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Down syndrome: Prenatal screening overview

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INTRODUCTION — Down syndrome is the most common chromosome abnormality among live births and the most frequent form of intellectual disability caused by a demonstrable chromosomal abnormality. The syndrome is characterized by moderate to severe learning disability (average IQ approximately 40) in combination with short stature, characteristic facial features, heart defects (40 to 50 percent of cases), intestinal malformations (10 percent of cases), problems with vision and hearing (50 percent of cases), an increased frequency of infection, and other health problems [1]. (See "Down syndrome: Clinical features and diagnosis".)

RATIONALE FOR SCREENING — Protocols for prenatal screening for Down syndrome have been implemented for several reasons:

- The prevalence of live Down syndrome births is predicted to be 1 in 634 births in the absence of selective termination of affected pregnancies [2]. The prevalence of Down syndrome is relatively high but depends on the maternal age range of the population. The prevalence in the population increases as the proportion of pregnancies in older women increases.

  The prevalence of Down syndrome is highest early in pregnancy and declines naturally across the rest of gestation [3]. About 40 percent of affected pregnancies will be lost spontaneously between the time of chorionic villus sampling (CVS) and birth [1,3-5]. In addition, many pregnancies with Down syndrome fetuses identified prenatally are electively terminated [3,6-8].

- There can be significant burden of disease for the affected individual and his/her family. Some individuals are profoundly impacted while others are healthy and able to live independently as adults.

- Diagnostic tests that detect the chromosomal abnormality are readily available.

- For couples who choose to prevent birth of an affected infant, safe and effective options are available.

- For families who want the opportunity to plan for the birth of an affected child, various Down syndrome associations offer support for families and individuals with Down syndrome and promote their participation in society.

The usefulness of detection of Down syndrome depends upon personal preferences and the options available to parents. There is evidence to support offering prenatal diagnosis to pregnant women at increased risk of having an affected child when a comprehensive prenatal diagnosis program is available that includes education, accurate interpretation of test results, and follow-up to discuss options [9].

All of the consequences of screening should be considered [9]. There is little high-quality information on personal and family outcomes after screening. Adverse psychological effects of screening tests include the fear of discovering an affected fetus and concern for the possible complications from diagnostic and therapeutic interventions, particularly procedure-related loss of a normal fetus. Most parents are anxious when they receive a positive screening test result, perhaps because they do not fully understand that

most positive results are associated with a normal pregnancy outcome. Although anxiety is reduced when a diagnostic procedure shows an unaffected pregnancy [10], women who experience a false-positive screening result are less likely to choose screening in a subsequent pregnancy [11].

BASIC APPROACH TO COUNSELING — Basic information on prenatal diagnosis can be given to patients individually, in a group session, or with decision aids. A randomized trial found that all three approaches were useful [12]. Couples were most satisfied with individual counseling, but those in group sessions showed a significantly greater increase in knowledge from pre- to post-intervention questionnaires than those exposed to the other approaches. However, the key principle is to provide patients with clear, detailed information that allows them to make informed, preference-based screening and diagnostic testing decisions [13].

A nondirective approach should be used when providing information about Down syndrome, and it should be clear that testing is voluntary. Nondirective information enables the parents to balance the risks, limitations, and benefits of prenatal screening and diagnostic testing with the issues involved in raising a child with Down syndrome or pregnancy termination.

The provision of written information is desirable to ensure that parents have a clear understanding of the tests and their accuracy. Consultation with a genetic counselor or a medical geneticist can be helpful to address the parents' concerns and facilitate their decision-making process, particularly after a diagnosis of Down syndrome. (See "Down syndrome: Management".)

Patients considering Down syndrome screening should be given the following information [14]. Women weigh this information differently and come to individual decisions regarding whether to undergo prenatal testing for chromosomal abnormalities and which test to undergo.

- An explanation of the difference between a screening test and a diagnostic test
- Screening sensitivity and specificity compared with diagnostic testing
- Description of the performance of various screening tests
- The option of diagnostic testing instead of screening
- The risks associated with prenatal diagnosis
- The psychological implications of prenatal screening and diagnosis
- The implications of having a child with Down syndrome (see "Down syndrome: Clinical features and diagnosis" and "Down syndrome: Management")
- The detection rate of chromosomal abnormalities other than Down syndrome, and the implications of having a child with one of these abnormalities
- Information about the length of time necessary to obtain results from screening and diagnostic testing
- Information about pregnancy termination (see "Surgical termination of pregnancy: First trimester" and "Second trimester pregnancy termination: Overview and surgical termination")

CANDIDATES FOR PRENATAL SCREENING AND DIAGNOSIS — Maternal age alone was the initial risk factor used for screening pregnancies for Down syndrome. The risk of giving birth to a baby with Down syndrome as a function of maternal age is nonlinear and ranges from approximately 1 in 1500 in young women to 1 in 10 in a 48-year-old (figure 1 and table 1). The risk is almost constant at ages 15 to 25, rises slowly between ages 25 to 35, and then increases approximately fourfold from ages 35 to 40 and 10-fold from ages 40 to 45; some data show that the risk of Down syndrome does not increase further beyond age 45 [2,15].

In 2002, almost 14 percent of pregnant women in the United States were age 35 or older, and these women accounted for 51 percent of Down syndrome pregnancies [16]. The oldest 5 percent of pregnant women (those over age 38 to 39) accounted for 30 percent of Down syndrome pregnancies. The effect of paternal age on Down syndrome risk is uncertain. (See "Effect of advanced paternal age on fertility and pregnancy".)

The use of Down syndrome risk at age 35 as a "threshold" for offering invasive testing was reached by consensus and chosen because this risk was believed to be about the same as the risk of procedure-related pregnancy loss from the invasive testing required for determining karyotype [17]. In addition, at this level of risk, the costs of diagnostic testing would be reasonably offset by savings accrued if the birth of an affected child was prevented [18,19].

However, these assumptions have been challenged [20-22]. Procedure-related risk is only one of many factors that need to be considered and may be lower than previously thought. The value that individual patients place on various outcomes, such as birth of a child with Down syndrome and loss of a normal pregnancy, needs to be incorporated into any risk-benefit equation. Many women are willing to assume a relatively high risk of a procedure-related loss of a normal fetus in order to have the ability to terminate an affected pregnancy. On the other hand, some older women, such as those who may have had difficulty conceiving or carrying a pregnancy, may choose a screening test over a diagnostic test to reduce the likelihood of an invasive test and consequent risk of fetal loss or injury [9].

Based on the arguments discussed above, in 2007, the American College of Obstetricians and Gynecologists (ACOG) recommended that (1) all women be offered aneuploidy screening before 20 weeks of gestation and that (2) all women should have the option of invasive testing, regardless of maternal age [14,23].

ACOG also stated that a prenatal diagnostic procedure for fetal karyotype, rather than serum screening, should be considered in women of any age at high risk of Down syndrome or other fetal aneuploidies. Such women include those with:

- A previous pregnancy complicated by fetal trisomy
- At least one major or two minor fetal structural anomalies in the current pregnancy
- Chromosomal translocation, inversion, or aneuploidy in themselves or their partner

The recurrence risk of an autosomal aneuploidy depends on the woman’s age: It is about 1 percent for all women under 35 years but is the maternal age-specific risk for women over 35 years (table 1). Previous pregnancies with aneuploidy of a sex chromosome are not at increased risk of recurrence unless the extra chromosome was a maternally derived X chromosome. Although this could be related to advanced maternal age, the derivation of the extra X chromosome is not usually known.

At this time, screening tests are most useful for identification of fetuses with Down syndrome and trisomy 18, but other aneuploidies may be suspected based on abnormal analyte levels (table 2) or ultrasound findings. (See "Sonographic findings associated with fetal aneuploidy".)

SCREENING TESTS — Noninvasive screening tests for Down syndrome involve measurement of maternal serum marker levels which are interpreted in the context of maternal age-related risk; some tests also utilize ultrasound findings [16]. The results of these tests are used to calculate a pregnant woman's risk of having a child with Down syndrome (and almost always trisomy 18), thereby allowing her to make an informed choice about invasive diagnostic testing, which is costly and associated with a risk of pregnancy loss. The reasons for altered maternal serum markers in Down syndrome pregnancy are poorly understood. One hypothesis is that the serum marker pattern is related to poorly functioning fetal tissue with compensatory placental hyperfunction. (See "Laboratory issues related to maternal serum screening for Down syndrome", section on 'Down syndrome'.)

Choosing the most appropriate screening test can be confusing [24-27]. Down syndrome screening tests are summarized below and in the table (table 3); detailed discussions of each test are provided separately. Multiple marker tests perform better than tests with fewer markers (figure 2), although a Cochrane review did not find that the differences in performance between multiple marker tests and single marker tests reached statistical significance [28].

First trimester combined test — The first trimester combined test involves sonographic determination of nuchal translucency (NT) and gestational age (by crown-rump length) combined with the serum markers pregnancy-associated plasma protein-A (PAPP-A) and free or total beta human chorionic gonadotropin (beta-hCG). Screening can be performed at 9 to 13 weeks of gestation with free beta-hCG or at 11 to 13 weeks with total beta-hCG. Chorionic villus sampling (CVS) for definitive prenatal diagnosis must be available to women who undertake first trimester screening and are screen-positive.

The combined test is the best screening test for women whose priority is privacy and early diagnosis; however, CVS, the diagnostic follow-up test, is associated with a higher risk of procedure-related loss per woman screened than second trimester amniocentesis (table 3). Screening for open fetal neural tube defects, if desired, is performed in the second trimester. (See "First trimester combined test and integrated tests for screening for Down syndrome and trisomy 18" and "Prenatal screening and diagnosis of neural tube defects".)

Integrated tests — Integrated screening tests require measurement of serum markers, with or without ultrasound, in both the first and second trimesters. These tests (table 3) include screening for open neural tube defects and are cost-effective [29,30]. (See "First trimester combined test and integrated tests for screening for Down syndrome and trisomy 18", section on 'Integrated tests'.)

- Full integrated test — The full integrated test consists of ultrasound measurement of nuchal translucency at 10 to 13 weeks, PAPP-A obtained at 10 to 13 weeks, and alpha fetoprotein (AFP), unconjugated estriol (uE3), hCG, and inhibin A obtained at 15 to 18 weeks. At detection rates of 85 or 95 percent, the full integrated test has the lowest false positive rate among Down syndrome screening tests, leading to the lowest rate of procedure-related losses per woman screened (table 3).
- Serum integrated test — The serum integrated test is the same as the full integrated test but without ultrasound measurement of nuchal translucency. This test provides an option to patients in areas where expertise in measurement of nuchal translucency is not available. At detection rates of 85 or 95 percent, it has the lowest false positive rate among Down syndrome screening tests that do not include nuchal translucency measurement (table 3).

Sequential and contingent testing — A disadvantage of integrated tests is that the patient has to wait until the second trimester to obtain her risk estimate. Sequential and contingent testing schemes have been developed to address this problem [29].

Step-wise sequential testing — The step-wise sequential screening process involves performing the first trimester portion of the integrated screen and then offering CVS only to women whose results place them at very high risk of an affected fetus (eg, ≥1 in 50). Those whose screen does not place them at very high risk go on to complete the second trimester portion of the test. (See "First trimester combined test and integrated tests for screening for Down syndrome and trisomy 18", section on 'Integrated tests'.)

Contingent testing — Contingent screening is defined in terms of three risk cut-offs: (1) women at very high risk (eg, ≥1 in 50) of having a fetus with Down syndrome after first trimester testing would be offered immediate invasive prenatal diagnosis, (2) women at very low risk (eg, <1 in 2000) would be provided with their risk estimate and would require no additional testing, and (3) women at intermediate risk (eg, >1 in 2000 but <1 in 50) would receive second trimester marker testing [31]. The risk of women

in group (3) would be reevaluated in the second trimester after integrating all first and second-trimester markers and comparing the result with a third risk cut-off. This model provides an early result in most pregnancies for only a small increase in the overall screen-positive rate compared with the integrated test [32]. It is cost-effective [33,34] and has the advantage of avoiding the difficulty of nondisclosure of first-trimester results.

The performance of the contingent test has not yet been proven in a prospective clinical trial. One concern is that women with an "intermediate" test risk may perceive their risk as high because of the recommendation for further screening, and may experience significant anxiety and request diagnostic testing despite their intermediate risk. (See "First trimester combined test and integrated tests for screening for Down syndrome and trisomy 18", section on 'Contingent sequential screening'.)

Quadruple test — The quadruple test is the best available screening test for women who present for prenatal care in the second trimester. At 15 to 18 weeks of gestation (but as late as 22 weeks), the serum markers AFP, uE3, hCG, and inhibin A are measured in maternal serum. In 2011 and 2012, it was the most common Down syndrome screening test performed in the United States [35]. (See "Second trimester maternal serum screening for Down syndrome".)

Genetic sonogram — Because of its late timing (18 to 20 weeks of gestation), the genetic sonogram is not appropriate as a primary screening test. The issues related to its use as a secondary screening test are described elsewhere. (See "Sonographic findings associated with fetal aneuploidy".)

Cell-free DNA in maternal blood — Laboratory testing of cell-free DNA in maternal plasma can identify common autosomal trisomies (chromosomes 21, 18, and 13), as well as select sex chromosome aneuploidies (45X, 47XXY, 47XYY, 47XXX). Some commercial laboratories also provide results for a subset of microdeletions and/or triploidy. Each company has developed its own proprietary technology for assessment of cell-free DNA in maternal blood and calculation of aneuploidy risk, thus sensitivity and specificity vary slightly. All of these are considered laboratory-developed tests (LDTs) and have not been subject to US Food and Drug Administration (FDA) approval. (See "Noninvasive prenatal testing using cell-free nucleic acids in maternal blood".)

Cell-free DNA can be used as a primary or secondary screening test. **It is not a diagnostic test**; confirmation of positive results by an invasive test should be performed after a positive test result if a major intervention, such as pregnancy termination, is planned because false positive results are possible (rate <0.1 percent [36]). Amniocentesis has an advantage over CVS because CVS results may be confounded by confined placental mosaicism (ie, the origin of the abnormal chromosomal cell line originates from the placenta alone and does not reflect the fetus).

A fetal or newborn karyotype is also important to distinguish individuals with 47,+21 from those with a translocation involving chromosome 21. The risk of recurrence is affected if one parent carries a balanced translocation involving chromosome 21.

Cell-free DNA testing is not indicated for screening women with structural fetal anomalies detected by ultrasound; in these cases, direct diagnostic testing for aneuploidy (as well as additional genetic disorders) is more appropriate. One exception might be the finding of isolated increased nuchal translucency.

Candidates for primary screening — The American College of Obstetricians and Gynecologists (ACOG) considers use of a cell-free fetal DNA test an option for primary screening in women with singleton gestations at increased risk of fetal aneuploidy, including [37]:

- Maternal age ≥35 years at delivery
- Presence of sonographic findings associated with fetal aneuploidy
- History of previous pregnancy with fetal trisomy

- Parental balanced Robertsonian translocation with increased risk of trisomy 21 or 13
- Screen-positive result for aneuploidy on screening tests such as the first trimester combined test, integrated test, sequential test, or quadruple test

It is important to note that most studies have found that such testing has an uninformative rate in the range of <1 percent to 3 to 5 percent. (See "Noninvasive prenatal testing using cell-free nucleic acids in maternal blood".)

Because of its high sensitivity and specificity for Down syndrome (detection rate >99 percent and false positive rate <0.1 percent [36]), this test performs very well for selecting patients who will benefit from invasive prenatal diagnosis [38,39]. (See 'Screening performance of tests used for primary screening' below.)

Women with a family history of chromosomal abnormalities other than trisomy 21 or 18 (and in some cases trisomy 13 and certain sex chromosome aneuploidies) or a fetal structural abnormality on ultrasound examination should be offered an invasive diagnostic test since cell-free DNA screening only detects trisomy 21, 18, and possibly 13, and some sex chromosome anomalies and is **not diagnostic** (karyotype of fetal tissue [amniocytes, chorionic villi, or blood] is diagnostic).

The International Society for Prenatal Diagnosis (ISPD) cautions against ad-hoc use of maternal plasma-based testing in women at lower risk [40]. They recommend including the following information during pretest counseling of individual women who might be considering cell-free DNA screening for Down syndrome:

- Reliable noninvasive maternal cell-free DNA aneuploidy screening methods have only been reported for trisomies 21 and 18; efficacy for trisomy 13 appears to be lower, and efficacy for sex chromosome aneuploidy is unacceptably low. All of these aneuploidies would be identified through amniocentesis or CVS.
- False negative results are possible. The test does not detect all cases of fetal trisomy 21, 18, and 13.
- False positive results are possible. A positive result should be confirmed by amniocentesis or CVS. Awaiting the results of follow-up diagnostic testing is likely to be stressful.
- In cases where mosaicism is present (including confined placental mosaicism), results may be inaccurate.
- There is insufficient information about test performance in multiple gestation pregnancies discordant for trisomy but, theoretically, the detection of affected pregnancies could be lower than in singletons. When there has been a known early demise of a co-twin (“vanishing twin”), results may be inaccurate.
- For some patients, a Massively Parallel Sequencing (MPS) test result may not be informative. For example, women with an increased body mass index (BMI) are at high risk of test failure or an inconclusive result.
- For women who are at increased risk of a child with a prenatally diagnosable disorder with Mendelian pattern of inheritance, microdeletion syndrome, and some other conditions, amniocentesis or CVS would still be indicated.

There are still a number of issues that preclude using the new DNA-based test (MPS) as a primary screening tool. The infrastructure to permit primary testing by assessment of cell-free DNA in maternal blood, issues related to the resources required, patient and provider education, and reimbursement have not been adequately addressed. These issues need to be addressed before this test can be

recommended as a primary screening tool in the general obstetrical population.

Candidates for secondary screening — Maternal plasma-based testing for cell-free DNA has been clinically validated [41-49] as a secondary screening test in women who are screen-positive for Down syndrome or other aneuploidies by standard primary biochemical and ultrasound based screening tests. (See 'Secondary screening by a maternal plasma based test for cell-free DNA' below.)

SCREENING PERFORMANCE OF TESTS USED FOR PRIMARY SCREENING — A summary of Down syndrome detection rates and false positive rates from various maternal analyte screening tests (with or without nuchal translucency assessment) and the associated procedure-related loss rates are summarized in the table (table 3).

In a 2014 systematic review of studies of cell-free DNA in maternal blood in screening for aneuploidies, 99 percent of cases of trisomy 21, 97 percent of cases of trisomy 18, and 92 percent of cases of trisomy 13 were detected [50]. Importantly, most of these studies used stored samples from pregnancies with known outcome or used samples from high-risk pregnancies undergoing invasive testing, thus they did not reflect screening performance in the general obstetric population.

Screening performance of cell-free DNA testing for primary screening in the general obstetric population has been evaluated in four large observational studies [51-54]:

- The first study reported that performance in a low-risk population was comparable to that in a high-risk population (for trisomy 21 and trisomy 18 detection rate [DR] >99 percent and false positive rate [FPR] <1 percent) [51].
- The second study examined stored plasma samples from 2049 singleton pregnancies that underwent combined screening at 11 to 13 weeks of gestation [53]. Cell-free DNA testing was performed in 95.1 percent of these pregnancies and correctly identified all eight cases of trisomy 21 and the two with trisomy 18, with a false positive rate of 0.1 percent.
- A third study compared the performance of DNA sequencing to standard maternal serum/ultrasound screening (maternal analyte assay with or without nuchal translucency measurement) in a general obstetrical population of 1914 women who underwent both screening tests [52]. The plasma samples were obtained, processed, and frozen, and the results were not reported to the women or their clinicians. Both screening tests detected **all** cases of trisomy 21 (5 cases) and trisomy 18 (2 cases).
- In the last study, 2905 singleton pregnancies were prospectively screened for trisomies by cell-free DNA sequencing in maternal blood at 10 to 11 weeks of gestation and by the combined test at 11 to 13 weeks of gestation [54]. Results from cell-free DNA analysis were provided for 98.1 percent of cases and identified all 32 cases with trisomy 21, nine of 10 with trisomy 18 and two of five with trisomy 13, with false-positive rates of 0.04, 0.19 and 0.07 percent, respectively.

These studies show that use of cell free DNA has a significant advantage over standard screening because of its low false-positive rate (trisomy 21: <0.3 versus 3.6 percent; trisomy 18: 0.2 versus 0.6 percent); thus, far fewer women would need to be offered invasive diagnostic testing (amniocentesis, chorionic villus sampling [CVS]) [54-57].

MANAGEMENT OF SCREENING RESULTS

Screen-negative test — A negative test result means the patient's risk of having a baby with Down syndrome is less than a chosen cut-off level (eg, Down syndrome risk <1 in 250). It does not exclude the possibility of Down syndrome nor the possibility of a fetus with a chromosomal abnormality not targeted by the screening test but detectable with diagnostic testing [58]. The patient's actual risk of Down syndrome is provided in the report (eg, Down syndrome risk 1 in 900), and this number should be given

to the patient. With regard to Down syndrome screening, no further testing is recommended.

It is not appropriate to tell screen-negative women that their test was "normal" or "negative," as they may interpret these terms to mean the fetus definitely has a normal karyotype.

Screen-positive test — A positive test result means the patient's risk of having a baby with Down syndrome is at or above a chosen cut-off level (eg, Down syndrome risk ≥1 in 250). The actual risk for the patient is provided in the report (eg, Down syndrome risk 1 in 10), and this number should be given to the patient.

If an ultrasound has not been done, it should be performed to confirm gestational age and exclude other causes of a screen-positive test (eg, multiple gestation, congenital anomalies). In addition, it is prudent to double check the laboratory form to make sure the woman's age, weight, gestational age information, etc, have been recorded correctly, as these affect the risk calculation. (See "Laboratory issues related to maternal serum screening for Down syndrome".)

We advise not repeating serum screening tests [59]. Repeat testing of the entire population would result in a small increase in detection rate but is not justified based upon the expense and risk of false reassurance. Repeat testing limited to only screen-positive women can reduce the false positive rate, but a small percentage of affected pregnancies will erroneously become screen-negative.

After a positive screening test, it is helpful to have the parents meet with a genetic counselor to inform them of their diagnostic and management options, including information about the natural history of Down syndrome.

Patients who screen positive are offered fetal karyotype determination for definitive diagnosis. In the first trimester, karyotype is obtained by chorionic villus sampling (CVS). Preliminary results can be obtained within two days if a direct preparation is performed; final results from cultured cells take 7 to 10 days. In the second trimester, amniocentesis is performed to obtain fetal cells for chromosomal analysis. A rapid targeted screening result may be available within two days, but complete karyotype results from cultured cells take about 8 to 14 days. (See "Chorionic villus sampling" and "Diagnostic amniocentesis".)

Fluorescent in situ hybridization (FISH) targets chromosomes 13, 18, 21, X, and Y. It is used for rapid aneuploidy screening after amniocentesis and can be performed on interphase cytotrophoblasts from CVS if the direct preparation fails to yield sufficient useable metaphases for a complete karyotype. Analysis of the full karyotype is generally performed to allow detection of any aneuploidy (not just trisomy 21) as well as detection of major structural chromosomal abnormalities (eg, translocations, inversions, marker chromosomes).

Chromosomal microarray analysis is the preferred option for further evaluation of fetuses with structural abnormalities and a normal karyotype, after fetal demise (particularly when chromosomal analysis is desired, but G-banding is not possible due to failure of cell culture), and when a marker chromosome is identified. However, some clinicians have advocated microarray as a first-line test whenever fetal chromosomal analysis is planned [60]. (See "Use of chromosomal microarray in obstetrics".)

Secondary screening by a maternal plasma based test for cell-free DNA — As discussed above, maternal plasma-based testing for cell-free DNA has been clinically validated as a secondary Down syndrome screening test in women who are screen-positive by any of the standard biochemical and/or ultrasound primary screening tests (see 'Candidates for secondary screening' above). Confirmation of positive results by an invasive test is still needed because false positive results are possible (rate <0.1 percent [36]).

In the largest study to date, the maternal plasma-based test for cell-free DNA had a Down syndrome detection rate of 98.6 percent with a false positive rate of 0.2 percent; in 0.8 percent of samples, the test failed to give a result [41]. A positive test result increased Down syndrome risk by 490-fold; a negative

result reduced risk by 72-fold. Thus, when applied to women identified as screen-positive by any current primary Down syndrome screening test (first trimester, second trimester, integrated screening; ultrasound findings; advanced maternal age), almost all women (95 percent or 19 in 20) who are also positive by the DNA-based test will, in fact, be carrying a Down syndrome fetus and can be offered an invasive test for confirmation. Conversely, almost all those who are screen-negative by secondary screening can be informed that the probability that their fetus has Down syndrome is low and they can avoid an invasive procedure. Thus, this approach minimizes the risk of a procedure-related loss of a fetus unaffected by Down syndrome.

However, some fetal chromosomal abnormalities associated with screen-positive maternal analyte Down syndrome screening would be missed if cell-free DNA testing is chosen as the next step (secondary screening) rather than a diagnostic test [61]. These abnormalities include trisomies of chromosomes other than 21 and 18, large deletions, unbalanced translocations, and low-level mosaicism.

IMPACT OF OFFERING SCREENING — The development of Down syndrome screening tests with high detection rates and low false positive rates has had a major effect on Down syndrome births. An early demonstration of the impact of screening was reported by investigators in Maine [62]. Before serum screening was implemented (1980 to 1985), there was a 7 percent reduction in Down syndrome births based on diagnosis by amniocentesis, primarily performed because of advanced maternal age. From 1986 to 1990, maternal serum screening with alpha fetoprotein (AFP) was offered to women younger than 35 years of age and Down syndrome births were reduced by 22 percent. In 1991, improved serum screening with multiple markers was implemented and the improvement in prenatal detection led to a 46.3 percent reduction in affected births (1991 to 1993). Data from England and Wales collected from 1989 to 2008 showed a 71 percent increase in prenatal and postnatal diagnosis of Down syndrome during this period. The number of live births with Down syndrome fell by 1 percent because of widespread prenatal screening and availability of pregnancy termination. Without prenatal screening and subsequent termination, the birth rate of babies with Down syndrome would have risen by 48 percent over this period because of the continued trend of women delaying pregnancy until they are older [7].

The implementation of national guidelines, such as the American College of Obstetricians and Gynecologists recommendation to offer Down syndrome screening to all pregnant women, regardless of maternal age, is also expected to influence the overall impact of screening. This is illustrated by a study from Denmark where a national policy offering pregnant women information on Down syndrome screening and, if desired, first trimester screening using nuchal translucency and maternal analytes was implemented in 2004 [6]. The proportion of Down syndrome diagnosed prenatally increased from 53 to 61 percent in the period from 2000 to 2004 to 79 to 81 percent in the period from 2005 to 2006. Despite increased utilization of screening, the number of invasive diagnostic procedures (amniocentesis, chorionic villus sampling) fell by 53 percent since older women who might have undergone a diagnostic test as their initial procedure chose to undergo screening as a first step. Thus, increased prenatal detection of affected fetuses did not lead to an increased number of unaffected fetuses lost as a complication of invasive procedures. However, the number of Down syndrome births fell from about 60 per year in the period from 2000 to 2004 to about 32 per year in the period from 2005 to 2006. In a systematic review of 24 United States studies (1995 to 2011) that reported data for pregnancies with definitive prenatal diagnosis of Down syndrome and subsequent pregnancy termination, the weighted mean termination rate was 67 percent (range 61 to 93 percent) [63].

DELIVERING THE DIAGNOSIS TO PATIENTS WITH AFFECTED PREGNANCIES — The National Society of Genetic Counselors has published a guideline for communicating a prenatal or postnatal diagnosis of Down syndrome to parents [64]. The following is a synopsis of their recommendations:

- Inform parents as soon as possible.
- Ideally, the diagnosis should be delivered in person to both parents by a healthcare professional

with sufficient knowledge of the condition. A professional medical interpreter should be present, when appropriate.

- Avoid using value judgments, such as "I'm sorry" or "Unfortunately, I have bad news," when starting the conversation. Use active listening and empathic responses to support the parents. Allow time for silence and time for tears and offer the family time alone. Answer their questions and make plans for a follow-up conversation.
- Provide up-to-date, accurate, verbal and written information with a balanced perspective and tailored to the parent's knowledge base and emotional needs. Include the range of cognitive and health concerns of individuals with Down syndrome and both the positive aspects and challenges related to the syndrome. (See "Down syndrome: Management".)
- Provide informational resources, including national and local support groups and local medical and educational resources. The National Down Syndrome Society web site is www.ndss.org (toll-free telephone number is 800-221-4602).
- When appropriate, provide referrals to other specialists (eg, medical geneticists, genetic counselors, cardiologists, neonatologists, pediatric surgeons).
- Discuss possible pregnancy outcomes, such as the increased risk of miscarriage and stillbirth. Medical and surgical issues that may require prompt attention after delivery should be addressed. (See 'Management of pregnancy' below.)
- Couples with an affected pregnancy have several options (continuing the pregnancy, pregnancy termination, giving the child up for adoption), which should be discussed with sensitivity to their beliefs and values. Offer an opportunity to meet with families who are raising a child with Down syndrome, those who have chosen to create an adoption plan, and/or those who have terminated a pregnancy.

MANAGEMENT OF PREGNANCY — There are no guidelines for obstetrical management of pregnancies complicated by Down syndrome. As discussed above, these couples should be referred to national and local support groups and local medical and educational resources for information about the wide range of variability in manifestations and prognosis. (See 'Delivering the diagnosis to patients with affected pregnancies' above.)

It is estimated that fetal demise between diagnostic amniocentesis and delivery occurs in up to 30 percent of Down syndrome pregnancies not electively terminated; fetal demise occurs in about 30 to 50 percent of pregnancies between chorionic villus sampling and delivery [1,3-5]. Presumably, many of these losses are related to severe structural anomalies and growth restriction [65].

There are no studies on use of nonstress testing, the biophysical profile, or other antepartum tests for fetal assessment to monitor the fetus with Down syndrome. It is reasonable to use these tests for the usual obstetrical indications (eg, fetal growth restriction, oligohydramnios, preeclampsia, decreased fetal movement). (See "Overview of antepartum fetal surveillance".)

The diagnosis of Down syndrome generally does not influence usual care practices related to route of delivery. Since these fetuses are at risk of antepartum death, labor is typically induced at 39 to 40 weeks.

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: Should I have a screening test for Down syndrome during pregnancy? (The Basics)")
- Beyond the Basics topics (see "Patient information: Should I have a screening test for Down syndrome during pregnancy? (Beyond the Basics)")

The following table can also be helpful (table 4).

SUMMARY AND RECOMMENDATIONS

- Down syndrome is the most common chromosome abnormality among live births and the most frequent form of intellectual disability caused by a demonstrable chromosomal aberration. (See 'Introduction' above.)
- We recommend offering all pregnant women prenatal screening for Down syndrome, regardless of age (**Grade 1C**). Women should have the option of invasive testing, regardless of maternal age. (See 'Rationale for screening' above and 'Candidates for prenatal screening and diagnosis' above.)
- A nondirective approach should be used when providing information about Down syndrome, and it should be clear that testing is voluntary. (See 'Basic approach to counseling' above.)
- After a positive screening test, it is helpful to have the parents meet with a genetic counselor to inform them of their diagnostic and management options, including information about the natural history of Down syndrome. Fetal karyotype determination is offered for definitive diagnosis. In the first trimester, karyotype is obtained by chorionic villus sampling. In the second trimester, amniocentesis is performed to obtain amniocytes for chromosomal analysis. (See 'Screen-positive test' above.)

Maternal serum analyte screening tests

- Prenatal screening programs based on maternal serum analyte tests can detect up to 95 percent of pregnancies affected by Down syndrome with a false positive rate of 5 percent. The most commonly used test in the United States is the second trimester quadruple test, which has a detection rate of about 80 percent at a 5 percent false positive rate. Serum test “failures” are extremely rare, while failure to obtain ultrasound measurements of nuchal translucency occurs occasionally (<2 percent). (See 'Screening performance of tests used for primary screening' above.)
- The first trimester combined test is the best option for women whose most important goal is to obtain their estimate of risk of Down syndrome early in pregnancy. Alpha-fetoprotein is still recommended in the second trimester for detection of neural tube defects. (See 'First trimester combined test' above.)
- The full integrated test has the highest detection rate for Down syndrome, the lowest rate of procedure-related losses per woman screened (table 3), and includes screening for open neural tube defects. The serum integrated test has the highest detection rate for any test in which nuchal translucency measurement is not used. (See 'Integrated tests' above.)
- Sequential and contingent screening offer the advantages of the integrated test but allow some women to get early diagnosis. (See 'Integrated tests' above.)

- The quadruple test is the best available screening test for women who present for prenatal care in the second trimester. (See 'Quadruple test' above.)
- A negative test result means the patient's risk of having a baby with Down syndrome is less than a specific cut-off level; it does not exclude the possibility of Down syndrome. (See 'Screen-negative test' above.)

Maternal plasma cell-free DNA screening test

- Maternal plasma cell-free DNA screening programs can detect up to 99 percent of pregnancies affected by Down syndrome with a screen-positive rate of <0.2 percent. However, 1 to 5 percent (or more) of samples fail to produce an interpretation, even after repeat testing. A Down syndrome sample could possibly fail and not be detected by cell-free DNA testing. (See 'Cell-free DNA in maternal blood' above and 'Candidates for secondary screening' above.)
- Measurement of maternal plasma free DNA is an option as a primary test in women at high risk of fetal aneuploidy and as a secondary screening test for certain aneuploidies in women who are screen-positive on maternal analyte testing, and thus can markedly reduce the need for invasive diagnostic testing. (See 'Cell-free DNA in maternal blood' above and 'Candidates for secondary screening' above.)
- Cell-free DNA testing is a screening test. **It is not a diagnostic test**; confirmation of positive results by an invasive test should be performed after a positive test result if a major intervention, such as pregnancy termination, is planned because false positive results are possible. Amniocentesis has an advantage over chorionic villus sampling (CVS) because CVS results may be confounded by confined placental mosaicism. (See 'Cell-free DNA in maternal blood' above.)

  A fetal or newborn karyotype is also important to distinguish individuals with 47,+21 from those with a translocation involving chromosome 21. The risk of recurrence is affected if one parent carries a balanced translocation involving chromosome 21.

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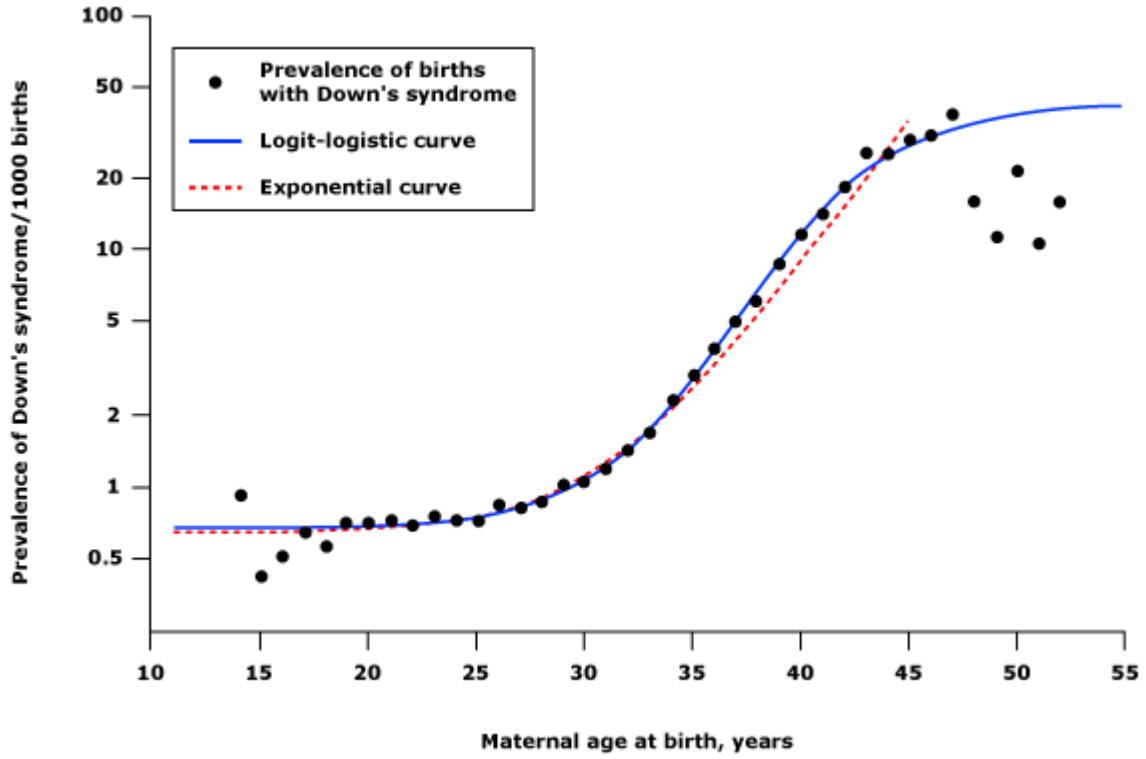
Topic 426 Version 45.0

GRAPHICS

Estimated prevalence of births with Down syndrome (95% CI) in the absence of antenatal screening in England and Wales 1990-1998: comparison of logit logistic curve with exponential curve



Reproduced with permission from: Morris, JK, Mutton, DE, Alberman, E. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. J Med Screen 2002; 9:2. Copyright ©2002 The Royal Society of Medicine Press, London.

Graphic 67614 Version 2.0

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

Maternal serum marker pattern in selected fetal syndromes

	Second trimester markers				First trimester markers	
Genetic disorder	**AFP**	**uE3**	**hCG**	**Inh A**	**PAPP-A**	**beta hCG**
Down syndrome	↓	↓	↑	↑	↓	↑
Trisomy 18	↓	↓ ↓	↓ ↓	↔	↓ ↓	↓ ↓
Trisomy 13	↔	↔	↔	↔	↓ ↓	↓
Turner syndrome with hydrops	↓	↓	↑	↑	↓ ↑	↓ ↑
Turner syndrome without hydrops	↓	↓	↓	↓	↓ ↑	↓ ↑
Triploidy (paternal)	↔	↓	↑	↑	↓ ↑	↑ ↑
Triploidy (maternal)	↔	↓	↓	↓	↓ ↑	↓ ↓
Smith-Lemli-Opitz syndrome	↓	↓ ↓	↓	NR	NR	NR

Second trimester markers: AFP (alpha-fetoprotein); uE3 (unconjugated estriol); hCG (human chorionic gonadotropin); inh A (inhibin A).
First trimester marker: PAPP-A (pregnancy-associate plasma protein A); beta hCG (beta human chorionic gonadotropin).

↑: increased; ↓: decreased; ↔: unaffected; ↓ ↑: variable; NR: not reported.

Graphic 71552 Version 3.0

Detection rate and false positive rate for Down syndrome screening tests - First and Second Trimester Evaluation of Risk Trial (FASTER) and Serum, Urine and Ultrasound Screening Study (SURUSS)

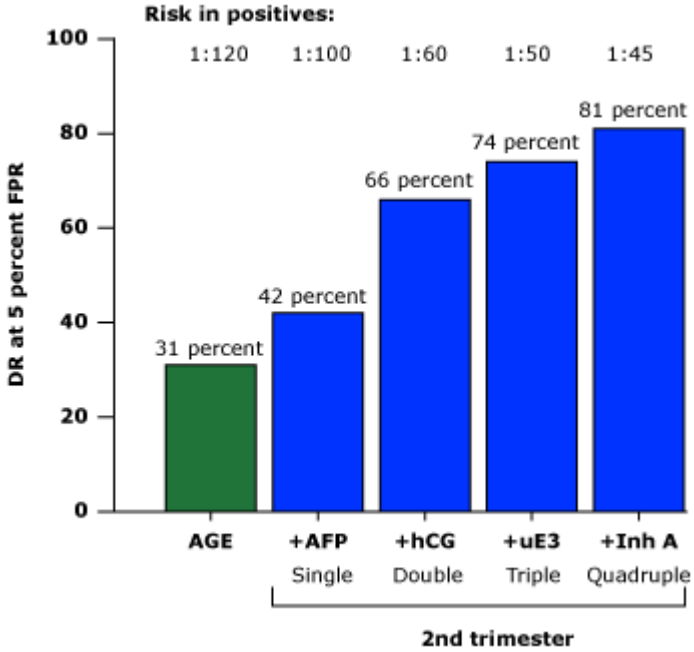
Test	FASTER*		SURUSS•		
	Detection rate, percent	FPR, percent	Detection rate, percent	FPR, percent	Procedure related losses per 100,000 women screened
Integrated	85	0.8	85	0.9	6
	95	5.0	90	2.1	15
Serum integrated	85	4.4	85	3.9	28
	95	17	90	7.4	53
Combined	85	4.8	85	4.3	35
	95	21	90	8.4	60
Quadruple	85	7.3	85	6.2	45
	95	22	90	10.6	76
Triple	85	14	85	9.3	67
	95	32	90	14.7	106

FPR: false positive rate.
* For FASTER, the first trimester combined test or first trimester component of the integrated test was done at 12 completed weeks of gestation.
• For SURUSS, the first trimester combined test or first trimester component of the integrated test was done at 11 completed weeks of gestation.

Adapted from: Wald NJ, Rodeck C, Hackshaw AK, et al. Health Technol Assess 2003; 7:1.

Graphic 57348 Version 4.0

Performance of maternal age and various second trimester maternal serum combinations in screening for Down syndrome



The bar graphs describe the detection rate (DR) attained at a fixed 5 percent false positive rate (FPR) for each of the screening tests. In addition, the risk in positives is given for each of the tests.

Data adapted from: Wald, NJ, Kennard, A, Hackshaw, A, et al. J Med Screen1997; 4:181.

Graphic 57445 Version 1.0

Select the statement that best describes your values and preferences to help decide which screening test is best for you

Statement	Screening test to consider
1. "I want the result of my screening test as early as possible in the pregnancy, while the pregnancy is still private and I have options of early prenatal diagnosis (chorionic villus sampling) because I would terminate an affected pregnancy."	First-trimester screening
2. "I want to have the test with the lowest chance of a screen positive result."	Integrated screening
3. "I would consider an amniocentesis if my test result shows a high chance of Down syndrome, but not a CVS because it has a higher risk for procedure-related complications."	Integrated screening
4. "I have been very anxious and want my results as soon as possible, whether or not I would terminate an affected pregnancy."	First-trimester screening
5. "I am already in my second trimester of pregnancy."	Triple or quad screening
6. "Nuchal translucency ultrasound is not available in my area."	Serum-only integrated screening
7. "Chorionic villus sampling is not available in my area."	Integrated screening
8. "My pregnancy is considered high risk for a chromosomal abnormality because of my age, my family history, a finding on my ultrasound exam, or a positive result on a screening test done on my blood."	Plasma DNA screening

Graphic 66116 Version 5.0

Disclosures

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Conflict of interest policy

Cystic fibrosis: Genetics and pathogenesis

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Literature review current through: Feb 2015. | **This topic last updated:** Sep 02, 2014.

INTRODUCTION — Cystic fibrosis (CF) is a multisystem disease affecting the digestive system, sweat glands, and the reproductive tract, but progressive lung disease continues to be the major cause of morbidity and mortality. Patients with CF have abnormal transport of chloride and sodium across the respiratory epithelium, resulting in thickened, viscous airway secretions [1,2]. Over a highly variable time course ranging from months to decades after birth, individuals eventually develop chronic infection of the respiratory tract with a characteristic array of bacterial flora, leading to progressive respiratory insufficiency and eventual respiratory failure [3].

The genetics and pathogenesis of cystic fibrosis are discussed here. Details of the clinical manifestations and effects of the disease process are discussed separately. (See "Cystic fibrosis: Overview of gastrointestinal disease" and "Cystic fibrosis: Clinical manifestations of pulmonary disease".)

GENETICS — CF is caused by mutations in a single large gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein [4-9]. Clinical disease requires disease-causing mutations in both copies of the CFTR gene.

The normal CFTR gene — CFTR belongs to the ABC (**A**TP-**B**inding **C**assette) family of proteins, a large group of related proteins that share transmembrane transport functions. ABC proteins include bacterial transporters for amino acids and other nutrients, surfactant transport proteins, and the mammalian multidrug resistance (MDR) protein (or P-glycoprotein).

CFTR functions as a regulated chloride channel, which, in turn, may regulate the activity of other chloride and sodium channels at the cell surface [10-13]. The CFTR gene spans 250 kilobases on chromosome 7, encoding 1480 amino acids in the mature protein (figure 1). The protein has two groups of six membrane-spanning regions, two intracellular nucleotide-binding folds (NBFs), and a highly charged "R domain" containing multiple phosphorylation sites. Activation of the chloride channel requires phosphokinase A-mediated phosphorylation of the R domain, and the continuous presence of ATP in the NBFs [14,15].

Genetic changes in CFTR — The phenotypic expression of disease varies widely, primarily as a function of the specific mutation (or mutations) present [16-21]. The Cystic Fibrosis Mutation Database lists more than 1900 different mutations in the CFTR gene with potential to cause disease.

The most common mutation is delta F508 (deletion of three DNA bases coding for the 508th amino acid residue phenylalanine), which is found in approximately 70 percent of Caucasian patients with CF in the United States. Certain mutations are found at higher frequency in some ethnic groups because of apparent founder effects. As an example, five mutations account for an estimated 97 percent of CF alleles in the Ashkenazi Jewish population [22]. A subset of the most frequent CFTR mutations is recommended for initial testing since the majority of individual mutations are very rare (table 1) [23]. (See "Cystic fibrosis: Clinical manifestations and diagnosis", section on 'Molecular diagnosis'.)

Mutations of the CFTR gene have been divided into five different classes (figure 2) [2,24]. In general,

mutations in classes I to III cause more severe disease than those in classes IV and V [19,25]. However, the clinical implications of a specific combination of mutations are often unclear, perhaps because of the influence of gene modifiers. Genotype-phenotype correlations are weak for pulmonary disease in CF, and somewhat stronger for the pancreatic insufficiency phenotype. (See 'Gene modifiers' below.)

In most cases, specific mutations should not be used to make assumptions about the severity of disease in an individual patient. Knowledge of the mutations may be useful to guide initial therapy, but clinical decisions should be guided by observable parameters of growth, lung function, and nutritional status. Some investigational therapies are directed at specific classes of CFTR mutation. (See "Cystic fibrosis: Investigational therapies", section on 'Reversing the consequences of CFTR mutations on protein function'.)

Class I mutations: Defective protein production — This defect is usually caused by nonsense, frameshift, or splice-site mutations, leading to premature termination of the mRNA and complete absence of CFTR protein. Examples include G542X, W1282X, R553X, 621+G>T, and 1717-1G>A [25]. This type of mutation accounts for two to five percent of cystic fibrosis cases worldwide. Some populations have a much higher frequency; as an example, 60 percent of Ashkenazi Jews with CF carry at least one copy of a nonsense mutation [26].

Class II mutations: Defective protein processing — Class II mutations in the CFTR sequence cause abnormal post-translational processing of the CFTR protein, which prevents the protein from trafficking to the correct cellular location. This category includes the delta F508 (F508del) mutation, which accounts for 70 percent of the disease-causing alleles in the United States. Fifty percent of CF patients are homozygous for F508del, and 90 percent will carry at least one copy of this mutation [25]. N1303Lys (N1303K) and A455E are also class II mutations; the latter is associated with relatively mild lung disease and pancreatic sufficiency.

Class III mutations: Defective regulation — Class III mutations lead to diminished channel activity in response to ATP. Many involve alterations of the NBF regions, NBO1 and NBO2, which may retain varying degrees of sensitivity to nucleotide binding (figure 2). Other CFTR mutations, mapped to the R domain, may also fall into this category. G551D is the most common class III mutation in Caucasian populations [25]

Class IV mutations: Defective conduction — With class IV mutations, the protein is produced and correctly localized to the cell surface. However, although chloride currents are generated in response to cAMP stimulation, the rate of ion flow and the duration of channel opening are reduced when compared to normal CFTR function. R117H is the most common class IV mutation in Caucasian populations [25].

Class V mutations: Reduced amounts of functional CFTR protein — This class of mutation is not included in some schemes. It includes mutations that alter the stability of mRNA and others that alter the stability of the mature CFTR protein (the latter is sometimes classified separately into a Class VI) [27,28]. The mutation A455E has been classified as Class II [25] or Class V [19,29,30].

GENE MODIFIERS — The inconsistent association between CF genotypes and phenotypes points to a role for gene modifiers. These genetic variations are not directly related to the CFTR gene but affect the severity or clinical manifestations of disease. Research into a variety of candidate genes is ongoing. There is good evidence that the following genes act as modifiers in CF, and that approximately 20 percent of patients with classic CF carry variants in one or both of these genes that exacerbates the pulmonary disease [31].

- TGF-beta 1 — Transforming growth factor-beta (TGF-beta) is a potent suppressor of T cell activation and can decrease T cell proliferation and cytokine production. In a study of 808 patients who were homozygous for the delta F 508 mutation, polymorphisms in the TGF-beta 1 gene were associated with more severe CF lung disease [32]. (See "Role of cytokines in the immune

system".)

- MBL — Mannose-binding lectin is an important component of the complement system, and deficiencies in this protein increase the risk for pyogenic infections. In individuals with CF, variant MBL alleles are associated with reduced lung function, increased risk for chronic Pseudomonas aeruginosa and Burkholderia cepacia complex infections, and early death [33]. In young patients with CF and pancreatic insufficiency, lower MBL-2 protein levels were associated with a steeper rate of decline in lung function and earlier age at first infection with P. aeruginosa [31]. These effects were exaggerated in individuals who also carried the TGF-beta 1 mutation described above. (See "Inherited disorders of the complement system".)

INCOMPLETE PHENOTYPE — In approximately 10 percent of patients with suspected CF, the disease manifestations appear to be unusually mild or limited to one organ system [34]. Although the term “nonclassic CF” has been applied to this group of patients, the term is preferably applied to patients who fulfill diagnostic criteria for disease but have intermediate sweat chloride results. (See "Cystic fibrosis: Clinical manifestations and diagnosis", section on 'Nonclassic CF'.)

The phenotypes and genetic causes of patients with this clinical presentation were described in a study of 158 patients who were referred for detailed genotyping [35]. Standard genetic testing for CF had been performed on each of these patients prior to inclusion in the study, and this panel had identified either no CFTR mutations or only one mutation. The characteristics of 74 of these patients had been previously published [36]. The subjects underwent detailed genetic testing using direct DNA sequencing and structured clinical phenotyping. The following findings were reported:

- On detailed genetic testing, 36 percent of patients proved to have two CFTR mutations, 24 percent had one mutation, and 40 percent did not have any detectable mutations despite exhaustive analysis. It is possible that undetected mutations in the introns, promoters, or regulatory regions of the gene contributed to the phenotypic findings in some of these individuals.
- Neither sweat chloride concentrations nor pulmonary function tests correlated with the number of CFTR mutations. However, 39 percent of the patients had intermediate sweat chloride concentrations (in the 40 to 60 mmol/L range) and 14 percent had normal sweat chloride concentrations (<40 mmol/L).
- Patients with two CFTR mutations were more likely to have absence of the vas deferens and the presence of P. aeruginosa in sputum as compared to those patients with zero CFTR mutations. Patients with zero CFTR mutations frequently presented with steatorrhea.

The pathogenetic mechanism responsible for clinical disease without CFTR mutations is unclear. The above findings suggest that factors other than CFTR mutations may lead to disease that is phenotypically similar to CF in some patients. Patients who do not have two CFTR mutations and/or have normal or borderline sweat chloride concentrations should be rigorously evaluated for other causes of their symptoms (eg, evaluation for Shwachman-Diamond syndrome in those with pancreatic insufficiency). (See "Shwachman-Diamond syndrome".)

CFTR-related metabolic syndrome – Newborn screening programs perform initial identification by screening for hypertrypsinogenemia, followed in most states by screening for common CFTR genotypes. These screening programs are increasingly identifying infants who have abnormal serum trypsinogen levels, sweat chloride levels that are either normal or in a borderline range (30 to 59 mmol/dl), and zero to two CFTR mutations, at least one of which is not recognized as a “CF causing mutation.” This combination of characteristics neither permits nor excludes the diagnosis of CF, so these infants are provisionally categorized as having “CFTR-related metabolic syndrome” (CRMS). Some of these infants will ultimately be found to have two disease-causing CFTR mutations, will develop signs and symptoms of CF, or will develop a diagnostic sweat chloride, and can be categorized as having true CF. Other

children may develop CFTR-related disorders such as chronic pancreatitis or male infertility, without meeting criteria for a CF diagnosis. Other children initially categorized as having CRMS may never develop any signs or symptoms of CFTR related disease. Because the natural history of infants with CRMS is unpredictable, these infants require continued evaluation and screening during the first few years of life [37]. (See "Cystic fibrosis: Clinical manifestations and diagnosis", section on 'CFTR-related metabolic syndrome'.)

DISEASE PATHOGENESIS — The pathogenesis of the organ dysfunction seen in CF has been studied in humans and CFTR-knockout mice, but remains incompletely understood [38,39]. It appears that the physical and chemical abnormalities of CF airway secretions result in chronic infection with phenotypically unique bacteria, particularly Pseudomonas species. Other genetic factors, including polymorphisms of the tumor necrosis alpha (TNF-a) gene, may increase susceptibility to P. aeruginosa infection and contribute to the clinical manifestations of CF [40].

Primary abnormalities in fatty acid metabolism have been noted in biopsies of CFTR-expressing tissue from patients with CF [41]. These changes, which result in increased tissue levels of arachidonic acid, also are present in the mouse model of CF, but are not seen in tissue from patients with inflammatory bowel disease. Thus, increased tissue expression of arachidonic acid and its metabolites may contribute to the abnormal inflammation characteristic of CF.

Abnormal secretions — CFTR malfunction in the respiratory epithelium is associated with a variety of changes in electrolyte and water transport. The mechanisms involved and ultimate electrolyte composition of airway surface fluid from normal and CF airways is a subject of ongoing research [11-13,42-45]. The net result of these changes is an alteration in the rheology of airway secretions, which become thick and difficult to clear [46]. An associated finding is an increased concentration of chloride in sweat secretions, which constitutes one of the methods of diagnosis of CF. (See "Cystic fibrosis: Clinical manifestations and diagnosis".)

Gastrointestinal effects — Thickened secretions caused by CFTR malfunction cause the gastrointestinal complications of CF. Impaired flow of bile and pancreatic secretions cause maldigestion and malabsorption, as well as progressive liver and pancreatic disease, leading to CF-related diabetes. Because of thickened intestinal secretions and maldigestion, CF patients are prone to intestinal obstruction (distal intestinal obstruction syndrome or intussusception) and to rectal prolapse. (See "Cystic fibrosis: Overview of gastrointestinal disease".)

Chronic lung infection — The chronic airway obstruction caused by viscous secretions is followed by progressive pulmonary colonization with pathogenic bacteria, including Haemophilus influenzae, Staphylococcus aureus, and eventually P. aeruginosa and/or Burkholderia cepacia complex bacteria. (See "Cystic fibrosis: Antibiotic therapy for lung disease", section on 'Pathogens'.)

Once infection is established, neutrophils are unable to control the bacteria, even though there is massive infiltration of these inflammatory cells into the lung tissue [47]. Recruited neutrophils subsequently release elastase, which overwhelms the antiproteases of the lung and contributes to tissue destruction in a process known as "prolonged endobronchial protease activity" [48]. In addition, large amounts of DNA and cytosol matrix proteins are released by degranulating neutrophils, contributing to the increased viscosity of the airway mucus [49].

Inflammation has been noted prior to the development of bacterial colonization, and may be triggered by viral infections [50]. In turn, chronic infection appears to be the major stimulus for an exuberant but ultimately ineffective inflammatory response that subsequently results in bronchiectasis [51,52]. The inflammatory response itself appears to contribute to the progression of pulmonary dysfunction; this mechanism is the basis for the use of some anti-inflammatory agents in treating CF lung disease [53,54]. (See "Clinical manifestations and diagnosis of bronchiectasis in adults" and "Cystic fibrosis: Overview of

the treatment of lung disease", section on 'Antiinflammatory therapy'.)

Individuals with cystic fibrosis are particularly prone to chronic infection with P. aeruginosa, due in part to increased oxygen utilization by epithelial cells, which results in an abnormally decreased oxygen tension within the hyperviscous mucous layer (figure 3) [55]. This local hypoxia induces the characteristic phenotypic changes in P. aeruginosa (and some other gram negative bacteria), including alginate production and loss of motility. This phenotype is consistent with the development of bacterial macrocolonies (or "biofilms") within the hypoxic regions of the airway mucus layer. Once this occurs, eradication of the organism is almost impossible. (See "Epidemiology, microbiology, and pathogenesis of Pseudomonas aeruginosa infection", section on 'Persistence of the organism in the airways'.)

