

Nadir hastalıkların tanısında yeni nesil dizi analizi uygulamalarına klinik yaklaşım: Sonuçların değerlendirilmesi

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Genetik Hastalıklar Tanı Merkezi

Tıbbi Genetik Eğitim Günleri
Ankara, 30.04.2016

- “**Nadir hastalık**” terimi dünyada yaygın hastalıklara oranla sayıca çok daha az insanı etkileyen, ama sonuçları masum olabildiği gibi en az diğer hastalıklar kadar ciddi veya hayatı tehdit edici de olabilen bir grup hastalığı tanımlamaktadır.

- Avrupa'da, 2000'de 1 kişide görülen hastalıklar nadir kabul edilmektedir.
- Nadir hastalıkların sanılanın aksine tek tek bakıldığında nadir ancak toplamda oldukça sık görülen bir problem olduğu dünyada 250 – 300 milyon, Türkiye'de ise yaklaşık 5 milyon insanı etkilediği tahmin edilmesi ile anlaşılabilmektedir.

- Nadir hastalıklarda Tıbbi genetiğinin en önemli görevlerinden biri patojen DNA dizisi değişimlerinin tespitidir.
- Yeni nesil dizileme (NGS) teknikleri yüzlerce aday gen, linkaj analizi ya da tüm ekzom sekanslama çalışmalarına olanak sağlamıştır.
- Analizler sonucunda çok sayıda varyasyon saptanabilmekte ancak bu varyasyonların hastalık nedeni olup olmadığı bilinmemektedir.
- Yakın zamanda yapılan çalışmalar sonucunda her bir bireyin genomunda her bir megabazda 1000 tane olmak üzere toplamda 3.500.000 varyasyon saptanmıştır.

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DNA ANALYSIS

Nadir genetik hastalıklar, yeni nesil dizi analizi uygulamaları arasında, sanger dizi analizine kıyasla, en avantajlı alanlardan biridir.

Bunun sebepleri arasında nadir genetik hastalıkların:

1. Nadir olduklarından dolayı haklarında az bilgiye sahip olunması
2. Genel olarak yaygın görülen mutasyonlarının olmaması
3. Önemli bir kısmının birden fazla genden oluşması
4. Keşfedilmiş genleri olmayan nadir genetik hastalıkların bulunması
5. Konvansiyonel yaklaşım sonucunda bir sonuca varılamayınca ekzom veya tüm genom dizi analizine olan ihtiyaç

- Bu sebeplerden dolayı yeni nesil dizileme teknolojisi nadir hastalıkların araştırılmasında çok büyük bir kapı açmıştır; eskiden mümkün olmayan çalışmalar mümkün hale gelmiş, mümkün olanlar da çok daha ucuza ve hızlı bir şekilde yapılabilir hale gelmiştir.
- Ancak yine de teori ve pratikte dezavantajları ve dikkat edilmesi gereken hususları bulunmaktadır. Bu hususlar sırf nadir hastalıklar ile ilgili değil, genel olarak yeni nesil dizi analizi ile ilgili olmakla beraber, nadir hastalıkların yukarıda bahsedilen hassasiyetinden dolayı bu alanda biraz daha önem kazanan hususlardır.

Dezavantajlar ve dikkat edilmesi gereken hususlar arasında şunlar sayılabilir:

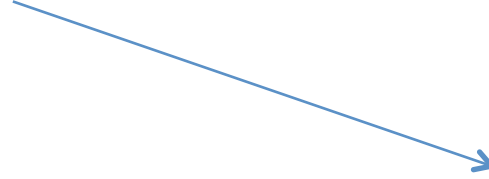
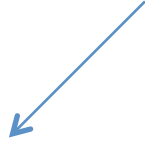
- Amplikon sekansının PCR bağımlı olması ve PCR kaynaklı sıkıntılar
 - Polimeraz hataları (yanlış baz bağlama, tekrar bölgeleri)
 - Asimetrik amplifikasyon
 - heterozigot büyük delesyonlar
- Alignment hataları
 - delesyon bölgeleri hataları
 - benzer bölgelerdeki hatalar (Alu tekrarları vb, pseudogenler)
- GC yüksek bölgelerdeki sıkıntılar
- Teknoloji kaynaklı hatalar
 - Homopolimer problemi
 - sinyal düzeltme problemi

- Çıkan varyasyonların nasıl değerlendireceğiz?
- Nasıl bir algoritma izlemeliyiz?
- Sonuca gitmemizde hangi veritabanları faydalı?
- Rutinde hangilerini kullanıyoruz?
- Bu veritabanlarına ne kadar güvenmeliyiz?
- En sağlıklı sonuca nasıl ulaşırız?

Laboratuvar Sonucu

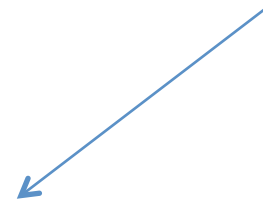
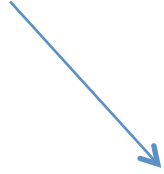


Varyant Değerlendirilmesi



Bulunan varyasyon literatürde var mı?
Kendi Laboratuvarınızda daha önce tespit edildi mi?

Populasyon frekansı ne kadar?



İnsiliko Değerlendirme

Bulunan varyasyon literatürde var mı?

- GeneReviews <http://www.ncbi.nlm.nih.gov/books/NBK1116/>
- Pubmed <http://www.ncbi.nlm.nih.gov/pubmed>
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GeneReviews currently comprises 609 chapters.

Published exclusively online, each chapter is: (1) reviewed for accuracy by editors expert in clinical genetics, laboratory genetics, and [genetic counseling](#); (2) [peer-reviewed](#) by internationally acknowledged subject experts; (3) [updated](#) by the author(s) in a formal comprehensive process every two to three years or as needed; and (4) [revised](#) by the author(s) or editorial staff whenever significant changes in clinically relevant information occur. Genetic counseling and testing terms used in *GeneReviews* are glossed and hyperlinked to additional information in the *GeneReviews* [Illustrated Glossary](#). *GeneReviews* are indexed in PubMed.

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Gaucher Disease

Synonyms: Glucocerebrosidase Deficiency, Glucosylceramidase Deficiency

Gregory M Pastores, MD and Derralynn A Hughes, MA, DPhil, FRCP, FRCPATH.

[Author Information](#)

Initial Posting: July 27, 2000; Last Revision: February 26, 2015.

Summary

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Clinical characteristics. **Gaucher** disease (GD) encompasses a continuum of clinical findings from a perinatal lethal disorder to an asymptomatic type. The identification of three major clinical types (1, 2, and 3) and two other subtypes (perinatal-lethal and cardiovascular) is useful in determining prognosis and management. GD type 1 is characterized by the presence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disease. GD types 2 and 3 are characterized by the presence of primary neurologic disease; in the past, they were distinguished by age of onset and rate of disease progression, but these distinctions are not absolute. Disease with onset before age two years, limited psychomotor development, and a rapidly progressive course with death by age two to four years is classified as GD type 2. Individuals with GD type 3 may have onset before age two years, but often have a more indolent course with onset at a later age. The clinical heterogeneity of GD is reflected in the wide range of clinical findings and the variable course of the disease. The clinical heterogeneity of GD is reflected in the wide range of clinical findings and the variable course of the disease.

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Table 2.

