et al. Dysmorphic features, simplified gyral pattern and 7q11.23 duplication reciprocal to the Williams-Beuren deletion. Eur J Hum Genet 2008; 16:880.
12. Baker P, Piven J, Schwartz S, Patil S. Brief report: duplication of chromosome 15q11-13 in two individuals with autistic disorder. J Autism Dev Disord 1994; 24:529.
13. Bolton PF, Dennis NR, Browne CE, et al. The phenotypic manifestations of interstitial duplications of proximal 15q with special reference to the autistic spectrum disorders. Am J Med Genet 2001; 105:675.
14. Piard J, Philippe C, Marvier M, et al. Clinical and molecular characterization of a large family with an interstitial 15q11q13 duplication. Am J Med Genet A 2010; 152A:1933.
15. Bundey S, Hardy C, Vickers S, et al. Duplication of the 15q11-13 region in a patient with autism, epilepsy and ataxia. Dev Med Child Neurol 1994; 36:736.
16. Flejter WL, Bennett-Baker PE, Ghaziuddin M, et al. Cytogenetic and molecular analysis of inv dup(15) chromosomes observed in two patients with autistic disorder and mental retardation. Am J Med Genet 1996; 61:182.
17. van Bon BW, Mefford HC, Menten B, et al. Further delineation of the 15q13 microdeletion and duplication syndromes: a clinical spectrum varying from non-pathogenic to a severe outcome. J Med Genet 2009; 46:511.
18. El-Hattab AW, Smolarek TA, Walker ME, et al. Redefined genomic architecture in 15q24 directed by patient deletion/duplication breakpoint mapping. Hum Genet 2009; 126:589.
19. Kiholm Lund AB, Hove HD, Kirchhoff M. A 15q24 microduplication, reciprocal to the recently described 15q24 microdeletion, in a boy sharing clinical features with 15q24 microdeletion syndrome patients. Eur J Med Genet 2008; 51:520.
20. Marangi G, Leuzzi V, Orteschi D, et al. Duplication of the Rubinstein-Taybi region on 16p13.3 is associated with a distinctive phenotype. Am J Med Genet A 2008; 146A:2313.
21. Thienpont B, Béna F, Breckpot J, et al. Duplications of the critical Rubinstein-Taybi deletion region on chromosome 16p13.3 cause a novel recognisable syndrome. J Med Genet 2010; 47:155.
22. Nagamani SC, Erez A, Bader P, et al. Phenotypic manifestations of copy number variation in chromosome 16p13.11. Eur J Hum Genet 2011; 19:280.
23. Ramalingam A, Zhou XG, Fiedler SD, et al. 16p13.11 duplication is a risk factor for a wide spectrum of neuropsychiatric disorders. J Hum Genet 2011; 56:541.

24. Fernandez BA, Roberts W, Chung B, et al. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11.2 in individuals ascertained for diagnosis of autism spectrum disorder. J Med Genet 2010; 47:195.
25. Weiss LA, Shen Y, Korn JM, et al. Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med 2008; 358:667.
26. Kumar RA, Marshall CR, Badner JA, et al. Association and mutation analyses of 16p11.2 autism candidate genes. PLoS One 2009; 4:e4582.
27. Kumar RA, KaraMohamed S, Sudi J, et al. Recurrent 16p11.2 microdeletions in autism. Hum Mol Genet 2008; 17:628.
28. McCarthy SE, Makarov V, Kirov G, et al. Microduplications of 16p11.2 are associated with schizophrenia. Nat Genet 2009; 41:1223.
29. Michaud JL, Lachance M, Hamdan FF, et al. The genetic landscape of infantile spasms. Hum Mol Genet 2014; 23:4846.
30. Reinthaler EM, Lal D, Lebon S, et al. 16p11.2 600 kb Duplications confer risk for typical and atypical Rolandic epilepsy. Hum Mol Genet 2014; 23:6069.
31. Schaaf CP, Goin-Kochel RP, Nowell KP, et al. Expanding the clinical spectrum of the 16p11.2 chromosomal rearrangements: three patients with syringomyelia. Eur J Hum Genet 2011; 19:152.
32. Bruno DL, Anderlid BM, Lindstrand A, et al. Further molecular and clinical delineation of co-locating 17p13.3 microdeletions and microduplications that show distinctive phenotypes. J Med Genet 2010; 47:299.
33. Bi W, Sapir T, Shchelochkov OA, et al. Increased LIS1 expression affects human and mouse brain development. Nat Genet 2009; 41:168.
34. Potocki L, Bi W, Treadwell-Deering D, et al. Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. Am J Hum Genet 2007; 80:633.
35. Potocki L, Chen KS, Park SS, et al. Molecular mechanism for duplication 17p11.2- the homologous recombination reciprocal of the Smith-Magenis microdeletion. Nat Genet 2000; 24:84.
36. Yusupov R, Roberts AE, Lacro RV, et al. Potocki-Lupski syndrome: an inherited dup(17)(p11.2p11.2) with hypoplastic left heart. Am J Med Genet A 2011; 155A:367.
37. Carmona-Mora P, Walz K. Retinoic Acid Induced 1, RAI1: A Dosage Sensitive Gene Related to Neurobehavioral Alterations Including Autistic Behavior. Curr Genomics 2010; 11:607.
38. Soler-Alfonso C, Motil KJ, Turk CL, et al. Potocki-Lupski syndrome: a microduplication syndrome associated with oropharyngeal dysphagia and failure to thrive. J Pediatr 2011; 158:655.
39. Sanchez-Valle A, Pierpont ME, Potocki L. The severe end of the spectrum: Hypoplastic left heart in Potocki-Lupski syndrome. Am J Med Genet A 2011; 155A:363.
40. Kirchhoff M, Bisgaard AM, Duno M, et al. A 17q21.31 microduplication, reciprocal to the newly described 17q21.31 microdeletion, in a girl with severe psychomotor developmental delay and dysmorphic craniofacial features. Eur J Med Genet 2007; 50:256.
41. Ensenauer RE, Adeyinka A, Flynn HC, et al. Microduplication 22q11.2, an emerging syndrome: clinical, cytogenetic, and molecular analysis of thirteen patients. Am J Hum Genet 2003; 73:1027.
42. Ou Z, Berg JS, Yonath H, et al. Microduplications of 22q11.2 are frequently inherited and are associated with variable phenotypes. Genet Med 2008; 10:267.
43. Yobb TM, Somerville MJ, Willatt L, et al. Microduplication and triplication of 22q11.2: a highly variable syndrome. Am J Hum Genet 2005; 76:865.
44. Courtens W, Schramme I, Laridon A. Microduplication 22q11.2: a benign polymorphism or a syndrome with a very large clinical variability and reduced penetrance?--Report of two families. Am

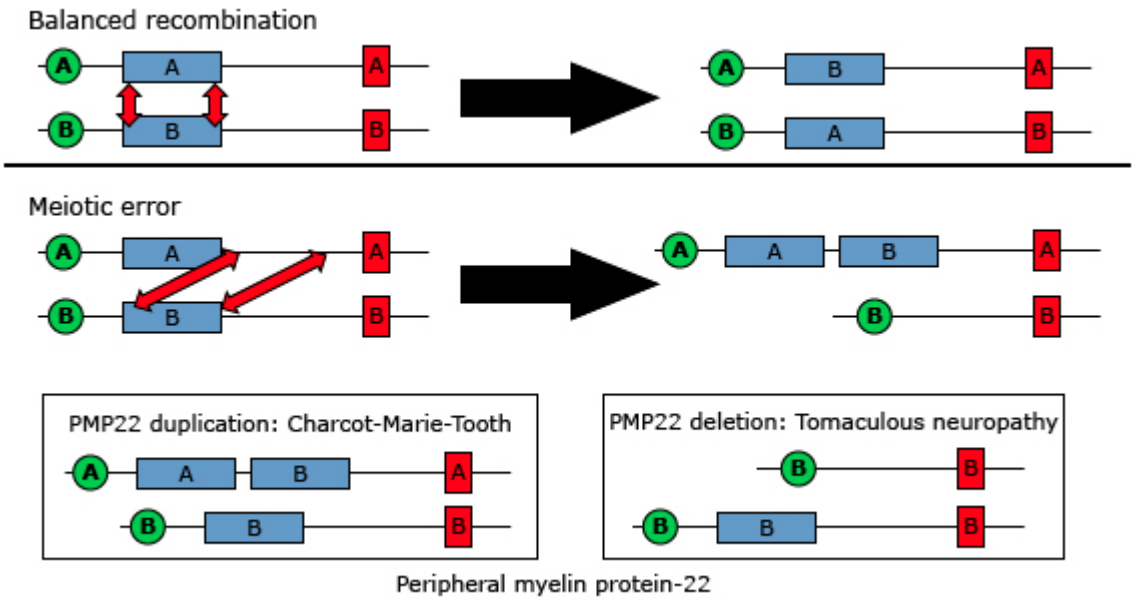
J Med Genet A 2008; 146A:758.

45. Wentzel C, Fernström M, Ohrner Y, et al. Clinical variability of the 22q11.2 duplication syndrome. Eur J Med Genet 2008; 51:501.
46. Okamoto N, Kubota T, Nakamura Y, et al. 22q13 Microduplication in two patients with common clinical manifestations: a recognizable syndrome? Am J Med Genet A 2007; 143A:2804.
47. Frye RE. Mitochondrial disease in 22q13 duplication syndrome. J Child Neurol 2012; 27:942.

Topic 13557 Version 2.0

GRAPHICS

Nonhomologous recombination resulting in copy number variation

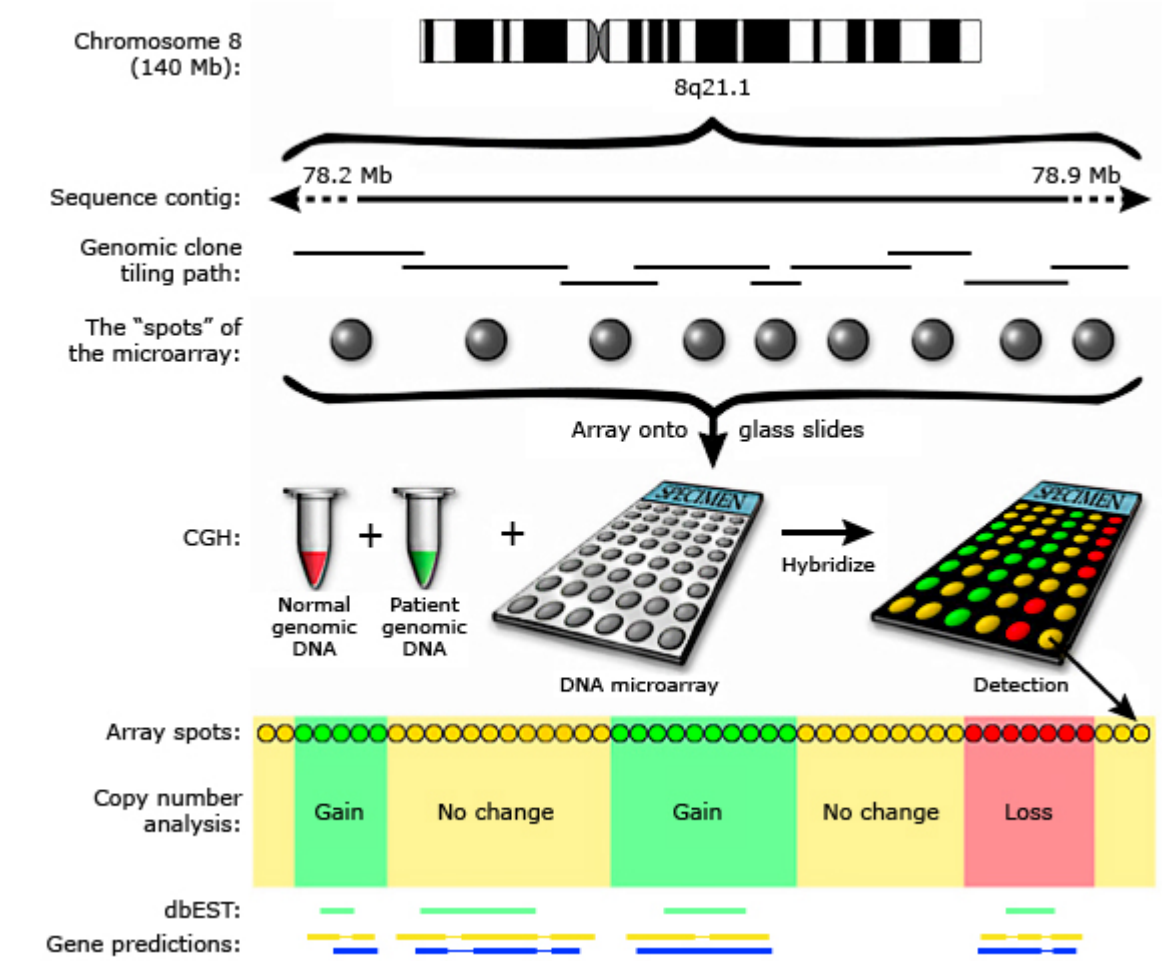


(Upper panel) Normal recombination of homologous region.
(Lower panel) Aberrant recombination, resulting in imbalanced swap of DNA between chromosomes.

PMP22: peripheral myelin protein 22.

Graphic 67644 Version 3.0

Schematic CGH for microarray setup



Schematic representation of the array CGH technique for a focused analysis of copy number imbalances along a region of interest (eg, 8q21.1). A tiling path of genomic clones (eg, BACs, PACs, PIs, cosmids) is generated to cover the region. After extraction and purification, these genomic DNA targets are arrayed onto glass slides.
Array CGH is performed by hybridizing labeled normal (Cy3) and tumor (Cy5) genomic DNA into the microarray and detected using a microarray scanner.
Each array spot, realigned *in silico* as a single contiguous map to correspond with the tiling path, can be analyzed by fluorescence ratio to identify the regions of copy number changes. These results may be correlated with *in silico* techniques to identify candidate genes of interest.

CGH: comparative genomic hybridization; BAC: bacterial artificial chromosome; PAC: P1 bacteriophage artificial chromosome; P1: P1 bacteriophage; Cy3: cyanine dye with green fluorescence; Cy5: cyanine dye with red fluorescence.

Graphic 58888 Version 10.0

Disclosures

Disclosures: **Carlos A Bacino, MD, FACMG** Nothing to disclose. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Elizabeth TePas, MD, MS** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Primary care of the adult with intellectual disability (mental retardation)

Author
Robert Baldor, MD

Section Editor
Thomas L Schwenk, MD

Deputy Editor
Lee Park, MD, MPH

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Oct 21, 2014.

INTRODUCTION — Developmental disabilities refer to a number of different conditions with onset in childhood; intellectual disability (ID) is a non-specific term that refers to a mental capacity below normal, due to any condition that impairs development of the brain before birth, during birth, or in the childhood years. ID (also referred to as cognitive impairment or cognitive adaptive disability) is replacing the older terminology “mental retardation.”

Intellectual disability affects 0.6 to 2.5 percent of people in the UK and the US [1,2]. People with intellectual disability are living longer than in the past and most are living in the community rather than in institutional settings. Patients with Down's syndrome live, on average, twice as long as they did 25 years ago [3]. Thus, the adult primary care clinician will be providing healthcare for increasing numbers of patients with intellectual disability and cognitive impairment.

Unfortunately, disparity exists in health services provided to those with intellectual disability, when compared to the general population [1,4]. Patients with ID are less likely to receive adequate medical care than the general population, despite their increased burden of chronic health problems [4,5]. Patients with ID have shortened life expectancy (ranging from 13 to 20 years shorter), increased numbers of medical problems, and decreased rates of recommended preventive health interventions. These issues can be attributed to multiple factors [2,5]:

- Genetic factors that result in both ID and a greater burden of somatic health problems.
- Communication difficulties involving the patient, caregivers, and health providers.
- Deficiencies in the structure and funding of health services for this population.

This topic will discuss the approach to an adult patient with intellectual disability who is being seen for primary care. A discussion of intellectual disability in pediatrics is presented separately. (See "Intellectual disability (mental retardation) in children: Management; outcomes; and prevention".)

DIAGNOSIS AND CLASSIFICATION — Individuals with ID are often characterized by their Intelligence Quotient (IQ). The IQ, a term first coined in the 1900s, is assessed by a variety of standardized tests including the Simon-Binet scale or the Wechsler Adult Intelligence scale. The normal range for IQ falls between 90 and 120. An IQ two standard deviations below the mean (ie, IQ <70) is consistent with intellectual disability. Intellectual disability is further classified as mild (IQ 50 to 69); moderate (IQ 35 to 49); severe (IQ 20 to 34); or profound (IQ <20).

The diagnosis of intellectual disability involves an assessment of the individual's cognitive and functional abilities that goes beyond simply determining the IQ. The American Association of Intellectual and Developmental Disabilities (AAIDD) advocates a three step evaluation process [6]:

- Measure the intelligence quotient.
- Assess behavior and emotional skills.
- Assess the impact of the individual's limitations on his or her ability to manage activities of daily living (ADLs).

The DSM V diagnostic criteria for ID are consistent with this assessment and require documentation of deficits in intellectual and adaptive functioning with onset during the developmental period [7]. (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs".)

The majority of individuals with intellectual disability are able to function well in childhood; limitations might not be apparent until they are challenged with learning upon entering school.

Many adults with mild ID are able to live independently in the community. However, those with IQ's below 50, accounting for approximately 10 to 12 percent of those with ID, will require significant support to perform ADL's (table 1).

EPIDEMIOLOGY — About 2.5 percent of the United States (US) population has an IQ below 70. The degree of disability within this group is considerably variable, as IQ is just one component for determining intellectual disability.

The US population prevalence of ID is 11.4 per 1000 in children and 6.6 per 1000 in adults [8]. There is up to a ninefold variation from state to state. (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs".)

ETIOLOGY — Conditions that impair intellectual development may be related to a genetic abnormality or to a brain injury occurring prenatally, perinatally, or in early childhood. Injuries resulting in impaired brain development may be related to trauma, metabolic abnormalities (eg, hypothyroidism), toxin exposure (eg, alcohol), or infections (eg, meningitis or encephalitis). The fetal alcohol syndrome is one of the three most common congenital causes of ID. In about one-third of cases, no cause can be determined. (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs" and "Intellectual disability (mental retardation) in children: Evaluation for a cause".)

Rates of brain injury in childhood have declined due to several initiatives: use of car seats and bicycle helmets, prenatal immunization for rubella, childhood HIB immunization to protect against H flu meningitis, and newborn blood screening to detect disorders such as hypothyroidism and PKU [9].

Genetic disorders — Over 500 different genetic defects have been associated with ID [10]. Genetic disorders are responsible for the majority of those with severe ID (IQ <50), while mild ID is more likely to be associated with nongenetic factors [11].

The two most common genetic etiologies of ID are Down syndrome and Fragile X Syndrome.

Down syndrome, the most common, is caused by a sporadic chromosomal disorder resulting in a third chromosome at the 21st position (Trisomy 21). (See "Down syndrome: Clinical features and diagnosis" and "Down syndrome: Management".)

X-linked disorders primarily affect males, with females being carriers and transmission through the maternal line. Fragile X Syndrome is caused by a single gene defect on the X chromosome. Other examples of X-linked inheritance associated with ID include Hunter syndrome, Lesch Nyhan syndrome, and Duchenne muscular dystrophy.

Many genetic defects do not cause mentation difficulties directly, but lead to metabolic disorders which then result in developmental impairment. Over 350 inborn errors of metabolism have been identified and affect 1 in 5000 births [12]. Phenylketonuria (PKU) is an example of a single gene disorder. PKU results in the production of a defective enzyme (phenylalanine hydroxylase) involved in protein metabolism, catalyzing the conversion of the amino acid phenylalanine to tyrosine. The resulting build up of phenylalanine causes developmental disability. However, if such individuals are placed on a phenylalanine free diet they can lead perfectly normal lives [13]. (See "Overview of phenylketonuria".)

Early identification of genetic metabolic disorders through state newborn screening programs has led to

improved survival and health status of individuals diagnosed with these conditions. Newborn screening programs in the US vary by state but always include PKU and congenital hypothyroidism (table 2) [14]. (See "Newborn screening".)

APPROACH TO THE PATIENT — There are multiple challenges to providing primary care for patients with intellectual disability. Patients are often not able to directly communicate their needs or concerns; caregivers who accompany them to an appointment may be unable to provide essential information; frequent relocations between group homes impedes the development of a trusting patient/provider relationship; and patients may be unusually fearful about components of the physical examination or diagnostic testing. Combining these barriers with an increased number of health issues among the intellectually disabled, and the extra clinician time needed to provide even routine care, can further compromise the ability to provide quality care. Nonetheless, the basic premise that must always be in the forefront is that these patients deserve the same intensity of preventive health services and medical intervention as all others.

Several aspects of providing care, including attention to specific social issues, are especially pertinent for the mentally retarded population.

- It is important to determine the nature of the living situation. Individuals with ID live in a variety of community settings, dependent on their ability to care for themselves. Many live with their parents throughout their life course. Disruptions in care occur as parents age, require care themselves, or die.
- Non-family settings range from living independently or in shared-living situations with friends to more structured residences such as supervised group homes to traditional nursing homes, or other intermediate care facilities. Individuals living in non-family licensed settings may have facility-related access to healthcare. Frequent changes in residential settings for insurance, age, or jurisdictional reasons often lead to fragmentation of care.
- It is important not to make assumptions about the degree of communication skills that an individual with ID possesses. Even when communication skills are limited, the patient should be addressed directly and treated in a respectful and caring manner. Acknowledge the patient's right to consent to examinations or tests, even if verbal communication is limited.
- Individuals who are non-verbal or have limited verbal communication skills are at greater risk for poor nutrition, overmedication, injury, and abuse. Abuse may be either physical or sexual, and may involve other patients or facility staff [15].
- For patients with limited communication, the medical history will come from the caregiver who is accompanying the patient. Physical complaints may be vague and the history limited. Contacting the caregiver who is closest to the patient is helpful in understanding what prompted the medical office visit. Two-way written communication between healthcare provider and caregiver is essential.
- It is best to approach frightened individuals slowly and perform a limited exam until they have become comfortable with the provider. For some patients, the white coat is problematic, while others may find it a reassuring sign that it is safe to be touched by this individual.
- In very difficult situations, pre-sedation with an anxiolytic (eg, lorazepam) may be required to obtain testing, such as an EKG, or to perform a pelvic exam. Home visits can provide the opportunity to pursue an exam in a more comfortable and safe environment for the patient.

Routine healthcare — General screening and immunization guidelines for routine health maintenance should be followed for individuals with ID [16]. Routine preventive services should include periodic dental exam, age appropriate cancer screening and immunizations. (See "Preventive care in adults: Recommendations".)

In addition to care routinely provided to the general population, particular interventions should be considered for patients with ID. The Massachusetts Department of Developmental Services has published guidelines specific to these patients [17].

Suggestions for routine healthcare in this population include:

- Evaluate for early stages of mental illness, which is more common in this population [18]. Early intervention may prevent more serious impairments and secondary disability.
- Screening laboratory studies (blood chemistries, complete blood count, TSH) should be considered at regular health maintenance visits to supplement the limited available information for patients with impaired communication [17,19]. Decisions to order laboratory studies should be balanced against the difficulty of obtaining a blood specimen, and the lower predictive value of positive test results in an asymptomatic population.
- People in institutional care should be periodically evaluated for evidence of infectious diseases such as tuberculosis and hepatitis C. Patients who do not have documentation of hepatitis B vaccination should be tested for hepatitis B and vaccinated if negative. Patients should be offered appropriate testing for sexually transmitted diseases, including HIV testing; legal guardians may need to be contacted for their decision and consent regarding HIV testing.

A common sense approach to routine health guidelines should be taken. As an example, a combative individual may need anesthesia to obtain an adequate pap smear. Risks of anesthesia need to be weighed against the risk of cervical cancer in the individual, especially if the patient is unlikely to have had consensual sexual activity and is considered low risk for sexual abuse.

Scheduling visits — While the periodic health examination in the general population may not be the most efficient way to provide primary care, and many advocate providing preventive health services in the context of sick visits, scheduled routine visits may have greater impact and be more important for patients with ID. A system of providing medical visits only on-demand is less effective for a population with limited ability to communicate who may not be able to express need. Additionally, these patients often require extra time for a visit because of the complexity of the patient/caregiver/clinician interaction and multiple underlying social, behavioral, and emotional difficulties.

In a study in the UK, for example, in which structured health checks were provided by 40 general practices for 180 patients with ID, 51 percent had new health problems identified; serious treatable health problems, including breast cancer, dementia, diabetes, and hypothyroidism were identified in sixteen patients [2].

Issues of special concern

Legal issues — Issues of guardianship should be clarified early on in the medical relationship. While many individuals with ID are their own guardian, often there is a need for a legal or medical guardian to be appointed. This may be a relative, designated representative, or social service agency as a "ward of the court". A successor guardian for an aging parent should be identified.

Understanding who has the ability to sign consent for medical interventions is important. Nevertheless, the medical provider can play an important role as a patient advocate when there is controversy over the approach to care.

End-of-life issues should be discussed prior to the development of a life-threatening event. Family concerns and preferences are important to solicit. ID itself is not a reason for a routine DNR status; such decisions should include the nature of the individual's terminal illness, likelihood of resuscitation success, and the family's religious and cultural beliefs.

Sexuality — Sexuality is an area often overlooked, as it is often assumed that individuals with ID are

not sexually active. Issues related to birth control and the possibility of sexually transmitted diseases should be considered and addressed with family and caregivers. Additionally, many individuals are living independently in the community and counseling regarding sexual abuse, alcohol, and substance abuse is important [20].

Victims of violence — Individuals with intellectual disability are at increased risk of experiencing interpersonal violence, including physical, sexual, and caregiver violence. In a systematic review and meta-analysis of three studies, there was a 60 percent increased risk for experiencing violence among persons with intellectual disability compared to the general population (OR 1.60, 95% CI 1.05-2.45) [21]. Another two studies cited in the systematic review but not included in the meta-analysis found that individuals with intellectual impairment had the highest rates of violence compared to individuals with other types of disability, including mental illness and physical or sensory impairments.

COMMON PROBLEMS — People with ID are at risk for a variety of social problems, and many also suffer from underlying congenital or metabolic abnormalities which may cause unique medical and physical problems. Common comorbid conditions include seizure disorders, cerebral palsy (CP), gastrointestinal motility problems, thyroid disease and behavioral disorders. Appropriate screening should be performed for cardiovascular risk. Unfortunately, this population is also participating in the obesity epidemic, with its resulting increase in diabetes. A table highlights conditions that are more common in this population (table 3).

Mental illness — The diagnosis and treatment of mental illnesses and other serious disorders in this population are often delayed, inadequate, or not provided at all. While behavioral issues are often the presenting complaint when patients with ID are brought in for psychologic evaluation, depression, anxiety and psychotic disorders often play a role. Psychiatric co-morbidities are common, affecting 31 percent of subjects with intellectual disability (mean age 22.6 years) who were followed over a course of 14 years [22]. In this Australian cohort, only 10 percent of those with psychopathology had received mental health intervention during the 14 year study period.

Seizure disorder — Seizure disorders are more prevalent in patients with ID than the general population. The incidence of seizures is highest in those with the lowest IQ and affect upwards of 50 percent of patients with ID and concurrent cerebral palsy [23]. A comorbid seizure disorder is associated with a death rate three times higher than for those without epilepsy [24]. It is important to discuss seizure safety with those that care for the patient.

It is not unusual for more than one anticonvulsive agent to be required in order to control seizures in a patient with severe ID. Periodic measurement of serum levels for anticonvulsants will help maintain therapeutic ranges, avoid breakthrough seizures, and avoid medication toxicity. A trial taper of anticonvulsants if the patient has not had a seizure in over a year has been advocated by some [25], although intellectual disability is a risk factor for seizure recurrence off medication. (See "Overview of the management of epilepsy in adults".)

Cerebral palsy — Cerebral palsy (CP) refers to the presence of a nonprogressive motor impairment and, like ID, is a nonspecific term. While not all individuals with CP suffer from intellectual disability, up to one-third of all mentally retarded individuals are affected by CP [26]. CP presents a variety of challenges to the patient and their caregivers, including spasticity and immobility, high rates of strabismus and cerebral visual impairment, bowel and bladder dysfunction, and altered growth and nutrition. (See "Clinical features of cerebral palsy".)

Pharmacologic treatment for spasticity includes the use of benzodiazepines or baclofen, which is less sedating [27]. Nerve blocks and botulinum toxin injections can be used for those with specific muscle group involvement or if medications have failed [28]. Such therapies need to be repeated three to four times a year. Orthopedic surgeries may be necessary. (See "Management and prognosis of cerebral

palsy".)

Careful skin hygiene is important for patients with CP or other significant movement limitations to prevent problems with pressure ulcers. Bone demineralization with consequent fractures, and decubitus ulcers, may occur secondary to long-standing immobility and nutritional deficiencies. A good relationship with a rehabilitation center can be important for assuring the proper fitting of wheelchairs and other supportive devices.

Dysphagia — Upper gastrointestinal dysmotility can cause dysphagia, esophageal reflux, and gastric emptying disorders. This may lead to dental erosion, esophagitis, anemia, feeding problems, aspiration, and pneumonia.

Dysphagia can be seen in up to 5 percent of patients with ID. The use of a modified barium swallow can be helpful to determine the degree of swallowing dysfunction and guide the use of specialized diets. (See "Oropharyngeal dysphagia: Clinical features, diagnosis, and management".)

Consultation with a speech or language pathologist can provide insight into feeding strategies and eating behaviors. Methods to minimize aspiration risk include modifying the consistency of foods to include pureed foods and compounds to thicken liquids to a honey-like consistency. Other important steps include feeding meals in a quiet non-stressful setting and feeding slowly in an upright position.

The use of gastrostomy tubes (G-tubes) or jejunostomy tubes (J-tubes) to decrease aspiration risk and provide adequate nutrition for those who are incapable of taking in enough calories to maintain weight may be considered. The use of such feeding tubes to prevent aspiration pneumonia is controversial. G-tube feeds can be given slowly while the individual sleeps to avoid the use of this disruptive technology during the day. It is important to instruct caregivers to keep the head of the bed elevated at a 30 degree angle to avoid reflux of stomach contents. J-tubes may be a better choice than G-tubes. (See "Enteral feeding: Gastric versus post-pyloric".)

Constipation — Constipation has been reported in up to 40 percent of individuals with ID, usually secondary to immobility and lack of exercise. However, specific gastrointestinal dysfunction may play a role and medical conditions such as hypothyroidism should be considered. Psychotropic and other medications with anticholinergic effects may also be contributing factors. Inadequately treated constipation may cause fecal impaction, intestinal obstruction, and even death. Since history of bowel function may be difficult to obtain, constipation may be missed as a cause of patient distress [15]. Plain films of the abdomen (KUB) can detect significant stool retention in the colon and may be helpful when the history is not reliable.

Strategies for dealing with this common condition include increasing fluids and stool softeners. Daily laxatives may be required. Tolerance to stimulant laxatives is uncommon [29]. For more significant problems stimulant suppositories or enemas given every three to four days may be necessary to avoid obstipation. (See "Management of chronic constipation in adults".)

Behavioral disorders — Behavioral disorders are frequent among people with ID and range from self-injurious actions to other aggressive activities which may be directed at other individuals and caregivers. The most common forms of these behaviors include head-banging, hand-biting, and excessive self-rubbing and scratching. Behavioral disruptions may be a normal reaction to minor changes in the patient's surroundings, appropriate for the developmental age of the patient. Patience and redirecting behavioral treatments should be tried before starting psychotropic medications.

Communication difficulties can significantly impede the evaluation of behavioral disorders. Any change in baseline behavior should prompt an investigation for an underlying source of pain, or other contributing medical factor [30]. In one report of secondary medical causes of behavioral change, constipation was the number one ranked problem [31]. Others have noted an association with menstrual discomfort [32].

Potential for unreported traumatic injuries should be considered.

A careful physical exam should be completed to look for sources of discomfort related to infection (respiratory, skin, urine), pain from minor annoyances such as skin irritation, or more serious conditions such as a fracture or testicular torsion. Potential causes for specific behavioral abnormalities should be evaluated (table 4).

A multidisciplinary approach is helpful in treating behavioral disorders. Behavioral modification therapies should be attempted, before medications are initiated. Behavioral techniques include providing alternative options for the individual to choose, and providing follow through with appropriate rewards or consequences.

Though antipsychotics are commonly used to treat aggressive behavior for non-psychotic individuals with ID, the use of antipsychotics for behavioral control should be reserved for resistant behaviors that result in significant self injury or potential harm to others. Medications should be weaned to the lowest effective doses once behaviors are stabilized [33]. Newer atypical antipsychotic agents minimize the risk of extrapyramidal side effects but carry an increased risk for inducing the metabolic syndrome, weight gain, and diabetes. Patients who are treated with psychotropic medications need frequent monitoring for potential side effects (table 5). (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

Rates of antipsychotic use are reported in up to 45 percent of individuals in institutions and 20 percent in the community [34]. A randomized trial compared treatment with a first generation antipsychotic (haloperidol), an atypical antipsychotic (risperidone), and placebo for 86 nonpsychotic patients with ID and aggressive behavior [34]. At four weeks, all three groups showed a marked decrease in aggression, determined by a quantitative score, with the greatest decrease in the group receiving placebo; this decline persisted at 12-week follow-up.

In addition, attention-deficit hyperactivity disorder (ADHD) is more prevalent in people with intellectual disability, compared to the general population. There is no evidence from randomized trials that risperidone is effective for management of ADHD in patients with intellectual disability [35], although it has been prescribed for this indication.

Dementia and cognitive decline — Adults with intellectual disability are presenting with late-life cognitive decline with increasing frequency; in this population, there are distinct challenges for evaluation, diagnosis and management. In particular, this is an issue for patients with Down syndrome who have a significantly increased risk for Alzheimer disease. (See 'Down syndrome' below and "Down syndrome: Clinical features and diagnosis", section on 'Dementia/Alzheimer disease'.)

There are no generally accepted criteria for memory or cognitive assessment in adults with intellectual disability. A diagnosis of dementia requires evidence of a change of function from a previous baseline; a family member or caregiver is an essential provider of this information. Asking specific questions about a change in participation in hobbies or activities, as well as documenting any changes in functional activities of daily living (ADLs) can be useful ways to elicit such information. While cognitive screening tools, such as the Mini-Mental State Examination have not been validated for diagnosing dementia in this population, administering an evaluation instrument, such as the Dementia Questionnaire for Persons with Mental Retardation and/or the IBR Mental Status Examination, may be helpful in establishing a baseline for follow-up examinations and providing some objective information [36-38]. It is also important to exclude possible treatable contributors to cognitive decline including adverse effects of medications, sleep problems, psychosocial and environmental stressors, as well as metabolic abnormalities. (See "Evaluation of cognitive impairment and dementia", section on 'Diagnostic approach'.)

Treatment involves both pharmacological and nonpharmacological approaches. These are discussed in

detail separately. (See "Treatment of dementia" and "Management of neuropsychiatric symptoms of dementia" and "Safety and societal issues related to dementia".)

Oral hygiene — Oral hygiene is often overlooked [39]. Periodontal disease is common. Mild sedation may be needed for outpatient dental visits; deeper sedation requiring monitoring is occasionally indicated for patients intolerant of outpatient care.

SYNDROME SPECIFIC ISSUES — When caring for an individual with ID, a search for the underlying cause is helpful, however in many instances the cause of the individual's disability is not discernible. Genetic testing can be helpful and may be useful for advising families to the possibilities of an inherited disorder.

Various conditions are associated with specific medical risks that may require special screening. The three major congenital etiologies of ID are Down syndrome, fetal alcohol syndrome, and fragile X syndrome.

Down syndrome — Down syndrome, resulting from an extra chromosome at the 21st position, is seen with increasing frequency with advancing maternal age [40]. The clinical features, diagnosis, and management of children with Down syndrome are discussed elsewhere. (See "Down syndrome: Clinical features and diagnosis" and "Down syndrome: Management".)

The median age of death for patients with Down syndrome has increased from <10 years to over 50 years of age [41]. The primary care of adult patients with Down syndrome is similar to the general adult population with additional screening for conditions specific to these patients.

Down syndrome is associated with cardiac abnormalities, particularly septal defects such as endocardial cushion defects, and tetralogy of Fallot. Children with Down syndrome are evaluated for the presence of cardiac abnormalities. If adult patients did not have an echocardiogram in childhood or results are not available, echocardiogram should be obtained once to rule out underlying cardiac defects. Patients with a normal echocardiogram do not need a repeat in adulthood unless there is a change in cardiac function or symptoms that suggest cardiac dysfunction [41]. The need for antibiotic prophylaxis prior to dental and other procedures is limited. (See "Antimicrobial prophylaxis for bacterial endocarditis".)

Thyroid dysfunction is common in patients with Down syndrome. Individuals with Down syndrome have a 30 percent lifetime risk of developing hypothyroidism and should be screened on an annual basis with a TSH.

Obstructive sleep apnea is also common in these patients and may be diagnosed in childhood. (See "Down syndrome: Management", section on 'Sleep apnea'.)

Visual impairments, including amblyopia, refractory errors, cataracts, and glaucoma, are common. Hearing impairments are also common. Annual ophthalmologic and auditory exams are recommended, and should be re-assessed in the workup of a newly developing behavioral problem.

Patients with Down syndrome have a decrease in cell-mediated immunity. Reduction in cell-mediated immunity results in a slightly higher rate of leukemia than in the general population, which is typically manifested in childhood. Additionally, these individuals are at increased risk for infection.

Ligamentous laxity is associated with Down syndrome and may cause problems if there is atlantoaxial instability with increased mobility at C1-2. This is seen in about 7 percent of Down syndrome patients; the majority are asymptomatic. Symptoms are due to cord compression and should be considered if there is torticollis, neck or shoulder pain, a gait change, or new incontinence. Preoperative neck Xrays (lateral cervical spine films: neutral, flexed, and extended views) should be obtained if general intubation is planned or if the individual plans to engage in contact sports or participate in the Special Olympics. (See "Down syndrome: Management", section on 'Atlantoaxial instability'.)

Patients with Down syndrome have a significantly increased risk for Alzheimer dementia which should be considered for the individual whose function begins to deteriorate. The occurrence of Alzheimer dementia occurs at a younger age in people with Down syndrome than the general population; it is not unusual to be seen in the 40s [42]. Almost 20 percent of patients with Down syndrome over age 45 have dementia, which is correlated with increased mortality risk in these individuals [43].

Alzheimer dementia is associated with neurofibrillary tangles and beta-amyloid plaques. The gene for beta-amyloid precursor protein (APP) is located on chromosome 21. It is thought that over expression of this gene, due to the extra chromosome, results in excess APP production. Additionally chromosome 21 codes for superoxide dismutase (SOD-1); increased activity of this enzyme may enhance the production of hydroxyl radicals and further contribute to neural damage [44].

Assessing dementia in the intellectually disabled patient is challenging. (See 'Dementia and cognitive decline' above.)

In general, patients with Down syndrome and Alzheimer disease should be managed similarly to other patients with dementia, although treatment trials in this population are limited. (See "Treatment of dementia".)

Fragile X syndrome — Fragile X syndrome is the most common form of inherited ID in males. A defect of the FMR1 (fragile X mental retardation) gene on the X chromosome leads to problems with the production of the FMR protein, assumed to be essential for normal brain functioning. Females, with two X chromosomes, are carriers, though may have some minor symptoms. This syndrome is seen in 1 of every 2000 male births.