P. aeruginosa also may acquire the ability to persist in the environment of the CF lung. One study found that 36 percent of CF patients were colonized with a hypermutable strain of P. aeruginosa that often persisted for years; such mutator strains were not isolated from patients with acute P. aeruginosa infection who did not have CF [56].

The frequent colonization and persistent infection caused by P. aeruginosa in CF patients is also related to the defective CFTR protein itself [47]. Normal CFTR protein serves as the receptor for binding of P. aeruginosa lipopolysaccharide (LPS) in vitro, and extracts LPS from the surface of the organism for endocytosis into epithelial cells [43,57,58]. This results in increased intranuclear translocation of the nuclear transcription factor NF kappa B and subsequent immunoactivation [57-59]. This process does **not** occur in the presence of abnormal CFTR or in CFTR-knockout mice [59], which may partially explain the inability of CF patients to control these infections. Disease-modifier genes appear to further affect the predisposition to P. aeruginosa infection, as described above. (See 'Gene modifiers' above and "Epidemiology, microbiology, and pathogenesis of Pseudomonas aeruginosa infection".)

SUMMARY

- Cystic fibrosis (CF) is caused by mutations in a single large gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Clinical disease requires disease-causing mutations in both copies of the CFTR gene. (See 'Genetics' above.)
- The phenotypic expression of disease varies widely, as a function of the specific mutations present and the presence of gene modifiers. (See 'Genetic changes in CFTR' above.)
- Mutations of the CFTR gene have been divided into five different classes (figure 2). In general, mutations in classes I to III cause more severe disease than those in classes IV and V [19,25]. However, the clinical implications of a specific combination of mutations are often unclear, and specific mutations should not be used to make assumptions about the severity of disease in an individual patient. (See 'Genetic changes in CFTR' above.)
- A subset of the most frequent CFTR mutations is recommended for initial testing, since the majority of individual mutations are very rare (table 1). (See 'Genetic changes in CFTR' above.)
- The most common mutation is delta F508 (deletion of three DNA bases coding for the 508th amino acid residue phenylalanine), which is found in approximately 70 percent of Caucasian patients with CF in the United States. (See 'Class II mutations: Defective protein processing' above.)
- Gene modifiers are genetic variations that are not directly related to the CFTR gene, but which nonetheless affect the severity or clinical manifestations of disease. Transforming growth factor-beta (TGF-beta) and Mannose-binding lectin are important gene modifiers in CF, and approximately 20 percent of CF patients carry variants in one or both of these genes that may exacerbate the pulmonary disease. (See 'Gene modifiers' above.)
- CFTR malfunction is associated with low water content in secretions from the respiratory,

pancreatic, and biliary epithelium, which causes the secretions to be viscous and difficult to clear. (See 'Abnormal secretions' above.)

- In the gastrointestinal tract, the abnormal bile and pancreatic secretions cause maldigestion and malabsorption, progressive liver and pancreatic disease, rectal prolapse, and intestinal obstruction (distal intestinal obstruction syndrome or intussusception). (See 'Gastrointestinal effects' above.)
- In the lung, the abnormal secretions cause chronic airway obstruction and reduce bacteriocidal killing, leading to progressive pulmonary colonization with pathogenic bacteria, and to the formation of bacterial biofilms. Chronic infection causes an inflammatory response and tissue destruction, causing bronchiectasis. Infection with P. aeruginosa is particularly favored in patients with CF, due to abnormally decreased oxygen tension within the hyperviscous mucous layer. (See 'Chronic lung infection' above.)

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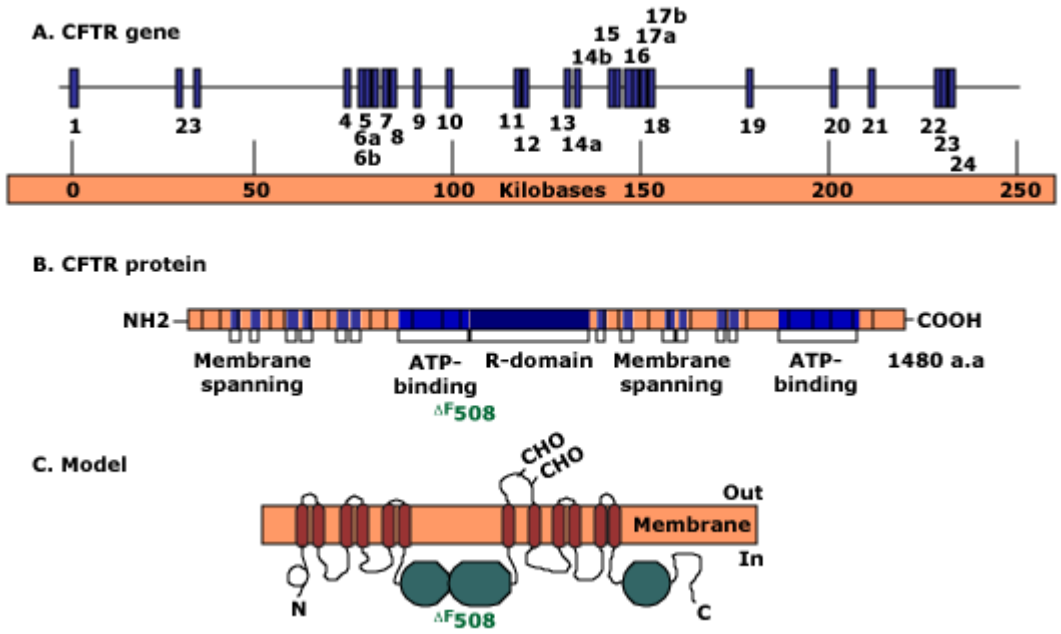
Topic 6368 Version 11.0

GRAPHICS

CFTR gene



Schematic representation of the CFTR gene and its encoded polypeptide. ΔF508 refers to the site of the most common mutation causing cystic fibrosis.

CFTR: cystic fibrosis transmembrane conductance regulator

Redrawn from Welsh, MJ, Tsui, L-C, Boat, T, Beaudet, AL. Cystic fibrosis. In: The Metabolic and Molecular Basis of Inherited Disease, Scriver, CR, Beaudet, AL, Sly, WS, et al (Eds), McGraw-Hill, New York, 1995, p. 3801.

Graphic 60265 Version 2.0

Genetic screening panels for cystic fibrosis

Standard or basic mutation panel
ΔF508, ΔI507, G542X, G551D, W1282X, N1303K, R553X, 621+1G>T, R117H, 1717-1G>A, A455E, R560T, R1162X, G85E, R334W, R347P, 711+1G>T, 1898+1G>A, 2184delA, 3849+10kbC>T, 2789+5G>A, 3659delC, 3120+1G>A
Expanded 32 mutation panel
G85E, ΔI507, R553X, 711+1G>T, 3659delC, R117H, ΔF508, R560T, 1078delT, 3849+10kbC>T, I148T, V520F, R1162X, 1717-1G>A, 3876delA, R334W, G542X, W1282X, 1898+1G>A, 3905insT, R347P, S549N, N1303K, 2184delA, R347H, S549R, 394delTT, 2789+5G>A, A455E, G551D, 621+1G>T, 3120+1G>A
Reflex tests
I506V*, I507V*, F508C*, 5T/7T/9T•

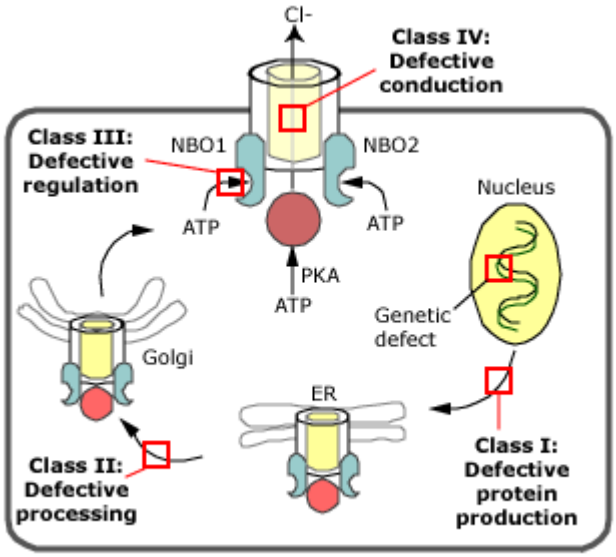
* Benign Variants. This test distinguishes between the ΔF508 CF mutation and these benign variants. I506V, I507V, and F508C testing is performed only as reflex tests for unexpected homozygosity for ΔF508 and/or ΔI507.

•5T / 7T /9T analysis is performed only when R117H is detected, for the following reasons: the R117H mutation can result in classic CF only if there is a 5T variant on the same chromosome and another CF mutation on the opposite chromosome. R117H on one chromosome and 5T or 7T on the opposite chromosome, or homozygosity for 5T (5T on each chromosome) can result in congenital bilateral absence of the vas deferens (CBAVD);

Technical Standards and Guidelines for CFTR Mutation Testing. American College of Medical Genetics, 2006 and ACOG Committee Opinion #325, Update on carrier screening for cystic fibrosis; December 2005

Graphic 65637 Version 2.0

Defects in the CFTR gene in cystic fibrosis



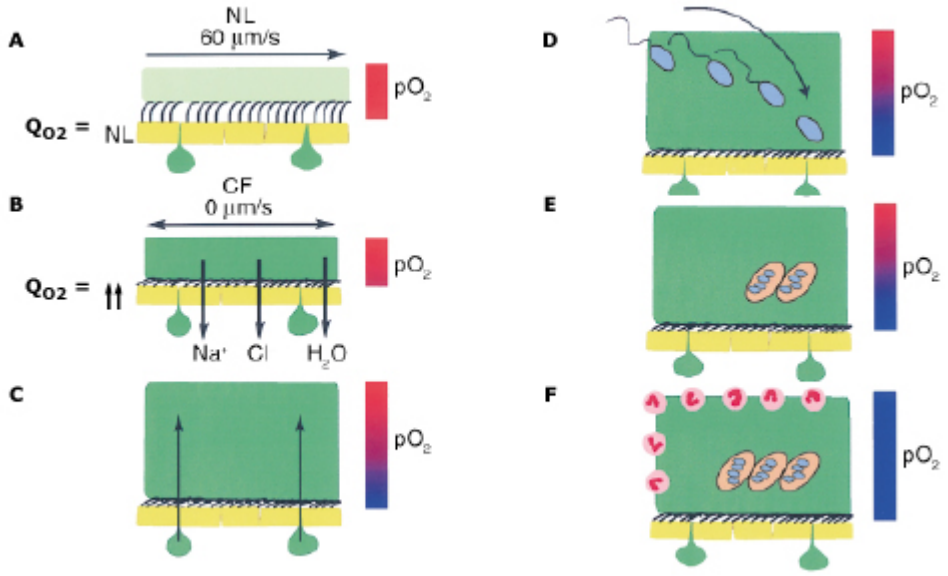
Schematic representation of the biosynthesis and function of CFTR in an epithelial cell and of mechanisms of dysfunction associated with different cystic fibrosis mutations.

CFTR: cystic fibrosis transmembrane conductance regulator; ER: endoplasmic reticulum; PKA: phosphokinase A; NB01 and NB02: nuclear binding folds.

Adapted from Welsh, MJ, Tsui, L-C, Boat, T, Beaudet, AL. Cystic fibrosis. In: The Metabolic and Molecular Basis of Inherited Disease, Scriver, CR, Beaudet, AL, Sly, WS, et al (Eds), McGraw-Hill, New York, 1995, p. 3801.

Graphic 80517 Version 2.0

Schematic model of the pathogenic events hypothesized to lead to chronic P. aeruginosa infection in airways of CF patients



(A) On normal airway epithelia, a thin mucus layer resides atop the periciliary liquid layer (PCL), shown as clear. The presence of the low-viscosity PCL facilitates efficient mucociliary clearance (denoted by vector). A normal rate of epithelial O_2 consumption (Q_{O2}; left) produces no O_2 gradients within this thin airway surface liquid (ASL) (denoted by bar). (B-F) CF airway epithelia. (B) Excessive CF volume depletion (denoted by vertical arrows) removes the PCL, mucus becomes adherent to epithelial surfaces, and mucus transport slows/stops (bidirectional vector). The raised O_2 consumption (left) associated with accelerated CF ion transport does not generate gradients in thin films of ASL. (C) Persistent mucus hypersecretion (denoted as mucus secretory gland/goblet cell units) with time increases the height of luminal mucus massages/plugs. The raised CF epithelial Q_{O2} generates steep hypoxic gradients in thickened mucus masses. (D) P. aeruginosa bacteria deposited on mucus surfaces penetrate actively and/or passively (due to mucus turbulence) into hypoxic zones within the mucus masses. (E) P. aeruginosa adapts to hypoxic niches within mucus masses with increased alginate formation and the creation of macrocolonies. (F) Macrocolonies resist secondary defenses, including neutrophils, setting the stage for chronic infection. The presence of increased macrocolony density and, to a lesser extent neutrophils, render the now mucopurulent mass hypoxic.

NL: normal; CF: cystic fibrosis.

Graphic 51872 Version 2.0

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Conflict of interest policy

Spinal muscular atrophy

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INTRODUCTION — Neuromuscular disorders that present in the newborn period with hypotonia and weakness are caused by a variety of conditions that affect the central nervous system (brain or spinal cord), peripheral nervous system, or skeletal muscle. Conditions that affect the anterior horn cells of the spinal cord are listed in the table (table 1).

This topic will review clinical aspects of spinal muscular atrophy (SMA).

CLINICAL FEATURES — SMA disorders are characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. These diseases are classified as types 1 through 4 depending upon the age of onset and clinical course.

The incidence of spinal muscular atrophy ranges from 4 to 10 per 100,000 live births, and the carrier frequency of disease-causing SMN1 mutations ranges from 1/90 to 1/50 [1]. (See 'Genetics' below.)

Classification — SMA type 1, also known as infantile spinal muscular atrophy or Werdnig-Hoffmann disease, is the most common and severe type of SMA. It typically presents in the neonatal period. However, mothers of affected patients may recognize a decrease or loss of fetal movement in late pregnancy. Some experts classify prenatal onset as SMA type 0 [2,3]. In these neonatal forms, symptoms progress rapidly, and the majority of infants die before one year of age from respiratory failure [4,5]. Nevertheless, long-term survivors have been reported [6-8]. This is perhaps due, in part, to advances in the care of chronic respiratory insufficiency and to more aggressive care. (See 'Management' below.)

SMA 2 (intermediate form) and SMA 3 (mild form; Kugelberg-Welander disease) have a later onset and a less severe course [9,10]. SMA 2 presents between 3 and 15 months of age, whereas SMA 3, the least severe, typically presents with signs of weakness at or after one year of age and progresses to a chronic course. In a study of children and adolescents with SMA 2 and SMA 3, muscle strength was reduced to a variable extent [11]. Although the muscle weakness affected motor function, walking, transfer from lying or sitting to the standing position, and stair-climbing were possible in some children. The outcome depends primarily upon the severity of muscle weakness at presentation rather than the age of onset, but earlier onset tends to correlate with greater weakness [12].

Adult onset of SMA (type 4) usually presents in the second or third decade of life and is otherwise similar to SMA type 3 [1,13-15].

Manifestations — Patients with all forms of SMA have diffuse symmetric proximal muscle weakness that is greater in the lower than upper limbs and absent or markedly decreased deep tendon reflexes [16]. Infants with SMA 1 have a severe symmetric flaccid paralysis and are unable to sit unsupported. Because the upper cranial nerves are spared, patients with SMA 1 typically have an alert expression, furrowed brow, and normal eye movements. However, weakness of the bulbar muscles results in a weak cry, poor suck and swallow reflexes, pooling of secretions, aspiration, and fasciculations of the tongue. Arthrogryposis (multiple joint contractures) may occasionally be present in those with a prenatal onset,

which is sometimes classified as SMA 0. Infants with SMA of neonatal onset may present with signs of fetal hypokinesia deformation sequence including polyhydramnios, intrauterine growth retardation, skeletal abnormalities with multiple articular contractures, and pulmonary hypoplasia.

All SMA types are associated with a restrictive, progressive respiratory insufficiency, particularly SMA 1 [17]. In SMA 1, respiratory muscle weakness leads to progressive respiratory failure. The intercostal muscles typically are more affected than the diaphragm, resulting in paradoxical breathing (inspiratory efforts cause the rib cage to move inward and the abdomen to move outward) and the development of a characteristic bell-shaped chest deformity. Cardiac muscle is not affected.

GENETICS — The inheritance pattern of 5q-related SMAs is autosomal recessive [1,18]. The different forms of 5q-SMA are caused by biallelic deletions or mutations in the survival motor neuron 1 (SMN1) gene on chromosome 5q13.2 [19-21]. The most common mutation of the SMN1 gene is a deletion of exon 7 [22]. Approximately 94 percent of patients with clinically typical SMA carry homozygous deletions of exon 7. SMN protein appears to play a role in mRNA synthesis in motor neurons and also may inhibit apoptosis [23,24]. The level of SMN protein correlates with severity of disease [25].

The differences in SMN protein and phenotypic expression appear to be related in part to a modifying gene, called SMN2. The SMN1 and SMN2 genes are more than 99 percent identical and lie within an inverted duplication on chromosome 5q13.2 [26]. The SMN1 gene lies telomeric of the SMN2 gene. Loss of the SMN1 protein is partially compensated by SMN2 protein synthesis, a mechanism that may explain some but not all of the phenotypic variability in patients with SMA [27]. The presence of three or more copies of SMN2 is associated with a milder phenotype [1,28].

While the most common forms of SMA are caused by deletions or mutations in the SMN1 gene on chromosome 5q (ie, 5q SMAs), there are a number of rare non-5q spinal muscular atrophies [29-31]. The non-5q SMAs are genetically and clinically heterogeneous (table 2).

Genetic counseling — Affected individuals with SMA and their parents should be referred for genetic counseling, which may be challenging. Occasionally, carriers have normal dosage studies for the SMN1 deletion because they have a deletion on one homologue and a SMN1 gene duplication on the other. There is also a significant de novo mutation rate (1.7 percent).

Genetic counseling, prenatal diagnosis, and carrier testing can be offered to those with a family history of SMA (or SMA-like disorders) in whom the genetic basis of the condition has been defined [32]. However, there is no consensus regarding the utility of preconception and prenatal screening for SMA in those without a family history. The American College of Medical Genetics recommends offering carrier testing to all couples regardless of race or ethnicity [33,34]. In contrast, the American College of Obstetricians and Gynecologists (ACOG) states that such screening is **not** recommended in the general population at this time, but should be offered to those who first have genetic counseling that includes discussion of the sensitivity, specificity, and limitations of screening [32].

DIAGNOSIS — Molecular genetic testing with targeted mutation analysis can confirm the diagnosis of SMA by detection of homozygous deletions of the telomeric exons 7 and 8 of the SMN1 gene [1,2,16]. The exon 7 deletion is by far the most common mutation in SMA, but point mutations also occur. Thus, sequencing of the SMN1 gene should be pursued if the diagnosis is typical of SMA and only a single deletion is identified.

In patients with suspected SMA who have a normal SMN1 gene by molecular genetic testing, the diagnosis of SMA is made clinically by electromyography and nerve conduction studies, and confirmed by muscle biopsy [1]. Nevertheless, absence of a deletion in SMN1 casts serious doubt on the diagnosis. In this situation, it is imperative to consider other conditions in the differential diagnosis (eg, spinal muscular atrophy with respiratory distress type 1) and/or sequencing of the SMN1 gene. (See 'Differential diagnosis' below.)

Electromyography — Electromyography in SMA shows abnormal spontaneous activity with fibrillations and positive sharp waves [35,36]. The mean duration and amplitude of motor unit action potentials are increased, and many are polyphasic. Nerve conduction velocities are normal or slightly decreased, and sensory nerve action potentials are normal. Serum creatine kinase concentration typically is normal or slightly elevated, although in rare cases it can be moderately elevated.

Muscle biopsy — Muscle biopsy reveals large groups of circular atrophic type 1 and 2 muscle fibers interspersed among fascicles of hypertrophied type 1 fibers [35]. The enlarged fibers have been reinnervated by the sprouting of surviving nerves and are three to four times larger than normal. Histologic diagnosis may be more difficult to make in the newborn infant because only widespread atrophy of muscle fibers may be seen. A later repeat biopsy is needed to demonstrate the mixture of hypertrophied and atrophic fibers seen after reinnervation occurs.

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of infantile SMA (types 0 and 1) includes other causes of floppy (hypotonic) infants [1]. Conditions that affect the anterior horn cells of the spinal cord are listed in the table (table 1).

Arthrogryposis multiplex congenita — Arthrogryposis multiplex congenita is a syndrome characterized by contractures of multiple joints [37,38]. It is associated with a heterogeneous group of disorders. Most cases are neurogenic (90 of 96 children in one study of pathologic features); the remaining cases have primary muscle disease [39]. Neurogenic arthrogryposis can result from disorders of the central nervous system, genetic syndromes, and chromosomal aberrations. The severity is variable. Bulbar and respiratory muscle functions are severely affected in some cases, which have a poor prognosis [40]. In others, muscle strength does not deteriorate and may improve.

The disorders that result in neurogenic arthrogryposis are genetically heterogeneous. Some patients (6 of 12 in one series) have deletions of the SMN1 gene that is associated with SMA [41,42].

X-linked infantile spinal muscular atrophy — X-linked infantile spinal muscular atrophy (XL-SMA or SMAX2) is a rare disorder characterized by congenital hypotonia, areflexia, congenital contractures and/or fractures, and loss of anterior horn cells [43,44]. The disease course in XL-SMA is similar to the severe forms of classic neonatal SMA (SMA types 0 and 1) [44]. The disorder is associated with mutations in the gene for ubiquitin activating enzyme 1 (called UBA1 gene or UBE1 gene) [45].

Spinal muscular atrophy with respiratory distress type 1 — Spinal muscular atrophy with respiratory distress type 1 (SMARD1), also known as autosomal recessive distal spinal muscular atrophy 1 (DSMA1), is characterized by diaphragmatic paralysis and respiratory failure that presents early in life, generally from one to six months of age [46,47]. There is a high frequency of intrauterine growth retardation and premature birth. Eventration of the diaphragm may be seen on chest radiographs. Clinical deterioration continues for the first two years of life, followed by stabilization or less often by some clinical improvement [47]. While all affected children remain dependent on mechanical ventilation and require full time care, some are able to participate in daily life activities and schooling. The disorder is caused by mutations in the immunoglobulin mu binding protein 2 (IGHMBP2) gene.

Congenital myasthenic syndromes — Newborns with congenital myasthenia frequently have ptosis, in contrast to patients with the transient disorder. In addition, they typically demonstrate ophthalmoplegia and bulbar and respiratory muscle weakness. Affected infants may have fluctuating generalized hypotonia, weakness, and life-threatening episodes of apnea. Arthrogryposis can be present at birth. (See "Neuromuscular junction disorders in newborns and infants", section on 'Congenital myasthenic syndromes'.)

Congenital myopathies — Congenital myopathies (eg, nemaline myopathy, central core disease, myotubular myopathy, and congenital fiber type disproportion) present with hypotonia and weakness that is greater proximally than distally. Tendon reflexes are decreased in proportion to the weakness. (See

"Congenital myopathies".)

Hypoxic-ischemic myelopathy — Severe hypoxic-ischemic injury can sometimes result in hypotonia or flaccid paralysis with diminished or absent reflexes caused by death of spinal motor neurons [48]. In these cases, infants typically have encephalopathy and may have seizures or signs of other end-organ damage. (See "Clinical features, diagnosis, and treatment of neonatal encephalopathy".)

Glycogen storage disease II — The classic infantile form of glycogen storage disease II (Pompe disease) is characterized by hypertrophic cardiomyopathy and severe generalized muscular hypotonia that presents during the first few months of life. The tongue may be enlarged. Hepatomegaly also may be present and is usually due to heart failure. (See "Lysosomal acid maltase deficiency (glycogen storage disease II, Pompe disease)".)

Prader-Willi syndrome — Neonatal hypotonia is one of the hallmark features of Prader-Willi syndrome. The profound hypotonia can lead to asphyxia. Affected infants often have feeding difficulties, including a poor suck, which may lead to failure to thrive. Other common features include a weak cry and genital hypoplasia. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome".)

The hypotonia associated with Prader-Willi syndrome improves gradually during infancy, unlike SMA type 1 in which progressive deterioration occurs.

Traumatic myelopathy — Myelopathy caused by trauma to the high cervical spinal cord is a rare cause of hypotonia in infants. This condition results in a flaccid paralysis, which may be asymmetric, and absent reflexes. Physical examination may reveal evidence of trauma, such as bruising or fractures. If no accompanying brain injury is present, the infant will be alert with no cranial nerve abnormalities. A pin prick on the face will elicit a facial grimace but no response below the neck. A useful sign is withdrawal to a noxious stimulus of a limb with no spontaneous activity. Bladder distension, priapism, and absence of sweating below the level of the spinal lesion typically will appear as the myelopathy evolves over several days.

Zellweger syndrome — Newborns with Zellweger syndrome present with a characteristic craniofacial dysmorphism. Neurologic abnormalities include hypotonia and weakness with absent reflexes, severe impairment of hearing and vision, neonatal seizures, and developmental delay. Hepatomegaly is common. (See "Peroxisomal disorders", section on 'Zellweger syndrome'.)

MANAGEMENT — Treatment for SMA is supportive and directed at providing nutrition and respiratory assistance as needed, and treating or preventing complications of weakness [16,49]. Physical therapy may be helpful. Spinal bracing can be used to delay the development of progressive scoliosis that is caused by muscle weakness. However, spinal bracing applied to patients with SMA types 1 or 2 while in the sitting position significantly reduces expiratory tidal volume, and thus it should be used cautiously [50].

Respiratory muscle weakness often results in difficulty clearing lower respiratory secretions and hypoventilation during sleep [51]. Important interventions include methods for mobilization and clearance of airway secretions, and respiratory support.

- Secretion mobilization and clearance techniques involve manual or mechanical chest physiotherapy with postural drainage, and manual cough assistance and/or use of a mechanical insufflation/exsufflation device [51].
- Noninvasive nasal ventilation is an alternative to tracheostomy and conventional ventilator support in some children with respiratory failure [17,52,53]. Decisions about initiating ventilator support should be individualized, taking into account the medical facts and the values of the family [54].

Limited data suggest that survival has increased in patients with SMA type 1 born from 1995 through

2006 compared with those born from 1980 to 1994 [8]. Ventilation for >16 hours a day, use of mechanical insufflation-exsufflation device, and gastrostomy tube feeding were significantly and independently associated with prolonged survival, while year of birth was not. Thus, longer survival in the later time period appears to be related to more aggressive care.

Treatments that enhance the level of SMN protein may be available in the future [55]. Gene therapy using an adeno-associated virus vector to augment spinal cord SMN expression has shown promise in a mouse model of SMA [56]. Another promising approach involves intracerebroventricular or systemic injection of antisense oligonucleotides that effectively restore SMN expression [57-59]. Drugs that selectively modify the splicing of the survival motor neuron gene 2 (SMN2) messenger RNA also have a potential therapeutic role [60,61].

Pregnancy — As noted earlier, all SMA types are associated with a restrictive, progressive respiratory insufficiency. Thus, pregnancy in women with SMA is associated with increased risk because of impaired respiratory function, which is further limited in many cases by kyphoscoliosis and wheel chair dependency [62]. In addition, limited retrospective data suggest that pregnancy in women with SMA is often complicated by preterm labor [63] and an increased frequency of urinary tract infections [64].

Despite these issues, no deleterious effects have been detected with respect to fetal outcome [62,63]. Successful pregnancies have been reported in women with SMA who have forced vital capacities of 50 to 70 percent of predicted values [65-67].

Ideally, such pregnancies should be managed by obstetricians and anesthesiologists familiar with neuromuscular disorders [62]. There are no guidelines regarding mode of delivery. Successful outcomes have been reported with both cesarean section and vaginal delivery [63,64]. Spinal and epidural anesthesia may be difficult because of severe spine deformity [64]. However, there is no evidence of an increased risk of malignant hyperthermia in SMA [62].

Women with SMA may experience worsening of muscle weakness after the second trimester and/or delayed postpartum recovery [63,66]. In one report, an uneventful pregnancy and cesarean section was followed by extreme muscle weakness with dyspnea and bulbar involvement lasting one to two weeks [66]. Motor function then improved to baseline.

Issues related to prenatal screening are discussed above. (See 'Genetic counseling' above.)

SUMMARY AND RECOMMENDATIONS

- Spinal muscular atrophy (SMA) disorders are characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. These diseases are classified as types 1 through 4 depending upon the age of onset and clinical course (see 'Clinical features' above).
    - SMA type 1 (infantile spinal muscular atrophy or Werdnig-Hoffmann disease) is the most common and severe type of SMA. It typically presents in the neonatal period. Symptoms progress rapidly, and the majority of infants die before one year of age from respiratory failure.
    - SMA type 2 (intermediate form) and type 3 (Kugelberg-Welander disease) have a less severe course. SMA 2 presents between three and 15 months of age. SMA 3, the least severe, typically presents at or after one year of age and progresses to a chronic course.
    - Adult onset of SMA (type 4) usually presents in the second or third decade of life and is otherwise similar to SMA type 3.
- Patients with all forms of SMA have diffuse symmetric proximal muscle weakness that is greater in the lower than upper limbs and absent or markedly decreased deep tendon reflexes. Infants with SMA 1 have a severe symmetric flaccid paralysis and are unable to sit unsupported. All SMA types,

particularly SMA 1, are associated with a restrictive, progressive respiratory insufficiency. (See 'Manifestations' above.)

- The inheritance pattern of the common forms of SMA is autosomal recessive. These forms are caused by biallelic deletions or mutations in the SMN1 gene on chromosome 5q13. The differences in SMN protein and phenotypic expression appear to be related in part to a modifying gene (SMN2) that lies close to the SMN1 gene. The rare non-5q spinal muscular atrophies, such as X-linked infantile spinal muscular atrophy, are genetically and clinically heterogeneous (table 2). Affected individuals with SMA and their parents should be referred for genetic counseling. (See 'Genetics' above and 'Genetic counseling' above.)
- Molecular genetic testing can confirm the diagnosis in infants and children with suspected SMA. In patients with suspected SMA who have a normal SMN1 gene by molecular genetic testing, the diagnosis of SMA is made clinically by electromyography, nerve conduction studies, and muscle biopsy. Nevertheless, absence of a deletion in SMN1 casts serious doubt on the diagnosis. (See 'Diagnosis' above.)
- The differential diagnosis of infantile SMA (types 0 and 1) includes other causes of floppy infants. Of particular importance are the following conditions (see 'Differential diagnosis' above):
  - Arthrogryposis multiplex congenita
  - X-linked infantile spinal muscular atrophy
  - Spinal muscular atrophy with respiratory distress type 1
  - Congenital myasthenic syndromes
  - Congenital myopathies
  - Hypoxic-ischemic myelopathy
  - Lysosomal acid maltase deficiency
  - Prader-Willi syndrome
  - Traumatic myelopathy
  - Zellweger syndrome

  Conditions that affect the anterior horn cells of the spinal cord are listed in the table (table 1).
- Treatment for SMA is supportive and directed at providing nutrition and respiratory assistance as needed, and treating or preventing complications of weakness. (See 'Management' above.)

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Topic 6146 Version 15.0

GRAPHICS

Neuromuscular disorders presenting in newborns

Anterior horn cell disorders
Acute infantile spinal muscular atrophy
Traumatic myelopathy
Hypoxic-ischemic myelopathy
Arthrogryposis multiplex congenita
Congenital motor or sensory neuropathies
Charcot-Marie-Tooth disease
Congenital hypomyelinating neuropathy
Dejerine-Sottas disease
Hereditary sensory and autonomic neuropathy
Neuromuscular junction disorders
Transient acquired neonatal myasthenia
Congenital myasthenia
Magnesium toxicity
Aminoglycoside toxicity
Infantile botulism
Congenital myopathies
Nemaline myopathy
Central core disease
Multiminicore disease
Centronuclear (myotubular) myopathies
Congenital fiber type disproportion myopathy

Muscular dystrophies
Dystrophinopathies (Duchenne and Becker muscular dystrophy)
Classic form of congenital muscular dystrophy
With merosin deficiency
Without merosin deficiency
Congenital muscular dystrophy-dystroglycanopathy with central nervous system abnormalities
Walker-Warburg disease
Muscle-eye-brain disease
Fukuyama disease
Congenital muscular dystrophy with cerebellar atrophy/hypoplasia
Congenital muscular dystrophy with occipital argyria
Early infantile facioscapulohumeral dystrophy
Congenital myotonic dystrophy
Metabolic and multisystem diseases
Disorders of glycogen metabolism
Acid maltase deficiency
Severe neonatal phosphofructokinase deficiency
Severe neonatal phosphorylase deficiency
Debrancher deficiency
Primary carnitine deficiency
Peroxisomal disorders
Neonatal adrenoleukodystrophy
Cerebrohepatorenal syndrome (Zellweger)
Disorders of creatine metabolism
Mitochondrial myopathies
Cytochrome c oxidase deficiency

Graphic 66572 Version 4.0

Simplified classification of non-5q spinal muscular atrophies

Disease/phenotype, selected distinguishing features	Inheritance	Gene/locus	OMIM designations	MIM numbe
Distal spinal muscular atrophy/distal hereditary motor neuropathy or neuronopathy				
SMA with respiratory distress or diaphragmatic SMA	AR	IGHMBP2	SMARD1/HMN6 /DSMA1	604320
Distal HMN	AR	9p21.1-p12	DSMA2/HMNJ	605726
Distal SMA	AR	11q13	DSMA3/HMN3/HMN4	607088
Lower motor neuron syndrome with childhood onset	AR	PLEKHG5	DSMA4	611067
Distal SMA with late adolescent or young adult onset	AR	DNAJB2	DSMA5	614881
Distal HMN/SMA, juvenile	AD	7q34-q36	HMN1	182960
Distal adult HMN, Type IIA	AD	HSPB8	HMN2A	158590
Distal HMN, Type IIB	AD	HSPB1	HMN2B	608634
Distal HMN, Type IIC	AD	HSPB3	HMN2C	613376
Distal SMA with upper-limb predominance, Type VA	AD	GARS	HMN5	600794
Charcot-Marie-Tooth disease 2D	AD	GARS	CMT2D	601472
Distal SMA with upper-limb predominance, Type VB	AD	BSCL2	HMN5	600794
Silver spastic paraplegia syndrome	AD	BSCL2	SPG17	270685
Distal HMN with vocal cord paralysis	AD	2q14	HMN7A	158580
Distal HMN with vocal cord paralysis	AD	DCTN1	HMN7B	607641
Proximal spinal muscular atrophy (+/- distal involvement)				
SMA with late-onset, Finkel type	AD	VAPB	SMAFK	608627
SMA, Jokela type	AD	22q11.2-q13.2	SMAJ	615048

Congenital SMA with contractures/SMA, congenital, nonprogressive, with lower limb predominance	AD	TRPV4		600175
Scapuloperoneal SMA	AD	TRPV4	SPSMA	181405
Charcot-Marie-Tooth, Type 2C	AD	TRPV4	HMSN2C	606071
SMA with lower extremity predominance 1 (early onset)	AD	DYNC1H1	SMALED1	158600
SMA with lower extremity predominance 2 (early onset)	AD	BICD2	SMALED2	615290
Hereditary motor and sensory neuropathy, Okinawa type	AD	TFG	HMSNO	604484
Other non-5q spinal and bulbar muscular atrophies, SMA plus types				
Lethal arthrogryposis with anterior horn cell disease	AR	GLE1	LAAHD	611890
Lethal congenital contracture syndrome 1	AR	GLE1	LCCS1	253310
Pontocerebellar hypoplasia type 1A	AR	VRK1	PCH1A	607596
Pontocerebellar hypoplasia type 1B	AR	EXOSC3	PCH1B	614678
Brown-Vialetto-Van Laere syndrome 1	AR	SLC52A3	BVVLS1	211530
Fazio-Londe disease, bulbar palsy	AR	SLC52A3		211500
Brown-Vialetto-Van Laere syndrome 2	AR	SLC52A2	BVVLS2	614707
Spinal muscular atrophy with progressive myoclonic epilepsy	AR	ASAH1	SMAPME	159950
Spinal and bulbar muscular atrophy (Kennedy disease)	XR	AR	SMAX1/SBMA	313200
Infantile SMA with arthrogryposis	XR	UBA1	SMAX2	301830
Distal SMA, X-linked	XR	ATP7A	SMAX3	300489

AD = autosomal dominant; AR = autosomal recessive; HMN = hereditary motor neuropathy or neuronopathy; DSMA = distal spinal muscular atrophy; SMA = spinal muscular atrophy; XR = X-linked recessive

Modified with permission from: Darras BT. Non-5q spinal muscular atrophies: the alphanumeric soup thickens. Neurology 2011; 77:31. Copyright © 2011 Lippincott Williams & Wilkins. Additional data from: Online Inheritance in Man

Graphic 73754 Version 8.0

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Conflict of interest policy

Genetics and clinical presentation of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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INTRODUCTION — Defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol accounts for more than 90 percent of cases of congenital adrenal hyperplasia [1-3]. This conversion is mediated by 21-hydroxylase, or in current terminology, CYP21A2.

The most severely affected individuals with classic congenital adrenal hyperplasia due to CYP21A2 deficiency present during the neonatal period and early infancy with adrenal insufficiency with or without salt wasting, or later, with virilization. Females have genital ambiguity.

"Nonclassic," or late-onset CYP21A2 deficiency, does not manifest with neonatal genital ambiguity; rather, it presents later in life with signs of androgen excess. Clinical features in late childhood include premature pubarche, acne, and accelerated bone age; adolescent and adult females present with acne, hirsutism, and menstrual irregularity [4-10].

The pathophysiology, genetics, and clinical manifestations of the nonclassic form of congenital adrenal hyperplasia due to CYP21A2 deficiency are reviewed here. The diagnosis and treatment of late onset CP21A2 deficiency, and the classic form of CYP21A2 deficiency are reviewed separately. (See "Diagnosis and treatment of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and "Diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and "Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults" and "Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in infants and children".)

PREVALENCE — Based upon neonatal screening studies that detect classic congenital adrenal hyperplasia, CYP21A2 deficiency is a common inherited disorder. The prevalence based upon such studies has been estimated to be about 1 in 14,200 live births, ranging from 1 in 28,000 in the Chinese to 1 in 280 in Yupik Eskimos. (See "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency", section on 'Prevalence'.)

The nonclassic form (late-onset) is one of the most common autosomal recessive diseases, and the frequency is ethnic-specific. Among whites, the prevalence of the nonclassic form may be as high as 1 in 1000 to 1 in 100 [11-13], with the prevalence being even higher among Mediterraneans, Hispanics, and Eastern European Jews [1]. Most patients with the nonclassic form will not be identified by the neonatal screening studies, which are based upon detection of very high levels of 17-hydroxyprogesterone [14].

Women with the nonclassic form typically present with oligomenorrhea and hyperandrogenism and, therefore, may be indistinguishable from polycystic ovary syndrome (PCOS). The prevalence of congenital adrenal hyperplasia in women who present with apparent PCOS is variable, depending upon the population studied. As an example, in two different regions of Turkey, the prevalence ranged from 9.5 to 66 percent [15,16]. In the United States, the disorder occurs in about 1 to 4 percent of white women with clinical evidence of androgen excess [1,17,18]. (See "Clinical manifestations of polycystic ovary

syndrome in adults".)

The frequency of heterozygote carriers has been reported to be about 1 in 60 to 80 in some studies [11,19], but closer to 1 in 10 in another study using mutation analysis in a European population [20].

In children who present with premature pubarche (premature development of pubic hair), the prevalence of nonclassic CYP21A2 deficiency has been reported to be very low [21], or as high as 30 percent, in high-risk ethnic groups [22]. In an unselected population of 31 such patients, none were found to have the disorder [23].

The prevalence in men with idiopathic oligospermia is not established. However, in one study of Jewish men presenting to an infertility clinic, there were no cases found in either 222 subjects with abnormal semen analysis or a concurrent control group of 262 men with normal semen analysis [24].

PATHOPHYSIOLOGY — The defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol in patients with CYP21A2 deficiency results in decreased cortisol synthesis and therefore increased corticotropin (ACTH) secretion (figure 1). The resulting adrenal stimulation leads to increased production of androgens. The severity of disease relates to the degree to which the mutations compromise enzyme activity. In patients with the nonclassic form, enzymatic activity is reduced but sufficient to maintain normal glucocorticoid and mineralocorticoid production, at the expense of excessive androgen production.

GENETICS — As with the other forms of congenital adrenal hyperplasia, CYP21A2 deficiency is transmitted as an autosomal recessive disorder. Humans have two CYP21A genes, a non-functional pseudogene (CYP21A1 or CYP21P) and the active gene (CYP21A2 or CYP21), both located in a 35-kilobase region of chromosome 6p21.3 within the major histocompatibility locus.

The two CYP21A genes are more than 90 percent homologous. This high degree of homology facilitates recombination events during meiosis, with consequent exchanges of segments of DNA between the two genes.

- Large or unequal cross-over exchanges can result in a large deletion of the active gene, or a non-functioning hybrid gene. Patients who are homozygous or heterozygous for such mutations have classic forms of CAH.
- The exchange of smaller amounts of material can result in hybrid CYP21A1/CYP21A2 gene products with reduced but not absent enzyme activity. A patient who is heterozygous for this and a typical large gene deletion may have nonclassic CYP21A2 deficiency [25]. (See "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency", section on 'Genetics'.)

Genotype versus phenotype — It is not always possible to predict the phenotype of these patients from the specific mutation(s) of the CYP21A2 gene, but there are general correlations between genotype and phenotype. Patients with CYP21A2 mutations can be divided into groups according to the predicted effect of the mutation on 21-hydroxylase enzymatic activity. (See "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency", section on 'Genotype versus phenotype'.)

Women with the late-onset form may be either compound heterozygotes (with a classic mutation and a variant allele) or heterozygotes with two variant alleles, allowing for 20 to 60 percent of normal enzymatic activity (eg, with point mutations leading to conservative amino acid substitutions such as Val281Leu).

Women who are compound heterozygotes for two different CYP21A2 mutations usually have the phenotype associated with the less severe of the two genetic defects [26].

Obligate heterozygote carriers (with one normal allele) may have mild biochemical abnormalities [27-29], but no clinically important endocrine disorder.

Despite these general correlations, the CYP21A2 deficiency phenotype does not always correlate precisely with the genotype, suggesting that other genes influence the clinical manifestations. (See "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency", section on 'Genotype versus phenotype'.)

Prenatal diagnosis, neonatal screening and genotyping for CYP21A2 deficiency are discussed separately. (See "Diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency".)

CLINICAL PRESENTATIONS

Children — Children with nonclassic congenital adrenal hyperplasia present after the neonatal period with signs of hyperandrogenism, without adrenal insufficiency. Clinical features may include:

- Premature pubarche. Children with nonclassic CYP21A2 deficiency typically differ from children with ordinary premature adrenarche in having a bone age advanced more than 2.0 SD for age. (See "Premature adrenarche", section on 'Virilizing congenital adrenal hyperplasia'.)
- Medication-resistant cystic acne [30].
- Accelerated growth with tall stature as children.

However, these children may enter puberty early, with early epiphyseal closure, leading to short stature as an adult, although short stature is not a consistent feature [1,10,31]. The management of children is discussed separately. (See "Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in infants and children".)

Female reproduction — Adolescent and adult women have acne, hirsutism, and menstrual irregularity that are indistinguishable from the polycystic ovary syndrome [8,32,33].

In one study of 220 females with nonclassic congenital adrenal hyperplasia the clinical presentation varied by the age of the patient [33]:

- Nearly all patients younger than 10 years presented with premature pubarche; clitoromegaly and acne were less common (20 percent).
- The presenting clinical features in adolescents and adult women included hirsutism (59 percent), oligomenorrhea (54 percent), acne (33 percent), infertility (13 percent), clitoromegaly (10 percent), alopecia (8 percent), and primary amenorrhea (4 percent).
- The prevalence of hirsutism increased significantly with age, from 70 percent in adolescents to 90 percent in 40 to 49 year old women. When present, the degree of hirsutism was similar at all ages.

The following features may help distinguish nonclassic congenital adrenal hyperplasia and polycystic ovary syndrome [33,34]:

- Nonclassic congenital adrenal hyperplasia is uncommon in African-American and Hispanic-Puerto Rican women [35,36].
- Insulin resistance may be more severe, but probably not more common in polycystic ovarian

syndrome [33,34].

- Polycystic ovaries on ultrasound are less common in nonclassic congenital adrenal hyperplasia (40 versus 70 percent) [33,34].
- Obesity is more common in women with polycystic ovary disease [18].

In a questionnaire-based study, women with nonclassic congenital adrenal hyperplasia show increased masculinization (defeminization) when compared to normal women [37]. These attributes were more extreme in women with the classic form of the disease. A second study using interviews and questionnaires in women with nonclassic and classic 21-hydroxylase deficiency extended these findings. Among 22 women with the classic disorder, none reported sexual fantasies or actual experience with same-sex partners, while 19 of 79 women with the nonclassic form reported sexual fantasies and 3 of 77 had same-sex encounters [38].

Fertility — Women with the classic form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency have low fertility rates that correlate with the severity of the mutation. (See "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency", section on 'Female reproduction'.)

In contrast, subfertility is milder in women with the nonclassic form of 21-hydroxylase deficiency. Many women conceive spontaneously, while others have anovulatory infertility that responds to glucocorticoids alone or combined with clomiphene citrate [39]. (See "Ovulation induction with clomiphene citrate".)

However, the risk of spontaneous abortion (SAB) appears to be high in these women compared to normal women (≥25 percent versus 10 to 15 percent, respectively) [32,40-44]. Treatment with glucocorticoids may lower this risk, as illustrated in a study of 85 women with the nonclassic form who were pursuing pregnancy. Women who had received therapy with glucocorticoids in order to conceive (n = 36), had a lower risk of SAB than those who had not received glucocorticoids (n = 49; 6.5 versus 26.3 percent, respectively) [43].

Risk of classic CAH in offspring — Women with the late-onset form who seek fertility should be aware of the potential risk of giving birth to an infant with classic CYP21A2 deficiency. Women who carry the classic (severe) mutation whose partner also carries the classic mutation are at risk of having an infant who is homozygous for the severe mutation. This was illustrated in a report of 162 live births in 101 women with the late-onset form [40]. At birth, 4 (2.5 percent) and 24 (15 percent) of the 162 infants were diagnosed with the classic form and the late-onset nonclassic form, respectively.

If genetic screening has not been performed by a couple prior to conception, the birth of an affected infant should prompt consideration of genotyping and consideration of prenatal diagnosis in subsequent pregnancies.

However, genotyping for CYP21 mutations is not widely available, usually not covered by insurance, and does not detect all mutations; as a result, recommendations for screening protocols for these couples have not been established [45].

Prenatal diagnosis, neonatal screening, and genotyping for CYP21A2 deficiency are discussed separately. (See "Diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency".)

Men — In males, it can be difficult to differentiate between simple virilizing forms of "classic" CYP21A2 deficiency and "non-classic" forms. Both can present in childhood with premature pubarche or adrenarche and eventual short stature. After puberty, nonclassic men usually present with acne or infertility. Asymptomatic individuals (obligate heterozygote carriers) may be diagnosed because of an

affected family member.

Boys and men with classic CYP21A2 deficiency often develop testicular masses (testicular adrenal rest tumors). During adulthood, these are often associated with oligospermia and infertility. Although most men with the nonclassic form are thought to have normal testicular function and normal fertility, some do present with testicular adrenal rests and infertility [9,10,46].

In general, treatment is not necessary for men with nonclassic CYP21A2 deficiency who do not desire future fertility. However, in men with a testicular mass and/or oligospermia, glucocorticoid therapy should be given until fertility is no longer desired [47]. (See "Diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and "Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults", section on 'Testicular adrenal rests'.)

Adrenal incidentalomas — Although 60 percent of patients with unilateral adrenal incidentalomas, and even more of those with bilateral incidentalomas, have exaggerated serum 17-hydroxyprogesterone responses to ACTH stimulation [1], the prevalence of germline CYP21A2 mutations is low. However, unilateral and bilateral adrenal incidentalomas were found in 10 of 12 patients with simple virilizing and five of seven patients with late-onset CAH, as well as 9 of 10 heterozygotic siblings [48]. Most tumors had a diameter of less than 2 cm, but three patients had masses more than 5 cm in size. Adrenal masses in children with CYP21A2 deficiency are usually benign [1].

SUMMARY — Nonclassic CYP21A2 deficiency is one of the most common autosomal recessive diseases, and the frequency is ethnic-specific. (See 'Prevalence' above.) The genetics of this disorder are discussed above. (See 'Genetics' above.)

- Children may present with precocious pubarche, medication-resistant acne, and accelerated growth. (See 'Clinical presentations' above.)
- In adolescent girls and adult women, nonclassic CYP21A2 deficiency is characterized by acne, hirsutism, and menstrual irregularity (oligoovulation) that are indistinguishable from the polycystic ovary syndrome. (See 'Children' above and 'Female reproduction' above.)
- Oligo/anovulatory infertility is common in women who are untreated. Most conceive with ovulation induction (glucocorticoids alone or combined with clomiphene citrate), and the rate of early pregnancy loss appears to be no higher than normal after treatment begins. (See 'Fertility' above.)
- Although most men with the nonclassic form are thought to have normal testicular function and normal fertility, some do present with testicular adrenal rests and infertility. (See 'Clinical presentations' above.)

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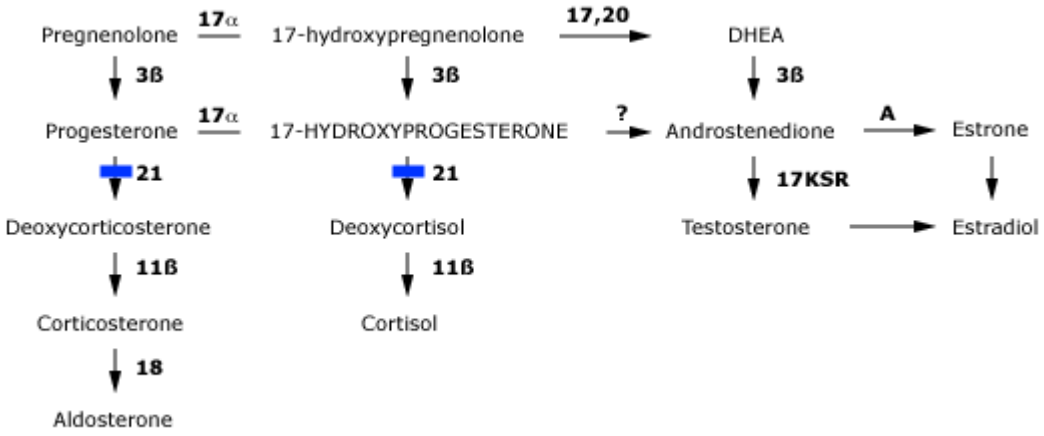
Topic 144 Version 5.0

GRAPHICS

Synthetic defect in CYP21A2 (21-hydroxylase) deficiency



Pathways of adrenal steroid synthesis. A synthetic defect in 21-hydroxylase leads to diminished cortisol synthesis, increased release of ACTH, accumulation of 17-hydroxyprogesterone (particularly after the administration of ACTH), possible virilization due to increased androgen production, and possible salt-wasting due to diminished production of aldosterone and deoxycorticosterone.

The numbers at the arrows refer to specific enzymes: 17α: 17α-hydroxylase (P450c17); 17,20: 17,20 lyase which is part of the P450c17 enzyme; 3β: 3β-hydroxysteroid dehydrogenase; 21: 21-hydroxylase (P450c21); 11β: 11β-hydroxylase; (P450c11); 18 refers to the two-step process of aldosterone synthase (P450c11as), resulting in the addition of an hydroxyl group that is then oxidized to an aldehyde group at the 18-carbon position; ?: unclear if pathway functions in vivo; DHEA: dehydroepiandrostenedione; 17KSR: 17-ketosteroid reductase; and A: aromatase.

Graphic 81907 Version 2.0

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Conflict of interest policy

Huntington disease: Genetics and pathogenesis

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INTRODUCTION — Unstable trinucleotide repeats are associated with a variety of neurodegenerative diseases. Nine of these disorders are associated with expansion of cytosine-adenine-guanine (CAG) repeats that encode for polyglutamine tracts in the protein products. Included in this group are Huntington disease (HD), spinobulbar muscular atrophy, dentatorubral pallidoluysian atrophy, and some of the spinocerebellar ataxias.

The most common presenting symptom of HD in adults is chorea (hence the name Huntington chorea). Other usual findings at presentation include memory deficits, affective disturbances, personality changes, and other manifestations of motor dysfunction such as parkinsonism and dystonia. Patients with juvenile-onset HD have minimal or no chorea, but develop myoclonus and seizures as well as cognitive and behavioral problems. Children also have a more rapidly progressive disease.

The genetics and pathogenesis of HD will be reviewed here. Clinical aspects and management of HD are discussed separately. (See "Huntington disease: Clinical features and diagnosis" and "Huntington disease: Management".)

CLINICAL GENETICS — Huntington disease (HD) is caused by expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene (also known as the HD or IT15 gene) located on chromosome 4p16.3 that encodes the protein huntingtin [1-3]. Mutant huntingtin contains an expanded tract of glutamine residues, which is located near its amino terminal. The disease is transmitted in an autosomal dominant manner.

HD shares several clinical features with the other polyglutamine diseases:

- They typically present in middle age, with progressive neuronal dysfunction and eventual neuronal loss over the ensuing 10 to 20 years.
- The greater the number of CAG repeats on expanded alleles, the earlier the age of onset and more severe the disease.
- The repeats show both somatic and germline instability. As a result of the latter, there can be expansion of the CAG repeat number over successive generations. This may cause earlier disease onset and a progressive worsening of the phenotype in subsequent generations, a phenomenon termed anticipation. Anticipation is more common following paternal transmission of the disease allele.
- A certain subset of neurons is preferentially vulnerable to dysfunction, even though the relevant protein is widely expressed throughout the brain and other tissues [4].

Wild-type HD alleles have 6 to 34 CAG repeat units. More than 35 repeats results in an unstable, expanded, disease-causing allele [3]. However, there is variable penetrance for expression of the HD phenotype with 35 to 39 CAG repeats. Full penetrance occurs with more than 40 repeats.

Trinucleotide repeat size is estimated to account for 30 to 70 percent of the variance in age of HD

symptom onset [3,5-7]. Alleles with 40 to 50 CAG repeats are found in most patients with the adult form of HD [3]. Juvenile HD is typically associated with alleles containing more than 60 CAG repeats, and some patients have more than 100 repeats. Additional factors predicting age of onset are thought to be environmental and other genetic determinants [8,9].

In addition to its effect on the age of presentation, it is generally believed that CAG repeat length is positively correlated with the rate of clinical disease progression [10-14]. There also appears to be a positive correlation between CAG repeat length and the severity of neuropathologic changes [15]. These findings suggest that large CAG expansions produce more widespread injury than smaller expansions and may affect neuronal subtypes that would otherwise be spared with smaller repeat sizes.

Anticipation and transmitting parent effect — Expansion of the CAG repeat number over successive generations causes an earlier and more severe phenotype, termed anticipation.

Intergenerational transmissions are associated with either slight increases of one to four CAG units or slight decreases of one to two units [1]. However, paternal transmission can sometimes produce much larger increases, on the order of seven or more CAG repeats [16,17]. The high number of cellular divisions that occur during spermatogenesis may account for the pronounced paternal-repeat instability [16,18].

Because of the tendency for paternal transmission to result in greater expansion of the CAG repeat size, anticipation shows a major transmitting parent effect, as approximately 70 to 88 percent of symptomatic patients with juvenile HD inherit the mutant HD gene from their father [19-21].

Toxic gain of function — Expansion of CAG repeats is thought to cause toxicity through a "gain of function" mechanism (ie, disease develops because the mutant form of the protein gains a function that is deleterious to the cell).

Three observations are compatible with HD being caused by a dominant gain of function rather than loss of function mechanism:

- Patients with homozygous disease have clinical manifestations and age of onset similar to those of heterozygous siblings [22,23]. In contrast, the data conflict on whether the clinical course is more severe with more rapid progression in those with homozygous disease [22,23].
- Reduction of normal huntingtin activity does **not** cause HD in both animal models and in humans. The clinical manifestations in mice with deletion or complete inactivation of wild-type Hdh, the homologue of the HD gene, are different from those in humans with HD. These mice die in gestation between days 8.5 and 10.5, before the emergence of the nervous system [24-26]. Thus, huntingtin is critical for early embryonic development. Mice heterozygous for Hdh inactivation are phenotypically normal [24,25].