Proportion of Individuals with *GBA* Pathogenic Variants Using the Panel of Four Common Variants

Variants ¹	% of Affected Individuals ^{2,3}
N370S/N370S	29%
N370S/?	20%
N370S/L444P	16%
N370S/84GG	12%
L444P/L444P ⁴	6%
L444P/?	3%
N370S/IVS2+1	3%

1. [Table 5](#) provides the variant name and [nucleotide](#) changes according to current nomenclature guidelines.
2. Based on data from 1097 individuals in the **Gaucher** Registry (International Collaborative **Gaucher** Group [October 1999]). In this population, 94% of individuals had type 1, 1% had type 2, and 5% type 3.
3. GD [mutation](#) detection rates based on [sequence analysis](#) available through the [ICGG Registry Program](#) (registration required)
4. Recombinant (Rec) alleles (i.e., the RecNciI [allele](#); see [Molecular Genetics](#)) contain two to four single [nucleotide](#) variants (including [L444P](#)) that arise as a result of [gene](#) rearrangements between exons 9 and 10 of the functional gene and [pseudogene](#). Thus, testing for the L444P variant alone does not allow distinction of the [isolated](#) L444P allele from Rec alleles, and may lead to an error in [genotype](#) designation [[Tayebi et al 2003a](#)].

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- GeneReviews <http://www.ncbi.nlm.nih.gov/books/NBK1116/>
- Pubmed <http://www.ncbi.nlm.nih.gov/pubmed>
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OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh. Its official home is omim.org.

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*182389

SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT; SCN1A

Alternative titles; symbols

SODIUM CHANNEL, BRAIN TYPE I, ALPHA SUBUNIT; NAC1
NAV1.1

HGNC Approved Gene Symbol: SCN1A

Cytogenetic location: 2q24.3 *Genomic coordinates (GRCh38):* 2:165,989,159-166,149,271 (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance (in progress)	Phenotype mapping key
2q24.3	Dravet syndrome	607208	AD	3
	Epilepsy, generalized, with febrile seizures plus, type 2	604403	AD	3
	Febrile seizures, familial, 3A	604403	AD	3
	Migraine, familial hemiplegic, 3	609634	AD	3

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potential therapeutic strategy for cognitive deficit and autism spectrum behaviors in Dravet syndrome. 

ALLELIC VARIANTS (24 Selected Examples):

.0001 GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS, TYPE 2

SCN1A, ARG1648HIS [dbSNP:rs121918622] [ClinVar]

In a 3-generation pedigree segregating autosomal dominant generalized epilepsy with febrile seizures plus, type 2 (604403) previously reported by Baulac et al. (1999), Escayg et al. (2000) identified a G-to-A transition at nucleotide 4943 in exon 26 of the **SCN1A** gene that resulted in an amino acid substitution, arg1648 to his. This mutation causes loss of the MaeII site and cosegregated with GEF5+2 in this family. The mutation was identified in 1 asymptomatic individual and was interpreted as an example of incomplete penetrance. One seemingly affected individual did not carry the mutation, suggesting it as a phenocopy; this was previously suggested by haplotype reconstruction. 

.0002 GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS, TYPE 2

SCN1A, THR875MET [dbSNP:rs121918623] [ClinVar]

In a family previously reported by Moulard et al. (1999) with GEF5+2 (604403), Escayg et al. (2000) identified a C-to-T transition at nucleotide 2624 of the **SCN1A** gene, resulting in an amino acid substitution thr875 to met. This mutation results from the loss of an AclI site. Eleven affected individuals and an obligate carrier were heterozygous for the mutation, whereas 4 unaffected relatives carried 2 normal alleles. 

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GATGGTATGGGGCCAAGAGATATAT
GTACGGCTGTCATCACTTAGACCTC
GGCTGGGCATAAAAGTCAGGGCAGA
TGGTGCATCTGACTCCTGAGGAGAA
GGTTGGTATCAAGGTTACAAGACAG
ACTGACTCTCTCTGCCTATTGGTCT

ClinVar

ClinVar aggregates information about sequence variation and its relationship to human health.

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Select ...

Clinical**significance**Variant of unknown
significance (1)

Pathogenic (18)

Review status

Single submitter (24)

Method type

Research (1)

Literature only (12)

Clinical testing (11)

Molecular**consequence**

Missense (15)

Variation type

Copy gain (1)

Deletion (4)

Single nucleotide (21)

Did you mean *ARSB* as a gene symbol? [Search ClinVar for ARSB](#)See [ARSB arylsulfatase B](#) in the Gene database**Results: 1 to 20 of 26**

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		Gene	Variation	Freq	Phenotype	Clinical Significance	Review Status	Chr
☐	See details	ARSB	ARSB:c.972A>G (p.Gly324=)	GMAF:0.0372	AllHighlyPenetrant	Benign	classified by single submitter	5
1.								
☐	See details	ARSB	ARSB:c.971G>T (p.Gly324Val)		not provided	Pathogenic	classified by single submitter	5
2.								
☐	See details	ARSB	ARSB:c.934T>C (p.Trp312Arg)		not provided	Uncertain significance	classified by single submitter	5
3.								
☐	See details	ARSB	ARSB:c.629A>G (p.Tyr210Cys)	GO-ESP:0.0002	not provided	Pathogenic	classified by single submitter	5
4.								
☐	See details	ARSB	ARSB:c.284G>A (p.Arg95Gln)		not provided	Pathogenic	classified by single submitter	5
5.								

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- Pubmed <http://www.ncbi.nlm.nih.gov/pubmed>
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The Human Gene Mutation Database
at the Institute of Medical Genetics in Cardiff

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Gene symbol Go!

Symbol: Missense/nonsense Go!

The Human Gene Mutation Database (HGMD®) represents an attempt to collate known (published) gene lesions responsible for human inherited disease, and is maintained in Cardiff by D.N. Cooper, E.V. Ball, P.D. Stenson, A.D. Phillips, K. Howells, S. Heywood, M.J. Hayden, M.E. Mort and M.P. Horan.



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Table:	Description:	Public entries: This site Academic non-profit users only	Total entries: HGMD Professional 2015.4
Mutation totals (as of 2016-04-19)		127836	179235
Gene symbol	The gene description, gene symbol (as recommended by the HUGO Nomenclature Committee) and chromosomal location is recorded for each gene. In cases where a gene symbol has not yet been made official, a provisional symbol has been adopted which is denoted by lower-case letters.	4860	7189
cDNA sequence	cDNA reference sequences are provided, numbered by codon.	4788	7421
Genomic coordinates	Genomic (chromosomal) coordinates have been calculated for missense/nonsense, splicing, regulatory, small deletions, small insertions and small indels.	0	157581
HGVs nomenclature	Standard HGVs nomenclature has been obtained for missense/nonsense, splicing, regulatory, small deletions, small insertions and small indels.	0	158606
Missense/nonsense	Single base-pair substitutions in coding regions are presented in terms of a triplet change with an additional flanking base included if the mutated base lies in either the first or third position in the triplet.	71196	100090
Splicing	Mutations with consequences for mRNA splicing are presented in brief with information specifying the relative position of the lesion with respect to a numbered intron donor or acceptor splice site. Positions given as positive integers refer to a 3' (downstream) location, negative integers refer to a 5' (upstream) location.	11875	16356
Regulatory	Substitutions causing regulatory abnormalities are logged in with thirty nucleotides flanking the site of the mutation on both sides. The location of the mutation relative to the transcriptional initiation site, initiation codon, polyadenylation site or termination codon is given.	2458	3414
Small deletions	Micro-deletions (20 bp or less) are presented in terms of the deleted bases in lower case plus, in upper case, 10 bp DNA sequence flanking both sides of the lesion. The numbered codon is preceded in the given sequence by the caret character (^).	19803	26623
Small insertions	Micro-insertions (20 bp or less) are presented in terms of the inserted bases in lower case plus, in upper case, 10 bp DNA sequence flanking both sides of the lesion. The numbered codon is preceded in the given sequence by the caret character (^).	8136	11184
Small indels	Micro-indels (20 bp or less) are presented in terms of the deleted/inserted bases in lower case plus, in upper case, 10 bp DNA sequence flanking both sides of the lesion. The numbered codon is preceded in the given sequence by the caret character (^).	1904	2553
Gross deletions	Information regarding the nature and location of each lesion is logged in narrative form because of the extremely variable quality of the original data reported.	8835	13556
Gross insertions	Information regarding the nature and location of each lesion is logged in narrative form because of the extremely variable quality of the original data reported.	1973	3272
Complex rearrangements	Information regarding the nature and location of each lesion is logged in narrative form because of the extremely variable quality of the original data reported.	1263	1699
Repeat variations	Information regarding the nature and location of each lesion is logged in narrative form because of the extremely variable quality of the original data reported.	393	488