Characteristic features include macrocephaly, large ears, strabismus, high palate, and hyperextensible fingers. Speech delays and behavioral problems, including attention deficit, are common with autistic-type behaviors seen in about a quarter of affected individuals. Physical symptoms, such as large testes, are more apparent after puberty. Hand biting or flapping and speech disturbances are also common. Cardiac valve defects may be present, particularly mitral valve prolapse.

Diagnosis is established by molecular testing for the FMR1 gene rather than routine chromosome analysis. No specific treatment other than genetic counseling is currently available.

Fetal alcohol syndrome — Fetal alcohol syndrome (FAS) is the leading cause of preventable intellectual disability. While not a genetic condition, fetal alcohol syndrome (FAS) is a common disorder, seen in about one to three per 1000 births in the US; incidence is likely higher in countries with higher rates of alcohol abuse. FAS is the extreme expression of prenatal alcohol consumption causing the abnormalities seen in fetal alcohol spectrum disorders (FASDs). In the US a 2002 survey revealed that approximately 10 percent of pregnant women used alcohol and 2 percent engaged in frequent use or binge drinking [45].

Ethanol acts as a toxin on newly forming embryonic cells, particularly during the first trimester when a woman may not yet realize she is pregnant. The history of alcoholism may be associated with multiparity, older maternal age at time of pregnancy, or maternal mental illness [45].

Characteristic facial features include a long philtrum, a wide and narrow upper lip, wide nasal bridge, and a small upturned nose. The "Lip-Philtrum Guide" is a useful tool [46] and is available through the University of Washington website. Central nervous system damage can include microcephaly, seizures, learning disabilities, and developmental delay. Growth deficiency, visual problems, hearing loss, heart defects, and genital urinary tract abnormalities are also seen.

Early identification of FAS can lead to intervention programs to prevent secondary complications. These secondary complications include educational difficulties, mental health problems including attention deficit, substance abuse, and trouble with the law. A stable and nurturing home, educational support

services, and consistent supportive environment are helpful in preventing these outcomes.

Prader-Willi syndrome — This most common form of obesity caused by a genetic disorder results from an abnormality of the long arm of chromosome 15. The Prader-Willi syndrome is characterized by infantile hypotonia and failure to thrive. Later in life hypogonadism, mental impairment, and short stature are seen and despite early trouble with maintaining weight, such patients experience hyperphagia, with resulting morbid obesity, which may lead to diabetes mellitus or premature congestive heart failure.

Strict food supervision, physical activity, and a special education program are the only treatments. Genetic testing is helpful with predicting the risk of recurrence so that appropriate counseling may be given.

SUMMARY AND RECOMMENDATIONS

- Intellectual disability (ID) affects up to 2.5 percent of the population. Adult primary care services are becoming more important for this population as people with intellectual disability are living longer and living in the community. (See 'Introduction' above.)
- The diagnosis of intellectual disability (ID, formerly referred to as mental retardation or MR) is based on assessment of the IQ (<70), an individual's behavioral and emotional skills, and their ability to manage activities of daily living (ADLs). (See 'Diagnosis and classification' above.)
- The most common genetic etiologies of ID are Down syndrome and Fragile X Syndrome. Fetal alcohol syndrome is the major non-genetic cause of ID. However, a specific etiology cannot be determined for many patients with ID. (See 'Etiology' above.)
- In providing care for patients with ID, it is important to understand the living situation, communicate with people who can provide medical historical information when the patient is unable to do so, recognize the potential for injury and abuse, and try to accommodate patient's fears while providing quality healthcare. Screening for infectious disease in institutionalized patients (TB, hepatitis B, C) and screening laboratory studies to supplement a limited patient history may be indicated. (See "Approach to the patient".)
- Medical problems common to this population include mental illness and behavioral disorders, seizure disorder, cerebral palsy, dysphagia, and constipation. Constipation may affect up to 40 percent of patients with ID and can be an unsuspected cause of behavioral change.
- Patients with Down syndrome should be evaluated for cardiac abnormalities, visual and hearing impairments, hypothyroidism, and early dementia. Atlantoaxial instability should be consideration when suggested by symptoms of neck pain or possible cord compression. (See 'Down syndrome' above.)
- The Fragile X syndrome is a sex-linked disorder causing macrocephaly and autistic-type behaviors. Fetal alcohol syndrome causes characteristic changes in facial configuration, developmental delay, and often behavioral difficulties. Prader-Willi syndrome can cause morbid obesity. (See 'Syndrome specific issues' above.)

REFERENCES

1. van Schrojenstein Lantman-De Valk HM, Metsemakers JF, Haveman MJ, Crebolder HF. Health problems in people with intellectual disability in general practice: a comparative study. Fam Pract 2000; 17:405.

2. Baxter H, Lowe K, Houston H, et al. Previously unidentified morbidity in patients with intellectual disability. Br J Gen Pract 2006; 56:93.
3. Fisher K, Kettl P. Aging with mental retardation: increasing population of older adults with MR require health interventions and prevention strategies. Geriatrics 2005; 60:26.
4. US Department of Health and Human Services. Closing the Gap: A National Blueprint to Improve the Health of Persons with Mental Retardation. Office of the Surgeon General. Rockville, MD 2002. Available at: www.nichd.nih.gov/publications/pubs/closingthegap/index.cfm (Accessed on December 22, 2012).
5. Heslop P, Blair PS, Fleming P, et al. The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK: a population-based study. Lancet 2014; 383:889.
6. American Association of Intellectual and Developmental Disabilities (AAIDD, formerly AAMR). Available at: www.aaidd.org (Accessed on December 22, 2012).
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.
8. Centers for Disease Control and Prevention (CDC). State-specific rates of mental retardation--United States, 1993. MMWR Morb Mortal Wkly Rep 1996; 45:61.
9. Alexander D. Prevention of mental retardation: Four decades of research. Ment Retard Dev Disabil Res Rev 1998; 4:50.
10. The National Human Genome Research Institute. Available at: www.genome.gov (Accessed on December 22, 2012).
11. Moser HG. A role for gene therapy in mental retardation. Mental Retardation and Developmental Disabilities Research Reviews. Gene Therapy 1995; 1:4.
12. Scriver CR. The metabolic and molecular bases of inherited disease, 7th ed, McGraw Hill, New York 1995.
13. Ding Z, Harding CO, Thöny B. State-of-the-art 2003 on PKU gene therapy. Mol Genet Metab 2004; 81:3.
14. National Newborn Screening and Genetics Center. Available at: genes-r-us.uthscsa.edu (Accessed on December 22, 2012).
15. Lennox N, Eastgate G. Adults with intellectual disability and the GP. Aust Fam Physician 2004; 33:601.
16. Down Syndrome Medical Interest Group (DSMIG), Cohen WI. Health care guidelines for individuals with Down syndrome. Down Syndrome Quart 1996; 1:1.
17. Massachusetts Health Quality Partners: Preventive health recommendations for adults with mental retardation. Available at: http://www.guidelines.gov/content.aspx?id=37906 (Accessed on December 22, 2012).
18. Chen CY, Lawlor JP, Duggan AK, et al. Mild cognitive impairment in early life and mental health problems in adulthood. Am J Public Health 2006; 96:1772.
19. World Health Organization. Healthy Ageing: Adults with Intellectual Disabilities, Physical Health Issues. Available at: http://who.int/mental_health/media/en/21.pdf (Accessed on December 22, 2012).
20. Cocco KM, Harper DC. Substance use in people with mental retardation: assessing potential problem areas. Ment Health Aspects Dev Disabil 2002; 5:101.
21. Hughes K, Bellis MA, Jones L, et al. Prevalence and risk of violence against adults with disabilities: a systematic review and meta-analysis of observational studies. Lancet 2012; 379:1621.
22. Einfeld SL, Piccinin AM, Mackinnon A, et al. Psychopathology in young people with intellectual disability. JAMA 2006; 296:1981.

23. Coulter DL. Epilepsy and mental retardation: an overview. Am J Ment Retard 1993; 98 Suppl:1.
24. McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. Am J Ment Retard 2000; 105:229.
25. Tyler CV Jr, Bourguet C. Primary care of adults with mental retardation. J Fam Pract 1997; 44:487.
26. Tilton AH, Butterbaugh G. Mental retardation and cerebral palsy. In: Neurological Therapeutics Principles and Practice, Noseworthy JH (Ed), Martin Dunitz, New York 2003.
27. Pranzatelli MR. Oral pharmacotherapy for the movement disorders of cerebral palsy. J Child Neurol 1996; 11 Suppl 1:S13.
28. Katz RT. Management of spasticity. Am J Phys Med Rehabil 1988; 67:108.
29. Müller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. Am J Gastroenterol 2005; 100:232.
30. Ryan R, Sunada K. Medical evaluation of persons with mental retardation referred for psychiatric assessment. Gen Hosp Psychiatry 1997; 19:274.
31. Charlot LR, Abend S, Silka V, et al.. A short stay inpatient unit for adults with development disabilities. In: Contemporary Dual Diagnosis MH/MR Service Models Volume 1: Residential and Day Services, NADD Press, Kingston, NY 2002.
32. Carr EG, Smith CE, Giacin TA, et al. Menstrual discomfort as a biological setting event for severe problem behavior: assessment and intervention. Am J Ment Retard 2003; 108:117.
33. Glover G, Bernard S, Branford D, et al. Use of medication for challenging behaviour in people with intellectual disability. Br J Psychiatry 2014; 205:6.
34. Tyrer P, Oliver-Africano PC, Ahmed Z, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. Lancet 2008; 371:57.
35. Thomson A, Maltezos S, Paliokosta E, Xenitidis K. Risperidone for attention-deficit hyperactivity disorder in people with intellectual disabilities. Cochrane Database Syst Rev 2009; :CD007011.
36. Moran JA, Rafii MS, Keller SM, et al. The National Task Group on Intellectual Disabilities and Dementia Practices consensus recommendations for the evaluation and management of dementia in adults with intellectual disabilities. Mayo Clin Proc 2013; 88:831.
37. Silverman W, Schupf N, Zigman W, et al. Dementia in adults with mental retardation: assessment at a single point in time. Am J Ment Retard 2004; 109:111.
38. National Down Syndrome Society. Available at: www.ndss.org (Accessed on December 22, 2012).
39. Prater CD, Zylstra RG. Medical care of adults with mental retardation. Am Fam Physician 2006; 73:2175.
40. Hultén MA, Patel S, Jonasson J, Iwarsson E. On the origin of the maternal age effect in trisomy 21 Down syndrome: the Oocyte Mosaicism Selection model. Reproduction 2010; 139:1.
41. Jensen KM, Bulova PD. Managing the care of adults with Down's syndrome. BMJ 2014; 349:g5596.
42. Bush A, Beail N. Risk factors for dementia in people with down syndrome: issues in assessment and diagnosis. Am J Ment Retard 2004; 109:83.
43. Coppus AM, Evenhuis HM, Verberne GJ, et al. Survival in elderly persons with Down syndrome. J Am Geriatr Soc 2008; 56:2311.
44. Cummings JL. Alzheimer's disease. N Engl J Med 2004; 351:56.
45. Centers for Disease Control and Prevention (CDC). Alcohol consumption among women who are pregnant or who might become pregnant--United States, 2002. MMWR Morb Mortal Wkly Rep 2004; 53:1178.

46. Astley SJ, Clarren SK. Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. Alcohol Alcohol 2000; 35:400.

Topic 2779 Version 22.0

GRAPHICS

Associated disability and level of mental retardation

MILD (IQ 50-69): Capable of personal independence with a little guidance and assistance.
MODERATE (IQ 35-49): Require assistance with more complex activities; communicate with simple sentences.
SEVERE (IQ 20-34): Require assistance with most ADLs; communicate with words and gestures.
PROFOUND (IQ <20): Require comprehensive care and assistance; usually non-verbal; high incidence of secondary disabilities.

Graphic 64507 Version 1.0

Commonly included components of state newborn screening programs for conditions that cause intellectual disability

Condition	Clinical syndrome	Treatment
Biotinidase deficiency	Seizures, skin disorders, hearing loss, MR, death	Daily biotin
Congenital hypothyroidism	Mental and growth retardation	Thyroid hormone replacement
Galactosemia	Cataracts, cirrhosis, MR, fatal sepsis	Eliminate lactose, use soy for newborn sepsis evaluation
Homocystinuria	MR, osteoporosis, thromboembolic disease	Dietary restrictions, supplemental medicines
Maple Syrup Urine disease	Feeding problems, vomiting, death; severe MR	Branched-chain amino acids/dietary restrictions
Phenylketonuria	MR, seizures, eczema	Phenylalanine restricted diet
Congenital toxoplasmosis	Hydrocephalus, MR, splenomegaly, ascites	One year of regimented antibiotics, ID consult
Newborn hearing screen	Global delay in cognitive and social development	Hearing aids Special Education

MR: mental retardation.

Graphic 76630 Version 3.0

Commonly missed conditions in patients with intellectual disability

Psychiatric disorders
Depression
Schizophrenia
Bipolar affective disorder
Anxiety disorders
Post-traumatic stress disorder
Gastrointestinal disorders
Constipation/atonic bowel
Bowel obstruction
Reflux oesophagitis
H. Pylori infection
Undescended testis/hypogonadism
Unrecognized pain or infection
Dental pathology
Chest infection
Urinary tract infection
Medication issues
Overuse of tranquilizers
Unrecognized side effects of medication
Epilepsy management
Inadequate review of anticonvulsant medication
Failure to consider medication interactions and toxicity
Sensory impairment
Hearing impairment
Visual impairment
Ear and eye pathology
Health maintenance activities
Immunization
Screening for infectious conditions including hepatitis B
Nutritional assessment (exclude malnutrition and obesity)
Breast checks and Pap tests

Blood pressure and skin checks
Screening for osteoporosis and vitamin D deficiency where appropriate
Physical activity assessment

Lennox N, Eastgate G. Adults with intellectual disability and the GP. Aust Fam Physician 2004; 33:601. Copyright to Australian Family Physician. Reproduced with permission. Permission to reproduce must be sought from the publisher, The Royal Australian College of General Practitioners.

Graphic 76615 Version 8.0

Treatment of self-injurious behaviors

Correct metabolic abnormalities	Evaluate for somatic pain: ear, GI (constipation)
Appropriate restricted diet: lactose, gluten	Behavior modification program
Evaluate for seizure activity	Consistency and follow-through
Increase activity levels if under-aroused	Protective gear: gloves, helmet
Reduce stimuli if over-aroused	Appropriate use of medications

Graphic 52451 Version 1.0

Monitoring for metabolic side effects of antipsychotic drugs

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	e Y
Personal or family history	X					X	
Weight (body mass index)	X	X	X	X	X		
Waist circumference	X			X		X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X	*		X			

* For patients taking olanzapine, quetiapine, clozapine.

Graphic 74435 Version 6.0

Disclosures

Disclosures: **Robert Baldor, MD** Nothing to disclose. **Thomas L Schwenk, MD** Nothing to disclose. **Lee Park, MD, MPH** Employment (Spouse): Novartis [Age-related macular degeneration (ranibizumab)].

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs

Authors
Penelope Pivalizza, MD
Seema R Lalani, MD

Section Editors
Marc C Patterson, MD, FRACP
Helen V Firth, DM, FRCP, DCH
Carolyn Bridgemohan, MD

Deputy Editor
Carrie Armsby, MD, MPH

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Jun 11, 2014.

INTRODUCTION — Intellectual disability (ID) is a neurodevelopmental disorder characterized by deficits in intellectual and adaptive functioning that present before 18 years of age [1]. ID is heterogeneous in etiology and encompasses a broad spectrum of functioning, disability, needs, and strengths. The term replaces and improves upon the older term of "mental retardation" [2]. The term "global developmental delay" (GDD) is usually used to describe children younger than age five who fail to meet expected developmental milestones in multiple areas of intellectual functioning and whose clinical severity level cannot be reliably assessed; not all children with GDD will meet criteria for ID as they grow older [1]. A variety of other terms are used outside of the United States to describe ID (table 1). Standardized intelligence quotient (IQ) testing is no longer used to classify severity of impairment in ID.

ID affects approximately 1 percent of the population. It is an important public health issue because of its prevalence and the need for extensive support services. Its management requires early diagnosis and intervention, coupled with access to health care and appropriate supports.

This topic review will discuss the definition and diagnosis of intellectual disability, including assessment of needs for support. Other aspects of intellectual disability are discussed in separate topic reviews:

- (See "Intellectual disability (mental retardation) in children: Evaluation for a cause".)
- (See "Intellectual disability (mental retardation) in children: Management; outcomes; and prevention".)

DEFINITIONS

Intellectual disability — Intellectual disability (ID) is a state of functioning that begins in childhood and is characterized by limitations in intelligence and adaptive skills. Two definitions are commonly used. One is published by the American Psychiatric Association (APA), in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and the other by the American Association on Intellectual and Developmental Disabilities (AAIDD). Although these definitions differed substantially in the past, current versions are similar [1,2].

Intellectual disability is characterized by significant limitations in **both** of the following, with onset during the developmental period [1] (or before 18 years of age [2]):

- Adaptive behavior – Limitations in adaptive functioning are linked to underlying intellectual impairment and affect participation in multiple settings, such as home, community, and school. Adaptive deficits include limitations in at least one of three domains: conceptual, social, and practical (table 2A-B). Ongoing support is required as compared with others in the same age group. The severity of ID is defined according to the level of supports needed in each of these domains. (See 'Adaptive function' below.)
- Intellectual functioning – Limitations in general mental capacity (intelligence) including learning,

reasoning, and problem solving, abstract thinking, and judgment. This limitation in intellectual ability typically corresponds to an intelligence quotient (IQ) less than 65 to 75. Although standardized IQ testing remains pertinent to the descriptive diagnostic profile, it is no longer used to classify the severity of impairment in ID. (See 'Intellectual function' below.)

The above definition of ID assumes that limitations in function must be assessed relative to the child's age, experience, and environment [1,2]. In addition, a valid assessment of adaptive and intellectual functioning considers differences in language and culture, as well as those in communication, motor, sensory, and behavioral factors. It is important to note that individuals with ID often have strengths as well as limitations. Defining ID severity by the level of support needed for adaptive functioning is valuable because appropriate individualized support usually will improve the life functioning of a person with intellectual disability. In addition, the combination of adaptive and intellectual function is more predictive of outcomes than intellectual function alone.

Syndromic versus nonsyndromic ID — ID may be further categorized as syndromic or nonsyndromic ID. The term syndromic ID is applied when a child presents with ID in addition to one or more clinical abnormalities or comorbidities of a known syndrome. The term nonsyndromic ID is usually applied when a child presents with ID alone [3]. The distinction between the two categories is not always clear-cut if the associated clinical abnormalities are subtle.

Global developmental delay — Global developmental delay (GDD) is the preferred term to describe intellectual and adaptive impairment in children younger than five years of age, based on failure to meet expected developmental milestones in several areas of intellectual functioning [1]. Not all children with GDD will meet criteria for ID as they grow older. The term intellectual disability (ID) usually is applied to children five years or older, when the clinical severity of impairment is more reliably assessed.

CLINICAL FEATURES

Presenting symptoms — Children with intellectual disability (ID) usually are brought to the attention of a pediatrician because of parental concerns of language delay, immature behavior, immature self-help skills, or difficulty in learning. Parents may first recognize delayed development when a younger sibling overtakes an older child in these skills. In other cases, the clinician may be alerted to the possibility of ID when a child fails to meet expected developmental milestones during developmental surveillance and screening.

Children with severe ID tend to come to medical attention earlier than those with mild ID. Most severely affected children are recognized before two years of age, whereas some children with mild ID may be undetected until school age. Individuals with a known genetic disorder and those presenting with obvious dysmorphic features and microcephaly may be diagnosed in infancy. (See "Microcephaly in infants and children: Etiology and evaluation".)

Most children with severe intellectual impairment will present with language delay. Language development is considered a reasonably good indicator of future intelligence in a child without hearing impairment. Thus, language delay associated with global developmental delay suggests cognitive impairment. This should be distinguished from isolated familial expressive language delay (without other deficits), which has a more favorable prognosis. In contrast, gross motor skills in children with ID are often less significantly delayed than intellectual and adaptive function, except when neuromuscular abnormalities result in delay. (See "Etiology of speech and language disorders in children" and "Overview of expressive language delay ("late talking") in young children".)

Associated conditions — As the severity of ID increases, other conditions are more likely to be associated. Common problems that occur in children with severe or profound ID include medical conditions, neurodevelopmental disorders including autism and other behavioral disorders, and obesity.

Medical conditions — Medical conditions commonly associated with ID include seizure disorders, motor impairment affecting gross, fine, and speech motor functions, structural abnormalities, dysmorphism, and vision, hearing, and other sensory impairments. In some cases, these other morbidities are the presenting features, while in others they may be unrecognized. Comorbid endocrine abnormalities may also be present such as abnormal thyroid function, short stature, and growth hormone deficiency [3-5].

Individuals with ID have greater rates of overweight and obesity as compared with typically developing peers. Risk factors that predispose to obesity include altered or inappropriate eating habits, underlying genetic syndromes, less physical activity, chronic health conditions, and psychotropic medication use. (See "Intellectual disability (mental retardation) in children: Management; outcomes; and prevention", section on 'Monitoring for associated disorders'.)

When a genetic cause is identified, the clinician should evaluate the patient for known associated conditions (eg, hypothyroidism in patients with Down syndrome). Such comorbidities may require specific management and also may alter the approach to diagnostic testing for ID (if they affect optimal participation or require test modification).

Other neurodevelopmental disorders and mental health problems — Other neurodevelopmental disorders in addition to ID affect approximately 30 to 70 percent of children with ID, occurring five times more often than in children without ID [6]. However, these associated disorders may be under-diagnosed in ID because developmental delay (especially poor language skills), medical problems, and personal/family circumstances make it challenging to apply the diagnostic behavioral criteria described in the Diagnostic and Statistical Manual (DSM–5) [7]. These neurodevelopmental disorders adversely affect functioning, quality of life, and adaptation.

Neurodevelopmental disorders associated with ID are reviewed in the practice parameter of the American Academy of Child and Adolescent Psychiatry (AACAP) [7] and include the following:

- Autism – Autism and autistic spectrum disorder may occur with ID. The disordered social and communication skills that characterize autism spectrum disorder must be distinguished from the developmentally delayed social and communication skills that typically affect children with ID (see "Autism spectrum disorder: Clinical features", section on 'Impaired social communication and interaction'). In addition, IQ scores may be less stable where both ID and autism are present, particularly in young children. In one study, 28 percent of children with ID had comorbid autistic disorder, and half of these cases were not diagnosed during routine care [8]. Autistic disorder occurs more commonly in syndromic ID (eg, in 25 to 47 percent of those with fragile X syndrome, 5 to 10 percent of those with Down syndrome); individuals with tuberous sclerosis, Angelman syndrome, Rett syndrome, Joubert syndrome, and Cohen syndrome are also more likely to have comorbid autism [3,9].

- ADHD – Some children with ID also have attention deficit hyperactivity disorder (ADHD). ADHD must be distinguished from situational inattentiveness at school where the demands may be too high, inability to comprehend and follow rules and expectations, or the effect of medication. (See "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Differential diagnosis'.)

- Learning disabilities – Varied difficulties in general and academic learning commonly occur with ID; these are pertinent to consider in each individual even if they are attributed to the underlying cause of the ID. For example, phonological difficulties frequently cause reading deficits in individuals with mild ID [10]. A *specific* learning disorder may be identified in addition to ID when a specific learning function is disproportionately affected, beyond expected for the child's ID profile, and not considered due to the underlying ID [1]. (See "Specific learning disabilities in children: Clinical

features".)

- Eating disorders – Associated eating disorders include pica (eating substances that are not food) and rumination (regurgitation of undigested food into the mouth, during or shortly after eating). (See "Eating disorders: Overview of epidemiology, diagnosis, and course of illness", section on 'Pica' and "Eating disorders: Overview of epidemiology, diagnosis, and course of illness", section on 'Rumination disorder'.)

- Depression and anxiety – Depression, anxiety, and posttraumatic stress disorder are common comorbid conditions. Depression may be manifested as aggressive or irritable externalizing behaviors. Depression and/or anxiety can be triggered by relocation, caregiver changes, and effects of medication (eg, beta blockers, neuroleptic drugs) or associated conditions (eg, hypothyroidism). It may be difficult to assess children with ID for these problems due to limited communication skills. Children with ID are at increased risk of suicidal ideation and for substance abuse. Screening for these problems is advised.

- Physical and sexual abuse – Children with ID are at increased risk of being victimized, manipulated, neglected and abused, including sexual abuse. They may be vulnerable to abuse because of cognitive, learning and communication deficits, gullibility, social naiveté, and the desire to please. Up to 14 percent of patients with ID admitted to hospitals have reported abuse [11]. Individuals with ID are more likely to experience frequent and persistent abuse, multiple abusers, and greater involvement of unfamiliar or non-family perpetrators compared with those without ID [12]. Abuse may cause other behavioral disorders, such as conduct disorder, post-traumatic stress disorder and depression. Sensitivity and a high index of suspicion for abuse are needed. Despite communication deficits, adolescents with severe ID often are able to disclose their victimization and abuse [11].

- Movement disorders – Stereotyped behaviors, stimulating movement and motor mannerisms, including tic disorders, are common in severe ID. (See "Hyperkinetic movement disorders in children", section on 'Stereotypies'.)

- Self-injurious behaviors – Self-injurious behavior frequently occurs and may suggest syndromes such as Lesch-Nyhan. Self-injurious and aggressive behaviors can also occur in individuals who have limited communication who are experiencing stress, depression or anxiety, or may result from side effects of sedative-hypnotic and neuroleptic medications.

CLINICAL EVALUATION — Developmental surveillance should be performed at well child visits with targeted screening at selected visits (9, 18, and 24 or 30 months), and whenever a parent or provider raises developmental concerns [13]. The goal is early identification of children with possible developmental delay or intellectual disability (ID) and prompt referral for further evaluation and early intervention services. (See "Developmental-behavioral surveillance and screening in primary care", section on 'When to perform developmental-behavioral screening'.)

Screening — A number of standardized screening tools are available (table 3). These vary in their sensitivity and specificity. The following are some of the screening tools in common use. Details about these tests, including their accuracy in identifying infants or children with developmental delays, are discussed in a separate topic review. (See "Developmental and behavioral screening tests in primary care".)

- Ages and Stages Questionnaires (ASQ) – The ASQ provide age-specific questions about the child that are completed by the child's parent, and can be used to screen development in children from 4 to 60 months of age. These are used in clinical and research settings and applied in some screening and intervention programs [13].

- Bayley Infant Neurodevelopmental Screener (BINS) – The BINS can be used to screen development in children 3 to 25 months. It uses 10 to 13 directly elicited items per three- to six-month age range to screen neurologic processes (reflexes and tone), neurodevelopmental skills (fine motor, language), and cognitive processes.
- Brigance Screens-II – The Brigance Screens-II can be used to screen development in children from 0 to 90 months. It consists of nine separate forms, one for each 12-month age range, each of which takes 10 to 15 minutes to administer. It uses parent report (in the 0- to 24-month age range), direct observation, and elicitation to screen speech-language, motor skills, and general knowledge at younger ages and reading and math at older ages.
- Denver Developmental Screening Test-II (DDST-II) – The DDST-II is a directly administered tool that is designed to screen expressive and receptive language, gross motor, fine motor, and personal-social skills in children zero to six years of age [14]. It has limited sensitivity and specificity to detect language delay, mild ID, learning disabilities, and functional developmental delay [15]. It is used to track developmental skills during longitudinal pediatric follow-up and to detect children who require further evaluation of delays.
- Infant-Toddler Checklist for Language and Communications – This tool can be used to screen language and communication development in children 6 to 24 months of age [16,17]. Early language delay may be the first sign of atypical development in intellectual disability.
- Parents' Evaluation of Developmental Status (PEDS) – The PEDS can be used as a brief developmental screen in children from birth to eight years. In addition to functioning as a screening test, it provides longitudinal surveillance and helps to determine when referrals are necessary and when patient education, in-office counseling, watchful waiting, or additional screening is needed.

Detailed evaluation — When a screening test suggests developmental delay, further evaluation is needed. This includes a focused history and physical examination that elicits characteristics that suggest a specific cause of the ID, and examines for possible co-morbidities or associated conditions (see "Intellectual disability (mental retardation) in children: Evaluation for a cause"). The history should incorporate a three-generation family pedigree. The evaluation also includes a comprehensive developmental assessment, including standardized testing of intellectual and adaptive functioning and assessment of behaviors. Evaluations apply both assessment tools and clinical judgment to establish the diagnosis of ID and to evaluate the child's needs for support and services. (See 'Diagnosis of ID and needs assessment' below.)

A multidisciplinary approach is recommended. Throughout the evaluation, it is important to use skilled professional communication and allow sufficient time for the interview, to elicit parent concerns, provide genetic counseling, and convey sufficient information to enable optimal understanding and informed collaborative decision-making with the child's parents [18].

- Referral to a developmental pediatrician, pediatric neurologist, and/or psychologist is usually needed, for a comprehensive developmental evaluation. This includes cognitive-adaptive and behavioral assessments to determine the need for intellectual and adaptive supports.
- Speech and language and adaptive functioning should be formally assessed. Adaptive functions are assessed in three domains of conceptual, social and practical functioning, so as to identify what ongoing supports are needed individually.
- Occupational and physical therapists can assist in assessing functional impairments, strengths, and needs.
- A social worker can assist in assessment of the family and family needs, provide counseling, and generate social supports and contribute to long-term planning.

- A geneticist can evaluate for suspected genetic disorders and provide genetic counseling.
- A neurologist can assist in the assessment and management of seizures and other neurological conditions.

The nature and timing of the evaluations are controversial, and there is no widely accepted standardized approach. The first step is a comprehensive history and physical examination. In three series, the history and physical examination identified the etiology of ID or developmental delay in 17 to 34 percent of cases [19-21].

History — A comprehensive history should be obtained. Ample time should be allocated for the evaluation. This should include an opportunity for the parents to communicate their concerns, perceptions, and misconceptions [18].

Details of the child's developmental, behavioral, social, and educational history should be elicited from the parents or caretakers, as well as a record of medications, treatments, and support services. Behaviors that are characteristic of a specific cause of ID or behaviors of other neurodevelopmental disorders (see above) should be noted. Developmental progress, stagnation or loss of skills should be elicited. Quality of life questions or measures provide further insight into the needs of a person with ID. Results of prior developmental, psychological, and psychiatric evaluations should be obtained [7]. A high index of suspicion for abuse and neglect is warranted, particularly in verbally inexpressive children. (See "Physical abuse in children: Epidemiology and clinical manifestations" and "Child neglect and emotional abuse".)

To guide the investigation for a cause of the ID, the results of any previous newborn metabolic and thyroid testing, neuroimaging, lead and iron screening, growth records, and vision and hearing surveillance should be reviewed. The evaluation also should include a detailed family history inquiring about any close family member with a neurodevelopmental or genetic disorder; and whether the mother has a history of miscarriages or stillbirth/neonatal death. A specific inquiry should be made about whether there is any known consanguinity. The prenatal, perinatal, and neonatal course should be reviewed, including an inquiry about alcohol intake during pregnancy, as well as a complete review of systems. (See "Intellectual disability (mental retardation) in children: Evaluation for a cause".)

Physical examination — A physical examination may help establish the etiology of ID and identify associated conditions. The examination should be comprehensive, with specific attention to the following (see "The pediatric physical examination: General principles and standard measurements"):

- Measurements of height, weight, and head circumference, including growth velocity.
- Dysmorphic features that may suggest genetic or syndromic etiologies to guide selection of genetic tests. (See "Intellectual disability (mental retardation) in children: Evaluation for a cause", section on 'Genetic testing for a specific suspected or suggested disorder'.)
- Examination of the ears, nose, and throat, including hearing assessment. (See "The pediatric physical examination: HEENT".)
- Eye examination, including, visual acuity, visual fields, extra-ocular movements, strabismus, and evaluation of the fundi. (See "The pediatric physical examination: HEENT".)
- Assessment of the heart, lungs, abdomen, genitourinary system, back, extremities, and skin. (See "The pediatric physical examination: Back, extremities, nervous system, skin, and lymph nodes" and "The pediatric physical examination: Chest and abdomen" and "The pediatric physical examination: The perineum".)
- Complete neurologic and neurodevelopmental assessment. (See "Detailed neurologic assessment of infants and children".)

- Detailed observation of the child's behavior, including attention, impulsivity, activity, affect, motor mannerisms, disordered social communication, internalizing (eg, anxiety, depression) and externalizing behaviors (eg, oppositional and aggressive behavior), and behavioral phenotype.
- Parent/family interactions and behaviors may be observed for any features suggesting parental depression, parenting characteristics, or suspicion of child abuse. Parental stress, depression, and other needs may be elicited by parent-report measures. In some cases, parents themselves are affected by a genetic disorder and exhibit signs and symptoms relevant to the child's evaluation, diagnosis, and intervention.

Sensory screening — Children with global developmental delay and/or ID are at high risk for sensory impairments. Vision disorders affect 13 to 50 percent of patients with ID, and approximately 18 percent have hearing impairment [22]. Thus, assessment of vision and hearing is an essential part of the initial evaluation. This should include a complete ophthalmologic examination and audiometry, preferably using brainstem auditory evoked response. (See "Visual development and vision assessment in infants and children" and "Hearing impairment in children: Evaluation".)

DIAGNOSIS OF ID AND NEEDS ASSESSMENT — Intellectual disability (ID) is diagnosed by documenting significant limitations in **both** adaptive and intellectual function with onset during the developmental period [1,2]. The steps to making the diagnosis of ID and assessing its severity will be discussed here. The evaluation of a child for underlying **causes** of ID is discussed in a separate topic review. (See "Intellectual disability (mental retardation) in children: Evaluation for a cause".)

Adaptive function — The diagnosis of ID requires the presence of deficits in both intellectual and adaptive functioning; the adaptive impairment must be directly related to the intellectual impairment [1]. The severity of ID is also defined by the degree of impairment in adaptive functioning, rather than by an intelligence quotient (IQ) score. This represents a change in the latest version of the Diagnostic and Statistical Manual (DSM-5) as compared with the DSM-IV, and is now similar to the definition used by the American Association on Intellectual and Developmental Disabilities (AAIDD) [1,2]. Although both intellectual and adaptive impairment measures are pertinent in describing ID, impaired adaptive functions are more likely to be the presenting feature of ID than low IQ; impaired adaptive skills that affect activities of daily living and the child's ability to respond to common situations are more readily perceived than impaired intellectual functioning.

The diagnosis of ID requires impaired functioning in at least one of the following three domains, affecting participation in multiple settings (eg, home, community and/or school) and requiring ongoing support (table 2A) [1,2]:

- Conceptual domain – These skills include language, reading, and writing (literacy); money, time, and number concepts (mathematics); reasoning; memory; self-direction; and judgment in novel situations.
- Social domain – These skills include interpersonal social communication, empathy, ability to relate to peers as friends and social problem-solving. Social responsibility, self-esteem, gullibility, the ability to follow rules and avoid being victimized may also be included.
- Practical domain – These skills include activities of personal care or daily living, such as eating, dressing, mobility, and toileting. Further skills may include following a schedule or routine, using a telephone, managing money, preparing meals, occupational skills, and abilities in transportation/travel, health care, and safety.

Both clinical assessment and individualized standardized testing are used to delineate adaptive functioning [1]. Impaired function is defined by a score or performance at least two standard deviations below the mean on a standardized test assessing these domains [2]. The symptoms of adaptive

impairment need to have begun during child development. The severity of the ID is defined according to the supports that are needed in each of these domains of adaptive functioning. The “support intensity” may vary from intermittent to pervasive [2].

Standardized assessment tools using established developmental criteria are available to measure adaptive function and provide a composite score. The most commonly used tool is the parent-reported Vineland Adaptive Behavior Scale (VABS-II). Other examples include the AAIDD’s Diagnostic Adaptive Behavior Scale (DABS), the Woodcock–Johnson Scales of Independent Behavior-Revised (SIB-R), and the Adaptive Behavior Assessment System (ABAS-2nd Ed, or ABAS-II). These tests vary in the adaptive areas that are measured and in the reliability of scores within adaptive domains.

The instrument that is used to measure adaptive functioning must be appropriate for the child's age, gender, socioeconomic, experience, culture, and disability profile, and the results must be interpreted accordingly. As an example, normative values on an adaptive scale may be invalidated by a child's disability or medical condition. The assessment must also be appropriate for chronological and developmental age, as not all adaptive skills are applicable to young children.

Intellectual function — In addition to impaired adaptive functioning as described above, the diagnosis of ID requires the presence of impaired intellectual functioning, which includes learning, reasoning, and problem solving, abstract thinking, and judgment. Both clinical assessment and individualized standardized testing are required to confirm deficits in intellectual functioning [1]. The degree of impairment in intellectual function that is consistent with a diagnosis of ID typically corresponds to an intelligence quotient (IQ) less than 65 to 75.

An IQ score provides a useful description of a child’s intellectual disability. However, the IQ score is no longer applied as the diagnostic measure of severity, and is not used alone to drive clinical or legal decision-making. Moreover, IQ determination alone is an imprecise measure of a child's true intellectual abilities. The intellectual profile obtained by comprehensive developmental assessment is frequently more helpful than a composite or global IQ score, and generates a better description of individual strengths, and impaired functions that need intervention.

Because the diagnosis of ID requires both intellectual and adaptive deficits, a child with an IQ less than 70 unaccompanied by an adaptive deficit would not be considered to have ID, while one with an IQ between 70 and 75 that is accompanied by significant adaptive deficit would be diagnosed with ID. Although most children with an IQ less than 70 have adaptive deficits, their adaptive skills may improve with appropriate interventions; over time, they may no longer meet the severity of adaptive impairment criteria needed for an ID diagnosis.

Standardized intelligence tests — Intellectual function is typically measured by the administration of standardized tests to compare measured performance to that expected for age. The most commonly used tests for children are the Wechsler Scales. The instrument used for testing intellectual function must be appropriate for the child’s level of adaptive function (see 'Adaptive function' above). In order to be valid, the test must take into account the child's age, culture, language, socioeconomic status, and profile of motor, sensory, and communication functioning [1]. Tests must use currently applicable norms, as out-of-date norms falsely inflate scores (“Flynn effect”).

The following are some of the commonly used tests to assess children over specific age ranges (where y:years; m:months):

- Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV) – ages 2y 6m to 7y 7m [23]
- Wechsler Intelligence Scales for Children (WISC-V) – ages 6 years to 16y 11m [23]
- Wechsler Adult Intelligence Scale (WAIS-IV) – ages 16 to 90 years [23]

- Stanford-Binet Intelligence Scales (SB-5) – 2 to 85 years [24]
- Kaufman Assessment Battery for Children (KABC-II) – 3 to 18 years [23]
- Differential Abilities Scales (DAS-II) – 2y 6m to 17 years [23]
- Leiter International Performance Scale-Revised (Leiter-R) – 2 to 20 years [25]; this tests nonverbal intelligence only.
- Test of Nonverbal Intelligence-4th Ed (TONI 4) – 6 to 89 years [23]

Evaluation of individuals with suspected ID during infancy and early childhood is valuable to detect and define discrepancies needing early intervention. However, early assessment is not considered accurate in predicting long-term future intelligence [22,26]. With appropriate supportive services, some mildly affected children progress into typical range functioning by five years of age and do not meet criteria for ID.

Tests used to evaluate infants include the Bayley Scales of Infant Development and the Griffiths Mental Development Scales (age zero to two years). The Bayley Scales are widely used as a standardized test of infant mental and psychomotor development up to age 42 months [23]. The Griffiths Mental Scales, revised in 1996, are widely used internationally for the standardized comprehensive evaluation of children 0 to 24 months [27]. Griffith's criteria have been restandardized, extended, and revised for children from birth to eight years old [28]. These criteria are applicable for low functioning infants and children with global developmental delay (GDD) or those with severely or profoundly impaired intellect.