  Similar findings have been noted in humans, providing further support for a gain-of-function mechanism. In addition, a patient with a breakpoint in the HD gene that led to reduced expression of huntingtin was phenotypically normal [27].
- In mice, replacing wild-type Hdh with a mutant Hdh allele containing 50 glutamine repeats results in normal embryonic and brain development [28]. This finding indicates that the HD defect in humans does not mimic complete or partial Hdh inactivation.

Of note, htt residues outside of the polyglutamine tract impact disease severity, suggesting that the toxic gain of function is related to a normal function of huntingtin [29,30].

Distribution and function of huntingtin — Huntingtin is widely expressed throughout the brain, and is present in a large number of tissues throughout the body. However, the pathology of HD appears to be

limited to the central nervous system, with neuronal cell loss and atrophy of the caudate and putamen (the neostriatum) being most prominent [15]. Thus, the distribution of huntingtin does not correlate with the pattern of neuronal cell loss seen in HD.

Wild-type huntingtin exists primarily as a soluble cytoplasmic protein in somatodendritic regions and in axons [4,31]. It is associated with cellular organelles including the Golgi apparatus, mitochondria, endoplasmic reticulum, cytoskeleton, and synaptic vesicles, and is also present to a lesser degree in the nucleus [12].

Although it is essential for normal embryonic development, the role of wild-type huntingtin in the adult is poorly understood [2]. Huntingtin interacts with numerous proteins, raising the possibility that huntingtin is involved in multiple cellular events. Proposed functions for wild-type huntingtin include roles in the regulation of ciliogenesis, protein trafficking, vesicular transport and anchoring to the cytoskeleton, endocytosis, and postsynaptic signaling [3,32-34]. In addition, wild-type huntingtin may have a prosurvival (anti-apoptotic) function.

Mutant huntingtin — Mutant huntingtin is expressed in the brain [4,35,36]. A key neuropathologic feature of HD is selective neuronal loss in the caudate and putamen (striatum).

In HD, electron microscopy reveals both cytoplasmic and nuclear abnormalities, including the presence of large neuronal intranuclear inclusions or aggregates similar to those in other polyglutamine disorders [37-39]. The aggregates are also found in dystrophic neurites. The aggregates consist of amino-terminus fragments of the expanded mutant huntingtin [37,40]. The degree of aggregation varies with the length of the polyglutamine expansion (ie, the number of CAG repeats) [40].

Formation of mutant huntingtin aggregates may occur by one or both of two proposed mechanisms [3]:

- The normal tertiary protein conformation of huntingtin may be destabilized by the presence of the expanded polyglutamine tract, leading to the formation of insoluble beta pleated sheets
- The expanded polyglutamine tract may result in increased transglutaminase-mediated crosslinking with other polyglutamine-containing proteins, including mutant and wild-type huntingtin

While aggregation of mutant huntingtin is a pathologic hallmark of the disease process, the precise role of aggregates in the pathogenesis of HD is controversial [3,41-43]. As discussed below, the interaction of Rhes with mutant huntingtin results in both neurotoxicity and diminished aggregation of mutant huntingtin. This finding suggests that aggregation is a protective rather than a deleterious mechanism. (See 'Rhes' below.)

Experimental evidence consistently shows that the phenotypic severity of HD is directly related to levels of mutant huntingtin [44]. This concept has promoted therapeutic efforts to reduce and even reverse HD pathology and symptoms by inhibiting huntingtin expression or by altering its clearance. This approach is discussed elsewhere. (See "Huntington disease: Management", section on 'Animal models'.)

Although the pathophysiology of neuronal loss is incompletely understood, there is evidence that mutant huntingtin may disrupt a number of intracellular pathways and thereby cause cellular demise by interfering with key components of these pathways and/or by sequestrating of normal proteins into the huntingtin aggregates [2,3].

Proteins and pathways that are potentially disrupted by mutant huntingtin include the following [2,3]:

- Transcription disruption. One study showed that mutant huntingtin binds to and inhibits specificity protein 1 (Sp1), a transcription factor for cystathionine gamma-lyase (CSE), thereby leading to depletion of CSE, an enzyme necessary for the biosynthesis of the amino acid cysteine in the brain [45]. Furthermore, profoundly low levels of CSE were found in the striatum in mouse models of HD and in humans with HD; supplementation with cysteine reduced cytotoxicity in cell cultures of HD

tissue and improved motor outcomes and survival in live mouse models of HD. These results suggest that mutant huntingtin causes cysteine depletion, which in turn mediates HD striatal neurodegeneration.

- Activation of proteases, leading to proteolysis.
- Inhibition of essential native proteins that contain polyglutamine repeats.
- Reduction in protein degradation, perhaps by blocking or overloading the proteosome degradation system [46]; the importance of this mechanism is related to the central role of the ubiquitin protease system in the removal of damaged, mutated, mislocated or misfolded proteins that could be toxic to the cell [47].
- Interference with axonal transport.
- Increased ciliogenesis [32].
- Disruption of synaptic transmission [48,49].
- Interference with the normal action of wild-type huntingtin [50].

Although not necessarily a direct consequence of mutant huntingtin, a variety of additional mechanisms may contribute to neurodegeneration and the clinical manifestations of HD [3,51-53]. These include:

- Excitotoxicity
- Metabolic dysfunction, mitochondrial dysfunction and oxidative stress
- Promotion of apoptosis and/or autophagy
- Dysfunction of neuronal interaction and circuits, primarily involving the corticostriatal and nigrostriatal pathways
- Abnormal cerebrospinal fluid flow and impaired neuroblast migration [32,33]

Rhes — A possible explanation for the restriction of HD pathology mainly to the neostriatum involves the role of Rhes (Ras homolog enriched in striatum), a small guanine nucleotide-binding protein that is selectively localized to the striatum. Rhes interacts with both wild-type and mutant huntingtin, but binds more strongly with mutant huntingtin [54]. In cultured lines of human embryonic and murine brain cells, Rhes induces the small ubiquitin-like modifier (SUMO) protein to covalently attach to mutant huntingtin in a process known as sumoylation. This process reduces the aggregation of mutant huntingtin and elicits neurotoxicity.

NEUROPATHOLOGY — The characteristic pathologic change in Huntington disease (HD) is diffuse, marked atrophy of the neostriatum that may be worse in the caudate than in the putamen [15,55]. The caudate atrophy can often be detected on brain imaging with CT scan or MRI. Caudate and putamen volume measurements by MRI suggest that striatal atrophy begins 9 to 20 years before the clinical diagnosis of HD [56,57].

Although a general correlation exists between clinical severity of motor impairment and the degree of neuronal loss [58,59], some symptomatic patients (5 of 163 in one postmortem series) with HD have no pathologic abnormalities [55]. Symptoms in such patients presumably are caused by cellular dysfunction related to mutant huntingtin and its associated biochemical changes.

The pathologic changes are more dramatic in early onset HD. Affected patients typically show generalized brain atrophy and loss of cerebellar Purkinje cells [15].

At the cellular level, protein aggregates are seen both in the cytoplasm and nucleus. (See 'Mutant huntingtin' above.)

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: Huntington disease (The Basics)")

SUMMARY

- Huntington disease (HD) is caused by expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene (also known as the HD or IT15 gene) located on chromosome 4p16.3 that encodes the protein huntingtin. The disease is transmitted in an autosomal dominant manner. Wild-type HD alleles have 6 to 34 CAG repeat units. More than 35 repeats results in an unstable, expanded, disease-causing allele. However, there is variable penetrance for expression of the HD phenotype with 35 to 39 CAG repeats. Full penetrance occurs at repeat sizes greater than 40. (See 'Clinical genetics' above.)
- Individuals with early-onset HD tend to have a large number of CAG repeats, while those developing HD late in life typically have a low repeat number. Alleles with 40 to 50 CAG repeats are found in most patients with the adult form of HD. In comparison, juvenile HD is typically associated with alleles containing more than 60 CAG repeats. (See 'Clinical genetics' above.)
- Expansion of the CAG repeat number over successive generations may cause an earlier and more severe phenotype, termed anticipation. (See 'Anticipation and transmitting parent effect' above.)
- Expansion of CAG repeats is thought to produce a toxic "gain of function" (ie, disease develops because the mutant form of the protein gains a new function that is deleterious to the cell). (See 'Toxic gain of function' above.)
- Wild-type huntingtin is essential for normal embryonic development. While its role in adults is not completely understood, wild-type huntingtin participates in the regulation of ciliogenesis, protein trafficking, vesicular transport and anchoring to the cytoskeleton, endocytosis, and postsynaptic signaling. (See 'Distribution and function of huntingtin' above.)
- Aggregation of mutant huntingtin is a pathologic hallmark of the disease process. However, the precise role of aggregates in the pathogenesis of HD is controversial. (See 'Mutant huntingtin' above.)
- While the pathophysiology of neuronal loss is incompletely understood, there is evidence that mutant huntingtin may disrupt a number of intracellular pathways and thereby cause cellular demise by interfering with key components of these pathways and/or by sequestration of normal proteins into the huntingtin aggregates. (See 'Mutant huntingtin' above.)
- The predominant localization of HD neuropathology to the striatum may be explained by the interaction of mutant huntingtin with Rhes, a small guanine nucleotide-binding protein that is selectively localized to the striatum. (See 'Rhes' above.)
- The characteristic pathologic change in HD is diffuse, marked atrophy of the neostriatum that may be worse in the caudate than in the putamen. (See 'Neuropathology' above.)

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Conflict of interest policy

Down syndrome: Management

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INTRODUCTION — Down syndrome (DS) is the most common chromosome abnormality among live born infants. It is the most frequent form of intellectual disability (mental retardation) caused by a microscopically demonstrable chromosomal aberration.

The Committee on Genetics of the American Academy of Pediatrics (AAP) has provided recommendations to assist clinicians in the care of children with DS [1]. The recommendations for medical evaluation are summarized in Appendix 1 of this document. Management requires an organized approach to the initial and ongoing evaluation and monitoring for associated abnormalities and prevention of common disorders [2,3].

The management and life expectancy of children with DS is presented here. The epidemiology, clinical features, and diagnosis are discussed separately. (See "Down syndrome: Prenatal screening overview" and "Congenital cytogenetic abnormalities", section on 'Trisomy 21 (Down syndrome)' and "Down syndrome: Clinical features and diagnosis".)

General issues related to management of adults with intellectual disability, and problems related to DS specifically, are discussed in detail separately. (See "Primary care of the adult with intellectual disability (mental retardation)".)

GROWTH — Anthropometric measurements should be plotted on standard National Center for Health Statistics or World Health Organization growth charts. Patients with Down syndrome (DS) should be monitored for disturbances of growth associated with other disorders, such as hypothyroidism or celiac disease, and for excessive weight gain. (See "Measurement of growth in children".)

Obesity prevention — A goal of growth monitoring is the prevention of obesity. Interventions beginning at 24 months of age should include attention to diet and promotion of physical activity. Caloric intake should be less than recommended for age in typical individuals and supplemental vitamins and minerals should be provided [4]. Calcium and vitamin D intake should be monitored closely to minimize bone loss, since adults with DS have lower bone mineral density than controls [5,6].

CARDIAC DISEASE — All newborns with Down syndrome (DS) should be evaluated for congenital heart disease in consultation with a pediatric cardiologist. An echocardiogram is recommended to detect abnormalities that may not be symptomatic or apparent on physical examination. Continued clinical cardiac evaluation is needed because of the high risk of mitral valve prolapse and aortic regurgitation in adolescents and young adults [2]. In a large retrospective cohort study of congenital heart surgery, patients with DS had similar mortality, but higher morbidity, compared with patients without DS [7]. (See "Congenital heart disease (CHD) in the newborn: Presentation and screening for critical CHD" and "Management and outcome of isolated atrial septal defects in children" and "Management of isolated ventricular septal defects in infants and children" and "Management of patent ductus arteriosus" and "Management and outcome of tetralogy of Fallot".)

HEARING — Newborns should have a newborn hearing screen with brainstem auditory evoked

response (BAER) or otoacoustic emission (OAE) [1]. Infants with Down syndrome (DS) should have repeat hearing screening at six months of age. Hearing should be evaluated regularly throughout childhood, typically every six months until four to five years of age and then yearly. Any child who fails screening should be referred to an otolaryngologist for further evaluation and management. (See "Screening the newborn for hearing loss" and "Hearing impairment in children: Evaluation" and "Screening tests in children and adolescents", section on 'Hearing screen'.)

Children should be evaluated and treated for otitis media, which occurs commonly [1]. (See "Acute otitis media in children: Epidemiology, microbiology, clinical manifestations, and complications".)

OPHTHALMOLOGIC DISORDERS — An ophthalmologic assessment should be performed in the newborn period or at least before six months of age to detect strabismus, nystagmus, and cataracts. The risk of refractive errors is approximately 50 percent between three and five years of age [1]. Affected children should have annual assessments of vision. Unaffected children should be examined annually before age five years to detect refractive errors that may occur during childhood, and every two years after age five (every three years after age 13) to screen for disorders, including keratoconus and lens opacities, that may develop in adolescents or adults. The examination should be performed by a pediatric ophthalmologist or ophthalmologist with expertise in infants with disabilities. (See "Visual development and vision assessment in infants and children" and "Evaluation and management of strabismus in children", section on 'Evaluation' and "Overview of nystagmus" and "Cataract in children".)

THYROID FUNCTION — Thyroid function testing should be obtained in the newborn period. The American Academy of Pediatrics (AAP) recommends that screening should be repeated at 6 and 12 months, and then annually [1]. However, there is debate regarding the optimal frequency of laboratory screening [8-11]. Height and weight should be measured yearly since the combination of deceleration of linear growth associated with weight gain is a sensitive indicator of hypothyroidism [10]. (See "Clinical features and detection of congenital hypothyroidism".)

CELIAC DISEASE — Screening for symptoms of celiac disease should begin at one year of age [1]. Laboratory screening is recommended if signs or symptoms develop. (See "Clinical manifestations and diagnosis of celiac disease in children".)

HEMATOLOGY — A complete blood count and differential should be obtained at birth to evaluate for myeloproliferative disorders and polycythemia. Infants with transient myeloproliferative disorders should be followed with a complete blood count and differential every three months until three years of age and then every six months until six years of age. This monitoring protocol is modified from that used in the prospective study of transient leukemia in Down syndrome (DS) conducted by the Pediatric Oncology Group [12]. Children DS are at increased risk for leukemia. Thus, there should be vigilance for signs of leukemia, such as anemia, increased infections, and excessive bruising. (See "Down syndrome: Clinical features and diagnosis", section on 'Hematologic disorders' and "Neonatal polycythemia" and "Overview of the presentation and diagnosis of acute lymphoblastic leukemia in children and adolescents".)

A hemoglobin level should be obtained annually from 1 to 13 years of age to screen for anemia [1]. The anemia is usually due to iron deficiency secondary to the restricted diet that many children with DS develop as a result of delayed oral motor skills and dysphagia. However, anemia may also be a sign of leukemia.

PERIODONTAL DISEASE — Periodontal disease is common in children and adults with Down syndrome (DS) and involves inflammation, periods of acute infection, and pain [13]. The increased frequency is thought to be due in part to alterations in mouth flora, with a higher frequency of Actinobacillus actinomycetemcomitans compared with controls [14]. Overlapping teeth, poor oral hygiene, and immunodeficiency may also play a role [15]. (See "Gingivitis and periodontitis in children and adolescents: An overview", section on 'Periodontitis' and "Periodontal disease in children:

Associated systemic conditions", section on 'Down syndrome'.)

Routine brushing should be encouraged. Dental visits are recommended every six months. Orthodontic problems, which occur in the majority of DS patients, should be evaluated and treated if possible. However, the cooperation necessary for many orthodontic procedures may make them impractical in this population.

ATLANTOAXIAL INSTABILITY — The American Academy of Pediatrics Committee on Genetics and the American Academy of Pediatrics (AAP) Committee on Sports Medicine and Fitness recommend careful neurologic evaluation for signs and symptoms consistent with spinal cord injury (eg, loss of motor skills, loss of bowel or bladder control, neck pain, neck stiffness) as the most important clinical predictor of symptomatic atlantoaxial instability (AAI) and dislocation [1,16]. The evaluating clinician should take a careful history and perform a thorough physical examination, looking for evidence of neurologic involvement. This clinical screening process should be done at least annually. Caution regarding contact sports and trampoline use should be discussed with families.

The AAP Committee on Genetics recommends obtaining lateral plain cervical spine radiographs in the neutral position with odontoid and anterior-posterior (A-P) views to examine for evidence of AAI or subluxation in patients with myopathic signs or symptoms [1]. Of note, children do not have adequate vertebral mineralization and epiphyseal development for accurate radiographic evaluation of the cervical spine until at least three years of age.

The patient should be placed in a collar and referred immediately to a pediatric neurosurgeon or pediatric orthopedic surgeon if significant radiographic abnormalities are noted. Flexion and extension radiographs may be performed prior to referral if no significant radiographic abnormalities are present. The AAP Committee on Sports Medicine and Fitness recommends that symptomatic children have magnetic resonance imaging (MRI) to clarify the extent of spinal cord compression, and that appropriate surgical consultation be obtained to evaluate the need for definitive treatment [16].

Nearly all people with AAI who have suffered a catastrophic injury to the spinal cord have had preceding neurologic symptoms [16]. Asymptomatic AAI is relatively uncommon, occurring in only 2.6 percent of patients with Down syndrome (DS) in one study [17]. Despite this, the Special Olympics requires screening neck radiographs in children with DS before participation. Children who are found to have AAI on these radiographs but who lack neurologic symptoms should be followed closely with repeat neurologic examinations (at least annually) [16].

BEHAVIOR AND PSYCHIATRIC PROBLEMS — Assessment and treatment of behavior and psychiatric problems should be expeditious and should include evaluation of the problem at school and at home, behavior management techniques, and medication as needed. (See "Developmental and behavioral screening tests in primary care" and "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Evaluation'.)

SLEEP APNEA — Children with Down syndrome (DS) have an increased risk of obstructive sleep apnea because of soft tissue and skeletal alterations that lead to upper airway obstruction. Symptoms related to sleep apnea (snoring, restless sleep, and sleep position) should be discussed at health supervision visits beginning at age one year and continuing throughout childhood [18]. Polysomnography is recommended in all children with DS by four years of age [1]. (See "Mechanisms and predisposing factors for sleep related breathing disorders in children" and "Evaluation of suspected obstructive sleep apnea in children" and "Management of obstructive sleep apnea in children".)

FERTILITY AND REPRODUCTION — Ages for the onset and completion of puberty are typical for individuals with Down syndrome (DS). However, the mean stretched penile length and the mean testicular volumes are significantly below average among adult men with DS compared with normal men. Fertility is impaired in individuals with DS, most likely secondary to primary gonadal deficiency [19]. Most

published data, however, suggests that 15 to 30 percent of women with DS are capable of becoming pregnant and their risk of having a child with DS is about 50 percent [20]. Offspring without trisomy 21 seem to have an increased risk for other congenital and developmental abnormalities. Limited research also suggests that women with DS may have an increased risk for miscarriages, premature births, and difficult labor [21]. Men with DS are generally thought to be infertile. However, there have been various published case reports of men with DS fathering children [22-24].

Individuals with various disabilities are at an increased risk for sexual abuse. It is important for parents to discuss matters of sexuality, social skills training, and measures to prevent pregnancy routinely with older children and adults with DS.

ALZHEIMER DISEASE — Dementia that resembles Alzheimer disease is more common and occurs at an earlier age in patients with Down syndrome (DS). A medical evaluation should be performed, including testing for thyroid disease, when the diagnosis of Alzheimer disease is considered. Possible depression should also be excluded. The diagnosis and treatment of dementia, including in patients with DS, is discussed in detail separately. (See "Down syndrome: Clinical features and diagnosis", section on 'Dementia/Alzheimer disease' and "Evaluation of cognitive impairment and dementia" and "Treatment of dementia".)

LIFE EXPECTANCY — Life expectancy in Down syndrome (DS) is shorter than that in the general population or in individuals with other causes of intellectual disability. However, survival has improved substantially [25-28]. In a Swedish study using national birth and death registries, the median age at death increased from 3.6 years from 1969 to 1973 to 56.8 years from 1999 to 2003 [28]. The most common main or contributing cause of death was pneumonia and other infections, followed by congenital malformations, circulatory disease, and dementia. In a similar study using United States death certificates from 1983 to 1997, the improvement in survival was thought to be due to increased placement of infants in homes rather than institutions, and to changes in treatment for common causes of death, especially congenital heart disease [25].

In a retrospective cohort study conducted on 16,506 infants with DS born in the United States between 1983 and 2003, the overall 1-month and 1-, 5-, and 20-year survival probabilities were 98, 93, 91, and 88 percent, respectively [29]. Survival improved modestly over the course of the study in all but the neonatal period.

In the study using death certificate data, malignancies other than leukemia were much less frequent in those with than without DS (standardized mortality odds ratio 0.07) [25]. Possible mechanisms suggested for the low rate of cancer include tumor suppressor genes on chromosome 21, a slower rate of replication or higher rate of apoptosis in DS cells, or less exposure to environmental risks.

Predictors of survival in DS may include race, gender, birth weight, gestational age at birth, and presence of heart defects and other structural anomalies [25,29-31]. In the death certificate study noted above, the median age at death was higher among whites than other races [25]. In contrast to the greater longevity of females in most populations, males with DS appear to have a survival advantage [32,33]. In a series from Western Australia, life expectancy was 58.6 years for the population, and 3.3 years longer for males than females [32].

BASIC SCIENCE RESEARCH AND FUTURE TREATMENT OPTIONS — The development of Down syndrome (DS) mouse models has provided an opportunity to study emerging pharmacotherapies that target intellectual disabilities common in DS [34-36]. The overexpression of many genes found on chromosome 21 contributes to learning deficits. Research has focused on hippocampus function related to memory and learning. Areas of interest include specific gamma-aminobutyric acid (GABA) receptor inhibitors, N-methyl-D-aspartic (NMDA) receptor antagonists, and hippocampal dentate gyrus neurogenesis. Preliminary basic science research shows medications such as pentylenetetrazole (PTZ),

memantine, and fluoxetine may enhance learning in the DS mouse model. Further studies and clinical trials are needed to show efficacy and safety of these medications in children with DS.

ALTERNATIVE TREATMENTS — Oxidative stress, the imbalance between production and removal of oxygen-derived free radicals, may contribute to some features of Down syndrome (DS), such as decreased immune function, premature aging, impaired mental function, and malignancy [37]. In particular, the activity of superoxide dismutase (the gene for which is located on chromosome 21) is increased [38]. Superoxide dismutase is usually regarded as a protective enzyme since it scavenges free superoxide molecules. However, in DS, the hydrogen peroxide generated by superoxide dismutase-1 may become toxic in the presence of ferrous iron (Fe2+). It forms the highly toxic hydroxyl radical (OH), which can result in profound cellular damage [39].

Supplementation with antioxidant nutrients has been proposed as potential therapy for DS. Treatments studied include supplementation with zinc, selenium, megavitamins and minerals, vitamin A, vitamin B6, 5-hydroxytryptamine, coenzyme Q10, and targeted nutritional intervention [37,40,41]. These studies have methodologic flaws and provide no convincing evidence that nutritional supplementation improves outcomes in DS. One randomized controlled trial evaluated psychomotor and language development in 156 infants treated for 18 months with daily oral supplementation with one of four programs: antioxidants (selenium, zinc, vitamin A, vitamin E, vitamin C), folinic acid, antioxidants and folinic acid combined, or placebo. This trial found no significant differences between the groups [41].

COUNSELING AND RESOURCES — Counseling may begin when a prenatal diagnosis of Down syndrome (DS) is made or suspected [1]. The discussion should include the wide range of variability in manifestations and prognosis. Medical and educational treatments and interventions should be discussed. Initial referrals should be made to early intervention, informative publications [42], parent groups, and advocacy groups. In the early teen years, discussion and plans for transition to adulthood should include employment, place of residence, and leisure activities.

Internet resources for parents and patients include the following:

- The Association for Children with Down Syndrome
- National Down Syndrome Society

A brochure entitled, "Your baby and Down syndrome: Answers to questions you might have," available in English and Spanish, can be downloaded from the National Down Syndrome Society website.

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 topic (see "Patient information: Down syndrome (The Basics)")
- Beyond the Basics topic (see "Patient information: Down syndrome (Beyond the Basics)")

SUMMARY

- Management of Down syndrome (DS) requires an organized approach to ongoing evaluation and

monitoring for associated abnormalities and prevention of common disorders. The Committee on Genetics of the American Academy of Pediatrics (AAP) has provided recommendations to assist clinicians in the care of children with DS. These recommendations are available on their website.

- The following evaluations are recommended:
  - Plot growth on standard National Center for Health Statistics or World Health Organization growth charts; monitor for disturbances of growth associated with other disorders, such as hypothyroidism or celiac disease, and for excessive weight gain.
  - Pediatric cardiology evaluation, including an echocardiogram, in the newborn period for congenital heart disease and continued clinical cardiac monitoring in adolescence and adulthood for mitral valve prolapse and aortic regurgitation.
  - Newborn hearing screen and ongoing hearing screening throughout childhood, plus monitoring for otitis media, which is a common cause of hearing loss in children with DS.
  - An ophthalmologic assessment before six months of age and then approximately annually to screen for ophthalmologic disorders.
  - Thyroid function testing in the newborn period with newborn state screens, and repeated at 6 months of age, 12 months of age, and then yearly thereafter.
  - Monitor for symptoms of celiac disease beginning at one year of age. Screening is recommended if signs or symptoms develop.
  - A complete blood count and differential at birth to evaluate for myeloproliferative disorders and polycythemia; ongoing monitoring for signs of leukemia.
  - Check hemoglobin level annually starting at one year of age to screen for iron deficiency anemia.
  - Neurologic evaluation for signs and symptoms consistent with spinal cord injury at each health supervision visit; symptomatic children should have magnetic resonance imaging (MRI) to clarify the extent of spinal cord compression.
  - Monitoring for symptoms related to sleep apnea at health supervision visits beginning at age one year; polysomnography is in all children with DS by four years of age.
- Life expectancy in DS is shorter than that in the general population or in individuals with other causes of intellectual disability. However, survival has improved substantially in the past two to three decades.
- Internet resources for parents and patients include the following:
  - The Association for Children with Down Syndrome
  - National Down Syndrome Society

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Fragile X syndrome: Clinical features and diagnosis in children and adolescents

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INTRODUCTION — The clinical features and diagnosis of fragile X syndrome (FXS) (previously called fragile X mental retardation syndrome, X-linked mental retardation and macroorchidism, and Martin-Bell syndrome) in children and adolescents will be discussed here. Prenatal screening and the management of FXS in children and adolescents are discussed separately. (See "Prenatal screening and diagnosis for fragile X syndrome" and "Fragile X syndrome: Management in children and adolescents".)

PREVALENCE — Fragile X syndrome (FXS, MIM #300624) is the most frequent form of inherited intellectual disability, with a prevalence between 1 in 4000 and 1 in 6000 in males [1,2]. The prevalence in females is approximately one-half of that in males [2]. The carrier rate is approximately 1 in 750 men and 1 in 250 women [1,3,4]. FXS has been diagnosed in up to 3 percent of boys with special needs (eg, autism, nonsyndromic intellectual disability) [5].

GENETICS AND ETIOLOGY — The genetics and molecular biology of fragile X syndrome (FXS) are discussed in detail separately. (See "Prenatal screening and diagnosis for fragile X syndrome", section on 'Genotype and inheritance' and "Genetic and environmental causes of birth defects", section on 'Unstable DNA and fragile X syndrome'.)

FXS is an X-linked disorder. It is caused by decreased or absent levels of fragile X mental retardation protein (FMRP) due to a loss of function mutation in the fragile X mental retardation 1 (FMR1) gene, located at Xq27.3 [6,7]. In more than 99 percent of cases, loss of function is caused by an unstable expansion of a trinucleotide (cytosine-guanine-guanine, CGG) repeat at the 5' untranslated region [2,8]. Deletions, point mutations, and missense mutation in FMR1 also may cause FXS, but are extremely rare (<1 percent of cases) [2,9,10].

There are two clinically significant levels of CGG expansion:

- Expansion of >200 repeats is known as full mutation and leads to methylation-coupled silencing of the FMR1 gene and absence of FMRP, causing the classical FXS phenotype. (See 'Full mutation in boys' below and 'Full mutation in girls' below.)
- Expansion between approximately 50 to 55 and 200 repeats is known as premutation. The FMR1 gene remains transcriptionally active, FMRP is produced, and the classic FXS phenotype does not occur. However, a spectrum of clinical findings is associated with the premutation. (See 'Premutation' below.)

NEUROANATOMY — Children with fragile X syndrome (FXS) have relative macrocephaly (head circumference >50th percentile for age and sex) [2]. Macrocephaly is related to underlying structural anomalies. Magnetic resonance imaging and quantitative morphometry demonstrate that individuals with an FMR1 full mutation have increased total brain volume, relatively increased caudate nucleus volume, decreased cerebellar vermis, increased fourth ventricle volume, and increased hippocampal volume [11-13]. In addition, boys with FXS have decreased lateral ventricle volume [11]. Caudate nucleus volume correlates with the methylation status of the fragile X mental retardation 1 (FMR1) gene, and

both caudate nucleus and lateral ventricular volumes correlate with intelligence quotient (IQ).

CLINICAL FEATURES

Overview — The clinical features of fragile X syndrome (FXS) vary depending upon the mutation state (full mutation versus premutation), degree of methylation, sex, tissue variation, and possibly magnitude of the fragile X mental retardation protein (FMRP) deficit (table 1) [2,5,8,14-16]. Males with the full mutation are usually significantly affected. In females with the full mutation, the degree of impairment varies widely.

Full mutation in boys — All males with full mutation FXS have manifestations of FXS, but there is a wide range of physical, cognitive, and behavioral features [17]. The physical features may be subtle. The diagnosis in young boys often is suspected because of global developmental delay and typical behavioral characteristics, described below. Approximately 15 percent present with symptoms of attention deficit hyperactivity disorder (ADHD) or specific learning disability [18].

Physical features — The physical features of FXS in males vary depending upon age. The classic physical manifestations are more obvious in adolescents: long and narrow face with prominent forehead and chin (prognathism), large ears, and testicular enlargement (volume >25 mL after puberty) with normal testicular function [5,19-23]. Testicular enlargement is not a useful clinical sign until the child is at least eight years old [20,24].

Physical manifestations are subtle in infants and young boys. Nonetheless, some craniofacial and connective tissue findings may be present from a young age (picture 1). These include [5,17,21,25-27]:

- Relative macrocephaly (head circumference >50th percentile for age and sex)
- Strabismus
- Pale blue irises
- Midface hypoplasia with sunken eyes
- Arched palate
- Mitral valve prolapse (seemingly benign)
- Joint hyperlaxity (particularly of the thumbs, fingers, and wrists)
- Hypotonia
- Soft skin over the dorsum of hands
- Flexible flat feet

Cognitive function — Developmental delay (including delayed attainment of motor and language milestones), intellectual disability (previously termed mental retardation), and learning disabilities are the most salient clinical features of FXS [28]. Boys with FXS typically sit alone at 10 months, walk at 20.6 months, and say their first clear words at 20 months (compared with approximately 7 months, 13 months, and 11 months, respectively, in typically developing children) [2].

Adult males typically have an intelligence quotient (IQ) in the moderate intellectual disability range, but intellectual disability ranges from mild to severe. (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs".)

Although individual strengths and weaknesses may vary from patient to patient, consistent strengths among boys with FXS include verbal skills (verbal reasoning, simple labeling, vocabulary, verbal comprehension) [17]. Consistent weaknesses include mathematics abilities, visuospatial abilities, attention and executive function (eg, the ability to organize information, plan ahead, problem solve), and visual-motor coordination [17,29-32].

Longitudinal analysis indicates that cognitive level and adaptive behavior skills decline after early childhood [33-35]. Prepubertal boys, and in particular preschool boys with FXS, generally have higher

IQs than adolescents and adults [36]. The decline occurs in all areas: quantitative skills, verbal reasoning, visual/abstract abilities, and short-term memory [34]. Declines in cognitive and adaptive skills reflect the slow acquisition of skills compared with other children of the same age, rather than a regression of skills [17,32,37]. These observations highlight the importance of early intervention to facilitate cognitive abilities and adaptive behavior skills [17,35]. (See 'Diagnosis' below and "Fragile X syndrome: Management in children and adolescents".)

Language and speech — Boys with FXS have delayed language development. Expressive language skills are achieved more slowly than receptive language skills, and the discrepancy between expressive and receptive skills increases with age [28,38]. Approximately 10 percent of boys with FXS are nonverbal [18].

Expressive language is often tangential (eg, responses or comments that do not relate to the topic of conversation) and perseverative, with inappropriate self-repetition, echolalia (involuntary parrot-like repetition), and pragmatic errors [17,28,39]. In contrast to individuals with autism, boys with FXS who often exhibit autistic-like features generally take appropriate turns during conversation [28].

Articulation is poor, and language is repetitive and characterized by short and fast utterances [36]. Cluttering is often present. Cluttering is a rapid, fluctuating rate of speech with repetitions of sounds, words, and phrases, and occasional garbled, slurred, or disorganized speech.

Behavioral features — The behavioral phenotype of boys with FXS shares features with ADHD, anxiety, and autism spectrum disorders (eg, hyperactivity, inattention, gaze aversion, and stereotypic movements, such as hand flapping, hyperarousal, social anxiety, unusual speech patterns) [32,40-43]. (See "Autism spectrum disorder: Clinical features", section on 'Restricted and repetitive behavior, interests, and activities' and "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Core symptoms' and "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Clinical features'.)

Boys with FXS are more inattentive, overactive, and impulsive than boys with other types of intellectual disability [40]. These symptoms may be related to sensory hyperreactivity and lack of stimulus inhibition. They may lead to a diagnosis of ADHD. The ADHD-like symptoms tend to decline with age, but many adult males with FXS remain hyperactive. Treatment with stimulant medication may be beneficial [8]. (See "Fragile X syndrome: Management in children and adolescents", section on 'Hyperactivity and inattention'.)

Boys with FXS may have avoidant behaviors, particularly when their intellectual disability is severe [41]. They tend to avoid new situations and to move away from new objects [40]. However, they do not remain socially withdrawn or avoid familiar people. Their social skills often correlate with their cognitive level [41].

Boys with FXS also may have anxiety symptoms (nervousness, obsessive compulsive disorder-like obsessions and perseverations), mood instability, aggressive behavior, and self-injurious behavior [44-46].

Prader-Willi phenotype — A subgroup of boys with FXS have a phenotype similar to that of Prader-Willi syndrome (ie, obesity and hyperphagia) but do not have the characteristic cytogenetic or methylation abnormalities at 15q11-13 [47-50]. Autism is more common in boys with FXS and the Prader-Willi phenotype than in boys with FXS without the Prader-Willi phenotype (54 versus approximately 30 percent) [50]. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome" and "Epidemiology and genetics of Prader-Willi syndrome".)

Full mutation in girls — The phenotype of full mutation FXS in girls is much more variable than in boys because of individual differences in inactivation of the fragile X chromosome [17]. Approximately 50

percent of girls with a full fragile X mutation have normal intellect. The remaining 50 percent usually have milder features than boys, but the full spectrum of cognitive, behavioral, and physical findings may occur [5].

As many as 50 percent of females with the full mutation have some of the characteristic physical features (eg, prominent ears) [51]. Approximately 50 percent of women with the full mutation have IQs in the borderline or mild intellectual disability range [51-54]. Cognitive impairment appears to correlate with the activation ratio of the fragile X chromosome, rather than the size of the amplification [55]. As in males with full mutation FXS, cognitive function may decline after early childhood. (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs".)

Many girls with the full mutation have associated behavioral or emotional problems [44,51,56]. They typically present with learning difficulties (especially in math), attention problems (or full ADHD), and shyness or social anxiety [18]. Deficits in visual-motor coordination, executive function (eg, the ability to organize information, plan ahead, problem solve), and language (including selective mutism) are common [18,57-59]. Girls with the full mutation are at risk for affective and schizophrenia spectrum disorders [44,60]. Autistic behaviors (eg, communication and social interaction deficits, stereotypies) are more commonly reported among 6- to 16-year-old girls with FXS than age- and IQ-matched controls [61]. (See "Specific learning disabilities in children: Clinical features", section on 'Clinical features' and "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Core symptoms' and "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Clinical features' and "Autism spectrum disorder: Clinical features".)

Premutation — Individuals with fragile X premutation have between 50 and 200 cytosine-guanine-guanine (CGG) repeats. At this level, the fragile X mental retardation 1 (FMR1) gene remains transcriptionally active, and the classic FXS phenotype does not occur. (See 'Genetics and etiology' above.)

There are three potential areas of concern for individuals with fragile X premutations:

- Premature ovarian insufficiency (POI) in women, which is discussed separately. (See "Clinical manifestations and evaluation of spontaneous primary ovarian insufficiency (premature ovarian failure)".)
- Fragile X-associated tremor-ataxia syndrome (FXTAS) later in life, which is discussed separately. (See "The spinocerebellar ataxias", section on 'Fragile X-associated tremor/ataxia syndrome'.)
- Neurocognitive deficits.

In the past, fragile X premutation was not thought to affect cognitive function. However, there are reports of individuals with premutation and neurobehavioral manifestations, including cognitive and social skills deficits, anxiety, executive dysfunction, and autism [8,62-65]. Decreased FMRP levels have been detected in some of these individuals, suggesting a spectrum of clinical severity related to relative FMRP deficit [62].

The author's clinical practice has identified several boys with fragile X premutation and learning problems, developmental delay, or autistic features. This may reflect an ascertainment bias. However, they have identified four times more premutations in boys younger than 16 years with developmental problems who were referred for FMR1 gene testing than would be expected based upon the known prevalence of the premutation in males (unpublished data). Larger and more longitudinal studies are necessary, but these data provide additional evidence that fragile X premutations may affect neurocognitive and behavioral functioning in children.

Associated disorders

Autism — It is estimated that approximately 25 to 30 percent of children with FXS meet the criteria for autism (using autism diagnostic scales), and another 20 percent meet criteria for pervasive developmental disorder not otherwise specified [18,66-68]. Boys with FXS and autism have greater impairments in cognitive skills, social interaction, academic achievement, language ability, and adaptive behavior than boys with FXS alone [8,66,69,70]. (See "Autism spectrum disorder: Diagnosis", section on 'Diagnosis' and "Autism spectrum disorder: Clinical features".)

Epilepsy — Approximately 10 to 20 percent of boys with FXS and 5 percent of girls with FXS develop seizures [71-73]. The risk of seizures seems to be highest in childhood (peak incidence between six months and four years; mean age of onset two years) [8,72,73]. Most are simple or complex partial seizures, including benign childhood epilepsy with centrotemporal spikes (also known as benign rolandic epilepsy), although other types can occur. The seizures are relatively easy to control and often spontaneously remit during childhood [8]. (See "Benign focal epilepsies of childhood", section on 'Benign epilepsy with centrotemporal spikes' and "Fragile X syndrome: Management in children and adolescents", section on 'Seizures'.)

DIAGNOSIS — It is important to make the diagnosis of fragile X syndrome (FXS) as early as possible so that appropriate interventions (eg, speech and language therapy, special education support, genetic counseling) can be initiated [18]. Surveys of parents of children diagnosed with FXS indicate a significant delay between the onset of their concerns (average age approximately 12 months) and the diagnosis of FXS (average age 35 to 37 months). Approximately one-fourth of families had a second child with a full mutation before the first child was diagnosed [74,75].

Clinical suspicion — In the absence of a family history of FXS, the diagnosis of FXS requires clinical suspicion based upon cognitive, developmental, or behavioral concerns, as described above. The diagnosis is confirmed by molecular testing. (See 'Clinical features' above and 'FMR1 DNA analysis' below.).

The American Academy of Pediatrics Committee on Genetics recommends testing for FXS in children with any of the following [76]:

- Developmental delay
- Borderline intellectual abilities
- Mental retardation
- Diagnosis of autism without a specific etiology

Genetic counseling and genetic testing are also suggested for at-risk family members of patients with FXS (even if asymptomatic). Genetic testing should also be offered to females with primary ovarian insufficiency and patients over 50 years of age with progressive cerebellar ataxia and intention tremor, after an appropriate explanation of the test and its potential implications for the patient and their family [76].

Testing is also recommended in adults with intellectual disability without a specific etiology and typical physical features.

Family history — Family history questions that are suggestive of FXS include [5]:

- Cognitive effects – Intellectual disability, developmental delay, learning disabilities, specific problems with mathematics
- Speech delay or unusual speech pattern
- Autism spectrum disorders or autistic-like behaviors
- Attention deficit or attention deficit hyperactivity disorder (ADHD)

- Dysmorphic features – Macrocephaly, large ears, long face, broad forehead, prominent jaw, strabismus, large testicles
- Features of loose connective tissue – Hyperextensible joints, flat feet, hypotonia, mitral valve prolapse, hernias
- Neurologic symptoms – Seizures, late-onset progressive tremor, ataxia, difficulty walking, balance problems, short-term memory loss, loss of sensation in limbs
- Mental illness/personality disorders – Depression, schizophrenia, bipolar disorder, obsessive compulsive disorder, schizoaffective disorder, schizoid personality
- Behavioral problems – Impulsiveness, anger outbursts, violent behavior, solitary behavior, counseling or medication for behavioral difficulties
- Shyness, social anxiety, excessive worrying, counseling or medication for emotional difficulties
- Premature menopause, fertility problems

FMR1 DNA analysis — The diagnosis of FXS is based upon detection of an alteration in the fragile X mental retardation 1 (FMR1) gene [2]. Testing methods and indications for prenatal screening are discussed separately. (See "Prenatal screening and diagnosis for fragile X syndrome", section on 'Diagnosis' and "Prenatal screening and diagnosis for fragile X syndrome", section on 'Screening'.)

The American College of Medical Genetics, American Academy of Pediatrics, and American Academy of Neurology suggest molecular testing for FXS in children with developmental delay, intellectual disability, or autism, particularly when associated with physical and behavioral characteristics of FXS or a relative with undiagnosed intellectual disability [77]. Although the yield of molecular testing in such individuals is low [78], early diagnosis is important for timely genetic counseling. (See "Prenatal screening and diagnosis for fragile X syndrome", section on 'Candidates for screening' and "Autism spectrum disorder: Diagnosis", section on 'Genetic testing' and "Intellectual disability (mental retardation) in children: Evaluation for a cause", section on 'Genetic testing'.)

Testing for mutations in the FMR1 gene is also suggested for individuals who had cytogenetic testing in the past if the results of the testing and the clinical/behavioral phenotype are inconsistent [77].

A detailed description of molecular genetic tests and the testing strategy for FMR1-related disorders is available through the Genetic Testing Registry (GTR).

Additional evaluation — Following initial diagnosis of FXS, children and adolescents should undergo a multidisciplinary evaluation to determine the extent of disease [2]. The evaluation should include:

- Complete developmental and educational assessments (including speech and language evaluation and physical and occupational evaluation) for educational planning.
- Behavioral and psychology assessment to evaluate cognitive abilities, concentration or attention problems, anxiety, obsessive compulsive disorder, aggression, and depression.
- Medical evaluation for feeding problems, gastroesophageal reflux, hypotonia, joint laxity, mitral valve prolapse, history of possible seizures, strabismus, evidence of recurrent otitis media, and scoliosis.

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of fragile X syndrome (FXS) includes [2,79,80]:

- Autism spectrum disorder. Children with FXS often have autistic behaviors and may have comorbid autism. (See "Autism spectrum disorder: Clinical features", section on 'Overview'.)

- Attention deficit hyperactivity disorder (ADHD). (See "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Clinical features' and "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation", section on 'Core symptoms'.)
- Other causes of intellectual disability or developmental delay, including:
    - Fragile XE syndrome (FRAXE). FRAXE, which is extremely rare, is characterized by mild intellectual disability without consistent physical features. It has been described in boys with expanded cytosine-cytosine-guanine (CCG) repeats in fragile X mental retardation 2 (FMR2) gene, near the fragile X mental retardation 1 (FMR1) gene.
    - XXY (Klinefelter syndrome). Boys with Klinefelter syndrome may have specific learning disabilities, particularly in expressive language. In contrast to postpubertal boys with FXS, boys with XXY usually have small testes. (See "The child with tall stature and/or abnormally rapid growth", section on 'Klinefelter syndrome'.)
    - Cerebral gigantism (also known as Sotos syndrome). Characteristic features of cerebral gigantism include typical facial appearance (macrocephaly, frontal bossing, prominent chin, pointed chin, downslanting palpebral fissures), overgrowth, learning disability, behavioral problems, and congenital cardiac anomalies. (See "The child with tall stature and/or abnormally rapid growth", section on 'Cerebral gigantism'.)
    - Prader-Willi syndrome. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome".)

(See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs".)

RESOURCES — Fragile X syndrome (FXS) resources for healthcare providers and families include:

- The National Fragile X Foundation
- FRAXA Research Foundation
- The National Institute of Child Health and Human Development
- Genetic Testing Registry (GTR)

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 topic (see "Patient information: Fragile X syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Fragile X syndrome (FXS) is the most frequent form of inherited intellectual disability, with a prevalence between 1 in 4000 and 1 in 6000 in males. The prevalence in females is approximately

one-half of that in males. (See 'Prevalence' above.)

- FXS is an X-linked disorder. It is caused by a loss of function mutation in the fragile X mental retardation 1 (FMR1) gene that leads to decreased or absent fragile X mental retardation protein (FMRP). (See 'Genetics and etiology' above.)
- The clinical features of FXS vary depending upon the mutation state (full mutation versus premutation), degree of methylation, sex, and tissue variation (table 1). (See 'Overview' above.)
- All males with full mutation FXS have manifestations of FXS, but there is a wide range of physical, cognitive, and behavioral features. (See 'Full mutation in boys' above.)
    - Classic physical features include long and narrow face with prominent forehead and chin, large ears, and testicular enlargement, but these features typically are not obvious until adolescence or adulthood. Physical features in younger males may include macrocephaly, strabismus, midface hypoplasia, arched palate, mitral valve prolapse, hyperextensible joints, hypotonia, soft skin, and flexible flat feet.
    - Intellectual disability is usually in the moderate range. Expressive language is more affected than receptive language.
    - Behavioral features may include hyperactivity, inattention, gaze aversion, stereotypic movements (eg, hand flapping, hand biting), hyperarousal, social anxiety, and unusual speech.
- Girls with the full mutation usually have milder features than boys, and 50 percent have normal cognitive function, but the full spectrum of cognitive, behavioral, and physical findings may occur. (See 'Full mutation in girls' above.)
- In the absence of a family history of FXS, diagnosis of FXS requires clinical suspicion based upon cognitive, developmental, or behavioral concerns, as described above. Diagnosis is confirmed by molecular testing. (See 'Diagnosis' above.)
- Following initial diagnosis of FXS, children and adolescents should undergo a multidisciplinary evaluation for educational planning, assessment of behavioral and emotional needs, and associated medical problems (eg, gastroesophageal reflux, hypotonia, joint laxity, mitral valve prolapse, seizures, strabismus, recurrent otitis media, scoliosis). (See 'Additional evaluation' above.)
- The differential diagnosis of FXS includes autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), and other causes of intellectual disability or developmental delay. (See 'Differential diagnosis' above.)

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Topic 2924 Version 12.0

GRAPHICS

Fragile X syndrome genotype-phenotype correlations

Mutation type	Number of CGG trinucleotide repeats	Methylation status of FMR1	Clinical status	
			Male	Female
Premutation	Approximately 59 to approximately 200	Unmethylated	At risk for FXTAS*	At risk for POI and FXTAS
Full mutation	>200	Completely methylated	100 percent with intellectual disability	Approximately 50 percent with intellectual disability, approximately 50 percent normal intellect
Repeat size mosaicism	Varies between premutation and full mutation in different cell lines	Partial: Unmethylated in the premutation cell line; methylated in the full mutation cell line	Nearly 100 percent affected with ID; may be higher functioning• than males with full mutation	Highly variable: Ranges from normal intellect to affected
Methylation mosaicism	>200	Partial: Mixture of methylated and unmethylated cell lines	Nearly 100 percent affected with ID; may be higher functioning• than males with full mutation	Highly variable: Ranges from normal intellect to affected
Unmethylated full mutation	>200	Unmethylated	Nearly all have ID but often have high functioning ID to low-normal intellect	Highly variable: Ranges from normal intellect to affected

CGG: cytosine-guanine-guanine; FMR1: fragile X mental retardation 1 gene; FXTAS: fragile X-associated tremor/ataxia syndrome; POI: premature ovarian insufficiency; ID: intellectual disability; IQ: intelligence quotient.

* Both males and females with premutations and manifestations of some symptoms of fragile X syndrome have been reported[1].

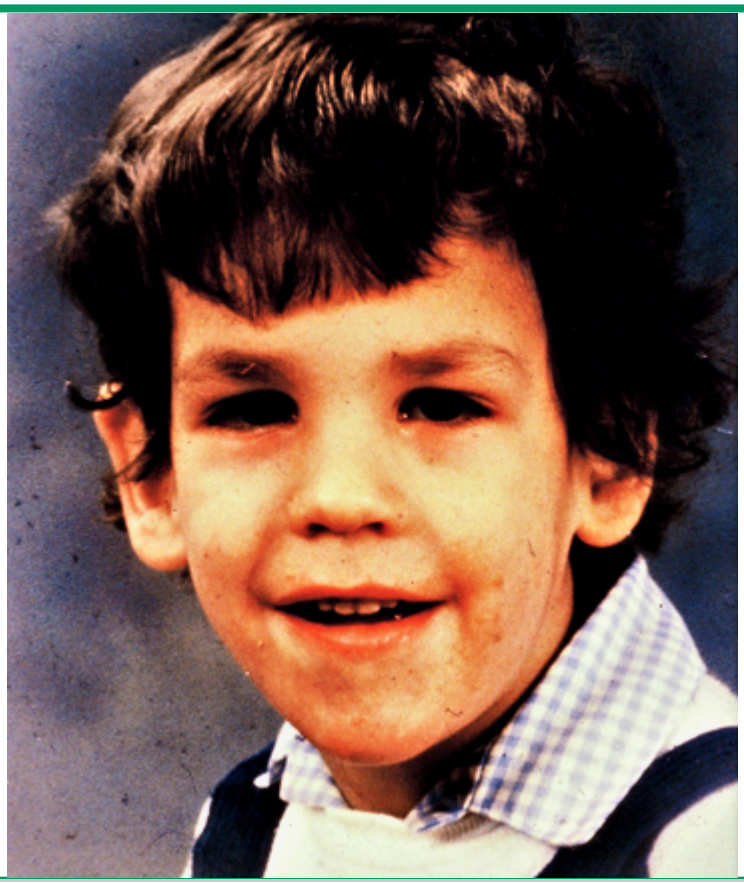
• FMR1 mutations are complex alterations involving nonclassic gene-disrupting alterations (trinucleotide repeat expansion) and abnormal gene methylation. This complexity at the gene level affects production of the FMR1 protein and may result in an atypical presentation in which affected individuals occasionally have an IQ above 70, the traditional demarcation denoting mental retardation.

Reference:

1. *Riddle JE, Cheema A, Sobesky WE, et al. Phenotypic involvement in females with the FMR1 gene mutation. Am J Ment Retard. 1998; 102:590.*

Graphic 73067 Version 9.0

Typical facial features in a patient with fragile X syndrome



A four-year-old boy with fragile X syndrome displays some of the typical facial features of the disorder including:

- A long and narrow face with prominent forehead and chin (prognathism)
- Large ears
- Midface hypoplasia with sunken eyes
- Strabismus

Graphic 60035 Version 4.0

Disclosures

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Conflict of interest policy

Fragile X syndrome: Management in children and adolescents

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All topics are updated as new evidence becomes available and our peer review process is complete.
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INTRODUCTION — The management of children and adolescents with fragile X syndrome (also called fragile X mental retardation syndrome, X-linked mental retardation and macroorchidism, and Martin-Bell syndrome) will be discussed here. The clinical features, diagnosis, and prenatal screening are discussed separately. (See "Fragile X syndrome: Clinical features and diagnosis in children and adolescents" and "Prenatal screening and diagnosis for fragile X syndrome".)

OVERVIEW — The management of children and adolescents with fragile X syndrome (FXS) is individualized according to the child's cognitive and behavioral symptoms, strengths, and weaknesses [1,2]. (See "Fragile X syndrome: Clinical features and diagnosis in children and adolescents", section on 'Additional evaluation'.)

Interventions may include individualized education plans, speech and language therapy, occupational therapy, behavior therapy, and pharmacotherapy. Few controlled trials have been performed to assess the effectiveness of these interventions in children with FXS [3,4]. However, they are effective in children with other cognitive or behavioral problems. (See "Intellectual disability (mental retardation) in children: Management; outcomes; and prevention" and "Specific learning disabilities in children: Educational management".)

GENETIC COUNSELING — Families of individuals with fragile X syndrome (FXS) should be referred to a geneticist or genetic counselor for a detailed discussion of the inheritance of the fragile X mental retardation-1 (FMR1) mutation and testing of other family members [5-8]. FXS test results should be interpreted for the family according to the guidelines established by the National Society of Genetic Counselors and the American Society of Human Genetics [5-7]. Family members at risk for premutation or full mutation of FMR1 should receive information about possible emotional, neurologic, and reproductive problems [5].

DEVELOPMENTAL AND EDUCATIONAL INTERVENTIONS — Children and adolescents with fragile X syndrome (FXS) usually have special educational needs and should be referred for early developmental stimulation and educational programs [8,9]. Most children with FXS have difficulties with mathematics and expressive language skills and relative strengths in receptive language skills [10]. However, developmental strengths and weaknesses must be assessed on an individual basis [9]. Children with FXS and autism require additional educational interventions. (See "Fragile X syndrome: Clinical features and diagnosis in children and adolescents".)

BEHAVIORAL INTERVENTIONS — Behavioral interventions may be effective in promoting coping skills and reducing problematic behaviors (eg, aggression, stereotypic behaviors, self-injury) [9,11,12]. There are few empirical studies of the effectiveness of behavioral interventions for children and adolescents with fragile X syndrome [13]. Treatment strategies are guided by the therapist's experience and understanding of factors associated with problematic behaviors [9,13]. Problematic behaviors often are precipitated and reinforced by social and/or environmental events (eg, anxiety, sensory overload, change in routine, the amount of attention the child is receiving, etc.) [9,14-17]. Environmental changes (eg, small class size, avoiding excessive stimulation, avoiding sudden changes) may reduce the frequency of

problem behaviors [1,18]. Individuals with fragile X syndrome can be taught to recognize stressful situations and use self-calming techniques before responding inappropriately [9].

Behavioral interventions for children with intellectual disability are discussed in greater detail separately. (See "Intellectual disability (mental retardation) in children: Management; outcomes; and prevention", section on 'Behavior intervention'.)

Children and adolescents with fragile X syndrome who have higher levels of function may benefit from counseling or psychotherapy to focus on anxiety reduction, socialization, and depression [13,19].

HEALTH SUPERVISION — Children and adolescents with fragile X syndrome (FXS) should receive routine health supervision and prompt referral for medical, therapeutic, educational, and consultative services (eg, early intervention services, speech therapy) [8,9,20]. Health supervision guidelines from the American Academy of Pediatrics Committee on Genetics are available online.

Support — Families with fragile X mutation or premutation benefit from parental and social supports [9]. Personal and family support should be reviewed at regularly scheduled health supervision visits [8]. Internet-based information and support resources are provided below. (See 'Resources' below.)

Surveillance — In addition to intellectual disability and language and behavior problems, children and adolescents with fragile X syndrome (FXS) are at risk for a number of medical problems, listed below. Surveillance for these problems and appropriate intervention and/or referral should occur at regularly scheduled health maintenance visits throughout childhood, adolescence, and young adulthood [8].