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Gene symbol ▼

Go!

Symbol:

Missense/nonsense

Gene Symbol	Chromosomal location	Gene name	cDNA sequence	Extended cDNA	Mutation viewer
GAA (Aliases: available to subscribers)	17q25.2-q25.3	Glucosidase, alpha acid (Aliases: available to subscribers)	NM_000152.3	Not available	BIOBASE Feature available to subscribers

Mutation type	Number of mutations	Mutation data by type (register or log in)
Missense/nonsense	214	Get mutations
Splicing	50	Get mutations
Regulatory	0	No mutations
Small deletions	60	Get mutations
Small insertions	23	Get mutations
Small indels	10	Get mutations
Gross deletions	11	Get mutations
Gross insertions/duplications	1	Get mutations
Complex rearrangements	0	No mutations
Repeat variations	0	No mutations
Get all mutations by type		BIOBASE Feature available to subscribers
Public total (HGMD Professional 2015.4 total)	369 (487)	

http://www.hgmd.cf.ac.uk/ac/index.php

Missense/nonsense	Splicing	Regulatory	Small deletions	Small insertions	Small indels	Gross deletions	Gross insertions	Complex	Repeats
274 mutations in HGMD professional 2013.4	47 mutations in HGMD professional 2013.4	8 mutations in HGMD professional 2013.4	21 mutations in HGMD professional 2013.4	13 mutations in HGMD professional 2013.4	13 mutations in HGMD professional 2013.4	4 mutations in HGMD professional 2013.4	No mutations	3 mutations in HGMD professional 2013.4	No mutations
Further options available in HGMD professional 2013.4									

Accession Number	Codon change	Amino acid change	Codon number	Genomic coordinates & HGVS nomenclature	Phenotype	Reference	Comments
CM951121	CCG-CTG	Pro-Leu	20	BIOBASE Feature available to subscribers	Hirschsprung disease	Angrist (1995) Hum Mol Genet 4, 821	
CM941217	TCG-TTG	Ser-Leu	32	BIOBASE Feature available to subscribers	Hirschsprung disease	Edery (1994) Nature 367, 378 Functional characterisation report available to subscribers	
CM961241	CTG-CCG	Leu-Pro	40	BIOBASE Feature available to subscribers	Hirschsprung disease	Yin (1994) Eur J Hum Genet 2, 272	
CM020759	GCGg-GCA	Ala-Ala	45	BIOBASE Feature available to subscribers	Hirschsprung disease, association with	Borrego (1999) J Med Genet 36, 771 Additional phenotype report available to subscribers Additional phenotype report available to subscribers Additional report available to subscribers Additional report available to subscribers Additional report available to subscribers	
CM001777	cCTG-ATG	Leu-Met	56	BIOBASE Feature available to subscribers	Hirschsprung disease	Hofstra (2000) Hum Mutat 15, 418 Functional characterisation report available to subscribers Additional phenotype report available to subscribers Additional report available to subscribers Additional report available to subscribers Additional report available to subscribers	
CM941218	CCC-CTC	Pro-Leu	64	BIOBASE Feature available to subscribers	Hirschsprung disease	Edery (1994) Nature 367, 378	
CM033450	CGC-CAC	Arg-His	67	BIOBASE Feature available to subscribers	Autonomic control, congenital failure of ?	Sasaki (2003) Hum Genet 114, 22 Additional phenotype report available to subscribers Additional phenotype report available to subscribers Additional report available to subscribers	
				BIOBASE		Bolt (2000) Proc Natl Acad Sci U S A 97	

http://www.hgmd.cf.ac.uk/ac/index.php

Missense/nonsense	Splicing	Regulatory	Small deletions	Small insertions	Small indels	Gross deletions	Gross insertions	Complex	Repeats
295 mutations in HGMD professional 2015.4	65 mutations in HGMD professional 2015.4	1 mutation in HGMD professional 2015.4	69 mutations in HGMD professional 2015.4	29 mutations in HGMD professional 2015.4	11 mutations in HGMD professional 2015.4	14 mutations in HGMD professional 2015.4	1 mutation in HGMD professional 2015.4	2 mutations in HGMD professional 2015.4	No mutations

Further options available in [HGMD professional 2015.4](#)

Accession Number	HGMD Splicing mutation	Genomic coordinates & HGVS nomenclature	Phenotype	Reference	Comments
CS941489	IVS1 as -13 T-G	BIOBASE Feature available to subscribers	Glycogen storage disease 2	Huie (1994) Hum Mol Genet 3, 2231 Additional report available to subscribers Additional report available to subscribers Additional report available to subscribers Additional report available to subscribers Functional characterisation report available to subscribers Additional report available to subscribers Additional report available to subscribers Additional phenotype report available to subscribers Additional report available to subscribers Additional report available to subscribers Functional characterisation report available to subscribers Additional phenotype report available to subscribers Functional characterisation report available to subscribers	aka c.45T>G.....
CS081916	IVS1 as -3 C-A	BIOBASE Feature available to subscribers	Glycogen storage disease 2	Pittis (2008) Hum Mutat 29, E27	
CS083928	IVS1 as -2 A-G	BIOBASE Feature available to subscribers	Glycogen storage disease 2	Kroos (2008) Hum Mutat 29, E13 Additional report available to subscribers	
CS040146	IVS2 ds -1 G-A	BIOBASE Feature available to subscribers	Glycogen storage disease 2	Hermans (2004) Hum Mutat 23, 47 Additional report available to subscribers	ACGa>ACA, Th.....
CS077363	IVS2 ds -1 G-C	BIOBASE Feature available to subscribers	Glycogen storage disease 2	Gort (2007) Mol Genet Metab 92, 183 Additional report available to subscribers	ACGa>ACC, Th.....
CS095579	IVS2 ds -1 G-T	BIOBASE Feature available to subscribers	Glycogen storage disease 2	Maimaiti (2009) J Hum Genet 54, 493 Additional phenotype report available to subscribers Functional characterisation report available to subscribers Additional report available to subscribers Additional report available to subscribers	ACGa>ACT, Th.....

http://www.hgmd.cf.ac.uk/ac/index.php

Missense/nonsense	Splicing	Regulatory	Small deletions	Small insertions	Small indels	Gross deletions	Gross insertions	Complex
295 mutations in HGMD professional 2015.4	65 mutations in HGMD professional 2015.4	1 mutation in HGMD professional 2015.4	69 mutations in HGMD professional 2015.4	29 mutations in HGMD professional 2015.4	11 mutations in HGMD professional 2015.4	14 mutations in HGMD professional 2015.4	1 mutation in HGMD professional 2015.4	2 mutations in HGMD professional 2015.4
Further options available in HGMD professional 2015.4								