Interpretation and limitations of IQ testing — Appropriate interpretation of the results is essential. An IQ score of 65 to 75 (two standard deviations below the mean) or less is considered below normal intelligence. In general, the standard measurement error in IQ testing is approximately five points, although this varies with the instrument used. As an example, the error in Wechsler IQ testing is 10 points, which means that a child with a score of 70 can have an IQ from 65 to 75.

Global IQ scores may be invalid if there are highly discrepant scores on the subtests. IQs derived from different tests are not interchangeable because of differences in the measurement error and the particular skills that are tested. Another limitation is that a child's test results may change over time [29]. As a result, while they provide information about abilities measured at the time of the test, they are not necessarily an accurate measurement of a child's long-term potential. IQ measures are less valid at lower values, and out-of-date norms falsely inflate scores ("Flynn effect").

Classification of severity — Although ID is highly heterogeneous and comprises a diverse spectrum of functioning, strengths, weaknesses, impairments, disabilities and needs, it is helpful to recognize categories of severity when assessing needs for supports. The severity of ID is currently defined according to the level of support needed to address impaired adaptive functioning in one or more settings (eg, school, home, work). The DSM-5 describes characteristic impairments in ID that affect one or more adaptive domains (conceptual, social, or practical), and categorizes levels of severity within a range of mild to profound (table 2B) [1]. The American Association on Intellectual and Developmental Disabilities (AAIDD) uses a scheme that is similar except that it classifies severity by describing the supports needed as intermittent, limited, extensive, and pervasive [2].

In the past, ID severity was categorized based on intellectual functioning alone, using the following ranges [30]:

- Mild – IQ between 50 to 55 and 70
- Moderate – IQ between 35 to 40 and 50 to 55
- Severe – IQ between 20 to 25 and 35 to 40
- Profound – IQ less than 20 to 25

SUMMARY AND RECOMMENDATIONS

- Intellectual disability (ID) is characterized by significant limitations both in intellectual functioning and in adaptive functioning that affect everyday social, conceptual and practical functioning, with onset in childhood (before 18 years of age). The term is preferred over the former term, mental retardation. (See 'Intellectual disability' above.)
- Global developmental delay (GDD) is the term applied to children under five years of age who fail to meet expected developmental milestones and have significant impairments in several areas of intellectual functioning. Not all children with GDD will meet criteria for ID as they grow older. (See 'Global developmental delay' above.)
- The cause of ID and the severity of impairment affect when and how a child presents with ID. Children with severe ID present earlier than those with mild ID. Most children with intellectual impairment present with language delay and delay or disorder in other developmental domains. Gross motor skills in affected children are often relatively preserved. (See 'Clinical features' above.)
- Problems that are commonly associated with most severely affected children with ID include seizure disorders, motor impairments, and vision, hearing, and other sensory impairments, as well as neurodevelopmental disorders including autism, attention deficit hyperactivity disorder (ADHD), depression and anxiety, and self-stimulating or self-injurious behaviors. Children with ID are also at increased risk of being victimized or abused. (See 'Associated conditions' above.)
- A number of standardized tests are available to screen for GDD or ID (table 3). When a screening test suggests developmental delay, further evaluation is needed. Evaluation for ID includes a comprehensive developmental assessment, including standardized testing of intellectual and adaptive functioning and assessment of behaviors. These assessments are used to establish the diagnosis of ID and to evaluate the child's needs for supports and services. (See 'Screening' above and 'Detailed evaluation' above.)
- ID is diagnosed when there are significant deficits in **both** intellectual and adaptive function, which are measured using clinical assessment and standardized tests. The adaptive deficits are directly associated with the underlying intellectual impairment. Selection of the appropriate testing instruments depends on the child's age, gender, culture, language, socioeconomic status, and neurodevelopmental profile including motor, sensory, and communication functioning. (See 'Intellectual disability' above.)
    - Tests of adaptive function are used to assess for deficits in conceptual skills, social skills, and practical daily living skills (table 2A). A diagnosis of ID requires impaired functioning in at least one of these domains, across multiple environments, requiring ongoing support. (See 'Adaptive function' above.)
    - The severity of ID is defined by the degree of impairment in adaptive functioning rather than by intellectual function or IQ score (table 2B). (See 'Classification of severity' above.)
    - For tests of intellectual function, the lower limit of normal is considered to be two standard deviations below the mean, or an intelligence quotient (IQ) of approximately 70. (See 'Intellectual function' above.)
- The evaluation of a child for underlying causes of ID is discussed in a separate topic review. (See "Intellectual disability (mental retardation) in children: Evaluation for a cause".)

REFERENCES

1. American Psychiatric Association. Intellectual Disability (Intellectual Developmental Disorder). In: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, American Psychiatric Association. (Ed), Arlington, VA 2013. p.33.
2. American Association of Intellectual and Developmental Disabilities (AAIDD), Definition of Intellectual Disability, available at: http://aaidd.org/intellectual-disability/definition (Accessed on July 11, 2013).
3. Kaufman L, Ayub M, Vincent JB. The genetic basis of non-syndromic intellectual disability: a review. J Neurodev Disord 2010; 2:182.
4. Chelly J, Khelfaoui M, Francis F, et al. Genetics and pathophysiology of mental retardation. Eur J Hum Genet 2006; 14:701.
5. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol 2010; 9:623.
6. Szymanski L, King BH. Summary of the Practice Parameters for the Assessment and Treatment of Children, Adolescents, and Adults with Mental Retardation and Comorbid Mental Disorders. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 1999; 38:1606.
7. Szymanski L, King BH. Practice parameters for the assessment and treatment of children, adolescents, and adults with mental retardation and comorbid mental disorders. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues. J Am Acad Child Adolesc Psychiatry 1999; 38:5S.
8. Bryson SE, Bradley EA, Thompson A, Wainwright A. Prevalence of autism among adolescents with intellectual disabilities. Can J Psychiatry 2008; 53:449.
9. Molloy CA, Murray DS, Kinsman A, et al. Differences in the clinical presentation of Trisomy 21 with and without autism. J Intellect Disabil Res 2009; 53:143.
10. Wise JC, Sevcik RA, Romski M, Morris RD. The relationship between phonological processing skills and word and nonword identification performance in children with mild intellectual disabilities. Res Dev Disabil 2010; 31:1170.
11. Balogh R, Bretherton K, Whibley S, et al. Sexual abuse in children and adolescents with intellectual disability. J Intellect Disabil Res 2001; 45:194.
12. Soylu N, Alpaslan AH, Ayaz M, et al. Psychiatric disorders and characteristics of abuse in sexually abused children and adolescents with and without intellectual disabilities. Res Dev Disabil 2013; 34:4334.
13. Council on Children With Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics 2006; 118:405.
14. Frankenburg WK, Dodds J, Archer P, et al. The Denver II: a major revision and restandardization of the Denver Developmental Screening Test. Pediatrics 1992; 89:91.
15. Glascoe FP, Byrne KE, Ashford LG, et al. Accuracy of the Denver-II in developmental screening. Pediatrics 1992; 89:1221.
16. Wetherby AM, Prizant BM. Communication and symbolic behavior scales: Developmental profile, Paul H. Brookes Publishing Company, Baltimore, MD 2002.
17. Eadie PA, Ukoumunne O, Skeat J, et al. Assessing early communication behaviours: structure and validity of the Communication and Symbolic Behaviour Scales-Developmental Profile (CSBS-DP)

in 12-month-old infants. Int J Lang Commun Disord 2010; 45:572.

18. Levetown M, American Academy of Pediatrics Committee on Bioethics. Communicating with children and families: from everyday interactions to skill in conveying distressing information. Pediatrics 2008; 121:e1441.
19. Majnemer A, Shevell MI. Diagnostic yield of the neurologic assessment of the developmentally delayed child. J Pediatr 1995; 127:193.
20. Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic yield of subspecialists' evaluation of young children with global developmental delay. J Pediatr 2000; 136:593.
21. Battaglia A, Bianchini E, Carey JC. Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. Am J Med Genet 1999; 82:60.
22. Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology 2003; 60:367.
23. Pearson website, Clinical Assessment. Available at: http://www.pearsonclinical.com/ (Accessed on April 08, 2014).
24. Houghton Mifflin Harcourt website, available at: http://www.riverpub.com/products/sb5/details.html (Accessed on April 08, 2014).
25. Available from the PAR website: http://www4.parinc.com/products /Product.aspx?ProductID=LEITER-3 (Accessed on April 08, 2014).
26. Stein MT, Lukasik MK. Developmental screening and assessment: infants, toddlers, and preschoolers. In: Developmental-Behavioral Pediatrics, 3rd, Levine MD, Carey WB, Crocker AC (Eds), Saunders Elsevier, Philadelphia 2009. p.785.
27. Griffiths mental development scales - revised: Birth to 2 years. Available from Hogrefe, at: http://www.hogrefe.co.uk/griffiths-mental-development-scales-revised-birth-to-2-years-gmds-0-2.html.
28. Luiz DM, Foxcroft CD, Stewart R. The construct validity of the Griffiths Scales of Mental Development. Child Care Health Dev 2001; 27:73.
29. Sattler JM. Assessment of Children: Cognitive Applications, 3rd, Jerome M (Ed), Sattler, San Diego 1988.
30. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), Fourth edition, Text revision, American Psychiatric Association, Washington, DC 2000.

Topic 6172 Version 19.0

GRAPHICS

Terminology used to describe intellectual disability in different countries

Country and/or language	Term
United States	Intellectual disability
Australia	Intellectual disability
Canada (English, French)	Mental deficiency, intellectual handicap
England	Learning disability*, intellectual disability, developmental disability•
France	Mental deficiency, mental apraxia
Germany	Mental handicap, mental retardation
Italy	Mental delay, mentally deficient
Estonia	Mental retardation
Puerto Rico	Mentally slowed down
Spain	Mental delay

* In the United States, the term "learning disability" usually denotes a specific learning disability (eg, dyslexia) rather than intellectual disability.
• In the United States, the term "developmental disability" does not necessarily involve intellectual disability. For example, a developmental disability could be limited to motor dysfunction or developmental-behavioral dysfunction, in the absence of intellectual disability.

Schroeder SR, Gerry M, Gertz G, Velazquez F. Usage of the Term "Mental Retardation:" Language, Image and Public Education. Kansas University Center on Developmental Disabilities; Center for the Study of Family, Neighborhood and Community Policy, The University of Kansas. 2002. p.86.

Graphic 57206 Version 5.0

Summary of adaptive skills used to define severity of intellectual disability

	Skills
Conceptual domain	These skills include language, reading, and writing (literacy); money, time, and number concepts (mathematics); reasoning; memory; self-direction; and judgment in novel situations.
Social domain	These skills include interpersonal social communication, empathy, ability to relate to peers as friends and social problem-solving. Social responsibility, self-esteem, gullibility, the ability to follow rules and avoid being victimized may also be included.
Practical domain	These skills include activities of personal care or daily living, such as eating, dressing, mobility, and toileting. Further skills may include following a schedule or routine, using a telephone, managing money, preparing meals, occupational skills, and abilities in transportation/travel, health care, and safety.

A diagnosis of intellectual disabilty (ID) requires impaired functioning in intellectual functions (intelligence), AND impaired functioning in at least one of the domains of adaptive functioning listed above, which affects participation in multiple settings (eg, home, community, and/or school), and requires ongoing support. The severity of ID is defined according to the level of supports needed.

Adapted from the following sources:

1. *American Psychiatric Association. Intellectual Disability (Intellectual Developmental Disorder). In: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, American Psychiatric Association.*
2. *American Association of Intellectual and Developmental Disabilities (AAIDD), Definition of Intellectual Disability, available at: http://aaidd.org/intellectual-disability/definition (Accessed on July 11, 2013).*

Graphic 90174 Version 1.0

Severity of intellectual disability

Severity level*	Proportion of individuals with ID●	Adaptive skill domains		
		Conceptual domainΔ	Social domainΔ	Practical domainΔ
Mild	85 percent	Children require academic supports to learn skills expected for age. Adults may have difficulties with functional academic skills such as planning, reading, and money management.	Social skills and personal judgement are immature for age. The individual is at risk of being manipulated by others (gullibility).	Most individuals are independent in daily living activities, employable in jobs requiring simple skills, and often able to live independently. They typically need support for making decisions in health care, nutrition, shopping, finances, and raising a family.
Moderate	10 percent	For children, conceptual and academic skills lag well behind those of peers. For adults, academic skills are typically at an elementary level. Complex tasks such as money management need substantial support.	Successful friendships with family/friends are possible using spoken language, but the individual is limited by deficits in social and communicative skills. Social cues, social judgment, social and life decisions regularly need support.	Most individuals are capable of personal care activities with sufficient teaching and support, and achieve independent self-care with moderate supports, such as available in a group home. Adults may be employable in a supported environment.
Severe	3 to 4 percent	Individuals have little understanding of written language, or number, time, and money concepts. Caretakers	Individuals benefit from healthy supportive interactions with family/familiar people and may use very basic	Individuals are trainable in some basic activities of daily living with significant ongoing support and supervision.

		provide extensive supports for problem-solving.	single words, phrases, or gestures pertinent to their direct experience.	
Profound	1 to 2 percent	Individuals may use objects in a goal-directed fashion for self-care and recreation.	Although understanding of symbolic communication is very limited, individuals may understand some gestures and emotional cues, and can express themselves non-verbally.	Individuals are typically dependent upon support for all activities of everyday living. Co-occurring sensory or physical limitations are common.

This table paraphrases the severity levels of ID as outlined by the American Psychiatric Association in the Diagnostic and Statistical Manual, 5th Edition (DSM-5). The American Association on Intellectual and Developmental Disabilities (AAIDD) uses a scheme that is similar except that it focuses on support needs, which are classified as intermittent, limited, extensive, and pervasive.

ID: intellectual disability.
* DSM-5-defined categories of severity.
• Estimates are based on IQ-derived levels of severity (which differ from DSM-5 defined categories of the same name).
Δ Examples of the needs and supports of each adaptive domain, with increasing categories of severity.

Adapted from the following sources:

1. *American Psychiatric Association. Intellectual Disability (Intellectual Developmental Disorder). In: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, American Psychiatric Association.*
2. *American Association of Intellectual and Developmental Disabilities (AAIDD), Definition of Intellectual Disability, available at: http://aaidd.org/intellectual-disability/definition (Accessed on July 11, 2013).*

Graphic 95384 Version 1.0

Selected developmental and behavioral screening tests for use in primary care*

Developmental and behavioral screening tests•
Parent report tests
Parents' Evaluations of Developmental Status (PEDS)
PEDS:Developmental Milestones (PEDS:DM)
Direct observation/elicitation tests
Battelle Developmental Inventory Screening Test (BDIST)
PEDS:Developmental Milestones (PEDS:DM)
Developmental screening tests•
Parent report tests
Ages and Stages Questionnaire
Infant-Toddler Checklist for Language and Communications
Direct observation/elicitation tests
Bayley Infant Neurodevelopmental Screen (BINS)
Brigance Screens-II
Safety Word Inventory and Literacy Screener (SWILS)
Behavioral screening tests
Broad-band tests (all involve parent report)
Ages and Stages Questionnaire:Social Emotional (ASQ:SE)
Brief Infant-Toddler Social Emotional Assessment (BITSEA)
Conners 3rd Edition (Conners 3)
Eyberg Child Behavior Inventory/Sutter-Eyberg Student Behavior Inventory
Pediatric Symptom Checklist
Narrow-band tests
Conners 3 Attention Deficit Hyperactivity Disorder (ADHD) index (Conners 3AI)
Modified Checklist for Autism in Toddlers (M-CHAT), Revised with follow-up (C-CHAT-R/F)
Vanderbilt ADHD Diagnostic Parent and Teacher Rating Scales

* Only those screening tests that have been validated against a "gold standard" instrument and have been found to be able to correctly identify at least 70 percent of children with and without developmental or behavioral disabilities are included.
• Screening tests that assess only one domain of development (eg, motor) are not included.

Adapted from: Glascoe FP and Robertshaw NR. PEDS:DM Professionals Manual PEDSTest.com, LLC, 1013 Austin Court, Nolensville, TN 37135, 2007.

Graphic 57703 Version 6.0

Disclosures

Disclosures: **Penelope Pivalizza, MD** Nothing to disclose. **Seema R Lalani, MD** Nothing to disclose. **Marc C Patterson, MD, FRACP** Grant/Research/Clinical Trial Support: Actelion [Lysosomal diseases (Miglustat)]. Consultant/Advisory Boards: Amicus; Agios; Cydan; Genzyme; Orphazyme; Shire HGT [Lysosomal diseases (Arimoclomol, cyclodextrin, glucocerebrosidase)]; Stem Cells, Inc; Vtesse [Lysosomal diseases (Human embryonic stem cells)]. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Carolyn Bridgemohan, MD** Equity Ownership/Stock Options: MEDCO [Autism (Prescription services)]; Merck [Autism (Vaccines)]. **Carrie Armsby, MD, MPH** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Intellectual disability (mental retardation) in children: Evaluation for a cause

Authors
Penelope Pivalizza, MD
Seema R Lalani, MD

Section Editors
Marc C Patterson, MD, FRACP
Helen V Firth, DM, FRCP, DCH
Carolyn Bridgemohan, MD

Deputy Editor
Carrie Armsby, MD, MPH

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Nov 20, 2014.

INTRODUCTION — Intellectual disability (ID) is a neurodevelopmental disorder with multiple etiologies that is characterized by deficits in intellectual and adaptive functioning presenting before 18 years of age. ID encompasses a broad spectrum of functioning, disability, and strengths [1]. The term improves upon and replaces the older term, mental retardation. The term global developmental delay is used to describe children younger than age five who fail to meet expected developmental milestones in multiple areas of intellectual functioning, and whose severity level of impairment cannot be reliably assessed; not all children with GDD will meet criteria for ID as they grow older [1]. A variety of other terms are used outside of the United States to capture intellectual deficits (table 1). Standardized IQ testing is no longer used to classify the severity of impairment in ID.

ID is an important public health issue because of its prevalence and the need for extensive support services. Its management requires early diagnosis and intervention, coupled with access to health care and appropriate supports. Identifying a cause enables focused interventions, treatments, surveillance, and appropriate counseling, with anticipation of possible medical or behavioral complications and a more specific prognosis [2].

This topic review will discuss the epidemiology of intellectual disability and evaluation of affected children for a specific cause. Other aspects of intellectual disability are discussed in separate topic reviews:

- (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs".)
- (See "Intellectual disability (mental retardation) in children: Management; outcomes; and prevention".)

EPIDEMIOLOGY

Prevalence — The prevalence of intellectual disability (ID) varies substantially among studies due to differences in study design, diagnostic approach, severity of the condition, and population characteristics, such as age. In the general population, the prevalence of ID (with deficits in both adaptive and intellectual functioning) is approximately 1 percent [3-7]. The prevalence of deficits in intellectual function only (as measured by IQ) is approximately 3 percent [3]. ID is mild in approximately 85 percent of affected individuals.

The prevalence of ID varies with age and gender, and is highest in school-age and male populations [8]. It is estimated that about 30 percent more males are diagnosed with ID as compared with females [9]. However, the gender difference diminishes with more severe ID. Prevalence of mild ID is more variable across populations than severe ID, varying with environmental factors of maternal education, educational access, or opportunities and access to healthcare [10]. ID, and mild ID in particular, is more prevalent in developing countries or areas with lower socioeconomic status [10].

Global developmental delay is the preferred term to describe intellectual and adaptive impairment in

children younger than five years of age. The prevalence of global developmental delay is estimated at 1 to 3 percent [11]. Global developmental delay does not necessarily predict later ID, although there is a strong correlation. (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs", section on 'Global developmental delay'.)

Risk factors — Genetic and biological factors are implicated in many cases of ID. A study from California identified risk factors for idiopathic ID according to the level of severity [12]. Increased risk for severe ID was seen in males, low-birth-weight infants (eg, premature infants), and children of Hispanic, Black, or Asian mothers, compared with White mothers. The risk for severe ID increased with higher maternal age and decreasing maternal education. The risk for ID also appears to be associated with advanced paternal age; one study demonstrated found that paternal age greater than 40 years is associated with an increased risk for mild to moderate ID [13].

The risk factors for mild ID with unknown cause were slightly different [12]. Increased risk was identified in multiple births and children born second or later. Compared with children born to White mothers, the risk of having a child with mild ID was greater for Black mothers, less for Asian mothers, and similar for Hispanic mothers.

Other reports also have identified maternal age and limited maternal education as important risk factors for ID. As an example, in a large birth cohort in Tennessee, low level of maternal education was the strongest predictor of mild ID, and a stronger predictor than maternal age [14]. The risk of ID in children of mothers with 12 years or less of education was seven times greater compared with mothers with some post-secondary education, and three times greater than those with a high school diploma. The risk for mild ID was slightly increased in children born to mothers 15 to 19 years old, while the risk of moderate to severe ID was greatest in those born to mothers 40 to 44 years of age.

CAUSES — The causes of ID are extensive and include any disorder that interferes with brain development and functioning. Among the known causes of ID, the majority are genetic abnormalities [15,16]. A minority of cases have environmental causes such as teratogens, toxins, infections, trauma, birth asphyxia, and nutritional deficiencies [17]. ID can occur in isolation or with neurological abnormalities such as epilepsy or structural brain defects, or with other congenital anomalies.

Genetic causes — Genetic conditions are increasingly being diagnosed by technological advances in genetic testing; a specific genetic cause can be identified in more than 50 percent of cases of ID referred for specialty evaluation [15,16,18]. The increasing use of techniques related to genome-wide sequencing of the coding regions (exome) promises to uncover many more genes involved in both syndromic and nonsyndromic ID. Chromosomal microarray analysis (CMA) is currently the most valuable tool in routine practice to identify the genetic causes of ID, as discussed below [10,19]. (See 'Chromosomal microarray analysis' below.)

A genetic abnormality may present as ID alone (nonsyndromic ID), or as ID associated with a clinical syndrome (syndromic ID) [20] (see "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs", section on 'Syndromic versus nonsyndromic ID'). Some genetic syndromes are genetically heterogeneous and may be caused by mutations in several genes with distinct roles in common biological pathways. Some examples of genetic conditions with genetic heterogeneity include Noonan syndrome [21], Cornelia de Lange syndrome [22], and Rubinstein-Taybi syndrome [23].

Detailed information about many genetic syndromes is available by searching for the disorder in the following open-access databases:

- On-line Mendelian Inheritance in Man (OMIM)
- GeneReviews

- Genetic Testing Registry

Some of the known genetic disorders or conditions causing ID include the following:

Chromosomal abnormalities — Chromosomal aberrations as a group are the most common known cause of ID [10]. Down syndrome, or trisomy 21, is the single most common known genetic cause of ID [10,24]. (See "Down syndrome: Clinical features and diagnosis".)

Genomic disorders resulting from genomic instability due to the innate genomic architecture have been recognized as a frequent cause of ID. A variety of syndromes have been described with deletions due to genomic rearrangements. These include Williams-Beuren syndrome (WBS) [25] (see "Microdeletion syndromes (chromosomes 1 to 11)"), Smith-Magenis syndrome [26], Angelman and Prader-Willi syndromes [27], and 22q11 deletion syndrome (DiGeorge syndrome) [28]. (See "Microdeletion syndromes (chromosomes 12 to 22)".)

Other such disorders include deletions at *NRXN1* [29], 1q21.1 [30], 15q13.3 [31], and 16p11.2 [32]. Less frequent copy number variations are observed as deletions of 1p36 [33], 3q29 [34], 9q34 [35], and 17q21.31 [36]. These are generally classified as syndromic forms of ID, occurring with comorbid disorders such as autism spectrum disorder, neuropsychiatric concerns, epilepsy, facial dysmorphisms, or congenital anomalies. Many of these loci have reciprocal duplications associated with ID including duplications of the WBS region [37], Potocki-Lupski syndrome [38], and 22q11.2 duplication syndrome [39]. Some other known pathological deletions detected by CMA include deletions in *SHANK2* [40], *ILRAPL1,* Neuroligin 4 (*NLGN4*) and *SHANK3* which are known causes of ID and autism [41,42].

Single-gene disorders

X-linked disorders — Mutations resulting in X-linked ID have been reported in over 100 genes and account for 10 to 12 percent of ID in males [43,44]. X-linked disorders are very heterogeneous and occur in syndromic or nonsyndromic forms.

- **Fragile X syndrome** – The most common X-linked single gene disorder causing ID is Fragile X syndrome, which occurs in approximately 2 to 3 percent of males with ID [24,45]. The prevalence of fragile X syndrome in males with ID is approximately twice that of females (due to variability of expression in females carrying a full mutation as a consequence of variation in X-inactivation). (See 'Testing for fragile X syndrome' below and "Fragile X syndrome: Clinical features and diagnosis in children and adolescents".)

- **MECP2-related disorders** – *MECP2* related disorders, including Rett syndrome and *MECP2* duplication/triplication, are important causes of X-linked ID.

  - **Rett syndrome** is a neurodevelopmental disorder caused by **mutations** in *MECP2* that occurs almost exclusively in females. After a period of initially normal development during the first 6 to 18 months of life, affected girls experience loss of speech and purposeful hand use, develop stereotypic hand movements, and gait abnormalities. (See 'Rett syndrome' below and "Rett syndrome".).

  - **MECP2 duplication syndrome** (MIM #300260), also known as Lubs X-linked mental retardation syndrome, is clinically and genetically distinct from Rett syndrome. It is characterized by duplications (or triplication) of the *MECP2* gene and is a cause of severe to profound intellectual disability in males [46]. Females with *MECP2* duplication are usually asymptomatic, although mild to severe cognitive impairment has been described [47,48]. *MECP2* duplications account for about 1 percent of unexplained X-linked ID [46]. *MECP2* duplication is suspected in males who have neonatal hypotonia progressing to spasticity, failure to thrive, severe language impairment, severe to profound ID, and seizures. CMA is the recommended test to identify *MECP2* duplications, as *MECP2* sequencing tests do not detect

duplications. (See 'Chromosomal microarray analysis' below.)

- **X-linked creatine transporter** deficiency is estimated to be responsible for approximately 1 to 2 percent of X-linked ID [49-51]. It is caused by mutations in *SLC6A8* and is characterized by mild to severe ID in males, with speech and motor delay, behavioral abnormalities, and seizures [52].
- **Pelizaeus Merzbacher disease** is a rare X-linked hypomyelinating disorder due to mutations in the *PLP1* gene that cause progressive motor and intellectual deterioration in a male infant [53,54]. Brain magnetic resonance imaging (MRI) and CMA testing are used to detect this condition.

Autosomal dominant disorders — "De novo" (new) mutations in dominantly inherited genes are increasingly identified as an important cause of severe ID [6,55]. In individuals with ID where standard genetic tests, including CMA, fail to identify a cause, next-generation whole exome sequencing can identify new mutations in 16 to 25 percent of cases [15,55,56]. These include mutations in *STXBP1, SYBGAP1, SCN2A, ANKRD11*, *KANSL1*, *KAT6B*, *MLL2*, *SHANK3*, *SPAST*, *SRCAP*, and *ZEB2* [15,56]. Trio exome analysis is particularly helpful in identifying de novo mutations, which are the commonest genetic cause of ID in nonconsanguineous populations.

Autosomal recessive disorders — Autosomal recessive disorders occur particularly in consanguineous families and include many inborn errors of metabolism [10,20]. Some examples of recessive disorders causing ID include mutations in *PRSS12* (encodes a serine protease probably involved in neural synapses) [57], *CRBN* (involved in the regulation of mitochondrial metabolism) [58], *CC2D1A* [59], *TUSC3* (involved in glycosylation) [60], and *GRIK2* (glutamate receptor 6) [61]. These disorders are increasingly identified by homozygous mapping and whole exome sequencing, where available. For children with ID, the yield of routine metabolic investigations for inborn errors of metabolism ranges from 0.8 to 2.5 percent [18,62]. (See 'Genome sequencing' below and 'Metabolic testing' below.)

Mitochondrial disorders — Mitochondrial disorders, caused by mutations of the mitochondrial DNA (mtDNA) or the nuclear DNA (nDNA) [63], are a heterogeneous group of diseases that frequently cause ID in association with neurologic, cardiopulmonary, ophthalmologic, renal, or hematological complications. The disorder may be nuclear encoded (autosomal recessive, autosomal dominant, X-linked), or encoded in the mitochondrial genome (maternally inherited). (See "Mitochondrial myopathies: Clinical features and diagnosis".)

Environmental causes

Prenatal causes — Important nongenetic prenatal causes of ID include congenital infections and environmental toxins or teratogens (eg, alcohol, lead, mercury, phenytoin, valproate). Prenatal exposure to alcohol is a relatively common cause of ID in many countries, and is potentially preventable. Radiation exposure, especially between 9 and 15 weeks gestation, is associated with ID [8]. (See "Approach to congenital malformations" and "Overview of TORCH infections", section on 'Clinical features of TORCH infections' and "Fetal alcohol spectrum disorder: Clinical features and diagnosis".)

Perinatal causes — Perinatal abnormalities that may lead to ID include preterm birth, hypoxia, infection, trauma, and intracranial hemorrhage. (See "Long-term neurodevelopmental outcome of premature infants" and "Management and complications of intraventricular hemorrhage in the newborn".)

Postnatal causes — Postnatal and acquired causes of ID may be easier to identify, as they typically occur in an individual who was previously normal. Etiologies include accidental or nonaccidental trauma, central nervous system (CNS) hemorrhage, hypoxia (eg, near-drowning), environmental toxins, psychosocial deprivation, malnutrition, intracranial infection, CNS malignancy, or acquired hypothyroidism. The extent to which concurrent exposures to multiple environmental toxins affect neurocognitive outcomes is not known.

Congenital hypothyroidism may cause cognitive delay if it is unrecognized and untreated. In Jordan, a country without a comprehensive newborn screening program, 3 percent of children in whom cognitive delay was detected at a mean age of 15 months, were found to have congenital hypothyroidism [64]. Where newborn screening is available, early screening and treatment has mostly eliminated ID caused by hypothyroidism and phenylketonuria. (See "Clinical features and detection of congenital hypothyroidism".)

APPROACH TO DIAGNOSTIC TESTING — Decisions about which laboratory studies should be performed are based upon clinical abnormalities identified during the history and physical examination and the diagnostic yield and availability of the specific tests [3,11,19]. Evidence-based consensus is still developing for which tests should be routinely performed to evaluate a child with unexplained ID or global developmental delay; tests may vary across clinical settings and among nations, especially where screening programs differ [65]. Studies analyzing cost-benefit, cost-effectiveness, and the evidence base for sequential or stepwise testing approaches are still needed.

The results of the laboratory studies may identify a particular disorder that would allow the clinician to provide more information to the family about the associated prognosis, comorbidities, anticipation of future needs, and whether any specific treatment is available. With the exception of metabolic disorders, which are rare, most causes of ID do not have specific treatments to rectify the cause. Genetic causes may have implications for future pregnancies, and there may also be reproductive implications for the extended family, which should be addressed with genetic counseling. Even if a specific diagnosis cannot be found, exclusion of certain disorders may be helpful for the parents and other family members.

GENETIC TESTING — Selection and sequence of genetic tests is guided by a focused history (including a family history as this may suggest a particular pattern of inheritance) and a physical examination. If there are dysmorphic features or clinical characteristics that suggest a specific genetic disorder, then the first step is specific testing for that disorder, as outlined below. (See 'Genetic testing for a specific suspected or suggested disorder' below.)

Where no specific disorder is clinically suggested or suspected, then genetic testing for idiopathic or unexplained intellectual disability is recommended, starting with a chromosomal microarray analysis (CMA) (algorithm 1) [2,3,11,19]. The use of genome sequencing for this purpose is rapidly evolving. (See 'Chromosomal microarray analysis' below and 'Genome sequencing' below.)

Genetic testing for a specific suspected or suggested disorder — Patients with characteristics suggesting a particular syndrome should undergo specific genetic testing to confirm or rule out that disorder. Tests may be done on the parents as well as the child. Parental testing is usually deferred until after a possible diagnostic variant has been identified in the child, except in the case of trio exome analysis where parental samples may be helpful to identify de novo variants. If the clinical features described below are absent, then testing for fragile X may still be appropriate in some cases, as a second step in the evaluation of unexplained ID. (See 'Genetic tests for unexplained intellectual disability' below.)

Examples of suspected disorders for which specific tests are recommended as an initial step include:

Down syndrome or other common aneuploidy — For children with clinical features suggesting Down syndrome or other common aneuploidy (trisomy 18 or a sex chromosome aneuploidy), we suggest a G-banded karyotype analysis. (See "Down syndrome: Clinical features and diagnosis" and "Congenital cytogenetic abnormalities" and "Sex chromosome abnormalities".)

Fragile X syndrome — Fragile X syndrome (full *FMR1* mutation) should be suspected in males with moderate to severe ID, macrocephaly, large ears, enlarged testes, perseverative speech, and poor eye contact. Males with unexplained ID **and** a family history of ID should also be evaluated for the syndrome. Females with characteristic clinical features or a family history of ID also should be tested for fragile X

syndrome because females with full *FMR1* mutation present with ID in about half of the cases. (See 'Testing for fragile X syndrome' below and "Fragile X syndrome: Clinical features and diagnosis in children and adolescents".)

Rett syndrome — Rett syndrome should be suspected in girls with unexplained moderate to severe ID who were normal during the first six months of life then experienced a period of regression or developmental stagnation usually beginning in the second year of life, especially if there are stereotypic hand movements. (See "Rett syndrome".)

Muscular dystrophy — For boys with unexplained global developmental delay or ID, and especially those with proximal muscle weakness, we suggest measurement of serum creatine kinase to screen for Duchenne muscular dystrophy. If the creatine kinase is elevated, specific genetic testing is then performed. This is because boys with Duchenne muscular dystrophy may present with unexplained global developmental delay/ID, so screening is appropriate for boys with clinical features that suggest this diagnosis [66,67]. Early identification of this disorder enables early intervention and family counseling. Becker muscular dystrophy also may be associated with ID, but the muscular dysfunction tends to be milder. (See "Clinical features and diagnosis of Duchenne and Becker muscular dystrophy".)

Genetic tests for unexplained intellectual disability — Genetic tests are recommended for unexplained ID because they can provide diagnostic and prognostic information and allow for informative genetic counseling of the parents and other family members. Although diagnostic tests for chromosome abnormalities and single gene disorders have the highest yield if dysmorphic features, congenital anomalies, or findings suggestive of a specific syndrome are present, testing has a diagnostic yield even if such features are absent (algorithm 1). The diagnostic yields of different tests or testing approaches are summarized in the tables (table 2A-C); the reported diagnostic yields are estimated based on meta-analysis of different patient groups rather than representative population-based samples [45]. This analysis does not include the yield from genome sequencing, which is rapidly becoming an important diagnostic technique in specialty centers. (See 'Genome sequencing' below.)

Chromosomal microarray analysis — Current evidence supports the use of CMA as a first-line genetic test for unexplained ID, in preference to G-banded karyotype analysis [2,19,68-70] or subtelomeric fluorescence in-situ hybridization (stFISH) [19,71]. CMA is also known as molecular karyotyping, microarray-based genomic copy-number analysis, or array-based comparative genomic hybridization (aCGH). A list of laboratories that perform CMA testing is available at the GeneTests website. (See "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Array comparative genomic hybridization'.)

The use of CMA leads to a genetic diagnosis in 15 to 20 percent of patients with unexplained ID, which is substantially higher than G-banded karyotype analysis (table 2A). The higher yield of CMA is primarily because of its sensitivity for submicroscopic deletions and duplications (deletion and duplications are also known as copy number variations) [72]. In a meta-analysis of 33 studies of patients with ID, autism spectrum disorders, or multiple congenital anomalies, the average diagnostic yield of CMA was 12 percent [19]. In another study of more than 35,000 patients with ID, CMA detected a pathogenic abnormality in nearly 19 percent of patients [73].

G-banded karyotype analysis should be reserved for patients when a common aneuploidy is suspected (such as Down syndrome, trisomy 18, or a sex chromosome aneuploidy), or where CMA is unavailable. CMA will not identify balanced translocations, such as translocations or inversions and may not detect low-level mosaicism, but these are relatively infrequent causes of abnormal phenotypes in this population. As a result, karyotyping is still recommended if there is concern for balanced translocation (eg, a history of frequent miscarriages, or a family history of translocation) [19]. CMA has a lower resolution than sequencing and therefore does not detect point mutations (sequence variants)

responsible for single-gene disorders. (See "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Chromosomal analysis'.)

Clinicians should be aware that there are different platforms for CMA studies. Oligonucleotide-based arrays provide a superb means of detecting DNA copy number changes, including single exon deletions on certain platforms [74,75]. There are a large number of designs of CMA with different levels of resolution (from ~1 Mb to several kb) and different approaches to probe location (eg, evenly spaced across the genome, or targeted to the exome [coding portion of the genome] or hybrid [gene-focused but with a genome-wide backbone]). Single nucleotide polymorphism (SNP) arrays can detect copy number changes, as well as long contiguous stretches of copy number neutral regions of absence of heterozygosity that can be associated with uniparental disomy (UPD) or parental consanguinity. Both of these findings increase the risk for autosomal recessive conditions. In addition, SNP arrays detect triploidy, low-level mosaicism, and chimerism [76]. Combined oligonucleotide/SNP arrays are also available to pool the advantages of each method [77].

If the CMA testing result is normal or yields a known benign variant, then further evaluation using specific tests may be considered, as recommended in a consensus statement [19]. Where CMA fails to find a cause of ID, whole exome sequencing can be applied to identify causative mutations [15,55]. Deciphering variants of uncertain clinical significance may be challenging. Interpretation of a CMA result requires expert review to determine whether a copy-number variant is clinically significant. In many cases, testing of the patient's parents is necessary to fully assess the clinical significance of a result to enable appropriate genetic counseling [19,78].

Testing for fragile X syndrome — Fragile X syndrome is caused by an abnormal expansion mutation of a CGG triplet repeat in the FMR1 gene (typically >200) and is the most prevalent form of inherited ID [79]. Most affected males and approximately one-half of females with a full FRAX mutation have ID. Males generally have moderate to severe ID and may not have the characteristic appearance; affected females tend to have mild ID. (See "Fragile X syndrome: Clinical features and diagnosis in children and adolescents".)

Selection criteria for fragile X testing varies among authorities. Most experts recommend fragile X testing for all children in the following groups (table 2B) [19,79]:

- Males and females with ID and clinical features suggesting fragile X syndrome (eg, macrocephaly, large ears, enlarged testes in case of males, perseverative speech, and poor eye contact)
- Males and females with unexplained ID or developmental delay **and** a family history of ID

In addition, many authorities suggest fragile X testing for all children with the following characteristics:

- Males and females with ID whose initial microarray testing is normal or benign [19]
- Males and females with unexplained ID (because of a 1 to 3 percent diagnostic yield [45])
- Males and females with unexplained autism [79,80]
- Males and females with borderline ID [79]

Testing for subtelomeric chromosomal rearrangements — Chromosomal rearrangements in the gene-rich subtelomeric region are identified in approximately 4 to 6 percent of children with ID [81].