Associated medical concerns in children and adolescents with fragile X syndrome include [8,14,21]:

- Flat feet (80 percent) and other connective tissue manifestations (eg, ligamentous laxity, inguinal hernia) [21,22]. (See "Clinical features and management of foot pain in the child or adolescent athlete", section on 'Flexible pes planus'.)
- Gastroesophageal reflux. (See "Gastroesophageal reflux in infants" and "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents".)
- Mitral valve prolapse (typically develops during adolescence or adulthood; present in 50 to 80 percent of adults) [21]. (See "Definition and diagnosis of mitral valve prolapse".)
- Recurrent otitis media (60 percent) [21,23]. (See "Acute otitis media in children: Epidemiology, microbiology, clinical manifestations, and complications" and "Acute otitis media in children: Diagnosis".)
- Refractive errors (20 percent), strabismus (8 to 30 percent), and nystagmus [21]. (See "Refractive errors in children" and "Evaluation and management of strabismus in children", section on 'Evaluation'.)
- Seizures (as many as 20 percent) [24-26]. The peak incidence is between six months and four years [13,25,26]. The possibility of seizures should be considered in older children and adolescents if school performance is declining or when a disturbed sleep pattern occurs. (See "Clinical and laboratory diagnosis of seizures in infants and children".)
- Scoliosis (<20 percent) [21].
- Depression [14]. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis" and "Overview of treatment for pediatric depression".)
- Anxiety [14].

Anticipatory guidance — The American Academy of Pediatrics guidelines for health supervision of

children with fragile X syndrome suggest providing anticipatory guidance according to the following schedule [8]:

- Birth to 1 month — Infants in this age group generally are identified through prenatal testing because of a positive family history. Review support groups and available services. Discuss how and what to tell family members and friends [6].
- 1 month to 1 year — Discuss irritability and tantrums. Refer for early intervention services (in the United States).
- 1 to 5 years — Review the preschool program. Refer for speech and language therapy, physical therapy, and occupational therapy as indicated. Formal developmental evaluation may be warranted.
- 5 to 13 years — Assess effectiveness of behavioral interventions. Discuss how parents and siblings address behavioral problems. Review development and appropriateness of school placement (eg, visual presentation of information, small classroom size, individualized attention, speech and language therapy, occupational therapy). (See 'Developmental and educational interventions' above and 'Behavioral interventions' above.)
- 13 to 21 years — Review behavioral concerns (eg, violent outbursts). Assess psychosocial development, physical and sexual development, and fertility in boys and girls. Discuss the need for and level of supervision, and discuss the need for birth control. The National Fragile X Foundation (www.fragilex.org) provides resources for discussing sexuality with children and adolescents with FXS. Discuss the need for vocational training and group home placement if appropriate. Facilitate transition to adult medical care as appropriate or desired.

PHARMACOTHERAPY

General principles — Psychopharmacologic therapy may be necessary for children and adolescents with fragile X (FXS) syndrome and attention deficit hyperactivity disorder, anxiety, mood instability, or maladaptive behaviors (eg, perseveration, aggression, self-injury) that significantly affect social interaction and are not controlled with environmental or behavioral interventions. There is no specific therapy for enhancing cognitive abilities [4].

Psychopharmacologic intervention is individualized according to symptoms; it must be closely monitored [1]. Specific agents may help with some problematic behaviors but exacerbate others [4].

There are few controlled studies evaluating the use of psychopharmacologic interventions in children and adolescents with FXS. Evidence to support their use is derived from observational surveys of clinical populations [13].

Hyperactivity and inattention — Inattention and hyperactivity in children with FXS are typically treated with stimulants [4]. Observational studies suggest that stimulants are beneficial in approximately 70 percent of boys with FXS [4,27]. In a small placebo-controlled crossover trial, methylphenidate in addition to behavioral interventions and individualized therapy was associated with improved teacher ratings of socialization skills and attention span [27].

Benefits of stimulants may include increased attention span and decreased distractibility, motor activity, fidgeting, and impulsivity [4]. Adverse effects of stimulants may include appetite suppression, insomnia, moodiness, increased aggressiveness or irritability, and aggravation of anxiety or perseveration. (See "Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents", section on 'Stimulant adverse effects'.)

In children younger than five years, stimulants may exacerbate irritability or other behavior problems. Nonstimulant therapies (eg, alpha-2 agonists such as guanfacine and clonidine) often are used in this

age group to treat hyperactivity, inattention, and hyperarousal [4,13]. In observational studies, alpha-2 agonists are beneficial in approximately 60 to 70 percent of patients [4,28,29]. Adverse effects of alpha-2 agonists include decreased blood pressure and sedation [28].

Other behaviors — Anxiety, compulsive, perseverative behaviors, and mood symptoms may be managed with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs). Observational studies suggest that treatment with SSRIs relieves anxiety in approximately 50 percent of patients with FXS [4,30]. However, approximately 20 percent of treated patients reported activation (restlessness, mood change, disinhibited behavior, aggression) with SSRIs [30].

Benefits of SSRIs may include decreased fixations and compulsive behaviors, decreased irritability, easier transitions, increased comfort in social situations, and ability to tolerate environmental stimuli [4]. Adverse effects may include activation, changes in appetite, insomnia, nausea, and suicidal ideation. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Adverse side effects'.)

Irritability, aggression, mood instability, and perseverative behaviors may respond to treatment with antipsychotic agents (eg, risperidone, aripiprazole) [4,13]. In controlled trials in children with autism, risperidone has been shown to be beneficial in controlling aggressive and aberrant behavior [31-33]. Aripiprazole also may target distractibility, anxiety, mood instability, and aberrant social behaviors.

Benefits of antipsychotics may include improved sleep and decreased anxiety, agitation, perseveration, and aggression [4]. Adverse effects may include sedation, nausea, constipation, dystonic and extrapyramidal reactions, gynecomastia, and weight gain [34].

Seizures — Seizures in children with FXS generally are controlled with a single anticonvulsant (eg, carbamazepine, valproic acid, lamotrigine, oxcarbazepine, zonisamide) [13]. (See "Overview of the treatment of seizures and epileptic syndromes in children" and "Antiepileptic drugs: Mechanism of action, pharmacology, and adverse effects".)

Anticonvulsants with adverse effects that include hypotonia, clumsiness, cognitive dulling, and daytime sedation should be avoided [4,13]. Phenytoin is usually avoided because it is associated with gingival hypertrophy, and it is difficult to manage dental problems in children with FXS because of their hypersensitivity. Phenobarbital and gabapentin may exacerbate behavior problems and also should be avoided in children with FXS.

Investigational therapies — A number of investigational therapies target biochemical pathways that are thought to play a role in the clinical manifestations of fragile X syndrome (FXS). These include:

- Metabotropic glutamate receptor 5 (mGluR5) antagonists — Excessive mGluR5 signaling is thought to contribute to some of the behavioral abnormalities and cognitive deficits of FXS [3,13,35]. In animal models, mGluR5 antagonists have demonstrated improvements in behavior and cognition; reduction of anxiety, depression, and seizures; and correction of underlying abnormal cellular processes such as aberrant cell signaling [3,36-38]. A small randomized trial in 30 adult patients showed significant improvement on the Aberrant Behaviour Checklist-Community Edition (ABC-C) score, but only in the subset of patients with a fully methylated promotor [39]. Two different mGluR5 antagonists are under study in large multicentric phase 2 trials. (See clinicaltrials.gov for information about clinical studies).
- Lithium — Lithium downregulates the phospholipase C signaling pathway, which is used by mGluR5 and other receptors to activate dendritic translation and has the potential to correct excessive dendritic protein synthesis in FXS [13]. A small open-labeled trial of lithium in 15 males with FXS (6 to 23 years) found significant improvement in behavioral functioning, adaptive behavior, and verbal memory [40]. Larger randomized trials are needed to confirm these results.

- Minocycline — Matrix metalloproteinases (MMP) modulate synaptic physiology and plasticity, and MMP9 levels are elevated in the hippocampus in patients with FXS [41]. Open-label studies of minocycline in patients with FXS demonstrated improvements in language, attention, social communication, anxiety, and behavior [42,43]. A subsequent randomized trial of minocycline in 55 individuals (aged 3.5 to 16 years) showed improvement on the Clinical Global Impression Scale [44]. However, the potential benefits of this therapy should be weighed against the potential side effects, especially in children, who would require long-term treatment.

- Gamma-aminobutyric acid (GABA) system agonists — GABA is the primary inhibitory neurotransmitter in the central nervous system. The GABA system is downregulated in FXS [45]. Social function and behavior, but not irritability, improved in patients with FXS in a phase 2 trial of the GABA agonist arbaclofen [46]. Two other clinical trials are ongoing: a phase 2 study with ganaxolone, a GABA-A receptor agonist, and a phase 3 study with acamprosate, both a GABA agonist and an NMDA antagonist [47].

- Chloride importer antagonists — As noted above, GABAergic signaling is deficient in FXS [45]. However, GABA actions are shifted from inhibitory to excitatory with elevated levels of intracellular chloride seen in many disorders including FXS. Bumetanide, a diuretic NKCC1 chloride importer antagonist that decreases intracellular chloride and has shown efficacy in treating autism, improved autistic features in a patient with FXS [48].

- Ampakines (positive AMPA receptor modulators) — Excessive mGluR activity contributes to reduced synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and excessive internalization of AMPA receptors [13]. Reduced AMPA receptor signaling is another potential target for therapy. In a controlled trial, treatment with CX516 (an ampakine) had no effect on cognitive function in a cohort of subjects with FXS [49].

- Cannabinoid receptor antagonists — Activation of mGluR5 enhances production of endocannabinoids, leading to depression of excitatory and inhibitory transmission and amplification of the mammalian target of rapamycin (mTOR) signaling pathway mediated via cannabinoid receptor 1 (CNR1, also called CB1R). In a mouse model, CNR1 blockade with rimonabant normalized cognitive performance, nociception, and seizure susceptibility [50]. CNR2 blockade reduced anxiolytic-like behavior.

- Mammalian target of rapamycin (mTOR) inhibitors — Enhanced mTOR signaling is thought to contribute to some of the cognitive deficits seen in patients with FXS [51]. Both acute and chronic administration of an mTOR inhibitor, temsirolimus, prevented memory impairment in a murine model [50].

- p21-activated kinase (PAK) inhibitors — The density and morphology of dendritic spines are abnormal in FXS [52,53]. PAK is involved in the structural integrity and functionality of dendritic spines via modulation of actin cytoskeleton dynamics. A single dose of a group I PAK inhibitor ameliorated the dendritic spine aberrations and also seizure susceptibility and behavioral abnormalities in mice [54].

PRADER-WILLI PHENOTYPE — Treatment of children with the Prader-Willi phenotype of FXS is similar to that for children with Prader-Willi syndrome without FXS. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome", section on 'Evaluation and management of comorbidities' and "Clinical features, diagnosis, and treatment of Prader-Willi syndrome", section on 'Growth hormone treatment' and "Clinical features, diagnosis, and treatment of Prader-Willi syndrome", section on 'Management of feeding and obesity'.)

OUTCOME — Life expectancy for individuals with fragile X syndrome is normal [9]. Adult males typically have an intelligence quotient (IQ) in the moderate intellectual disability range (the average IQ in adult

males with a completely methylated full mutation is approximately 40) [3,55]. However, IQ may vary from mild to severe. Males with incomplete methylation of FMR1 may have IQ in the borderline or low normal range. Adult females with the full mutation usually have IQ in the normal or mild intellectual disability range. (See "Intellectual disability (mental retardation) in children: Definition; diagnosis; and assessment of needs".)

RESOURCES — Internet-based resources for healthcare providers, patients, and families of with fragile X syndrome include [6]:

- The National Fragile X Foundation
- FRAXA Research Foundation Inc
- The National Institute of Child Health and Human Development
- Genetic Testing Registry (GTR)

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 topic (see "Patient information: Fragile X syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- The management of children and adolescents with fragile X syndrome (FXS) is individualized according to the child's cognitive and behavioral symptoms, strengths, and weaknesses. Interventions may include individualized education plans, speech and language therapy, occupational therapy, behavior therapy, and pharmacotherapy. (See 'Overview' above.)
- Families of individuals with FXS should be referred to a geneticist or genetic counselor for a detailed discussion of the inheritance of the fragile X mental retardation-1 (FMR1) mutation and testing of other family members. (See 'Genetic counseling' above.)
- Children and adolescents with FXS usually have special educational needs and should be referred for early developmental stimulation and educational programs. (See 'Developmental and educational interventions' above.)
- Behavioral interventions may be effective in promoting coping skills and reducing problematic behaviors (eg, aggression, stereotypic behaviors, self-injury). (See 'Behavioral interventions' above.)
- Health supervision of children with FXS involves surveillance for a number of associated medical problems, including flat feet, hyperextensible joints, inguinal hernia, gastroesophageal reflux, mitral valve prolapse, recurrent otitis media, refractive errors, strabismus, nystagmus, seizures, scoliosis, depression, and anxiety. (See 'Surveillance' above.)
- Psychopharmacologic intervention is individualized according to symptoms (eg, inattention, hyperactivity, anxiety, mood instability) and must be closely monitored. (See 'Pharmacotherapy'

above.)

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Clinical manifestations and diagnosis of the thalassemias

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All topics are updated as new evidence becomes available and our peer review process is complete.
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INTRODUCTION — The major hemoglobin in adults is hemoglobin A, a tetramer consisting of one pair of alpha globin chains and one pair of beta globin chains. In normal subjects, globin chain synthesis is very tightly controlled, such that the ratio of production of alpha to non-alpha chains is 1.00 ± 0.05. Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one or more globin chains, thus disrupting this closely regulated ratio. (See "Molecular pathology of the thalassemic syndromes".)

- The vast majority of adult patients with alpha or beta thalassemia **minor** are asymptomatic and may be diagnosed because of the presence of microcytic, hypochromic red cells, with or without minor degrees of anemia.
- Thalassemias of intermediate degrees of severity (**thalassemia intermedia**) are common throughout the world, and may be due to the presence of more than one hemoglobin mutation in the same patient (eg, sickle cell thalassemia, hemoglobin E/beta thalassemia) or to the presence of an abnormal hemoglobin with a reduced (ie, thalassemic) production rate (eg, hemoglobin Lepore, hemoglobin Constant Spring).
- Beta thalassemia **major** and alpha thalassemia **major** are on the other end of this spectrum. The former is associated with life-long transfusion-dependent anemia, while the latter is incompatible with extra-uterine life.

The clinical manifestations and diagnosis of the thalassemias will be reviewed here [1]. The management of beta thalassemia is discussed separately. (See "Treatment of beta thalassemia" and "Efficacy of hematopoietic cell transplantation in beta thalassemia major".)

BETA THALASSEMIA MAJOR

Overview — Beta thalassemia is due to impaired production of beta globin chains, leading to a relative excess of alpha globin chains. Excess alpha globin chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within the cell, leading to a variety of clinical manifestations. The degree of alpha globin chain excess determines the severity of subsequent clinical manifestations, which are profound in patients homozygous for impaired beta globin synthesis (ie, beta thalassemia major) and much less pronounced in heterozygotes, who generally have minimal or mild anemia and no symptoms. (See "Pathophysiology of beta thalassemia".)

Infants with severe beta thalassemia major (BTM) are well at birth, because the production of beta globin is not essential during fetal life or the immediate perinatal period. The major non-alpha globin produced at the time of birth is gamma globin, such that the major hemoglobin in early postnatal life is fetal hemoglobin (Hb F, alpha2/gamma2).

Symptoms emerge during the second six months of life when gamma globin chain production decreases and is normally replaced with the production of beta globin to form adult hemoglobin (Hb A, alpha2/beta2). However, since newborns with BTM are unable to produce beta chains, they develop chronic anemia, the stigmata of profound hemolysis, and suffer the noxious effects of massive ineffective

erythropoiesis upon the body. The clinical expression of the severe phenotype is remarkably heterogeneous, depending upon a variety of factors that alter the burden of alpha-globin inclusions in the individual patient [2-6].

When BTM becomes clinically apparent during the second six months of life, pallor, irritability, growth retardation, abdominal swelling due to hepatosplenomegaly, and jaundice reflect the onset and sequelae of severe hemolytic anemia. The symptoms associated with ineffective erythropoiesis (eg, bony abnormalities and abnormal skeletal development) soon follow. Eighty percent of untreated children will die within the first five years of life, due directly to the consequences of severe anemia, high output heart failure, inanition, and unusual susceptibility to infection [4,7,8].

The clinical features outlined below describe the most severe manifestations of BTM, most of which are rarely seen in the United States or other countries with highly developed medical care systems [3]. (See "Community public health issues and the thalassemic syndromes: Lessons from other countries".)

The clinical manifestations of BTM are multifactorial. Even though the primary genetic defect resides in a single gene (ie, beta globin) expressed only during terminal maturation of red cell progenitors, many organ systems are affected. Understanding of the symptomatology of BTM requires recognition that patients suffer simultaneously from the following:

- The effects of severe and chronic anemia
- The stigmata of chronic hemolysis
- Organ damage from transfusional iron overload
- The profound local and systemic effects of a rapidly and relentlessly expanding mass of erythroid bone marrow progenitors

The application of modern forms of hypertransfusion therapy, which can suppress many of the adverse effects of anemia and extramedullary hematopoiesis; marked reduction in the risk of transfusion-associated hepatitis; rigorous use of iron chelation to reverse transfusion-related iron overload; and the use of hematopoietic cell transplantation have ameliorated most of these features [9].

However, in many areas of the world where genetic counseling and/or intensive therapy are not available, patients with severe symptoms are still encountered. Indeed, management of the iron stores in these patients has become the overriding challenge, since most of the manifestations of anemia and hemolysis can be controlled by aggressive hypertransfusion regimens. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload'.)

Clinical manifestations — The direct effects of BTM on other organs and tissues in the body are due to the deleterious effects of the profound anemia, the byproducts of hemolysis, and the intramedullary and extramedullary expansion of erythroid marrow progenitors [2,4-6,10]. However, in actual practice, patients exhibit both direct and indirect abnormalities of a number of organ systems. Indirect effects include the accumulation of end-organ damage due to iron overload either from blood transfusions or accelerated iron turnover [11], blood-borne infections (eg, viral hepatitis from blood transfusions), or progressive diversion of caloric resources to bone marrow expansion.

Skeletal changes — Skeletal abnormalities are dramatic in these patients and frequently lead to marked changes in the facial structure and body habitus, producing the characteristic "chipmunk facies" and delayed skeletal maturation. Skeletal changes are due largely to the expansion and invasion of erythroid bone marrow, which widen the marrow spaces, attenuate the cortex, and produce osteoporosis.

The skull and facial bones are strikingly abnormal. Marrow expansion causes dramatic widening of the diploic spaces and produces a characteristic "hair-on-end" radiographic appearance of the skull [12]. In addition, there is prominent frontal bossing, delayed pneumatization of the sinuses, and marked

overgrowth of the maxillae. As a result, the upper incisors are "jumbled" and the malar eminences are especially prominent, producing malocclusion and the characteristic facies.

The ribs and the bones of the extremities become box-like and eventually convex, due to expansion of the bone marrow. Premature fusion of the epiphyses can result in characteristic shortening of the limbs, particularly the arms. Of equal concern is the thinning of the cortices due to marrow expansion, which often results in pathologic fractures. Compression fractures of the spine, often with spinal cord compression and neurologic deficits, have been reported in these children.

As children reach the end of the first decade of life, the greatly expanded hematopoietically active ("red") marrow is replaced at the periphery of the skeleton by inactive ("yellow") marrow as in unaffected preadolescent children. The changes in the hands and feet thus become somewhat less prominent in the second decade of life if the child survives. However, changes in the pelvis, skull, and spine become more pronounced, due to the continuation of active erythropoiesis at these sites. It is often in the second decade of life, not surprisingly, that compression fractures and paravertebral expansion of extramedullary masses become particularly prominent. These changes may lead to complications such as back pain, spinal asymmetry and scoliosis, cord compression from intraspinal collections of hematopoietic tissue, and intervertebral disc degeneration [13].

Osteopenia with cortical thinning, increased trabeculation of the spine, severe osteoporosis with fractures, including vertebral fractures in adolescents and young adults, remain serious complications, even in well-transfused and iron-chelated patients [14-16]. The mechanism(s) underlying this observation are unclear. Different studies have identified the following possible contributing factors [13,17-23]:

- The Sp1 polymorphism of the COLIA1 collagen gene, which may predispose to vertebral osteoporosis [17] (see "Pathogenesis of osteoporosis", section on 'Genetics')
- Increased bone resorption that may be related to vitamin D deficiency of uncertain etiology [18,19] (see 'Endocrine and metabolic abnormalities' below). Bone formation may not be impaired [20].
- Failure to progress normally through puberty [21], most likely secondary to hypogonadism [20,22] (see 'Endocrine and metabolic abnormalities' below)
- A direct effect of iron overload on bone, possibly due to iron-induced oxidative stress [24] or activation of osteoclasts [25]
- A direct toxicity of deferoxamine, leading to skeletal dysplasia [26,27]
- Zinc deficiency [28-30] (see 'Vitamin and mineral levels' below)

Liver and gallbladder — Hepatomegaly is prominent early in the disease, due to increased red cell destruction as well as extramedullary erythropoiesis in this organ. Liver enlargement tends to be somewhat more prominent in children with BTM than in others with other causes for congenital hemolytic anemia. Later in the first decade of life, hepatomegaly becomes fixed and not reducible by blood transfusion, due to development of cirrhosis secondary to increased iron deposition.

Even in the absence of transfusion, the accelerated rate of erythropoiesis enhances dietary iron absorption from the gut, resulting in a chronic state of iron overload. In the liver, iron first infiltrates Kupffer cells and then engorges hepatocytes, ultimately provoking fibrosis and, potentially, end-stage liver disease, in a manner analogous to that seen in hereditary hemochromatosis.

A curious feature of deranged iron homeostasis in individuals with BTM is that hepcidin levels remain low despite massive iron overload [31]. Such reduced hepcidin production enhances the absorption of iron from the diet, increasing the already high iron burden. Serum from thalassemic subjects blocks

hepcidin synthesis in cultured liver cells [32], suggesting that thalassemic serum contains a circulating repressor of hepcidin [33]. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Anemia due to ineffective erythropoiesis' and "Regulation of iron balance", section on 'Hepcidin'.)

Liver changes consistent with viral hepatitis, both hepatitis B and hepatitis C, are frequent, even in children who have received little or no transfusion therapy. While hepatitis as a complication of transfusion is readily understandable, the prevalence in non-transfused children suggests additional susceptibility factors. Iron overload is one situation thought to favor susceptibility to viral hepatitis.

In view of the above, it is not surprising that liver function abnormalities are highly prevalent, but variable, given the multiplicity of underlying causes. Hyperbilirubinemia is nearly universal. Most affected children also have hypergammaglobulinemia and abnormal hepatocellular enzyme markers. In advanced stages of the disease, probably as the result of hemochromatosis and exposure to hepatitis B and C viruses through multiple blood transfusions, hypoalbuminemia, coagulation factor abnormalities, and other stigmata of end-stage liver disease (eg, hepatocellular carcinoma) may appear [34].

A prominent feature of children with chronic hemolytic anemia is the development of premature bilirubin gallstone disease and biliary tract inflammation. This is particularly true of children with BTM. Two-thirds of these patients have multiple calcified bilirubin stones by the age of 15 [35]. Fortunately, true episodes of cholecystitis or cholangitis are rare. Gall bladder removal is thus rarely indicated in the absence of clear-cut symptoms.

Splenomegaly — Massive splenomegaly develops early in the course of BTM due to increased red cell destruction and the presence of splenic extramedullary hematopoiesis. Splenomegaly is progressive and can produce characteristic symptoms such as early satiety and hypersplenism. Shortened survival of transfused red cells or progressive worsening of the anemia or other cytopenias in non-transfused patients are indications that removal of the spleen may palliate symptoms by reducing splenic consumption of red cells. However, children often require splenectomy whether or not they are transfused. (See "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism", section on 'Extravascular nonimmune hemolysis due to hypersplenism'.)

Before and after splenectomy, children with BTM suffer immune deficits as the result of premature loss of splenic function [2]. Splenic monocytes and macrophage are particularly important for clearance of bacteria and other particulate matter, and splenic leukocytes appear to be important in early life for the maturation of the alternative pathway of complement activation. Iron overload within the spleen and engorgement of splenic reticuloendothelial cells are both thought to contribute to abnormal splenic function, even when the spleen is anatomically present.

Splenectomy — If splenectomy is performed, children with BTM, like all other splenectomized patients, are at considerable risk for overwhelming sepsis. Vaccination against pneumococcus and prophylactic use of antibiotics are essential. (See "Prevention of sepsis in the asplenic patient".)

Patients with BTM or thalassemia intermedia may also be at increased risk for developing thromboembolic phenomena, including stroke, following splenectomy [36-38].

Kidneys — The kidneys are frequently enlarged in thalassemia, due to the presence of extramedullary hematopoiesis. Less well understood is the tendency for the renal tubules to be dilated. The urine is frequently dark, due to increased concentrations of bile pigments; large amounts of urate, uric acid, and oxalate are also seen.

Because of the high rate of cellular turnover in this disease, hyperuricemia is encountered in children with BTM, and they are at risk for development of gouty nephropathy. However, true attacks of gouty arthritis are rare before the second or third decade of life. (See "Asymptomatic hyperuricemia".)

Endocrine and metabolic abnormalities — Endocrine and metabolic abnormalities are quite common in patients with BTM, attributable, at least in part, to chronic iron overload [39]. In a study of 56 patients with transfusional iron overload (52 with either thalassemia major or intermedia), pituitary iron overload was detected by magnetic resonance imaging during the first decade of life, while clinically significant pituitary volume loss was not observed until the second decade of life [40]. Both pituitary iron overload and volume loss were independently predictive of hypogonadism, which was defined clinically based upon the timing of secondary sexual characteristics or the need for sex hormone replacement therapy.

In two studies comprising over 800 patients with transfusion-dependent thalassemia, the following endocrine/metabolic abnormalities were noted [39,41]:

- Hypogonadism – 40 to 55 percent
- Growth failure – 33 percent
- Diabetes – 6 to 13 percent
- Hypothyroidism – 10 to 11 percent

There is increasing evidence that chelation therapy can arrest the **progression** of these endocrine abnormalities [41-45]. However, it is not yet entirely clear whether actual **reversal** of endocrine dysfunction can be achieved by chelation. At least one report suggests that intensive chelation therapy with two agents (eg, deferoxamine plus deferiprone) might accomplish this latter goal [46]. (See "Chelation therapy for thalassemia and other iron overload states".)

Growth retardation is frequently profound in these children. This reflects, in part, the diversion of caloric resources for erythropoiesis, along with the effects of anemia, since hypertransfusion frequently restores growth rates to normal. However, the adolescent growth spurt is often delayed, even in children who are hypertransfused, unless intensive iron chelation therapy is instituted early in life.

Primary and secondary characteristics of sexual development are usually delayed for both boys and girls [22]. While there is increasing evidence that hypogonadism may be primarily due to iron overload, zinc deficiency may also play a role.

- Menarche is frequently delayed, breast development is often poor, and patients are frequently oligomenorrheic or amenorrheic, even if menarche occurs.
- Boys frequently develop no or sparse facial and body hair and tend to have decreased libido, even if sperm production does occur.

A report from the Thalassemia Clinical Research Network reported on the following findings in 361 subjects with thalassemia (mean age 23, range: 6 to 75 years) living in North America and receiving current therapy [47]:

- Approximately 25 percent of children and adults, regardless of their thalassemia syndrome, had short stature. Overall growth in children was mildly affected and final height was close to midparental height.
- Patients with beta thalassemia major had higher rates of multiple endocrinopathies, worse hyperglycemia, subclinical hypoparathyroidism, and hypercalciuria. All were found to correlate with higher ferritin concentrations.
- Hypogonadism, the most frequent endocrinopathy, was frequently undertreated. Among hypogonadal girls, menarche was delayed to 17 years.
- Low levels of vitamin D were common, especially among adolescents.

Diabetes mellitus — Abnormal carbohydrate metabolism is another major endocrine abnormality

encountered in these children [48]. Glucose intolerance usually develops during the second decade of life, even though baseline blood sugar levels are frequently normal. Interestingly, the early lesion appears to be related more to insulin resistance than to defective insulin production. The latter is a complication that occurs only during the late stages of development of hemosiderosis. More effective iron chelation appears to improve glucose intolerance [49].

A retrospective historical study evaluated the incidence of diabetes mellitus (DM) in 957 patients with BTM as well as the effect of DM on cardiac complications. Results included the following [50]:

- The incidence of DM in this population was 9 percent. When compared with those without DM, patients with BTM and DM were older, had started chelation at an older age, and had a higher incidence of endocrine co-morbidity (eg, hypogonadism, hypothyroidism, hypoparathyroidism).
- Although there were no significant differences between DM and non-DM patients for global cardiac T2*, those with DM had significantly increased frequencies of heart failure, hyperkinetic (atrial) arrhythmias, and myocardial fibrosis.

These results are concordant with the increased vulnerability in the general population of the diabetic heart to failure and arrhythmia, and are relevant for the prevention of disorders of glucose metabolism, particularly in young patients. They also stress the need to intensify chelation therapy in patients with BTM in whom excess pancreatic iron is found by MRI (where available) and/or when such patients develop disorders of glucose metabolism, since improvement is possible with enhanced chelation therapy [49]. (See "Heart failure in diabetes mellitus", section on 'Epidemiology'.)

Cardiac complications — Cardiac abnormalities are a major feature of BTM [51,52]. Cardiac malfunction, including heart failure and fatal arrhythmias, are frequent causes of death, and cardiac dilatation secondary to anemia is nearly universal. Transfusion usually corrects the latter abnormality, but may lead to cardiac hemosiderosis due to myocardial iron deposition. Cardiomegaly, non-specific electrocardiographic changes (eg, bradycardia, repolarization abnormalities), and atrial as well as left ventricular dysfunction ensue in the untreated child [53-56], leading to end-stage cardiomyopathy. (See "Clinical utility of cardiovascular magnetic resonance imaging", section on 'Iron overload'.)

Additional risk factors for the development of cardiovascular complications may include:

- Vascular endothelial dysfunction and increased arterial stiffness have been found in children with hemoglobin E beta thalassemia despite treatment with periodic blood transfusions and iron chelation therapy, and have been attributed, at least in part, to the presence of oxidative stress markers and increased levels of non transferrin bound iron [57].
- Presence of the epsilon-4 allele of apolipoprotein E [58], which has decreased antioxidant and iron-binding activity compared with the epsilon-2 and epsilon-3 alleles [59].
- Presence of the null (deleted) genotype for glutathione S-transferase M1, an enzyme which, when present, may help reduce some of the oxidant damage due to increased iron deposition in tissues [60].
- A relationship among vitamin D deficiency, cardiac iron uptake, and ventricular dysfunction has been suggested, although the mechanism involved is not clear [61].
- In an MRI-based study, there was a significant incidence of myocardial fibrosis/necrosis, correlating best with presence of cardiovascular risk factors, a history of cardiac complications, and anti-HCV antibodies, rather than myocardial iron overloading [62].
- In a study of135 transfusion-dependent patients with beta thalassemia, 18 (13 percent) satisfied MRI criteria for the rare cardiomyopathy left ventricular noncompaction (LVNC) [63]. There were no statistically significant differences between patients with and without LVNC with respect to

demographics, hemoglobin levels, splenectomy status, iron overload status, liver disease, infection, or iron chelator type. (See "Isolated left ventricular noncompaction".)

In transfused patients with BTM, cardiac hemosiderosis is the most feared complication. Without early institution of iron chelation therapy, a characteristic cardiomyopathy due to iron overload develops. These patients develop a sterile pericarditis, arrhythmias (both supraventricular and ventricular), poor exercise performance [64], and end-stage restrictive cardiomyopathy leading to heart failure [55,65,66].

Fatal ventricular arrhythmias are a frequent cause of death. Rhythm disturbances begin with the characteristic prolongation of the PR interval, then first degree heart block, premature atrial beats, and, later, ST segment depression and ventricular ectopy.

Magnetic resonance imaging — Cardiovascular magnetic resonance imaging (MRI) is considered the "gold standard" for measurement of all left and right ventricular indices, while myocardial iron deposition can be quantified reproducibly with myocardial T2*, a relaxation parameter that arises on MRI principally from local magnetic field inhomogeneities that are increased with iron deposition [55]. (See "Clinical utility of cardiovascular magnetic resonance imaging", section on 'Iron overload' and "Treatment of beta thalassemia", section on 'Cardiac monitoring'.)

The importance of T2* cardiovascular MRI for determining myocardial iron loading and the development of heart failure and cardiac death in transfused patients with BTM was demonstrated in an international survey of 3095 patients in 27 worldwide centers. Results included the following [67]:

- At first scan, 20.6 percent had severe myocardial iron loading (T2* ≤10 ms), 22.8 percent had moderate myocardial iron loading (T2* 10 to 20 ms), and 56.6 percent had no iron loading (T2* >20 ms).
- At first scan, 85 of 2915 patients (2.9 percent) were reported to have heart failure. Of these, 81 percent had a T2* <10 ms and 99 percent had a T2* <20 ms.
- During follow-up, 108 of 2830 patients (3.8 percent) developed new heart failure. Of these, T2* at first scan had been <10 ms in 96 percent and <20 ms in 100 percent.
- There were 35 cardiac deaths (1.1 percent). Of these, T2* at first scan had been <10 ms in 86 percent and <20 ms in 97 percent.

Ninety-seven percent of those undergoing their first T2* scan in this report were taking regular iron chelation, and 93 percent had been taking iron chelation therapy for more than five years. Since a cardiac T2* <20 ms, which was present in over 40 percent of the subjects in this study, indicates inadequate chelation, issues such as compliance and intensification of treatment must be addressed in all patients with BTM undergoing iron chelation therapy [68]. (See "Chelation therapy for thalassemia and other iron overload states", section on 'Overall goals of iron chelation therapy'.)

Pulmonary complications — For poorly understood reasons, most patients with BTM have mild abnormalities of pulmonary function, including restrictive and small airway obstructive defects, hyperinflation, decreased maximal oxygen uptake, and abnormal anaerobic thresholds. These abnormalities are not corrected by transfusion and do not correlate with somatic iron burden, blood counts, or hemolysis [69]. After splenectomy, profound thrombocytosis places these patients at risk for pulmonary vascular obstruction.

Pulmonary hypertension — Although primary pulmonary symptoms are relatively infrequent in thalassemia, adult patients may develop pulmonary hypertension (PAH), the cause of which is not entirely clear [70], but may be related to such factors as prior splenectomy, older age, chronic hemolysis, iron overload, platelet activation, and smoking [71-74]. (See "Pulmonary hypertension associated with sickle cell disease", section on 'Introduction'.)

As an example, in a multicenter cross-sectional study of 1309 patients with beta thalassemia, those with a tricuspid valve regurgitant jet velocity ≥3.2 m/sec on transthoracic echocardiography underwent right heart catheterization to confirm the diagnosis of PAH (mean pulmonary arterial pressure ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg). Results included the following [74]:

- The positive predictive value for a tricuspid valve regurgitant jet velocity ≥3.2 m/sec threshold for the diagnosis of PAH was 94 percent. The confirmed PAH prevalence on right heart catheterization was 2.1 percent (95% CI 1.4-3.0) and was four times higher in those with thalassemia intermedia than in those with thalassemia major (4.8 versus 1.1 percent).
- Considerable functional limitation and decrease in the six-minute walk distance were noted in patients with confirmed PAH. On multivariate analysis, independent risk factors for confirmed PAH were increasing age (OR 1.1 per one-year increase) and prior splenectomy (OR 9.3; 95% CI 2.6-34).

Aplastic crisis — Parvovirus B19 infects erythroid precursor stem cells. In normal children, this results in a very mild transient erythrocytopenia because the impairment of marrow function is transitory and the 120-day survival of normal red blood cells protects them from acute drops in the red cell count. (See "Clinical manifestations and diagnosis of human parvovirus B19 infection".)

In patients with extremely shortened red cell survival, as in BTM, the effect is far more profound. These patients depend on very high rates of red cell production; moreover, the shortened red cell survival (four to eight days) causes the red cell count to fall rapidly when production is stopped. Children with BTM who develop B19 infection thus develop dramatic, often life threatening drops in hematocrit with reticulocyte counts of nearly zero. This "aplastic crisis" often requires emergent transfusion support [2,4].

Milder decreases in rates of red cell production frequently accompany other infections (hypoplastic crises), probably due to the amplified effects of the short red cell survival on transient partial suppression of erythropoiesis occurring in association with infection.

Chronic pain — A multicenter prospective study of 258 thalassemia patients (mean age 29; range 12 to 71) receiving care at 12 Thalassemia Clinical Research Network sites has revealed that 81 percent reported having pain for ≥1 year, and 31 percent reported pain for ≥5 years [75]. Patients with pain reported an average number of four sites of pain, which included the lower back (82 percent), leg (56 percent), head (48 percent), and midback (47 percent). Of those questioned about pain during the prior four-week period, 36 percent had no pain, while it was considered mild, moderate, or severe in 36, 19, and 9 percent, respectively. Regression analysis demonstrated a significant correlation of increased age with increased pain, irrespective of the type of thalassemia, transfusion status, gender, bone density, chelator type, or degree of iron overload. Although this pain syndrome appears to be a major cause of morbidity [76], its etiology and predictors remain unexplained.

Laboratory findings

Red blood cells — Profound hypochromic, microcytic anemia accompanied by bizarre red cell morphology is a hallmark of beta thalassemia major (BTM) [2,3]. The hemoglobin level may be as low as 3 to 4 g/dL. Red cell morphology is dramatically abnormal in most patients, with extreme hypochromia and poikilocytosis, a predominance of microcytes, tear drop and target cells (picture 1), and the visibility, even in routine stains, of clumped inclusion bodies representing precipitates of alpha globin within the red cell. These precipitates (Heinz bodies) can be more readily appreciated by staining with methyl violet or other supravital stains.

The white blood cell (WBC) count is often strikingly high, and the reticulocyte count surprisingly low. The latter reflects the severe degree of ineffective erythropoiesis underlying the disorder, resulting in many fewer than the expected number of reticulocytes being released from the bone marrow. The high white

count may be misleading, since these patients release many nucleated red blood cells (NRBC) into the peripheral blood. Depending on the counting method used, NRBC can be miscounted as leukocytes. However, even when corrected for this phenomenon, a true neutrophilia is often encountered.

The platelet count is usually normal. However, hypersplenism can lower both white cell and platelet counts. Splenectomy usually produces exaggerated rises in circulating NRBC, WBC, and platelets in the peripheral blood. (See 'Splenomegaly' above.)

Iron studies — Because of the high rate of erythroid cell turnover, the serum iron level is usually elevated; the transferrin saturation, expressed as the ratio of serum iron to total iron binding capacity (or transferrin), is very high [2].

Serum ferritin levels in those with thalassemia major may be quite elevated, reflecting the presence of iron overload primarily from multiple blood transfusions, but to a lesser extent from increased absorption of dietary iron from the gastrointestinal tract. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Anemia due to ineffective erythropoiesis' and "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload'.)

Other laboratory studies — The serum is often icteric; increased concentrations of indirect (unconjugated) bilirubin and lactate dehydrogenase, and low levels of haptoglobin, findings typical of hemolytic disease, are usually present. (See "Approach to the diagnosis of hemolytic anemia in the adult".)

Vitamin and mineral levels — Vitamin and mineral levels relevant to bone marrow homeostasis, such as folate, vitamin B12, and pyridoxine, are usually normal.

- Folate deficiency can develop in these patients, due to the high rate of cellular turnover.
- Serum zinc levels tend to be particularly low in these patients, likely due to increased requirements for this essential element and/or increased excretion subsequent to the use of iron chelating agents [28,77-79].
- Serum and leukocyte ascorbic acid levels are reduced, possibly as a result of accelerated catabolism in the face of iron overload. Serum levels of vitamin E are also sometimes low, perhaps for the same reasons.

Bone marrow examination — Bone marrow examination reveals profound erythroid hyperplasia that is unusual for the degree of immaturity and bizarre morphology of the erythroid progenitors. Early erythroblasts are abundant, and often appear megaloblastic, likely reflecting limited supplies of folate and other nutrients. Later erythroid progenitors are less abundant than expected, due to their intramedullary destruction (ie, ineffective erythropoiesis), producing a marked "left shift" that was erroneously interpreted as leukemic in the late 19th and early 20th century descriptions of this disease. Alpha globin inclusions are readily apparent, particularly if supravital dyes are used.

Extramedullary hematopoiesis — A dramatic abnormality of the bone marrow, rarely seen in other forms of chronic anemia, is extramedullary erythropoiesis. In the most severely symptomatic children, erythroid bone marrow may invade the bony cortex and break through bone, setting up masses of ectopic erythroid cell colonies in the thoracic or pelvic cavities or sinuses (image 1). These expanding masses can behave clinically like tumors, causing spinal cord compression and other abnormalities [80].

Hemoglobin electrophoresis patterns — Patients with homozygous beta (0) thalassemia are unable to make any Hb A. In untransfused patients only Hb F and Hb A2 are present on hemoglobin electrophoresis. When transfused, they will have variable amounts of Hb A from the transfused blood, but will still have increased amounts of Hb F and Hb A2 (table 1). Patients with combined heterozygosity for beta (0) and beta (+) thalassemia may produce small amounts of Hb A.

A more complete discussion of hemoglobin separation techniques is presented separately. (See "Laboratory diagnosis of the hemoglobinopathies".)

Diagnosis — The diagnosis of beta thalassemia major will have been made in all patients at around 6 to 12 months of age due to the presence of pallor, irritability, growth retardation, abdominal swelling due to hepatosplenomegaly, and jaundice. The laboratory examination at that time will show severe anemia with markedly abnormal hypochromic, microcytic red cells (picture 1) and with all of the classical findings of severe hemolytic anemia (eg, increased indirect bilirubin and lactate dehydrogenase and reduced or absent haptoglobin).

The diagnosis is confirmed on hemoglobin electrophoresis (table 1). Hemoglobin A is absent or severely reduced; only hemoglobins F and A2 are present. Variable amounts of hemoglobin A will be present in those who are subsequently treated with red cell transfusions, but levels of hemoglobins F and A2 will remain elevated.

CLINICAL HETEROGENEITY OF BETA THALASSEMIA

Overview — The beta thalassemia syndromes are remarkable for their heterogeneity, particularly in terms of clinical severity (table 2) [2,3]. Some of the factors contributing to this variability have been identified on the basis of differences in the mutations producing the beta thalassemic lesion (eg, beta (+) or beta (0) mutations that produce some or no beta globin, respectively), as well as interactions that modify the alpha-globin inclusion burden (eg, an accompanying alpha thalassemia).

- The genetic basis for the variability in clinical severity of homozygous beta (0) thalassemia was studied in a cohort of 316 Sardinian patients [81]. Clinical severity was assessed via the age at first transfusion. Phenotypic severity (ie, earlier age at the time of first transfusion) was explained to a large extent by genetic variants affecting fetal hemoglobin production (HBG2:g.-158C>T, BCL11A, HBS1L-MYB), with the remainder due to alpha globin gene defects and gender. (See "Clinical variability in sickle cell anemia", section on 'Fetal hemoglobin'.)

- Patients "homozygous" for beta thalassemia mutations (that is, inheriting a beta thalassemia mutation on each chromosome, even if they are not identical) usually exhibit some degree of alpha globin inclusion body formation, with consequent anemia, hemolysis, and varying degrees of ineffective erythropoiesis. The amount of alpha globin inclusion body formation and the degree of ineffective erythropoiesis correlate best with overall severity. The terms "beta thalassemia minor" and "beta thalassemia intermedia," attempt to reflect the fact that individuals carrying beta thalassemia mutations exhibit considerable clinical heterogeneity, requiring differences in approach to management. (See "Pathophysiology of beta thalassemia".)

- The vast majority of heterozygotes for beta thalassemia (eg, beta thalassemia trait) are asymptomatic [2]. This is thought to reflect the ability of the erythrocyte to catabolize some of the excess unpaired alpha-globin chains effectively; the burden is less because the patient is capable of producing approximately half the normal amount of beta globin.

Beta thalassemia minor — The terms beta thalassemia minor, beta thalassemia trait, and silent carrier of beta thalassemia are used to describe heterozygotes who carry one normal beta globin allele and one beta globin thalassemic allele. The vast majority of these patients are entirely asymptomatic, but do present an abnormal blood picture that is sometimes erroneously diagnosed as iron deficiency anemia.

Although the splenic volume, as assessed by ultrasonography, is 29 to 67 percent greater in those with thalassemia minor than in comparable controls [82,83], the spleen is palpable in less than 20 percent of subjects [82,84].

Typically, the blood count and peripheral blood film exhibit features similar to those seen in iron deficiency anemia (eg, hypochromia and microcytosis) (picture 2). However, as a rule, the microcytosis

is much more profound, and the anemia much milder, than that seen in iron deficiency anemia. Patients with beta thalassemia minor/trait also tend to have total red blood cell counts higher than normal, often into the "polycythemic" range.

Patients with beta thalassemia trait almost always have a hematocrit >30 percent, and a mean corpuscular volume of the red cells (MCV) <75 fL. In contrast, patients with iron deficiency rarely become microcytic (MCV <80 fL) until the hematocrit has dropped below 30. Another potentially useful indicator is the red cell distribution width (RDW). The RDW in patients with thalassemia trait tends to be normal, since virtually all cells are hypochromic and microcytic. In contrast, there is considerable heterogeneity in cell size in the early and intermediate stages of iron deficiency, producing an increased RDW. (See "Mean corpuscular volume".)

The peripheral blood smear often reveals a large number of target cells, more dramatic than is seen in all but the most profound cases of iron deficiency, as well as teardrop-shaped red cells (dacrocytes), which are not seen in iron deficiency. Red blood cell survival is either normal or only slightly shortened; reticulocyte counts are normal or only slightly increased, and overt hemolysis is generally not present.

During pregnancy, women with beta thalassemia trait sometimes exhibit a tendency to develop a more profound "physiologic" anemia of pregnancy than normal mothers, and may require transfusion. However, pregnancy outcomes are generally favorable [85].

Some rare forms of heterozygous beta thalassemia are due to mutations that alter the structure of the beta globin chain near its carboxy terminus, producing elongated or truncated beta globin chains. Even though their initial rate of synthesis is normal, these mutant chains combine abnormally with alpha globin to produce highly insoluble hemoglobin dimers or tetramers. The precipitates generate severe inclusion body formation and a phenotype more like severe beta thalassemia. These rare patients require management like patients with beta thalassemia major or intermedia. (See "Molecular pathology of the thalassemic syndromes", section on 'Dominant thalassemia trait due to nonsense codons in the final exon'.)

Protection against arterial thromboembolic events — A number of studies and a meta-analysis have indicated that beta thalassemia trait has a protective effect against arterial cardiovascular and cerebrovascular disease in male subjects [86,87]. This beneficial effect has been attributed to low serum cholesterol levels, slight anemia, and microcytosis, with a concomitant decrease in blood viscosity [88,89]. These intriguing hypotheses require further prospective follow-up studies.

Hemoglobin electrophoresis — On electrophoresis or high performance liquid chromatography (HPLC) in patients with beta thalassemia trait, over 90 percent of the hemoglobin will be hemoglobin A along with an elevation in the hemoglobin A2 value, sometime as high as 7 or 8 percent, and an increase in Hb F in about 50 percent of patients (table 1 and table 3).

As an example, in a study of 444 Chinese individuals with beta thalassemia trait, hemoglobin A2 levels, when measured by HPLC, were in the range of 5.6 ± 0.5 percent [90]. While mean hemoglobin A2 levels were slightly lower in those with both beta thalassemia trait and iron deficiency anemia (5.3 percent), all subjects with both conditions had hemoglobin A2 levels ≥3.5 percent. While others have agreed that the presence of iron deficiency does not compromise the diagnosis of high hemoglobin A2 beta thalassemia trait [91], this has not been a universal conclusion [92].

However, some forms of beta thalassemia trait are not associated with an elevated hemoglobin A2 level, such as those with delta-beta or gamma-delta-beta thalassemia trait or when beta thalassemia trait is co-inherited with a delta globin gene mutation [90,93,94]. Therefore, a normal concentration of hemoglobin A2 does not rule out the presence of beta thalassemia trait. (See "Structure and function of normal human hemoglobins", section on 'Hemoglobin A2'.)

More complex hemoglobin electrophoretic patterns may be seen in patients with beta thalassemia trait who have co-inherited a gene for sickle cell anemia (eg, sickle cell/thalassemia) (table 3 and table 4). These combinations are discussed in detail separately. (See "Variant sickle cell syndromes" and 'Effect of concomitant alpha thalassemia' below.)

Beta thalassemia intermedia

Overview — The term "beta thalassemia intermedia" (TI) refers to patients with symptomatic beta thalassemia who do not require transfusion during at least the first few years of life, and are able to survive into the second decade of life without chronic hypertransfusion therapy (eg, non-transfusion-dependent thalassemia) [95].

The term "beta thalassemia intermedia" is losing favor because it fails to address the genetic or clinical mechanisms for the phenotype of intermediate clinical severity [3]. However, it remains useful to refer to a category of patients who present special challenges in management, especially when these individuals are divided into those who require or do not require frequent blood transfusions.

The understanding that alpha globin inclusion burden is the predominant driver of clinical severity in patients with beta thalassemia has provided a useful paradigm for understanding some of the factors that contribute to the extraordinary clinical variability of this disease (table 2) [96]. As an example, some beta thalassemia mutations entirely ablate beta globin synthesis (ie, the beta(0) variants), while others are compatible with the production of up to 35 or 40 percent of the normal output of beta globin (ie, the beta(+) variants). Clearly, compound heterozygosity for a "severe" and a "mild" mutation, in terms of the degree to which beta-globin production is impaired, should result in a somewhat milder syndrome than homozygosity for a mutation that permits no beta-globin synthesis whatsoever.

Complications — Subjects with TI, while they may not require transfusion therapy at all, or as often as those with thalassemia major, have increased absorption of dietary iron, and may ultimately develop signs, symptoms, and complications of iron overload (eg, cardiac dysfunction, end-stage liver disease including hepatocellular carcinoma, endocrine dysfunction) [97-101]. They may also suffer from the complications of chronic hypoxia, such as high cardiac output, increased pulmonary vascular resistance, pulmonary hypertension, and heart failure, and may also be prone to thrombotic complications. As a result, such patients should be monitored frequently for these complications. (See "Pathogenesis of pulmonary hypertension" and "Treatment of beta thalassemia", section on 'Beta thalassemia intermedia'.)

In one study of 584 patients with TI, older age and prior splenectomy were independently associated with an increased risk of most disease-related complications; splenectomy was protective only against the development of extramedullary hematopoiesis [101]. In this report, in which 70 percent of the subjects were over the age of 18 years, 56 percent had undergone splenectomy, and 76 percent were receiving either occasional or regular transfusions, complications included the following:

- Osteoporosis – 23 percent
- Extramedullary hematopoiesis – 21 percent
- Hypogonadism – 17 percent
- Cholelithiasis – 17 percent
- Thrombosis – 14 percent
- Pulmonary hypertension – 11 percent
- Abnormal liver function – 10 percent
- Leg ulcers – 8 percent [102]
- Hypothyroidism – 6 percent
- Heart failure – 4 percent

- Diabetes mellitus – 2 percent

Thus, while most patients with TI do not need regular blood transfusions in order to survive, the stigmata of the disease, including bone marrow expansion, hepatosplenomegaly, and chronic hemolytic anemia are present, even in milder forms of the disorder.

- At the milder end of the scale of TI, some of these patients will undergo normal puberty and survive into adult life. However, they may be subject to a number of complications with advancing age (eg, leg ulcers, thrombosis, extramedullary hematopoiesis, pulmonary hypertension, hypothyroidism, osteoporosis) [100].
- At the more severe end of the spectrum, children with TI develop a need for transfusions or splenectomy at earlier times, often at the onset of or during adolescence. This may reflect the increased demands of puberty and the prepubertal growth spurt on the production of red cells.

These patients present a therapeutic dilemma, namely, when to institute chronic transfusion therapy with its attendant complications [2]. Delay for the longest possible time is clearly desirable, given the life-long problems associated with transfusion therapy. On the other hand, excessive delay can lead to significant morbidity, similar to that seen in younger children with beta thalassemia major. It is important to realize, however, that progressive iron overload can develop in many of these children, even in the absence of chronic transfusion therapy, requiring consideration for the use of iron chelating agents.

Iron overload — As already noted, expansion of the erythroid marrow and accelerated erythroid turnover stimulate iron absorption from the gut, leading to excessive iron accumulation in the body in patients incapable of utilizing the excess iron to manufacture hemoglobin. When patients with non-transfusion-dependent thalassemia develop signs and symptoms of iron overload, they are similar in virtually all respects to those with beta thalassemia major. (See "Pathophysiology of beta thalassemia", section on 'Non-transferrin bound iron'.)

As an example, in a cross-sectional study of 168 subjects with TI and a mean age of 35 years, mean liver iron concentration, as determined by magnetic resonance imaging, was 8.4 ± 6.7 mg Fe/g dry weight (normal: <2; iron overload: >4) [103]. After adjusting for age, gender, splenectomy and transfusion status, and laboratory indices, a 1 mg Fe/g dry weight increase in liver iron concentration was independently and significantly associated with higher odds of thrombosis, pulmonary hypertension, hypothyroidism, osteoporosis, and hypogonadism.

The above results from a cross sectional study were confirmed in the ORIENT study, a retrospective longitudinal cohort study in 52 subjects with non-transfusion-dependent thalassemia, using data from five Middle East comprehensive care centers. Observations included the following [104]:

- Thirty-six subjects (69 percent) had at least one morbidity, while 17 (33 percent) had multiple morbidities. The most common morbidities were osteoporosis (48 percent), extramedullary hematopoiesis (19 percent), liver disease (17 percent), hypothyroidism (10 percent), hypogonadism (8 percent), and diabetes mellitus (8 percent).
- The cumulative incidence of at least one morbidity was zero, 53, and 100 percent for those with mean overall serum ferritins ≤300, 300 to <800, and ≥800 ng/mL, respectively. The cumulative incidence of multiple morbidities was 0, 5.9, and 59 percent for those with mean overall serum ferritins ≤300, 300 to <800, and ≥800 ng/mL, respectively.
- Kaplan-Meier survival curves for time-to-first morbidity indicated that morbidity-free survival at 10 years for subjects with an overall serum ferritin level ≤300 or ≥800 ng/mL were 100 and zero percent, respectively.

These results confirm the damaging effects of iron overload in this patient population, and support the

use of a ferritin level ≥800 ng/mL to initiate iron chelation therapy in those with beta thalassemia intermedia. (See "Chelation therapy for thalassemia and other iron overload states", section on 'Iron chelation in transfusion-independent thalassemia'.)

Effect of concomitant alpha thalassemia — Alpha thalassemia is common in the same populations in which beta thalassemia is prevalent. Coinheritance of alpha thalassemia trait clearly ameliorates the severity of beta thalassemia, since the reduction in alpha globin synthesis (from the alpha thalassemia component) reduces the burden of alpha globin inclusions (from the beta thalassemia component) without greatly affecting the amount of actual hemoglobin made.

Effect of fetal hemoglobin levels — Fetal hemoglobin (HbF) synthesis persists to some degree in most patients with symptomatic beta thalassemia. In part, this reflects the tendency of "erythropoietic stress" to stimulate HbF production, even in adults. Elevated levels of HbF also appear to vary in the population via polymorphisms for heterocellular hereditary persistence of fetal hemoglobin, as well as mutations in the erythroid-enriched transcription factor KLF1. This important subject is discussed in depth separately. (See "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Acquired increases in HbF' and "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'HbF in the thalassemias and hereditary persistence of fetal hemoglobin' and "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Kruppel-like factor 1 (KLF1)'.)

Persistent synthesis of HbF has two beneficial effects: it provides additional oxygen carrying capacity and the gamma globin chain binds some of the free alpha globin, thus reducing alpha globin inclusions. In some ethnic groups and locations thalassemia also tends to be milder, presumably because of increased HbF levels [105]. As an example, the effect of HbF levels on 10 measures of morbidity was assessed in 63 untransfused subjects with thalassemia intermedia who had never received HbF induction therapy [106]. The following observations were made:

- Levels of HbF correlated positively with total hemoglobin and negatively with non-transferrin bound iron.
- There was a strong negative correlation between the HbF level and the total number of morbidities (eg, extramedullary hematopoiesis, pulmonary hypertension, venous thromboembolism, heart failure, leg ulcers, abnormal liver function, endocrinopathy, osteoporosis).
- A HbF threshold of 63.7 percent had 95.5 and 100 percent sensitivity and specificity, respectively, for ensuring the absence of morbidity.

Other causes of disease variability — Although features of the globin genotype in families with thalassemia account for some of the clinical variability encountered in this disorder, much remains to be explained. For example, siblings in some families appear to have identical globin genotypes, yet exhibit rather notable differences in clinical severity or in the prominence of individual manifestations of the disease. There is thus a substantial effort underway to use gene expression profiling, study of single nucleotide polymorphisms, and other technologies in an effort to associate polymorphic variations in other genes with altered clinical phenotype. To date, despite a considerable accumulation of preliminary data, no definitive leads are available. (See "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Hemoglobin switching: genetic basis of HbF expression' and "Clinical variability in sickle cell anemia".)