Accession Number	Deletion (^codon number)	Genomic coordinates & HGVS nomenclature	Phenotype	Reference
CD099726	TGAGG^(5)CACCCgccctgctCCCACCGGCT	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Oba-Shinjo (2009) J Neurol 256, 1881
CD082115	CCCGCCC^(8)TGctCCCACCGGCT	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Nascimbeni (2008) Neurology 70, 617
CD071347	AGAGCA^(78)GTGccacacagtgcGACGTCCCCC	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Palmer (2007) Neuromuscul Disord 17, 16
CD983801	CAGCCGC^(90)TTCgATTGCGCCCC	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Vorgerd (1998) Neurogenetics 1, 205
CD106339	GGAGCC^(121)CAGatGGGGCAGCCC	BIOMASE Feature available to subscribers	Glycogen storage disease 2, late-onset	Bernstein (2010) Mol Genet Metab 101, 130
CD982667	GCAGCCC^(126)TGgtgCTTCTTCCCA	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Kroos (1998) Clin Genet 53, 379
CD101756	GGAGAAC^(141)CTGagctcctctgaaatgggCTACACGGCC	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Labrousse (2010) Mol Genet Metab 99, 379
CD084143	GGCCACC^(152)CTGaccCGTACCACCC	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Kroos (2008) Hum Mutat 29, E13
CD085127	ACCTTG^(153)ACCCgtaccaccccACCTTCTT	BIOMASE Feature available to subscribers	Glycogen storage disease 2	van der Beek (2008) J Neurol Sci 275, 46
CD120546	CACCTTG^(153)ACCcgtaccACCCACCT	BIOMASE Feature available to subscribers	Glycogen storage disease 2, infantile-onset ?	Bali (2012) Am J Med Genet C Semin Med Genet 160, 40
CD972217	CACCTTC^(160)TTCccCAGGACATC	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Nicolino (1997) Biochem Biophys Res Commun 235, 138
CD100606	GGACGTG^(172)ATGatgGAGACTGAGA	BIOMASE Feature available to subscribers	Glycogen storage disease 2, late-onset	Laforêt (2010) Neuromuscul Disord 20, 128
CD941680	TGATG^(174)GAGACTGAGAACCGCC	BIOMASE Feature available to subscribers	Glycogen storage disease 2	Hermans (1994) Hum Mol Genet 3, 2213 Additional report available to subscribers Additional report available to subscribers Additional report available to subscribers Functional characterisation report available to subscribers

Literatürde bildirilmemiş

Literatürde bildirilmiş

İnsiliko Değerlendirme

Patojen olma ihtimali zayıf

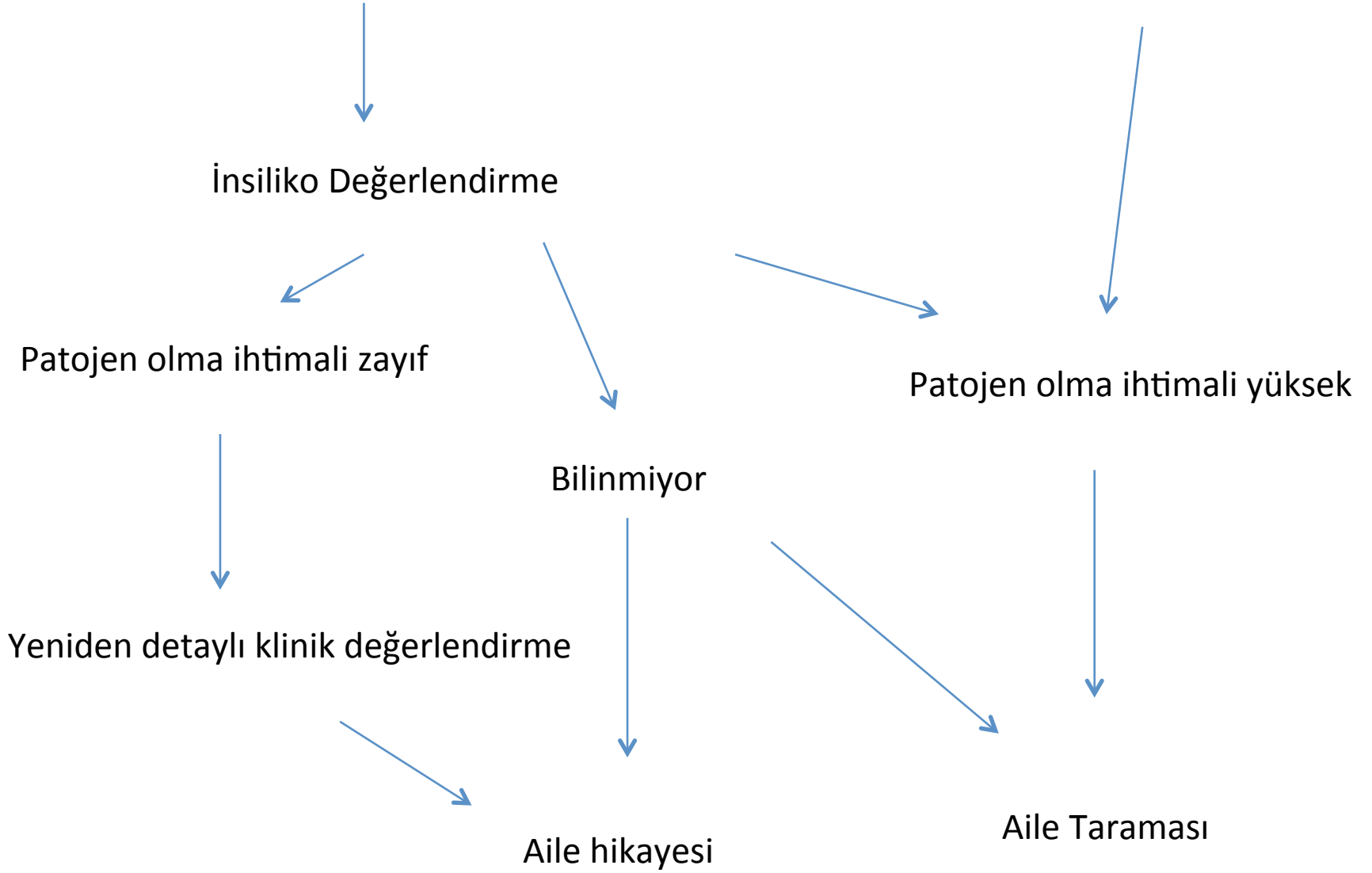
Patojen olma ihtimali yüksek

Bilinmiyor

Yeniden detaylı klinik değerlendirme

Aile hikayesi

Aile Taraması



BÜTÜN SÜLALE
AKRABA EVLİLİĞİ
YAPMIŞ BANA
NİYE İZİN VERMİ-
YOSUNUZ?!!!