Currently, CMA is the test of choice to detect subtelomeric chromosomal rearrangements, as the majority of diagnostic CMA arrays offer dense coverage of subtelomeric regions (table 2A). Molecular screening using fluorescence in situ hybridization (FISH) of subtelomeric probes was used widely for evaluation of ID prior to the institution of CMA. FISH may still be substituted if array diagnosis is not available or if a specific telomeric disorder (eg, 1p36 monosomy, or Cri-du-chat syndrome) is strongly suspected clinically. (See "Tools for genetics and genomics: Cytogenetics and molecular genetics", section on 'Fluorescence in situ hybridization' and "Microdeletion syndromes (chromosomes 1 to 11)", section on

'1p36 deletion syndrome' and "Congenital cytogenetic abnormalities", section on '5p deletion syndrome (cri-du-chat syndrome)'.)

Genome sequencing — Whole genome sequencing or whole exome sequencing (WES) may be considered for patients with features suggesting that genetic disease is likely and other recommended genetic tests have failed to find the cause for ID (algorithm 1). The diagnostic yield of WES is estimated to be between 16 to 25 percent for individuals with severe ID or those in whom a genetic disorder is suspected despite negative testing [55,56]. Due to the falling costs of sequencing and its high diagnostic yield, WES is rapidly becoming a clinical tool for the evaluation of ID, especially at specialty centers. Adoption of WES testing into the diagnostic process will depend on its cost, availability, access to expert interpretation, and the allocation of resources within each health care setting [82]. (See "Principles and clinical applications of next-generation DNA sequencing".)

OTHER TESTS

Metabolic testing — ID is a clinical feature of some inborn errors of metabolism. Most affected children have other manifestations of metabolic disease, such as episodic decompensation, seizures, developmental regression, failure to thrive, or physical findings, such as abnormal neurological exam and hepatomegaly. In addition, screening programs in the United States identify many newborns with these conditions.

For children with unexplained ID, the yield of routine metabolic investigations is low, ranging from 0.8 to 2.5 percent (table 2C), but the potential for improved outcomes after diagnosis and treatment is high [2]. These laboratory tests are appropriate for children with ID and clinical features suggestive of metabolic disease, as outlined above. Some biochemical tests are helpful not only for diagnosis, but also for management of the disorders (eg, calcium assays in 22q11.2 deletion [DiGeorge syndrome], Williams syndrome). (See "Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features" and "Inborn errors of metabolism: Metabolic emergencies" and "Newborn screening".)

Indications for metabolic testing — The results of newborn screening for metabolic disorders should be reviewed as part of the initial evaluation. Additional testing should be performed if these results are not available, or in children with a positive family history of metabolic disorders, parental consanguinity, episodic decompensation, or developmental regression. The presence of these features increases the likelihood of identification of a disorder compared with nonselective screening [83].

To perform metabolic screening, concentrations of serum amino acids, urine organic and orotic acids, serum ammonia, and lactate are most often measured; very long chain fatty acids and carnitine may also be measured on blood samples [19]. Electrolytes are measured to detect acidosis. If further metabolic testing is performed and guided by a specialist, the diagnostic yield increases to at least 3 percent, particularly in children with suggestive clinical features [45]. Other possible tests include urine creatine and guanidinoacetate (for creatine synthesis and transport disorders), blood homocysteine and transferrin electrophoresis, urine glycosaminoglycans, and oligosaccharides [45,65]. (See "Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features", section on 'Developmental delay'.)

Biotinidase deficiency — Clinical symptoms of biotinidase deficiency (MIM #253260) may include seizures, hypotonia, ataxia, developmental delay, and cutaneous abnormalities (alopecia and rashes), although the disorder may present with global developmental delay alone. Biotinidase deficiency is rare but important to detect as it is readily treatable. Biotinidase deficiency is included in the newborn screen in all 50 US states. This is also known as late-onset biotin-responsive multiple carboxylase deficiency. (See "Overview of the hereditary ataxias", section on 'Disorders of pyruvate and lactate metabolism'.)

Thyroid screening — In countries without newborn screening programs, unrecognized congenital hypothyroidism can result in ID [64]. In these countries, thyroid testing has been recommended for infants and children presenting with ID [65]. In these cases, the majority of children have systemic signs

of hypothyroidism. (See "Clinical features and detection of congenital hypothyroidism".)

In countries in which newborn screening for hypothyroidism is routinely performed, thyroid testing is not indicated unless clinical features suggest thyroid dysfunction.

Lead screening — Lead is the most common environmental neurotoxin. Lead exposure can harm cognitive function, even at levels below 10 mcg/dL (0.48 micromol/L) [84]. Accordingly, the upper limit of normal in United States children is now defined as the 97.5th percentile of blood lead levels (5 mcg/dL [0.24 micromol/L], as of 2012). (See "Childhood lead poisoning: Clinical manifestations and diagnosis".)

In the United States, blood lead screening is recommended for **all** children with ID. Although lead toxicity is an uncommon cause of ID in the United States, case identification is essential to allow for treatment and for evaluation of other children who may have been similarly exposed. In addition, children with ID or developmental delay from other causes are at increased risk for lead exposure because they often have persistent mouthing behavior. In one report, blood lead levels >10 mcg/dL occurred in a greater proportion of children with behavioral and/or developmental problems than in controls (12 versus 0.7 percent) [85]. Additional risk factors for lead exposure include living in a house or child care facility built before 1950, recent immigration or home renovation, folk remedies, and some parental occupations including smelting, soldering, and auto body repair. Routine screening for lead toxicity is particularly important for children who fall into one of these high risk groups. (See "Screening tests in children and adolescents", section on 'Lead poisoning'.)

Neuroimaging — If the history or physical examination suggests central nervous system (CNS) malformation or injury (such as microcephaly, seizures, or focal neurologic signs, or suspicion of a hypomyelinating or demyelinating disorder), we recommend neuroimaging in the evaluation of ID [2]. Magnetic resonance imaging (MRI) is preferred, although computerized tomography (CT) scanning may be acceptable if MRI is not available; potential radiation exposure and risk of sedation should be considered as part of informed decision-making. (See "Approach to neuroimaging in children".)

In patients with these features, neuroimaging has a reasonably high yield for detecting an abnormality [83,86-89]. As an example, in a retrospective study MRI abnormalities were found in 109 of 224 (49 percent) of children with developmental delay [88]. The most common lesions identified were CNS malformations, white matter abnormalities, and cerebral atrophy. The yield is likely to be higher in children with specific physical features such as microcephaly, epilepsy, or abnormal motor signs [89,90]. Many of these MRI abnormalities are nonspecific, and often do not lead to a specific diagnosis or alter clinical management.

The sensitivity of MRI is greater than CT in the evaluation of ID. This was illustrated by a series of children with moderate to severe developmental delay but without major neurologic symptoms, in which all patients had a CT scan and some also had an MRI [87]. Abnormalities were found in 51 of 170 (30 percent) who had CT scanning and 19 of 28 (65 percent) who had MRI.

Electroencephalogram — We do **not** routinely obtain an electroencephalogram (EEG) in the evaluation of ID. An EEG may be helpful if epilepsy is present or an epileptic syndrome, neurodegenerative disorder, or speech regression is suspected (such as occurs in Landau-Kleffner syndrome) [65].

Routine EEG evaluation contributes little to the diagnosis of ID. This is illustrated by the following reports:

- In a study of 224 children with global developmental delay, EEGs performed in 60 did not contribute to determining the etiology [83].
- In another report, 10 of 120 children had abnormal EEGs associated with epileptic syndromes, although it is likely that they already had a recognized seizure disorder [11,91].

SUMMARY AND RECOMMENDATIONS — The optimal order or timing of tests to identify the etiology of intellectual disability (ID) is not certain. A staged approach is recommended by the practice parameter of the American Academy of Neurology and the Child Neurology Society for the evaluation of the child with global developmental delay or ID [45].

- A genetic cause can be identified in more than 50 percent of cases of ID in populations referred for specialty evaluation. (See 'Causes' above.)
    - Down syndrome is the single most common genetic cause of ID; fragile X syndrome and Rett syndrome are other genetic causes of ID. (See 'Chromosomal abnormalities' above and 'X-linked disorders' above.)
    - X-chromosome genetic disorders account for approximately 10 to 12 percent of ID in males. (See 'X-linked disorders' above.)
    - De novo dominant mutations are an important cause of severe ID. (See 'Autosomal dominant disorders' above.)
- Nongenetic prenatal causes of ID include congenital infections, and teratogens including alcohol, lead, and valproate. Perinatal abnormalities account for up to 5 percent of ID and include preterm birth, hypoxia, infection, trauma, and intracranial hemorrhage. Postnatal and acquired causes of ID include accidental or nonaccidental trauma, central nervous system (CNS) hemorrhage, congenital hypothyroidism, hypoxia (eg, near-drowning), environmental toxins, psychosocial deprivation, malnutrition, intracranial infection, and CNS malignancy. (See 'Environmental causes' above.)

Features suggesting a specific test — In children with features that suggest a specific diagnosis, the following testing is recommended:

- If the history or physical examination suggests Down syndrome, fragile X, Rett, syndrome or other genetic disorders obtain specific tests for the disorder. Some muscular dystrophies, including Duchenne, occasionally present with nonspecific developmental delay and should be considered in children presenting with otherwise unexplained ID and proximal muscle weakness. (See 'Genetic testing for a specific suspected or suggested disorder' above.)
    - Fragile X testing is recommended for male and female children with clinical features suggesting fragile X syndrome (eg, macrocephaly, large ears, enlarged testes in males, perseverative speech, and poor eye contact). (See 'Testing for fragile X syndrome' above.)
    - Rett syndrome should be suspected in girls with unexplained moderate to severe ID who were normal during the first six months of life then experienced a period of regression or developmental stagnation, especially if there are stereotypic hand movements. (See 'Rett syndrome' above.)
- If results are not available from newborn screening or if the history or clinical signs suggest a metabolic disorder or hypothyroidism, obtain metabolic studies (concentrations of serum amino acids, urine organic acids, serum ammonia, and lactate) and thyroid screen (T4, thyroid stimulating hormone [TSH]). Features that suggest the possibility of metabolic disease include episodic decompensation, seizures, developmental regression, failure to thrive, or physical findings such as abnormal neurological exam and hepatomegaly. (See 'Metabolic testing' above and 'Thyroid screening' above.)
- We suggest neuroimaging in patients with symptoms or signs that suggest a malformation or injury of the CNS, such as microcephaly, seizures, or focal neurologic signs. For this purpose, magnetic resonance imaging (MRI) is the preferred test. (See 'Neuroimaging' above.)
- If the child has seizures or is suspected to have a syndrome that is associated with epilepsy,

perform an electroencephalogram. (See 'Electroencephalogram' above.)

Children with unexplained ID — For children without features suggesting a specific diagnosis, or for those with negative results of specific tests, we suggest the following screens for genetic disorders (algorithm 1):

- Perform a chromosomal microarray (CMA), in preference to G-banded karyotype or subtelomeric fluorescence in situ hybridization (FISH). CMA currently detects a cause in 15 to 20 percent of the cases of ID (table 2A). Abnormalities that can be detected by CMA include submicroscopic deletions and duplications. If CMA is not available, then G-banded karyotype and FISH testing may be applied instead. (See 'Chromosomal microarray analysis' above.)
- For features that suggest the possibility of a balanced translocation, such as a history of frequent miscarriages or a family history of translocation, perform G-banded karyotyping either before or in addition to CMA [19]. This is because CMA does not detect balanced translocations, which are relatively infrequent causes of abnormal phenotypes in this population. (See 'Chromosomal microarray analysis' above.)
- If the initial CMA is normal, or for male and female children with unexplained ID **and** a family history of ID, perform fragile X testing. Fragile X testing also should be performed for children with clinical features suggesting fragile X syndrome, as described above. In addition, many authorities recommend fragile X testing in all children with unexplained ID or autism, since fragile X syndrome often presents with non-specific global developmental delay in young children. (See 'Testing for fragile X syndrome' above.)
- In addition, all children with ID should have a review of newborn screening results and blood lead screening. (See 'Lead screening' above.)
- Where an increased risk of genetic disease is suggested (eg, parental consanguinity, prior unexplained infant death, multiple miscarriages, loss or regression of developmental milestones), metabolic testing and genetics consultation are advised in addition to CMA. (See 'Metabolic testing' above.)
- Referral to a pediatric geneticist is valuable for many children with ID, and especially for those with severe ID who remain undiagnosed despite appropriate investigation. The consultation may yield a definitive diagnosis and facilitate genetic counseling to the family and appropriate management of the patient.

REFERENCES

1. American Psychiatric Association. Intellectual Disability (Intellectual Developmental Disorder). In: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, American Psychiatric Association. (Ed), Arlington, VA 2013. p.33.
2. Moeschler JB, Shevell M, Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics 2014; 134:e903.
3. Szymanski L, King BH. Practice parameters for the assessment and treatment of children, adolescents, and adults with mental retardation and comorbid mental disorders. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues. J Am Acad Child Adolesc Psychiatry 1999; 38:5S.
4. Szymanski L, King BH. Summary of the Practice Parameters for the Assessment and Treatment of

Children, Adolescents, and Adults with Mental Retardation and Comorbid Mental Disorders. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 1999; 38:1606.

5. Harris JC. The classification of intellectual disability. In: Intellectual disability: Understanding its development, causes, classification, evaluation, and treatment, Oxford University Press, New York 2006. p.42.
6. Veltman JA, Brunner HG. De novo mutations in human genetic disease. Nat Rev Genet 2012; 13:565.
7. Maulik PK, Mascarenhas MN, Mathers CD, et al. Prevalence of intellectual disability: a meta-analysis of population-based studies. Res Dev Disabil 2011; 32:419.
8. Ramer JC, Miller G. Overview of Mental Retardation. In: Static Encephalopathies of Infancy and Childhood, Miller G, Ramer JC (Eds), Raven Press, New York 1992.
9. McLaren J, Bryson SE. Review of recent epidemiological studies of mental retardation: prevalence, associated disorders, and etiology. Am J Ment Retard 1987; 92:243.
10. Kaufman L, Ayub M, Vincent JB. The genetic basis of non-syndromic intellectual disability: a review. J Neurodev Disord 2010; 2:182.
11. Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology 2003; 60:367.
12. Croen LA, Grether JK, Selvin S. The epidemiology of mental retardation of unknown cause. Pediatrics 2001; 107:E86.
13. Leonard H, Glasson E, Nassar N, et al. Autism and intellectual disability are differentially related to sociodemographic background at birth. PLoS One 2011; 6:e17875.
14. Chapman DA, Scott KG, Mason CA. Early risk factors for mental retardation: role of maternal age and maternal education. Am J Ment Retard 2002; 107:46.
15. Rauch A, Wieczorek D, Graf E, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet 2012; 380:1674.
16. Moeschler JB. Genetic evaluation of intellectual disabilities. Semin Pediatr Neurol 2008; 15:2.
17. Leonard H, Wen X. The epidemiology of mental retardation: challenges and opportunities in the new millennium. Ment Retard Dev Disabil Res Rev 2002; 8:117.
18. van Karnebeek CD, Scheper FY, Abeling NG, et al. Etiology of mental retardation in children referred to a tertiary care center: a prospective study. Am J Ment Retard 2005; 110:253.
19. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010; 86:749.
20. Chelly J, Khelfaoui M, Francis F, et al. Genetics and pathophysiology of mental retardation. Eur J Hum Genet 2006; 14:701.
21. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet 2013; 381:333.
22. Liu J, Krantz ID. Cornelia de Lange syndrome, cohesin, and beyond. Clin Genet 2009; 76:303.
23. van Belzen M, Bartsch O, Lacombe D, et al. Rubinstein-Taybi syndrome (CREBBP, EP300). Eur J Hum Genet 2011; 19:preceeding 118.
24. Rauch A, Hoyer J, Guth S, et al. Diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation. Am J Med Genet A 2006; 140:2063.
25. Merla G, Brunetti-Pierri N, Micale L, Fusco C. Copy number variants at Williams-Beuren syndrome 7q11.23 region. Hum Genet 2010; 128:3.

26. Elsea SH, Girirajan S. Smith-Magenis syndrome. Eur J Hum Genet 2008; 16:412.
27. Buiting K. Prader-Willi syndrome and Angelman syndrome. Am J Med Genet C Semin Med Genet 2010; 154C:365.
28. Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet 2007; 370:1443.
29. Béna F, Bruno DL, Eriksson M, et al. Molecular and clinical characterization of 25 individuals with exonic deletions of NRXN1 and comprehensive review of the literature. Am J Med Genet B Neuropsychiatr Genet 2013; 162B:388.
30. Brunetti-Pierri N, Berg JS, Scaglia F, et al. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet 2008; 40:1466.
31. Shinawi M, Schaaf CP, Bhatt SS, et al. A small recurrent deletion within 15q13.3 is associated with a range of neurodevelopmental phenotypes. Nat Genet 2009; 41:1269.
32. Shinawi M, Liu P, Kang SH, et al. Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. J Med Genet 2010; 47:332.
33. Gajecka M, Mackay KL, Shaffer LG. Monosomy 1p36 deletion syndrome. Am J Med Genet C Semin Med Genet 2007; 145C:346.
34. Willatt L, Cox J, Barber J, et al. 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome. Am J Hum Genet 2005; 77:154.
35. Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet 2007; 145C:383.
36. Koolen DA, Vissers LE, Pfundt R, et al. A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. Nat Genet 2006; 38:999.
37. Somerville MJ, Mervis CB, Young EJ, et al. Severe expressive-language delay related to duplication of the Williams-Beuren locus. N Engl J Med 2005; 353:1694.
38. Zhang F, Potocki L, Sampson JB, et al. Identification of uncommon recurrent Potocki-Lupski syndrome-associated duplications and the distribution of rearrangement types and mechanisms in PTLS. Am J Hum Genet 2010; 86:462.
39. Portnoï MF. Microduplication 22q11.2: a new chromosomal syndrome. Eur J Med Genet 2009; 52:88.
40. Berkel S, Marshall CR, Weiss B, et al. Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. Nat Genet 2010; 42:489.
41. Pinto D, Pagnamenta AT, Klei L, et al. Functional impact of global rare copy number variation in autism spectrum disorders. Nature 2010; 466:368.
42. Marshall CR, Young EJ, Pani AM, et al. Infantile spasms is associated with deletion of the MAGI2 gene on chromosome 7q11.23-q21.11. Am J Hum Genet 2008; 83:106.
43. Ropers HH. Genetics of early onset cognitive impairment. Annu Rev Genomics Hum Genet 2010; 11:161.
44. Stevenson RE, Charles E, Schwartz R, Rogers RC. Atlas of X-Linked Intellectual Disability Syndromes, Oxford University Press, New York 2012.
45. Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2011; 77:1629.
46. Lugtenberg D, Kleefstra T, Oudakker AR, et al. Structural variation in Xq28: MECP2 duplications in

1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy. Eur J Hum Genet 2009; 17:444.

47. Grasshoff U, Bonin M, Goehring I, et al. De novo MECP2 duplication in two females with random X-inactivation and moderate mental retardation. Eur J Hum Genet 2011; 19:507.
48. Scott Schwoerer J, Laffin J, Haun J, et al. MECP2 duplication: possible cause of severe phenotype in females. Am J Med Genet A 2014; 164A:1029.
49. Lion-François L, Cheillan D, Pitelet G, et al. High frequency of creatine deficiency syndromes in patients with unexplained mental retardation. Neurology 2006; 67:1713.
50. Rosenberg EH, Almeida LS, Kleefstra T, et al. High prevalence of SLC6A8 deficiency in X-linked mental retardation. Am J Hum Genet 2004; 75:97.
51. Clark AJ, Rosenberg EH, Almeida LS, et al. X-linked creatine transporter (SLC6A8) mutations in about 1% of males with mental retardation of unknown etiology. Hum Genet 2006; 119:604.
52. van de Kamp JM, Betsalel OT, Mercimek-Mahmutoglu S, et al. Phenotype and genotype in 101 males with X-linked creatine transporter deficiency. J Med Genet 2013; 50:463.
53. Hoffman-Zacharska D, Mierzewska H, Szczepanik E, et al. The spectrum of PLP1 gene mutations in patients with the classical form of the Pelizaeus-Merzbacher disease. Med Wieku Rozwoj 2013; 17:293.
54. Hoffman-Zacharska D, Kmieć T, Poznański J, et al. Mutations in the PLP1 gene residue p. Gly198 as the molecular basis of Pelizeaus-Merzbacher phenotype. Brain Dev 2013; 35:877.
55. de Ligt J, Willemsen MH, van Bon BW, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med 2012; 367:1921.
56. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 2013; 369:1502.
57. Molinari F, Rio M, Meskenaite V, et al. Truncating neurotrypsin mutation in autosomal recessive nonsyndromic mental retardation. Science 2002; 298:1779.
58. Higgins JJ, Pucilowska J, Lombardi RQ, Rooney JP. A mutation in a novel ATP-dependent Lon protease gene in a kindred with mild mental retardation. Neurology 2004; 63:1927.
59. Basel-Vanagaite L, Attia R, Yahav M, et al. The CC2D1A, a member of a new gene family with C2 domains, is involved in autosomal recessive non-syndromic mental retardation. J Med Genet 2006; 43:203.
60. Garshasbi M, Hadavi V, Habibi H, et al. A defect in the TUSC3 gene is associated with autosomal recessive mental retardation. Am J Hum Genet 2008; 82:1158.
61. Motazacker MM, Rost BR, Hucho T, et al. A defect in the ionotropic glutamate receptor 6 gene (GRIK2) is associated with autosomal recessive mental retardation. Am J Hum Genet 2007; 81:792.
62. van Karnebeek CD, Jansweijer MC, Leenders AG, et al. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. Eur J Hum Genet 2005; 13:6.
63. Wong LJ. Molecular genetics of mitochondrial disorders. Dev Disabil Res Rev 2010; 16:154.
64. al-Qudah AA. Screening for congenital hypothyroidism in cognitively delayed children. Ann Trop Paediatr 1998; 18:285.
65. McDonald L, Rennie A, Tolmie J, et al. Investigation of global developmental delay. Arch Dis Child 2006; 91:701.
66. Essex C, Roper H. Lesson of the week: late diagnosis of Duchenne's muscular dystrophy presenting as global developmental delay. BMJ 2001; 323:37.
67. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed diagnosis in duchenne muscular dystrophy: data

from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr 2009; 155:380.

68. Firth HV, Richards SM, Bevan AP, et al. DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. Am J Hum Genet 2009; 84:524.
69. Sagoo GS, Butterworth AS, Sanderson S, et al. Array CGH in patients with learning disability (mental retardation) and congenital anomalies: updated systematic review and meta-analysis of 19 studies and 13,926 subjects. Genet Med 2009; 11:139.
70. Moeschler JB. Medical genetics diagnostic evaluation of the child with global developmental delay or intellectual disability. Curr Opin Neurol 2008; 21:117.
71. Oostlander AE, Meijer GA, Ylstra B. Microarray-based comparative genomic hybridization and its applications in human genetics. Clin Genet 2004; 66:488.
72. Ropers HH. Genetics of intellectual disability. Curr Opin Genet Dev 2008; 18:241.
73. Hochstenbach R, van Binsbergen E, Engelen J, et al. Array analysis and karyotyping: workflow consequences based on a retrospective study of 36,325 patients with idiopathic developmental delay in the Netherlands. Eur J Med Genet 2009; 52:161.
74. Boone PM, Bacino CA, Shaw CA, et al. Detection of clinically relevant exonic copy-number changes by array CGH. Hum Mutat 2010; 31:1326.
75. Wiszniewski W, Hunter JV, Hanchard NA, et al. TM4SF20 ancestral deletion and susceptibility to a pediatric disorder of early language delay and cerebral white matter hyperintensities. Am J Hum Genet 2013; 93:197.
76. Conlin LK, Thiel BD, Bonnemann CG, et al. Mechanisms of mosaicism, chimerism and uniparental disomy identified by single nucleotide polymorphism array analysis. Hum Mol Genet 2010; 19:1263.
77. Wiszniewska J, Bi W, Shaw C, et al. Combined array CGH plus SNP genome analyses in a single assay for optimized clinical testing. Eur J Hum Genet 2014; 22:79.
78. Paciorkowski AR, Fang M. Chromosomal microarray interpretation: what is a child neurologist to do? Pediatr Neurol 2009; 41:391.
79. Hersh JH, Saul RA, Committee on Genetics. Health supervision for children with fragile X syndrome. Pediatrics 2011; 127:994.
80. Hall SS, Lightbody AA, Reiss AL. Compulsive, self-injurious, and autistic behavior in children and adolescents with fragile X syndrome. Am J Ment Retard 2008; 113:44.
81. De Vries BB, Winter R, Schinzel A, van Ravenswaaij-Arts C. Telomeres: a diagnosis at the end of the chromosomes. J Med Genet 2003; 40:385.
82. Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. JAMA Intern Med 2014; 174:275.
83. Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic yield of subspecialists' evaluation of young children with global developmental delay. J Pediatr 2000; 136:593.
84. CDC response to Advisory Committee on Childhood Lead Poisoning Prevention Recommendations in "Low Level Lead Exposure Harms Children: A Renewed Call of Primary Prevention" http://www.cdc.gov/nceh/lead/ACCLPP/activities.htm (Accessed on May 17, 2012).
85. Lewendon G, Kinra S, Nelder R, Cronin T. Should children with developmental and behavioural problems be routinely screened for lead? Arch Dis Child 2001; 85:286.
86. Majnemer A, Shevell MI. Diagnostic yield of the neurologic assessment of the developmentally delayed child. J Pediatr 1995; 127:193.
87. Demaerel P, Kingsley DP, Kendall BE. Isolated neurodevelopmental delay in childhood: clinicoradiological correlation in 170 patients. Pediatr Radiol 1993; 23:29.

88. Bouhadiba Z, Dacher J, Monroc M, et al. [MRI of the brain in the evaluation of children with developmental delay]. J Radiol 2000; 81:870.
89. Decobert F, Grabar S, Merzoug V, et al. Unexplained mental retardation: is brain MRI useful? Pediatr Radiol 2005; 35:587.
90. Moeschler JB, Shevell M, American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics 2006; 117:2304.
91. Battaglia A, Bianchini E, Carey JC. Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. Am J Med Genet 1999; 82:60.

Topic 6189 Version 20.0

GRAPHICS

Terminology used to describe intellectual disability in different countries

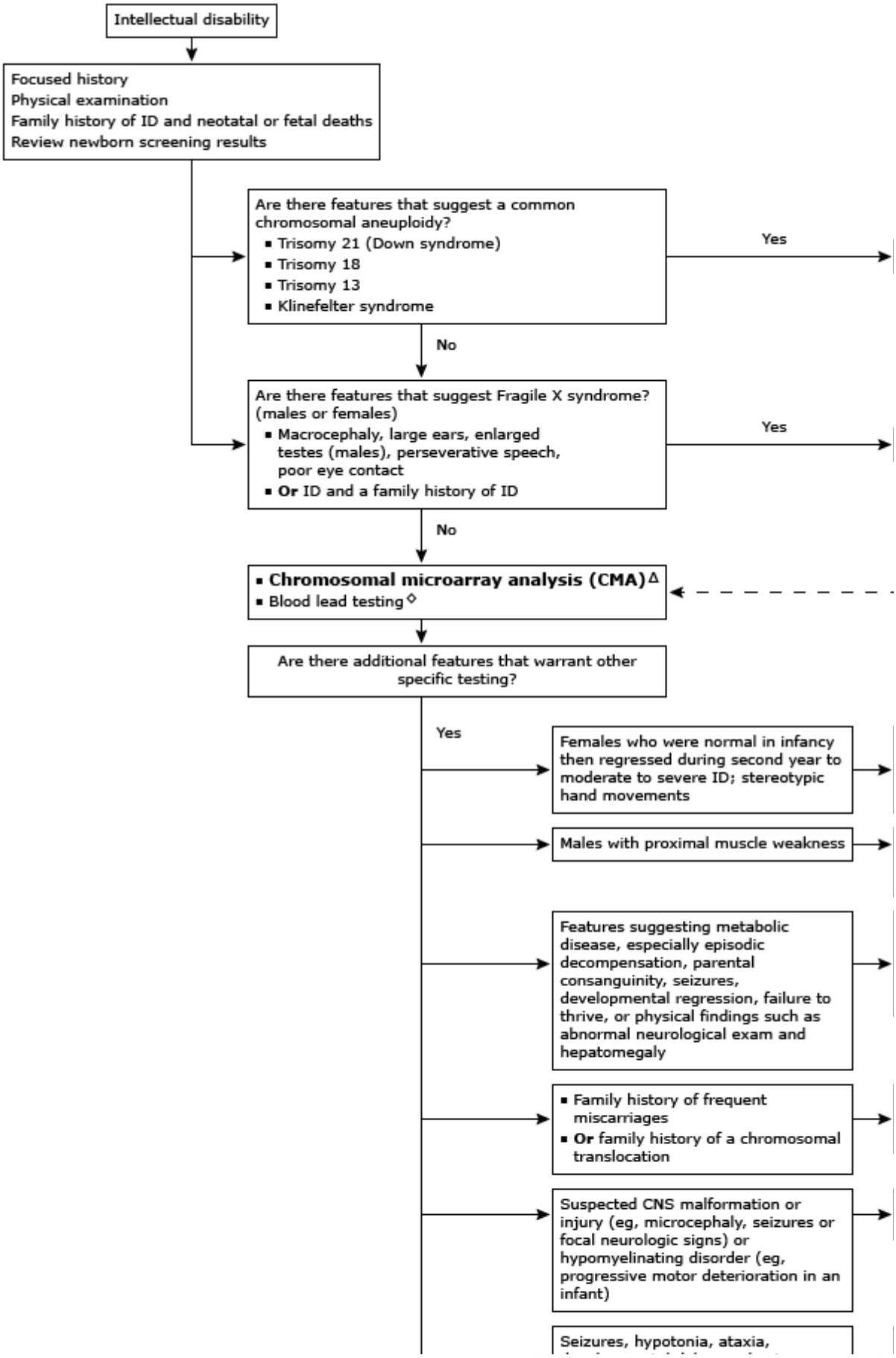
Country and/or language	Term
United States	Intellectual disability
Australia	Intellectual disability
Canada (English, French)	Mental deficiency, intellectual handicap
England	Learning disability*, intellectual disability, developmental disability•
France	Mental deficiency, mental apraxia
Germany	Mental handicap, mental retardation
Italy	Mental delay, mentally deficient
Estonia	Mental retardation
Puerto Rico	Mentally slowed down
Spain	Mental delay

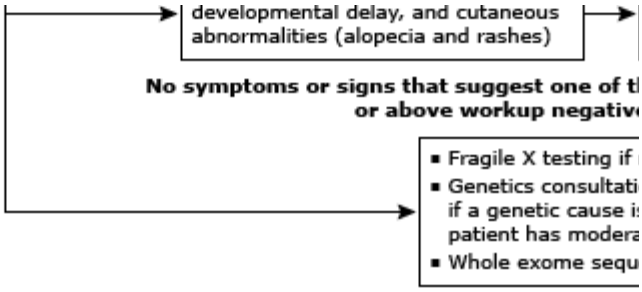
* In the United States, the term "learning disability" usually denotes a specific learning disability (eg, dyslexia) rather than intellectual disability.
• In the United States, the term "developmental disability" does not necessarily involve intellectual disability. For example, a developmental disability could be limited to motor dysfunction or developmental-behavioral dysfunction, in the absence of intellectual disability.

Schroeder SR, Gerry M, Gertz G, Velazquez F. Usage of the Term "Mental Retardation:" Language, Image and Public Education. Kansas University Center on Developmental Disabilities; Center for the Study of Family, Neighborhood and Community Policy, The University of Kansas. 2002. p.86.

Graphic 57206 Version 5.0

Staged laboratory evaluation for causes of intellectual disability





CNS: central nervous system; CMA: chromosomal microarray; FISH: fluorescence in situ hybridizatior magnetic resonance imaging.

* Many authorities recommend fragile X testing in all children with unexplained ID or autism, since fra with non-specific global developmental delay in young children.

Δ Where CMA is unavailable, G band karyotype and FISH testing are applied.

◇ Blood lead testing is recommended for all children with ID. Children with ID and prolonged mouthin for lead exposure. Lead toxicity is an uncommon cause of ID in the United States.

§ Features that suggest a high risk for genetic disease include parental consanguinity, prior unexplain miscarriages, or loss or regression of developmental milestones. Genetics consultation is also recomm moderate, severe, or profound ID with no obvious cause, even if these features are not present.

Graphic 95374 Version 2.0

Yield of screening for chromosomal anomalies in individuals with intellectual disability

Population tested	Diagnostic yield* (percent of patients with positive results)	Comments
Chromosomal microarray analysis (CMA)Δ		
Unexplained GDD/ID	15 to 20[1]	CMA is recommended as first-line test for most patients with GDD/ID, unless the patient has features suggesting a specific disorder, as described below.
Karyotype		
Unexplained GDD/ID	10 to 15[2]	Recommended as first-line test for the following: ■ Patients with features of Down or other chromosomal syndrome ■ Family history of chromosomal abnormalities ■ Parent with multiple miscarriages
Subtelomeric fluorescence in situ hybridization (StFISH)		
Unexplained GDD/ID or MCA	4 to 6	Where available, microarray analysis is generally recommended to replace StFISH testing.
Mild GDD/ID	1 to 2	

GDD: global developmental delay; ID: intellectual disability; MCA: multiple congenital anomalies; XL: X-linked.
* Represents approximate diagnostic yield, based on a meta-analysis of population studies. Most of the included studies were "class III," defined as a sample of patients studied during the course of a condition, rather than a population-based sample.
Δ Chromosomal microarray analysis (CMA) is also known as comparative genomic hybridization (CGH).

References:

1. *Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010; 86:749.*
2. *van Karnebeek CD, Jansweijer MC, Leenders AG, et al. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. Eur J Hum Genet 2005; 13:6.*

Data from: Michelson DJ, Shevell MI, Sherr EH, Moeschler JB, Gropman AL, Ashwal S. Evidence report: Genetic and metabolic testing on children with global developmental delay. Neurology 2011; 77:1629.

Graphic 72211 Version 3.0

Yield of screening for X linked disorders in individuals with intellectual disability

Population tested	Diagnostic yield* (percent of patients with positive results)	Comments
Testing the whole X chromosome or testing multiple X-linked genes specifically:		
Definitely X-linked	42	Testing the whole X chromosome or multiple X-linked ID genes specifically is recommended in male patients with a family history suggestive of X-linked inheritance of ID Mutations in X-linked genes account for 10 percent of all cases with ID
Possibly X-linked	17	
Specific testing for fragile X (trinucleotide repeat expansion of the *FMR1* gene):		
Males with clinical features of fragile X syndrome [1]	15	Testing is suggested in children with the following characteristics: [1,2] ■ Male or female children with ID and clinical features suggestive of fragile X syndrome, such as macrocephaly, large ears, enlarged testes, perseverative speech, lack of eye contact ■ Male or female children with ID and a family history of ID ■ Children with unexplained ID whose first-line CMA testing is normal (or benign)
Males with unexplained GDD/ID	3	
Males or females with mild to moderate unexplained GDD/ID	2-3	
Females with unexplained GDD/ID	1	
Specific testing for Rett syndrome (*MeCP2* testing)		
Females with moderate to severe GDD/ID	2	Recommended in patients with the following: ■ Girls with severe ID ■ Girls with clinical features of Rett syndrome
Males with moderate to severe GDD/ID	<1	
Specific testing for *JARID1C:*		
Unrelated males	1	
Specific testing for *ARX:*		

Possibly X-linked	1	
Specific testing for *SLC6A8:*		
Unrelated males	<1	

GDD: global developmental delay; ID: intellectual disability; CMA: chromosomal microarray analysis (also known as comparative genomic hybridization).
* Represents approximate diagnostic yield, based on a meta-analysis of population studies. Most of the included studies were "class III" defined as a sample of patients studied during the course of a condition, rather than a population-based sample.

References:

1. *Hagerman RJ, Amiri K, Cronister A. Fragile X chechlist. Am J Med Genet 1991; 38:283.*
2. *Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010; 86:749.*

Data from: Michelson DJ, Shevell MI, Sherr EH, Moeschler JB, Gropman AL, Ashwal S. Evidence report: Genetic and metabolic testing on children with global developmental delay. Neurology 2011; 77:1629.

Graphic 51263 Version 1.0

Diagnostic yield of screening for inborn errors of metabolism in individuals with intellectual disability

Population studied	Diagnostic yield* (percent of patients with positive results)	Comments
General metabolic screening Δ [1]	<1 to 5 ◇	Recommended (in addition to CMA) in patients with the following features: ■ Parental consanguinity ■ Family with other children with similar problems, or unexplained fetal demise ■ Episodic symptoms, including seizures or encephalopathy ■ Multiple organ dysfunction ■ Failure to thrive, dietary selectivity, unusual body odor, hearing loss, hepatomegaly ■ Developmental regression
Creatine synthesis and transport disorders [1]	up to 3	
Congenital disorders of glycosylation	up to 1.5	

CMA: chromosomal microarray analysis (also known as comparative genomic hybridization).
* Represents approximate diagnostic yield, based on a meta-analysis of population studies. Most of the included studies were "class III," defined as a sample of patients studied during the course of a condition, rather than a population-based sample.
Δ Screening for metabolic disorders varies among institutions. It typically includes urine for amino acids, organic acids, mucopolysaccharides, oligosaccharides, uric acid, sialic acid, purines, and pyrimidines; and plasma for amino acids, acylcarnitines, and sialotransferrins.
◇ The diagnostic yield depends on the presence of clinical indicators of metabolic disease and the range of testing performed. Initial metabolic screening does not definitively exclude some diagnoses such as mucopolysaccharidosis and a congenital disorder of glycosylation, and some tests should be repeated if the clinical features are suspicious for one of these disorders.

References:

1. *Engbers HM, Berger R, van Hasselt P, et al. Yield of additional metabolic studies in neurodevelopmental disorders. Ann Neurol 2008; 64:212.*

Data from: Michelson DJ, Shevell MI, Sherr EH, Moeschler JB, Gropman AL, Ashwal S. Evidence report: Genetic and metabolic testing on children with global developmental delay. Neurology 2011; 77:1629.

Graphic 62940 Version 5.0

Disclosures

Disclosures: **Penelope Pivalizza, MD** Nothing to disclose. **Seema R Lalani, MD** Nothing to disclose. **Marc C Patterson, MD, FRACP** Grant/Research/Clinical Trial Support: Actelion [Lysosomal diseases (Miglustat)]. Consultant/Advisory Boards: Amicus; Agios; Cydan; Genzyme; Orphazyme; Shire HGT [Lysosomal diseases (Arimoclomol, cyclodextrin, glucocerebrosidase)]; Stem Cells, Inc; Vtesse [Lysosomal diseases (Human embryonic stem cells)]. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Carolyn Bridgemohan, MD** Equity Ownership/Stock Options: MEDCO [Autism (Prescription services)]; Merck [Autism (Vaccines)]. **Carrie Armsby, MD, MPH** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Microcephaly in infants and children: Etiology and evaluation

Author
Julie A Boom, MD

Section Editors
Jan E Drutz, MD
Helen V Firth, DM, FRCP, DCH
Marc C Patterson, MD, FRACP

Deputy Editor
Mary M Torchia, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Mar 12, 2015.

INTRODUCTION — The measurement of head circumference (also called occipitofrontal circumference [OFC]), a direct reflection of head growth, is an important step in the evaluation of childhood growth and development. Deviations from normal head growth may be the first indication of an underlying congenital, genetic, or acquired problem (eg, congenital infection, genetic syndrome) [1-4]. Many genetic conditions are associated with an abnormal pattern of head growth; the earlier these conditions are detected, the earlier appropriate treatment, services, and genetic counseling can be provided [5].