Diagnosis and differential diagnosis — The diagnosis of beta thalassemia minor or intermedia should be entertained in patients of any age with microcytic, hypochromic red cells (picture 3). As the beta thalassemias show considerable heterogeneity, patients may or may not have symptoms referable to anemia, may have variable degrees of splenomegaly and variable degrees of hemolysis.

The major differential diagnosis in patients with microcytic, hypochromic red cells includes iron deficiency

and the anemia of (chronic) inflammation, as follows:

- **Iron deficiency** – Patients with iron deficiency will have low levels of serum iron and ferritin and increased levels of transferrin (total iron binding capacity). Those with iron deficiency rarely become microcytic (mean corpuscular volume (MCV) <80 fL) until the hematocrit has dropped below 30 percent. The red cell distribution width (RDW) is usually increased and the total red cell count is decreased in concert with the degree of anemia. A cause for blood loss will be obvious in most patients.
- **Anemia of inflammation** – Patients with the anemia of chronic inflammation will have low levels of serum iron and transferrin. Levels of ferritin will be normal or increased. An inflammatory, infectious, or malignant disease is usually the underlying cause.
- **Thalassemia** – Patients with thalassemia will have normal to increased levels of serum iron and ferritin. Levels of transferrin will be normal or decreased. Patients with beta thalassemia trait almost always have a hematocrit >30 percent, and a mean corpuscular volume (MCV) <75 fL. The RDW tends to be normal. The total red cell count is usually normal to increased in those with beta thalassemia trait, reflecting the presence of an increased number of smaller than normal red cells. At least one of the patient's parents will also be affected. A family history of "iron deficiency anemia not responding to treatment with iron" is common.

The diagnosis of a beta thalassemic condition is confirmed on hemoglobin electrophoresis (table 1 and table 3). Hemoglobin A will be the major hemoglobin present. Levels of hemoglobin A2 are increased in virtually all patients, while levels of hemoglobin F are increased in about 50 percent of patients. (See "Laboratory diagnosis of the hemoglobinopathies".)

If hemoglobin S is present on electrophoresis along with hypochromic, microcytic red cells, and iron deficiency is absent, one of the sickle cell/thalassemia conditions is present (table 3 and table 4). (See "Variant sickle cell syndromes".)

THE ALPHA THALASSEMIA SYNDROMES — Alpha thalassemia is due to impaired production of alpha globin chains, leading to a relative excess of beta globin chains. The toxicity of the excess beta globin chains on the red cell membrane skeleton appears to be less than that of the excess partially oxidized alpha globin chains in beta thalassemia. (See "Pathophysiology of alpha thalassemia", section on 'Definitions'.)

Nomenclature and diagnostic patterns — The normal subject has four functional alpha globin genes, two on each chromosome 16 (ie, aa/aa). There are four deletional alpha thalassemia syndromes, reflecting the loss of one, two, three, or all four of these alpha chain genes (table 1):

- **Alpha thalassemia minima** (silent carrier of alpha thalassemia, heterozygosity for alpha (+) thalassemia, heterozygosity for the alpha thalassemia-2 trait) is due to the loss of **one** of the four alpha globin genes (ie, aa/a-).
- **Alpha thalassemia minor** is due to the loss of **two** of the four alpha globin genes. This can come about in two different ways, as follows:
    - Heterozygosity for the alpha thalassemia-1 trait (heterozygosity for alpha (0) thalassemia), in which both alpha genes on one of the two chromosomes have been deleted (ie, cis deletional form, aa/--)
    - Homozygosity for the alpha thalassemia-2 trait (homozygosity for alpha (+) thalassemia), in which one of the alpha genes has been deleted on each of the two chromosomes (ie, trans deletional form, a-/a-)
- **The deletional form of hemoglobin H disease** is due to the loss of **three** of the four alpha globin

loci, due to compound heterozygosity for both the alpha thalassemia-2 trait and the alpha thalassemia-1 trait (ie, a-/--).

- **The non-deletional form of hemoglobin H disease** is due to the loss of **two** of the four alpha globin loci along with an alpha chain mutation in one of the two remaining loci, due to compound heterozygosity for both the alpha thalassemia-1 trait and hemoglobin Constant Spring (ie, --/aa^{CS}).
- **Hydrops fetalis with Hb Barts** is due to loss of all **four** alpha globin loci secondary to homozygosity for the alpha thalassemia-1 trait (ie, --/--).

The majority of patients with alpha thalassemia, especially in Asia and Africa, have lost alpha globin gene function because of deletion of one, two, three, or all four structural alleles [107,108]. However, non-deletion alleles are also common, especially in the Mediterranean area, as are mutations producing highly unstable alpha globin variants that lead to failure to produce intact hemoglobin during erythropoiesis. (See "Pathophysiology of alpha thalassemia".)

A major clinical feature associated with inheritance of alpha thalassemia is the interaction of alpha thalassemia trait with beta globin hemoglobinopathies, including beta thalassemia and sickle cell anemia. (See 'Effect of concomitant alpha thalassemia' above and "Variant sickle cell syndromes", section on 'Sickle-alpha thalassemia'.)

Alpha thalassemia minima — Alpha thalassemia minima is essentially asymptomatic. Adult patients with alpha thalassemia minima are not anemic, their red cells are not microcytic, and their hemoglobin electrophoresis pattern is normal. The complete blood count and peripheral smear are usually normal, although very slight hypochromia and microcytosis might be evident by microscopic examination. Alpha thalassemia minima becomes apparent in families usually because individuals carrying this allele can, when mating with a partner carrying the alpha thalassemia-1 allele, give rise to an infant with HbH disease. The diagnosis of alpha thalassemia minima can be reliably made only via DNA analysis.

Alpha thalassemia minor — Alpha thalassemia minor resembles mild beta thalassemia trait. Adult patients with alpha thalassemia minor may have mild anemia, their red cells are hypochromic and microcytic and target cells are present. Hemoglobin electrophoresis pattern is normal. In contrast to patients with beta thalassemia, elevation of HbA2 is not seen in the alpha thalassemias; slight elevations of HbF have been reported.

Alpha thalassemia minor in individuals of African origin usually arises from the homozygous state for the alpha-thalassemia-2 allele (ie, a-/a-). Deletion of both alleles from one chromosome (the "cis" deletion) rarely occurs in this population. Moreover, the deletion usually involves the less active of the two normal alpha-globin alleles, so that alpha thalassemia minor (a-/a-) in this group tends to be milder than alpha thalassemia minor in Asian populations (aa/--). This diagnosis can be definitively made only through the use of molecular genetic techniques, which are not generally available.

Hemoglobin H disease — The clinical manifestations of HbH disease are more severe than those seen in alpha thalassemia minor and less severe that those seen in neonates with hydrops fetalis and hemoglobin Barts [109]. As a result, HbH disease has also been called alpha thalassemia intermedia and has been classified among the non-transfusion-dependent thalassemias [98].

Hemoglobin H, composed of four beta chains, forms because the marked impairment in alpha globin production results in accumulation of excess unpaired beta globin chains. In contrast to free alpha globin chains, which are exceptionally insoluble, free beta globin chains are soluble enough to form the homotetrameric HbH. Adult patients have a moderate degree of anemia, their red cells are microcytic, and their hemoglobin electrophoresis pattern shows 5 to 30 percent hemoglobin H (beta-4 tetramers).

HbH exhibits a dramatically left-shifted oxygen disassociation curve, such that it is virtually useless for oxygen transport. Moreover, it is rather insoluble, so that it behaves as an unstable hemoglobin during

the latter stages of erythropoiesis and during the circulating life span of the red cell. Inclusion body formation during the early stages of erythropoiesis is less prominent because of the somewhat higher solubility of unpaired beta globin, so that ineffective erythropoiesis in most patients with HbH disease is less severe than that seen in beta thalassemia. Rather, these patients suffer from a chronic hemolytic anemia, due to the formation of inclusion bodies in circulating red cells as HbH precipitates.

Clinical features — Individuals with HbH disease suffer from hemolytic anemia throughout much of gestation and are symptomatic at birth, often presenting with neonatal jaundice and anemia, and occasionally with hydrops fetalis [110]. This occurs because alpha globin synthesis is required in utero for the production of the major hemoglobin found during late gestation: hemoglobin F (alpha2/gamma2). Patients with beta thalassemia, on the other hand, do not have these difficulties until a few months after birth, when HbF production (and gamma globin production) decreases markedly and there is a need for increased production of beta globin chains for HbA (alpha2/beta2).

Patients with HbH disease exhibit all of the stigmata of chronic hemolytic anemia, including hepatosplenomegaly, indirect hyperbilirubinemia, elevated LDH, reduced haptoglobin, leg ulcers, osteopenia, and premature biliary tract disease, as described for severe beta thalassemia (see 'Laboratory findings' above) [109,111,112].

The skeletal, developmental, and metabolic changes due primarily to ineffective erythropoiesis tend, in general, to be less severe in this patient population for reasons already stated. However, for poorly understood reasons, some of these patients can exhibit clinical phenotypes strongly resembling severe beta thalassemia intermedia or beta thalassemia major. Most patients, however, do not require chronic transfusion support during the first decade of life.

The typical patient with HbH disease resembles patients with beta thalassemia intermedia. Even though transfusion support is not necessary early in life, splenectomy or institution of transfusion support during the second or third decade of life is often necessary [112]. Iron overload due to increased iron absorption is also as significant an issue as it is in beta thalassemia intermedia [109,111,113]. Measures to delay the onset of hepatic and cardiac damage due to iron deposition must therefore be employed as in patients with beta thalassemia intermedia [114]. (See "Chelation therapy for thalassemia and other iron overload states", section on 'Iron chelation in transfusion-independent thalassemia'.)

Hemoglobin H is readily oxidized. Thus, patients with HbH disease, as in patients inheriting unstable hemoglobins or glucose-6-phosphate dehydrogenase deficiency, are at risk for exacerbations of their hemolytic process and anemia when exposed to oxidant stressors, such as infection or oxidizing drugs (eg, antimalarials, certain sulfa drugs). (See "Pathophysiology of alpha thalassemia", section on 'Role of oxidant injury'.)

HbH disease patients are also, similar to other patients with chronic hemolytic anemias, particularly susceptible to aplastic or hypoplastic crises by the same mechanisms described for beta thalassemia (see 'Aplastic crisis' above) [113].

Diagnosis — The peripheral blood film in HbH disease shows hypochromia and microcytosis (picture 4) with readily detectable inclusion bodies, especially if the smear is stained with a supravital dye such as methyl violet or brilliant cresyl blue (picture 3) [115]. Bone marrow examination reveals erythroid hyperplasia with poorly hemoglobinized erythroblasts carrying inclusion bodies.

The diagnosis is confirmed by finding HbH in circulating red cells, using a number of hemoglobin electrophoretic or chromatographic techniques (table 1 and figure 1). In one study, for example, median levels of HbH were 6.9 percent (range 2.2 to 21) in 26 subjects with deletional HbH disease and 29 percent (range 10 to 50) in 9 subjects with non-deletional HbH disease [112].

In addition, Hb Barts (gamma-4), a fast-moving hemoglobin, can be detected in concentrations of

approximately 20 to 40 percent at the time of birth of a child with hemoglobin H disease [109]. This latter test has been successfully employed in California as a screening test for HbH disease [116]. DNA-based genotyping is required for precise diagnosis, and is especially important in prenatal testing and genetic counseling (see 'Genetic counseling and antenatal diagnosis' below).

Acquired hemoglobin H disease — Hemoglobin H disease can be acquired during the course of several hematologic malignancies, most notably the myelodysplastic syndrome. (See "Clinical manifestations and diagnosis of the myelodysplastic syndromes", section on 'Acquired hemoglobin H disease'.)

Hydrops fetalis and hemoglobin Barts — This condition is incompatible with extrauterine life since normal neonatal and adult hemoglobins (ie, hemoglobins A, F, and A2) cannot be made and Hb Barts (gamma-4 tetramers) cannot release oxygen to tissues because its affinity for oxygen is at least 10 times greater than that of HbA. (See "Pathophysiology of alpha thalassemia", section on 'Hydrops fetalis and hemoglobin Bart's'.)

These patients produce no alpha globin, which is essential for the formation of fetal hemoglobin, the predominant hemoglobin normally produced after the first six to eight weeks of gestation. Hb Barts, a homotetramer composed of four gamma globin chains (gamma-4), exhibits an extremely left-shifted oxygen dissociation curve. It fails to deliver any oxygen to tissues, resulting in profound tissue hypoxia. The deficit in oxygen delivery, coupled with anemia due to mechanisms similar to HbH disease, causes massive tissue ischemia in the developing fetus. (See "Nonimmune hydrops fetalis", section on 'Anemia'.)

The hydropic state in the fetus reflects the existence of massive total body edema due to high output heart failure. Fetal death usually occurs during the late second through mid-third trimester of pregnancy. However, occasional live births have been reported, sometimes at full term, following use of intrauterine transfusion [117,118]. (See "Intrauterine fetal transfusion of red blood cells".)

These infants usually die within a few hours after birth, unless supported with massive total exchange transfusions. Rarely, infants have survived the perinatal period [119] and need to be maintained on a chronic intensive hypertransfusion regimen with iron chelation. However, survival beyond the perinatal period almost never occurs, except in rare circumstances [120,121]. Mothers of fetuses with hydrops fetalis are at risk for the development of polyhydramnios, and a variety of other obstetrical complications.

In populations of African origin, this severe form of alpha thalassemia almost never occurs because the "cis" deletion, in which both loci are absent from the same chromosome (ie, aa/--), occurs very rarely. Inheritance of the cis deletion chromosome from each of the two parents, which occurs most commonly in populations of Asian origin, is necessary for development of hydrops fetalis. On the other hand, inheritance of the cis deletion from one parent (aa/--) and alpha thalassemia-2 trait from the other (ie, either a-/a- or aa/a-) is necessary for the development of HbH disease (ie, a-/--).

Hemoglobin Constant Spring — Hemoglobin (Hb) Constant Spring (CS) is a particularly common structural variant associated with alpha thalassemia in Asia [108]. It is always inherited in association with a normal alpha chain (eg, aa/aa^{CS}). An additional feature in these patients is the presence of a minor, very slowly migrating abnormal hemoglobin component on hemoglobin electrophoresis; this is the Hb Constant Spring band.

The alpha(CS) gene contains a mutation that abolishes the normal translation termination codon, so that polyribosomes "read through" the normal translation termination site on alpha(CS) mRNA, translating an additional 31 residues from the normally untranslated 3' extremity of the mRNA, until another in frame termination codon is reached. This "read through" process disrupts normal alpha globin mRNA stability, resulting in a highly unstable alpha(CS) mRNA that accumulates to only 1 percent of the normal level. The alpha(CS) allele thus functions as a severe alpha thalassemia gene.

Non-deletional Hemoglobin H disease — Co-inheritance of the cis deletional form of alpha thalassemia minor from one parent and hemoglobin Constant Spring from the other (ie, --/aa^{CS}) results in a form of hemoglobin H disease (eg, non-deletional HbH disease), which is often more severe than that seen in subjects with deletional HbH disease [122]. (See "Molecular pathology of the thalassemic syndromes", section on 'Failed translation termination: Hb constant spring'.)

Suspecting and diagnosing alpha thalassemia — Alpha thalassemia due to deletion of one or two of the four loci present in the developing erythroblast is difficult to detect on clinical or laboratory grounds alone. Anemia, hypochromia and microcytosis may be minimal or non-existent, especially if only one locus is deleted (ie, alpha thalassemia minima, silent carrier state). All too often, the existence of alpha thalassemia trait is recognized in family members because of the birth or prior family history of an individual with more severe alpha thalassemia (eg, HbH disease or hydrops fetalis with Hb Barts).

Accordingly, family history is important in raising suspicion of this condition in family members. In the absence of a positive family history, the condition should be considered in individuals from ethnic groups with a very high incidence of alpha thalassemia (eg, Asians and people of Mediterranean origin; African Americans almost never have severe alpha thalassemia despite a high incidence of a single gene deletion).

The presence of microcytosis with minimal or mild anemia is a major clue, but, in many individuals, hypochromic and/or microcytic cells on peripheral blood films, in the absence of overt microcytic indices or anemia is the only clue. In newborns, small amounts of Hb Barts may be present; in children and adults, low levels of HbH may be found, although the analysis of hemoglobin in circulating red cells can be normal (table 1). Unlike the beta thalassemic disorders, hemoglobin A2 levels are not increased in the alpha thalassemias.

Measurement of the relative rates of alpha and beta globin synthesis by isotopic labeling methods is diagnostic but is not available in clinical laboratories. The only certain way to determine the alpha thalassemia genotype of an individual with suspected alpha thalassemia is direct sequencing DNA analysis of the globin genes. In a single test, this will identify the number of loci deleted, whether the deletions are in the cis (both copies deleted from one chromosome) or trans (one copy deleted from each chromosome) configuration in individuals with 2 loci deleted, and any mutations causing non-deletion forms of alpha thalassemia. This analysis is available in most reference laboratories. (See "Laboratory diagnosis of the hemoglobinopathies", section on 'Definitive evaluation'.)

Management — Alpha thalassemia minima and alpha thalassemia minor require no specific therapy. Inappropriate use of iron should be avoided in patients with detectable hypochromia and microcytosis; proper diagnosis and distinction of these patients from patients with iron deficiency is crucial.

Individuals carrying alpha thalassemia trait alleles require especially careful genetic counseling, given the complex patterns of inheritance that could affect the clinical phenotype of their offspring [2,108]. (See "Mean corpuscular volume", section on 'Causes of microcytosis'.)

The management of patients with HbH disease parallels in many respects the approach described for patients with beta thalassemia intermedia. Because of the tendency of HbH to suffer oxidative damage, close monitoring of the blood count and possible transfusional intervention may be required during periods of oxidant stress, such as infection or exposure to oxidant drugs. Patients must be monitored carefully for signs that institution of chronic transfusion or iron chelation support are needed, especially during the second and third decades of life. A role for bone marrow transplantation in the treatment of HbH disease has not yet been established. Fetal hemoglobin manipulation plays no role in this disorder, and no effective means of gene therapy has been developed. (See "Treatment of beta thalassemia".)

Hydrops fetalis with hemoglobin Barts is, as noted above, almost always lethal in utero. The possibility for survival of these fetuses by institution of chronic total exchange transfusional support exists, but is

not practical and not usually recommended [117,118]. However, combinations of transfusion, iron chelation, and hematopoietic cell transplantation have allowed a small number of these children to survive [118,120,121]. Because of the high risk of maternal morbidity, early consideration of therapeutic termination of pregnancy is an issue that must be discussed with mothers at risk.

GENETIC COUNSELING AND ANTENATAL DIAGNOSIS — Families in which a patient with heterozygous or homozygous thalassemia is discovered require intensive education and genetic counseling.

Beta thalassemia — Since the beta globin gene exists as a single copy, the odds of two parents, each carrying beta thalassemia trait, giving rise to a child with homozygous beta thalassemia are one in four, since the gene follows straightforward Mendelian rules of inheritance. The odds of their child having heterozygous thalassemia (thalassemia trait) are one in two, and the odds are one in four that the child's hemoglobin profile will be normal.

Mothers with heterozygous thalassemia require particularly close monitoring during pregnancy because of the occasional incidence of especially severe physiologic anemia of pregnancy. Screening of the family for beta thalassemia trait can usually be accomplished through a combination of a routine CBC, with particular attention being paid to measurement of the mean corpuscular volume (MCV), as well as results of a hemoglobin electrophoresis, including the level of Hb A2. A characteristic smear exhibiting hypochromia and microcytosis is clearly helpful. If microcytosis is encountered, iron deficiency should be ruled out, especially if the hematocrit is less than 30 to 33 percent.

Couples at risk for giving birth to a child with homozygous thalassemia should be apprised of the availability of antenatal diagnosis by direct gene analysis [123]. A small chorionic villus biopsy sample, or amniocytes from a routine amniocentesis provide adequate DNA for comprehensive globin gene analysis. The fact that thalassemia mutations have been thoroughly characterized and categorized within individual populations allows for nearly unambiguous diagnosis of homozygous thalassemia, heterozygous thalassemia, compound heterozygous states, and normal hemoglobin genotypes by use of PCR amplification and allele-specific oligonucleotide hybridization probes designed to detect the most prevalent mutations [123].

Although these methods require referral to a laboratory equipped with the appropriate technology, the procedures can routinely be done by these facilities with a rapid turnaround time. Hematology divisions at most academic medical centers in the Western world are familiar with ways to access these reference labs. (See "Fetal blood sampling" and "Prenatal screening and testing for hemoglobinopathy", section on 'Prenatal diagnosis'.)

Families in whom a fetus homozygous for beta thalassemia is identified face the difficult choice of whether to undergo elective termination of pregnancy. One study has raised the possibility of an alternative to pregnancy termination. When there are family members available who are HLA compatible with the fetus, early hematopoietic cell transplantation appears to be efficacious [124]. This is a highly individualized decision that must be made in light of a thorough discussion of the known facts. The considerable burden of disease morbidity and the elaborate therapies required must be weighed against the potential for long-term survival with a reasonable quality of life. Individual moral, ethical, and religious views must be taken into account during this discussion.

In certain regions, such as Cyprus, Sardinia, Northern Italy, and parts of Greece, the introduction of DNA-based antenatal diagnosis and genetic counseling has led to a nearly complete eradication of new cases of severe beta thalassemia. In other areas of the world, the impact has been less dramatic but still significant. Genetic counseling and antenatal diagnosis should be attempted only in collaboration with genetic counselors familiar with the hemoglobinopathies. (See "Community public health issues and the thalassemic syndromes: Lessons from other countries".)

Pre-implantation genetic testing, by which the genotype of the fetus can be ascertained from polar bodies created during ovulation, without damage to the potential fertilized egg, is a rapidly emerging technology. This approach has a clear potential for application to families at risk to conceive a child with severe thalassemia. At the present time, this method is prohibitively expensive and competently performed in only a few centers.

Alpha thalassemia — The genetics of alpha thalassemia are somewhat more complex because of the duplicated nature of the alpha globin genes on chromosome 16. Since uncomplicated alpha thalassemia trait is frequently asymptomatic and barely detectable, prospective identification of families at risk is less likely.

- Individuals of African descent are rarely at risk for giving birth to infants with severe forms of alpha thalassemia. Counseling to make individuals aware of the condition is usually adequate.
- More intensive counseling is needed if the individual partners are non-African individuals from alpha thalassemia endemic areas, in whom there is the risk of having a fetus with hydrops fetalis or hemoglobin H disease. (See "Fetal blood sampling".)

Hemoglobin H disease or hydrops fetalis — Families in which HbH or hydrops fetalis has previously occurred are clearly at risk of giving birth to additional infants with these conditions [109]. The principles of genetic counseling and antenatal diagnosis that should be followed are similar to those outlined above for beta thalassemia. Early monitoring of pregnancies at risk for the presence of a hydropic fetus is important, because of the increased risk for polyhydramnios and other obstetrical complications. (See "Polyhydramnios".)

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 5^{th} to 6^{th} 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 10^{th} to 12^{th} 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 topic (see "Patient information: Thalassemia (The Basics)")

SUMMARY — The major hemoglobin in adults is hemoglobin A, consisting of one pair of alpha globin chains and one pair of beta globin chains. Globin chain synthesis is very tightly controlled, such that the ratio of production of alpha to non-alpha chains is 1.00 ± 0.05. Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of alpha (alpha thalassemia) or beta (beta thalassemia) globin chains, disrupting this closely-regulated ratio.

- Beta thalassemia – There are three major forms of beta thalassemia, as follows:
  - Beta thalassemia minor – These subjects carry one normal beta globin allele and one beta globin thalassemic allele. The vast majority are asymptomatic. On electrophoresis, over 90 percent of the hemoglobin will be hemoglobin A along with an elevation in the hemoglobin A_2 value, and an increase in Hb F in about 50 percent of patients (table 1 and table 3). (See 'Beta thalassemia minor' above.)
  - Beta thalassemia intermedia – These subjects are compound heterozygotes for two different beta globin chain mutations and have a disease that is intermediate in severity between beta

thalassemia minor and beta thalassemia major. (See 'Beta thalassemia intermedia' above.)

- Beta thalassemia major – These severely affected subjects are homozygous for mutations associated with absent (or very severely reduced) production of beta chains. The diagnosis is usually made at around 6 to 12 months of age due to the presence of pallor, irritability, growth retardation, abdominal swelling due to hepatosplenomegaly, and jaundice. The laboratory examination shows severe hemolytic anemia with markedly abnormal hypochromic, microcytic red cells (picture 1). The diagnosis is confirmed on hemoglobin electrophoresis (table 1). Hemoglobin A is absent or very severely reduced; only hemoglobins F and A_2 are present. (See 'Beta thalassemia major' above.)

- Alpha thalassemia – The normal individual has a complement of four alpha globin chain genes. Accordingly, there are four major forms of alpha thalassemia, due to loss of one, two, three, or four of these genes, as follows:

  - Alpha thalassemia minima – These subjects have inherited three normal alpha globin chain genes, are asymptomatic, and have normal blood counts and red blood cell indices. The diagnosis of alpha thalassemia minima can be reliably made only via DNA analysis. (See 'Alpha thalassemia minima' above.)

  - Alpha thalassemia trait – These subjects have inherited two normal alpha globin chain genes. Adults may have mild anemia, their red cells are hypochromic and microcytic and target cells are present. Hemoglobin electrophoresis pattern is normal. Elevation of HbA_2 is not seen in the alpha thalassemias; slight elevations of HbF have been reported. The diagnosis of alpha thalassemia trait can be reliably made only via DNA analysis. (See 'Alpha thalassemia minor' above.)

  - Hemoglobin H disease – These subjects have inherited only one functional alpha globin chain gene and are symptomatic at birth, with neonatal jaundice and life-long hemolytic anemia. The diagnosis is confirmed by finding hemoglobin H, a tetramer of beta globin chains, in circulating red cells (table 1 and figure 1). Hemoglobin Barts (a tetramer of gamma globin chains) can be detected at the time of birth of a child with hemoglobin H disease. Hemoglobin H disease can also be acquired in some patients with myeloid malignancies. (See 'Hemoglobin H disease' above.)

  - Hydrops fetalis and hemoglobin Barts – These subjects have inherited no alpha globin chain genes. Without treatment (eg, exchange transfusion) this condition is incompatible with extrauterine life. (See 'Hydrops fetalis and hemoglobin Barts' above.)

- Differential diagnosis – The peripheral blood in thalassemia demonstrates hypochromic, microcytic red cells, a picture often confused with iron deficiency. Routine laboratory tests (complete blood count, red cell indices, iron studies) will serve to differentiate these two disorders from one another. (See 'Diagnosis and differential diagnosis' above.)

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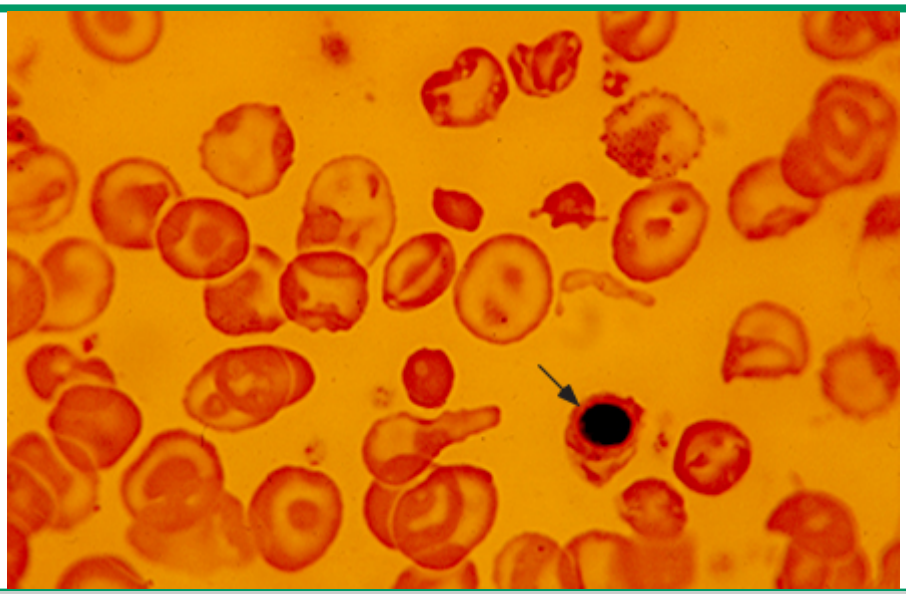
Topic 7116 Version 49.0

GRAPHICS

Peripheral blood smear in beta thalassemia intermedia

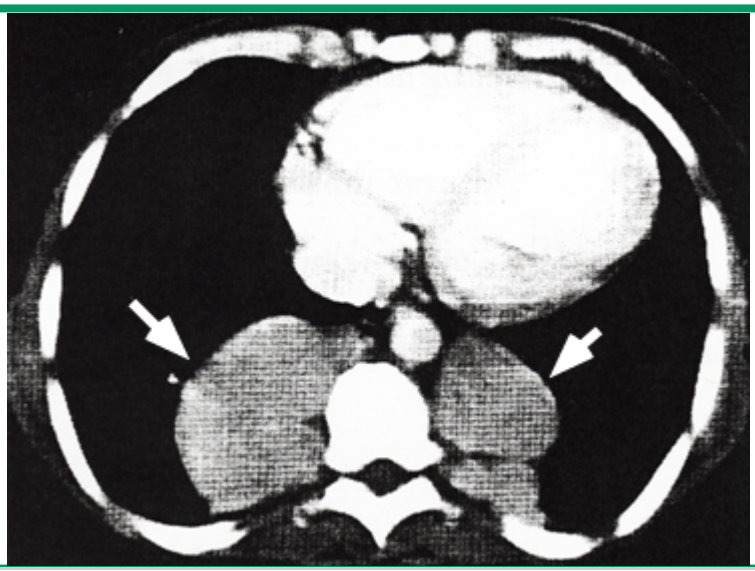


Peripheral smear from a patient with beta thalassemia intermedia post-splenectomy. This field shows target cells, hypochromic cells, microcytic cells, red cell fragments, red cells with bizarre shapes, and a single nucleated red cell (arrow).

Courtesy of Stanley Schrier, MD.

Graphic 76666 Version 2.0

Extramedullary hematopoiesis (paraspinal masses) on CT scan in thalassemia



This is an axial contrast-enhanced CT scan through the level of the chest in a 23-year-old thalassemic woman, showing uniformly enhancing paraspinal hematopoietic masses with no bony erosion (arrows).

From: Georgiades CS, Neyman EG, Francis IR, et al. Typical and atypical presentations of extramedullary hemopoiesis. AJR Am J Roentgenol 2002; 179:1239. Reprinted with permission from the American Journal of Roentgenology.

Graphic 53353 Version 12.0

The thalassemias: Genetic, clinical, and laboratory findings

Disorder	Genotype	MCV	Anemia	Hemoglobin electrophoresis
Alpha thalassemia				
Silent carrier	α α / α -	NL	None	Normal <3 percent Hb Barts at birth
Minor	α α / - - or α - / α -	Low	Mild	Normal 3 to 8 percent Hb Barts at birth
Hb H disease (deletional)	α - / - -	Low	Moderate	5 to 30 percent HbH present in adults 20 to 40 percent Hb Barts at birth
Major (fetal hydrops)	- - / - -	Low	Fatal	Hb Barts, Hb Portland, and HbH present HbA, HbF, and HbA_2 are absent
Beta thalassemia				
Minor (trait)	β / β^{o} or β / β^{+}	Low	Mild	HbA_2 increased (3.5 to 7 percent)
Intermedia	β^{+} / β^{+} and others*	Low	Moderate	HbF increased in about 50 percent of patients
Major	$\beta^{\circ} / \beta^{\circ}$	Low	Severe	HbA absent Only HbA_2 and HbF are present

MCV: mean corpuscular volume; Hb: hemoglobin; NL: normal; β^{+}: thalassemic gene producing some β-chain; β°: thalassemic gene producing no β-chain.
* See text for multiple other genotypes.

Courtesy of Stephen A Landaw, MD, PhD.

Graphic 50393 Version 6.0

Thalassemia variants which may present as Beta Thalassemia intermedia

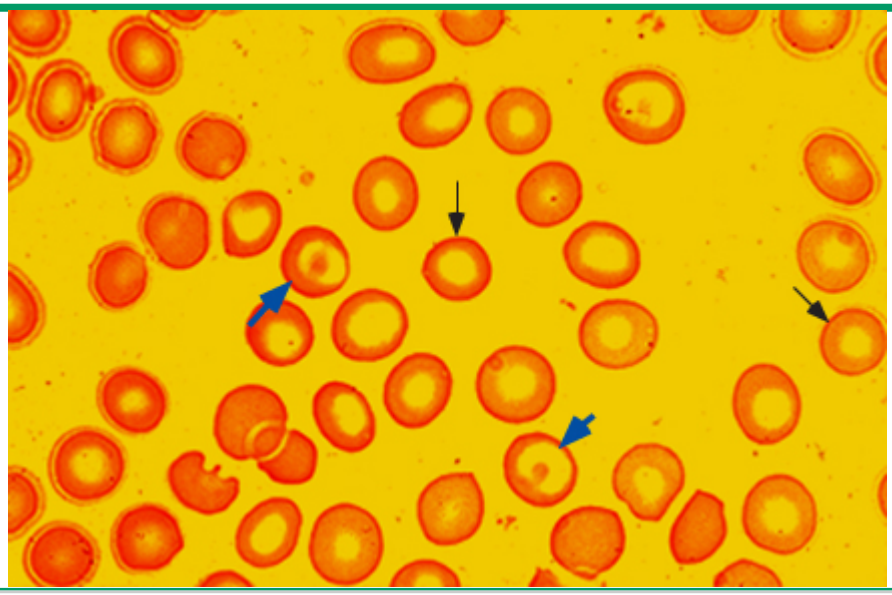
General principles: The pathophysiology of beta thalassemia depends absolutely on the amount of excess unpaired alpha globin chains. Therefore any genetic variant that increases or decreases the amount of these unpaired alpha chains (eg, by altering the rate of alpha or beta chain production, or by substituting for the missing beta chains) will modify the phenotype. Disorders that present as β-thalassemia intermedia, rather than as the major or minor variants, are listed below:
Homozygosity for mild forms of β+ thalassemia
Compound heterozygosity for β+/βº thalassemia
Compound heterozygosity for β thalassemia and another beta chain variant (eg, β-thal/Hgb E)
Coinheritance of homozygous β thalassemia with genes for increased gamma chain synthesis (ie, HPFH)
Coinheritance of homozygous β+ thalassemia with alpha thalassemia (eg, β+/β+ with -a/-a, --/aa, -a/aa, or --/-a)
Coinheritance of heterozygous β thalassemia and triplicated or quadruplicated alpha genes (eg, aa/aaa or aa/aaaa)
Dominant forms of beta thalassemia

β º thalassemia: no production of beta chains; β + thalassemia: reduced production of beta chains (may be mild, moderate, or severely reduced); HPFH: Hereditary persistence of fetal hemoglobin.

Table provided by Stanley L. Schrier, MD.

Graphic 69490 Version 3.0

Beta thalassemia trait

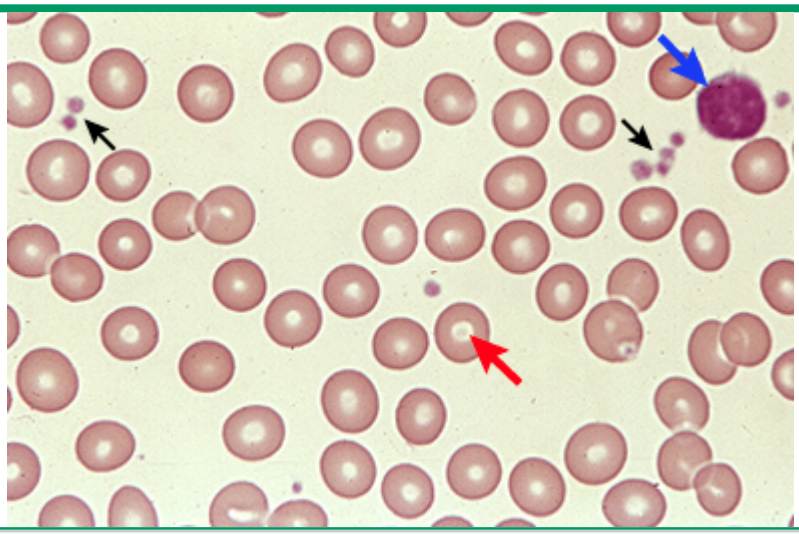


Peripheral smear from a patient with beta thalassemia trait. The field shows numerous hypochromic and microcytic red cells (thin arrows), some of which are also target cells (blue arrows).

Courtesy of Stanley Schrier, MD

Graphic 56728 Version 1.0

Normal peripheral blood smear



High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Electrophoretic patterns in common hemoglobinopathies

Condition	HbA	HbS	HbC	HbF	HbA2
Normal	95 to 98*	0	0	<1	2.5 ± 0.2
Beta thalassemia minor	90 to 95	0	0	1 to 3	>3.5 ¶
Sickle cell trait	50 to 60	35 to 45 Δ	0	<2	<3.5
Sickle-beta(+) thalassemia	5 to 30	65 to 90	0	2 to 10	>3.5
Sickle-beta(0) thalassemia	0	80 to 92	0	2 to 15	>3.5
Sickle-HbC disease	0	45 to 50	45 to 50	1 to 8	<3.5
Homozygous sickle cell disease	0	85 to 95	0	2 to 15	<3.5

Hb: hemoglobin.
* Numbers indicate the percent of total hemoglobin for an untransfused adult patient. Ranges are approximate and may vary depending upon the particular laboratory and method of determination. There may be overlap of levels between the various sickle cell variants.
¶ Beta thalassemia minor, due to Hbδβ thalassemia, have normal or low HbA2 levels with markedly increased HbF levels.
Δ Percent HbS can be as low as 21 percent in patients with sickle cell trait in conjunction with alpha thalassemia.

Graphic 64715 Version 8.0

Hematologic parameters in sickle cell trait-alpha thalassemia

Alpha globin genes	Hemoglobin (g/dL)	MCV (fL)	Hemoglobin S (percent)
4	13 to 15	80 to 90	35 to 45
3	13 to 14	75 to 85	30 to 35
2	12 to 13	70 to 75	25 to 30
1	7 to 10	50 to 55	17 to 25

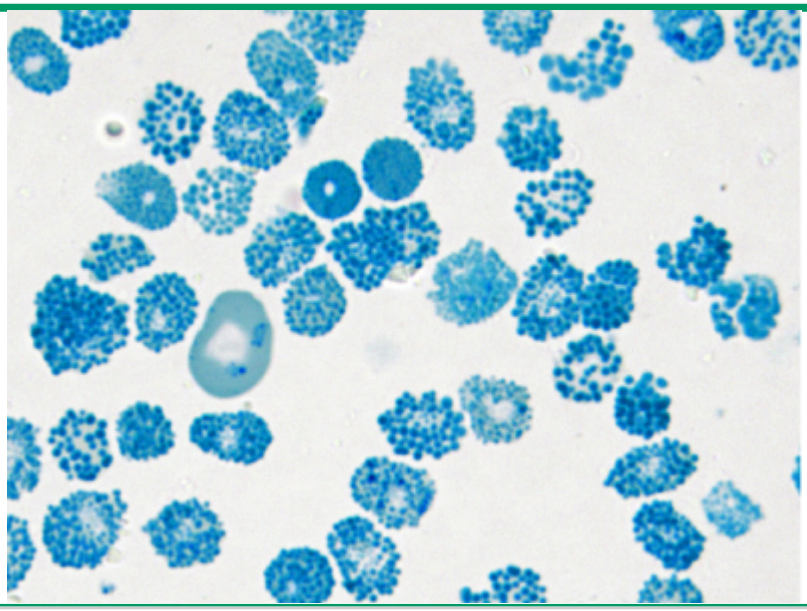
This table shows the effect of the number of functioning alpha globin genes on hematologic parameters in patients with the combination of alpha thalassemia and sickle cell trait. (The absence of any functional alpha globin genes is incompatible with extrauterine life; the normal complement is four.)

MCV: mean corpuscular volume.

Data from: Steinberg MH, Embury SH. Alpha-thalassemia in blacks: genetic and clinical aspects and interactions with the sickle hemoglobin gene. Blood 1986; 68:985.

Graphic 70184 Version 3.0

Hgb H inclusions

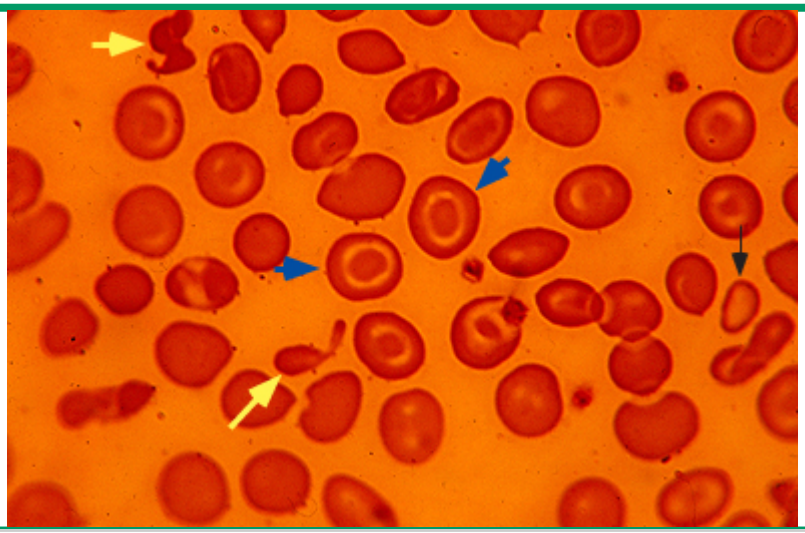


Red cells from a patient with acquired hemoglobin H disease were incubated in vitro with new methylene blue. Multiple ("golf ball-like") small inclusions due to precipitation of hemoglobin H are seen as a result of interaction with this dye.

Kindly provided by Dr. German Pihan, Pathology Department, Beth Israel Deaconess Medical Center, Boston.

Graphic 77536 Version 1.0

Hemoglobin H disease

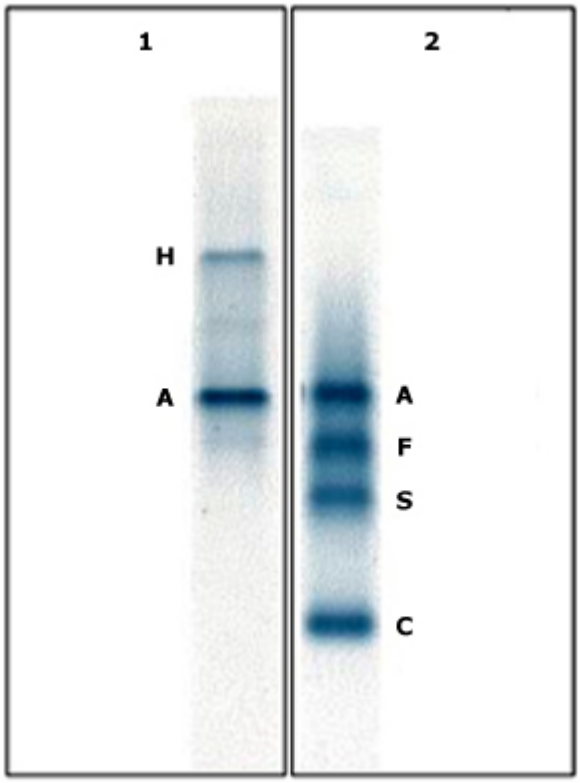


Peripheral blood smear from a patient with hemoglobin H disease and an intact spleen. The smear shows target cells (blue arrows), microcytic red cells (black arrow), and red cell fragments (yellow arrows).

Courtesy of Stanley Schrier, MD.

Graphic 80776 Version 1.0

Electrophoresis for hemoglobin H: Alkaline cellulose acetate gel



This is a hemoglobin electrophoresis run at alkaline pH on cellulose acetate gel. Lane 2 is a commercial standard containing approximately equal amounts of hemoglobins A, F, S, and C. Lane 1 is a hemoglobin sample from a patient with myelodysplastic syndrome/acute myeloid leukemia, a population of hypochromic-microcytic red cells, and acquired hemoglobin H disease. A minor fast-migrating band, hemoglobin H, is seen along with hemoglobin A.

Kindly supplied by Dr. German Pihan, Department of Pathology, Beth Israel Deaconess Medical Center.

Graphic 50325 Version 2.0

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Conflict of interest policy

Genetics, clinical features, and diagnosis of Marfan syndrome and related disorders

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INTRODUCTION — One of the most common inherited disorders of connective tissue, Marfan syndrome (MFS, MIM #154700) is an autosomal dominant condition with a reported incidence of 1 in 3000 to 5000 individuals [1,2]. There is a broad range of clinical severity associated with MFS and related disorders, ranging from isolated features of MFS to neonatal presentation of severe and rapidly progressive disease involving multiple organ systems [3]. Although many clinicians view the disorder in terms of classic ocular, cardiovascular, and musculoskeletal abnormalities, manifestations also include involvement of the lung, skin, and central nervous system.

The genetics, pathogenesis, clinical manifestations, and diagnosis of MFS and related disorders will be reviewed here. The management of patients with MFS and related disorders and issues related to pregnancy are discussed separately. (See "Management of Marfan syndrome and related disorders" and "Pregnancy and Marfan syndrome".)

GENETICS — MFS is a highly variable systemic tissue disorder with clinical characteristics similar to a variety of other hereditary disorders from which it should be distinguished. MFS is almost exclusively inherited in an autosomal dominant manner, although rare case reports have described recessive fibrillin 1 gene (FBN1) mutations [4]. While most individuals with MFS have an affected parent, 25 percent or more of probands have MFS as the result of a de novo mutation.

Most patients with the typical Marfan phenotype harbor mutations involving the gene (FBN1) encoding the connective tissue protein fibrillin-1 [5-7]. However, FBN1 mutations also cause a wide range of milder phenotypes that often show at least some overlap with the classic Marfan phenotype. (See 'FBN1/2 phenotypes' below.)

In a minority of cases (less than 10 percent) with typical Marfan phenotype, no mutation in FBN1 is identified [3]. Studies have suggested that at least some of these cases are due to a complete allele deletion, more complex rearrangements, or alterations in regulatory sequences involving the FBN1 gene. In some of these individuals with atypical presentations reminiscent of MFS, an inactivating mutation in a gene encoding for transforming growth factor-beta receptor (TGFBR) may be responsible. (See 'TGFBR mutations' below.)

FBN1 mutations — FBN1 is a large gene (65 exons) located at chromosome 15q-21.1. The fibrillin-1 protein contains many cysteine-rich domains homologous to those observed in epidermal growth factor (EGF) and the latent transforming growth factor beta binding proteins (LTBPs) [8,9]. Fibrillin-1 is an important matrix component of both elastic and nonelastic tissues. It is the main constituent protein of extracellular microfibrils that are thought to contribute to the formation and maintenance of elastic fibers [10,11].

Since the first report of an FBN1 mutation in 1991, more than 1800 different mutations involving this protein have been registered for MFS and associated disorders in the Universal Mutation Database for FBN1 (UMD-FBN1). The majority of the mutations are nonrecurrent and distributed throughout the gene without striking phenotype-genotype correlations. One possible exception involves apparent clustering of

mutations between exons 24 and 32 associated with cases of severe rapidly progressive MFS (previously known as “neonatal MFS”) [12]. However, some patients with severe MFS lack mutations in this region and many patients with mutations in this region have classic or mild variants of MFS [3].

Of note, mutations in FBN1 have been identified in some patients with isolated features of the Marfan phenotype who do not have MFS [13]. (See 'FBN1/2 phenotypes' below.)

Mutations involving a second fibrillin protein, fibrillin-2, a product of the FBN2 gene located on chromosome 5, have been described and are associated with a phenotype different from the Marfan phenotype. (See 'Congenital contractural arachnodactyly' below.)

Causal FBN1 mutations — Criteria have been developed to identify FBN1 mutations that are likely causal and thus can contribute to the diagnosis of MFS when used together with other criteria [14] (see 'Revised Ghent nosology' below):

- A mutation previously shown to segregate with disease in a Marfan family
- De novo mutation in association with sporadic disease (proven paternity and absence of disease in parents) in one of five categories:
    - In-frame and out-of-frame deletion/insertion
    - Splice site mutations affecting canonical splice sequence or shown to alter splicing on the mRNA/cDNA level
    - Missense mutations substituting/creating cysteine residues
    - Missense affecting conserved residues of the EGF consensus sequence (D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable numbers of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, and F phenylalanine.
- Hereditary missense mutations that are absent in at least 400 ethnically matched control chromosomes (with segregation in family, if possible to determine) within the categories described above.
- Linkage of haplotype for n≥6 meioses to the FBN1 locus

TGFBR mutations — A minority of patients with the Marfan phenotype have no identifiable mutation in the FBN1 gene. Mutations in TGF-beta receptor 2 (TGFBR2) and TGFBR1 genes have been linked to the Marfan phenotype in some patients and may be responsible for up to 10 percent of cases with the Marfan phenotype [7,15,16].

Some individuals with TGFBR1 or TGFBR2 mutations have clinical features consistent with MFS, while others have features of one of two other syndromes: Loeys-Dietz syndrome (LDS) or familial thoracic aortic aneurysm (FTAA) syndrome. Autosomal dominant inheritance with variable penetrance has been observed in families with a variety of TGFBR mutations [17]. There are no apparent phenotype-genotype correlations and the identical mutations described as causing MFS are observed in patients and families with classic and severe LDS, including widespread and aggressive vascular disease. The clinical characteristics of these syndromes are discussed below. (See 'TGFBR1/2 phenotypes' below.)

Some experts have proposed that patients with the Marfan phenotype and TGFBR1 or TGFBR2 mutations be classified as having LDS (rather than MFS) as a means of highlighting the potential for more aggressive vascular disease than seen in MFS with an FBN1 mutation [3,14].

Prenatal genetic testing — Prenatal diagnostic testing is feasible if a disease-causing mutation has been identified in the family. However, the severity of disease in a child who inherits a mutant FBN1 (or TGFBR1/2) gene is unpredictable. Linkage analysis and direct sequencing of the FBN1 (or TGFBR1/2)

genes from cells or tissue obtained by amniocentesis or chorionic villus sampling can be informative. Resources for genetic testing are discussed in more detail elsewhere. However, such analyses are time consuming and planning for them should ideally be done prior to conception. (See "Genetic counseling and testing".)

Role of genetic testing — There are currently limited outcome data on genetic testing in patients with suspected MFS. Not all patients with suspected MFS require genetic testing given the cost and potential limitations. Mutation analysis of 93 patients with MFS found FBN1 mutations in 86 (93 percent) [18]. Even in the presence of an FBN1 mutation, the diagnosis of MFS relies on fulfillment of clinical diagnostic criteria.

Genetic testing, however, may be beneficial in the following circumstances:

- Identification of FBN1 mutation will change medical management of the affected patient
- Identification of FBN1 mutation will change follow-up frequency of the affected patient
- Identification of FBN1 mutation will help identify potentially affected family members
- Identification of FBN1 mutation will facilitate prenatal diagnostic testing
- Identification of another disorder (eg, Loeys-Dietz or familial aortic aneurysmal disease) will change medical or surgical management or follow-up for the affected patient.

HISTOPATHOLOGY — Histologic features of the medial layer of the aortic root in patients with Marfan syndrome (MFS) include fragmentation of elastic lamellae, cystic medial necrosis, fibrosis, and loss of smooth muscle cells [19-23]. The term cystic medial necrosis was coined by Erdheim to describe the lacunar appearance of medial degeneration in MFS; however no actual cysts or overt necrosis is present [19,20]. Cystic medial necrosis and the other histologic findings are not specific for MFS, although greater elastin fragmentation has been described in patients with aortic root aneurysms with MFS compared to those without a connective tissue diagnosis; this distinction may not apply in patients with other vascular connective tissue disorders [19,20,23]. The histologic changes are thought to reflect injury and repair [20].

PATHOGENESIS — How FBN1 or transforming growth factor-beta receptor mutations lead to disease is not well understood at a molecular level. Among the proposed mechanisms are alterations in:

- A structural role of microfibrils in coordinating tissue morphogenesis, homeostasis, and/or response to hemodynamic stress [24].
- Increased bioavailability of transforming growth factor (TGF)-beta [25].

Support for the importance of TGF-beta signaling comes from study of an animal model of an FBN1-targeted mouse model of MFS as well as clinical studies in which inhibition of TGF-beta attenuated the clinical manifestations of the disease [26-30]. The administration of the angiotensin II type 1 receptor blocker losartan (an antagonist of TGF-beta signaling) in a mouse model prevented aortic dilation and improved disease manifestations in the aortic wall and the lungs [26]. This effect was not due to altered hemodynamics since a similar benefit was not seen with a beta blocker, which is used clinically to slow the rate of aortic growth. (See "Management of Marfan syndrome and related disorders", section on 'Beta blocker'.) Clinical evidence for this mechanism was provided by two randomized controlled trials in which losartan therapy reduced the rate of aortic root dilatation [29,30] and one small randomized trial in which perindopril therapy reduced aortic root diameters and TGF-beta levels [28,31]. In addition, many conditions with pronounced clinical overlap with MFS are caused by primary mutations in genes encoding direct effectors and/or regulators of TGF-beta signaling, including Loeys-Dietz syndrome caused by heterozygous mutations in TGFBR1, TGFBR2, SMAD3, or TGFB2 (LDS1-4, respectively); and Shprintzen-Goldberg syndrome (SGS) caused by heterozygous loss-of-function mutations in SKI that encode a prototypical repressor of TGF-beta signaling. (See "Management

of Marfan syndrome and related disorders", section on 'Therapy targeting the renin-angiotensin system'.)

CRITERIA FOR DIAGNOSIS OF MFS

Older criteria — Although there is variable phenotypic expression of Marfan syndrome (MFS), aortic root dilatation and ectopia lentis are cardinal features of the disease and various systemic features support the diagnosis [14]. Other symptoms and signs of MFS, such as joint hypermobility, are much more commonly seen in patients without the disease. Previous reliance on less specific features led to a tendency to over-diagnose MFS in index cases or family members. As a result, stringent criteria for the diagnosis of MFS (Ghent nosology) were proposed in 1996 [32]. These criteria relied on the recognition of both "major" and "minor" clinical manifestations involving the skeletal, cardiovascular, and ocular systems, and the dura [32]. Major criteria included: ectopia lentis, aortic root dilatation involving the sinuses of Valsalva or aortic dissection, and lumbosacral dural ectasia by computed tomography or magnetic resonance imaging, family or genetic history, and four of eight typical skeletal manifestations.

Limitations of some of the 1996 Ghent criteria included insufficient validation, limited applicability to children, a requirement of expensive and specialized evaluation, and the recognition that dural ectasia is often seen in other connective tissue disorders, including both LDS and SGS [14].

Revised Ghent nosology — The 2010 revised Ghent nosology puts greater weight on aortic root dilatation/dissection and ectopia lentis as the cardinal clinical features of MFS and on testing for mutations in FBN1 [14]. For the aortic criteria, aortic root Z score calculators are available.

- In the absence of family history of MFS, the presence of one of any of the following criteria is diagnostic for MFS:
    - Aortic criterion (aortic diameter Z ≥2 or aortic root dissection) **and** ectopia lentis* (see 'Ocular abnormalities' below)
    - Aortic criterion (aortic diameter Z ≥2 or aortic root dissection) **and** a causal FBN1 mutation as defined above (see 'Causal FBN1 mutations' above)
    - Aortic criterion (aortic diameter Z ≥2 or aortic root dissection) **and** a systemic score ≥7 (see 'Systemic score' below)*
    - Ectopia lentis **and** a causal FBN1 mutation as defined above (see 'Causal FBN1 mutations' above) that has been identified in an individual with aortic aneurysm
- In the presence of family history of MFS (as defined by the above criteria), the presence of one of any of the following criteria is diagnostic for MFS:
    - Ectopia lentis
    - Systemic score ≥7 points*
    - Aortic criterion (aortic diameter Z ≥2 above 20 years old, Z ≥3 below 20 years, or aortic root dissection)*

For criteria with an asterisk (*), the diagnosis of MFS can be made only in the absence of discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome (table 1) **and** after TGFBR1/2, collagen biochemistry, or COL3A1 testing if indicated. Later data suggest that additional gene mutations should also be excluded, including those in SMAD3, TGFB2, and SKI.