ÇÜNKÜ DERSİMİZİ
ALDIK!!! YILLARCA SAKAT
YA DA HASTALIKLI ÇOCUK-
LARIMIZ OLDU!!!... SEN
ŞANSLIYDIN!!!!... AY SAMET
SEN DE BİŞEYLER
SÖYLESENE!!!





http://www.mutationtaster.org/



mutation t@sting

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- [query chromosomal positions](#)
- [QueryEngine](#)
- [other applications](#) | [team](#)

Gene

HGNC gene symbol, NCBI Gene ID, Ensembl gene ID [show](#)

[available transcripts](#)

clear input

Transcript

Ensembl transcript ID

Position / snippet
refers to

☒ coding sequence (ORF)

(genomic sequence)

☐ transcript (cDNA sequence)

☐ gene

Alteration

all types by sequence

enter a few bases around your alteration

Format:

ACTGTC[A/T] GTGTF

A substituted by T

ACTGTC[AG/T] GTGTF

AG substituted by T

ACTGTC[ACGT/-] GTGTF

ACGT deleted

ACTGTC[-/AA] GTGTF

AA inserted

options

☐ show nucleotide alignment

single base exchange by position

enter **position**

and **new base**

insertion or deletion by position

AGL geni c.3980 G>A



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- [documentation](#) | [FAQs](#)
- [single query](#)
- [query chromosomal positions](#)
- [QueryEngine](#)
- [other applications](#) | [team](#)

Gene

AGL HGNC gene symbol, NCBI Gene ID, Ensembl gene ID [show](#)
[available transcripts](#)

Transcript

ENST00000294724 Ensembl transcript ID

Position / snippet
refers to

☒ coding sequence (ORF) ☐ transcript (cDNA sequence) ☐ gene
(genomic sequence)

Alteration

all types by sequence

enter a few bases around your alteration

Format:

ACTGTC[A/T] GTGTF

A substituted by T

ACTGTC[AG/T] GTGTF

AG substituted by T

ACTGTC[ACGT/-] GTGTF

ACGT deleted

ACTGTC[-/AA] GTGTF

AA inserted

options

☐ show nucleotide alignment

single base exchange by position

enter **position**
and **new base**

insertion or deletion by position

enter **positions** of

AGL geni c.3980 G>A



[documentation](#)

mutation t@sting

Prediction disease causing Model: *complex_aae*, prob: 1 (classification due to NMD, [real probability](#) is shown anyway) [\(exp](#)

Summary

- NMD
- amino acid sequence changed
- known disease mutation at this position (HGMD CM023324)
- protein features (might be) affected
- splice site changes

<u>analysed issue</u>	<u>analysis result</u>
-----------------------	------------------------

name of alteration	no title
alteration (phys. location)	chr1:100379113G>A
HGNC symbol	AGL
Ensembl transcript ID	ENST00000294724
UniProt peptide	P35573
alteration type	single base exchange
alteration region	CDS
DNA changes	c.3980G>A

AGL geni c.3980 G>A

- protein features (might be) affected
- splice site changes

analysed issue analysis result

name of alteration	no title
alteration (phys. location)	chr1:100379113G>A
HGNC symbol	AGL
Ensembl transcript ID	ENST00000294724
UniProt peptide	P35573
alteration type	single base exchange
alteration region	CDS
DNA changes	c.3980G>A cDNA.4458G>A g.63474G>A
AA changes	W1327* Score: 6.0 explain score(s)
position(s) of altered AA if AA alteration in CDS	1327 (frameshift or PTC - further changes downstream)
frameshift	no
dbSNP / TGP / HGMD(public) / ClinVar	known disease mutation at this position, please check HGMD for details (HGMD ID CM023324)
regulatory features	H3K36me3, Histone, Histone 3 Lysine 36 Tri-Methylation
phyloP / phastCons	4.784, 1 (flanking) 5.777, 1 5.777, 1 (flanking) explain score(s) and/or inspect your position(s) in in UCSC Genome Browser
splice sites	effect gDNA position score wt detection sequence

AGL geni c.3980 G>A

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Code release

License

Source Code JCVI-SIFT v. 1.03
Code & exe (Sun, Linux)

FTP download

SIFT Human DB (release 63)
SIFT dbSNP DB (build 132)

Related links

Human genome assembly
GRCh37
Ensembl annotation release 63
NCBI dbSNP Build 132
NCBI BLink

Updates

Aug 2011: SIFT Human DB
updated to support GRCh37
Ensembl release 63

Apr 2011: SIFT dbSNP DB
updated to support NCBI dbSNP
build 132

SIFT predicts whether an **amino acid substitution affects protein function**. SIFT prediction is based on the degree of conservation of amino acid residues in sequence alignments derived from closely related sequences, collected through PSI-BLAST. SIFT can be applied to naturally occurring **nonsynonymous polymorphisms or laboratory-induced missense mutations**.

**** PROVEAN project New ****

Visit our new [PROVEAN project](#) to get functional predictions from multiple tools. We welcome your [feedback or questions](#).

New features in [PROVEAN Human Genome Variants DB](#):

- Single submission returns functional predictions from **SIFT** and **PROVEAN**. PROVEAN is a new prediction tool which works for **both SNPs and indels**. (Choi et al., 2012, PLOS ONE)
- Updated versions of Ensembl gene annotation (GRCh37 Ensembl 66) and NCBI dbSNP database (Build 137).
- New database structure to support fast retrieval for genome-wide analysis.

Referencing SIFT

Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc*. 2009;4(7):1073-81. [PubMed PDF](#)

Ng PC, Henikoff S. Predicting the Effects of Amino Acid Substitutions on Protein Function *Annu Rev Genomics Hum Genet*. 2006;7:61-80. [PubMed PDF Supp](#)

Ng PC, Henikoff S. SIFT: predicting amino acid changes that affect protein function. *Nucleic Acids Res*. 2003 Jul 1;31(13):3812-4. [PubMed](#)

Ng PC, Henikoff S. Accounting for Human Polymorphisms Predicted to Affect Protein Function. *Genome Res*. 2002 Mar;12(3):436-46. [PubMed Data](#)

Human Genome DB

Tool Description

[SIFT/PROVEAN Human SNPs](#)

Get **SIFT** and **PROVEAN** predictions for SNPs and indels (Ensembl 66) ([Sample format](#))

AGL geni c.3980 G>A



[documentation](#)

mutation t@sting

Prediction disease causing Model: *complex_aae*, prob: 1 (classification due to NMD, [real probability](#) is shown anyway) [\(exp\)](#)

Summary

- NMD
- amino acid sequence changed
- known disease mutation at this position (HGMD CM023324)
- protein features (might be) affected
- splice site changes

analysed issue analysis result

name of alteration	no title
alteration (phys. location)	chr1:100379113G>A
HGNC symbol	AGL
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alteration type	single base exchange
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DNA changes	c.3980G>A

AGL geni c.3980 G>A

Transcript-based displays

- Transcript summary
- Supporting evidence (35)
- Sequence
 - Exons (34)
 - cDNA
 - Protein
- External References
 - General identifiers (36)
 - Oligo probes (57)
- Ontology
 - Ontology graph (21)
 - Ontology table (21)
- Genetic Variation
 - Variation table
 - Variation image
 - Population comparison
 - Comparison image
- Protein Information
 - Protein summary
 - Domains & features (5)
 - Variations (285)
- External data
 - Personal annotation
- ID History
 - Transcript history
 - Protein history

Configure this page

Manage your data

Transcript: AGL-004 ENST00000294724

Description

amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase [Source:HGNC Symbol;Acc:321]

Location

[Chromosome 1: 100,316,045-100,389,576](#) forward strand.