The etiology and evaluation of microcephaly in infants and children will be reviewed here. The etiology and evaluation of macrocephaly and the clinical genetics approach to microcephaly are discussed separately. (See "Microcephaly: A clinical genetics approach" and "Macrocephaly in infants and children: Etiology and evaluation", section on 'Etiology'.)

NORMAL HEAD GROWTH — Normal head growth in infants and children is discussed separately. (See "Normal growth patterns in infants and prepubertal children", section on 'Head growth' and "The pediatric physical examination: HEENT", section on 'Anterior and posterior fontanelles'.)

Measurement — Occipitofrontal circumference (OFC) should be measured at health maintenance visits between birth and three years of age and in any child with neurologic symptoms. The measuring tape should encircle the head and include an area 1 to 2 cm above the glabella anteriorly and the most prominent portion of the occiput posteriorly (picture 1). Measurement of OFC in the newborn may be unreliable until the third or fourth day of life since it may be affected by caput succedaneum, cephalohematoma, or molding [6]. In older infants, the accuracy of the measurement may be affected by thick hair and deformation or hypertrophy of the cranial bone.

Monitoring — OFC measurements are most informative when plotted over time [7]. Standards have been determined for head growth in healthy children between 0 and 18 years of age [8-11]. Most clinicians use the standard growth curves to monitor the head growth of premature infants, with an adjustment for prematurity (ie, corrected age), until approximately 12 to 24 months of age [12,13]. (See "Growth management in preterm infants", section on 'Monitoring of growth'.)

Head circumference charts — Several standardized charts are available for monitoring head circumference. These include:

- The Centers for Disease Control and Prevention (CDC) National Center for Health Statistics head circumference charts for children 0 to 36 months of age (CDC growth charts) (figure 1A-B) (calculator 1). These charts are based on a nationally representative demographic sample.
- The World Health Organization (WHO) head circumference charts for children zero to five years of age (WHO growth standards). These charts are based on data from the Multicentre Growth Reference Study of breastfed children living under optimal environmental conditions.
- The Nellhaus head circumference charts for children 0 to 18 years of age. These charts are based

on a 1968 international meta-analysis [8]. They are available in the full text of reference [8].

- The Fels head circumference charts for children 0 to 18 years. These charts are based on data from the Fels Longitudinal Study of 888 white children from the United States [9]. They are available in the full text of reference [9].
- The United States Head Circumference Growth Reference charts for children 0 to 21 years of age. These charts combine growth reference data from the CDC, Nellhaus, the Fels Longitudinal Study, and others [10]. They are available in the full text of reference [10].
- The Bushby charts for adults. These charts are based on data from 354 white adults (median age 40 years, range 17 to 83 years) in two British centers; OFC percentiles are related to height [14]. Bushby charts are available in the full text of reference [14].

In September 2010, the CDC recommended that the WHO growth charts be used for children zero to two years (figure 2A-B) (calculator 2), and the CDC growth charts for children older than two years [11]. The clinical consequences of using the WHO standards for children younger than two years of age and a different standard for older children will need to be monitored over time [11]. The particular chart that is chosen for young children may affect the categorization of head size, particularly at the higher percentiles [15,16]. In a retrospective cohort study of 75,412 children in a primary care network, the proportion of children with OFC >95th percentile was 8.6 percent with the CDC curve and 14 percent with the WHO curve [15]. The proportion of subjects with OFC <5th percentile was 2.9 percent using the CDC curves and 2.3 percent using the WHO curve. Another potential problem is that changing from one curve to another after age two years may change the way a particular child's head growth is classified. The United States Head Circumference Growth Reference charts, published in 2010, address this problem but require additional validation before their use can be widely adopted [10].

It may be inappropriate to use a single head circumference standard for children in all countries or ethnic groups. A study that compared mean head circumference from a variety of studies including >11,000,000 children from economically advantaged populations (1988 to 2013) with the WHO reference standards found that the mean head circumferences in certain national or ethnic groups were sufficiently different from the WHO means to affect diagnosis of microcephaly or macrocephaly [17].

The standard growth curves are not appropriate for monitoring the head size of children with craniosynostosis, craniofacial syndromes, and children with certain medical conditions associated with microcephaly (eg, Williams-Beuren syndrome). Growth curves for children with Williams-Beuren syndrome are available through the American Academy of Pediatrics.

DEFINITIONS

Microcephaly — The definition of microcephaly is somewhat controversial [18-21]. Some authors define microcephaly as an occipitofrontal circumference (OFC) more than 2 standard deviations (SD) below the mean for a given age, sex, and gestation (ie, <3rd percentile) [5,7,22]. Some require that the measurement be adjusted as necessary for prematurity or parental head circumference [9,20]. Other authors define microcephaly as an OFC more than 3 SD below the mean [6,23-25]. Still others introduce qualifying terms: mild microcephaly or borderline microcephaly (between 2 and 3 SD below the mean), and severe microcephaly (more than 3 SD below the mean) [26]. The American Academy of Neurology (AAN) practice parameter defines microcephaly as OFC >2 SD below the mean [21]. These distinctions are somewhat related to prognosis, as described below [6,27-29]. (See 'Prognosis' below.)

Using the definition of more than 2 SD below the mean, approximately 2 percent of the general population would be considered microcephalic even though many of these individuals are simply at the low end of the population distribution [18,30].

Given that microcephaly is a sign rather than a diagnosis, we prefer to use the qualifying terms, defining

borderline microcephaly as an OFC between 2 and 3 SD below the mean, moderate microcephaly as an OFC between 3 and 5 SD below the mean, and severe microcephaly as an OFC ≥5 SD below the mean.

Classification — Microcephaly can be classified in a number of ways [18-20,23]:

- By time of onset – Congenital microcephaly is present at birth or by 36 weeks' gestation. It is sometimes called "primary microcephaly", but “primary microcephaly” also refers to a particular microcephaly phenotype, so “congenital microcephaly” is preferred. (See "Microcephaly: A clinical genetics approach", section on 'Classification'.)

  Postnatal microcephaly refers to failure of normal growth in a brain that was of normal size at birth. It is sometimes called "secondary microcephaly". Time of onset is the most commonly used classification system.

- By etiology – Genetic or environmental. (See 'Etiology' below.)

- By relation to other growth parameters – Symmetric (proportionate) or asymmetric (disproportionate). Microcephaly is considered symmetric (or proportionate) when the OFC is more than 2 to 3 SD below the mean, but proportionate to weight and length (or height) which also are below the mean [19].

- By association with other anomalies – Isolated (or pure) microcephaly is not associated with any other anomalies. Syndromal (or complex) microcephaly is associated with one or more additional anomalies (table 1). These categories tend to overlap.

Microencephaly — Microencephaly (micrencephaly) is an abnormally small brain. Microencephaly is a neuroimaging or neuropathologic diagnosis [31]. However, because head growth is driven by brain growth, microcephaly usually implies microencephaly (except in cases of generalized craniosynostosis in which skull growth is restricted) [19,22,24,26,31].

Although microcephaly always implies microencephaly [5], the reverse is not true. Microencephaly may be present in children with normal OFC [31].

PATHOGENESIS — Microencephaly has two major mechanisms:

- Lack of brain development or abnormal brain development related to a developmental insult during the time-specific period of induction and major cellular migration [31]; this type of microcephaly is thought to result from a reduction in the number of neurons generated during neurogenesis [24]; the forebrain is most severely affected (eg, holoprosencephaly) [6]

- Injury or insult to a previously normal brain (sometimes called secondary microcephaly); this type of microcephaly is thought to result from a reduction in the number of dendritic processes and synaptic connections [24]

ETIOLOGY — A variety of genetic abnormalities and environmental insults can affect brain development, resulting in microencephaly and/or microcephaly of congenital or postnatal onset (table 2) [31,32].

In a retrospective series of 680 children with microcephaly who presented for pediatric neurology evaluation at two centers in Germany, the etiologic distribution was as follows [33]:

- Genetic or presumably genetic (eg, numerical chromosome aberrations, microdeletions/duplications, monogenic disorders, genetic syndromes) – 29 percent
- Prenatal and perinatal brain injury (eg, teratogenic exposure, maternal disease, birth complication) – 27 percent
- Craniosynostosis – 2 percent

- Postnatal brain injury (eg, infarct, encephalitis, nonaccidental trauma) – 2 percent
- Unknown etiology – 41 percent (it is likely that many of these patients had a genetic etiology)

The majority of patients in this series had neurologic findings (eg, intellectual disability, epilepsy). The distribution of causes in primary care patients is likely to differ.

Isolated microcephaly — Isolated microcephaly ("microcephaly vera", “primary microcephaly”, or "true microcephaly") is present at birth and uncomplicated by other anomalies. The brain may have normal architecture but is small (more than 3 standard deviations [SD] below the mean) [18]. Isolated microcephaly is discussed separately. (See "Microcephaly: A clinical genetics approach", section on 'Primary microcephaly'.)

Syndromic microcephaly — Numerous syndromes have microcephaly as one of their features [18]. A complete listing or description of such syndromes is beyond the scope of this review. However, Online Mendelian Inheritance in Man is an online database that permits searching according to combinations of clinical features (eg, microcephaly, syndactyly, cataracts). Select microcephaly syndromes that have recognizable phenotypes are described in the table (table 1) [18,23]. Syndromic microcephaly is discussed separately. (See "Microcephaly: A clinical genetics approach", section on 'Microcephaly with dysmorphism'.)

Neuroanatomic abnormalities — Neuroanatomic abnormalities that are associated with microcephaly include neural tube defects, holoprosencephaly, atelencephaly, lissencephaly, schizencephaly, polymicrogyria, macrogyria, and fetal brain disruption sequence [5].

- Neural tube defects – Encephalocele (protrusion of a portion of the cerebral hemisphere or meninges through a skull defect) or spinal neural tube defects can be associated with abnormal development of the brain and microcephaly. (See "Primary (congenital) encephalocele".)
- Holoprosencephaly – Holoprosencephaly results from incomplete development and septation of the midline central nervous system structures. It may occur as an isolated abnormality in association with other brain defects, or as part of a multiple-anomalies syndrome [18]. It is characterized by varying degrees of brain separation, hypotelorism, facial clefts, and nasal malformations (figure 3). The clinical manifestations range from an isolated single maxillary incisor to cebocephaly (eg, small mouth, single nostril, and close-set eyes (picture 2)), or cyclopia. (See "Facial clefts and holoprosencephaly", section on 'Holoprosencephaly' and "Congenital anomalies of the nose", section on 'Holoprosencephaly'.)
- Atelencephaly – Atelencephaly (or aprosencephaly) is a rare brain malformation without any telencephalon derived brain structures (the cerebrum and related structures) [34].
- Lissencephaly – In lissencephaly, the six cortical layers do not form normally due to impaired migration of neurons from the germinal matrix lining the ventricles. The surface of the brain appears completely or partially smooth with loss or reduction of sulci (image 1) [19]. Lissencephaly is usually genetic in origin but may also be caused by infection, intrauterine perfusion failure. Microcephaly develops in all patients with lissencephaly by the first year; a minority is microcephalic at birth [19].
- Schizencephaly – Schizencephaly is characterized by asymmetric infolding of cortical gray matter along the primary brain cleft in the perisylvian region (image 2) [19].
- Polymicrogyria – Polymicrogyria is a developmental malformation characterized by excessive gyri on the surface of the brain (image 3).
- Pachygyria – Pachygyria (macrogyria) is a developmental malformation characterized by a reduction in the number of sulci of the cerebrum and is often seen in lissencephaly.

- Fetal brain disruption sequence – Fetal brain disruption sequence is characterized by severe microcephaly of prenatal onset (average occipitofrontal circumference [OFC] 5.8 standard deviations [SD] below the mean), overlapping cranial sutures, prominence of the occipital bone, and scalp rugae [26,35-39]. It is thought to result from destruction or necrosis of the brain tissue secondary to prenatal insult (eg, vascular disruption, intrauterine infection) some of which may be genetic in origin (eg, mutations in COL4A1/2) [39].
- Hydranencephaly – Hydranencephaly is vascular insult to the brain in which fluid-filled cavities replace the cerebral hemispheres; cerebellum, midbrain, thalami, and basal ganglia are usually preserved.

Metabolic disorders — Various metabolic disorders may be associated with microcephaly, but the prevalence of metabolic disorders among children with microcephaly is low (estimated to be 1 to 5 percent) [21]. Metabolic disorders associated with microcephaly include aminoacidurias (eg, phenylketonuria [PKU]), organic acidurias (eg, methylmalonic aciduria), urea cycle disorders (eg, citrullinemia), and certain storage diseases (eg, neuronal ceroid lipofuscinosis) (table 2). (See appropriate topic reviews). With the exception of maternal phenylketonuria, phosphoglycerate dehydrogenase deficiency, and Amish lethal microcephaly, metabolic disorders rarely present with microcephaly [21].

Environmental factors — Environmental factors that may result in decreased brain size include [5,26,27,40,41]:

- Antenatal, perinatal, and postnatal central nervous system infections. (See "Overview of TORCH infections", section on 'Clinical features of TORCH infections'.)
- In utero drug or toxin exposure. Characteristic features of fetal alcohol exposure include pre- and postnatal growth retardation, short palpebral fissures, flat philtrum, and thin upper lip. (See "Fetal alcohol spectrum disorder: Clinical features and diagnosis", section on 'Clinical features'.)
- Hypoxic-ischemic insults. (See "Etiology and pathogenesis of neonatal encephalopathy" and "Clinical features, diagnosis, and treatment of neonatal encephalopathy".)
- Intraventricular hemorrhage or stroke resulting in ischemic destruction. (See "Clinical manifestations and diagnosis of intraventricular hemorrhage in the newborn" and "Stroke in the newborn".)
- Severe malnutrition [42].
- Systemic disease that is often genetic in origin (eg, polycystic kidneys, biliary atresia, renal failure).

POSTNATAL EVALUATION

Overview of approach — Evaluation for microcephaly should be initiated when a single OFC measurement is more than 2 to 3 standard deviations (SD) below the mean or when serial measurements reveal progressive decrease in head size (ie, crossing of several major percentile lines [eg, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}] between health supervision visits) [6].

The evaluation of microcephaly includes a thorough history and physical examination of the child and parents (in consideration of familial variation in head size) [6,7,19,21,23,33]. (See 'History' below and 'Physical examination' below and 'Parental OFC' below.)

Ancillary testing, which is directed by clinical findings from the history and examination, may include laboratory studies and imaging (algorithm 1). (See 'Diagnostic testing' below and 'Neuroimaging' below.)

Factors that determine the need for laboratory and radiologic evaluation include:

- Age at onset, although the birth OFC measurement often is not available
- History of antenatal insult (infection, toxin, drug, etc) (table 2)
- Associated features (eg, proportionality, syndromic features)
- Family history

The approach outlined below is largely consistent with that outlined in the practice parameter developed by the American Academy of Neurology and the Child Neurology Society [21].

Syndromic features or signs of metabolic disease — If syndromic features (table 1) or symptoms of metabolic disease are present, consultation with, or referral to, a clinical geneticist should be initiated to determine the appropriate diagnostic evaluation. (See 'Diagnostic testing' below and "Microcephaly: A clinical genetics approach", section on 'Initial genetics consultation'.)

No syndromic features

- Occipitofrontal circumference (OFC) more than 3 SD below the mean – If syndromic features are absent and the OFC was more than 3 SD below the mean at birth (ie, congenital microcephaly), evaluation for isolated microcephaly, congenital infection and neuroimaging may be warranted [6,23]. If syndromic features are absent and the OFC is more than 3 SD below the mean with postnatal onset, neuroimaging may be warranted.

  Consultation with, or referral to, a specialist in pediatric infectious diseases, pediatric genetics, pediatric neurology, and/or pediatric radiologist may be helpful in planning the diagnostic evaluation.

- OFC 2 to 3 SD below the mean – If syndromic features are absent and the OFC is between 2 and 3 SD below the mean, measurement of parental head circumference is helpful in evaluating autosomal dominant microcephaly [23]. (See 'Parental OFC' below.)

Abnormal development — Additional evaluation (ie, neuroimaging or diagnostic testing) may be warranted in children with microcephaly and abnormal development. Testing may include genetic studies, evaluation for congenital infection, and evaluation for metabolic disease or storage disorder. Consultation with a clinical geneticist, specialist in pediatric infectious diseases, or pediatric neurology is suggested to determine the most appropriate testing strategy.

History — Important aspects of the history in a child with microcephaly include [7,18,21,23,33]:

- Prenatal history, particularly with respect to maternal medical problems (eg, diabetes, epilepsy, phenylketonuria [PKU]), medications, infections, tobacco, alcohol, or substance use, radiation exposure; findings of antenatal ultrasonography if it was performed.
- Birth history (eg, perinatal complications, infections, metabolic issues).
- Weight, length, and OFC at birth to establish the onset of microcephaly and to determine if it is proportionate to weight and length.
- OFC trajectory to determine whether microcephaly is static or progressive.
- History of seizures, developmental history (regression of milestones may indicate metabolic disease).
- Family history of consanguinity or similarly affected individuals. The family history should include three generations to detect recessive disorders, which may skip a generation.
- For children who were born prematurely, abnormal head ultrasonography findings. In a retrospective review of 923 preterm infants (<28 weeks), microcephaly at age two years was more common among those with intraventricular hemorrhage, ventriculomegaly, or an echolucent lesion

than among those with normal ultrasonography (15 to 20 versus 6 percent) [43].

Physical examination — Important aspects of the physical examination of the child with microcephaly include [18,23,31,33]:

- General appearance – Dysmorphic features may suggest a particular syndrome (table 1). However, facial dysmorphism may be distorted by microcephaly. Congenital microcephaly is usually associated with a sloping forehead and small anterior fontanelle [6].
- OFC – The OFC should be measured and compared with previous measurements. The severity of microcephaly should be assessed by determining the number of SD below the mean (ie, the z score). The z scores for children younger than two years can be determined by using the following calculators for the World Health Organization (WHO) OFC chart (calculator 2) and the Centers for Disease Control and Prevention (CDC) growth chart (calculator 1).
- Weight and length trajectories – The child's weight and length (or height) should also be measured and plotted on standard curves. The weight and length percentiles should be compared with the OFC percentile. (See "Normal growth patterns in infants and prepubertal children", section on 'CDC growth charts'.)

  Several causes of microcephaly may be associated with postnatal growth failure and/or short stature (eg, Seckel syndrome, Rubinstein-Taybi syndrome).
- Head – In addition to measuring the OFC, examination of the head should include assessment of the head shape. In infants, assessment of the fontanelles and palpation of the cranial sutures also should be performed.

  The anterior fontanelle usually closes between 10 and 24 months. Early closure can be a normal finding but also is associated with microcephaly, craniosynostosis, hyperthyroidism, or hypoparathyroidism. Persistent enlargement of the anterior fontanelle in children with microcephaly may be due to a syndrome (eg, Down syndrome, trisomy 13 or 18, 5p- [cri-du-chat], Rubinstein-Taybi) or toxins. (See appropriate topic reviews).

  An abnormal head shape and ridges along the suture lines are suggestive of craniosynostosis. Overriding sutures and a prominent occiput is suggestive of fetal disruption sequence. (See "Overview of craniosynostosis".)
- Eyes – Examination of the eyes may provide clues to intrauterine infection (eg, chorioretinitis, cataract) or metabolic disease (cataract). (See "Cataract in children", section on 'Clinical features' and "Overview of TORCH infections", section on 'Clinical features of TORCH infections'.)
- Oropharynx – The oropharynx should be examined for single maxillary incisor (characteristic of holoprosencephaly) and other midline defects of the eyes, nose, and palate (eg, cleft lip or palate, bifid uvula, etc).
- Skin – Examination of the skin may provide clues to intrauterine infection (eg, petechiae and/or jaundice in the newborn) or metabolic disease (eg, eczematous rash in PKU). (See "Overview of phenylketonuria".)
- Abdomen – Hepatomegaly or splenomegaly are suggestive of congenital infection.
- Neurologic assessment – Neurologic evaluation, including assessment of tone, reflexes, and intellectual/developmental ability. Children with microcephaly are at risk for cerebral palsy and intellectual/developmental disability [21]. Cerebral palsy is common in children with microcephaly, and children with microcephaly are at risk for intellectual/developmental disability. (See "Clinical

features of cerebral palsy", section on 'Clinical features' and "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs", section on 'Clinical evaluation'.)

Parental OFC — Parents' OFC measurements should be obtained if possible to assess familial variation in head size [19]. This is particularly true if the microcephaly is between 2 and 3 SD below the mean [23]. The genetic contribution to microcephaly can be assessed by using the Weaver curve [18,44].

Weaver curve — The Weaver curve helps to determine whether genetic influences contribute to a child's microcephaly [44]. A standard score is calculated for the child and each of the parents using the following formula:

Standard score (SS) = (OFC - mean value)/SD

The mean values and SD for age and sex are listed in the table (table 3). In calculating the parents' standard scores, the mean value and standard deviation for an 18-year-old should be used.

The average of the parents' SS and the child's SS are plotted on the Weaver curve (figure 4). A genetic contribution to microcephaly is suggested if the child's standard score is within the range determined by the average parental score, permitting the evaluation to be tailored appropriately [44].

Diagnostic testing — Diagnostic testing may be warranted in children with microcephaly and abnormal development or associated clinical findings (algorithm 1). Testing may include [6,7,21,23,31,33]:

- Genetic studies if the child has dysmorphic features unless there is an obvious cause of the microcephaly in a child with OFC <3 SD below the mean. Consultation with a clinical geneticist is suggested to determine the most appropriate testing strategy, but will usually include a genomic array unless there is a readily identifiable syndromic diagnosis. (See "Microcephaly: A clinical genetics approach", section on 'Initial genetics consultation'.)
- Evaluation for congenital infection. Consultation with a specialist in pediatric infectious diseases is suggested to determine the most appropriate testing strategy. (See "Overview of TORCH infections", section on 'Screening for TORCH infections'.)
- Evaluation for metabolic disease or storage disorder. This may include testing for amino- and organic acidurias, lactate and/or very-long-chain fatty acids if the infant is hypotonic, or plasma 7-dehydrocholesterol if the infant has features suggestive of Smith-Lemli-Opitz syndrome (table 1). Consultation with a clinical geneticist is suggested to determine the most appropriate testing strategy. (See "Inborn errors of metabolism: Metabolic emergencies", section on 'Initial evaluation' and "Inborn errors of metabolism: Identifying the specific disorder", section on 'Laboratory evaluation' and "Organic acidemias".)
- Ophthalmology referral. Ophthalmologic examination may provide clues to congenital infection or genetic disease.

Neuroimaging — Neuroimaging studies, which may identify structural causes of microcephaly, are most useful in microcephalic children with abnormal development [5,21]. Most children with symptomatic microcephaly have abnormal neuroimaging [45,46].

In a retrospective series of 680 children with symptomatic microcephaly who presented for pediatric neurology evaluation at two centers in Germany, 299 underwent cranial magnetic resonance imaging [33]. Seventy-six percent had abnormal findings, including anomalies of white matter (eg, periventricular leukomalacia, delayed or disturbed myelination) in 40 percent and gyration defects in 14 percent. In another study of 55 children with symptomatic microcephaly, MRI revealed abnormalities in 68 percent of the children with genetic microcephaly and 100 percent of the children with acquired microcephaly (intrauterine or postnatally acquired) [46]. Migrational abnormalities were the most common findings in

children with genetic microcephaly. Hydranencephaly and infarction were the most common findings in children with acquired microcephaly.

Neuroimaging may include:

- CT scan of the head for intracranial calcification (a clue to intrauterine infection) (see "Overview of TORCH infections")
- MRI scan to delineate abnormalities in CNS architecture (eg, migration abnormalities) [22,26,31]

PRENATAL EVALUATION — Prenatally, microcephaly is diagnosed by ultrasound examination and is defined as head circumference <3 standard deviations below the mean or below the 2nd percentile for gestational age (image 4) [47-49]. The diagnosis is complicated by limitations in accuracy of head circumference measurements and inconsistency between prenatal and postnatal head circumference growth curves. Although there are reference values for fetal head circumference [50], standards have not been developed for specific populations (eg, based on sex, race/ethnicity) [51].

The approach to evaluation of prenatal microcephaly depends upon the presence of associated ultrasonographic anomalies, appropriateness of other fetal biometric parameters (eg, length of bones, abdominal circumference) in relation to gestational age, historical features (eg, consanguinity, intrauterine infection), and head circumference measurements of parents and siblings. Associated ultrasonographic anomalies may indicate syndromic microcephaly. (See "Prenatal diagnosis of CNS anomalies other than neural tube defects and ventriculomegaly".)

Additional evaluation (eg, karyotype, fetal brain MRI, intrauterine infection) may be obtained if a specific diagnosis is desired to help with pregnancy management. Indications for these evaluations may include:

- Parental consanguinity
- Family members with microcephaly and stigmata of autosomal dominant conditions that include microcephaly (table 1)
- Other CNS and non CNS morphologic abnormalities that suggest a chromosomal disorder
- Otherwise unexplained fetal microcephaly (eg, family members with normal head circumference and fetal biometric parameters other than head circumference appropriate for gestational age)
- Signs of intrauterine infection (eg, intracranial calcifications or ascites)

The developmental outcome of prenatal microcephaly depends upon the underlying etiology and associated abnormalities [52].

If there has been a previously affected child, prenatal assessment includes a level II (high risk) fetal sonogram at 20 weeks to assess anatomy. Fetal MRI may be an adjunct to sonography. Consultation with a specialist is recommended. Repeat sonogram at 32 weeks can be obtained if repeat head measurements are desired later in pregnancy. However, severe postnatal microcephaly may not be evident on sonogram during the second trimester and may not be apparent until very late in pregnancy or even postnatally [53].

PROGNOSIS — The prognosis for children with microcephaly depends upon the underlying cause. The prognosis usually is worse for children whose microcephaly is part of a wider pattern of malformation (eg, trisomy 13, trisomy 18) and for those with intrauterine infection [6,52]. In a retrospective series of 680 children with microcephaly, most of whom had neurologic symptoms, 65 percent had intellectual disability or developmental delay and 43 percent had epilepsy [33].

The severity of cognitive impairment is generally related to the severity of microcephaly, as illustrated below:

- In a study of 212 children with microcephaly, median intelligence quotient (IQ) decreased with decreasing occipitofrontal circumference (OFC) (median IQ 35 versus 62 in children with OFC more than 3.9 standard deviations [SD] below the mean and between 2.0 and 2.1 SD below the mean, respectively) [28].
- In another study, IQ scores in seven-year-old children with OFC more than 3 SD below the mean were more likely to have IQ scores <70 than children with OFC between 2 and 3 SD below the mean (51 versus 11 percent) [29]. None of the children with OFC more than 3 SD below the mean had IQ scores greater than 100.

However, individuals with autosomal recessive primary microcephaly, Seckel syndrome, and other primary microcephaly syndromes generally fare better intellectually than would be predicted on the basis of their head circumference (see "Microcephaly: A clinical genetics approach", section on 'Primary microcephaly and its syndromes'). Most children with postnatal-onset microcephaly have poor developmental outcome. In a longitudinal cohort of 57 children with postnatal-onset microcephaly who were followed for an average of four years, only 23 percent had a normal developmental quotient [54]. Maintenance of postnatal growth (weight and height) was associated with more favorable developmental outcomes, independent of underlying etiology.

SUMMARY AND RECOMMENDATIONS

- Head circumference (occipitofrontal circumference [OFC]) should be measured at health maintenance visits between birth and three years of age and in any child with neurologic symptoms. OFC measurements are most informative when plotted over time. (See 'Measurement' above and 'Monitoring' above.)
- Microcephaly is an OFC greater than 2 standard deviations (SD) below the mean for a given age, sex, and gestation. Microcephaly is borderline when the OFC is between 2 and 3 SD below the mean, moderate when the OFC is between 3 and 5 SD below the mean, and severe when the OFC is ≥5 SD below the mean. Microencephaly is an abnormally small brain. (See 'Definitions' above and 'Head circumference charts' above.)
- A variety of genetic abnormalities and environmental insults can affect brain development resulting in microencephaly and/or microcephaly (table 2). (See 'Etiology' above.)
- Evaluation for microcephaly should be initiated when a single OFC measurement is more than 2 to 3 SD below the mean (after confirmation that the measurement was accurate) or when serial measurements reveal progressive decrease in head size. (See 'Overview of approach' above.)
- The initial evaluation includes a history and physical examination of the child and parents. Factors that determine the urgency and extent of the ancillary evaluation of include age at onset; history of central nervous system trauma or infection; associated symptoms, neurodevelopmental abnormalities or syndromic features (table 1); and family history (algorithm 1). (See 'Overview of approach' above.)
- Consultation with or referral to a clinical geneticist, pediatric neurologist, or specialist in pediatric infectious diseases can be helpful in determining the appropriate studies for the ancillary evaluation. (See 'Diagnostic testing' above and 'Neuroimaging' above and "Microcephaly: A clinical genetics approach", section on 'Initial genetics consultation'.)

REFERENCES

1. Stoll C. Problems in the diagnosis of fragile X syndrome in young children are still present. Am J Med Genet 2001; 100:110.
2. Zvulunov A, Weitz R, Metzker A. Neurofibromatosis type 1 in childhood: evaluation of clinical and epidemiologic features as predictive factors for severity. Clin Pediatr (Phila) 1998; 37:295.
3. Furuta T, Tabuchi A, Adachi Y, et al. Primary brain tumors in children under age 3 years. Brain Tumor Pathol 1998; 15:7.
4. Tomita T, McLone DG. Brain tumors during the first twenty-four months of life. Neurosurgery 1985; 17:913.
5. Nard JA. Abnormal head size and shape. In: Common & Chronic Symptoms in Pediatrics, Gartner JC, Zitelli BJ (Eds), Mosby, St. Louis 1997.
6. Rios A. Microcephaly. Pediatr Rev 1996; 17:386.
7. Fenichel GM. Disorders of cranial volume and shape. In: Clinical Pediatric Neurology: A Signs and Symptoms Approach, 5th, Elsevier Saunders, Philadelphia 2005. p.353.
8. Nellhaus G. Head circumference from birth to eighteen years. Practical composite international and interracial graphs. Pediatrics 1968; 41:106.
9. Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: birth to 18 years. Pediatrics 1987; 79:706.
10. Rollins JD, Collins JS, Holden KR. United States head circumference growth reference charts: birth to 21 years. J Pediatr 2010; 156:907.
11. Grummer-Strawn LM, Reinold C, Krebs NF, Centers for Disease Control and Prevention (CDC). Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States. MMWR Recomm Rep 2010; 59:1.
12. Wright CM, Williams AF, Elliman D, et al. Using the new UK-WHO growth charts. BMJ 2010; 340:c1140.
13. American Academy of Pediatrics Committee on Nutrition. Failure to thrive. In: Pediatric Nutrition, 7th, Kleinman RE, Greer FR. (Eds), American Academy of Pediatrics, Elk Grove Village, IL 2014. p.663.
14. Bushby KM, Cole T, Matthews JN, Goodship JA. Centiles for adult head circumference. Arch Dis Child 1992; 67:1286.
15. Daymont C, Hwang WT, Feudtner C, Rubin D. Head-circumference distribution in a large primary care network differs from CDC and WHO curves. Pediatrics 2010; 126:e836.
16. Wright CM, Inskip HM, Godfrey K, et al. Monitoring head size and growth using the new UK-WHO growth standard. Arch Dis Child 2011; 96:386.
17. Natale V, Rajagopalan A. Worldwide variation in human growth and the World Health Organization growth standards: a systematic review. BMJ Open 2014; 4:e003735.
18. Abuelo D. Microcephaly syndromes. Semin Pediatr Neurol 2007; 14:118.
19. Leroy JG, Frías JL. Nonsyndromic microcephaly: an overview. Adv Pediatr 2005; 52:261.
20. Opitz JM, Holt MC. Microcephaly: general considerations and aids to nosology. J Craniofac Genet Dev Biol 1990; 10:175.
21. Ashwal S, Michelson D, Plawner L, et al. Practice parameter: Evaluation of the child with microcephaly (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2009; 73:887.
22. Varma R, William, SD, Wessel HB. Neurology. In: Atlas of Pediatric Physical Diagnosis, 5th, Zitelli BJ, Davis HW (Eds), Mosby Elsevier, Philadelphia 2007. p.563.

23. Firth HV, Hurst JA, Hall JG. Microcephaly. In: Oxford Desk Reference: Clinical Genetics, 1st ed, Oxford University Press, Oxford 2005. p.172.
24. Woods CG. Human microcephaly. Curr Opin Neurobiol 2004; 14:112.
25. Leviton A, Holmes LB, Allred EN, Vargas J. Methodologic issues in epidemiologic studies of congenital microcephaly. Early Hum Dev 2002; 69:91.
26. Gleeson JG, Dobyns WB, Plawner L, Ashwal S. Congenital structural defects. In: Pediatric Neurology Principles and Practice, 4th ed, Swaiman KF, Ashwal S, Ferriero DM (Eds), Mosby Elsevier, Philadelphia 2006. p.399.
27. Avery GB, Meneses L, Lodge A. The clinical significance of "measurement microcephaly". Am J Dis Child 1972; 123:214.
28. Pryor HB, Thelander H. Abnormally small head size and intellect in children. J Pediatr 1968; 73:593.
29. Dolk H. The predictive value of microcephaly during the first year of life for mental retardation at seven years. Dev Med Child Neurol 1991; 33:974.
30. Sells CJ. Microcephaly in a normal school population. Pediatrics 1977; 59:262.
31. Menkes JH, Sarnat HB, Flores-Sarnat L. Malformations of the central nervous system. In: Child Neurology, 7th, Menkes JH, Sarnat HB, Maria BL (Eds), Lippincott Williams & Wilkins, Philadelphia 2006. p.284.
32. Mochida GH, Walsh CA. Molecular genetics of human microcephaly. Curr Opin Neurol 2001; 14:151.
33. von der Hagen M, Pivarcsi M, Liebe J, et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. Dev Med Child Neurol 2014; 56:732.
34. Garcia CA, Duncan C. Atelencephalic microcephaly. Dev Med Child Neurol 1977; 19:227.
35. Russell LJ, Weaver DD, Bull MJ, Weinbaum M. In utero brain destruction resulting in collapse of the fetal skull, microcephaly, scalp rugae, and neurologic impairment: the fetal brain disruption sequence. Am J Med Genet 1984; 17:509.
36. Villó N, Beceiro J, Cebrero M, de Frias EG. Fetal brain disruption sequence in a newborn infant with a history of cordocentesis at 21 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 84:F63.
37. Bönnemann CG, Meinecke P. Fetal brain disruption sequence: a milder variant. J Med Genet 1990; 27:273.
38. Moore CA, Weaver DD, Bull MJ. Fetal brain disruption sequence. J Pediatr 1990; 116:383.
39. Corona-Rivera JR, Corona-Rivera E, Romero-Velarde E, et al. Report and review of the fetal brain disruption sequence. Eur J Pediatr 2001; 160:664.
40. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001; 344:1132.
41. Spohr HL, Willms J, Steinhausen HC. Prenatal alcohol exposure and long-term developmental consequences. Lancet 1993; 341:907.
42. Skull SA, Ruben AR, Walker AC. Malnutrition and microcephaly in Australian aboriginal children. Med J Aust 1997; 166:412.
43. Krishnamoorthy KS, Kuban KC, O'Shea TM, et al. Early cranial ultrasound lesions predict microcephaly at age 2 years in preterm infants. J Child Neurol 2011; 26:188.
44. Weaver DD, Christian JC. Familial variation of head size and adjustment for parental head circumference. J Pediatr 1980; 96:990.
45. Custer DA, Vezina LG, Vaught DR, et al. Neurodevelopmental and neuroimaging correlates in

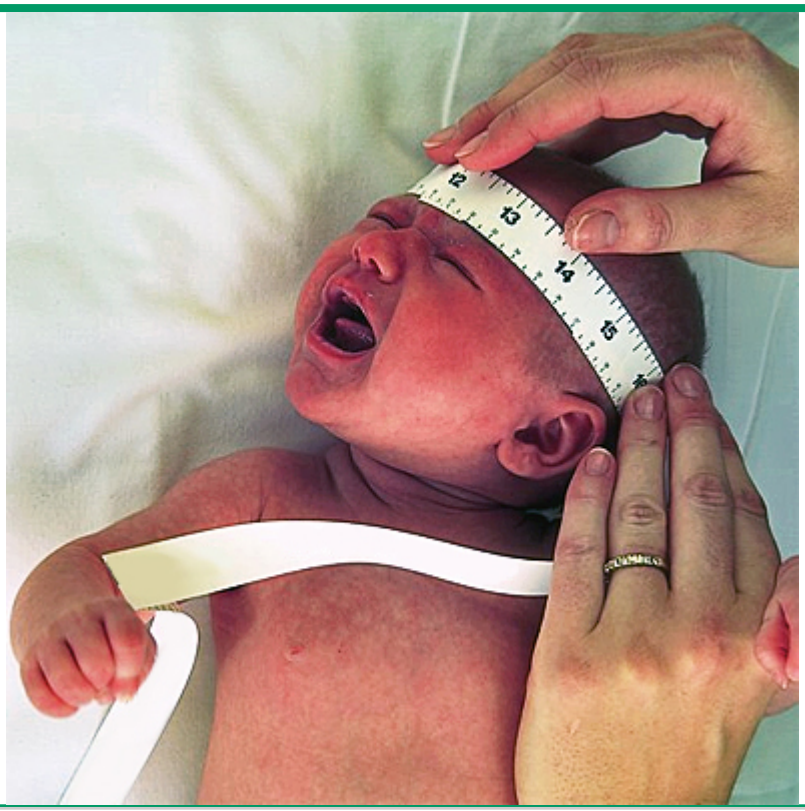
nonsyndromal microcephalic children. J Dev Behav Pediatr 2000; 21:12.

46. Sugimoto T, Yasuhara A, Nishida N, et al. MRI of the head in the evaluation of microcephaly. Neuropediatrics 1993; 24:4.
47. Chervenak FA, Jeanty P, Cantraine F, et al. The diagnosis of fetal microcephaly. Am J Obstet Gynecol 1984; 149:512.
48. Chervenak FA, Rosenberg J, Brightman RC, et al. A prospective study of the accuracy of ultrasound in predicting fetal microcephaly. Obstet Gynecol 1987; 69:908.
49. Kurtz AB, Wapner RJ, Rubin CS, et al. Ultrasound criteria for in utero diagnosis of microcephaly. J Clin Ultrasound 1980; 8:11.
50. Kurmanavicius J, Wright EM, Royston P, et al. Fetal ultrasound biometry: 1. Head reference values. Br J Obstet Gynaecol 1999; 106:126.
51. Berger I. Prenatal microcephaly: can we be more accurate? J Child Neurol 2009; 24:97.
52. Deloison B, Chalouhi GE, Bernard JP, et al. Outcomes of fetuses with small head circumference on second-trimester ultrasonography. Prenat Diagn 2012; 32:869.
53. Tolmie JL, McNay M, Stephenson JB, et al. Microcephaly: genetic counselling and antenatal diagnosis after the birth of an affected child. Am J Med Genet 1987; 27:583.
54. Rosman NP, Tarquinio DC, Datseris M, et al. Postnatal-onset microcephaly: pathogenesis, patterns of growth, and prediction of outcome. Pediatrics 2011; 127:665.