Systemic score — The revised Ghent nosology includes the following scoring system for systemic features [14]:

- Wrist (picture 1) **AND** thumb sign (picture 2): 3 points (wrist **OR** thumb sign: 1 point) (see

'Arachnodactyly' below)

- Pectus carinatum deformity: 2 (pectus excavatum or chest asymmetry: 1 point) (see 'Pectus deformity' below)
- Hindfoot deformity: 2 points (plain pes planus:1 point) (see 'Hindfoot valgus' below)
- Pneumothorax: 2 points (see 'Pulmonary disease' below)
- Dural ectasia: 2 points (see 'Dural ectasia' below)
- Protrusio acetabuli: 2 points (see 'Protrusio acetabuli' below)
- Reduced upper segment/lower segment ratio **AND** increased arm span/height **AND** no severe scoliosis: 1 point (see 'Abnormal US/LS and arm span/height' below)
- Scoliosis or thoracolumbar kyphosis: 1 point (see 'Scoliosis and kyphosis' below)
- Reduced elbow extension (≤170 degrees with full extension): 1 point (see 'Skeletal findings' below)
- Facial features (at least three of the following five features: dolichocephaly [reduced cephalic index or head width/length ratio], enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia): 1 point. (See 'Facial features' below.)
- Skin striae: 1 point (see 'Skin striae' below)
- Myopia >3 diopters: 1 point (see 'Ocular abnormalities' below)
- Mitral valve prolapse (all types): 1 point (see 'Cardiac disease' below)

A systemic score ≥7 indicates major systemic involvement.

Diagnosis in the young — Application of diagnostic criteria to individuals <20 years old, particularly those with sporadic disease, requires special care since additional clinical features may subsequently emerge.

The revised Ghent nosology recommends the following categories for individuals <20 years old with features of MFS who do not meet diagnostic criteria for MFS [14]:

- “Nonspecific connective tissue disorder” applies if the systemic score is less than 7 and/or aortic root measurements are borderline (Z<3) in the absence of an FBN1 mutation.
- “Potential MFS” applies if an FBN1 mutation is identified in a sporadic or familial cases but the aortic root Z-score is less than 3.

Individuals under 20 years of age with systemic findings suggestive of MFS but without cardiovascular involvement should also have annual echocardiograms due to the potential risk of development of aortic disease [14].

Critique of the revised Ghent nosology — Among 180 adult patients with MFS according to the original Ghent criteria, 164 (91 percent) met criteria for MFS using the revised Ghent criteria [33]. In 13 of the 16 patients in which the diagnosis of MFS was rejected using the revised criteria, the reason for rejection was a Z-score of the aortic root <2, although the aortic diameter was greater than 40 mm in six of them. Although Z-score data are based on assuming a linear relationship between body surface area (BSA) and aortic root size [34], subsequent studies suggest that all aortic roots with diameter ≥ 40 mm are dilated [33]. In contrast to this position, however, other studies have documented aortic measurements in excess of 40 mm in unselected individuals with larger body size and advanced age (>40 years). Further work in this area should help to clarify this important issue.

CLINICAL MANIFESTATIONS OF MFS

Aortic disease — Aortic root disease, leading to aneurysmal dilatation, aortic regurgitation, and dissection, is the main cause of morbidity and mortality in the Marfan syndrome (MFS) (movie 1 and image 1A-E) [35]. There can be poor correlation between the severity of the cardiovascular and the ocular or skeletal manifestations [36]. Although dilated, the aorta in MFS tends to be stiffer and less distensible than in controls, and these changes increase with age [37-40].

Dilatation of the aorta is found in approximately 50 percent of young children with MFS and progresses with time. Approximately 60 to 80 percent of adult patients with MFS have dilatation of the aortic root (with normal range adjusted for patient body surface area and age) by echocardiography [41], often accompanied by aortic regurgitation [36]. Importantly, all patients diagnosed with MFS using the revised criteria must have aortic root dilatation, a family history of aortic root dilatation, or an FBN1 mutation previously associated with aortic root dilatation, highlighting the strong predisposition for emergence of vascular disease. Dilatation may also involve other segments of the thoracic aorta, the abdominal aorta, the root of the pulmonary artery or even the carotid and intracranial arteries, although this is much less frequent than observed in LDS.

As recommended in the 2010 American College of Cardiology/American Heart Association/American Association for Thoracic Surgery thoracic aorta guidelines, echocardiography is recommended at initial diagnosis and at six months to assess the aortic root and ascending aorta in patients with MFS [42]. The normal range for aortic diameter varies with body size and age so nomograms and Z-scores are used to identify aortic dilatation [14,34]. Monitoring should be performed at least annually as discussed separately. (See "Management of Marfan syndrome and related disorders", section on 'Monitoring MFS'.)

Undiagnosed and untreated MFS is frequently associated with aortic dissection (image 2 and image 1E). The dissection generally begins just above the coronary ostia and can extend the entire length of the aorta; it is a type I dissection in the DeBakey classification or a type A in the Dailey scheme. Approximately 10 percent of dissections begin distal to the left subclavian (type III or type B) but dissection is rarely limited to just the abdominal aorta. Many patients with MFS and aortic dissection have a family history of dissection. (See "Clinical manifestations and diagnosis of aortic dissection".)

The frequency with which MFS is responsible for aortic dissection was addressed in a review from the International Registry of Aortic Dissection (IRAD) [43]. The frequency varied with age. MFS was present in 50 percent of those under age 40, compared to only 2 percent of older patients with aortic dissection and, in another report from IRAD, no patient over age 70 [44]. The potential for these observations to be influenced by age-specific ascertainment bias should be considered.

The degree of aortic disease also has implications for women who would like to become pregnant and for management during pregnancy. These issues are discussed separately. (See "Pregnancy and Marfan syndrome".)

Cardiac disease — Mitral valve prolapse (MVP) is frequently identified in patients with MFS (eg, 40 and 54 percent in two series of MFS patients [45,46]). However, only one point in the systemic score is assigned for MVP since it is a nonspecific feature and most patients with MVP do not have MFS [41]. The frequency of MVP in MFS increases with age and is greater in women. Tricuspid valve prolapse may also occur.

On echocardiography, the mitral leaflets have an elongated and redundant appearance and either or both leaflets may prolapse. Patients with MFS and MVP have no to severe mitral regurgitation, with most having mild or less regurgitation [45]. Approximately 25 percent of patients with MVP have progressive disease as defined by the appearance or worsening of clinical symptoms of mitral regurgitation or worsening on echocardiography. In some of these cases, worsening of mitral regurgitation is due to spontaneous rupture of the chordae tendineae or the result of infective endocarditis. Heart failure

attributable to mitral valve prolapse and regurgitation represents a major source of morbidity and mortality in young children with the most extreme and rapidly progressive presentation of MFS. (See "Natural history of chronic mitral regurgitation in mitral valve prolapse and flail mitral leaflet", section on 'Natural history of mitral valve prolapse'.)

Care should be taken to distinguish MFS from MVP syndrome, which is defined as MVP associated with a limited systemic features score (<5), as discussed below. (See 'Mitral valve prolapse syndrome' below.)

A preliminary report suggested that some patients with MFS may have a cardiomyopathy with biventricular enlargement and generally asymptomatic mild systolic dysfunction unrelated to valvular disease [47].

Skeletal findings — Individuals with MFS have excess linear growth of the long bones and joint laxity [3]. Individuals with MFS are taller than predicted by their genetic background (aside from the FBN1 mutation) (picture 3), which is generally, but not necessarily, tall compared to general population standards [48].

Paradoxically, some individuals with MFS have reduced joint mobility, particularly of the elbow and digits [3]. The presence of reduced elbow extension (≤170 degrees with full extension) contributes one point to the systemic score [14].

Arachnodactyly — Patients with MFS typically have arachnodactyly with positive thumb and wrist signs. A positive thumb sign indicates that the entire distal phalanx protrudes beyond the ulnar border of a clenched fist with or without the assistance of the patient or examiner to achieve maximum adduction (picture 2). A positive wrist sign means that the top of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist (picture 1). Three points are assigned if both thumb and wrist signs are positive; only one point is assigned if only one of these signs is positive.

Generalized joint hypermobility also may occur, producing findings that overlap with the much more common benign joint hypermobility syndrome. (See "Joint hypermobility syndrome".)

Pectus deformity — Pectus carinatum (picture 3) is assigned two points since it is thought to be more specific for MFS than pectus excavatum or chest asymmetry, which is assigned one point [14]. (See "Pectus carinatum" and "Pectus excavatum: Etiology and evaluation".)

Hindfoot valgus — Hindfoot valgus is assigned two points. It occurs with forefoot abduction and lowering of the midfoot and should be evaluated from anterior and posterior views. Pes planus (flat foot) without hindfoot valgus is assigned one point.

Abnormal US/LS and arm span/height — Individuals with MFS have disproportionately long extremities in comparison to the length of the trunk (dolichostenomelia), so the upper segment to lower segment (US/LS) ratio is decreased and the arm span to height ratio is increased. In determining the US/LS ratio, the lower segment is defined as the distance from the top of the symphysis pubis to the floor in the standing position and the upper segment is the height minus the lower segment [14]. Thresholds for abnormal US/LS and arm span/height vary with age and ethnicity. Reduced US/LS is <0.85 for white adults and <0.78 for black adults. For children, reduced US/LS is <1 for age 0 to 5 years, <0.95 for 6 to 7 years, <0.9 for 8 to 9 years, and <0.85 above age 10 years. Increased arm span to height ratio is >1.05 for white adults. Scoliosis can artifactually influence body measurements and hence ratios.

Scoliosis and kyphosis — Presence of either of the following findings is diagnostic for scoliosis [14]:

- With the patient bending forward, observation of a vertical difference of ≥1.5 cm between the ribs of

the left and right hemithorax.

- A Cobb's angle (on an anterior-posterior radiographic view of the spine, the angle between a line drawn along the superior end plate of the superior end vertebra and a second line drawn along the inferior end plate of the inferior end vertebra of the scoliosis) of at least 20 degrees.

If scoliosis is absent, one point can be attributed to kyphosis if there is exaggerated kyphotic thoracolumbar spinal curvature.

Protrusio acetabuli — Acetabular protrusion can be diagnosed by plain radiograph, computed tomography (CT), or magnetic resonance imaging (MRI). On an anterior-posterior pelvic film, medial protrusion of the acetabulum ≥3 mm beyond the ilio-ischial (Kohler) line is diagnostic. Criteria on CT or MRI are not as precisely defined but involve loss of the normal oval shape of the pelvic inlet at the level of the acetabulum.

Facial features — One point is added to the systemic score if at least three of the following five facial features are present: dolichocephaly (reduced cephalic index or head width/length ratio), enophthalmos, downslanting palpebral fissures, malar hypoplasia, and retrognathia.

Ocular abnormalities — Annual ophthalmologic evaluation is recommended for all patients with MFS. Urgent assessment is recommended for patients with sudden change in vision.

Ectopia lentis occurs in 50 to 80 percent with MFS [49]. The finding of iridodonesis (vibration of the iris with eye movement) on external inspection of the eye should raise the concern for ectopia lentis. Ectopia lentis is detected on slit-lamp examination after maximal dilatation of the pupil and the lens is usually displaced upward and temporally (picture 4). It is caused by failure of the supporting ciliary zonules.

Ectopia lentis is the only cardinal ocular criterion for MFS. (See 'Revised Ghent nosology' above.) However FBN1 mutations have been identified in some patients with ectopia lentis who do not have MFS [50], so the ectopia lentis syndrome should be carefully distinguished from MFS. (See 'Ectopia lentis syndrome' below and "Ectopia lentis (dislocated lens) in children".)

The finding of myopia >3 diopters contributes one point to the systemic score. Patients with MFS develop secondary myopia due to increased axis globe length. Other ocular findings in MFS include flat cornea (measured by keratometry) [51], hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis, retinal detachment, glaucoma, and early cataract formation [3]. Retinal tears and detachment are commonly bilateral in MFS and may be associated with proliferative retinopathy [52].

Dural ectasia — Dural ectasia results from enlargement of the spinal canal owing to progressive ectasia of dura and neural foramina and to erosion of vertebral bone (image 3). This abnormality usually involves the lumbosacral spine and was identified in 63 and 92 percent of patients with MFS in case series using CT and MR scanning [53,54]. Dural ectasia is a sensitive but not specific sign of MFS and is commonly seen in Loeys-Dietz syndrome and Shprintzen-Goldberg syndrome and has been reported in the vascular form of Ehlers-Danlos syndrome. (See 'Spectrum of phenotypes and differential diagnosis' below.)

Several modalities have been utilized to help identify dural ectasia, including CT scanning and MRI. The latter technique appears to be the most sensitive [54]. No correlation appears to exist between the severity of dural ectasia and the degree of aortic dilatation.

Pulmonary disease — Some patients with MFS develop emphysematous changes with lung bullae predominantly in the upper lobes, which can predispose to spontaneous pneumothorax (which contributes two points to the systemic score) (image 1C and image 2) [3,14,55].

Skin striae — The presence of striae atrophicae contributes one point to the systemic score if they are not associated with pronounced weight changes or pregnancy and if they have an uncommon location

such as the mid back, lumbar region, upper arm, axillary region, or thigh [14].

Other — Recurrent or incisional herniae, joint hypermobility, and high arched palate may occur but are not included in the systemic score since these clinical features are considered nonspecific [14].

SPECTRUM OF PHENOTYPES AND DIFFERENTIAL DIAGNOSIS — As reflected in the above revised Ghent criteria, patients with MFS present with a spectrum of aortic, ocular, cardiac, and systemic features. The differential diagnosis for MFS includes a variety of conditions with phenotypic features that partially overlap the Marfan phenotype including disorders associated with FBN1/2 or TGFBR1/2 mutations as well as a variety of other genetic disorders (table 1). As noted above, exclusion of MFS is particularly difficult in individuals <20 years old. (See 'Diagnosis in the young' above.)

Imaging those at risk for aortic enlargement — The differential diagnosis for MFS includes other conditions associated with aortic complications. Patients with Loeys-Dietz syndrome (LDS) or a genetic mutation known to predispose to aortic aneurysms/dissections (TGFBR1, TGFBR2, FBN1, ACTA2, or MYH11) should undergo complete aortic imaging at initial diagnosis and six months thereafter to establish if enlargement is occurring, as recommended in the 2010 American College of Cardiology/American Heart Association/American Association for Thoracic Surgery guidelines [42]. Monitoring is discussed separately. (See "Management of Marfan syndrome and related disorders", section on 'Aortic monitoring'.)

As noted above, individuals under 20 years of age with systemic findings suggestive of MFS but without cardiovascular involvement should also have annual echocardiograms due to the potential risk of rapid development of aortic disease [14]. Adults with repeatedly normal aortic root measurements can be seen at two- to three-year intervals.

FBN1/2 phenotypes — To date, no correlation between the specific type of FBN1 mutation and clinical phenotype has been recognized. As a general rule, patients with exon skipping tend to have more severe disease, while those showing premature termination causing reduced levels of mutant transcript and protein can show milder disease, often with absence of ectopia lentis [56]. Some families have members with both classic MFS and a milder but related phenotype without aortic involvement [57]. These differences may be due to different genetic alterations rather than single FBN1 mutations and/or the influence of genetic modifiers.

Rare patients with FBN1 mutations have one predominant manifestation such as isolated ectopia lentis syndrome, isolated ascending aortic aneurysm and/or dissection, or isolated skeletal features [58]. (See 'Conditions related to MFS' below.)

Mutations involving a second fibrillin protein, fibrillin-2 (encoded by FBN2), have been linked to congenital contractural arachnodactyly (Beals syndrome). (See 'Congenital contractural arachnodactyly' below.)

TGFBR1/2 phenotypes — A spectrum of clinical features and outcomes are seen in patients with TGFBR1 or TGFBR2 mutations [17,59]. Some individuals with TGFBR1 or TGFBR2 mutations have clinical features consistent with MFS, while others have features of one of two other syndromes with overlapping clinical manifestations: LDS or familial thoracic aortic aneurysm syndrome. Some have proposed classifying patients with Marfan-like phenotypes and TGFBR1 or TGFBR2 mutations as LDS (rather than as MFS) as a means of highlighting the potential for more aggressive vascular disease than seen in MFS with an FBN1 mutation and the potential for unique LDS features in existing family members or future offspring [3,14].

The degree of aortic dilatation in individuals with TGFBR1 or TGFBR2 mutations is highly variable, and aortic dissection in patients with normal aortic diameters has been reported in some series but not others [17,59]. Skeletal features are also variable.

Loeys-Dietz syndrome — Most patients with a TGFBR1 or TGFBR2 mutation have Loeys-Dietz syndrome, which is often characterized by hypertelorism (widely spaced eyes), a split uvula or cleft palate, tortuous arteries, and aortic aneurysms [16,17]. Associated findings may include premature fusion of the skull, structural heart disease and aneurysms affecting vessels other than the aorta. LDS-like phenotypes have now also been reported in patients with heterozygous mutations in SMAD3, TGFB2, and TGFB3.

The prognosis in patients with LDS is variable and appears to depend upon clinical disease expression as well as treatment [17,59]. Initial reports documented more widespread and aggressive vascular disease, earlier ages of surgery and dissection, and earlier mortality in patients with the full clinical spectrum of LDS, when compared to MFS. However, different observations were made in 71 individuals who were diagnosed with TGFBR2 mutations in adulthood, when compared with 50 age- and sex-matched unaffected family members (controls) and 243 patients with FBN1 mutations [59]. Seven (10 percent) patients with TGFBR2 mutations met diagnostic criteria for MFS, including two who had equivocal features suggestive of ectopia lentis.

- The frequency of aortic dilation was similar in the TGFBR2 and FBN1 groups (78 and 79 percent)
- The two groups also had a similar incidence and average age for both thoracic aortic surgery (31 versus 27 percent and 35 versus 39 years) and aortic dissection (14 versus 10 percent and 38 versus 39 years).
- The TGFBR2 group had a lower rate of mitral valve disease (myxomatous, prolapse, or regurgitation)
- The mortality rate was higher in TGFBR2 than FBN1 families if patients who were not treated were included; the difference in mortality rate disappeared if only treated patients were included.

These observations highlight the importance of considering ascertainment bias when considering the natural history of disease.

Conditions related to MFS — The ectopia lentis syndrome, MASS phenotype, and mitral valve prolapse syndrome each include some features of MFS but do not meet diagnostic criteria for MFS [14]. These should be distinguished from MFS with care since emerging MFS may include similar features.

Ectopia lentis syndrome — An autosomal dominant form of familial ectopia lentis syndrome (ELS) is caused by FBN1 mutations and recessive forms are caused by LTBP2 and ADAMTSL4 mutations [14]. The revised Ghent criteria for ELS are ectopia lentis with or without systemic features **and** either an FBN1 mutation not known to be associated with aortic dilatation/dissection or no FBN1 mutation.

Thus, the syndrome includes some skeletal features of MFS as well as ectopia lentis but does not include aortic aneurysm. MFS rather than ELS should be diagnosed if the patient has aortic dilation, family history of aortic dilation or aneurysm, or an FBN1 mutation previously associated with aortic dilation [14]. It can be difficult to distinguish ELS from emerging MFS since aortic aneurysm may emerge later, so vigilance for aortic aneurysm is required and the diagnosis of ELS cannot be made before the patient is 20 years of age.

MASS phenotype — MASS phenotype is a familial disorder that includes the following features that partially overlap with MFS: **m**itral valve prolapse, borderline but no progressive **a**ortic dilatation, **s**triae atrophica, and at least one **s**keletal feature [60]. The revised Ghent criteria for diagnosis of MASS are an aortic diameter Z <2 **and** systemic score ≥5 including at least one skeletal feature **and** absence of ectopia lentis [14].

The MASS phenotype is most difficult to distinguish from emerging MFS in a young individual without a contributory family history and careful follow-up is required for appropriate diagnosis [2]. FBN1 mutations

have been found in some patients with the MASS phenotype [61] but the potential risk of progression to aortic complications has not been characterized.

Mitral valve prolapse syndrome — The revised Ghent criteria for mitral valve prolapse syndrome (MVPS) are mitral valve prolapse **and** systemic features (score <5) **and** aortic diameter Z<2 and absence of ectopia lentis [14]. Some common systemic features are pectus excavatum, scoliosis, and mild arachnodactyly.

Homocystinuria — Homocystinuria is associated with a Marfanoid body habitus and severe myopia and/or ectopia lentis, although the lens is typically dislocated downward rather than upward as in MFS [14]. Distinguishing features of homocystinuria include intellectual disability and thrombotic events. The diagnosis of homocystinuria can be established or excluded by measuring homocystine levels [62]. (See "Ectopia lentis (dislocated lens) in children", section on 'Systemic causes'.)

Congenital contractural arachnodactyly — Mutations in the FBN2 gene, the gene encoding the extracellular matrix protein fibrillin-2, have been described in patients with congenital contractural arachnodactyly (CCA, MIM# 121050, Beals-Hecht or Beals syndrome), which is an autosomal dominant disorder characterized by a marfanoid habitus with arachnodactyly, kyphosis/scoliosis, contractures of knees and ankles, flexion contractures of the proximal interphalangeal joints of the fingers and toes (camptodactyly), and crumpled ears (folded upper helix) [14,49,63,64]. Rare individuals with this syndrome have mild enlargement of the sinuses of Valsalva that does not progress to aortic dissection.

Certain Ehlers Danlos types — A number of forms of Ehlers Danlos syndrome (EDS) are associated with joint hypermobility. Arterial aneurysms and dissection are seen particularly in EDS vascular type. EDS is discussed in detail separately. (See "Clinical manifestations and diagnosis of Ehlers-Danlos syndromes" and "Joint hypermobility syndrome", section on 'Ehlers-Danlos syndrome'.)

Stickler syndrome — Type II and type XI collagen mutations have been identified in the Stickler syndrome [65,66].

Additional disorders in the differential diagnosis

- Congenital bicuspid aortic valve disease with associated aortopathy. Aortic dilation may involve primarily the aortic root or the mid-ascending aorta.
- Aortic coarctation with associated ascending aortic enlargement
- Familial thoracic aortic aneurysm or aortopathy

SCREENING RELATIVES — Recommendations for screening relatives are also included in the 2010 American College of Cardiology/American Heart Association/American Association for Thoracic Surgery guidelines [42]. First-degree relatives of patients with a gene mutation associated with aortic aneurysms and/or dissection (eg, FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) should undergo counseling and genetic testing. Those found to have the genetic mutation should then undergo aortic imaging. (See "Genetic counseling and testing".)

The risk of Marfan syndrome (MFS) in the siblings of an individual with MFS depends upon whether a parent has MFS [3]. If a parent has MFS, the risk of MFS in a sibling is 50 percent. If neither parent has MFS, the risk of MFS in a sibling is far less than 50 percent (since the mutation in the proband is likely de novo) but greater than general population risk since there are rare cases of somatic and germline mosaicism which could lead to MFS in siblings without manifestation of MFS in the parents.

For patients with aortic aneurysm and/or dissection without a known mutation, aortic imaging is recommended for first-degree relatives to identify those with asymptomatic disease. If one or more first-degree relatives are found to have thoracic aortic dilatation, aneurysm, or dissection, then imaging of second-degree relatives is reasonable.

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 topic (see "Patient information: Marfan syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- The diagnosis of Marfan syndrome (MFS) in familial and sporadic cases are based upon the presence of characteristic manifestations, particularly aortic root dilatation/dissection and ectopia lentis, as well as other systemic features including skeletal findings, mitral valve prolapse, dural ectasia, pneumothorax, and skin striae. The presence of a likely causal FBN1 mutation lends strong support to the diagnosis in combination with certain clinical features. (See 'Revised Ghent nosology' above.)
- MFS is caused by a variety of mutations in the FBN1 gene. FBN1 mutations have been identified in over 90 percent of patients with MFS. (See 'FBN1 mutations' above.)
    - About 10 percent of individuals with suspected MFS have no defined FBN1 mutation. Some of these individuals may have TGFBR1 or TGFBR2 mutations. TGFBR1/TGFBR2 mutations more typically cause Loeys-Dietz syndrome (LDS), with rare reports in association with familial thoracic aortic aneurysm (FTAA) syndrome. We suggest categorizing individuals with the Marfan phenotype with a TGFBR1 or TGFBR2 mutation as LDS since they may be at risk for more aggressive vascular disease than seen in MFS. (See 'TGFBR mutations' above.)
    - Some patients with FBN1 gene mutations do not have MFS and instead have a related disorder such as ectopia lentis syndrome or other diseases such as Shprintzen-Goldberg syndrome, Weill-Marchesani syndrome, or stiff skin syndrome. (See 'FBN1/2 phenotypes' above.)
- Application of diagnostic criteria to individuals <20 years old requires special care since some clinical features may have not yet emerged. (See 'Diagnosis in the young' above.)
- The aortic root Z-score is used to identify aortic dilatation since aortic size varies with body size. However, use of Z-scores may underestimate aortic size, particularly in individuals with large body surface area. (See 'Aortic disease' above and 'Critique of the revised Ghent nosology' above.)
- The differential diagnosis for MFS includes a variety of conditions with phenotypic features that partially overlap the Marfan phenotype, including disorders associated with FBN1/2 or TGFBR1/2 mutations, as well as a variety of other genetic disorders (table 1). (See 'Spectrum of phenotypes and differential diagnosis' above.)
- First-degree relatives of patients with a gene mutation associated with aortic aneurysms and/or dissection (eg, FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) should undergo counseling and genetic testing. Those found to have the genetic mutation should then undergo aortic imaging. (See 'Screening relatives' above.)
- For patients with aortic aneurysm and/or dissection without a known mutation, aortic imaging is

recommended for first-degree relatives to identify those with asymptomatic disease. If one or more first-degree relatives are found to have thoracic aortic dilatation, aneurysm, or dissection, then imaging of second-degree relatives is reasonable. (See 'Screening relatives' above.)

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Topic 8150 Version 15.0

GRAPHICS

Differential diagnosis of Marfan syndrome

Differential diagnosis	Gene	Features similar to Marfan syndrome	Discriminating features
Loeys-Dietz syndrome (LDS)	TGFBR1/2	Aortic aneurysm/dissection	Bifid uvula/cleft palate, arterial tortuosity, hypertelorism, diffuse aortic and arterial aneurysms, craniosynostosis, clubfoot, cervical spine instability, thin and velvety skin, easy bruising
Shprintzen-Goldberg syndrome (SGS)	FBN1 and other	Pectus abnormalities, scoliosis, arachnodactyly	Craniosynostosis, mental retardation
MASS phenotype*	FBN1* and other	Mitral valve prolapse, mild aortic dilatation, striae atrophica, and at least one skeletal feature; systemic score ≥5	Aortic root size Z<2; no ectopia lentis
Mitral valve prolapse syndrome	Several candidate gene loci	Mitral valve prolapse, pectus excavatum, scoliosis, mild arachnodactyly	Lack of aortic enlargement, lack of ectopia lentis, systemic score <5
Congenital contractural arachnodactyly (CCA)	FBN2	Marfanoid habitus, arachnodactyly, kyphosis/scoliosis, mild enlargement of the sinuses of Valsalva	Crumpled ears (folded upper helix), contractures of major joints (knees and ankles) at birth, flexion contractures of the proximal interphalangeal joints (camptodactyly), absence of aortic dissection or rupture
Weill-Marchesani syndrome (WMS)	FBN1 and ADAMTS10	Ectopia lentis	Microspherophakia, brachydactyly, joint stiffness

Ectopia lentis syndrome (ELS)	FBN1, LTBP2, ADAMTSL4	Ectopia lentis, may have mild skeletal findings	Lack of aortic root dilatation
Familial thoracic aortic aneurysm and dissection syndrome (FTAAD/FTAA)	TGFBR1/2, ACTA2	Aortic dilatation and dissection	Livedo reticularis, iris flocculi, lack of Marfanoid skeletal features
FTAAD with bicuspid aortic valve	ACTA2	Aortic aneurysm and dissection	Livedo reticularis, iris flocculi, cerebral aneurysm, premature ischemic strokes, Moyamoya disease, premature coronary artery disease, bicuspid aortic valve, patent ductus arteriosus
FTAAD with patent ductus arteriosus	MYH11	Aortic root aneurysm	Patent ductus arteriosus
Homocystinuria	CBS	Marfanoid habitus, ectopia lentis	Thrombosis, mental retardation
Arterial tortuosity syndrome (ATS)	SLC2A10	Aortic aneurysm	Generalized arterial tortuosity, arterial stenosis, facial dysmorphism
Ehlers-Danlos syndrome (vascular type)	COL3A1	Aortic aneurysm/dissection occurs in some	Middle sized artery aneurysm, translucent skin, dystrophic scars, intestinal or uterine rupture
Ehlers-Danlos syndrome (cardiac valvular subtype)	COL1A2	Mitral valve prolapse, joint hypermobility	Severe aortic and/or mitral valvular regurgitation, atrophic scars, skin hyperelasticity
Ehlers-Danlos syndrome (kyphoscoliotic type)	PLOD1	Aortic dilatation/dissection, kyphoscoliosis, joint laxity	Middle sized artery aneurysm/rupture
Stickler syndrome (hereditary arthroophthalmopathy)	COL2A1, COL11A1	Marfinoid habitus, mitral valve prolapse, retrognathia	Vitreal degeneration, retinal detachment, myopia, open angle glaucoma, early cataracts, cleft palate, hearing loss, epiphysial changes

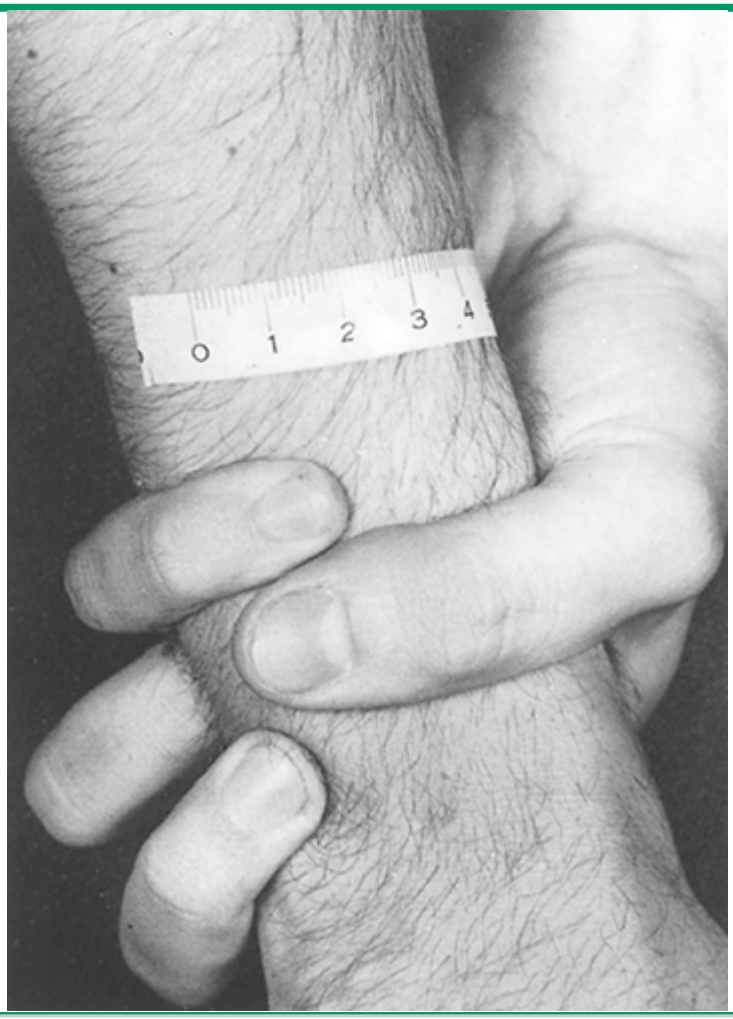
Klinefelter's syndrome	47,XXY (and other X>1 genotypes in men)	Marfanoid habitus	Small testes and genitalia, cognitive impairment
Congenital bicuspid aortic valve disease with associated aortopathy	NOTCH1, KCNJ2, and putative loci on chromosomes 18q, 5q and 13q	Ascending aortic aneurysm, some have pectus deformity, scoliosis	Bicuspid aortic valve (may occur together with or separately from aortic aneurysm in various family members); lack of ocular and other systemic findings of Marfan syndrome; aortic dilatation is commonly maximal or exclusively above the sinotubular junction
Aortic coarctation with associated ascending aortic enlargement	NOTCH1, ERBB4, largely unknown	Aortic dilatation	Coarctation of the aorta

TGFBR: TGF-beta receptor.
* An individual with MASS phenotype with an FBN1 mutation may subsequently transition to Marfan syndrome, but the probability of such transition is not known.

Adapted in part from: Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010; 47:476.

Graphic 59476 Version 4.0

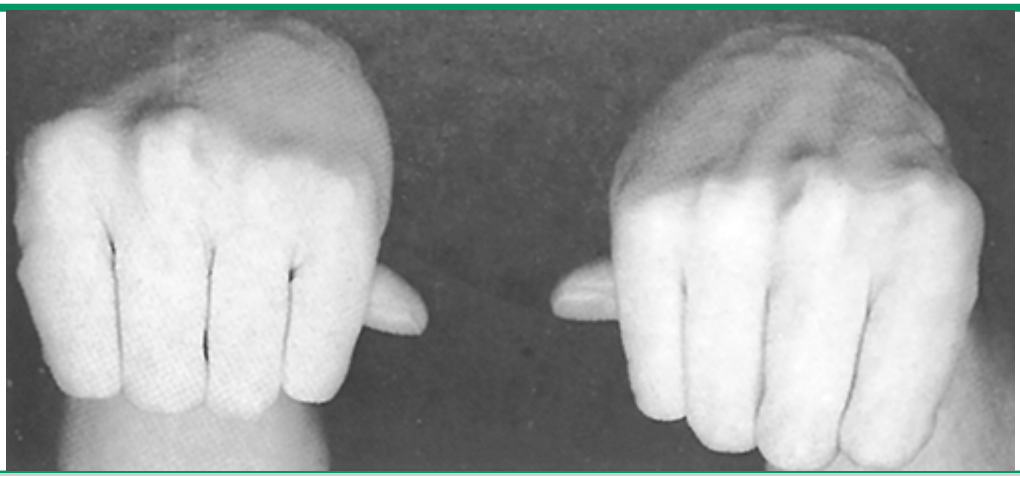
Wrist sign in a patient with Marfan syndrome



The wrist sign in a patient with Marfan syndrome. In a positive test, the first phalanges of the thumb and fifth digit substantially overlap when wrapped around the opposite wrist.

Graphic 86854 Version 1.0

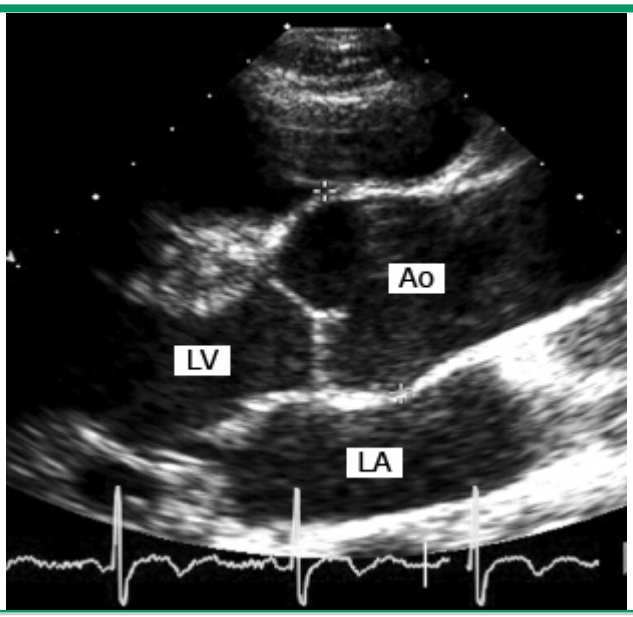
Steinberg thumb sign in a patient with Marfan syndrome



Steinberg thumb sign in a patient with Marfan syndrome. A positive test, such as this, consists of the distal phalanx of the thumb protruding beyond the ulnar border of the clenched fist and reflects both longitudinal laxity of the hand and a long thumb.

Graphic 86853 Version 1.0

Echocardiogram of dilated aortic root in a patient with Marfan syndrome



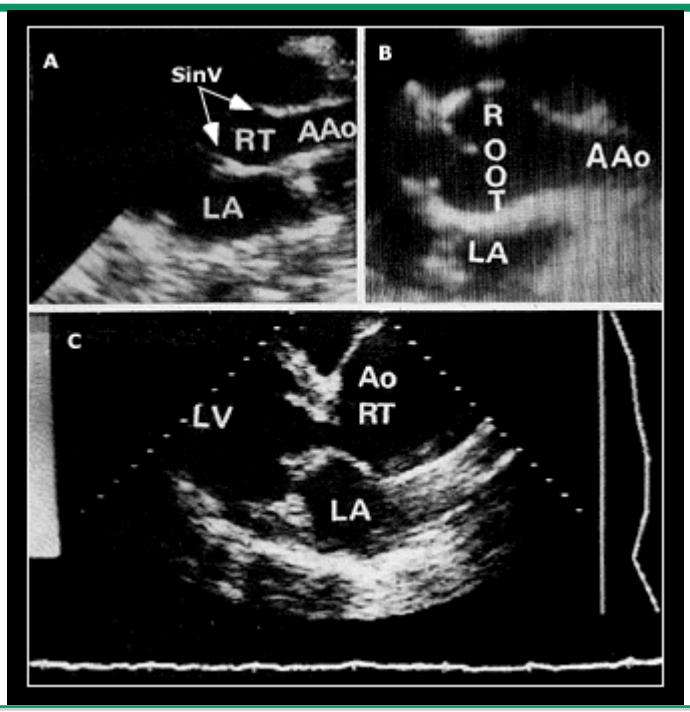
In this parasternal long-axis echocardiographic view of a patient with Marfan syndrome, the aortic root is dilated at the level of the sinuses of Valsalva. The sinotubular junction is preserved with a normal ascending aorta diameter above the sinuses.

Ao: ascending aorta; LA: left atrium; LV: left ventricle.

Courtesy of Heidi Connolly, MD.

Graphic 87118 Version 1.0

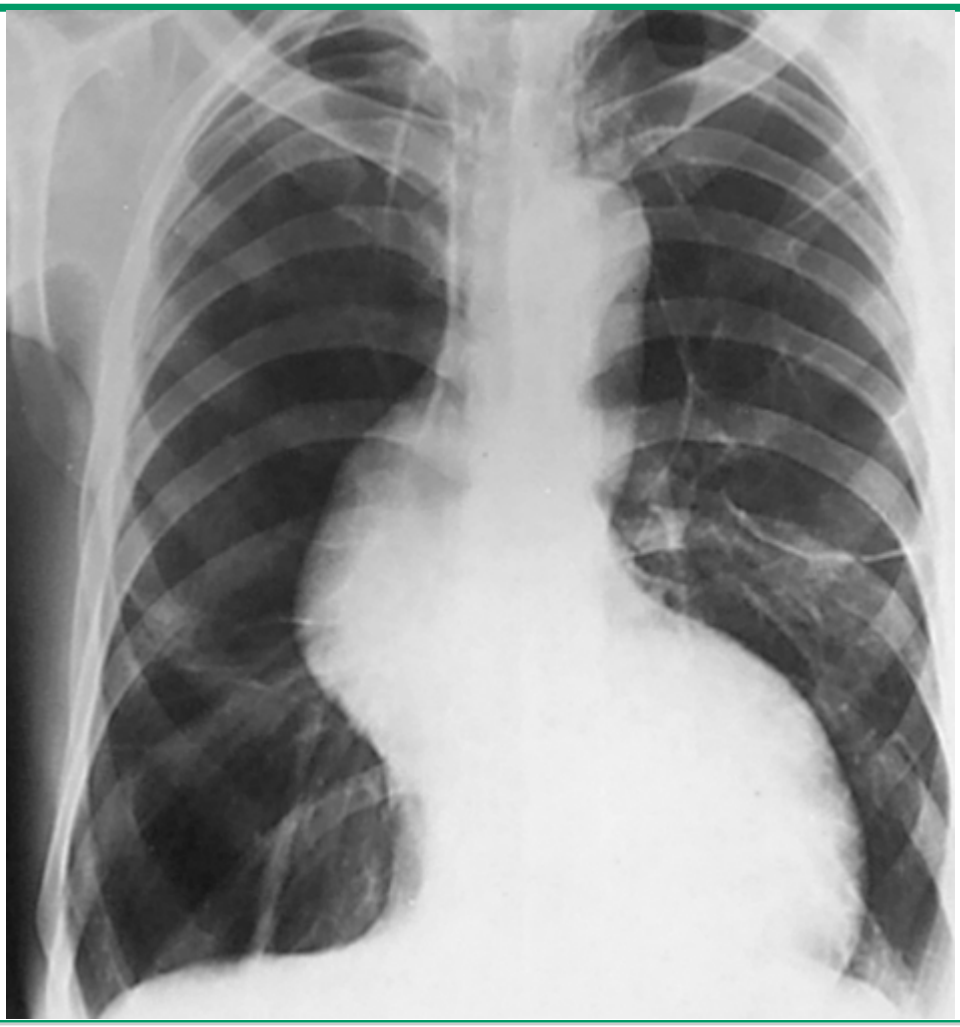
Aortic root enlargement



The normal aortic root (RT) and ascending aorta (AAo) are seen in panel A; slight prominence of the sinuses of Valsalva (SinV) can be appreciated. Panel B is the aortic RT and AAo from a patient with the Marfan syndrome; the SinV are large while the AAo is relatively normal, a pattern that seems unique to the Marfan syndrome. In panel C, a greatly enlarged aortic (Ao) RT is also seen, but the pattern differs from that seen in the Marfan patient; the dilatation begins at the aortic ring and continues beyond the sinotubular junction well into the AAo, considered to represent aortoannular ectasia.

Graphic 50641 Version 3.0

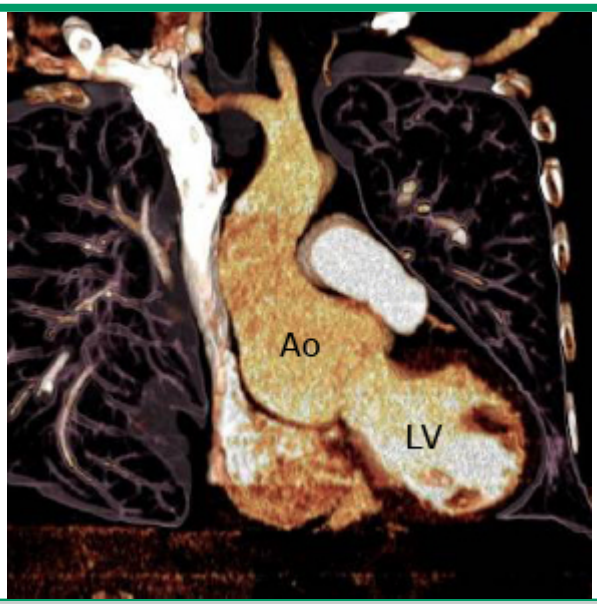
Chest radiograph in a patient with Marfan syndrome



Chest radiograph in a patient with Marfan syndrome. Features include hyperinflation, bullous changes, dilated tortuous aorta, and "tall" lungs.

Graphic 86855 Version 1.0

Computed tomographic (CT) image of the ascending aorta in a patient with Marfan syndrome.



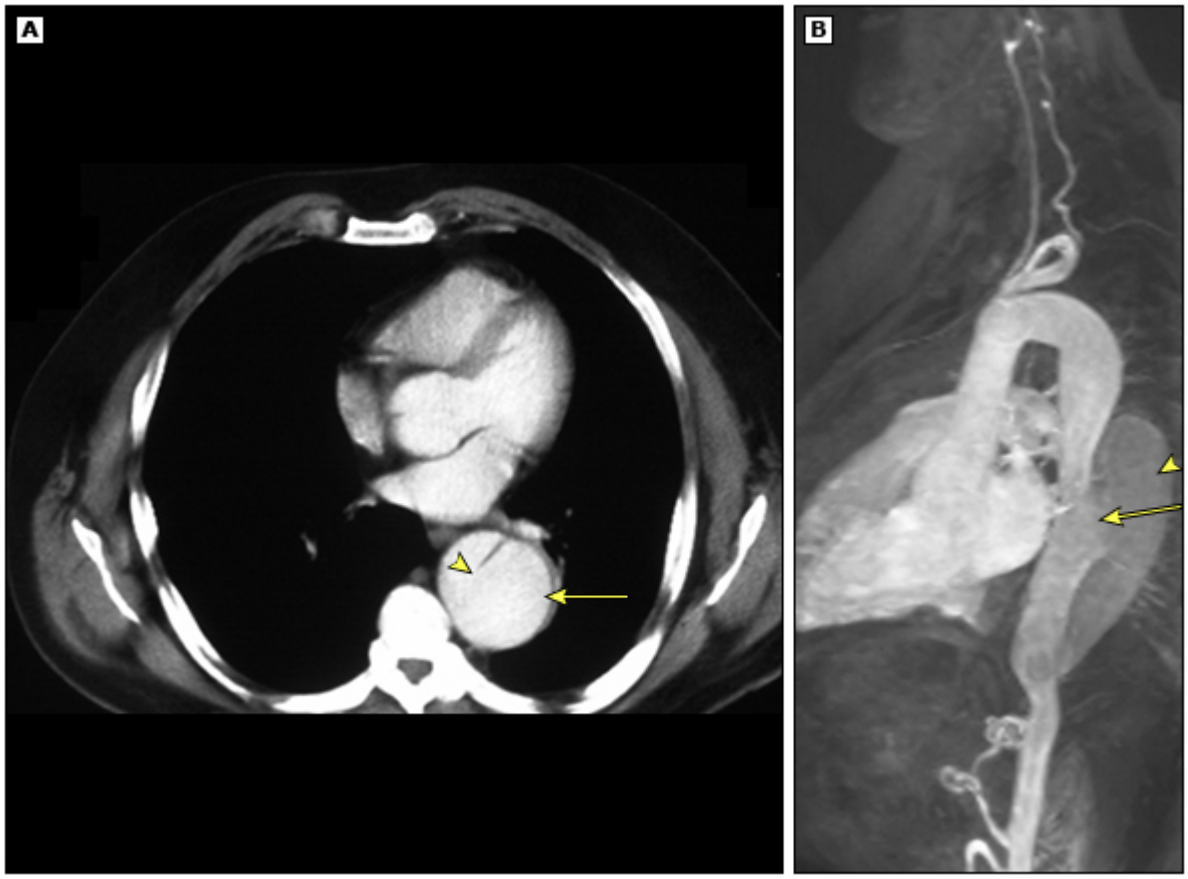
In this coronal CT view, the aortic root is dilated at the level of the sinuses of Valsalva.

Ao: ascending aorta; LV: left ventricle.

Courtesy of Heidi Connolly, MD.

Graphic 87119 Version 2.0

Focal dissection of the descending aorta in Marfan syndrome on CT and MRI

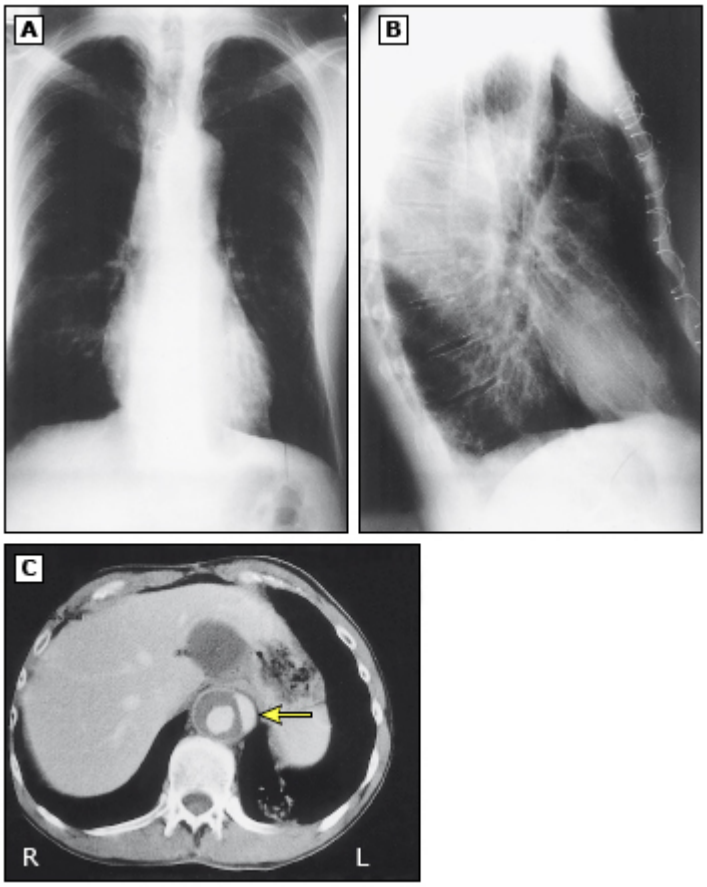


A CT image through the heart (A) shows a communication (arrowhead) between the true lumen of the thoracic aorta and a large compressive false lumen (arrow). Image B is an MRI of the aorta in the lateral projection and shows a focal dissection with communication at mid aortic level (arrow) between the true lumen and the false lumen (arrowhead).

CT: computed tomography; MRI: magnetic resonance.

Graphic 93363 Version 2.0

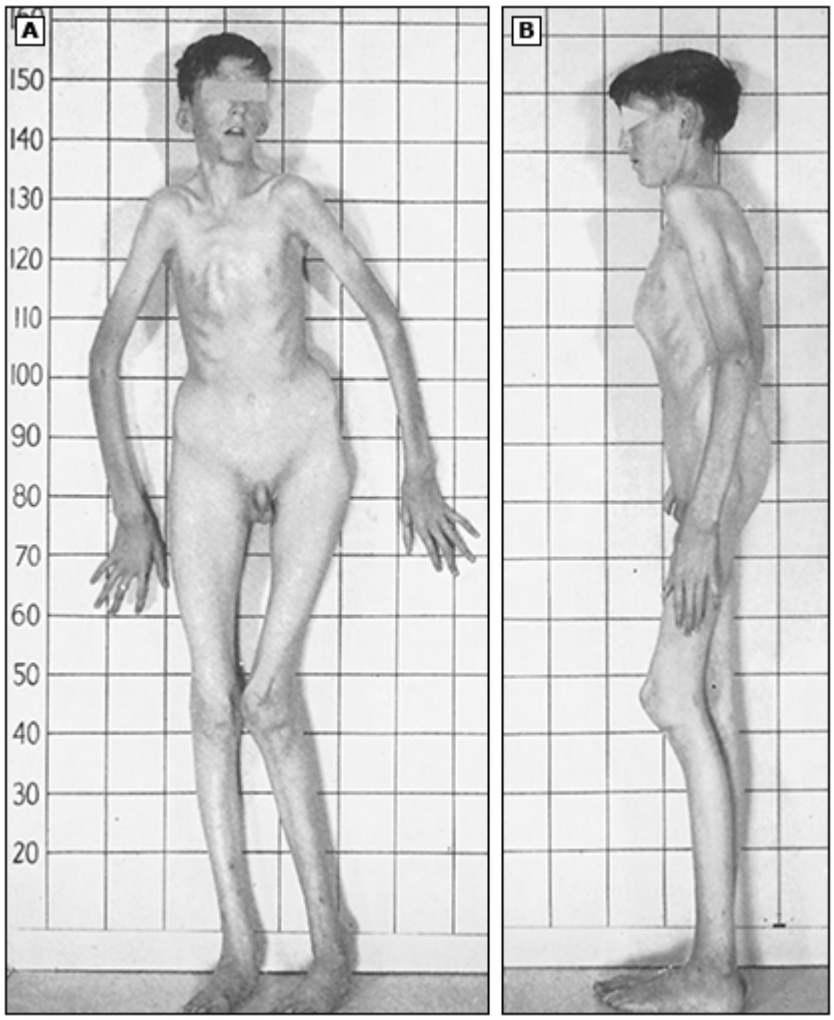
Emphysema and aortic dissection in Marfan syndrome



This 25-year-old male patient with a history of Marfan syndrome had undergone prior dissecting aneurysm repair and presented with acute chest pain.
(A) PA chest x-ray.
(B) Lateral chest x-ray. Note the gracile osteopenic appearance of the ribs, consistent with Marfans syndrome. Note also the hyperinflated lungs consistent with emphysema. These studies were taken after surgery for a dissecting aortic aneurysm; note the metallic surgical sutures in the sternum.
(C) CT, mid-thorax. Note the descending aortic dissection with a false lumen with contrast (arrow) and non-effaced true lumen with contrast and surrounding thrombus.

Graphic 86924 Version 7.0

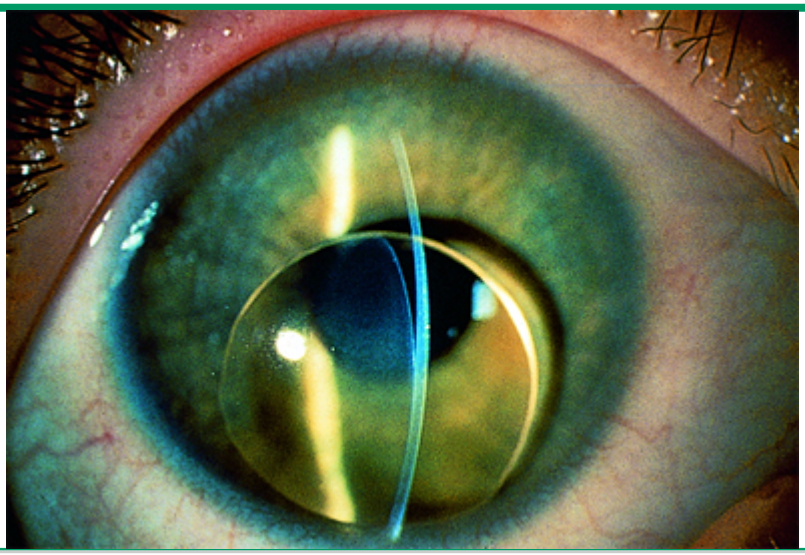
Example of skeletal features in Marfan syndrome



Marfan syndrome in a 14-year-old boy. Note arachnodactyly, relatively long limbs (dolichostenomelia), pectus carinatum, sparse subcutaneous fat, unilateral genu valgum, and pes planus. Ectopia lentis and scoliosis also were present. This patient died of aortic rupture at age 15 years.

Graphic 86852 Version 1.0

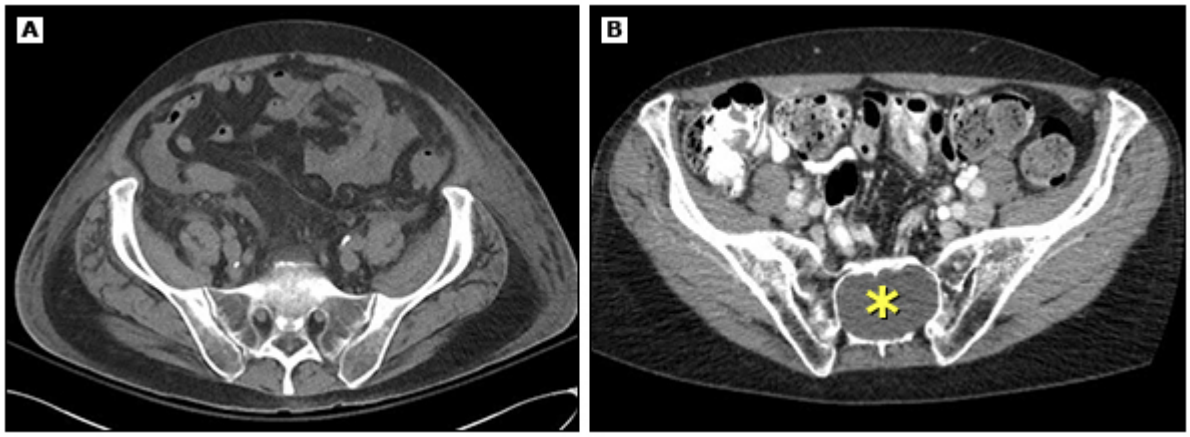
Ectopia lentis (dislocated lens) in Marfan syndrome



Slit-lamp photomicrography shows ectopia lentis with microspherophakia; the lens is completely luxated into the anterior chamber, predisposing to pupillary block glaucoma.

Graphic 67015 Version 2.0

Dural ectasia



Computerized tomography of the pelvis demonstrates (A) normal spinal canal and (B) features of lumbosacral dural ectasia (asterisk). Note dilation of the spinal canal. This may be associatec with pain and headaches.

Courtesy of Heidi M. Connolly, MD.