Gene

This transcript is a product of gene [ENSG00000162688](#) - This gene has 8 transcripts

Show/hide columns				Filter		
Name	Transcript ID	Length (bp)	Protein ID	Length (aa)	Biotype	CCDS
AGL-001	ENST00000361915	7368	ENSP00000355106	1532	Protein coding	CCDS759
AGL-002	ENST00000370165	7106	ENSP00000359184	1532	Protein coding	CCDS759
AGL-003	ENST00000370163	7166	ENSP00000359182	1532	Protein coding	CCDS759
AGL-004	ENST00000294724	7446	ENSP00000294724	1532	Protein coding	CCDS759
AGL-005	ENST00000361302	7179	ENSP00000354971	1516	Protein coding	CCDS760
AGL-006	ENST00000361522	7179	ENSP00000354635	1515	Protein coding	CCDS761
AGL-201	ENST00000370161	6923	ENSP00000359180	1516	Protein coding	CCDS760
AGL-007	ENST00000477753	682	No protein product	-	Processed transcript	-

Transcript and Gene level displays

Views in Archive Ensembl are separated into gene based views and transcript based views according to which level the information is more appropriately associated with. This view is a transcript level view. To flip between the two sets of views you can click on the Gene and Transcript tabs in the menu bar at the top of the page.

AGL geni c.3980 G>A

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SIFT Human Protein provides SIFT predictions for all Ensembl transcripts with an assigned ENSP number and returns tolerated/intolerated mutations for selected amino acid substitutions. If no substitutions are provided then all substitutions are shown.

User Input

Enter your email address if you want the results through email :
Please check that your address is correct and your mailbox is not full.

Protein Ensembl ENSP IDs

One ENSP number (starting with ENSP) per line (Limit 1000 proteins, please!).

[\[Sample format\]](#)

Paste in ENSP numbers, and any substitutions

ENSP00000294724, 1327

AGL geni c.3980 G>A

SIFT: PREDICTIONS

User Input	ENSP	Pos	Ref	Subst	Prediction	SIFT Score	Median Information Content	# Seqs
ENSP00000294724, 1327	ENSP00000294724	1327	W	A	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	C	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	D	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	E	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	F	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	G	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	H	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	I	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	K	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	L	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	M	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	N	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	P	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	Q	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	R	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	S	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	T	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	V	DAMAGING	0	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	W	TOLERATED	1	2.45	74
ENSP00000294724, 1327	ENSP00000294724	1327	W	Y	DAMAGING	0	2.45	74

SCN1A geni c.243 C>A



PolyPhen-2 prediction of functional effects of human nsSNPs

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PolyPhen-2 (Polymorphism Phenotyping v2) is a tool which predicts possible impact of an amino acid substitution on the structure and function of a human protein using straightforward physical and comparative considerations. Please, use the form below to submit your query.

15-Feb-2012: PolyPhen-2 server has been updated to utilize **version 2.2.2** of the software, protein sequences from **UniProtKB/UniRef100** Release 2011_12 (14-Dec-2011), structures from **PDB/DSSP** Snapshot 03-Jan-2012 (78,304 entries) and **UCSC** MultiZ multiple alignments of 45 vertebrate genomes with hg19/GRCh37 human genome (08-Oct-2009)

Query Data

Protein or SNP identifier

Protein sequence
in FASTA format

Position

Substitution

AA₁ A R N D C E Q G H I L K M F P S T W Y V
AA₂ A R N D C E Q G H I L K M F P S T W Y V

Query description

Display advanced query options

SCN1A geni c.243 C>A



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WHESS.db provides quick access to precomputed set of **PolyPhen-2** predictions for whole human exome sequence space (**WHESS**). It contains annotations for all single-nucleotide non-synonymous (missense) codon changes enumerated at each CDS codon position in the exons of 43,043 UCSC knownGene transcripts (hg19/GRCh37) with maximum sequence overlap and identity to known UniProtKB proteins.

Query WHESS.db

Enter search:

Note:

*Use genomic coordinates for GRCh37/hg19 with
allele nucleotides in plus strand orientation*

Search Examples

P06241 445 I F

FYN_HUMAN 410 G R

NP_005792 59 L P

rs1801108

chr1:1267483 G/A

chr1:1158631 A/C,G,T

http://www.mutationtaster.org/
SCN1A geni c.243 C>A



[documentation](#)

mutation t@sting

Prediction

disease causing

Model: *simple_aae*, prob: 0.982810410377209

[\(explain\)](#)

Summary

- amino acid sequence changed

analysed issue

analysis result

name of alteration	no title
alteration (phys. location)	chr2:166929889G>T
HGNC symbol	SCN1A
Ensembl transcript ID	ENST00000303395
UniProt peptide	P35498
alteration type	single base exchange
alteration region	CDS
DNA changes	c.243C>A cDNA.243C>A g.261C>A
AA changes	D81E Score: 45 explain score(s)
position(s) of altered AA if AA alteration in CDS	81
frameshift	no

SCN1A geni c.243 C>A



PolyPhen-2 prediction of functional effects of human nsSNPs

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PolyPhen-2 (Polymorphism Phenotyping v2) is a tool which predicts possible impact of an amino acid substitution on the structure and function of a human protein using straightforward physical and comparative considerations. Please, use the form below to submit your query.

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Query WHESS.db

Enter search:

Note:

*Use genomic coordinates for GRCh37/hg19 with
allele nucleotides in plus strand orientation*

Search Examples

P06241 445 I F
FYN_HUMAN 410 G R
NP_005792 59 L P
rs1801108
chr1:1267483 G/A
chr1:1158631 A/C,G,T

SCN1A geni c.243 C>A



PolyPhen-2 prediction of functional effects of human nsSNPs

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WHESS.db: chr2:166929889 G/T

ChrPos	Ref / Allele	Gene	Transcript	Str	Observed	RefSNP	Protein	Pos	AA1 / AA2	HDivPred	HDivProb	HVarPred	HVarProb
chr2:166929889	G / T	SCN1A	uc010zcz.1	-	C / A		P35498-2	81	D / E	benign	0.306	benign	0.29

Software & web support: [ivan adzhubey](#)

Web design & development: [biobyte solutions](#)

Drowned in next generation sequencing data

HELP!



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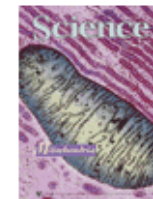
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MITOMAP

A human mitochondrial genome database

A compendium of polymorphisms and mutations in human mitochondrial DNA

MITOMAP reports published and unpublished data on human mitochondrial DNA variation. Most of the data is hand-curated and, due to the massive volume of sequencing data being produced world wide, there is always a backlog of papers and data to be added. If you would like to fast-track inclusion of a paper and its data into MITOMAP, please email a pdf to mitomap@email.chop.edu. We appreciate your help. Thanks.



MITOMAP Quick Reference

- To search for point mutations, click [here](#). The info button on the search page has more information.
- The rCRS is GenBank number **NC_012920**. Click [here](#) for details.

General References

[The Annotated Human Mitochondrial DNA Sequence](#)

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MITOMAP

A human mitochondrial genome database

A compendium of polymorphisms and mutations in human mitochondrial DNA

MITOMAP reports published and unpublished data on human mitochondrial DNA variation. Currently our variant tables report frequencies from 30589 human mitochondrial DNA sequences. If you would like to add a paper and its data into MITOMAP, please email a pdf to mitomap@email.chop.edu. We appreciate your help. Thanks.



Mitomap has moved to an upgraded server. This should result in improved performance and better security. Please [let us know](#) if you encounter problems!

MITOMAP Quick Reference

- To search for point mutations, click [here](#). The help button on the search page has more information.
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 31 March 2014: The Allele Search Function has been repaired. Thanks for your patience.