Topic 2839 Version 12.0

GRAPHICS

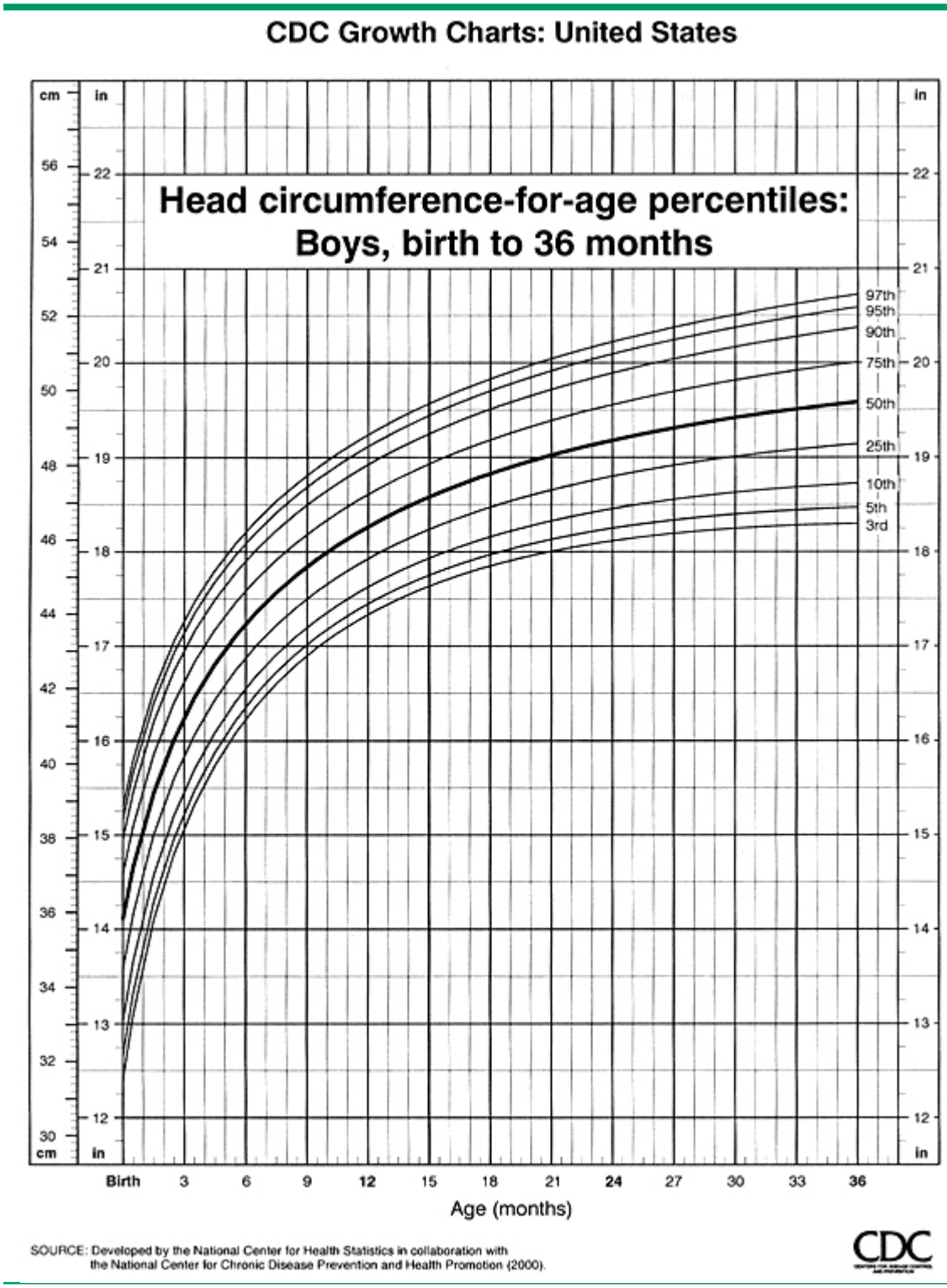
Measurement of head circumference



Measuring head circumference. The measuring tape passes just above the eyebrows and around the prominent posterior aspect of the head.

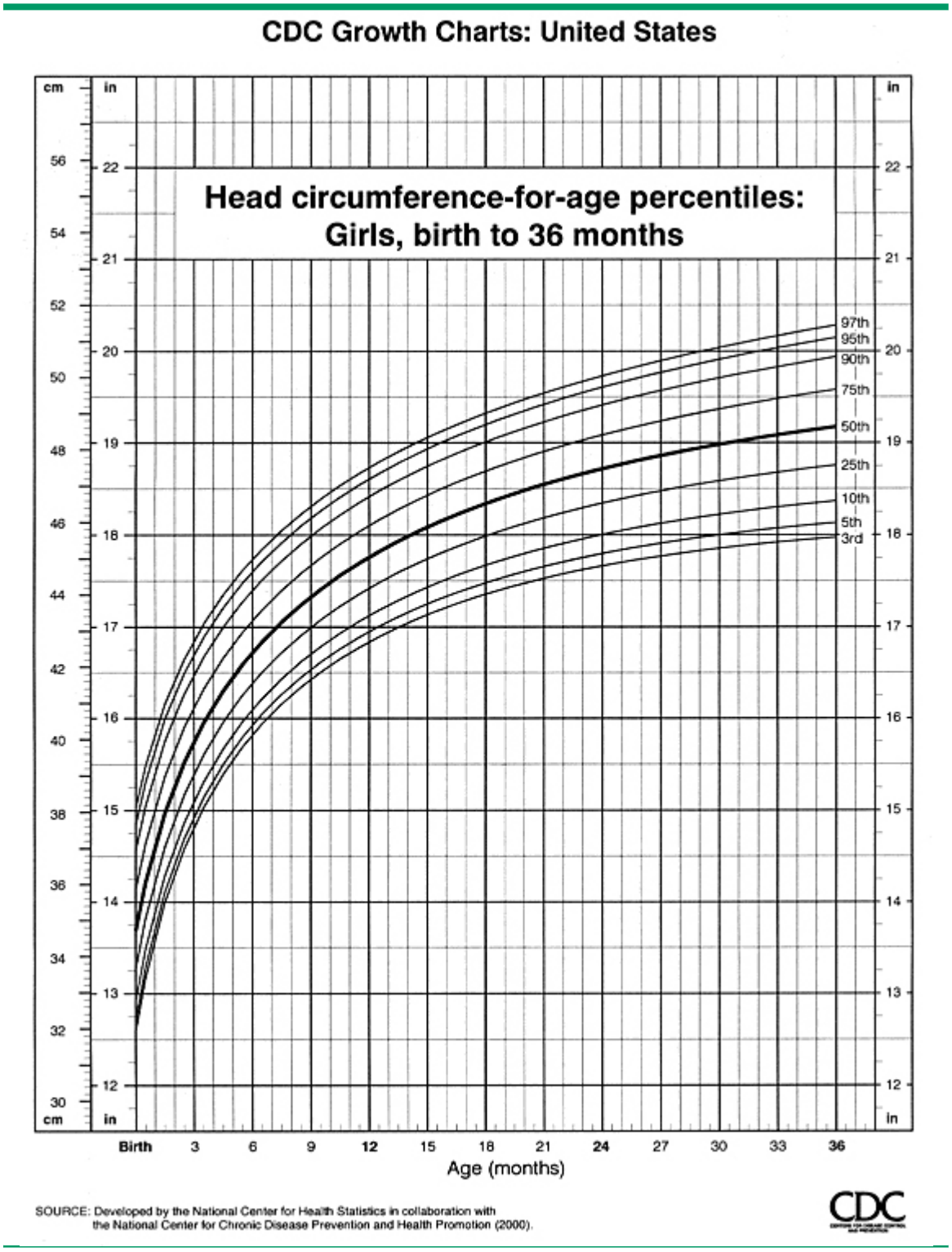
Graphic 70799 Version 2.0

Head circumference-for-age percentiles, boys birth to 36 months, CDC growth charts



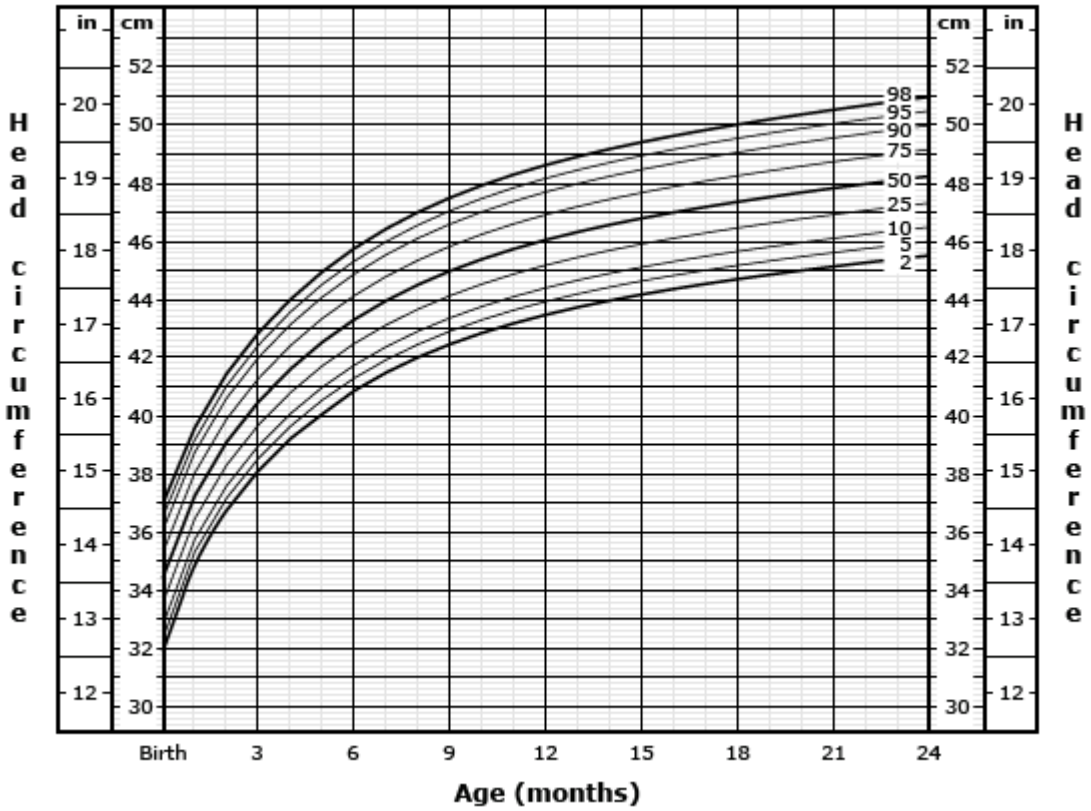
Graphic 80863 Version 3.0

Head circumference-for-age percentiles, girls 0 to 36 months, CDC growth charts



Graphic 59076 Version 3.0

Head circumference-for-age percentiles, boys 0 to 24 months, WHO growth standards

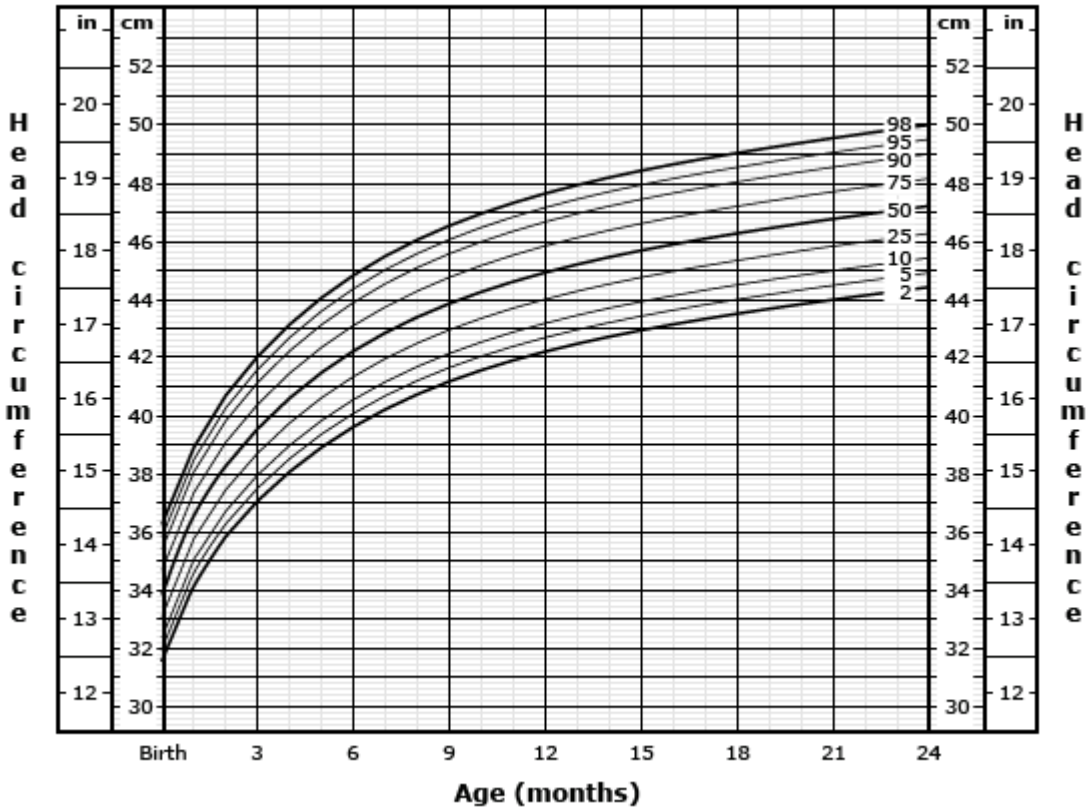


WHO: World Health Organization.

Reproduced from: Centers for Disease Control and Prevention based on data from the WHO Child Growth Standards.

Graphic 58632 Version 3.0

Head circumference-for-age percentiles, girls 0 to 24 months, WHO growth standards



WHO: World Health Organization.

Reproduced from: Centers for Disease Control and Prevention based on data from the WHO Child Growth Standards.

Graphic 74503 Version 3.0

Selected syndromes with microcephaly as a characteristic feature

Syndrome	Clinical features
Down syndrome MIM #190685	Brachycephaly, upslanting palpebral fissures, epicanthal folds, short neck, transverse palmar crease, space between first and second toes, hypotonia
Trisomy 18	Prominent occiput, narrow bifrontal diameter, hypoplastic supraorbital ridge, short palpebral fissures, micrognathia, structural cardiac lesions (ventricular septal defect, atrial septal defect, patent ductus arteriosus)
Trisomy 13	Holoprosencephaly, wide sagittal suture, cleft lip, cleft palate, loose skin, transverse palmar crease, polydactyly, posterior prominence of heel; structural cardiac lesions (ventricular septal defect, patent ductus arteriosus, atrial septal defect, dextrocardia)
Fetal alcohol syndrome	Pre- and postnatal growth retardation, short palpebral fissures, flat philtrum, thin upper lip
Seckel syndrome MIM #210600	Pre- and postnatal growth retardation, average birth weight approximately 1540 g, proportionate short stature; micrognathia, facial asymmetry, downslanting palpebral fissures, prominent beaked nose; limb hypoplasia; gap between first and second toes
Smith-Lemli-Opitz MIM #270400	Ptosis, broad nasal tip, anteverted nostrils, cleft palate, micrognathia, congenital heart defects, syndactyly of second and third toes, postaxial polydactyly, hypospadias or cryptorchidism (in boys)
Williams-Beuren (7q11.23 deletion) MIM #194050	Cardiovascular disease (supravalvular aortic stenosis), idiopathic hypercalcemia, periorbital fullness, short upturned nose, long philtrum, wide mouth, full lips
Cornelia de Lange MIM 122470, 300590, 610759	Pre- and postnatal growth retardation, generalized hirsutism, fusion of eyebrows (synophrys), arched brows, long eyelashes, small upturned nose, thin lips, midline beaking of the upper lip; limb reduction defects, missing fingers, syndactyly of second and third toes
Miller-Dieker lissencephaly (17p13.3 deletion) MIM #247200	Bitemporal narrowing, upturned nose, small jaw, vertical furrowing of forehead, micrognathia, genitourinary anomalies
Wolf-Hirschhorn (4p deletion) MIM #194190	Congenital heart disease, hearing loss, prominent glabella, hypertelorism, wide nasal bridge, beaked nose, short philtrum, down-turned upper lip
Cri-du-chat (5p15.2 deletion)	Round face, hypertelorism, micrognathia, epicanthal folds, hypotonia, high-pitched cry

MIM #123450	
Monosomy 1p36 deletion MIM #607872	Brachycephaly, large fontanelle, pointed chin, hearing loss, flat nasal bridge, flat nose, cleft lip, cleft palate, short fifth finger
Mowat-Wilson MIM #235730	Pre- or postnatal microcephaly, short stature, hypertelorism, iris coloboma, deep-set eyes, downslanting palpebral fissures, cupped ears, pointed chin, seizures, hypospadias (in boys), Hirschsprung's disease, congenital heart disease
Rubinstein-Taybi MIM #180849	Postnatal short stature, low anterior hairline, hypoplastic maxilla, micrognathia, heavy eyebrows, long eyelashes, broad thumbs and big toes
Aicardi-Goutières syndrome MIM #225750	Congenital microcephaly, abnormal eye movements, hepatosplenomegaly, cerebral calcification, thrombocytopenia, spasticity, seizures

Data from:

1. *Abuelo D. Microcephaly syndromes. Semin Pediatr Neurol 2007; 14:118.*
2. *Firth HV, Hurst JA, Hall JG. Microcephaly. In: Oxford Desk Reference: Clinical Genetics, 1st ed. Oxford University Press, Oxford 2005. p.172.*

Graphic 61045 Version 8.0

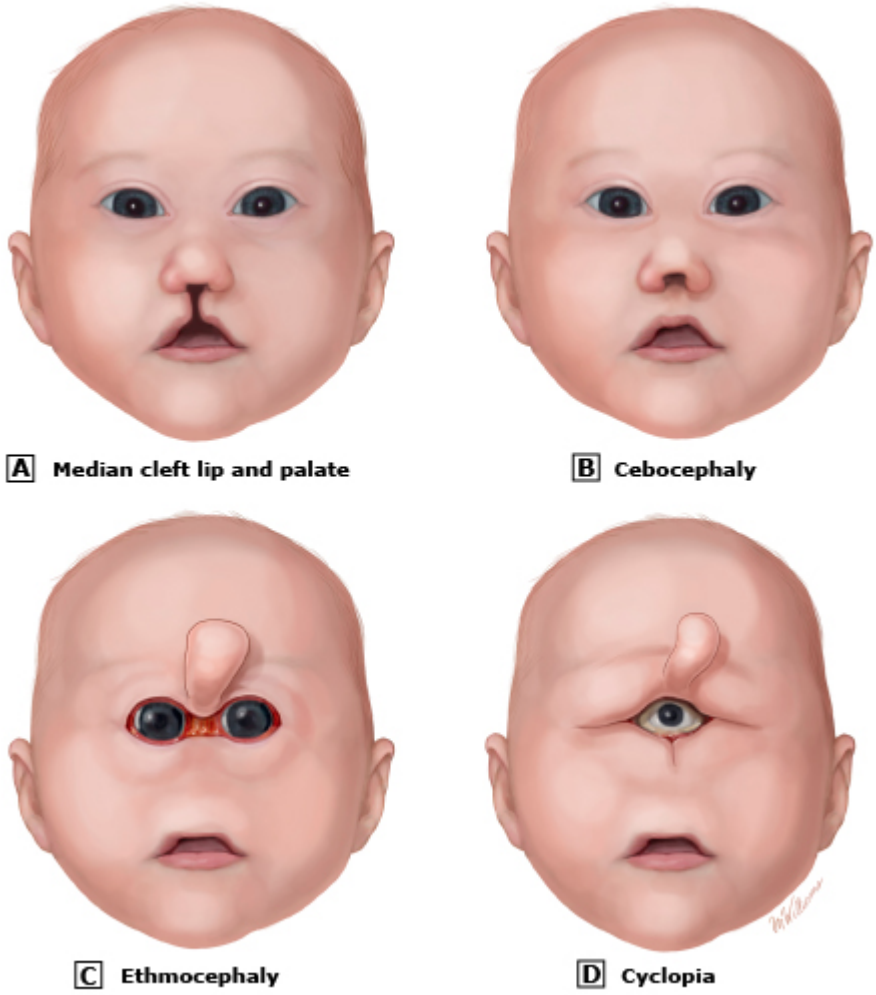
Selected causes of microcephaly

Isolated microcephaly (true microcephaly, microcephaly vera)
Autosomal recessive (eg, autosomal recessive primary microcephaly types 1 through 6, Amish lethal microcephaly)
Autosomal dominant
X-linked microcephaly
Chromosomal abnormalities and syndromes
Trisomies (eg, 21, 18, 13)
Monosomy 1p36 deletion
Seckel syndrome
Smith-Lemli-Opitz syndrome
Williams-Beuren syndrome (7q11.23 deletion)
Cornelia de Lange syndrome
Miller-Dieker lissencephaly syndrome (17p13.3 deletion)
Wolf-Hirschhorn syndrome (4p deletion)
Cri-du-chat syndrome (5p15.2 deletion)
Mowat-Wilson syndrome
Rubinstein-Taybi syndrome
Aicardi-Goutières syndrome
Cockayne syndrome
Bloom syndrome
Angelman syndrome

Neuroanatomic abnormalities
Neural tube defects (eg, anencephaly, hydranencephaly, encephalocele)
Holoprosencephaly
Atelencephaly (aprosencephaly)
Lissencephaly
Schizencephaly
Polymicrogyria
Pachygyria (macrogyria)
Fetal brain disruption sequence
Metabolic disorders
Maternal diabetes mellitus
Untreated maternal phenylketonuria
Phenylketonuria
Methylmalonic aciduria
Citrullinemia
Neuronal ceroid lipofuscinosis
Environmental causes
Congenital infection (eg, cytomegalovirus, herpes simplex virus, rubella, varicella, toxoplasmosis, human immunodeficiency virus, syphilis, enterovirus)
Meningitis
In utero drug or toxin exposure (eg, alcohol, tobacco, marijuana, cocaine, heroin, antineoplastic agents, antiepileptic agents, radiation, toluene)
Perinatal insult (eg, hypoglycemia, hypothyroidism, hypopituitarism, hypoadrenalism)
Anoxia/ischemia

Graphic 75479 Version 6.0

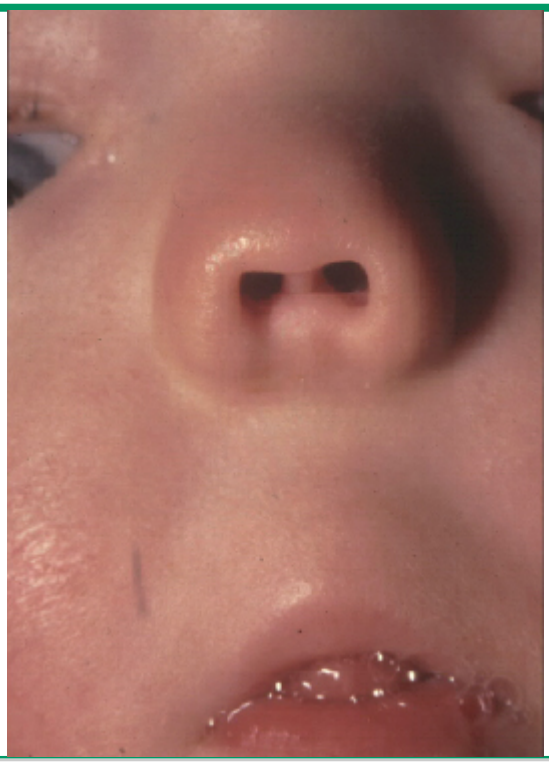
Holoprosencephaly spectrum



Features of cebocephaly include an absent or defective single-nostril nose and closely-set eyes (hypotelorism). Ethmocephaly is characterized by small, narrow-set eyes (hypotelorism and microphthalmia) separated by a primative, nonfunctioning nasal structure (proboscis). Cyclopia is marked by a single central orbital fossa and proboscis. The globe can be absent, underdeveloped, or apparently normal, and there can be one or two globes.

Graphic 70880 Version 6.0

Cebocephaly

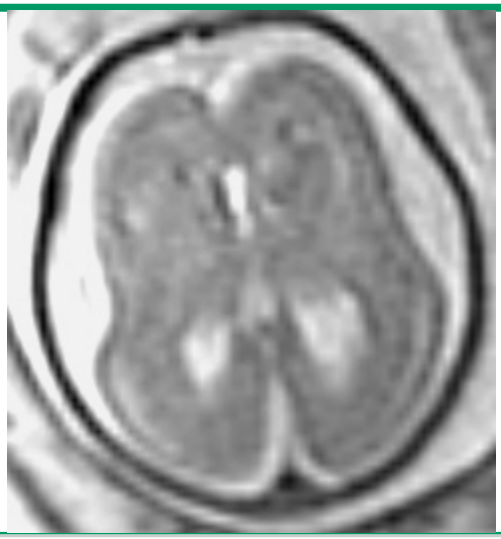


The closely-approximated nostrils, small mouth, and hypotelorism in this infant are clinical manifestations of holoprosencephaly.

Courtesy of Glenn C Isaacson, MD, FAAP, FACS.

Graphic 60138 Version 2.0

Fetal lissencephaly

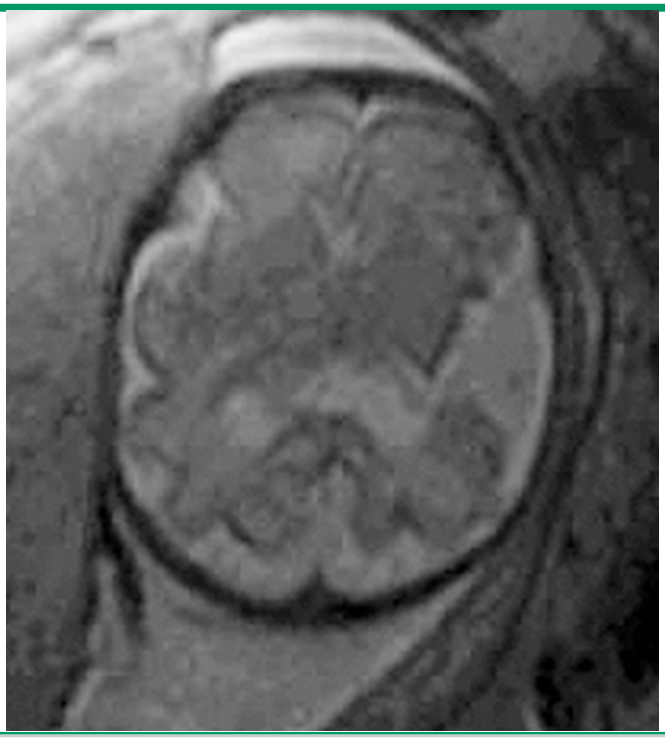


Axial magnetic resonance image of fetus at 29 weeks with diffusely smooth cortex, compatible with lissencephaly.

Courtesy of Deborah Levine, MD.

Graphic 67398 Version 1.0

Fetal schizencephaly

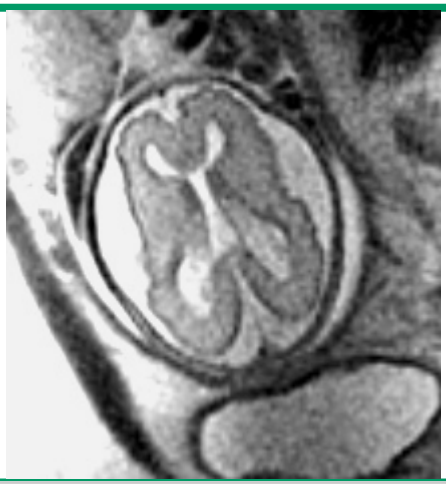


Fetus at 31 weeks with schizencephaly. Note the cleft in the brain.

Courtesy of Deborah Levine, MD.

Graphic 74979 Version 1.0

Fetal polymicrogyria

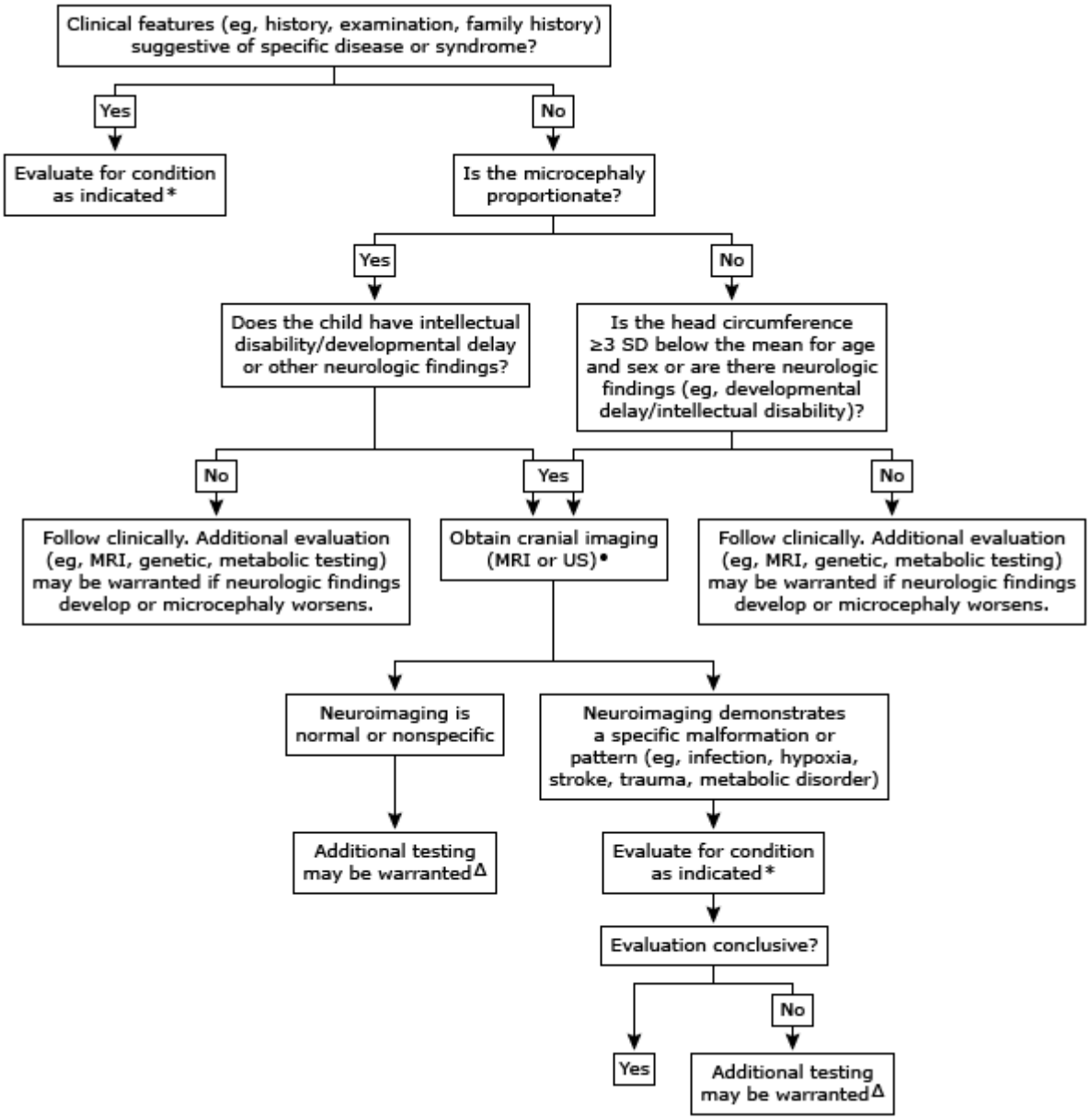


Third trimester fetus with diffusely dysmorphic sawtooth pattern of the gyri over the convexities compatible with polymicrogyria.

Courtesy of Deborah Levine, MD.

Graphic 57657 Version 1.0

Evaluation of microcephaly in infants and children



SD: standard deviation; MRI: magnetic resonance imaging; US: ultrasonography; CMV: cytomegalovirus.

* Consultation with a specialist in pediatric infectious diseases, pediatric genetics, pediatric neurology, and/or pediatric radiology may be helpful in planning the evaluation.

• Consultation with a pediatric radiologist may be helpful in planning neuroimaging.

Δ Additional testing may include evaluation for genetic or metabolic studies, ophthalmology evaluation and/or tests for congenital infection. Consultation with a specialist in pediatric infectious diseases, pediatric genetics, or pediatric neurology may be helpful in planning the evaluation.

Adapted from:

1. *Ashwal S, Michelson D, Plawner L, et al. Practice parameter: Evaluation of the child with microcephaly (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2009; 73:887.*
2. *von der Hagen M, Pivarcsi M, Liebe J, et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. Dev Med Child Neurol 2014; Epub ahead of print*

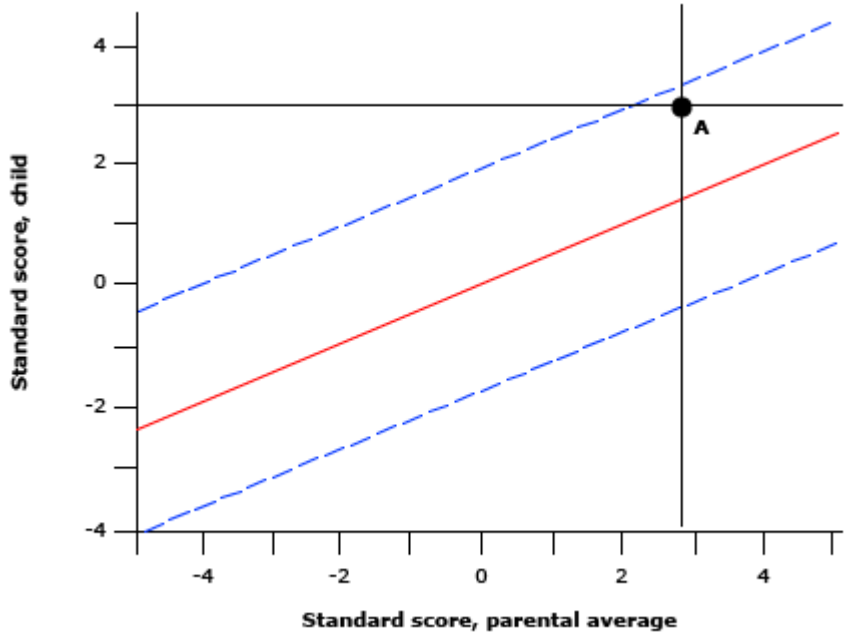
Graphic 94816 Version 1.0

Head circumference data of Nellhaus

Age	Males		Females	
	Mean (cm)	1 SD	Mean (cm)	1 SD
Birth	34.74	1.33	34.02	1.22
1 mo	37.30	1.30	36.43	1.22
3 mo	40.62	1.23	39.71	1.20
6 mo	43.76	1.29	42.68	1.38
9 mo	45.75	1.28	44.69	1.30
12 mo	47.00	1.31	45.81	1.29
18 mo	48.31	1.36	47.27	1.36
2 yr	49.19	1.39	48.02	1.29
3 yr	50.63	1.38	49.25	1.36
4 yr	50.91	1.39	50.10	1.37
5 yr	51.41	1.37	50.55	1.32
6 yr	51.40	1.41	50.52	1.31
7 vr	52.24	1.52	51.46	1.35
8 yr	52.35	1.40	51.64	1.44
9 yr	52.58	1.44	51.87	1.33
10 yr	53.16	1.41	52.15	1.50
11 yr	53.25	1.53	52.64	1.39
12 vr	53.71	1.52	53.01	1.50
13 yr	54.14	1.57	53.70	1.37
14 yr	54.59	1.30	54.04	1.39
15 yr	54.95	1.51	54.39	1.34
16 yr	55.37	1.11	54.64	1.16
17 yr	55.77	1.32	54.78	1.35
18 yrs and older	55.95	1.34	54.94	1.40

Graphic 61299 Version 4.0

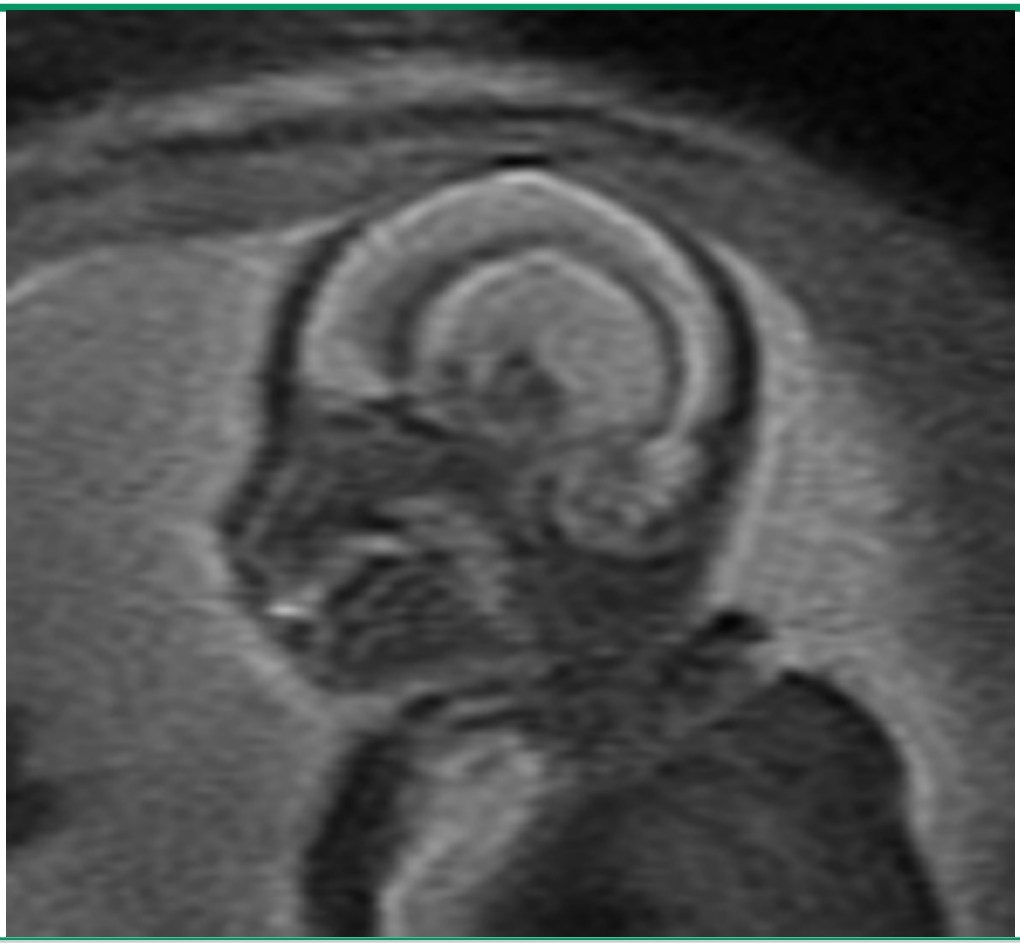
Weaver curve



Plotted above is an example of the use of the Weaver curve. The child's OFC was 49.5 cm at the age of 9 months, placing him well above the 97th percentile on Nellhaus's head circumference chart. His standard score (SS) was calculated to be +2.93. The father had an OFC of 59.5 cm, and the mother's was 59.0 cm with SS of +2.65 and +2.90, respectively. Their average parental SS was +2.78. When plotted, the intercept (A) of lines from the SS falls below the +2 SD regression line. Thus, the child's head size in relationship to that of his parents is judged to be normal.

Graphic 80059 Version 5.0

Fetal microcephaly



Fetus with microcephaly at 18 weeks gestational age. Note the small brain and sloping appearance of the forebrain.

Courtesy of Deborah Levine, MD.