Graphic 95679 Version 1.0

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Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis

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INTRODUCTION — There are three major clinically and genetically distinct forms of neurofibromatosis: neurofibromatosis types 1 and 2 (NF1 and NF2) and schwannomatosis. Neurofibromatosis type 1, also known as von Recklinghausen disease or NF1, is the most common type. The hallmarks of NF1 are the multiple café-au-lait macules and neurofibromas. The condition is called segmental NF1 when clinical features are limited to one area of the body.

The pathogenesis, clinical features, and diagnosis of NF1 are reviewed here. Management and prognosis are discussed separately (see "Neurofibromatosis type 1 (NF1): Management and prognosis"). The other two forms of neurofibromatosis, neurofibromatosis type 2 (NF2) and schwannomatosis, are also discussed in detail separately. (See "Neurofibromatosis type 2" and "Schwannomatosis".)

EPIDEMIOLOGY — NF1 is an autosomal dominant genetic disorder with an incidence of approximately 1 in 2600 to 1 in 3000 individuals [1,2]. Approximately one-half of the cases are familial (inherited). The remainder are the result of de novo (sporadic) mutations [2]. The de novo mutations occur primarily in paternally-derived chromosomes and the likelihood of de novo NF1 increases with advanced paternal age [3]. The incidence of segmental NF1 is estimated at 1 in 36,000 to 40,000 [4].

PATHOGENESIS — NF1 is due to mutations in the *NF1* gene located at chromosome 17q11.2 [5,6]. Neurofibromin, the protein product encoded by the gene, is expressed in many tissues, including brain, kidney, spleen, and thymus [7]. It belongs to a family of guanosine triphosphate hydrolase (GTPase)-activating proteins (GAPs), the ras p21 family (21 kD rat sarcoma viral oncogene homologs), that downregulate the cellular proto-oncogenes and are important determinants of cell growth and regulation [8-10]. Ras activates a number of signaling pathways that includes the stem cell factor (SCF)/c-kit signaling, mechanistic target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK) pathways. *NF1* plays a role as a tumor suppressor gene [11].

Mutations in the *NF1* gene result in reduced amounts of functional protein, causing the wide spectrum of clinical findings, including NF1-associated tumors [7]. Penetrance, or the likelihood that the individual carrying the mutation will manifest the disease, is complete. However, NF1 is highly variable in its expression (ie, the severity of and specific manifestations of the disorder vary among affected individuals within the same family and from one family to another) [12]. Somatic mutation or loss of heterozygosity at the *NF1* locus, in combination with a germline NF1 mutation, leads to complete loss of neurofibromin expression that is seen in NF1 lesions such as pseudoarthrosis [13] and neurofibromas [14].

No obvious genotype-phenotype correlation have been demonstrated in patients with small mutations (<20 base pairs) of the *NF1* gene, with the exception of the c.2970-2972 delAAT (p.M990del) mutation that is associated with a very mild phenotype in the majority of cases [15]. These patients have a paucity of cutaneous, subcutaneous, and superficial plexiform neurofibromas that may relate to the fact that this mutation only deletes a single amino acid, unlike most other mutations that truncate or prevent neurofibromin formation. Patients with a phenotype referred to as "spinal NF," who have internal and paraspinal neurofibromas but few cutaneous tumors, tend to have splicing or missense mutations [16].

About 1 to 5 percent of patients with NF1 have large deletions that encompass more than 700 kb of DNA and include the entire *NF1* gene [7,17,18]. Such patients have a higher incidence of intellectual disability, developmental delay, some dysmorphic facial features, earlier appearance of cutaneous neurofibromas, and connective tissue abnormalities [19,20]. Data are conflicting as to whether individuals with large gene deletions also have an increased risk of malignant peripheral nerve sheath tumors (MPNSTs) [21,22].

Segmental NF1 is caused by somatic mosaicism due to a postzygotic mutation in the *NF1* gene [23]. This results in some cells having two normal *NF1* genes and other cells containing a mutation in one copy of the *NF1* gene. In most cases, patients with segmental NF1 have no affected relatives. When an adult with localized NF1 who has mosaicism within both somatic and gonadal tissues transmits the mutation to a child, this offspring will carry the *NF1* mutation in all of his/her cells and will not have segmental disease [4,24].

CLINICAL MANIFESTATIONS — The typical order of appearance of clinical manifestations is café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules (iris hamartomas), and neurofibromas [25]. Osseous lesions, if present, usually appear during the patient's first year after birth, and symptomatic optic pathway glioma (OPG) usually occurs by the time the patient is three years of age (table 1). Other tumors and neurologic complications typically begin to appear after the first year of life. Hypertension may occur in childhood, and malignant transformation of tumors may occur in adolescence and adulthood.

Café-au-lait macules — Café-au-lait macules are flat, uniformly hyperpigmented macules that appear during the first year after birth and usually increase in number during early childhood (picture 1). The number of café-au-lait macules then stabilizes over time. Up to 15 percent of the normal population have one to three café-au-lait macules. However, the presence of six or more café-au-lait macules is highly suggestive of NF1 [26,27]. (See "Benign pigmented skin lesions other than melanocytic nevi (moles)", section on 'Café-au-lait macule'.)

Approximately 95 percent of adults with NF1 have café-au-lait macules (picture 2), but they tend to fade later in life and may be difficult to distinguish in elderly individuals. A Wood's lamp often is useful to visualize these macules when they are not readily discernible by gross inspection [28], although the diagnostic criteria specify examination in ordinary room lighting. (See "Dermatologic procedures", section on 'Wood's lamp examination (black light)'.)

Freckling — Freckling is a diagnostic criterion distinct from café-au-lait macules. It occurs mostly in regions of skin apposition, especially the axillary (picture 3) and inguinal areas. Freckling usually is not apparent at birth, but often appears by age three to five years, typically first in the inguinal region [26]. Freckling may also occur in other intertriginous areas, such as the neckline or inframammary areas in women.

Lisch nodules — Lisch nodules characteristically are raised, tan-colored hamartomas of the iris and represent a specific finding for NF1. These do not affect vision in any manner.

Lisch nodules are useful both in establishing a diagnosis of NF1 in a child and determining whether a parent is affected. These lesions are detected in fewer than 10 percent of affected children younger than six years of age, but are seen in greater than 90 percent of adults. They may be seen with a direct ophthalmoscope if the nodules are large or numerous and the iris is light (picture 4), but are best seen thorough slit-lamp examination by an ophthalmologist to detect the lesions and to distinguish them from iris nevi [29].

Tumors — Patients with NF1 develop both benign and malignant tumors at increased frequency throughout life [30,31]. Neurofibromas are the most common type of benign tumor that develops in patients with NF1. OPGs are the predominant type of intracranial neoplasms, but other central nervous

system (CNS) and non-CNS tumors can occur.

The overall risk of malignancy in NF1 is increased in patients under 50 years of age, with a rate that is approximately 2.5- to 4-fold higher than that of the general population [32-34].

Peripheral neurofibromas — Neurofibromas are benign peripheral nerve sheath tumors that are comprised of a mixture of Schwann cells, fibroblasts, perineurial cells, and mast cells [35]. The Schwann cells may be abnormal in NF1 patients, and they can have angiogenic and invasive properties in plexiform neurofibromas (picture 5) [36]. (See 'Soft tissue sarcomas' below.)

Neurofibromas may appear as focal growths or extend longitudinally along a nerve and involve multiple fascicles. The latter are referred to as plexiform neurofibromas. Neurofibromas may be located in the skin (cutaneous neurofibromas), along peripheral nerves under the skin or deeper inside the body, and along nerve roots adjacent to the spine.

Cutaneous — Discrete cutaneous neurofibromas are the most common type. They consist of soft, fleshy, sessile or pedunculated tumors (picture 6) [37]. They move with the skin on examination and are not tender. Some are located within the dermis and can be palpated as a soft spot in the skin, often with an overlying violaceous discoloration. These dermal lesions usually begin to appear just before or during adolescence, although small lesions can be seen in younger children, especially if the skin is viewed with side lighting. They tend to increase in size and number with age. They vary in number from just a few to thousands, with the highest density occurring over the trunk. Pregnancy can also affect the number and size of all types of neurofibromas, suggesting that these tumors have a hormone-responsive component. In a report of 247 pregnancies in 105 women, growth of new lesions and enlargement of existing lesions was reported in 60 and 55 percent of cases, respectively [38].

Cutaneous neurofibromas are benign and do not carry an increased risk of developing malignant transformation but they often represent a major cosmetic problem in adults (picture 7). Pruritus associated with accelerated growth of neurofibromas may be a prominent and distressing symptom.

Plexiform — Plexiform neurofibromas may be located superficially and associated with overgrowth of skin and soft tissues (picture 8), may be located deep inside the body, or may have both superficial and deep components. Cutaneous involvement tends to be diffuse, with no discernible nerve fibers, although small plaques of cutaneous plexiform tumors may have palpable cords of thickened nerves. Deeper plexiform neurofibromas tend to appear as thickened nerves and can grow into a complex mass consisting of a network of enlarged nerves. The lesions are usually congenital and tend to grow most rapidly during childhood [39]. Whole body imaging reveals plexiform neurofibromas in approximately 50 percent of patients with NF1 [40].

Plexiform neurofibromas represent a major cause of morbidity and disfigurement in individuals with NF1, and symptomatic plexiform neurofibromas are associated with increased mortality [41]. Plexiform neurofibromas may compress the airway or spinal cord, and can transform into malignant peripheral nerve sheath tumors (MPNSTs). The most common feature of malignant transformation of an existing plexiform neurofibroma is a painful, expanding lesion [42]. (See 'Malignant peripheral nerve sheath tumors' below.)

Nodular — Nodular neurofibromas are discrete lesions that may grow under the skin, where they appear as firm, rubbery masses that may be tender, or occur deeper inside the body. Some can enlarge to the point where they compress surrounding structures or cause pain, but they do not tend to invade surrounding tissues like plexiform neurofibromas. Nodular neurofibromas can also transform into MPNST.

Optic pathway gliomas — OPGs occur in 15 percent of children younger than six years of age with NF1 [43]. They rarely occur in older children and adults [44,45]. OPGs are typically low-grade pilocytic

astrocytomas [46]. They can arise anywhere along the anterior visual pathway to the optic radiations and involve the optic nerves, chiasm, and postchiasmal optic tracts. (See "Optic pathway glioma" and "Neurofibromatosis type 1 (NF1): Management and prognosis", section on 'Optic pathway gliomas'.)

Many children with NF1 and OPGs have normal vision. A minority of children become symptomatic with progressive vision loss associated with an expanding lesion [43,47-49]. Symptoms and signs of OPG may include decreased visual acuity or color vision, abnormal pupillary function, proptosis, and optic nerve atrophy [50-52].

Children with advanced tumors involving the optic chiasm occasionally present with either premature or delayed puberty caused by hypothalamic involvement [49]. Detecting precocious puberty early in patients with NF1 is important because it may indicate the presence of a clinically significant OPG. In addition, treatment can minimize the complications of accelerated linear bone growth and premature development of secondary sexual characteristics. One of the earliest signs of precocious puberty is accelerated linear growth, which highlights the importance of maintaining accurate growth charts using standards for children with NF1 [53-56]. (See "Definition, etiology, and evaluation of precocious puberty".)

Other CNS neoplasms — In addition to OPGs, individuals with NF1 are at an increased risk for developing other CNS neoplasms, particularly astrocytomas and brainstem gliomas [49,57,58]. Although astrocytomas usually arise in early childhood (mean age at diagnosis 4.5 years), the risk persists into adulthood [44]. The most frequent clinical presentation is that of increased intracranial pressure [49], although lesions are often asymptomatic and are noted as incidental findings if brain imaging is performed.

Soft tissue sarcomas — Patients with NF1 are at an increased risk of developing soft tissue sarcomas, such as MPNSTs, rhabdomyosarcoma (RMS), and gastrointestinal stromal tumors (GISTs).

Malignant peripheral nerve sheath tumors — MPNSTs, previously called neurofibrosarcomas, usually arise within preexisting plexiform or nodular neurofibromas that have undergone malignant transformation. The primary care provider should be alert to the possibility of this highly malignant tumor, particularly in teenagers and young adults. The first presentation of malignant transformation often is development of significant and constant pain, change in consistency, or rapid growth of a nodule within an existing plexiform neurofibroma [17,59]. Positron emission tomography (PET) imaging with fluorodeoxyglucose may be helpful in distinguishing MPNST from benign plexiform or nodular neurofibromas [60]. The lifetime risk of developing an MPNST in patients with NF1 ranges from 5 to 13 percent [61-64]. Among children with MPNSTs, 20 to 50 percent have NF1 [59,61,65]. Patients with NF1 tend to have larger tumors at diagnosis [66,67]. MPNSTs are discussed in greater detail separately. (See "Peripheral nerve tumors", section on 'Malignant peripheral nerve sheath tumors' and "Neurofibromatosis type 1 (NF1): Management and prognosis", section on 'Malignant peripheral nerve sheath tumors'.)

Rhabdomyosarcoma — RMS is encountered more frequently in patients with NF1 than in the general population [68-70]. RMS tends to present at an early age and often arises in a genitourinary site [68]. (See "Rhabdomyosarcoma in childhood and adolescence: Epidemiology, pathology, and molecular pathogenesis".)

Gastrointestinal stromal tumors — Patients with NF1 are also at an increased risk of developing soft tissue sarcomas that arise within the stromal compartment of the gastrointestinal tract, termed GISTs [71-73]. In the setting of NF1, GISTs frequently occur in the small intestine (more than 70 percent), are often multiple, and have a different molecular pathology. (See "Epidemiology, classification, clinical presentation, prognostic features, and diagnostic work-up of gastrointestinal mesenchymal neoplasms including GIST".)

Glomus tumors — Glomus tumors arise in the tips of the fingers and toes under the nail bed and

present with pain, tenderness, and sensitivity to cold. They are associated with NF1 [74] and are important to recognize because the pain is readily relieved by surgical removal of the tumor.

Other tumors — Whether other common malignancies occur at higher rates in patients with NF1 is uncertain [34,75]. NF1 patients have an increased risk of certain other malignancies, such as juvenile myelomonocytic leukemia of childhood and pheochromocytoma, although genetic etiologies other than NF1 are more common causes of these malignancies [4]. Women with NF1 may be at increased risk of breast cancer [32,76-78]. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Juvenile myelomonocytic leukemia'.)

Bone abnormalities — Bony abnormalities in NF1 include pseudoarthrosis and bone dysplasia, which are part of the United States National Institutes of Health (NIH) Consensus Conference criteria for the disease [25,79,80], as well as short stature, scoliosis, and osteoporosis [81,82]. (See 'Diagnostic criteria' below.)

Long bone dysplasia and pseudoarthrosis — Long bone dysplasia typically presents in infants or young children as anterolateral bowing of the tibia, which progresses to narrowing of the medullary canal, cortical thickening, and fracture [83,84]. The diagnosis may be overlooked until pathologic fractures occur with weight bearing or when walking is first attempted in toddlers. Approximately one-half of fractures occur before the patient is two years of age.

A pseudoarthrosis is a false joint that forms when there is nonunion of bone fragments at the site of a long bone fracture. It severely compromises function in the affected limb. Pseudoarthrosis in NF1 results from impaired healing due to bone dysplasia [17]. Long bone pseudoarthrosis occurs in infancy in approximately 5 percent of patients with NF1 [83]. It has a male predominance (1.7:1). NF1 is the most common cause of long bone pseudoarthrosis, accounting for 50 to 80 percent of cases. Thus, evaluation for NF1 should be performed in a child with this condition. Management is complex and may necessitate amputation to allow the toddler to walk. The Children's Tumor Foundation has published guidelines for management of children with NF1 and pseudoarthrosis [85].

Other bone lesions — Other skeletal lesions include vertebral defects, such as scalloping caused by dural ectasia, nonossifying fibromas within long bones, and sphenoid wing dysplasia, which may present as facial asymmetry [80]. Young children with NF1 may have a hair whorl overlying an area of vertebral dysplasia [86].

Short stature — Children with NF1 frequently have short stature. In a database of 569 white North American patients with NF1, 13 percent had a height ≥2 standard deviations below the population mean [53]. Growth curves for children with NF1 are available and can aid the clinician in determining if the degree of short stature is consistent with the diagnosis of NF1 or is more severe [53,54]. The latter suggests an additional cause and requires evaluation. (See "Diagnostic approach to children and adolescents with short stature" and "Causes of short stature".)

Scoliosis — Scoliosis occurs in 10 to 25 percent of individuals with NF1 [28,47]. This condition frequently becomes apparent at 6 to 10 years of age or in early adolescence. Scoliosis in children with NF1 most commonly affects the thoracic spine. (See "Adolescent idiopathic scoliosis: Clinical features, evaluation, and diagnosis".)

Osteoporosis — Individuals with NF1 have lower bone density per age compared with general population controls. Characterization of 74 NF1 patients (children and young adults) by dual energy x-ray absorptiometry (DEXA) scans found statistically significant and generalized reduction in bone mass [81]. The severity of decreased bone density can range from osteopenia to osteoporosis. The etiology of this decrease in bone density is unknown. A survey from Finland revealed that an increased risk of fractures in both children and adults over the age of 40 with NF1 (threefold and fivefold increased relative risk, respectively) compared with population controls of similar age and gender distribution [87].

Neurologic abnormalities — Neurologic disorders include cognitive deficits, learning disabilities, and seizures. Gross and fine motor developmental delays are also seen [88]. Macrocephaly is a common feature.

Cognitive deficits and learning disabilities — Cognitive deficits and learning disabilities occur with higher frequency in children with NF1 [89]. A study of 81 children with NF1 found moderate-to-severe impairment involving one or more domains of cognitive function in 66 (81 percent) [90]. Intelligence quotient (IQ) scores are 5 to 10 points lower in children with NF1 compared with the general population or unaffected sibling controls [91]. The incidence of intellectual disability (full scale IQ <70) in this disorder is 4 to 8 percent, only slightly higher than that of the general population (2 to 3 percent). Thus, a child with NF1 and intellectual disability should be evaluated for other causes of cognitive impairment (eg, fragile X syndrome). (See "Fragile X syndrome: Clinical features and diagnosis in children and adolescents".)

One-half of the children in one series performed poorly on tasks of reading, spelling, and mathematics, but only 20 percent had specific learning disabilities (defined by discrepancy between ability [IQ] and academic achievement) [90]. Specific learning disabilities occur in up to 65 percent of patients with NF1 in other series [89,91]. Affected children demonstrate a range of neuropsychologic impairments, including poor performance on nonverbal learning problems (ie, difficulty with written work, poor attention, and decreased organizational skills), tests of visuospatial function, and language-based learning tasks (ie, reading and spelling) [91]. Attention-deficit hyperactivity disorder (ADHD) occurs in 38 to 39 percent of children with NF1 [90,92]. Executive function impairment in the areas of planning and problem solving that are not directly related to inattention level are also seen [93]. Problems with speech articulation are also common. (See "Neurofibromatosis type 1 (NF1): Management and prognosis", section on 'Cognitive and learning deficits' and "Specific learning disabilities in children: Clinical features" and "Specific learning disabilities in children: Evaluation" and "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation".)

Seizures — Seizures are about twice as common in patients with NF1 compared with the general population, with a prevalence of about 4 to 6 percent [94-96]. Seizures can be of any type and begin at any age. Focal seizures are often due to an intracranial neoplasm [96]. Thus, new seizures should prompt repeat neuroimaging, even if previous imaging was normal. (See "Overview of the classification, etiology, and clinical features of pediatric seizures and epilepsy".)

Macrocephaly — Head size is generally larger in persons with NF1. This may present as relative macrocephaly compared with height or absolute macrocephaly [53,97]. It is caused by increased brain volume due to inherent skeletal features of the disorder and may be associated with cognitive problems. Rarely, hydrocephalus may occur due to aqueductal stenosis. (See 'Increased brain volume (megalencephaly)' below.)

Peripheral neuropathy — Peripheral neuropathy is much less common in NF1 than in neurofibromatosis type 2 (NF2), with reports of nerve compression in up to 4 percent of patients and spinal root compression in up to 3 percent in patients with NF1 [28,47,57,98]. By comparison, clinical symptoms of peripheral neuropathy occur in almost 50 percent of patients with NF2 [98]. Nevertheless, peripheral neuropathy can be a severe complication of NF1 that is associated with frequent morbidity related to spinal complications and development of MPNSTs [99]. (See "Neurofibromatosis type 2" and 'Malignant peripheral nerve sheath tumors' above.)

Hypertension — Hypertension is a frequent finding in adults with NF1 and may develop during childhood. Hypertension is considered essential in most cases, but vascular lesions producing renovascular hypertension are more frequent in NF1 patients. Thus, evaluation for renovascular causes should be initiated in children with NF1 and hypertension [47,100]. Renovascular lesions can be detected in patients who are still normotensive. The frequency with which such patients will develop

hypertension is not known. A much less common cause of hypertension in NF1 is pheochromocytoma, which has been clinically identified in 0.1 to 5.7 percent of patients. (See "Definition and diagnosis of hypertension in children and adolescents" and "Overview of hypertension in adults" and "Pheochromocytoma in children" and 'Other tumors' above and "Neurofibromatosis type 1 (NF1): Management and prognosis", section on 'In patients with severe hypertension'.)

Other manifestations — Very rarely, patients may develop cardiovascular complaints or airway compromise due to mediastinal neurofibromas or MPNST metastases to the heart and lung [101-103]. Pulmonary hypertension [104-106], pulmonary artery stenosis [107], interstitial lung disease [108], and bullous lung disease [109] have also been reported. Pulmonary embolism and acute myocardial infarction have occurred in patients with both NF1 and pheochromocytoma [110,111]. (See 'Plexiform' above and 'Malignant peripheral nerve sheath tumors' above and 'Other tumors' above.)

Segmental NF1 — Segmental NF1 is due to mosaicism for an *NF1* gene mutation. The presentation of segmental and generalized NF1 is similar with regard to the age of appearance of the specific features, with a few exceptions [4,112]. In segmental NF1, pigmentary features and plexiform neurofibromas tend to present in children, while dermal neurofibromas develop in adults. Lisch nodules may be present in one or both eyes. In most patients, the affected area is limited to one side, with involvement ranging from a narrow strip to one-half of the body [4]. More serious complications of NF1, such as OPGs, pseudoarthrosis, plexiform neurofibromas, and learning difficulties, are uncommon in patients with segmental NF1, occurring in 5.6 percent in one series of 124 patients [4].

NEUROIMAGING FINDINGS — Neuroimaging abnormalities are frequently detected in patients with NF1 [113]. These include NF-associated bright spots and increased brain volume.

NF-associated bright spots — Focal areas of increased signal intensity were first identified on T2 weighted magnetic resonance imaging (MRI) of the brain in children with NF1. The term "unidentified bright objects" (UBOs) is discouraged because it can be upsetting to parents. Bright spots are seen commonly in children with NF1, but may disappear in adulthood [7]. They occur most often in the basal ganglia, cerebellum, brainstem, and subcortical white matter and are thought to represent increased fluid within the myelin associated with dysplastic glial proliferation [114,115]. They do not behave in a malignant or premalignant manner and are not associated with focal neurologic deficits. They are not part of the United States National Institutes of Health (NIH) diagnostic criteria [115,116].

Data are conflicting on the relationship between NF-associated bright spots and cognitive function. In one report, 25 of 40 children (62 percent) with NF1 had bright spots present on MRI [117]. These patients had significantly lower intelligence quotient (IQ) and language scores and impaired visuomotor integration and coordination, compared with children without them. In another study, the number of locations containing spots accounted for much of the lowering of IQ scores in NF1 patients compared with unaffected siblings [118]. However, in a third series, these lesions were not associated with intellectual impairment [115]. (See 'Cognitive deficits and learning disabilities' above.)

Increased brain volume (megalencephaly) — Brain volumes are increased in patients with NF1 and may be related to cognitive abnormalities [97,113,119,120]. (See 'Macrocephaly' above and 'Cognitive deficits and learning disabilities' above.)

Cerebrovascular dysplasia — Several retrospective series have noted abnormal cerebral vasculature (eg, moyamoya syndrome, intracranial aneurysm) in 2 to 6 percent of children with NF1 who underwent neuroimaging [121-123]. Most patients were asymptomatic despite angiographic progression, but some required surgery for revascularization.

DIAGNOSIS — The diagnosis of NF1 is based upon the presence of characteristic clinical features (table 2). Genetic testing is often not required to make the diagnosis, but can be helpful in confirming the diagnosis for children who do not meet diagnostic criteria or only demonstrate café-au-lait macules and

axillary freckling.

Children suspected of having NF1 should be evaluated by a multidisciplinary team that includes pediatric neurology, genetics, and ophthalmology. This team should examine the child for diagnostic criteria and treatable complications, provide anticipatory guidance, and refer to specialists as needed. Both an expert panel [79] and the Genetics Committee of the American Academy of Pediatrics have published diagnostic and health supervision guidelines for children with NF1 [56].

The initial screening evaluation should confirm the diagnosis by identifying clinical features of NF1. History should be obtained regarding symptoms associated with the disorder, such as pain, visual complaints, weakness or neurologic deficits, headaches, and seizures. The developmental history and school progress should be reviewed. Physical examination should focus on skin, skeletal, and neurologic systems. Ophthalmologic evaluation should be performed to identify Lisch nodules and early signs of optic pathway glioma (OPG). (See 'Clinical manifestations' above and 'Diagnostic criteria' below.)

Diagnostic criteria — The diagnostic criteria developed by the United States National Institutes of Health (NIH) Consensus Conference in 1987 and updated in 1997 are based upon specific clinical features of NF1 (table 2) [25,79,80]. According to these criteria, **at least two** of the following clinical features must be present to make the diagnosis of NF1:

- Six or more café-au-lait macules >5 mm in diameter in prepubertal and >15 mm in diameter in postpubertal individuals. For each lesion, the longest diameter is measured.
- Two or more neurofibromas of any type or one plexiform neurofibroma (picture 5).
- Freckling in the axillary or inguinal regions.
- Optic glioma.
- Two or more Lisch nodules (iris hamartomas).
- A distinctive bony lesion, such as sphenoid dysplasia or thickening of the long bone cortex with or without pseudoarthrosis.
- A first-degree relative (parent, sibling, or offspring) with NF1 based upon the above criteria.

The NIH diagnostic criteria are both highly specific and sensitive in all but the youngest children [25,28], with 97 percent of patients meeting the diagnostic criteria by eight years of age and the remainder meeting criteria by 20 years of age in a study of 1893 NF1 patients younger than 21 years of age [25]. Approximately 46 percent of sporadic NF1 patients failed to meet the criteria by one year of age. Thus, young children who have only one clinical manifestation and no family history of NF1 should continue to be monitored for appearance of other manifestations, since a definitive diagnosis usually can be made by the time the child is four years of age. Genetic testing can be considered to make a molecular diagnosis. In one report of 41 children one month to 14 years of age with six or more café-au-lait macules on the initial visit, a diagnosis of NF1 was eventually made in approximately 50 percent [26].

Genetic testing — Genetic testing can be performed to confirm the diagnosis in questionable cases and to help direct screening of family members (ie, perform targeted testing for the mutation identified in the proband rather than a comprehensive mutation analysis of the entire gene). It is required for prenatal or preimplantation diagnosis. A positive *NF1* mutation test does not predict the severity or complications of the disorder. (See 'Pathogenesis' above.)

Mutations associated with the clinical diagnosis of NF1 disrupt the function of the *NF1* gene. Because of the large size of the gene and the heterogeneity of mutations, molecular testing includes sequencing of all of the coding exons as well as tests for deletions or rearrangements of a portion or the entire gene. Molecular testing is clinically available and is reported to find the causative DNA mutation in

approximately 95 percent of patients who carry the clinical diagnosis of NF1 [124]. Thus, a negative test does not completely exclude the diagnosis. A negative test may also represent mosaicism for the mutation (for example, in segmental NF1 where blood maybe negative) or the possibility of a different disorder. (See 'Differential diagnosis' below.)

Individuals with other conditions, including Legius syndrome [125,126] and constitutional mismatch repair deficiency syndrome [127], may manifest both café-au-lait macules and axillary freckling. Thus, there is increasing use of genetic testing in the diagnosis of NF1 for patients who meet only these two NIH criteria in addition to those with only one NIH criterion. A positive genetic test may shorten the period of diagnostic uncertainly. In addition, appropriate screening evaluations (eg, ophthalmic screens) are initiated promptly if the test is positive for an *NF1* mutation. If the *NF1* mutation testing is negative, then the diagnostic laboratory may perform *SPRED1* (sprouty-related EVH1 [enabled/vasodilator-stimulated phosphoprotein homology 1] domain-containing protein 1) mutation testing to evaluate for Legius syndrome. If both are negative, then genetic testing of the four mismatch repair genes or Noonan syndrome should be considered. The parents of young children with multiple café-au-lait macules alone should understand the risks and benefits of genetic analysis before proceeding with testing. (See 'Differential diagnosis' below.)

Screening family members — A detailed family history should be obtained to detect possible symptoms of NF1 when the diagnosis is made in a child. When possible, parents and siblings should be examined for the characteristic signs (table 2) [79]. This evaluation includes a complete examination of the skin and a slit-lamp examination of the eyes because of the variable expressivity characteristic of this disorder. (See 'Pathogenesis' above.)

Genetic screening of family members is discussed above. (See 'Genetic testing' above.)

Prenatal testing — Amniocentesis or chorionic villus sampling can be performed to obtain a sample for genotyping the fetus if the precise mutation of an affected family member with NF1 is known. Preimplantation genetic diagnosis (PGD) to identify those embryos that do not carry a known familial *NF1* mutation is also possible [128]. (See "Neurofibromatosis type 1 (NF1): Management and prognosis", section on 'Genetic counseling'.)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of NF1 includes Legius syndrome, constitutional mismatch repair-deficiency (CMMR-D) syndrome, neurofibromatosis type 2 (NF2), and Noonan syndrome.

Legius syndrome — Legius syndrome, an autosomal dominant NF1-like disorder, results from germline loss-of-function mutations in *SPRED1* (sprouty-related EVH1 [enabled/vasodilator-stimulated phosphoprotein homology 1] domain-containing protein 1) [125,126]. SPRED1 is a member of the SPROUTY/SPRED family of proteins that act as negative regulators of RAS-RAF kinase interaction and mitogen-activated protein kinase (MAPK) signaling. The clinical features include a subset of those of NF1 (multiple café-au-lait macules, axillary freckling, and macrocephaly), but importantly lack neurofibromas and central nervous system (CNS) tumors [126,129]. Melanocytes from a café-au-lait spot demonstrated both the germline *SPRED1* mutation and an acquired somatic mutation in the wild-type *SPRED1* allele, suggesting that complete SPRED1 inactivation is needed to generate a café-au-lait spot in this syndrome [125].

Constitutional mismatch repair-deficiency syndrome — CMMR-D syndrome is a rare autosomal recessive disorder caused by inheritance of deleterious mutations in both copies of one of the four mismatch repair genes [127]. The main clinical manifestation that CMMR-D shares with NF1 is café-au-lait macules. Axillary freckling and Lisch nodules have also been reported in CMMR-D. The primary clinical difference between the two disorders is the types of malignancies seen with each. In CMMR-D, hematologic malignancies typically develop in infancy to early childhood, brain tumors

(primarily glioblastoma) in mid-childhood, and colorectal cancer in adolescence to young adulthood. A variety of other tumors (eg, rhabdomyosarcoma [RMS] and optic pathway glioma [OPG]) are less commonly seen in CMMR-D [127,130,131]. Heterozygous mutations in one of the MMR genes cause Lynch syndrome (hereditary nonpolyposis colon cancer). (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis".)

Neurofibromatosis type 2 — NF2 and NF1 are caused by mutations in genes on different chromosomes which encode proteins of distinct function. Nonetheless, partial overlap in the clinical manifestations of these inherited disorders can occasionally lead to confusion. (See "Neurofibromatosis type 2".)

Key differences between NF1 and NF2 include:

- Café-au-lait macules are much less frequent in NF2 and Lisch nodules are not seen.
- The schwannomas associated with NF2 rarely undergo malignant transformation into a malignant peripheral nerve sheath tumor (MPNST).
- The spinal root tumors that are seen with both NF2 and NF1 are schwannomas in NF2 and neurofibromas in NF1.
- NF2 is not associated with the cognitive impairment that is often seen with NF1.
- NF2 is associated with a very high prevalence of bilateral acoustic schwannomas.

Noonan syndrome — Noonan syndrome is characterized principally by short stature, webbed neck, characteristic facial features, and pulmonic stenosis [132]. Affected individuals may have café-au-lait spots, sometimes more than six that are larger than 5 mm, which fulfills a diagnostic criterion for NF1 in children. In addition, the facial features of Noonan syndrome are sometimes also seen in individuals with NF1. Noonan syndrome is due to mutation in one of several genes in the Ras signaling pathway, especially *PTPN11* (protein-tyrosine phosphatase, nonreceptor-type, 11). (See "Causes of short stature", section on 'Noonan syndrome' and "Pulmonic stenosis (PS) in neonates, infants, and children".)

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 topic (see "Patient information: Neurofibromatosis type 1 (The Basics)")

Information for patients about NF1 is available online through the Children's Tumor Foundation.

SUMMARY

- There are three major clinically and genetically distinct forms of neurofibromatosis, neurofibromatosis types 1 and 2 (NF1 and NF2) and schwannomatosis. NF1, also known as von Recklinghausen disease, is the most common type. The hallmarks of NF1 are the multiple café-au-lait macules and associated cutaneous neurofibromas (picture 2). The condition is called segmental NF1 when clinical features are limited to one area of the body. (See 'Introduction'

above.)

- NF1 is an autosomal dominant disorder caused by mutations in the *NF1* gene that encodes the protein neurofibromin. Penetrance is complete, but expression is highly variable. Segmental NF1 is caused by somatic mosaicism due to a postzygotic mutation in the *NF1* gene. (See 'Pathogenesis' above.)
- The typical order of appearance of clinical manifestations is café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules (iris hamartomas), and neurofibromas. Osseous lesions, if present, usually appear during the patient's first year after birth, and symptomatic optic pathway glioma (OPG) usually occurs by the time the patient is three years of age (table 1). Other tumors and neurologic complications typically begin to appear after the first year of life, and hypertension and malignant transformation of tumors may occur in adolescence and adulthood. (See 'Clinical manifestations' above.)
- The diagnosis of NF1 is based upon the presence of characteristic clinical features (table 2). Genetic testing is not required to make the diagnosis, but can be helpful in confirming the diagnosis for children who do not meet diagnostic criteria or only demonstrate café-au-lait macules and axillary freckling. Children suspected of having NF1 should be evaluated by a multidisciplinary team that includes pediatric neurology, genetics, and ophthalmology. This team should examine the child for diagnostic criteria and treatable complications, and also provide anticipatory guidance. (See 'Diagnosis' above.)
- The differential diagnosis of NF1 includes Legius syndrome, constitutional mismatch repair-deficiency (CMMR-D) syndrome, NF2, and Noonan syndrome. (See 'Differential diagnosis' above.)

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Topic 2939 Version 26.0

GRAPHICS

Features of neurofibromatosis type 1 as a function of the age when they may first be apparent

Birth through age 2
Café-au-lait spots, pseudoarthrosis, sphenoid wing dysplasia, optic pathway gliomas, plexiform neurofibromas (rarely)
Ages 2 through 6
Axillary freckling, Lisch nodules, optic pathway gliomas, other CNS tumors, learning disabilities or speech delay, plexiform neurofibromas
6 to 10 years
Learning disabilites, attention deficit disorders, scoliosis, plexiform neurofibromas, increased risk of other cancer types (eg, rhabdomyosarcomas), headaches
Adolescence
Subcutaneous and cutaneous neurofibromas, malignant transformation of preexisting plexiform neurofibromas, isolated MPNST, hypertension
Adulthood
Increasing number of cutaneous and subcutaneous neurofibromas, MPNST, hypertension

CNS: central nervous system; MPNST: malignant peripheral nerve sheath tumors.

Modified and updated from: Plon SE, Riccardo VM. In: Oksi's Pediatrics: Principles and Practice, McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB (Eds), Lippincott Williams & Wilkins, Philadelphia 1999. Copyright © 1999 Lippincott Williams & Wilkins.

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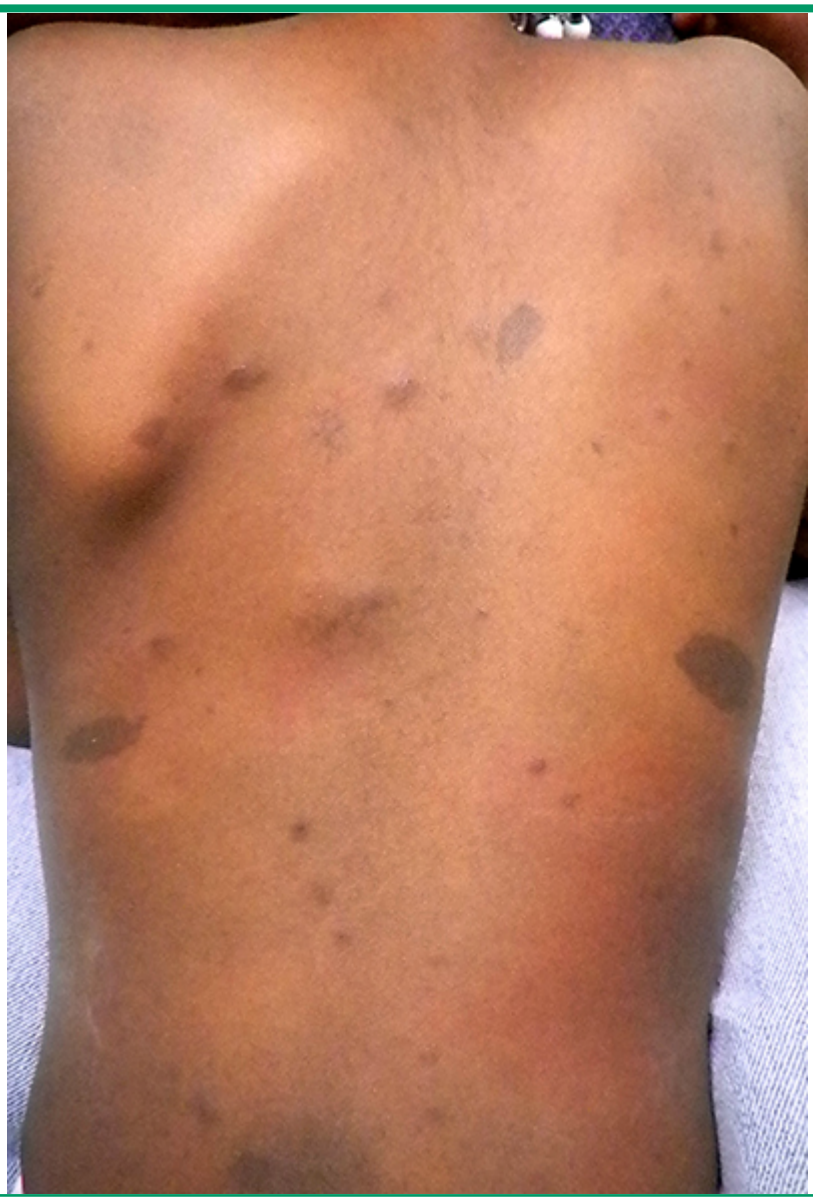
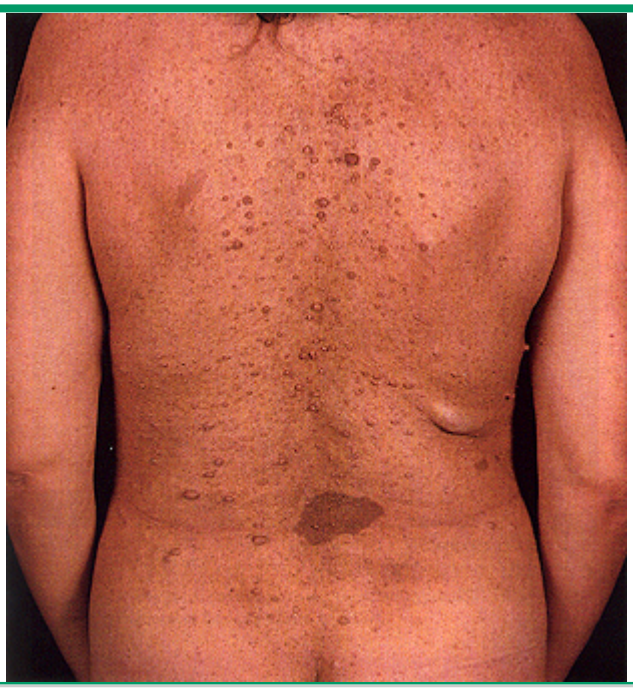
Graphic 53064 Version 8.0

Multiple cafe-au-lait spots in a patient with neurofibromatosis 1



Graphic 96125 Version 1.0

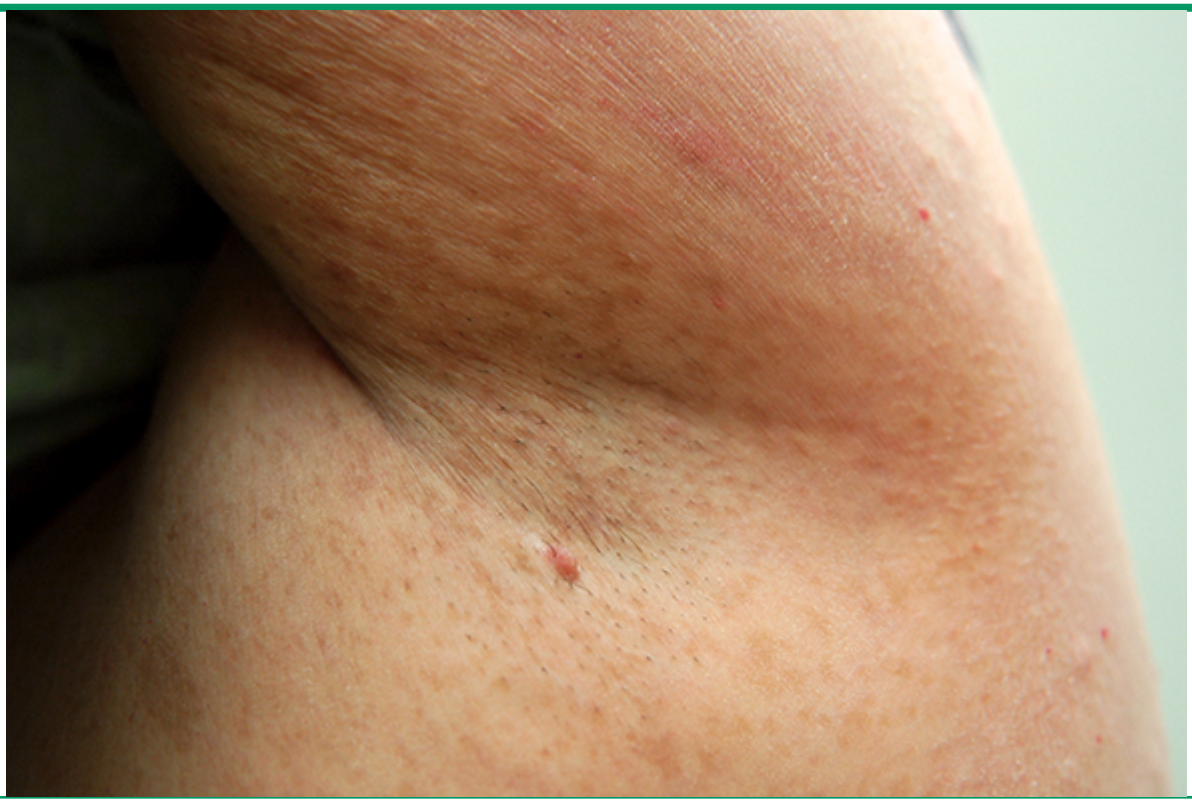
Neurofibromata and café-au-lait macules in a patient with neurofibromatosis 1 (NF1)



Skin-colored and pink-tan, soft papules and nodules on the back are neurofibromata. These lesions first appeared during late childhood. The large, soft, ill-defined, subcutaneous nodule on the right lower back is a plexiform neuroma. The café-au-lait macules appeared earlier in childhood. A large one is visible on the middle lower back.

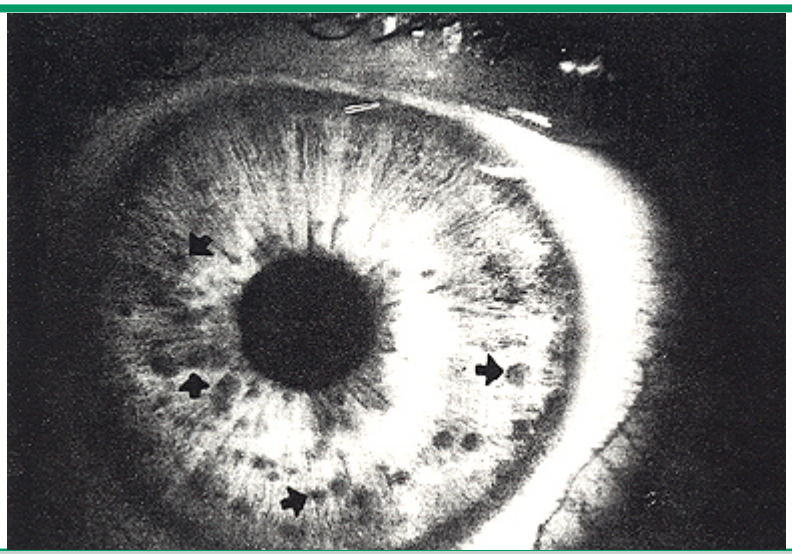
Graphic 69606 Version 3.0

Axillary freckling in a patient with neurofibromatosis 1



Graphic 96124 Version 1.0

Lisch nodules in a patient with neurofibromatosis type 1

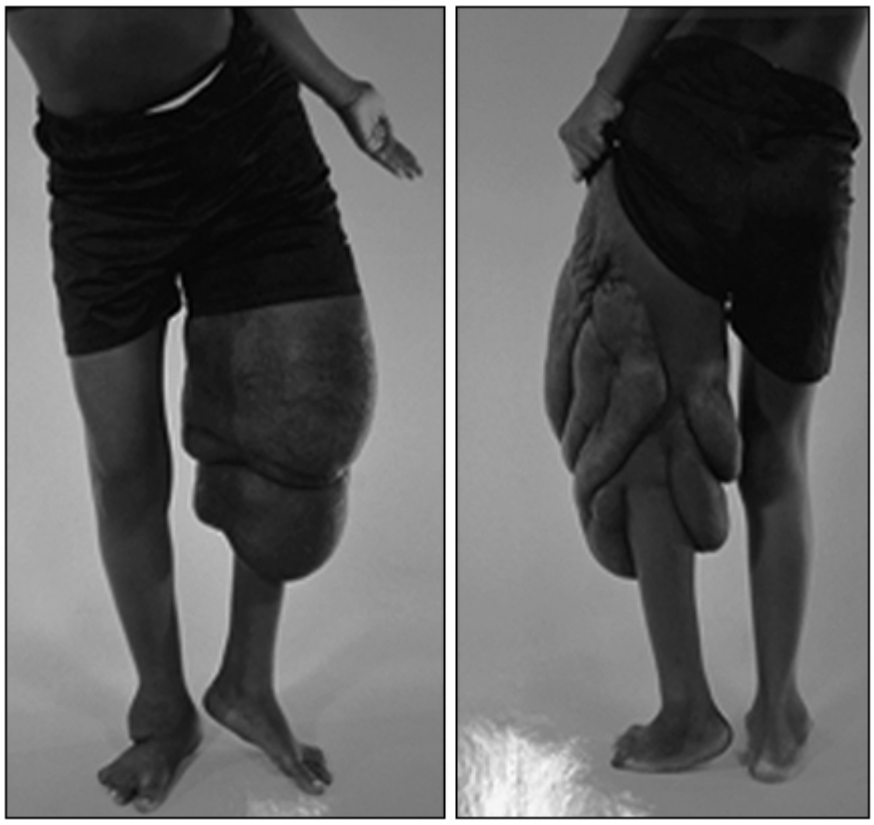


The iris of a patient with neurofibromatosis type 1 (NF1), showing multiple Lisch nodules (arrows).

Reproduced with permission from: Friedman JM, Gutmann H, MacCollin M, Riccardi VM (Eds). Neurofibromatosis: Phenotype, Natural History, and Pathogenesis, 3rd ed, Johns Hopkins University Press, Baltimore 1999. Photograph courtesy of RA Lewis, MD.

Graphic 74414 Version 4.0

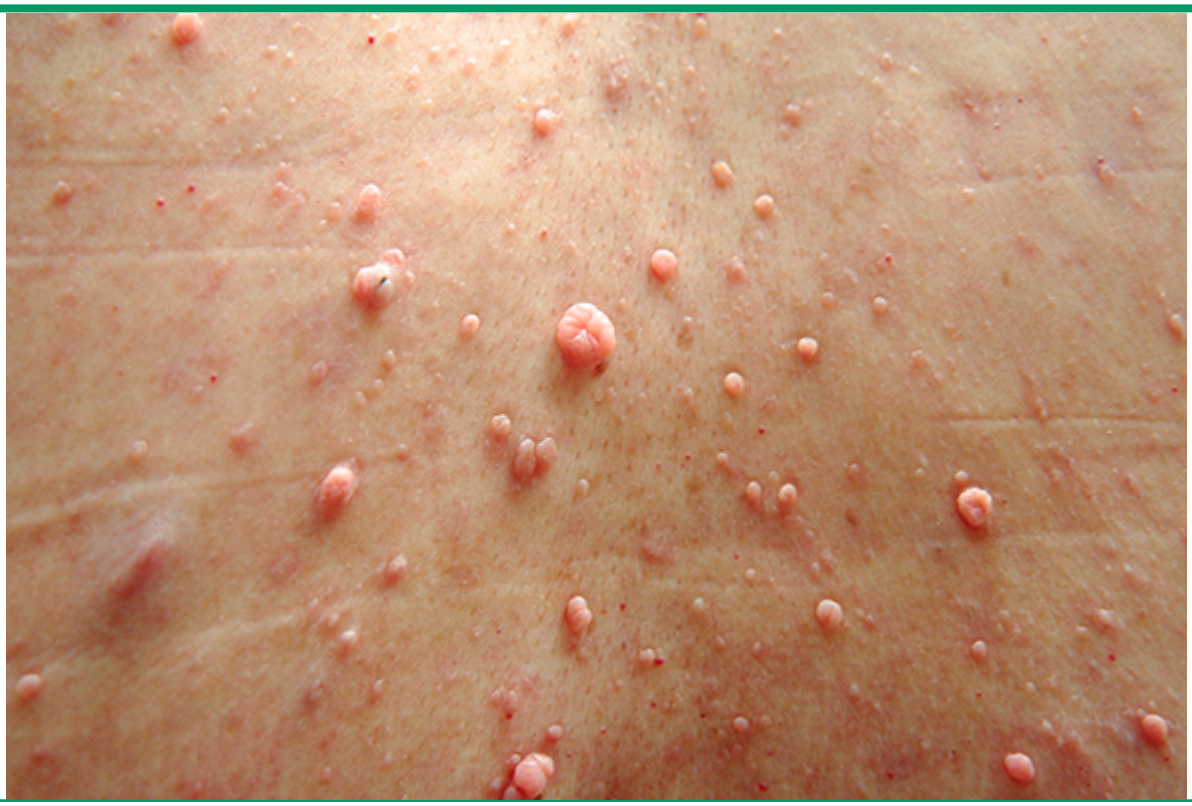
Plexiform neurofibroma in a child with neurofibromatosis type 1



Clinical picture of a child with plexiform neurofibroma of the thigh in the distribution of the femoral nerve. This patient was subsequently operated on.

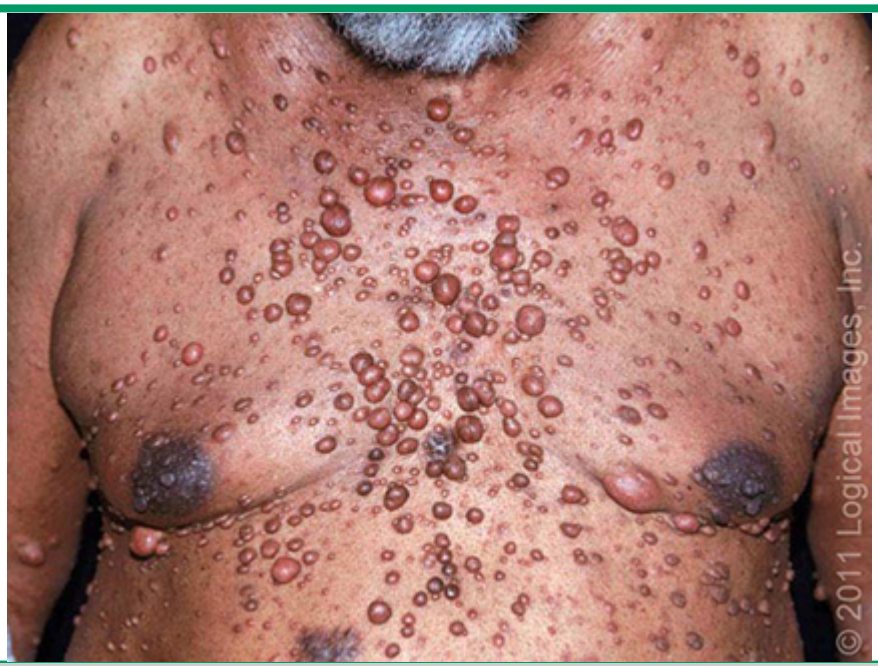
Graphic 55032 Version 9.0

Multiple cutaneous neurofibromas in a patient with neurofibromatosis 1



Graphic 96127 Version 1.0

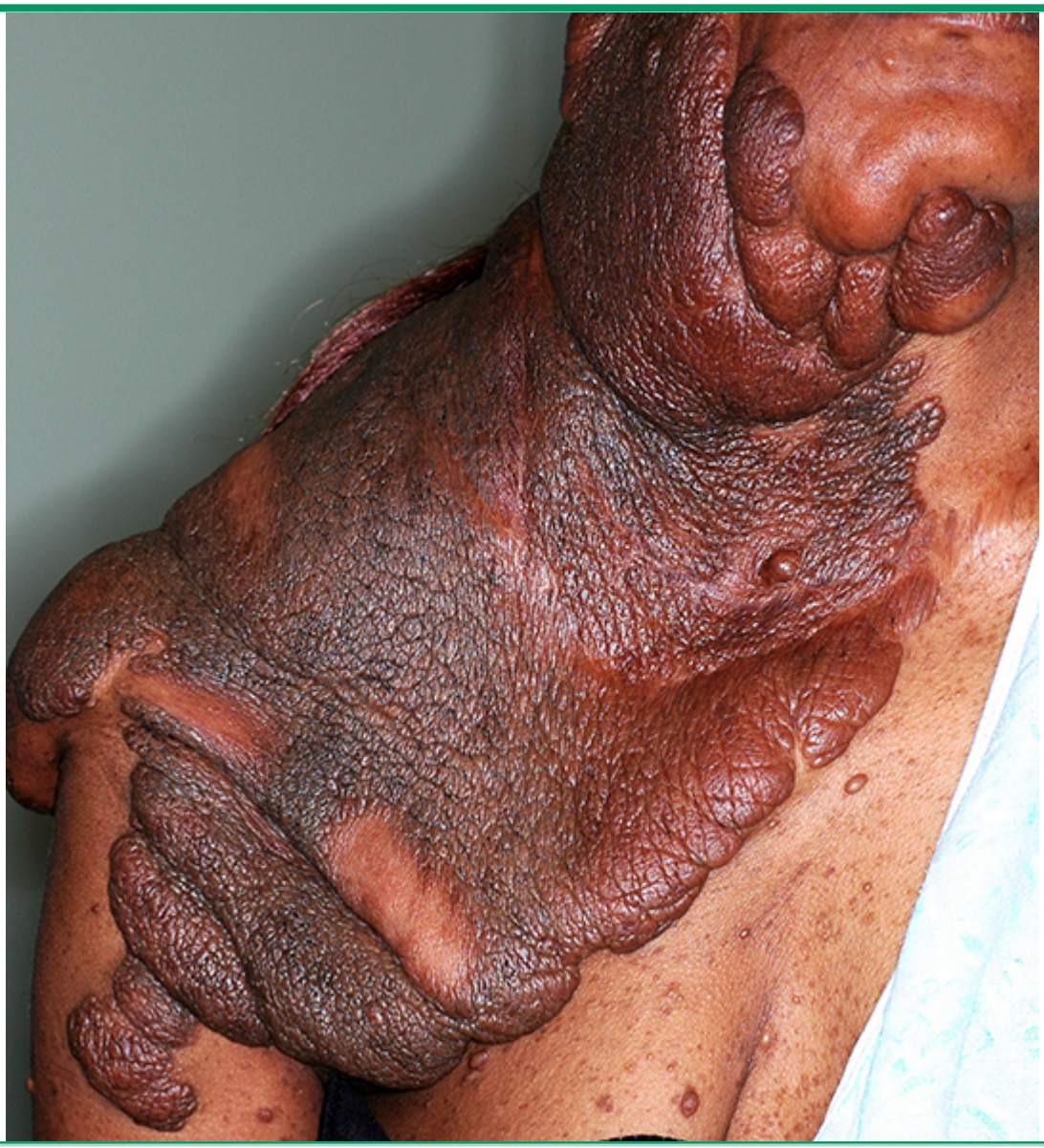
Multiple neurofibromas in an adult patient with neurofibromatosis type 1



Multiple papules and nodules consistent with neurofibromas are present on the trunk.