Allele Search

Searched nucleotide position(s): **10406**

MITOMAP: Reported Mitochondrial DNA Base Substitution Diseases: rRNA/tRNA Mutations

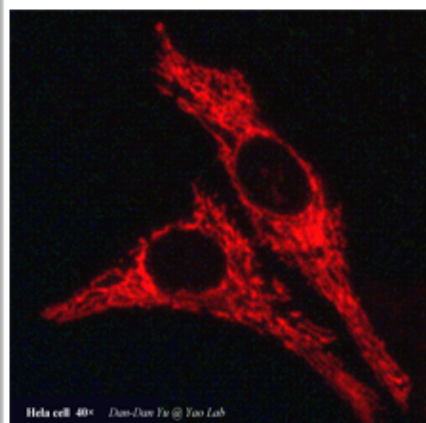
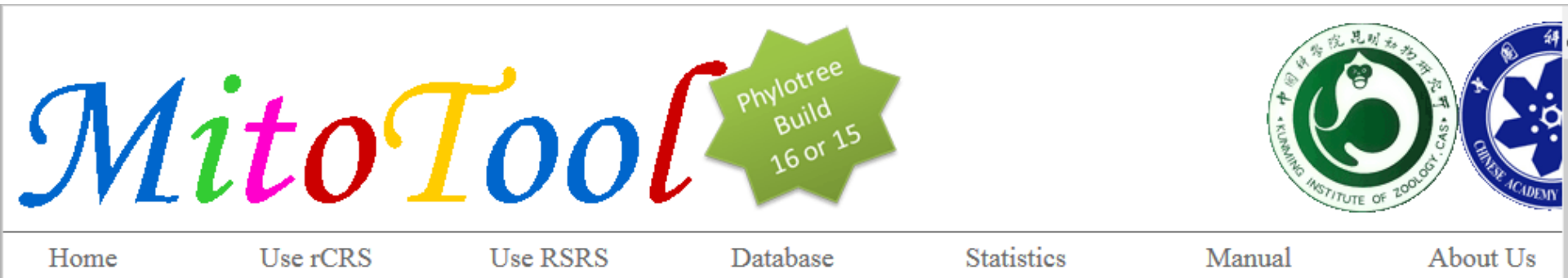
Locus	Disease	Allele	RNA	Homoplasmy	Heteroplasmy	Status	Refer
MT-IR	Mitochondrial Myopathy	G10406A	tRNA Arg	-	+	Reported	refere

Start: End:

Search [Reference Search](#) | [Site Search](#)

Enter a single nucleotide position or a range(up to 100 bps). Values must be positive integers from 1 to 16569.

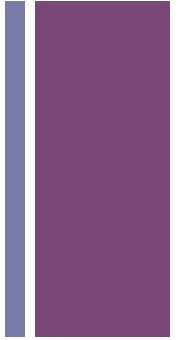
Mitokondri gen analizleri



MitoTool, a web-based bioinformatics platform, provides a convenient, user-friendly interface for handling human mtDNA sequence data. It contains multiple modules to cover a wide array of functions: (i) to automatically yield a list of the variants in cell mtDNA relative to the revised Cambridge Reference Sequence (rCRS) recommended by the Reconstructed Sapiens Reference Sequence (RSRS) and determine the haplogroup status of that lineage according to Phylotree (www.phylotree.org), (ii) to detect missing sequence variants in certain mtDNA with claimed haplogroup status, (iii) to display the location of the variant, interspecies conservation index and change of amino acid status, (iv) to identify potentially pathogenic mutations based on the reported data, (v) to conduct statistical analysis for haplogroup distribution frequency between case and control groups, and (vi) to retrieve and batch download analytical output of mitochondrion-related data of interest. It is unique in its ability to recognize four types of mtDNA data, to pro



Mitokondrial genom analizi



- **CYTB** geninde mt.15166C>A (%15) (**LHON**)
- **TRNR** geninde mt.10406G>A (%3) (**Mitokondrial myopati**) (**Kan örneği- kas dokusu önerildi**)
- **ATP6** geninde mt.9176T>C (%95) (**LEIGH sendromu**)

Search COSMIC v68

Search

[By Cancer](#)

[By Gene](#)

[By Sample](#)

Search Gene name, Mutation, Tissue,
Sample ..

Go

eg. BRAF, V600E, lung, COLO-829

Search via [Cancer Browser](#)

COSMIC

All cancers arise as a result of the acquisition of a series of fixed DNA sequence abnormalities, mutations, many of which ultimately confer a growth advantage upon... [\[More\]](#)

Cosmic Release v68

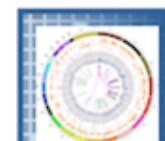
The COSMIC system was first released to the public on 4th February 2004, and this 68th release marks our 10th anniversary. From an initial release containing only 4 genes, our latest version presents full mutation spectra across 132 known cancer genes, 208 fusion gene pairs and almost 8000 cancer genomes...[\[More\]](#)

Statistics

Genes	25660
Samples	981720
Mutations	1627878
Papers	18465
Unique Variants	1292597

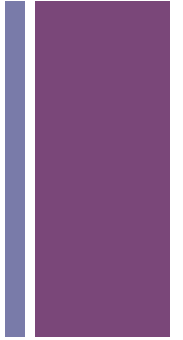
Fusions	10251
Genomic Rearrangements	7584
Whole Genomes	8236
Copy Number	425776

Cancer Genome Project Links





Kanser genetiği



EGFR

- p.S695R (c.2083A>C) (%5) mutasyonunun Gefinitib'e yanıtı etkilemesi beklenmediği rapor edilmiştir (Modern Pathology 2006, 19 (986-998).
- p.M766V(c.2296A>G) (%4) mutasyonunun Gefinitib'e direnç yol açabileceği bildirilmiştir (Biochemical Journal 495, 2 (2008) 197-206).
- p.V802A (c.2405T>C) (%30) değişiklik daha önce bildirilmemiştir. Ancak aynı bölgede p.V802I bulunan diğer bir değişiklik TKI grubu ile ilişkilendirilmiştir ve TKI grubu ilaçların etkinliğini arttırmaktadır.
- p.A722T (c.2164G>A) (%100) değişikliğinin ise TKI grubu ilaçları ile ilişkisi bilinmemektedir.
- **p.P733S (c.2197C>T) (%3):** Hastada yapılan çalışmalarda 19. ekzonda saptanan değişiklik daha önce tanımlanmış ve tirozin kinaz domaini içinde yer alan bir değişiklik olup, TKI grubu ilaçların etkinliğini arttırmaktadır.