Graphic 78619 Version 1.0

Disclosures

Disclosures: **Julie A Boom, MD** Nothing to disclose. **Jan E Drutz, MD** Nothing to disclose. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Marc C Patterson, MD, FRACP** Grant/Research/Clinical Trial Support: Actelion [Lysosomal diseases (Miglustat)]. Consultant/Advisory Boards: Amicus; Agios; Cydan; Genzyme; Orphazyme; Shire HGT [Lysosomal diseases (Arimoclomol, cyclodextrin, glucocerebrosidase)]; Stem Cells, Inc; Vtesse [Lysosomal diseases (Human embryonic stem cells)]. **Mary M Torchia, MD** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Microcephaly: A clinical genetics approach

Author
Geoff Woods, ChB, MB, MD, FRCP, FMedSci

Section Editor
Helen V Firth, DM, FRCP, DCH

Deputy Editor
Mary M Torchia, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Feb 13, 2015.

INTRODUCTION — Microcephaly is an important neurologic sign. Deviations from normal head growth may be the first indication of an underlying congenital, genetic, or acquired problem. Many genetic conditions are associated with an abnormal pattern of head growth; the earlier these conditions are detected, the earlier appropriate treatment, services, and genetic counseling can be provided [1].

A clinical genetics approach to microcephaly in infants and children will be presented here. At the heart of this approach is an attempt in each case to formulate a diagnosis that gives at least an indication of the sibling recurrence risk. The etiology and primary care evaluation of microcephaly in infants and children are discussed separately. (See "Microcephaly in infants and children: Etiology and evaluation".)

DEFINITION — The definition of microcephaly is not standardized. It is sometimes defined as an occipitofrontal circumference (OFC) more than 3 standard deviations (SD) below the mean for a given age, sex, and gestation. Other times, it is defined as an OFC more than 2 SD below the appropriate mean (ie, less than the 3rd percentile). It is important to record measurements rather than percentiles – as head circumference charts vary, especially up to the age of three years, and to use the most recent culturally and ethnically relevant charts to determine percentiles [2].

If microcephaly is defined as a head size less than 3 SD below the appropriate mean, it is more likely to be associated with genetic and non-genetic disorders affecting brain development. In contrast, if microcephaly is defined as more than 2 SD below the mean, many intellectually normal individuals who have a head circumference at the low end of the population distribution will be included.

Whatever definition is employed, measurement and appropriate charting of OFC is part of the evaluation of individuals who have a developmental delay or learning disability. The results of population-based studies indicate that it is important to measure OFC in all infants when height and weight are measured, inasmuch as reduced head circumference growth in early life is associated with diminished cognitive abilities thereafter [3-6]. (See "Specific learning disabilities in children: Role of the primary care provider", section on 'Medical evaluation' and "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs", section on 'Clinical evaluation'.)

CLASSIFICATION — The terminology used to describe different types of microcephaly can be confusing, and the genetic implications of particular terms must be critically considered. For example, the term “secondary microcephaly” is easily misconstrued as the non-genetic opposite of genetic, “primary microcephaly,” when in fact, secondary microcephaly is merely a descriptive term that denotes genetic and non-genetic disorders in which head growth slows **after** birth. (See 'Acquired microcephaly' below.)

Primary microcephaly — The term "primary microcephaly" was originally associated with one particular autosomal recessive microcephaly phenotype (**m**icro**c**ephaly **p**rimary **h**ereditary, MCPH) (picture 1) [7]. Broadly, primary microcephaly is thought to result from failure to produce enough neurons. However, defective production of neurons with secondary degeneration also may occur (eg, MCPH10, caused by homozygous mutation in *ZNF335*) [8]. Therefore, the primary microcephaly phenotype is clinically and genetically heterogeneous. Several gene loci, designated MCPH1, MCPH2, etc, have been identified,

and more are yet to be discovered [9]. (See 'Primary microcephaly and its syndromes' below.)

Classic primary microcephaly includes the following clinical features:

- Reduced occipito-frontal circumference (OFC) at birth leading to greatly reduced OFC in adulthood
- Relatively normal brain anatomy
- Relative absence of neurologic signs
- Nonprogressive mild, moderate, or (less commonly) severe learning difficulties

Several newly reported varieties of autosomal recessive microcephaly have been added to an expanding list of primary microcephalies and this has broadened the range of associated phenotypes beyond the original clinical description. For example, microcephaly with early onset epilepsy (MCSZ, MIM #613402), Amish microcephaly (MCPHA, MIM #607196), microcephaly with or without other brain malformations caused by nonsense or missense mutations, respectively (MCPH2, MIM #604317), and microcephaly with simplified gyral pattern, cerebellar and/or brain stem hypoplasia (MIM %603802) are sometimes listed under the heading primary microcephaly because they are each inherited in an autosomal recessive fashion [10,11]. (See 'Primary microcephaly and its syndromes' below.)

Genetic complexities also bedevil orderly classification. As an example, different mutations in the Amish microcephaly gene, *SLC25A19*, result in a metabolic disorder affecting the mitochondrial thiamine pyrophosphate carrier with a variable phenotype ranging from early, lethal Amish microcephaly to an adult condition with normal OFC and cognition, striatal necrosis, and polyneuropathy [12].

Acquired microcephaly — The term "acquired microcephaly" is synonymous with such terms as secondary microcephaly and postnatal microcephaly. These terms refer to the brain that had normal or near-normal size at birth and grows abnormally slowly thereafter. A possible implication is that neuronal degeneration occurs for any genetic or non-genetic reason. Many cases of acquired microcephaly go undiagnosed [13].

Relative microcephaly — "Relative microcephaly" is a shorthand expression that usually is used to describe the child with neurologic impairments who has reduced head circumference relative to his somatic size, or relative to the head circumferences of his (normal) parents (figure 1). The term is best avoided.

INITIAL GENETICS CONSULTATION — The objective of genetics consultation for a family with a child or relative affected by microcephaly is to formulate a diagnosis, even an incomplete diagnosis, if that is at all possible (eg, primary, syndromic, metabolic, neurologic), and to estimate the chance of recurrence of the condition in another child. The clinical geneticist must distinguish syndromic from nonsyndromic microcephaly and collaborate with colleagues to diagnose metabolic and neurologic conditions that may cause microcephaly.

At first consultation, it is uncommon for the geneticist to make a confident diagnosis of a specific condition and additional evaluation generally is necessary [13-16]. The subsequent clinical and laboratory evaluation are best determined on a case-by-case basis. Factors to be considered include the onset of microcephaly, associated dysmorphism or congenital anomalies, maternal/environmental factors, and progressive neurologic abnormalities [2].

History — A comprehensive approach to history taking, including the family history, and clinical examination of the child with microcephaly are described separately. (See "Microcephaly in infants and children: Etiology and evaluation", section on 'Postnatal evaluation'.)

Points worth highlighting include:

- The age at which microcephaly was first observed
- History of antenatal insult or maternal illness, such as epilepsy [17]

- Fetal exposures, including alcohol, drugs, infections, and toxins (eg, undiagnosed maternal hyperphenylalaninemia [18,19])
- Whether other relatives are affected
- Parental consanguinity

Several consultations, a trusting clinician-patient relationship, and tact often are required to assess factors such as prenatal infection, the exact quantities of alcohol consumed at different stages in gestation in suspected fetal alcohol syndrome, or the intellectual attainments of parents and relatives.

Examination — Physical examination should include an assessment of the genetic contribution to microcephaly by measuring the parents' occipitofrontal circumferences (OFC) and plotting these measurements on head circumference charts appropriate for sex. A new head circumference reference chart for birth to adulthood was published in 2010 [20]. For direct comparison, simultaneously plot the OFC measurements of the child, parents, and any siblings on such a chart (figure 1). For most normal children, when the head sizes of the parents and the child are plotted and compared, the child's OFC lies between the SD or centile plots of both parents, just as the midparental height is a guide to the expected height of a child. Although the Weaver curve [21] achieves the same goal with greater precision, it takes a little longer to complete. (See "Microcephaly in infants and children: Etiology and evaluation", section on 'Weaver curve'.)

Laboratory evaluation — The laboratory evaluation is best determined on a case-by-case basis, bearing in mind that the objective is to formulate a diagnosis and estimate the chance of recurrence of the condition in another child. If there is a suspicion of a metabolic cause for microcephaly, appropriate referral to the metabolic service should be made at an early stage in case there is an underlying, treatable inborn error of metabolism. (See 'Metabolic microcephaly' below.)

Chromosome studies are important in all cases. Array comparative genomic hybridization (CGH) studies have replaced traditional cytogenetic tests as the first-line genetic test in children with neurodevelopmental disorders, particularly when there is less severe microcephaly, malformation, or dysmorphism. Array CGH has a higher abnormality detection rate than traditional cytogenetic studies. Although traditional cytogenetic studies can detect abnormal, prophase-like cells suggesting severe microcephaly due to microcephalin (*MCPH1*) mutation (a very rare event), the increased resolution of array CGH permits detection of much smaller chromosomal deletions and duplications. (See 'Array comparative genomic hybridization' below.)

Neuroimaging — When there is a request for accurate genetic counseling, magnetic resonance imaging (MRI) of the brain usually is undertaken despite the requirement for sedation or general anesthesia in very young or uncooperative individuals. Simultaneous magnetic resonance spectroscopy may be warranted if rare neurometabolic causes of microcephaly are suspected (eg, brain creatine deficiency syndromes) [22].

Categorization after initial consultation — After the initial genetics assessment, most children with microcephaly can be assigned to one of the following broad clinical categories, although some patients have features of more than one category:

- Microcephaly (OFC -2SD to -4SD) with an undiagnosed pattern of dysmorphism – In such children it is important to rule out chromosomal defects, specific dysmorphic syndromes, and environmental factors such as prenatal alcohol exposure. This category usually has a low empiric risk of recurrence, except in families where one parent is likely affected. (See 'Microcephaly with dysmorphism' below.)
- Primary microcephaly phenotype (OFC -4SD to -11 SD) – Classic cases of primary microcephaly have minimal dysmorphism and normal neurologic examination. This category usually has a high

risk of recurrence because the primary microcephaly phenotype is usually due to an autosomal recessive condition. Note that the phenotype is not always classic; in such cases brain MRI findings may help to identify a particular type of genetic microcephaly. (See 'Neuroimaging' above and 'Primary microcephaly and its syndromes' below.)

- Microcephaly with prominent neurologic abnormalities (OFC -2 to -4SD) – This category frequently includes postnatal reduction in brain growth with spasticity, global developmental impairments, seizures including epileptic encephalopathy, and diverse brain MRI abnormalities. There are few data on empiric risk of recurrence because this category includes an admixture of recessive disorders including metabolic conditions, new dominant mutations (especially in some, but not all, cases with early infantile epileptic encephalopathy), and, occasionally, difficult to identify adverse prenatal events. (See 'Microcephaly with prominent neurologic abnormalities' below.)

SUBSEQUENT GENETICS ASSESSMENT — The initial genetic assessment may result in the patient being assigned informally to one of the broad categories described in the previous section (see 'Categorization after initial consultation' above). Thereafter, the need for further laboratory investigations is driven by consultations with colleagues—metabolic physicians, pediatric neurologists, and neuroradiologists—and by the desire of parents to have more information on recurrence risks and options for future pregnancies.

Microcephaly with dysmorphism — Microcephaly with dysmorphism is a common scenario in the genetic clinic. The occipitofrontal circumference (OFC) at birth may be normal or mildly reduced. Subsequently, the OFC may follow a trajectory between 2 and 4 SD below the mean for age, sex, and gestational age. Decreased head circumference may be noted at the child's first presentation with developmental impairments. Developmental impairments often are global, but the severity across domains (eg, motor, language) is not necessarily uniform. Other clinical problems, such as organ malformation, visual impairments, or hearing loss can lead to an earlier presentation. The risk of recurrence depends upon the underlying diagnosis.

Genetic assessment is vital when seeking an underlying syndrome. Sometimes, a subtle pattern of dysmorphisms suggests a "gestalt" diagnosis, such as Angelman syndrome, Rubinstein-Taybi syndrome, or Cornelia de Lange syndrome types 1 through 5 (MIM #122470, MIM #300590, MIM #610759, MIM#614701, MIM #300882).

Williams syndrome and Angelman syndrome are two relatively common conditions, with well-defined molecular genetic pathologies on chromosome 7 and chromosome 15, respectively, that cause mildly reduced head circumference. Such well-known syndromes increasingly act as clinical cornerstones for development of new knowledge. As an example, recognition of the clinical overlap between Rett and Angelman syndrome preceded the expanding spectrum of Angelman syndrome-like and Rett syndrome-like conditions with various combinations of severe learning difficulties, epilepsy, movement disorder or ataxia, irregular breathing, and reduced OFC (table 1) [23-28]. The phenotypes of affected adults with less familiar gestalt conditions are now being explored as a result of easier molecular diagnostic confirmation with new DNA sequencing technologies [29]. (See 'Genetic testing' below.)

Rarely, the phenotype of a dysmorphic infant is so striking that diagnosis readily follows. A good example is the autosomal recessive microcephaly-capillary malformation syndrome due to mutations in *STAMBP* [30]. More often, however, there is no firm clinical diagnosis. Difficulties arise in cases where the clinical evidence is weak or just suggestive. In some cases, family history is crucial (eg, consanguinity, ethnic background, affected relatives). Family history should always be investigated in detail, if possible. Confirmed information from the family history may be the only evidence for reliable diagnosis of a hitherto unknown autosomal dominant, recessive, or X-chromosome-linked microcephaly syndrome.

Evaluation by a geneticist is also important to assess less common clinical signs such as body

asymmetries, pigmentary rash along Blaschko lines (linear streaks on limbs and whorled patterns around the trunk (figure 2)), and unusual dysmorphisms (eg, affecting the digits in diploid/triploid mosaicism (picture 2) or the hairline in tetrasomy 12p [Pallister-Killian syndrome]). These signs indicate mosaic genetic abnormalities that may be identified through cytogenetic studies on tissue samples (eg, skin or scrapings from the buccal mucosa).

If the pattern of dysmorphisms and other clinical signs does not suggest a diagnosis, which commonly happens, the clinician is faced with the challenge of scrutinizing hundreds of case reports seeking evidence for a specific microcephaly syndrome [31]. This process requires:

- Detailed examination by a clinical dysmorphologist to identify the obvious and not-so-obvious clinical features
- Interrogation of computerized syndrome and medical publication databases for candidate diagnoses featuring one, a few, or any combination of the noted clinical features
- Discussion of cases with experienced colleagues at clinical dysmorphology meetings especially when there are clues of uncertain clinical significance

The computerized database provides a list of diagnoses that should be considered. However, the dysmorphologist must decide which of the candidate diagnoses are more plausible in the patient. This judgment requires extensive clinical experience. In one child, the presence of a "hard" diagnostic finding, such as choanal atresia, may narrow the number of candidate diagnoses. However, in another child, the absence of choanal atresia does not necessarily exclude these same conditions. "Soft" features, such as ptosis, epicanthus, clinodactyly (picture 3), or single palmar crease (picture 4), are common and nonspecific (they may even be inherited and totally unrelated to the presenting complaint (picture 3)) but, in certain combinations a "gestalt" diagnosis is suggested: the classic example is immediate recognition of Down syndrome, yet all genetics practitioners will have missed what is, with hindsight, such an obvious diagnosis. (See "Down syndrome: Clinical features and diagnosis", section on 'Dysmorphic features'.)

Primary microcephaly and its syndromes — Characteristic clinical features of the classic primary microcephaly phenotype include (picture 1):

- Reduced OFC at birth leading to greatly reduced OFC in adulthood
- Relatively normal brain anatomy
- Relative absence of neurologic signs
- Nonprogressive mild, moderate or (less commonly) severe learning difficulties

However, the classic primary microcephaly phenotype is not as pure or homogeneous as was originally thought. The OFC is not always markedly reduced; brain architecture is not always normal; and spasticity and seizures are not always absent [9,32-35]. The MCPH1 phenotype includes short stature and the cytogenetic finding of increased prophase-like cells (see 'Laboratory evaluation' above). The emerging biology of many primary microcephaly genes is that they control fundamental cell functions including cell division and cell cycle checkpoints, DNA damage repair, and chromatin remodeling [36].

Despite expanding knowledge, what is currently known about the clinical genetics of primary microcephalies represents only a small proportion of the information necessary to provide accurate genetic counseling for all families who have a child with greatly reduced OFC for no apparent reason. In most such cases, there is a high empirical risk of recurrence in siblings [37,38], which seems mostly due to autosomal recessive gene mutations. Molecular genetic testing may facilitate identification of an underlying diagnosis. The introduction of NextGeneration sequencing, which allows simultaneous analysis of many/all MCPH genes, has lessened the difficulties of sequential testing. (See 'Second or "next generation" sequencing' below and 'Approach to molecular or DNA testing for microcephaly'

below.)

From a clinical standpoint, when the OFC is more than 4 standard deviations (SD) below the appropriate mean with the classic primary microcephaly (MCPH) phenotype (ie, a nondysmorphic child with severe microcephaly, yet relatively normal brain anatomy; relative absence of neurologic signs; short stature; and nonprogressive, moderate learning difficulties), genetic analysis of *ASPM* (abnormal spindle-like, microcephaly associated, MIM *605481), the gene responsible for **MCPH5** (MIM #608716), is most likely to detect mutations. (See 'First generation sequencing' below.)

After *ASPM*, the next most frequently encountered MCPH gene is probably *WDR62* (WD repeat-containing protein 62, MIM *613583), the gene responsible for **MCPH2** (MIM #604317). Mutations in *WDR62,* a spindle pole protein expressed in neuronal precursor cells undergoing mitosis in embryonic neuroepithelium, cause microcephaly with a structurally normal brain if the mutations are missense; with nonsense mutations, the phenotype is more severe and may involve a spectrum of cerebral malformations including lissencephaly, schizencephaly, polymicrogyria, heterotopias, and cerebellar abnormality [39].

Early onset and severe epilepsy is featured in the complex **MCSZ** phenotype (microcephaly, seizures, and variable cognitive impairment, MIM #613402) that was identified in affected patients from different ethnic backgrounds. Mutations in the gene for MCSZ (polynucleotide kinase 3'-phosphatase [*PNKP*, MIM *605610]) cause cellular sensitivity to radiation. The reporting of two additional cases expanded the MCSZ phenotype to include progressive polyneuropathy and cerebellar atrophy with less severe epilepsy [40].

Primary microcephaly syndromes that are associated with **defective DNA repair** include **MCPH1** (MIM #251200) due to mutations in *MCPH1* (also known as microcephalin and *BRIT1*) [41], **Nijmegen breakage syndrome** (MIM #251260), and **ligase-4 syndrome** (LIG4 syndrome, MIM #606593). LIG4 syndrome is very rare. Both Nijmegen breakage syndrome and LIG4 syndrome feature microcephaly with dysmorphisms, growth retardation, cellular radiosensitivity, and variable predispositions to immunodeficiency and malignancy with relatively normal cognition in some cases. Chromosomal breakage studies demonstrating increased cellular sensitivity to ionizing radiation may still be the best screening test when investigating patients who are possibly affected by a DNA repair disorder. (See "Nijmegen breakage syndrome".)

The autosomal recessive **microcephaly primordial dwarfism syndromes** are a group of unmistakable conditions that cause profound microcephaly with equally profound short stature [42]. The identified gene defects lie in fundamental cellular processes such as genome replication, DNA damage response, and centrosome function. In some rare cases, despite profoundly reduced OFC, there is normal cognition (eg, **Bloom syndrome** [MIM #210900]). **Seckel syndrome** (MIM #210600) is the archetypal phenotype, exhibiting extreme pre- and post-natal growth retardation, microcephaly, sloping forehead, prominent nose, and small chin. Seckel syndrome is usually due to recessive mutations in gene encoding ATR (ataxia telangiectasia and Rad3-related), a protein kinase that plays a central role in the DNA damage response pathway. A similar phenotype is caused by mutations in the gene encoding ATR-Interacting Protein (*ATRIP*), partner protein of ATR required for ATR stability and recruitment to the site of DNA damage [43]. Some individuals with *CDK5RAP2* (MCPH3) and *CPAP* (MCPH6) mutations can have a Seckel syndrome phenotype. A milder version of the Seckel syndrome phenotype has been diagnosed in patients who have mutations in a primary microcephaly gene *Cep152* (MCPH9) [44].

Clinically related to Seckel syndrome are **microcephalic primordial dwarfism type II** (MOPD II, MIM #210720) and **Meier-Gorlin syndrome type 1** (MGORS 1, MIM #224690) due mutations in pericentrin (*PCNT*) and origin recognition complex 1 (*ORC1*), respectively. Underlying these syndromes are defective genetic processes for cilia formation, centrosome function and DNA replication licensing [45]. Precise diagnosis of such conditions is important; otherwise, newly recognized and potentially treatable

clinical complications such as Moya Moya disease in MOPD II are unappreciated [46]. As another example, autosomal recessive insulin-like growth factor deficiency (MIM #608747) is a partially treatable cause of microcephaly, sensorineural deafness and intellectual disability.

Microcephaly with prominent neurologic abnormalities — Children with microcephaly and neurologic abnormalities but with a normal appearance are affected by a wide range of static and degenerative disorders. Presentations are diverse including delayed development or developmental regression, sensory impairments, seizures, movement disorders and ataxia, acute coma or encephalopathy. In such patients, microcephaly may not be present at birth and the development of microcephaly in the first year leads to descriptions such as acquired, secondary, or postnatal. The risk of recurrence depends upon the underlying diagnosis.

Logical progression through a series of biochemical tests and brain imaging studies is required for diagnosis. Chromosome studies early in the evaluation are supplemented by metabolic and genetic studies. For chromosome investigations, array comparative genomic hybridization (CGH) studies are the first choice but conventional cytogenetic studies supplemented by fluorescence in situ hybridization (FISH) examination may still be best to exclude the ring chromosome 20 syndrome, which causes epileptic regression in a child whose development may have been normal until the time of presentation [47]. (See 'Array comparative genomic hybridization' below and 'Traditional cytogenetic studies' below.)

Discussion with the neuroradiologist is critical when brain abnormalities are detected by magnetic resonance imaging (MRI). More detailed classification of clinical-neuroradiologic phenotypes combined with genetic studies has led to identification of new brain development syndromes and greatly improved genetic advice for families [48,49]. As examples:

- The autosomal recessive, prenatal onset, neurodegenerative pontocerebellar hypoplasias are diagnosed by brain MRI findings. In more than one-half of carefully selected cases, gene mutations are identified in either transfer RNA splicing endonuclease subunit gene (*TSEN54)* or nuclear encoded mitochondrial arginyl transfer RNA synthetase gene (*RARS2)* [50,51].
- Microcephaly due to mutations in calcium/calmodulin-dependent serine protein kinase (*CASK*, MIM *300172), an X-linked gene. *CASK* mutations cause microcephaly, optic atrophy, and pontine and cerebellar hypoplasia and nystagmus in affected males (MICPCH syndrome, MIM #300749) [52,53]. Epilepsy is common. Heterozygous females can be severely affected with abnormal brain MRI and postnatal microcephaly [54,55].
- Biallelic mutations were identified in *ARFGEF2* in a syndrome of acquired microcephaly with nodular heterotopia, regression, dystonic quadriplegia, and obstructive cardiomyopathy [56].
- Profound microcephaly (OFC -11SD) with underlying microlissencephaly (MIM #614019) is caused by *NDE1* biallelic mutations that lead to defective progress through mitosis, emphasizing that normal cerebral cortical neurogenesis is dependent on intact mitotic mechanisms, as exemplified in other primary microcephalies.

In the unexplained cases without clinical, laboratory, or neuroradiological clues, there are a small number of autosomal recessive nonsyndromic mental retardation genes that might cause postnatal-onset microcephaly (eg, trafficking protein particle complex, subunit 9 [*TRAPPC9*, MIM *611966]) [57-59].

For the few cases with microcephaly and evidence pointing to environmental factors (eg, MRI features indicating vascular damage, cerebral destruction, or prenatal infection), there are some inherited mimics, including the not uncommon Aicardi-Goutierès syndrome, that have high risk of recurrence (table 2) [60-70].

Metabolic microcephaly — Metabolic microcephaly usually causes postnatal or acquired microcephaly. Although microcephaly is neither a sensitive nor specific indicator of inborn errors of metabolism, it is

important not to miss a treatable metabolic disorder. A 2012 review identified over 80 treatable inborn errors of metabolism that can cause intellectual disability [71]. The authors of the review developed a tool to facilitate detection of these disorders. The tool is accessible online and on mobile devices (Treatable ID) [72].

Examples of metabolic microcephaly syndromes include:

- Maternal phenylketonuria – Among metabolic microcephaly syndromes, maternal phenylketonuria is the only condition that, when undiagnosed, has 100 percent chance of recurrence, and yet it is uniquely preventable [18,19]. (See "Overview of phenylketonuria", section on 'Phenylalanine embryopathy (maternal PKU)'.)
- Adenylosuccinate lyase deficiency – Adenylosuccinate lyase deficiency (MIM #103050), a disorder of purine biosynthesis, is not treatable [73]. However, it may be underdiagnosed in its severe and attenuated forms because diagnosis requires specific examination of urinary purine metabolites.
- Cerebral glucose transporter deficiency – Cerebral glucose transporter (GLUT1) deficiency (MIM #606777) is a treatable condition with a variable phenotype [74,75]. Postnatal microcephaly and seizures are prominent features in the earliest presenting cases, but movement disorders with progressive neurological signs and normal OFC are more likely in late presenting cases. Diagnosis of this autosomal dominant condition is most conveniently made by analysis of the *SLC2A1* gene (MIM *138140).
- 3-Phosphoglycerate dehydrogenase deficiency (MIM #601815) is an autosomal recessive disorder caused by a defect in the synthesis of L-serine. Congenital microcephaly, intractable seizures, and irritability are prominent in the first months of life. White matter volume loss is evident on brain MRI and spastic quadriplegia ensues. Treatment with serine lessens epilepsy severity and irritability but does not seem to improve psychomotor development. Not all cases are severely affected, highlighting the need to obtain plasma amino acids if the diagnosis is considered [76].

Uncertain diagnosis — When there is no metabolic or molecular diagnosis, the empiric recurrence risk for severe microcephaly is high; autosomal recessive inheritance is assumed in many cases.

Autosomal dominant microcephaly is usually milder in all respects and should only be diagnosed if there is a compatible family history (ie, equal frequency in males and females, parent-child transmission, multiple affected generations). One type of autosomal dominant microcephaly is microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR, MIM #152950) due to mutations in KIF11 (kinesin family member 11). The risk of lymphedema is life-long, and the chorioretinitis rarely, if ever, causes visual problems).

X-chromosome linked forms of microcephaly do exist and this inheritance mechanism must be considered in the case of the solitary affected male.

Clinical genetic follow-up is appropriate when there is no final diagnosis and clinical genetic dilemmas persist. As an example, determining the recurrence risk that is most appropriate for young parents whose first child has severe microcephaly (frequently autosomal recessive, 25 percent recurrence risk) and early onset epileptic encephalopathy (frequently due to de novo, autosomal dominant mutations, less than 5 percent recurrence risk). Detailed DNA sequencing studies (eg, whole genome or whole exome sequencing) may help resolve this type of dilemma. (See 'Second or "next generation" sequencing' below.)

GENETIC TESTING

Traditional cytogenetic studies — Cytogenetic studies that have been used to detect chromosome disorders at successively higher resolutions include conventional G-banded chromosome studies and

chromosome breakage studies (for DNA repair disorders), fluorescence in situ hybridization (FISH) studies, supplemented by multiplex ligation-dependent probe amplification (MLPA) studies [77,78]. However, these tests have in total a diagnostic yield of about 10 percent in individuals with neurodevelopmental impairments [77].

Array comparative genomic hybridization — Array comparative genomic hybridization (array CGH) is the cost-efficient, first choice test to seek the large and small genome imbalances that are pathogenic in 10 percent to 20 percent of cases depending on phenotype selection, with the highest diagnostic yield in children with congenital malformation and dysmorphism [79,80].

The microdeletions and microduplications that are beyond the resolution of conventional microscopy but which are detected by array CGH are collectively known as **copy number variants** (CNVs). Some CNVs have well-defined microcephaly phenotypes, whereas others are only tenuously associated or are thought to confer “genetic susceptibility” to a broad range of neurodevelopmental disorders including cognitive impairments, autism, and schizophrenia [81,82]. In families, it often transpires that a CNV, initially thought to be pathogenic, turns out to be inherited from an unaffected parent or a parent who is unaware that he or she is mildly affected by a developmental disorder or learning disability. Thus, inheritance studies often are required for the interpretation of abnormal results and clinical interpretation of array CGH results requires genetics expertise including familiarity with international, collaborative databases of chromosomal variants and their known and potential phenotypes [83]. (See "Microdeletion syndromes (chromosomes 1 to 11)" and "Microdeletion syndromes (chromosomes 12 to 22)" and "Microduplication syndromes".)

Some chromosome microdeletion and microduplication syndromes that are diagnosed through array CGH and can feature microcephaly (typically between 2 and 3 SD below the mean) are listed in the Table (table 3) [84-91].

Molecular genetic testing

First generation sequencing — First generation methodology (ie, Sanger sequencing) has been the method of choice for molecular genetic testing in accredited laboratories that analyze patients’ DNA seeking single gene mutations that cause neurodevelopmental disorders.

Second or "next generation" sequencing — Next generation (“Next Gen”) sequencing also known as massively parallel sequencing permits the examination of many genes simultaneously. The application of this new technology along with huge reductions in cost, presage a new era in molecular genetic testing where it is possible to sequence the entire human genome (whole genome sequencing), just the DNA sequences that are transcribed into RNA and translated into protein (exome sequencing), or subsets of specific disease-relevant protein-coding genes (gene panels). A present day challenge for clinicians who receive next generation sequencing results is to foster an essential working relationship with the scientists and bioinformaticians, who analyze and filter the many DNA sequence variants each individual carries. Despite the technological advances, the clinician’s skills remain essential to the whole process, interpreting family tree data, and undertaking phenotype analysis, all the time having an awareness of pitfalls such as genetic heterogeneity, variable expression of mutant genes, and novel patterns of inheritance. (See "Principles and clinical applications of next-generation DNA sequencing".)

The initial successes of next generation sequencing involved identification of genes for distinctive and exceptionally rare syndromes that there were only ever going to have one or two candidate genes. However, in 2012, independent researchers in Holland, Germany, and the United States demonstrated that “Next Gen,” is powerful enough to be used in common clinical settings to identify mutations in genes that cause severe but nonspecific developmental disorders, such as microcephaly, that have many candidate genes [92,93].

Approach to molecular or DNA testing for microcephaly — Molecular genetic testing may be

indicated in patients with microcephaly in whom the diagnosis remains uncertain after array CGH.

In children and adults with occipito-frontal circumference (OFC) more than 4 SD below the mean for age, sex, and gestational age and classic primary microcephaly (MCPH) phenotype (ie, reduced OFC from birth, relatively normal brain anatomy, relative absence of neurologic signs, and nonprogressive moderate to severe learning difficulties), first generation or Sanger sequencing analysis of MCPH5 (ie, seeking mutations in *ASPM*) may be warranted.

However, if this result is negative, the increasing number of microcephaly genes with overlapping phenotypes makes it difficult to formulate a plan for subsequent testing of single genes. Practical considerations, including cost, tend to limit evaluation to one or two microcephaly genes, usually *ASPM* (for MCPH5) and *WDR62* (for MCPH2). Mutations in *ASPM* are more common. Note that conventional cytogenetic karyotyping may provide a clue to mutation in microcephalin (for MCPH1) with premature chromosome condensation and a high number of prophase-like cells being noted if the cytogenetic laboratory is forewarned to look for these signs [41]. However, this clue will be less frequently encountered with the trend to replace conventional cytogenetic karyotyping with array CGH studies.

For the inexperienced practitioner, pitfalls of choosing the most appropriate one or two microcephaly gene tests abound. For example, MCPH4 (MIM #604321), a rare variety of primary microcephaly identified in families of North African descent, was initially thought to be due to mutation in the *CEP152* gene on chromosome 15q21 [94]. However, a mutation in the cancer susceptibility candidate 5 (*CASC5)* gene (MIM *609173) on chromosome 15q14 was subsequently identified in the original family with MCPH4 [95,96]. Microcephaly caused by mutation in the *CEP152* gene is now designated MCPH9 (MIM #614852), sometimes described as “mild” Seckel syndrome. (See MIM 210600 for a discussion of the genetic heterogeneity in Seckel syndrome.)

Analysis of additional MCPH genes is more cost efficient if it is performed by next generation DNA sequencing of a “microcephaly gene panel.” One such panel that is currently available offers analyses of 15 microcephaly genes. (See 'Primary microcephaly and its syndromes' above and 'Second or "next generation" sequencing' above.)

SUMMARY

- The definition of microcephaly is not standardized. Microcephaly is variably defined as an occipitofrontal circumference (OFC) more than 2 or 3 standard deviations (SD) below the mean for a given age, sex, and gestation. Microcephaly is more likely to be associated with disorders affecting brain development if it is defined as more than 3 SD below the appropriate mean. (See 'Definition' above.)
- The objective of a genetics consultation for a family with a child or relative affected by microcephaly is to formulate a diagnosis, the more precise the better, and estimate the chance of recurrence of the condition in another child. (See 'Initial genetics consultation' above.)
- Chromosome studies are important in all cases, but the method of evaluation is best determined on a case-by-case basis. An array comparative genomic hybridization study (a microarray) is generally the first-line genetic test, particularly when there is less severe microcephaly with dysmorphism. (See 'Laboratory evaluation' above and 'Array comparative genomic hybridization' above.)
- In children and adults with OFC more than 4 SD below the mean for age, sex, and gestational age and classic primary microcephaly (MCPH) phenotype (ie, reduced OFC from birth, relatively normal brain anatomy, relative absence of neurologic signs, and nonprogressive moderate to severe learning difficulties (picture 1)), first generation genetic analysis for MCPH5 (ie, sequencing for mutations in *ASPM)* is warranted. Analyses of additional MCPH genes is most cost efficient if performed by next generation DNA sequencing with a “microcephaly gene panel” (if available).

(See 'Primary microcephaly and its syndromes' above and 'Approach to molecular or DNA testing for microcephaly' above.)

- In children and adults with OFC between 2 and 3 SD below the mean and static neurologic impairments, learning disability, and dysmorphism, primary microcephaly is unlikely. Chromosome testing by array CGH is the first-line test. Subsequent clinical evaluation is led by the dysmorphologist. (See 'Microcephaly with dysmorphism' above and 'Array comparative genomic hybridization' above.)
- The evaluation for children with microcephaly and neurologic abnormalities generally progresses through a series of genetic, radiologic, and biochemical tests, usually led by the neurologist and/or metabolic medicine specialist. (See 'Microcephaly with prominent neurologic abnormalities' above and 'Neuroimaging' above.)
- When there is no molecular diagnosis, the empiric recurrence risk for severe microcephaly is high; autosomal recessive inheritance is assumed in many cases. Clinical genetic follow-up is appropriate when there is no final diagnosis and clinical genetic dilemmas persist. (See 'Uncertain diagnosis' above.)

ACKNOWLEDGMENT — We are saddened by the untimely death of John Tolmie, MB, ChB, FRCP, who passed away in March 2014. UpToDate wishes to acknowledge Dr. Tolmie's many contributions to clinical genetics, and in particular his contributions to previous versions of this topic review.

REFERENCES

1. Nard JA. Abnormal head size and shape. In: Common & Chronic Symptoms in Pediatrics, Gartner JC, Zitelli BJ (Eds), Mosby, St. Louis 1997.
2. Woods CG, Parker A. Investigating microcephaly. Arch Dis Child 2013; 98:707.
3. Lorenz JM, Whitaker AH, Feldman JF, et al. Indices of body and brain size at birth and at the age of 2 years: relations to cognitive outcome at the age of 16 years in low birth weight infants. J Dev Behav Pediatr 2009; 30:535.
4. Räikkönen K, Forsén T, Henriksson M, et al. Growth trajectories and intellectual abilities in young adulthood: The Helsinki Birth Cohort study. Am J Epidemiol 2009; 170:447.
5. Gale CR, O'Callaghan FJ, Bredow M, et al. The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. Pediatrics 2006; 118:1486.
6. Heinonen K, Räikkönen K, Pesonen AK, et al. Prenatal and postnatal growth and cognitive abilities at 56 months of age: a longitudinal study of infants born at term. Pediatrics 2008; 121:e1325.
7. Woods CG, Bond J, Enard W. Autosomal recessive primary microcephaly (MCPH): a review of clinical, molecular, and evolutionary findings. Am J Hum Genet 2005; 76:717.
8. Yang YJ, Baltus AE, Mathew RS, et al. Microcephaly gene links trithorax and REST/NRSF to control neural stem cell proliferation and differentiation. Cell 2012; 151:1097.
9. Mahmood S, Ahmad W, Hassan MJ. Autosomal Recessive Primary Microcephaly (MCPH): clinical manifestations, genetic heterogeneity and mutation continuum. Orphanet J Rare Dis 2011; 6:39.
10. Kelley RI, Robinson D, Puffenberger EG, et al. Amish lethal microcephaly: a new metabolic disorder with severe congenital microcephaly and 2-ketoglutaric aciduria. Am J Med Genet 2002; 112:318.
11. Rajab A, Manzini MC, Mochida GH, et al. A novel form of lethal microcephaly with simplified gyral

pattern and brain stem hypoplasia. Am J Med Genet A 2007; 143A:2761.

12. Spiegel R, Shaag A, Edvardson S, et al. SLC25A19 mutation as a cause of neuropathy and bilateral striatal necrosis. Ann Neurol 2009; 66:419.
13. Baxter PS, Rigby AS, Rotsaert MH, Wright I. Acquired microcephaly: causes, patterns, motor and IQ effects, and associated growth changes. Pediatrics 2009; 124:590.
14. Abuelo D. Microcephaly syndromes. Semin Pediatr Neurol 2007; 14:118.
15. Opitz JM, Holt MC. Microcephaly: general considerations and aids to nosology. J Craniofac Genet Dev Biol 1990; 10:175.
16. Vargas JE, Allred EN, Leviton A, Holmes LB. Congenital microcephaly: phenotypic features in a consecutive sample of newborn infants. J Pediatr 2001; 139:210.
17. Almgren M, Källén B, Lavebratt C. Population-based study of antiepileptic drug exposure in utero--influence on head circumference in newborns. Seizure 2009; 18:672.
18. Hanley WB. Finding the fertile woman with phenylketonuria. Eur J Obstet Gynecol Reprod Biol 2008; 137:131.
19. Prick BW, Hop WC, Duvekot JJ. Maternal phenylketonuria and hyperphenylalaninemia in pregnancy: pregnancy complications and neonatal sequelae in untreated and treated pregnancies. Am J Clin Nutr 2012; 95:374.
20. Rollins JD, Collins JS, Holden KR. United States head circumference growth reference charts: birth to 21 years. J Pediatr 2010; 156:907.
21. Weaver DD, Christian JC. Familial variation of head size and adjustment for parental head circumference. J Pediatr 1980; 96:990.
22. Comeaux MS, Wang J, Wang G, et al. Biochemical, molecular, and clinical diagnoses of patients with cerebral creatine deficiency syndromes. Mol Genet Metab 2013; 109:260.
23. Williams SR, Mullegama SV, Rosenfeld JA, et al. Haploinsufficiency of MBD5 associated with a syndrome involving microcephaly, intellectual disabilities, severe speech impairment, and seizures. Eur J Hum Genet 2010; 18:436.
24. Jacob FD, Ramaswamy V, Andersen J, Bolduc FV. Atypical Rett syndrome with selective FOXG1 deletion detected by comparative genomic hybridization: case report and review of literature. Eur J Hum Genet 2009; 17:1577.
25. Bahi-Buisson N, Nectoux J, Girard B, et al. Revisiting the phenotype associated with FOXG1 mutations: two novel cases of congenital Rett variant. Neurogenetics 2010; 11:241.
26. Gilfillan GD, Selmer KK, Roxrud I, et al. SLC9A6 mutations cause X-linked mental retardation, microcephaly, epilepsy, and ataxia, a phenotype mimicking Angelman syndrome. Am J Hum Genet 2008; 82:1003.
27. Zweier C, Peippo MM, Hoyer J, et al. Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). Am J Hum Genet 2007; 80:994.
28. Gitiaux C, Ceballos-Picot I, Marie S, et al. Misleading behavioural phenotype with adenylosuccinate lyase deficiency. Eur J Hum Genet 2009; 17:133.
29. Willemsen MH, Rensen JH, van Schrojenstein-Lantman de Valk HM, et al. Adult Phenotypes in Angelman- and Rett-Like Syndromes. Mol Syndromol 2012; 2:217.
30. McDonell LM, Mirzaa GM, Alcantara D, et al. Mutations in STAMBP, encoding a deubiquitinating enzyme, cause microcephaly-capillary malformation syndrome. Nat Genet 2013; 45:556.
31. Reardon W, Donnai D. Dysmorphology demystified. Arch Dis Child Fetal Neonatal Ed 2007; 92:F225.
32. Shen J, Eyaid W, Mochida GH, et al. ASPM mutations identified in patients with primary

microcephaly and seizures. J Med Genet 2005; 42:725.