Graphic 82613 Version 4.0

Plexiform neurofibroma with tissue hypertrophy in a patient with neurofibromatosis 1



Lesion involves the side of the face, neck, upper chest, and shoulder.

Graphic 96123 Version 1.0

NIH diagnostic criteria for neurofibromatosis type 1

Two or more of the following clinical features must be present:
Six or more café-au-lait macules of more than 5 mm in greatest diameter in prepubertal individuals, and more than 15 mm in greatest diameter in postpubertal individuals
Two or more neurofibromas of any type or one plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic glioma
Two or more iris hamartoma (Lisch nodules)
Distinctive bony lesion, such as sphenoid dysplasia, or thinning of the long bone cortex with or without pseudoarthrosis
A first-degree relative (parent, sibling, or offspring) with NF1 based on the above criteria

NF1: neurofibromatosis type 1.

Graphic 63696 Version 3.0

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Conflict of interest policy

Epidemiology and genetics of Prader-Willi syndrome

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INTRODUCTION — Prader-Willi syndrome (PWS), also known as Prader-Willi-Labhart syndrome, is the most common syndromic form of obesity and is caused by absence of expression of the paternally active genes in a discrete region on the long arm of chromosome 15, either due to deletions from the paternal chromosome or maternal disomy. The vast majority of cases occur sporadically. In adults and children, the primary clinical features are hyperphagia, usually leading to early-onset obesity, hypogonadism, developmental delay, and characteristic facial features. In infants, the most prominent findings are hypotonia and feeding difficulties.

The epidemiology and genetics of PWS will be reviewed here. The clinical features, diagnosis, and approaches to treatment of this disorder are discussed separately. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome".)

HISTORY — In 1887, Langdon-Down described the first girl with probable Prader-Willi syndrome (PWS), manifest by mental impairment, short stature, hypogonadism, and obesity; he termed the condition polysarcia [1]. Seventy years later, Prader and colleagues reported a series of patients with similar phenotypes [2]. In 1981, Ledbetter, et al, identified microdeletions within chromosome 15 as the site for PWS [3].

EPIDEMIOLOGY — Prader-Willi syndrome (PWS) is the most common syndromic form of obesity and affects between 350,000 and 400,000 individuals worldwide. Both sexes are affected equally [4].

Although prevalence estimates differ among studies, this is likely due to using different methods for case identification, and there is no strong evidence for increased risk in specific countries or gene pools. Within the United States, the rate of prevalence has been reported between 1 in 16,062 [5] to 1 in 25,000 [6]. Outside of the United States, reported prevalence rates for PWS range from 1 per 8,000 in rural Sweden [7] to 1 per 16,000 in Western Japan [8], and a birth incidence of 1 per 27,000 in Flanders [9]. Within the United Kingdom, a lower population prevalence of 1 in 52,000 was estimated, with a proposed true prevalence of 1 in 45,000 [10]. In each of these populations, PWS represents a very small fraction of children with obesity, or even severe obesity.

The prevalence of PWS is higher in populations referred for the key clinical features. One study reported PWS in 11 percent of infants referred for hypotonia [11]. The prevalence of PWS among individuals with intellectual disability is less than 1 percent [12].

GENETICS AND PATHOGENESIS

Genetics — Prader-Willi syndrome (PWS) was the first genetic disorder attributed to genomic imprinting, meaning that the expression of the gene depends on the gender of the parent donating the gene. PWS arises due to the loss of the paternal copy of the PWS “critical region” on chromosome 15q11.2-13, whereas loss of the maternal copy of 15q11.2-13 results in Angelman syndrome. The majority of cases of PWS arise sporadically. Monozygotic twins are concordantly affected. (See "Basic principles of genetic disease", section on 'Imprinting' and "Microdeletion syndromes (chromosomes 12 to 22)",

section on '15q11-13 paternal deletion syndrome (Prader-Willi syndrome)'.)

Between 65 and 75 percent of cases of PWS arise from deletion of paternal 15q11.2-13, and 20 to 30 percent of cases arise from maternal uniparental disomy (table 1). About 2 percent of cases are caused by a defect in the imprinting center; most of these are epimutations, and a small fraction (<0.5 percent of PWS cases) are caused by deletions. Very rarely, PWS is caused by a balanced translocation (<0.1 percent of cases) [13]. Determining the type of mutation has implications for recurrence risk. (See 'Risk of recurrence in future pregnancies' below.)

There appears to be some association between the type of genetic defect and the phenotypic features seen in an individual with PWS. Individuals with uniparental disomy generally have less distinct physical features, higher intelligence quotients (IQs), and milder behavioral problems than individuals with PWS caused by deletions. However, patients with uniparental disomy are also more likely to exhibit autistic-like behaviors and psychosis [14,15].

Maternal uniparental disomy of chromosome 14 or microdeletions of the 14q32.2 imprinted region has been associated with a PWS-like phenotype, especially during infancy [16,17].

Risk of recurrence in future pregnancies — The risk of PWS in siblings of an affected child depends on the type of molecular defect causing PWS in that individual. Thus, genetic testing is important not only to establish the diagnosis of PWS, but to determine the risk of recurrence in future pregnancies.

The recurrence risk is less than one percent if the affected child has a deletion or maternal disomy, or an imprinting defect without a deletion (an epimutation). Two rare molecular defects that cause PWS are associated with a higher recurrence risk: if the affected child has a deletion of the imprinting control center (representing a small fraction of those with imprinting defects and less than 0.5 percent of PWS cases), the recurrence risk for siblings is up to 50 percent; if the affected child has a parental chromosomal rearrangement (representing less than 1 percent of PWS cases), the recurrence risk for siblings is up to 25 percent (table 1) [14,18]. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome", section on 'Genetic testing'.)

Molecular pathogenesis — Several genes have been mapped to the 15q11.2-13 region. Genetic analysis of many different individuals with PWS progressively narrowed the candidate region, and it now appears that the major manifestations of PWS are caused by paternal deficiency for SNORD116-1 (HBII-85) "small nucleolar RNA" (snoRNA) cluster [19,20]. SnoRNAs are noncoding molecules that guide post-transcriptional modification of ribosomal RNA and other small nuclear RNAs. The modifications include methylation, which is the mechanism for sex-specific imprinting. The precise mechanisms through which HBII-85 deletions cause the clinical features of PWS have not been established.

SNORD116-1 and several other snoRNA clusters are located just downstream of the SNURF-SNRPN, NDN (necdin), MAGEL2, and MKRN3 genes, explaining the apparent association of PWS with these candidate genes in previous studies [14,18]. These genes, or others in the PWS region, may account for some associated features but are unlikely to be exclusive causes. As an example, truncating mutations in MAGEL2 have been identified in four patients with autism spectrum disorder and some or all of the clinical features of PWS [21]. Also, the P gene encodes for tyrosinase-positive albinism and is likely responsible for the hypopigmentation observed in 30 percent of individuals with PWS.

MOLECULAR GENETIC TESTING — Molecular testing for Prader-Willi syndrome (PWS) is highly sensitive, as standard panels with a methylation analysis will detect over 99 percent of PWS cases [14]. For probands with a strong clinical suspicion of PWS, the testing is done in a sequence that allows identification of all potential genetic defects. (See "Clinical features, diagnosis, and treatment of Prader-Willi syndrome", section on 'Indications for genetic testing'.)

Diagnostic panel — Molecular testing is a stepwise process designed to detect the most common

molecular defects causing PWS with the fewest steps (algorithm 1).

Diagnosis — The first and most important step in molecular diagnosis is a methylation analysis, which detects abnormal parent-specific methylation imprinting within the PWS critical region on 15q11.2-13. This can be done by the Southern method using a methylation-sensitive probe (SNRPN or PW71B) or by polymerase chain reaction (PCR) using parent-specific primers.

Mutation identification — If abnormal methylation is detected, further studies are performed to determine the type of mutation, which is important for the purposes of genetic counseling:

- Deletion — (65 to 75 percent of PWS cases). Deletions of the PWS-critical region are detected by fluorescence in situ hybridization (FISH) using the probe SNRPN, or by chromosomal microarray (CMA). If FISH or CMA are positive, then other family members should be evaluated to exclude the possibility of a translocation.
- Uniparental disomy — (20 to 30 percent of PWS cases). Testing for uniparental disomy (DNA polymorphism analysis) involves microsatellite probes or single nucleotide polymorphisms (SNPs), and is conducted on the parents and affected child.
- Imprinting center defects — (2 percent of PWS cases). If microsatellite markers detect no uniparental disomy, then a mutation or deletion in the imprinting center is suspected. Further sequencing diagnostic studies may be required to determine the risk of recurrence in future pregnancies. The majority of imprinting defects are "epimutations", in which the imprint, but not the underlying DNA sequence, is abnormal; in these cases the recurrence risk for future pregnancies is low [14,22]. A minority of imprinting defects (<1 percent of PWS cases) are caused by deletions in the imprinting center, which carry a higher risk of recurrence.

SUMMARY

- Prader-Willi syndrome (PWS) is caused by the absence of expression of the paternally active genes in the "Prader-Willi syndrome-critical" region of chromosome 15q11.2-13. This dependence of the phenotype on the gender of the parent of origin is known as "genomic imprinting". (See 'Genetics' above.)
- The prevalence of PWS is approximately 1 in 25,000 live births, and both sexes are affected equally. The vast majority of cases are sporadic rather than familial. (See 'Epidemiology' above.)
- Between 65 and 75 percent of cases of PWS are caused by deletions within the PWS-critical chromosome region, and 20 to 30 percent are caused by uniparental disomy (in which the paternal copy of the gene is replaced by a second maternal copy). The remaining PWS cases are caused by defects in the imprinting process or chromosomal translocations. (See 'Genetics' above.)
- The risk of PWS occurring in a sibling of an affected individual is very low unless a deletion affecting the imprinting center is present (table 1) (less than one percent of PWS cases). (See 'Risk of recurrence in future pregnancies' above.)
- The diagnosis of PWS is made by genetic testing of individuals that exhibit typical clinical features. Genetic testing is highly sensitive and detects PWS in over 99 percent of cases. The first and most important step in molecular diagnosis is a methylation analysis, which detects abnormal parent-specific methylation imprinting within the PWS critical region on 15q11.2-13 (algorithm 1). (See 'Molecular genetic testing' above and "Clinical features, diagnosis, and treatment of Prader-Willi syndrome".)

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Topic 5875 Version 9.0

GRAPHICS

Genetic test panel for Prader-Willi syndrome

Defect causing PWS	Percent of PWS cases	Molecular findings	Risk of recurrence in future siblings, percent
Deletions of PWS-critical region on paternal 15q11-q13	65 to 75	Methylation studies abnormal	<1*
		Deletion analysis abnormal (FISH or CMA)	
Maternal uniparental disomy	20 to 30	Methylation studies abnormal	<1*
		Deletion analysis normal (FISH or CMA)	
		Uniparental disomy (UPD) analysis abnormal (DNA polymorphism analysis using microsatellite probes or SNPs). This requires testing of parents and child	
Imprinting center defects			
Epimutations without deletion	2	Methylation studies abnormal	<1
		Deletion analysis normal (FISH or CMA)	
		Uniparental disomy (UPD) analysis normal	
Deletion	<0.5	Above, plus DNA sequence analysis	Up to 50

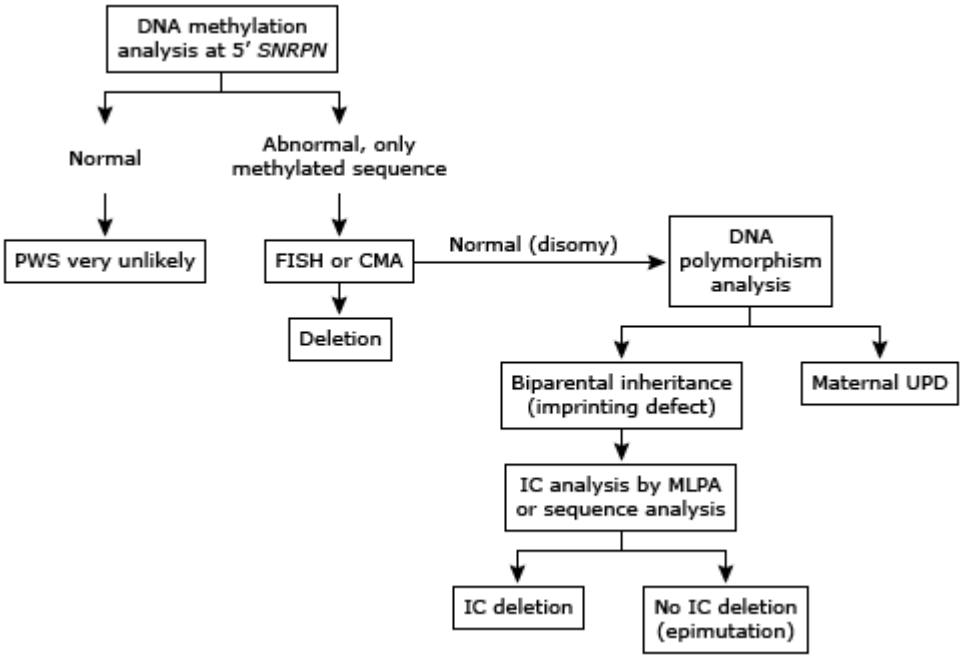
Molecular defects associated with Prader-Willi syndrome and associated risk for recurrence in siblings of an affected child.

PWS: Prader-Willi syndrome; FISH: fluorescent in-situ hybridization; CMA: chromosomal microarray; SNP: single nucleotide polymorphism.
* Rare defects with a substantial risk of recurrence in a sibling are chromosomal rearrangement (<1 percent of PWS cases) and maternal uniparental disomy (UPD) with predisposing parental translocation or marker chromosome (< 1 percent of PWS cases).

Data from Driscoll DJ, Miller JL, Schwartz S, and Cassidy SB. Prader-Willi Syndrome (1998 Oct 6 [Updated 2014 Jan 23]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1330/

Graphic 61992 Version 6.0

Algorithm for molecular diagnosis of Prader-Willi syndrome



FISH: fluorescence in situ hybridization; CMA: chromosomal microarray; UPD: uniparental disomy; IC: imprinting center; MLPA: multiplex ligation probe amplification.

Graphic 94207 Version 1.0

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Beckwith-Wiedemann syndrome

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INTRODUCTION — Beckwith-Wiedemann syndrome (BWS, MIM #130650) is a pediatric overgrowth disorder involving a predisposition to tumor development [1]. The clinical presentation is highly variable and some cases lack the characteristic features originally described by Beckwith and Wiedemann [2,3]. BWS exhibits etiologic molecular heterogeneity and some molecular alterations correlate with specific phenotypic features of BWS.

The epidemiology, genetics, pathogenesis, clinical manifestations, diagnosis, management, and prognosis of BWS are reviewed in this topic.

EPIDEMIOLOGY — Beckwith-Wiedemann syndrome (BWS) is a panethnic disorder with an estimated population prevalence of 1 in 13,700 [4]. This figure most likely represents an underestimate because milder phenotypes may not be ascertained. The prevalence is equal in males and females, with the notable exception of an increased frequency of female monozygotic twins versus male monozygotic twins [5]. BWS usually occurs sporadically (85 percent), but familial transmission occurs in approximately 15 percent of cases.

GENETICS AND PATHOGENESIS — Generally, both the maternally and paternally inherited alleles of each autosomal gene pair are expressed. Less than 100 genes across the genome are imprinted and expressed monoallelically in a parent of origin-specific manner (figure 1). That is, for a given imprinted gene pair, one parental allele is consistently expressed, whereas the other allele is silenced. Genomic imprinting is regulated by epigenetic mechanisms. These include noncoding RNAs and chemical modifications extrinsic to the primary nucleotide sequence, such as DNA methylation and histone modifications. Different DNA methylation and histone modification states underpin the expression or silencing of imprinted alleles. Thus, imprinted genes demonstrate differential DNA methylation. Imprinted genes occur in clusters referred to as imprinted domains and are regulated *in cis* (on the same chromosome) by imprinting centers (ICs). ICs are comprised of differentially methylated regions (DMRs) of DNA. (See "Overview of Mendelian inheritance", section on 'Parent-of-origin effects'.)

Deregulation of imprinted gene expression in the chromosome 11p15.5 region can result in the BWS phenotype [6-8]. The critical BWS genes in that region include insulin-like growth factor 2 (IGF2), H19, cyclin-dependent kinase inhibitor 1C (CDKN1C), potassium channel voltage-gated KQT-like subfamily member 1 (KCNQ1), and KCNQ1-overlapping transcript 1 (KCNQ1OT1, or long QT intronic transcript 1). A chromosome 11p15 molecular alteration is identified in only about 80 percent of individuals with BWS. This is due, in part, to somatic mosaicism for some of the molecular alterations.

Genomic loci outside of the chromosome 11p15.5 region have also been implicated in the etiology of BWS [9]. Molecular studies have demonstrated that NALP2 on chromosome 19 [10] can modulate imprinting in the chromosome 11p15.5 region. In addition, an infant with features of BWS was found to

have a large chromosome 7 deletion [11]. This deletion included the growth factor receptor-bound protein 10 gene (GRB10), an imprinted gene that inhibits the growth-promoting activities of insulin and insulin-like growth factors 1 and 2 by binding to the receptors for these molecules (insulin receptor and insulin-like growth factor 1 receptor). Chromosome 18q deletions were reported in individuals with some features of BWS and developmental delay [12].

Domain 1 of the chromosome 11p15.5 region is the telomeric imprinted domain that contains the imprinted genes H19 and IGF2. H19 is a nontranslated RNA that may function as a tumor suppressor gene. IGF2 is a potent fetal growth factor. IGF2 overexpression is considered to be a key determinant in the development of BWS. H19 and IGF2 are reciprocally expressed imprinted genes, with H19 maternally expressed and IGF2 paternally expressed. The expression of genes within this domain is regulated by an IC upstream of H19 called imprinting center 1 (IC1). IC1 is normally methylated on the paternal allele and unmethylated on the maternal allele. Regulation of transcription is accomplished by binding of the zinc-finger insulator protein CCCTC-binding factor (CTCF) to its consensus sequence within IC1. CTCF only binds to the unmethylated sequence (maternal allele) and interferes with downstream enhancers interacting with the IGF2 promoters [13].

Domain 2 is the centromeric imprinted domain that contains the imprinted genes CDKN1C, KCNQ1, and KCNQ1OT1. Regulation of this domain is controlled by an imprinting center, IC2, located in intron 10 of the KCNQ1 gene. IC2 is a differentially methylated region [14] that contains the promoter for KCNQ1OT1 - a noncoding RNA with regulatory function. In BWS, loss of methylation at IC2 results in biallelic expression of the normally paternally expressed KCNQ1OT1. Individuals with BWS and loss of methylation at IC2 have reduced CDKN1C expression [15]. In some BWS cases, loss of methylation at IC2 is associated with loss of methylation at multiple imprinted regions across the genome.

A number of different mechanisms can lead to BWS via either epigenetic and/or genetic alterations in the chromosome 11p15.5 imprinted domains. These modifications change the relative contributions of parental alleles [6-8] and include parent of origin specific duplications, translocations/inversions, microdeletions, microduplications, DNA methylation changes at IC1 or IC2, and uniparental disomy (UPD). UPD refers to the presence of two chromosomal regions from one parent and none from the other.

The following molecular alterations can be detected in individuals with BWS [8,16] (the percentage of cases with each type of alteration is quoted [17-20]):

- Loss of methylation at IC2 (50 percent)
- Paternal uniparental disomy 11 (20 percent)
- Gain of methylation at IC1 (5 percent)
- Mutation of CDKN1C (5 percent in sporadic cases)
- Paternal duplication, maternal inversion, or translocation involving the p15.5 band of chromosome 11 (less than 1 percent)

In some BWS cases, DNA methylation changes are associated with genomic alterations (microdeletions or microduplications); these usually involve IC1 and only rarely IC2 [18-21]. Genomic alterations with or without changes in methylation are important because of their heritability. Epigenetic alterations that involve both IC1 and IC2 generally indicate paternal UPD for a chromosomal segment including the 11p15.5 region [6,17]. Segmental UPD of chromosome 11 is thought to arise from a postzygotic somatic recombination event and therefore has a mosaic distribution in most cases.

CLINICAL MANIFESTATIONS — The hallmark features of Beckwith-Wiedemann syndrome (BWS) include omphalocele (exomphalos), macroglossia, and macrosomia (gigantism) [2,3]; however, there is significant clinical heterogeneity. Incidence figures for the specific individual clinical findings in BWS vary widely in published reports, probably representing different ascertainment biases. (See 'Diagnosis'

below.)

Findings associated with BWS include [22]:

- Macrosomia (traditionally defined as height and weight >97th percentile)
- Hemihyperplasia (asymmetric overgrowth of one or more regions of the body due to an abnormality of cell proliferation, ie, increased cell number) (picture 1)
- Macroglossia (picture 2)
- Omphalocele/umbilical hernia/diastasis recti (figure 2 and picture 3)
- Anterior linear ear lobe creases/posterior helical ear pits (picture 4)
- Visceromegaly involving one or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and pancreas
- Embryonal tumors (eg, Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma) in childhood (see "Presentation, diagnosis, and staging of Wilms tumor" and "Rhabdomyosarcoma in childhood and adolescence: Epidemiology, pathology, and molecular pathogenesis" and "Clinical presentation, diagnosis, and staging evaluation of neuroblastoma" and "Pathology of malignant liver tumors", section on 'Hepatoblastoma')
- Cytomegaly of the fetal adrenal cortex
- Renal abnormalities including structural anomalies, nephromegaly, nephrocalcinosis, later development of medullary sponge kidney
- Cleft palate (rare)
- Neonatal hypoglycemia (see "Neonatal hypoglycemia")
- Facial nevus flammeus, other vascular malformations (see "Vascular lesions in the newborn")
- Characteristic facies, including midface hypoplasia and infraorbital creases (picture 2)
- Cardiomegaly/structural cardiac anomalies; cardiomyopathy (rare)
- Advanced bone age

These and other features that are part of the phenotype are discussed in greater detail in the sections that follow.

Prenatal and perinatal — The most common features of BWS observed prenatally are macrosomia (90 percent) and polyhydramnios (50 percent) [23,24]. Fifty percent of affected infants are born preterm. The umbilical cord can be long and the placenta can average almost twice the normal weight for gestational age. Manifestations of BWS have been observed in about one-third of fetuses/liveborn infants from pregnancies complicated by placental mesenchymal dysplasia, which is distinctive cystic placental phenotype [25].

Growth — Macroglossia and macrosomia are generally present at birth, although postnatal onset of each of these features is sometimes observed [26,27]. Adult height typically remains at the upper range of normal despite rapid growth in early childhood. The growth rate usually slows around age seven to eight years of age.

When present, hemihyperplasia (sometimes mislabeled hemihypertrophy) is generally appreciated at birth, but may become more or less evident as the child grows. Hemihyperplasia may affect segmental regions of the body and/or specific organs and tissues. When several segments are involved, hemihyperplasia may be limited to one side of the body (ipsilateral) or involve opposite sides of the body (contralateral) [28].

Metabolic abnormalities — Neonatal hypoglycemia is well documented [4,29]. It poses a significant risk for developmental sequelae if severe and undetected or untreated. In those pregnancies deemed at increased risk for BWS either because of a positive family history or detection of fetal omphalocele on ultrasound, the newborn should be evaluated for hypoglycemia. Most cases of hypoglycemia are mild

and transient; however, rarely, hypoglycemia can persist and be refractory to treatment. Delayed onset of hypoglycemia (ie, beyond the first two weeks of life) is also rarely observed.

Other less common endocrine/metabolic/hematologic findings include hypothyroidism, hyperlipidemia/hypercholesterolemia, and polycythemia [29,30].

Structural anomalies — Anterior abdominal wall defects, including omphalocele, umbilical hernia, and diastasis recti, are common [1,8].

Much of the information regarding cardiovascular problems in BWS is anecdotal. Cardiomegaly is commonly detected in infancy if a chest x-ray is done, but this typically resolves without treatment. There are rare reports of cardiomyopathy.

Renal anomalies include medullary dysplasia, duplicated collecting system, nephrocalcinosis, nephrolithiasis, medullary sponge kidney, cystic changes, and nephromegaly [31-35]. Hypercalciuria can be found in children with BWS even in the absence of renal abnormalities visualized by ultrasound [31].

Rare cases of posterior fossa brain abnormalities have been reported in patients with BWS who have involvement of the centromeric imprinted domain (domain 2) [36]. (See 'Genetics and pathogenesis' above and 'Development' below.)

Neoplasia — Children with BWS have an increased risk of mortality associated with neoplasia. Most commonly observed are Wilms tumor and hepatoblastoma, but also neuroblastoma, adrenocortical carcinoma, and rhabdomyosarcoma, as well as a wide variety of other tumors, both malignant and benign [37]. The estimated risk for tumor development in children with BWS is 7.5 percent, with a range of risks between 4 percent and 21 percent [4,23,24,37-42]. This increased risk for neoplasia is concentrated in the first eight years of life. Tumor development is uncommon in affected individuals older than eight years of age.

Development — Development is usually normal in children with BWS unless there is a chromosome abnormality [36,43] or a history of hypoxia or significant, untreated hypoglycemia. Neurobehavioral issues, such as autism spectrum disorder, have been reported with increased frequency in children with BWS [44]; however, these cases were ascertained by parental report only. Additional studies, including formal neurodevelopmental assessments, are needed to assess the frequencies of these issues in BWS.

PHENOTYPE-(EPI)GENOTYPE CORRELATIONS — A number of genetic and/or epigenetic alterations in growth regulatory genes on chromosome 11p15.5 are associated with specific phenotype-(epi)genotype correlations and different inheritance risks.

Tumor development — Individuals with uniparental disomy (UPD) of 11p15.5 or gain of methylation at the H19 imprinting center (IC1), carry the highest risk of developing Wilms tumor or hepatoblastoma (approximately 30 percent) [6,45-50]. Those with loss of maternal methylation at IC2 also carry a moderately increased risk for tumors other than Wilms tumor (approximately 5 percent). Individuals with mutations in cyclin-dependent kinase inhibitor 1C (CDKN1C) appear to have the lowest risk of tumor formation, with only a small number of cases of neuroblastoma reported. In addition, those with cytogenetically visible alterations have a very low risk for tumor development. Of note, children clinically suspected to have, or diagnosed with, Beckwith Wiedemann syndrome (BWS) who have no detectable molecular alteration have a significant risk for tumor development of approximately 20 percent. This is likely due to somatic mosaicism for chromosome 11p15.5 UPD or other molecular anomalies.

Hemihyperplasia — Somatic mosaicism for UPD of chromosome 11p15.5 resulting in methylation alterations at IC2 or IC1 is associated with hemihyperplasia [7,51]. Less frequently, alterations in IC1 and IC2 are also seen in hemihyperplasia.

Omphalocele — IC2 alterations and CDKN1C mutations are associated with omphalocele [52].

Cleft palate — Only CDKN1C mutations have been reported in patients with BWS who have cleft palate [53,54].

Developmental delay — Developmental delay is associated with cytogenetically detectable duplications involving the paternal copy of chromosome 11p15.5 [7,43,55], although it may also be due to significant neonatal hypoglycemia or other perinatal complications, such as prematurity. In addition, developmental delay with posterior fossa brain abnormalities occur rarely in association with IC2 alterations or CDKN1C mutations [36].

Severe BWS phenotype — Cases of severe BWS have been reported in association with very high levels of somatic mosaicism for paternal UPD for chromosome 11p15.5 [56,57].

Positive family history — Most familial cases of BWS are due to mutations in CDKN1C or microdeletions of IC1 or, very rarely, IC2 microduplications [7,17,19,20,53,58-60]. Vertical transmission of BWS can also occur with chromosome 11p15.5 translocations or inversions.

Female monozygotic twins — There is a larger than expected number of female monozygotic twins discordant for BWS [5]. The affected females usually demonstrate loss of methylation at IC2. In contrast, the less frequently observed male monozygotic twins show a broad spectrum of BWS-associated molecular alterations [56].

Subfertility/assisted reproductive technology — Subfertility with or without use of assisted reproductive technology (ART) is associated with an increased risk of BWS cases due to loss of methylation at IC2 [51,61-63]. It is not clear what specific aspects of subfertility or its treatment drive this association.

DIAGNOSIS — No consensus diagnostic criteria exist for Beckwith-Wiedemann syndrome (BWS), although the presence of a subset of characteristic findings is used to confer a clinical diagnosis. The phenotype of BWS is highly variable and may include as few as two of the recognized clinical features. Approximately 15 percent of cases of BWS are familial. Thus, targeted information should be elicited regarding family history, including parental features during childhood, since these may normalize over time. In addition, type of conception (ie, natural versus assisted conception) and pregnancy-related findings, such as polyhydramnios, placental mesenchymal dysplasia [25], and prematurity should be ascertained. (See 'Clinical manifestations' above and 'Epidemiology' above.)

Notably, children with mild phenotypes (eg, macroglossia and umbilical hernia) are still at increased risk for tumor development. Thus, there should be a high index of suspicion when evaluating children with minimal clinical features in the BWS phenotypic spectrum, particularly if there is a positive family history (one or more family members with a clinical diagnosis of BWS or a history or features suggestive of BWS). In such cases anticipatory medical management (eg, tumor surveillance) and molecular testing should be considered (see 'Management' below). As noted above, tumor surveillance should not be discontinued in the absence of a detectable molecular alteration.

Genetic testing — Methylation-sensitive multiplex ligation probe analysis (MS-MLPA) is the most robust method clinically available for detecting the majority of epigenetic and genetic etiologies associated with BWS. MS-MLPA detects microdeletions/microduplications and alterations in gene dosage and DNA methylation including uniparental disomy (UPD) [58]. Somatic mosaicism associated with UPD may lead to weak signals on MS-MLPA. UPD can be confirmed by analysis of short tandem repeats when it is suggested by methylation alterations at both imprinting centers 1 and 2 (IC1 and IC2). In addition, failure to detect a methylation alteration or UPD in one tissue (usually leukocytes) is not conclusive, especially in cases involving hemihyperplasia. Thus, testing of at least two tissues/cell populations, for example leukocytes and skin, should be considered.

Karyotype analysis is required to detect the rare *de novo* and maternally transmitted

translocations/inversions and will also detect paternally derived duplications of chromosome 11p15.5 associated with BWS. Translocations/inversions almost always disrupt the gene KCNQ1 [14] and are not usually detectable by MS-MLPA because most do not demonstrate DNA copy number changes or DNA methylation changes.

DNA sequencing is required to detect genomic alterations in the cyclin-dependent kinase inhibitor 1C (CDKN1C) gene associated with BWS. CDKN1C mutations are seen both sporadically (5 percent of cases) and in autosomal dominant pedigrees modified by preferential parent of origin-specific transmission (40 percent of cases) [54].

Prenatal diagnosis — Indications for prenatal testing may include a previous child with BWS or a positive family history of BWS. Prenatal testing may be undertaken by chorionic villus sampling (CVS) or amniocentesis, if the cytogenetic or genomic abnormality (eg, microdeletion, CDKN1C mutation) in the affected family member is known. Epigenetic analysis of chromosome 11p15.5 in amniocytes is sufficiently reliable for prenatal diagnosis [64]. However, analysis of methylation alterations in CVS requires further validation before this can be offered as a clinical test.

Prenatal testing via amniocentesis may also be indicated for BWS-associated findings detected on fetal ultrasound, such as omphalocele, renal enlargement, or macroglossia [65]. A follow-up study of apparently isolated fetal omphalocele (ie, no known family history of BWS and no additional findings detected on fetal ultrasound) reported BWS in 20 percent of cases based upon subsequent clinical evaluation and/or molecular testing [66]. Thus, molecular testing is suggested in such cases.

Prenatal screening is an option if the molecular defect is not known or if invasive prenatal testing is not undertaken. This screening includes measurement of maternal serum alpha fetoprotein (AFP) to detect abdominal wall defects and ultrasound evaluation for assessment of growth parameters that may become advanced for gestational age (usually after 24 weeks), abdominal wall defects, organomegaly, renal abnormalities, cleft palate, cardiac anomalies, and macroglossia. Nuchal translucency measurements between 10 to 14 weeks can be informative [67] and detailed ultrasound is typically performed at 18 to 20 weeks and again at 25 to 32 weeks gestation.

DIFFERENTIAL DIAGNOSIS — The presentation of a newborn with large growth parameters (table 1 and table 2), macroglossia and/or hypoglycemia, should prompt a comprehensive clinical examination followed by relevant investigations. A number of endocrine disorders and overgrowth syndromes should be considered in the differential diagnosis, including maternal diabetes mellitus and congenital hypothyroidism. (See "Infant of a diabetic mother".)

Several genetic syndromes have features in common with Beckwith-Wiedemann syndrome (BWS), but can be distinguished by genetic testing, ancillary tests (eg, brain imaging, molecular, and/or biochemical testing), and follow-up for the appearance of defining features. The differential diagnosis includes:

- Simpson-Golabi-Behmel syndrome (type 1 MIM #312870, type 2 MIM #300209)
- Costello syndrome (MIM #218040)
- Perlman syndrome (MIM #267000)
- Sotos syndrome (MIM #117550)
- Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome, MIM #253200)

For cases involving asymmetry as an isolated finding, it is important to determine if the asymmetry represents overgrowth (hemihyperplasia) [28,68-70] or decreased growth (hemihypoplasia), since the latter is not associated with an increased risk for tumor development. Molecular testing may provide clarification in that hemihypoplasia may be associated with hypomethylation of imprinting center 1 (IC1) as opposed to hemihyperplasia with hypermethylation of IC1 or chromosome 11p15.5 uniparental disomy (UPD) [71]. (See 'Growth' above and 'Genetic testing' above.)

MANAGEMENT

Evaluation following initial diagnosis — The following evaluations are advised to establish the extent of disease in an individual diagnosed with Beckwith-Wiedemann syndrome (BWS):

- Assessment for airway sufficiency in the presence of macroglossia.
- Evaluation by a feeding specialist if macroglossia causes significant feeding difficulties.
- Assessment of neonates for hypoglycemia; evaluation by a pediatric endocrinologist if hypoglycemia is severe or persists beyond the first few days of life.
- Abdominal ultrasound examination to assess for organomegaly, structural abnormality, and tumors. A baseline magnetic resonance imaging (MRI) or computed tomography (CT) examination of the abdomen to screen for tumors may be considered at the time of diagnosis or later [72].
- Comprehensive cardiac evaluation including electrocardiogram (ECG) and echocardiogram prior to any surgical procedures or when a cardiac abnormality is suspected on clinical evaluation.
- Alpha fetoprotein (AFP) assay at the time of initial diagnosis to assess for hepatoblastoma.

Treatment of manifestations — The following measures are advised for disease manifestations that may appear throughout the course of the disease:

- Prompt treatment of hypoglycemia to reduce the risk of central nervous system complications. The onset of hypoglycemia is variable, and therefore parents should be informed of the symptoms of hypoglycemia so that they know when to seek appropriate medical attention for their child.
- Abdominal wall repair soon after birth for omphalocele. This surgery is generally well tolerated.
- Management of difficulties arising from macroglossia:
    - Anticipation of difficulties with endotracheal intubation [73].
    - Pulmonary assessment, possibly including sleep study, to address concerns regarding potential sleep apnea.
    - Management of feeding difficulties using specialized nipples, such as the longer nipple recommended for babies with cleft palate or, rarely, short-term use of nasogastric tube feedings.
    - Follow-up by a craniofacial team including plastic surgeons, orthodontists, and speech pathologists familiar with the natural history of BWS. Tongue growth slows over time and jaw growth can accelerate to accommodate the enlarged tongue. Some children benefit from tongue reduction surgery; however, surgical reduction typically impacts tongue length not thickness. Residual cosmetic, orthodontic, and speech issues may require further assessment/treatment [74].
- Consultation with an orthopedic surgeon if hemihyperplasia results in a significant difference in leg length. Surgery may be necessary during early puberty to close the growth plate of the longer leg in order to equalize the final leg lengths.
- Referral to a craniofacial surgeon if facial hemihyperplasia is significant.
- Treatment of neoplasia following standard pediatric oncology protocols.
- Standard interventions, such as infant stimulation programs, occupational and physical therapy, and individualized education programs for children with developmental delay.
- Referral of children with structural renal or gastrointestinal tract abnormalities to the relevant specialists.

Surveillance — The following surveillance is advised in patients with BWS:

- Monitor for hypoglycemia in the first few days of life by random blood glucose measurements to detect asymptomatic hypoglycemia and have a higher index of suspicion for/awareness of clinical signs of hypoglycemia.
- Screen for developmental issues as part of routine childcare, especially when there is a history of hypoglycemia, prematurity, or evidence of chromosome 11p15.5 duplication.
- Screen for embryonal tumors [75]. This screening protocol outlined should be applied to all children with BWS diagnosed either clinically and/or molecularly. We do not recommend modifying this protocol based upon different tumor risks ascribed to the various molecular subtypes of BWS. This type of stratification may be possible in the future once more data are available.
    - Abdominal ultrasound examination every three months until age eight years [41,72,76,77].
    - Measure serum AFP concentration every two to three months in the first four years of life for early detection of hepatoblastoma [76]. AFP serum concentration may be mildly elevated in children with BWS in the first year of life in the absence of a hepatoblastoma [78]. If the AFP is elevated in the absence of a suspicious lesion on imaging, follow-up measurement of serum AFP concentration plus baseline liver function tests four to six weeks later can be used to determine the trend in serum AFP concentrations over time. If a decline in AFP concentration is not seen, it is appropriate to refer to an oncologist and/or undertake an exhaustive search for an underlying tumor [79].
    - Periodic chest x-ray and urinary homovanillic acid (HVA) and vanilmandelic acid (VMA) assays to screen for neuroblastoma have been suggested, but have not been incorporated into most screening protocols because of their low yield.
- Assess for renal anomalies as part of the abdominal ultrasound examination for embryonal tumor screening in patients eight years of age and under. Assess individuals over eight years of age through adolescence with annual or biannual renal ultrasound examination to identify those requiring further evaluation/management, since nephrocalcinosis, nephrolithiasis, and medullary sponge kidney develop at a later age.
- Consider measurement of urinary calcium/creatinine ratio annually or biannually, since it may be abnormal in individuals with renal disease who have normal renal ultrasound examinations [31].
- Consideration should be given to offering tumor surveillance for those cases presenting with a "mild" phenotype (see 'Diagnosis' above). Additionally, tumor surveillance is suggested for the clinically unaffected monozygotic twin of a child with BWS because of the possibility of low-level mosaicism and shared-fetal circulation.

Genetic counseling — Genetic counseling regarding BWS etiology and recurrence risk (ie, risk of a subsequent affected child) is most accurate if data from a complete diagnostic evaluation are available, including molecular testing. These data include family history, clinical findings, karyotype, methylation-sensitive multiplex ligation probe analysis (MS-MLPA), and cyclin-dependent kinase inhibitor 1C (CDKN1C) mutation analysis if indicated. (See "Basic principles of genetic counseling for the obstetrical provider".)

The recurrence risk is low if molecular testing reveals uniparental disomy (UPD) or a methylation alteration in the absence of a transmissible genomic alteration. Information regarding recurrence risk for some of the molecular subtypes remains theoretical, since there is a paucity of confirmatory empiric data. This is especially relevant when providing genetic counseling for affected individuals with theoretically low recurrence risk (eg, UPD for chromosome 11p15, methylation alterations at imprinting

center 2 [IC2]). Molecular testing is typically not indicated for parents or other family members when UPD is found, since these cases arise via postzygotic somatic recombination. Parental studies are recommended if genomic alterations are found (eg, karyotype abnormalities, CDKN1C mutations, or microduplications or microdeletions of the chromosome 11p15.5 region).

Molecular alterations that are associated with significant recurrence risk include:

- Maternal transmission of chromosome 11p15.5 translocation/inversion [4]
- Maternal transmission of CDKN1C mutation [59]
- Chromosome 11p15.5 duplication of paternal origin [55]
- 11p15.5 microdeletion/microduplication [19]

Molecular testing or chromosome analysis is indicated for both parents and potentially other family members if either a translocation or inversion involving chromosome 11p15.5 or a CDKN1C mutation is found in the proband. The recurrence risk is 50 percent for CDKN1C mutations and for translocations or inversions involving chromosome 11p15.5 if the transmitting parent is the mother [59]. The risk is low if the CDKN1C mutation is found in the father, however, at least one case of BWS and paternal transmission of a CDKN1C mutation has been reported in the literature [60]. The recurrence risk for paternally derived duplications is not specifically defined, but is probably significant if the father carries a translocation. Familial transmissions involving microdeletions of IC1, and rarely of IC2, have been reported. Thus, parental testing is indicated when these alterations are identified [19,20,58].

The recurrence risk can be estimated empirically in the case of a positive family history in the absence of an abnormal genetic test result. Information incorporated into such estimates includes the sex and potential carrier status of the transmitting parent. All potential etiologies consistent with the positive family history should be considered. The recurrence risk for BWS in cases where there is no identified cause may be as high as 50 percent. Gonadal mosaicism remains a possibility, although it has not been reported to date. It should be considered when there is more than one affected offspring and/or the parents are not found to carry a transmissible microdeletion or mutation associated with BWS.

PROGNOSIS — Infants with Beckwith-Wiedemann syndrome (BWS) are at increased risk for mortality mainly due to complications of prematurity, macroglossia, hypoglycemia, tumors, and, rarely, cardiomyopathy. A previously reported mortality rate of 20 percent may be an overestimate given the improvements in syndrome recognition and treatment [4,24,57]. Prognosis is generally favorable after childhood. However, complications in adolescence/adulthood can occur (eg, renal medullary dysplasia, subfertility in males). Such issues may be associated with specific molecular subtypes [80]. (See 'Phenotype-(epi)genotype correlations' above.)

SUMMARY

- Beckwith-Wiedemann syndrome (BWS) is a pediatric overgrowth disorder involving a predisposition to tumor development. (See 'Introduction' above.)
- BWS usually occurs sporadically, but familial transmission occurs in approximately 15 percent of cases. (See 'Epidemiology' above.)
- Deregulation of imprinted genes within the chromosome 11p15.5 region results in the BWS phenotype. However, a chromosome 11p15 molecular alteration is identified in only about 80 percent of individuals with BWS. This may be due to low-level somatic mosaicism in the tissue sampled for testing or to other genomic loci that are probably involved in the etiology of BWS. (See 'Genetics and pathogenesis' above.)
- The hallmark features of BWS are omphalocele (exomphalos), macroglossia, and macrosomia (gigantism). However, the clinical presentation is highly variable, and some cases lack these

characteristic features. (See 'Clinical manifestations' above.)

- A number of genetic and/or epigenetic alterations in growth regulatory genes on chromosome 11p15.5 are associated with specific phenotype-(epi)genotype correlations and different recurrence risks. (See 'Phenotype-(epi)genotype correlations' above.)
- No consensus diagnostic criteria exist for BWS, although the presence of a subset of associated findings are used to confer a clinical diagnosis. Molecular testing can then be incorporated to determine the precise genetic defect and confirm the diagnosis. Methylation-sensitive multiplex ligation probe analysis (MS-MLPA) is the most robust method available for detecting the majority of epigenetic and genetic etiologies associated with BWS. Prenatal testing is available. (See 'Diagnosis' above.)
- The differential diagnosis includes both genetic and nongenetic causes of macrosomia (table 1 and table 2). (See 'Differential diagnosis' above.)
- Initial evaluation includes assessment for hypoglycemia, airway sufficiency, feeding difficulties, and screening for tumors. Surveillance includes monitoring for hypoglycemia, tumors, developmental issues, and renal disease. (See 'Management' above.)
- Cases involving uniparental disomy (UPD) arise from postzygotic somatic recombination and are therefore not known to be associated with a significantly increased risk for recurrence. Parental studies are recommended if genomic alterations are found (eg, karyotype abnormalities, cyclin-dependent kinase inhibitor 1C [CDKN1C] mutations, or microduplications or microdeletions of the chromosome 11p15.5 region) and these test results are then incorporated into estimates of recurrence risks. (See 'Genetic counseling' above.)
- Infants with BWS are at increased risk for mortality mainly due to complications of prematurity, macroglossia, hypoglycemia, tumors, and, rarely, cardiomyopathy. The increased risk for neoplasia is concentrated in the first eight years of life. Thus, prognosis is generally favorable after early childhood. (See 'Prognosis' above.)

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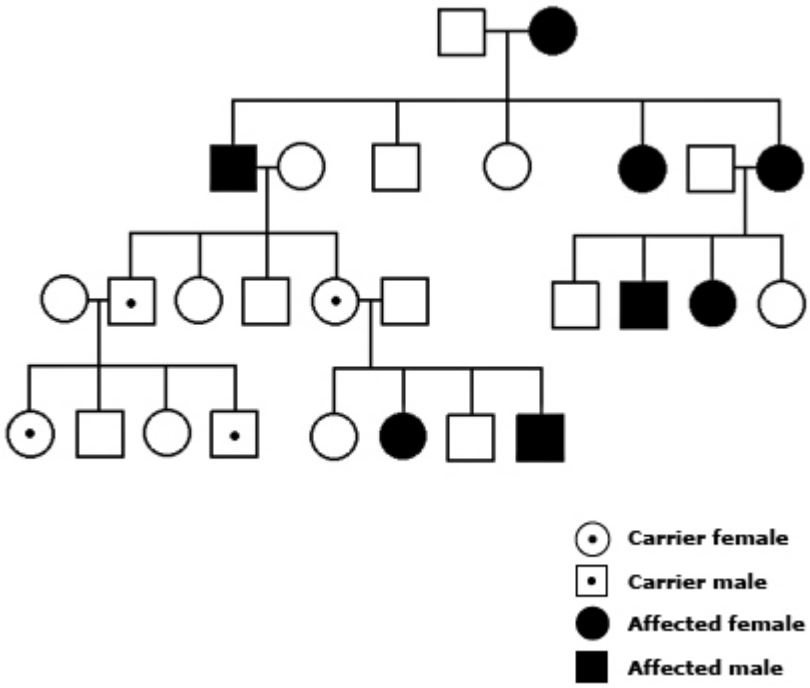
Topic 13555 Version 9.0

GRAPHICS

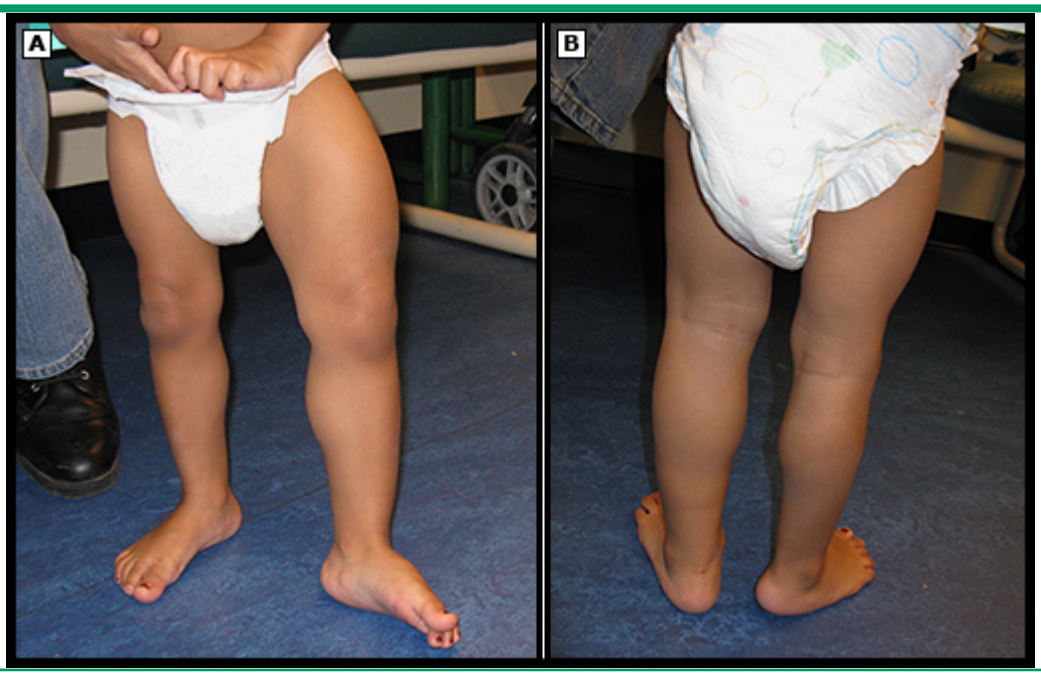
Example of a pedigree showing imprinting



Imprinting. An example of a pedigree demonstrating genomic imprinting is presented. At this locus, the paternal allele is normally repressed and the maternal allele is normally expressed. Approximately 50 percent of offspring of affected women are themselves affected, whereas no offspring of affected men are affected. However, the grandchildren of affected males will be affected if the mutation is passed through a carrier (unaffected) daughter, but not if passed through a carrier son.

Graphic 54712 Version 6.0

Hemihyperplasia in a patient with Beckwith-Wiedemann syndrome

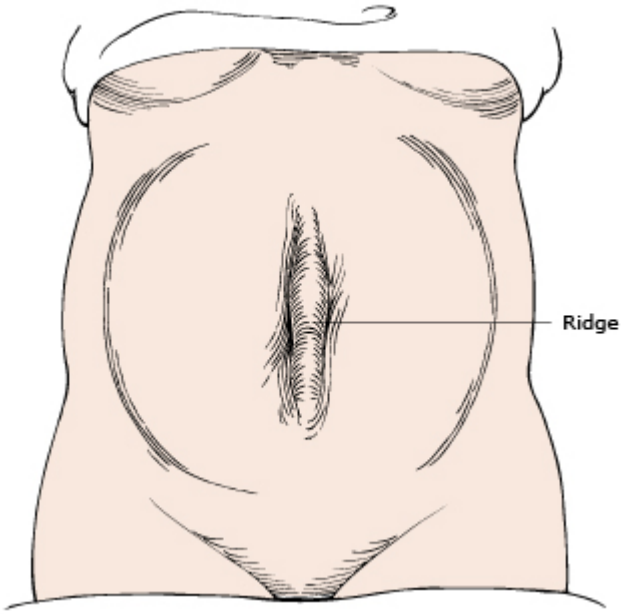


Graphic 66409 Version 1.0

Macroglossia in a patient with Beckwith-Wiedemann syndrome

Graphic 80654 Version 1.0

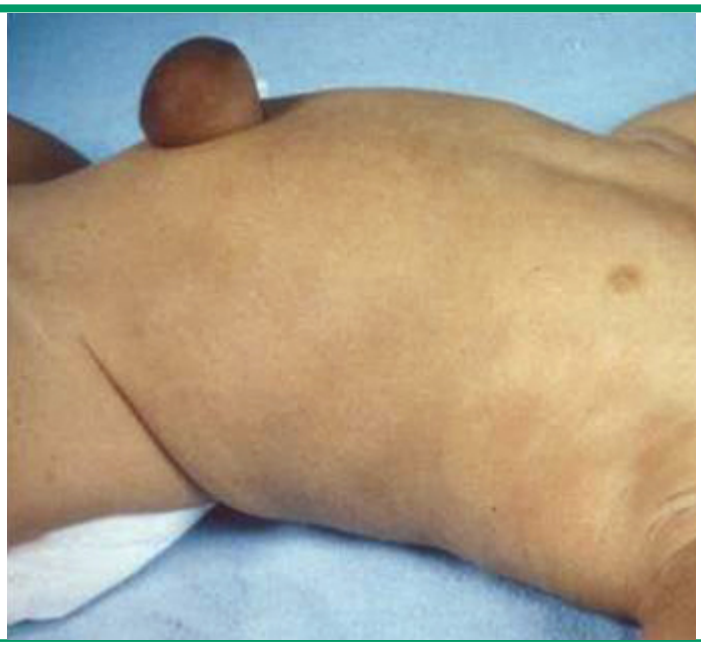
Diastasis recti



Diastasis recti occurs when bowel protrudes through a separation between the two rectus abdominis muscles. It appears as a midline ridge. The bulge may appear only when client raises head or coughs. The condition is of little significance.

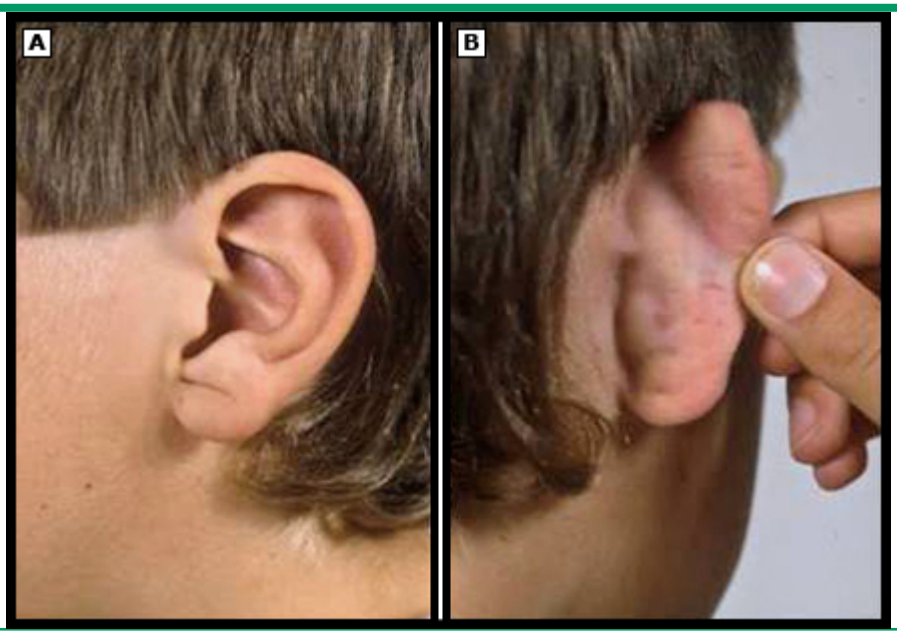
Graphic 69049 Version 2.0

Umbilical hernia in a patient with Beckwith-Wiedemann syndrome



Graphic 81489 Version 1.0

Anterior ear lobe crease and posterior helical ear pits in a patient with Beckwith-Wiedemann syndrome



Graphic 77586 Version 1.0

Risk factors for fetal macrosomia

Diabetes
Obesity
Multiparity
Prolonged gestation
Male fetus
Previous delivery of an infant weighing more than 4000 g
Race and ethnicity
Genetic syndromes

Courtesy of George T Mandy, MD.

Graphic 53324 Version 1.0

Differential diagnosis of Beckwith-Wiedemann syndrome - Genetic disorders

Syndrome	Diagnostic testing	Main characteristics
Simpson-Golabi-Behmel syndrome	Yes	Macrocephaly, coarse facies, ocular hypertelorism, broad flat nose, macrostomia, macroglossia, cleft lip, nail hypoplasia, macrosomia, visceromegaly, skeletal abnormalities, increased risk for embryonal tumor(s)
Costello syndrome	Yes	Coarse facies, loose skin, diffuse hypotonia, joint laxity, sparse fine hair, failure to thrive, increased risk for malignant solid tumors
Perlman syndrome	No	Macrosomia, unusual facies (depressed nasal bridge, anteverted upper lip, mild micrognathia), intellectual disability, increased risk for Wilms tumor
Sotos syndrome (cerebral gigantism)	Yes	Macrosomia, macrocephaly, ventriculomegaly, typical facial appearance, advanced bone age, intellectual disability
Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)	Yes	Macrocephaly, mildly coarse facies, skeletal abnormalities, short stature

Graphic 62919 Version 1.0

Disclosures

Disclosures: **Brian Chung Hon-Yin, MD, FCCMG** Nothing to disclose. **Cheryl Shuman, MS, CGC** Nothing to disclose. **Sanaa Choufani, PhD** Nothing to disclose. **Rosanna Weksberg, MD, PhD, FRCPC, FCCMG, 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