- Yeni nesil dizileme teknolojisi nadir hastalıkların araştırılmasında çok büyük bir kapı açmıştır; eskiden mümkün olmayan çalışmalar mümkün hale gelmiştir.
- Ancak sonuçların değerlendirilmesi çoğu zaman çok kolay olmamaktadır. En büyük sorun ise ülkemizin polimorfizm verilerinin henüz bilinmemesidir.
- Birçok nadir hastalıkta saptanan yeni varyasyonların mutasyon mu yoksa polimorfizm mi olduğunun araştırılması gerekmektedir.



boğaziçi university
molecular biology
& genetics
department

Ana Sayfa

Proje Özeti

TGP Sorulara Cevaplar

Basın Bildirisi

TGP Video

TR-Genom Çalıştayı

Proje Ekibi

Proje Desteği

TR-Genom Server

Veri Tabanı

Teşekkürler

İletişim

MBG-Bridge

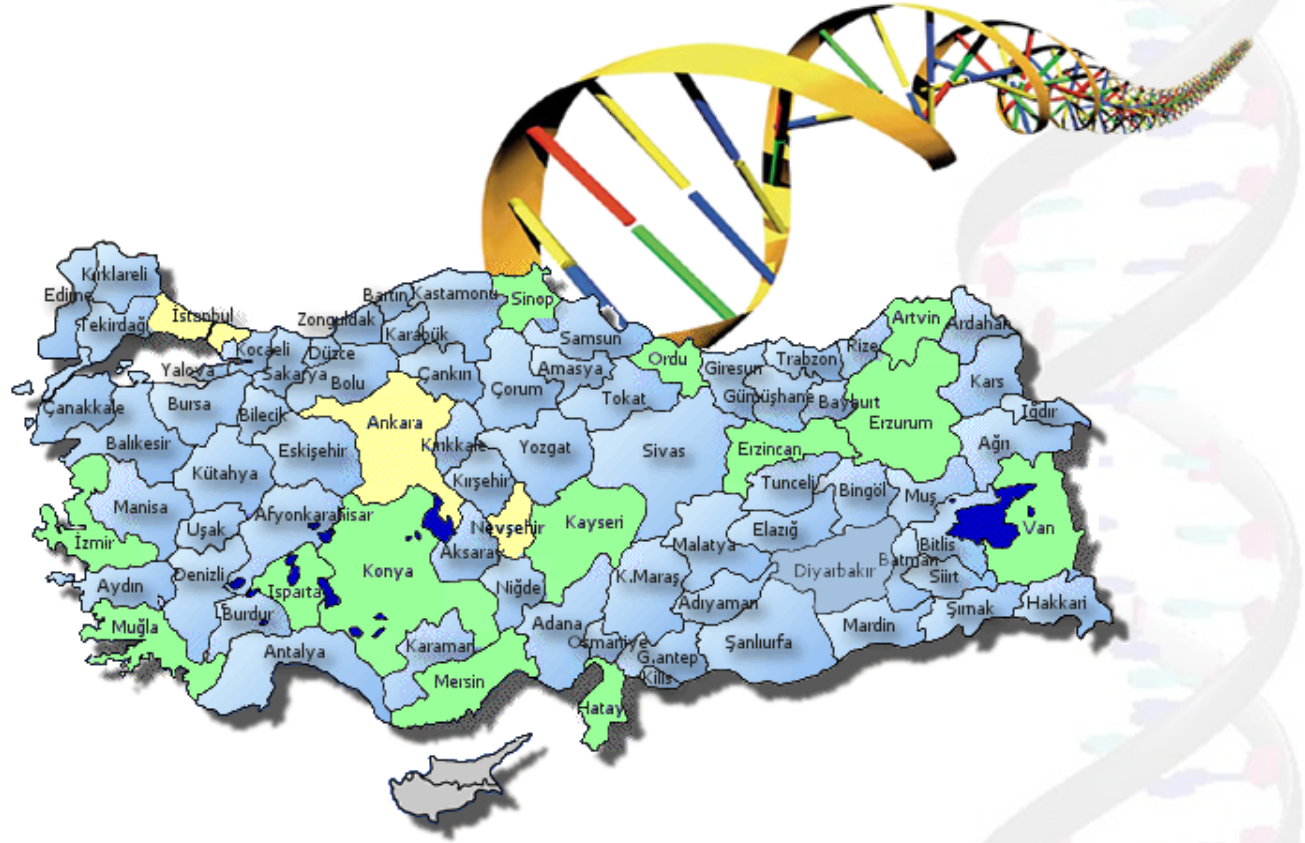
English



Lütfen kısa bir yol seçiniz ▼

Webmaster: C. Bekpen

Boğaziçi Üniversitesi Türkiye Genom Araştırması



- Tüm Genom Dizileme ve Bioinformatik Analizi Tamamlanan İller
- Tüm Genom Dizileme Analizi Tamamlanmış ve halen Bioinformatik analizleri devam eden iller

Genom analizi ayrıntıları için lütfen şehirlerin üstüne tıklayınız.



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Webmaster: C. Bekpen



İlk analizlerimizin ayrıntılı sonuçları 20-21 Ocak 2012 tarihinde açıklanacaktır.

Cinsiyet	Erkek
Toplam Read Sayısı	1.514.778.102
Ortalama Read Uzunluğu	89.86
Ortalama Dizi Derinliği	42.37
Genomun Dizileme Oranı %	99.64
Duplikasyon Değeri %	1.79
Toplam TNP (Tek Nükleotid Polimorfizm) sayısı	3.707.699

RESEARCH ARTICLE

Open Access

Whole genome sequencing of Turkish genomes reveals functional private alleles and impact of genetic interactions with Europe, Asia and Africa

Can Alkan^{1,2}, Pinar Kavak^{3,4}, Mehmet Somel^{5,6}, Omer Gokcumen⁷, Serkan Ugurlu⁸, Ceren Saygi⁸, Elif Dal², Kuyas Bugra⁸, Tunga Güngör³, S Cenk Sahinalp⁹, Nesrin Özören^{8*} and Cemalettin Bekpen^{8,10*}

Abstract

Background: Turkey is a crossroads of major population movements throughout history and has been a hotspot of cultural interactions. Several studies have investigated the complex population history of Turkey through a limited set of genetic markers. However, to date, there have been no studies to assess the genetic variation at the whole genome level using whole genome sequencing. Here, we present whole genome sequences of 16 Turkish individuals resequenced at high coverage (32 × –48×).

Results: We show that the genetic variation of the contemporary Turkish population clusters with South European populations, as expected, but also shows signatures of relatively recent contribution from ancestral East Asian populations. In addition, we document a significant enrichment of non-synonymous private alleles, consistent with recent observations in European populations. A number of variants associated with skin color and total cholesterol levels show frequency differentiation between the Turkish populations and European populations. Furthermore, we have analyzed the 17q21.31 inversion polymorphism region (*MAPT* locus) and found increased allele frequency of 31.25% for H1/H2 inversion polymorphism when compared to European populations that show about 25% of allele frequency.

Conclusion: This study provides the first map of common genetic variation from 16 western Asian individuals and thus helps fill an important geographical gap in analyzing natural human variation and human migration. Our data will help develop population-specific experimental designs for studies investigating disease associations and demographic history in Turkey.

- Türkiye Sağlık Enstitüleri Başkanlığı (TUSEB)-Biyoteknoloji Enstitüsü'nün T.C. Cumhurbaşkanlığı Himayelerinde 12-13 Şubat 2016 tarihinde İstanbul'da gerçekleştirdiği "Türkiye Genom Projesi Hazırlık Çalıştayı" sonrasında yapılan grup çalışmalarında, Genom Projesinin iki ana başlık altında değerlendirilerek bir "Yol Haritası" oluşturulması kanaati oluşmuştur.

"Referans Genomun" oluşturulması: Türkiye nüfusunu temsil edebilecek sayıda sağlıklı bireylerin tüm genom sekans ve analizlerinin yapılması, Hastalıkların Genetik etiyolojisinin saptanması:

Yaygın görülen kalıtsal hastalıklarda Türkiye nüfusunu temsil edecek, nadir hastalıklarda mümkün olan tüm hastaların genom sekanslarının yapılarak (tüm genom / ekzom) mutasyon profillerinin saptanması.

- Sonuç olarak Türk toplumunun tüm genom verileri ile elde edilecek varyasyon bilgileri ile sonuçların daha sağlıklı ve hızlı değerlendirilmesi mümkün olacaktır.