33. Desir J, Cassart M, David P, et al. Primary microcephaly with ASPM mutation shows simplified cortical gyration with antero-posterior gradient pre- and post-natally. Am J Med Genet A 2008; 146A:1439.
34. Passemard S, Titomanlio L, Elmaleh M, et al. Expanding the clinical and neuroradiologic phenotype of primary microcephaly due to ASPM mutations. Neurology 2009; 73:962.
35. Nicholas AK, Swanson EA, Cox JJ, et al. The molecular landscape of ASPM mutations in primary microcephaly. J Med Genet 2009; 46:249.
36. Awad S, Al-Dosari MS, Al-Yacoub N, et al. Mutation in PHC1 implicates chromatin remodeling in primary microcephaly pathogenesis. Hum Mol Genet 2013; 22:2200.
37. Bundey S, Carter CO. Recurrence risks in severe undiagnosed mental deficiency. J Ment Defic Res 1974; 18:115.
38. Tolmie JL, McNay M, Stephenson JB, et al. Microcephaly: genetic counselling and antenatal diagnosis after the birth of an affected child. Am J Med Genet 1987; 27:583.
39. Nicholas AK, Khurshid M, Désir J, et al. WDR62 is associated with the spindle pole and is mutated in human microcephaly. Nat Genet 2010; 42:1010.
40. Poulton C, Oegema R, Heijsman D, et al. Progressive cerebellar atrophy and polyneuropathy: expanding the spectrum of PNKP mutations. Neurogenetics 2013; 14:43.
41. O'Driscoll M, Jackson AP, Jeggo PA. Microcephalin: a causal link between impaired damage response signalling and microcephaly. Cell Cycle 2006; 5:2339.
42. Klingseisen A, Jackson AP. Mechanisms and pathways of growth failure in primordial dwarfism. Genes Dev 2011; 25:2011.
43. Ogi T, Walker S, Stiff T, et al. Identification of the first ATRIP-deficient patient and novel mutations in ATR define a clinical spectrum for ATR-ATRIP Seckel Syndrome. PLoS Genet 2012; 8:e1002945.
44. Kalay E, Yigit G, Aslan Y, et al. CEP152 is a genome maintenance protein disrupted in Seckel syndrome. Nat Genet 2011; 43:23.
45. Stiff T, Alagoz M, Alcantara D, et al. Deficiency in origin licensing proteins impairs cilia formation: implications for the aetiology of Meier-Gorlin syndrome. PLoS Genet 2013; 9:e1003360.
46. Perry LD, Robertson F, Ganesan V. Screening for cerebrovascular disease in microcephalic osteodysplastic primordial dwarfism type II (MOPD II): an evidence-based proposal. Pediatr Neurol 2013; 48:294.
47. Daber RD, Conlin LK, Leonard LD, et al. Ring chromosome 20. Eur J Med Genet 2012; 55:381.
48. Guerrini R, Parrini E. Neuronal migration disorders. Neurobiol Dis 2010; 38:154.
49. Barkovich AJ, Millen KJ, Dobyns WB. A developmental and genetic classification for midbrain-hindbrain malformations. Brain 2009; 132:3199.
50. Namavar Y, Barth PG, Poll-The BT, Baas F. Classification, diagnosis and potential mechanisms in pontocerebellar hypoplasia. Orphanet J Rare Dis 2011; 6:50.
51. Namavar Y, Barth PG, Kasher PR, et al. Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia. Brain 2011; 134:143.
52. Najm J, Horn D, Wimplinger I, et al. Mutations of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum. Nat Genet 2008; 40:1065.
53. Hackett A, Tarpey PS, Licata A, et al. CASK mutations are frequent in males and cause X-linked nystagmus and variable XLMR phenotypes. Eur J Hum Genet 2010; 18:544.

54. Moog U, Kutsche K, Kortüm F, et al. Phenotypic spectrum associated with CASK loss-of-function mutations. J Med Genet 2011; 48:741.
55. Takanashi J, Okamoto N, Yamamoto Y, et al. Clinical and radiological features of Japanese patients with a severe phenotype due to CASK mutations. Am J Med Genet A 2012; 158A:3112.
56. Tanyalçin I, Verhelst H, Halley DJ, et al. Elaborating the phenotypic spectrum associated with mutations in ARFGEF2: case study and literature review. Eur J Paediatr Neurol 2013; 17:666.
57. Mir A, Kaufman L, Noor A, et al. Identification of mutations in TRAPPC9, which encodes the NIK- and IKK-beta-binding protein, in nonsyndromic autosomal-recessive mental retardation. Am J Hum Genet 2009; 85:909.
58. Philippe O, Rio M, Carioux A, et al. Combination of linkage mapping and microarray-expression analysis identifies NF-kappaB signaling defect as a cause of autosomal-recessive mental retardation. Am J Hum Genet 2009; 85:903.
59. Mochida GH, Mahajnah M, Hill AD, et al. A truncating mutation of TRAPPC9 is associated with autosomal-recessive intellectual disability and postnatal microcephaly. Am J Hum Genet 2009; 85:897.
60. Stephenson JB. Aicardi-Goutières syndrome (AGS). Eur J Paediatr Neurol 2008; 12:355.
61. Briggs TA, Wolf NI, D'Arrigo S, et al. Band-like intracranial calcification with simplified gyration and polymicrogyria: a distinct "pseudo-TORCH" phenotype. Am J Med Genet A 2008; 146A:3173.
62. Hobson EE, Thomas S, Crofton PM, et al. Isolated sulphite oxidase deficiency mimics the features of hypoxic ischaemic encephalopathy. Eur J Pediatr 2005; 164:655.
63. Hoffmann C, Ben-Zeev B, Anikster Y, et al. Magnetic resonance imaging and magnetic resonance spectroscopy in isolated sulfite oxidase deficiency. J Child Neurol 2007; 22:1214.
64. van Straaten HL, van Tintelen JP, Trijbels JM, et al. Neonatal lactic acidosis, complex I/IV deficiency, and fetal cerebral disruption. Neuropediatrics 2005; 36:193.
65. Samson JF, Barth PG, de Vries JI, et al. Familial mitochondrial encephalopathy with fetal ultrasonographic ventriculomegaly and intracerebral calcifications. Eur J Pediatr 1994; 153:510.
66. Longman C, Tolmie J, McWilliam R, MacLennan A. Cranial magnetic resonance imaging mistakenly suggests prenatal ischaemia in PEHO-like syndrome. Clin Dysmorphol 2003; 12:133.
67. Schram A, Kroes HY, Sollie K, et al. Hereditary fetal brain degeneration resembling fetal brain disruption sequence in two sibships. Am J Med Genet A 2004; 127A:172.
68. Henneke M, Diekmann S, Ohlenbusch A, et al. RNASET2-deficient cystic leukoencephalopathy resembles congenital cytomegalovirus brain infection. Nat Genet 2009; 41:773.
69. Bönnemann CG, Meinecke P. Bilateral porencephaly, cerebellar hypoplasia, and internal malformations: two siblings representing a probably new autosomal recessive entity. Am J Med Genet 1996; 63:428.
70. Behunova J, Zavadilikova E, Bozoglu TM, et al. Familial microhydranencephaly, a family that does not map to 16p13.13-p12.2: relationship with hereditary fetal brain degeneration and fetal brain disruption sequence. Clin Dysmorphol 2010; 19:107.
71. van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. Mol Genet Metab 2012; 105:368.
72. van Karnebeek CD, Houben RF, Lafek M, et al. The treatable intellectual disability APP www.treatable-id.org: a digital tool to enhance diagnosis & care for rare diseases. Orphanet J Rare Dis 2012; 7:47.
73. Jurecka A, Jurkiewicz E, Tylki-Szymanska A. Magnetic resonance imaging of the brain in adenylosuccinate lyase deficiency: a report of seven cases and a review of the literature. Eur J Pediatr 2012; 171:131.

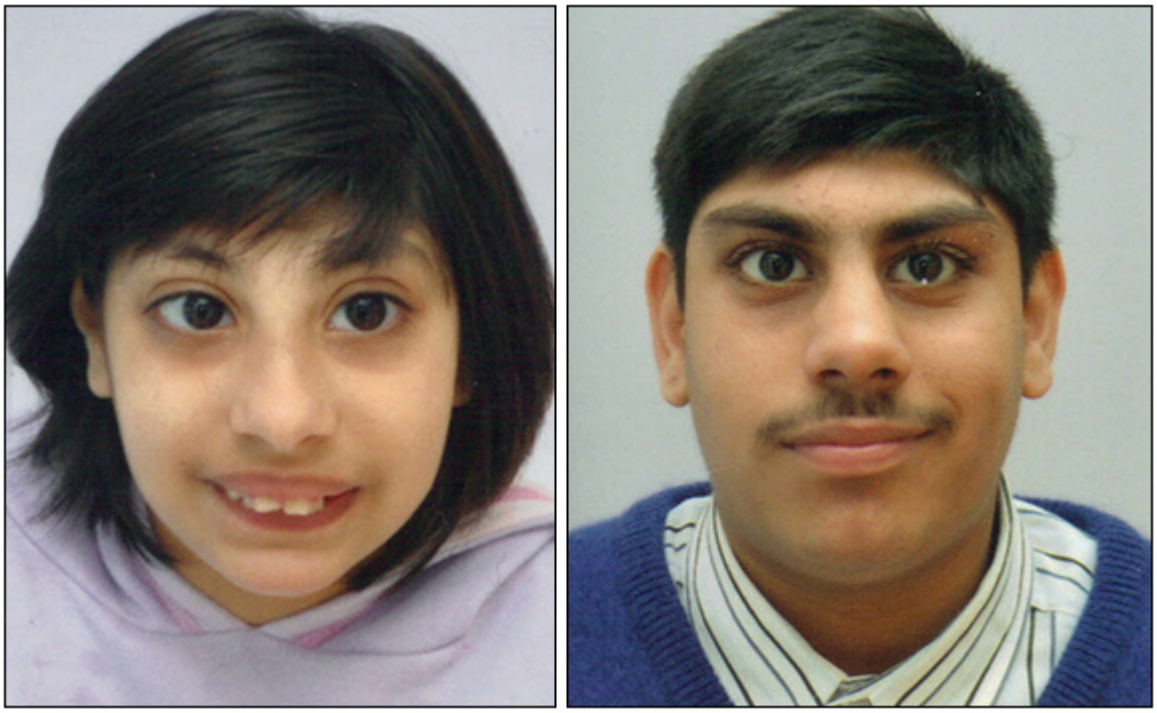
74. Verrotti A, D'Egidio C, Agostinelli S, Gobbi G. Glut1 deficiency: when to suspect and how to diagnose? Eur J Paediatr Neurol 2012; 16:3.
75. Brockmann K. The expanding phenotype of GLUT1-deficiency syndrome. Brain Dev 2009; 31:545.
76. Tabatabaie L, Klomp LW, Rubio-Gozalbo ME, et al. Expanding the clinical spectrum of 3-phosphoglycerate dehydrogenase deficiency. J Inherit Metab Dis 2011; 34:181.
77. Stegmann AP, Jonker LM, Engelen JJ. Prospective screening of patients with unexplained mental retardation using subtelomeric MLPA strongly increases the detection rate of cryptic unbalanced chromosomal rearrangements. Eur J Med Genet 2008; 51:93.
78. Lu XY, Phung MT, Shaw CA, et al. Genomic imbalances in neonates with birth defects: high detection rates by using chromosomal microarray analysis. Pediatrics 2008; 122:1310.
79. Sagoo GS, Butterworth AS, Sanderson S, et al. Array CGH in patients with learning disability (mental retardation) and congenital anomalies: updated systematic review and meta-analysis of 19 studies and 13,926 subjects. Genet Med 2009; 11:139.
80. Shoukier M, Klein N, Auber B, et al. Array CGH in patients with developmental delay or intellectual disability: are there phenotypic clues to pathogenic copy number variants? Clin Genet 2013; 83:53.
81. Stankiewicz P, Lupski JR. Structural variation in the human genome and its role in disease. Annu Rev Med 2010; 61:437.
82. Dumas L, Sikela JM. DUF1220 domains, cognitive disease, and human brain evolution. Cold Spring Harb Symp Quant Biol 2009; 74:375.
83. Firth HV, Richards SM, Bevan AP, et al. DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. Am J Hum Genet 2009; 84:524.
84. Mefford HC, Sharp AJ, Baker C, et al. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. N Engl J Med 2008; 359:1685.
85. Brunetti-Pierri N, Berg JS, Scaglia F, et al. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet 2008; 40:1466.
86. van Bon BW, Koolen DA, Brueton L, et al. The 2q23.1 microdeletion syndrome: clinical and behavioural phenotype. Eur J Hum Genet 2010; 18:163.
87. Franco LM, de Ravel T, Graham BH, et al. A syndrome of short stature, microcephaly and speech delay is associated with duplications reciprocal to the common Sotos syndrome deletion. Eur J Hum Genet 2010; 18:258.
88. Kleefstra T, van Zelst-Stams WA, Nillesen WM, et al. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. J Med Genet 2009; 46:598.
89. Nagamani SC, Erez A, Eng C, et al. Interstitial deletion of 6q25.2-q25.3: a novel microdeletion syndrome associated with microcephaly, developmental delay, dysmorphic features and hearing loss. Eur J Hum Genet 2009; 17:573.
90. Shinawi M, Liu P, Kang SH, et al. Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. J Med Genet 2010; 47:332.
91. Wilson HL, Crolla JA, Walker D, et al. Interstitial 22q13 deletions: genes other than SHANK3 have major effects on cognitive and language development. Eur J Hum Genet 2008; 16:1301.
92. Dixon-Salazar TJ, Silhavy JL, Udpa N, et al. Exome sequencing can improve diagnosis and alter patient management. Sci Transl Med 2012; 4:138ra78.
93. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 2013; 369:1502.

94. Guernsey DL, Jiang H, Hussin J, et al. Mutations in centrosomal protein CEP152 in primary microcephaly families linked to MCPH4. Am J Hum Genet 2010; 87:40.
95. Genin A, Desir J, Lambert N, et al. Kinetochore KMN network gene CASC5 mutated in primary microcephaly. Hum Mol Genet 2012; 21:5306.
96. Jamieson CR, Govaerts C, Abramowicz MJ. Primary autosomal recessive microcephaly: homozygosity mapping of MCPH4 to chromosome 15. Am J Hum Genet 1999; 65:1465.

Topic 14392 Version 10.0

GRAPHICS

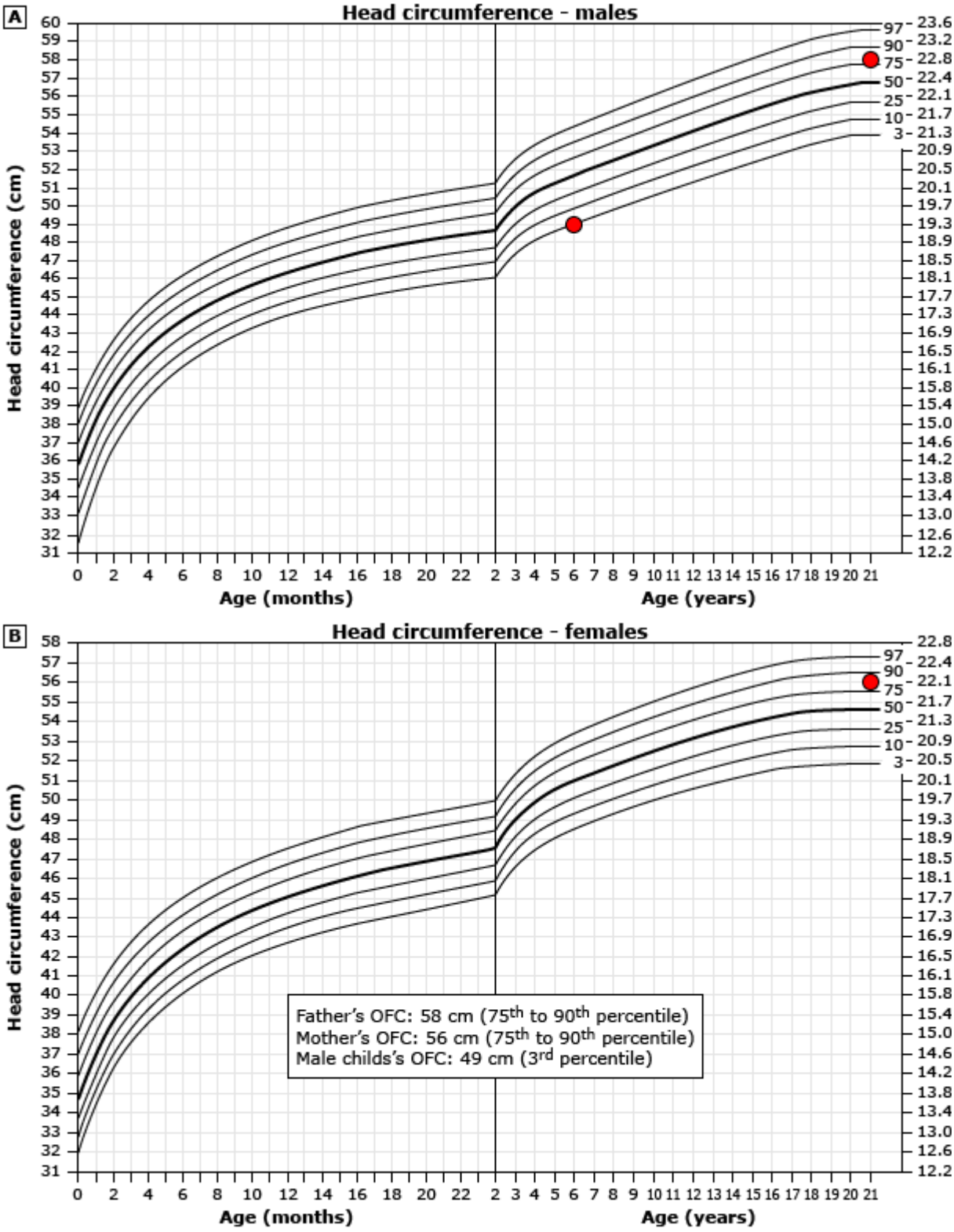
Primary microcephaly



Siblings with autosomal recessive primary microphaly, MCPH5, due to *ASPM* mutations.

Graphic 89983 Version 1.0

Comparing child and parent head circumference



It is helpful to simultaneously plot the child's and parents' occipitofrontal circumference (OFC) measurements to compare the percentile or standard deviation. For most normal children, the c OFC percentile is between that of the parents. In the example above, the child's OFC is certainly small relative to that of his parents.

Original figure modified for this publication. Rollins JD, Collins JS, Holden KR. United States head circumference growth reference charts: birth to 21 years. J Pediatr 2010; 156:907. Illustration used w the permission of Elsevier Inc. All rights reserved.

Graphic 57067 Version 1.0

Expanding spectrum of Rett syndrome-like and Angelman syndrome-like conditions

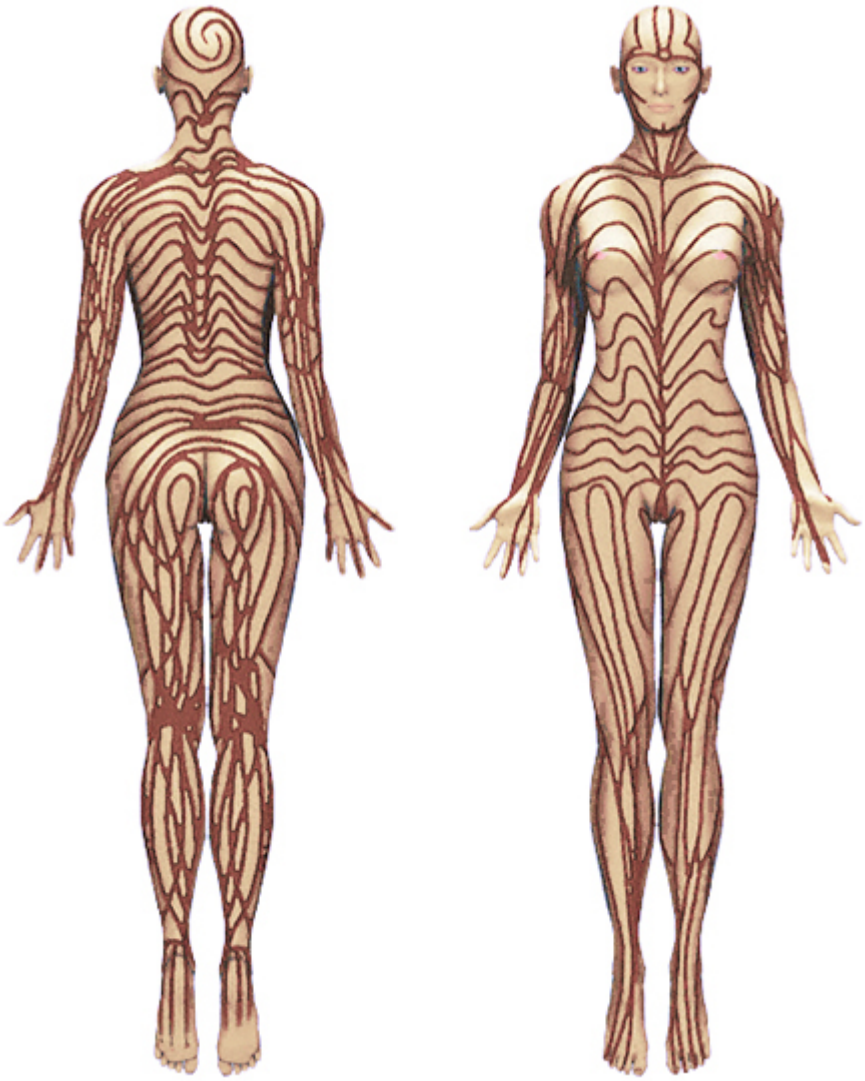
"Atypical" Rett or Angelman syndrome mimics	Features
MBD5/2q31.1 microdeletion	Minimal speech, seizures, microcephaly, behavioral disorders, short stature, coarse facies
FOXG1/chromosome 14 microdeletion	Congenital microcephaly, epilepsy, Rett-like phenotype, synophrys, dyskinesia
SLC9A6 (Christianson syndrome)	Epilepsy, ataxia, acquired microcephaly, lack of speech, slender body habitus
TCF4 Pitt-Hopkins syndrome/18q21.1 microdeletion	Wide mouth, fleshy lips, intermittent overbreathing
Atypical adenylosuccinate lyase deficiency	Hyperactivity, severe speech deficits, seizures, happy disposition, stereotypies

References:

1. *Williams SR, Mullegama SV, Rosenfeld JA, et al. Haploinsufficiency of MBD5 associated with a syndrome involving microcephaly, intellectual disabilities, severe speech impairment, and seizures. Eur J Hum Genet 2010; 18:436.*
2. *Jacob FD, Ramaswamy V, Andersen J, Bolduc FV. Atypical Rett syndrome with selective FOXG1 deletion detected by comparative genomic hybridization: case report and review of literature. Eur J Hum Genet 2009; 17:1577.*
3. *Bahi-Buisson N, Nectoux J, Girard B, et al. Revisiting the phenotype associated with FOXG1 mutations: two novel cases of congenital Rett variant. Neurogenetics 2010; 11:241.*
4. *Gilfillan GD, Selmer KK, Roxrud I, et al. SLC9A6 mutations cause X-linked mental retardation, microcephaly, epilepsy, and ataxia, a phenotype mimicking Angelman syndrome. Am J Hum Genet 2008; 82:1003.*
5. *Zweier C, Peippo MM, Hoyer J, et al. Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). Am J Hum Genet 2007; 80:994.*
6. *Gitiaux C, Ceballos-Picot I, Marie S, et al. Misleading behavioural phenotype with adenylosuccinate lyase deficiency. Eur J Hum Genet 2009; 17:133.*

Graphic 64060 Version 8.0

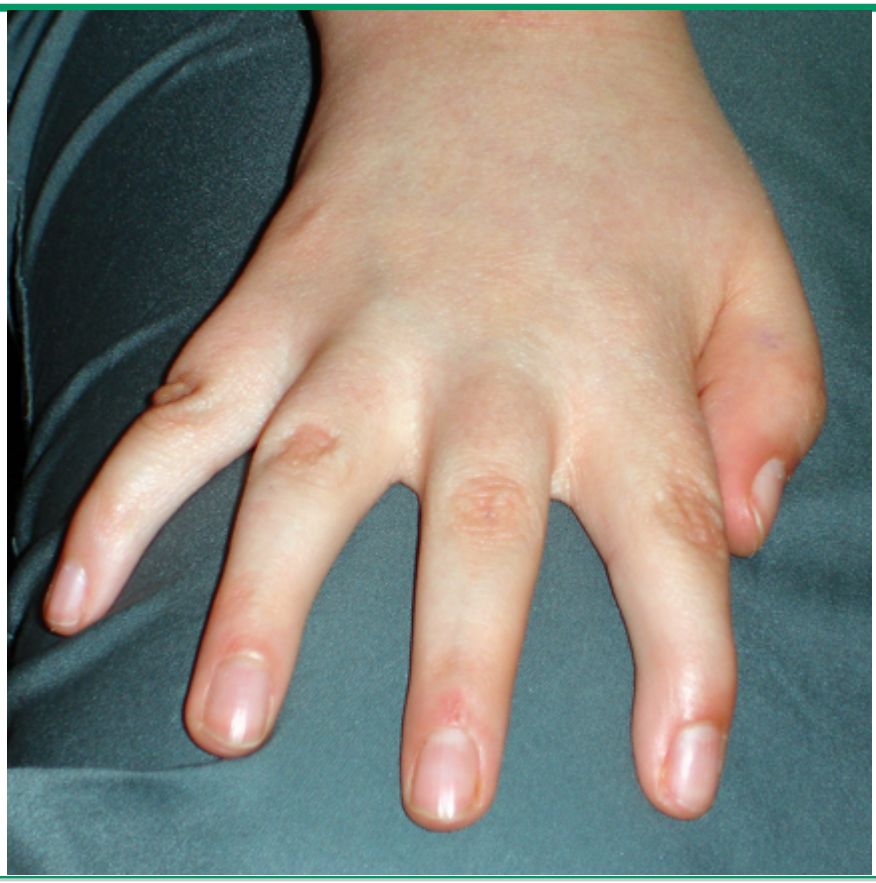
Lines of Blaschko



The pattern assumed by many different naevoid and acquired skin diseases on the human skin and mucosae. The cause of the pattern of Blaschko lines is unknown; they do not follow nerves, vessels, or lymphatics. The lines described by these conditions not only did not correspond to any known anatomical basis, but were remarkably consistent both from patient to patient and even from one disease to another. The lines may represent a clinical expression of a genetically programmed clone of altered cells, perhaps first expressed during embryogenesis.

Graphic 57219 Version 2.0

Diploid-triploid mosaicism

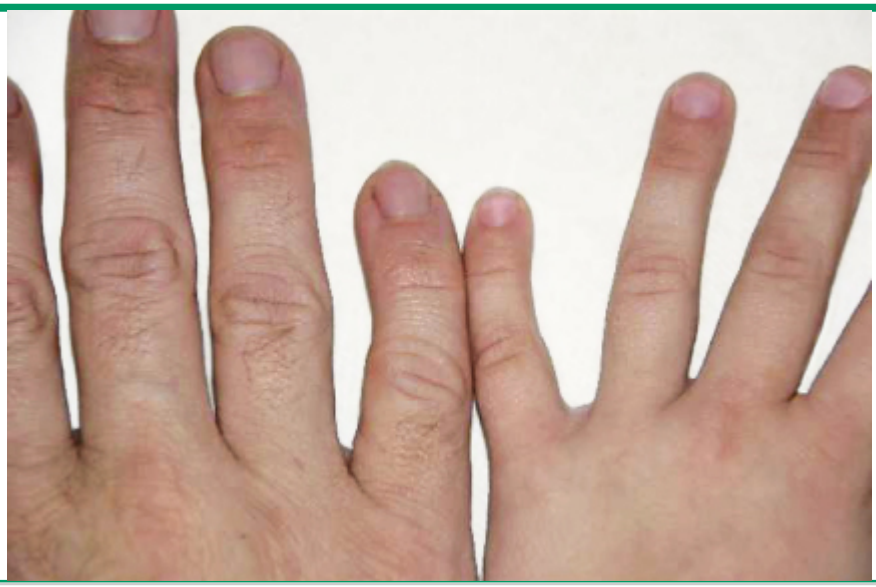


Diploid-triploid mosaicism. Note the skin syndactylies.

Courtesy of John Tolmie, MD.

Graphic 66227 Version 1.0

Clinodactyly

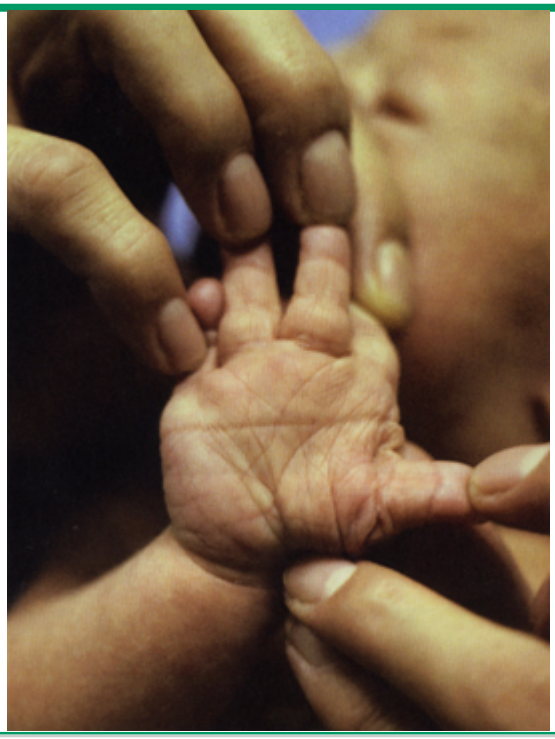


Inherited clinodactyly in a father (left) and son (right).

Reproduced with permission from: Julie Boom, MD and Lippincott Williams & Wilkins.

Graphic 54831 Version 2.0

Transverse palmar crease



Reproduced with permission from: Clark DA. Atlas of Neonatology, WB Saunders, Philadelphia 2000. Copyright © 2000 Elsevier.

Graphic 79414 Version 2.0

Genetic conditions associated with microcephaly and neuroradiologic abnormalities mimicking vascular damage or prenatal infection

Genetic condition	Phenocopy*
Aicardi-Goutierès syndrome (also known as pseudo-TORCH and allelic with Cree encephalitis [at least 5 genes, common])	Congenital infection with thrombocytopenia, increased production of alpha-interferon, ulcerative skin lesions
Pseudo-TORCH syndrome type b	Distinct pattern of band-like intracranial calcification, simplified gyration and polymicrogyria; severe postnatal microcephaly, seizures, developmental arrest
Sulfite oxidase deficiency	Neonatal encephalopathy; neuroradiology and pathology can mimic perinatal asphyxia
Mitochondrial/respiratory chain abnormality	Disrupted brain development with congenital infection-like calcifications, and a complex neuronal migration disorder
PEHO-like syndrome	Encephalopathy with hypoxic ischemic changes on MRI
Fetal brain disruption sequence	Traumatic brain destruction
Cystic leukoencephalopathy	Congenital CMV clinically and neuroradiologically
Bilateral porencephaly; cerebellar or vermis hypoplasia or aplasia; congenital heart defect	Bilateral porencephaly ("basket brain") may resemble middle cerebral artery infarct
16p13.11 unmasking NDE1 recessive mutation	Fetal brain disruption - severe microcephaly, callosal agenesis, cortical dysplasia, cysts

TORCH: toxoplasmosis, other (syphilis, varicella, etc), rubella, cytomegalovirus, herpes simplex virus; PEHO: progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy; MRI: magnetic resonance imaging; CMV: cytomegalovirus.
* Phenocopy: a nongenetic condition with an appearance that is similar to that caused by a specific genotype.

References:

1. *Stephenson JB. Aicardi-Goutierès syndrome (AGS). Eur J Paediatr Neurol 2008; 12:355.*
2. *Briggs TA, Wolf NI, D'Arrigo S, et al. Band-like intracranial calcification with simplified gyration and polymicrogyria: a distinct "pseudo-TORCH" phenotype. Am J Med Genet A 2008; 146A:3173.*
3. *Hobson EE, Thomas S, Crofton PM, et al. Isolated sulphite oxidase deficiency mimics the features of hypoxic ischaemic encephalopathy. Eur J Pediatr 2005; 164:655.*
4. *Hoffmann C, Ben-Zeev B, Anikster Y, et al. Magnetic resonance imaging and magnetic resonance spectroscopy in isolated sulfite oxidase deficiency. J Child Neurol 2007; 22:1214.*
5. *van Straaten HL, van Tintelen JP, Trijbels JM, et al. Neonatal lactic acidosis, complex I/IV deficiency, and fetal cerebral disruption. Neuropediatrics 2005; 36:193.*

6. *Samson JF, Barth PG, de Vries JI, et al. Familial mitochondrial encephalopathy with fetal ultrasonographic ventriculomegaly and intracerebral calcifications. Eur J Pediatr 1994; 153:510.*
7. *Longman C, Tolmie J, McWilliam R, MacLennan A. Cranial magnetic resonance imaging mistakenly suggests prenatal ischaemia in PEHO-like syndrome. Clin Dysmorphol 2003; 12:133.*
8. *Schram A, Kroes HY, Sollie K, et al. Hereditary fetal brain degeneration resembling fetal brain disruption sequence in two sibships. Am J Med Genet A 2004; 127A:172.*
9. *Behunova J, Zavadilikova E, Bozoglu TM, et al. Familial microhydranencephaly, a family that does not map to 16p13.13-p12.2:: relationship with hereditary fetal brain degeneration and fetal brain disruption sequence. Clin Dysmorphol 2010; 19:107.*
10. *Henneke M, Diekmann S, Ohlenbusch A, et al. RNASET2-deficient cystic leukoencephalopathy resembles congenital cytomegalovirus brain infection. Nat Genet 2009; 41:773.*
11. *Bonnemann CG, Meinecke P. Bilateral porencephaly, cerebellar hypoplasia, and internal malformations: two siblings representing a probably new autosomal recessive entity. Am J Med Genet 1996; 63:428.*
12. *Paciorkowksi AR, Keppler-Noreuil K, Robinson L, et al. Deletion 16p13.11 uncovers NDE1 mutations on the non-deleted homolog and extends the spectrum of severe microcephaly to include fetal brain disruption. Am J Med Genet A 2013; 161A:1523.*

Graphic 75778 Version 5.0

Selected microdeletion and microduplication syndromes that can feature microcephaly*

Chromosomal location	Features
1q21.1 deletion	Moderate/mild learning difficulties, heart defects, cataract (1q21.1 duplications associated with macrocephaly)
1q44 subtelomeric deletion	Callosal agenesis, severe microcephaly, epilepsy
2q31.1 deletion	Neurological and behavioral characteristics of MBD5 haploinsufficiency plus craniofacial dysmorphism, microcephaly, small hands and feet, hyperphagia
5q35 microduplication (reciprocal to the Sotos syndrome/NSD1 common deletion)	Short stature, delayed bone age, speech delay, and mild or no dysmorphism (opposite of Sotos syndrome?)
6q25 deletion	Callosal agenesis, facial dysmorphisms, hearing loss
9q34 deletion	Mental retardation, minor facial dysmorphisms, epilepsy; EHMT1 haploinsufficiency implicated
16p11.2 deletion and duplication	Autism and macrocephaly with deletion 16p11.2; attention deficit hyperactivity and microcephaly with duplication 16p11.2; epilepsy
17q23.1q23.2 microdeletion	Speech delay, microcephaly, growth retardation, dysmorphisms (heart, hands, limbs), abnormalities
22q13.3 deletion	Severe mental retardation and speech deficits, minimal dysmorphism (SHANK3 and other genes implicated)

* Note that the clinical findings other than microcephaly often are unremarkable, so array comparative genomic hybridization (CGH) is usually required for diagnosis. Additional information on emerging genomic disorders is available at: https://decipher.sanger.ac.uk/application/syndrome.

References:

1. *Mefford HC, Sharp AJ, Baker C, et al. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. N Engl J Med 2008; 359:1685.*
2. *Brunetti-Pierri N, Berg JS, Scaglia F, et al. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet 2008; 40:1466.*
3. *Shimojima K, Okamoto N, Suzuki Y, et al. Subtelomeric deletions of 1q43q44 and severe brain impairment associated with delayed myelination. J Hum Genet 2012; 57:593.*
4. *Talkowski ME, Mullegama SV, Rosenfeld JA, et al. Assessment of 2q23.1 microdeletion syndrome implactes MBD5 as a single causal locus of intellectual disability, epilepsy, and autism spectrum disorder. Am J Hum Genet 2011; 89:551.*
5. *Franco LM, de Ravel T, Graham BH, et al. A syndrome of short stature, microcephaly and speech delay is associated with duplications reciprocal to the common Sotos syndrome deletion. Eur J Hum Genet 2010; 18:258.*
6. *Kleefstra T, van Zelst-Stams WA, Nillesen WM, et al. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. J Med Genet 2009; 46:598.*

7. *Nagamani SC, Erez A, Eng C, et al. Interstitial deletion of 6q25.2-q25.3: a novel microdeletion syndrome associated with microcephaly, developmental delay, dysmorphic features and hearing loss. Eur J Hum Genet 2009; 17:573.*
8. *Shinawi M, Liu P, Kang SH, et al. Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioral problems, dysmorphism, epilepsy, and abnormal head size. J Med Genet 2010; 47:332.*
9. *Ballif BC, Theisen A, Rosenfeld JA, et al. Identification of a recurrent microdeletion at 17q23.1q23.2 flanked by segmental duplications associated with heart defects and limb abnormalities. Am J Hum Genet 2010; 86:454.*
10. *Wilson HL, Crolla JA, Walker D, et al. Interstitial 22q13 deletions: genes other than SHANK3 have major effects on cognitive and language development. Eur J Hum Genet 2008; 16:1301.*

Graphic 56397 Version 6.0

Disclosures

Disclosures: **Geoff Woods, ChB, MB, MD, FRCP, FMedSci** Nothing to disclose. **Helen V Firth, DM, FRCP, DCH** Nothing to disclose. **Mary M Torchia, MD** Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy