



**27. ULUSAL
ÇOCUK
NÖROLOJİSİ
KONGRESİ**

29 Nisan - 3 Mayıs 2026
Concorde Luxury Resort & Convention & Spa - KKTC

 Türkiye
ÇOCUK NÖROLOJİSİ
Derneği



VUS Değerlendirmede Kullanılan Veritabanları ve Araçlar

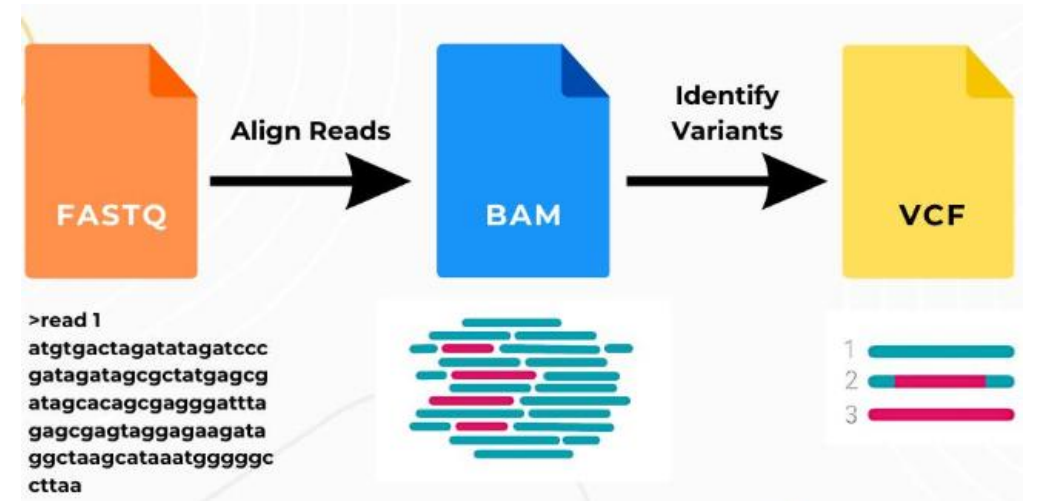
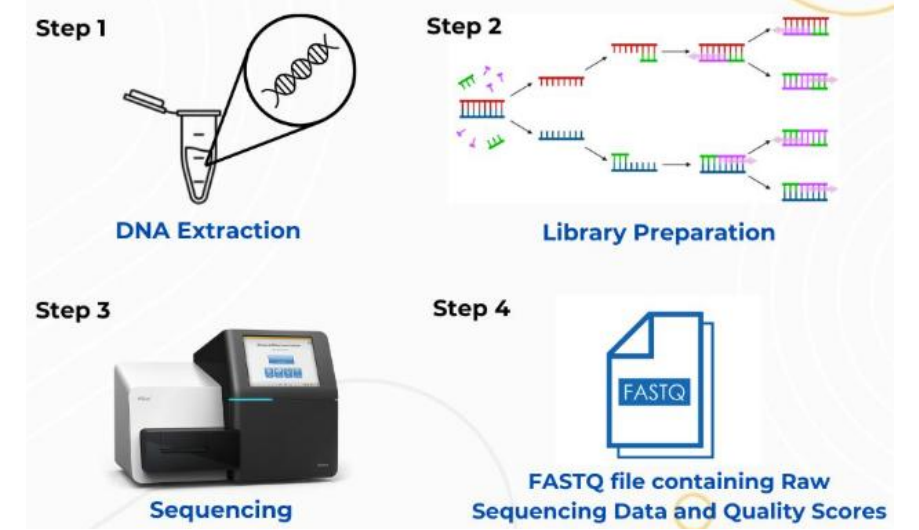
Dr. A. İpek POLAT

Dokuz Eylül Üniversitesi Tıp Fakültesi Çocuk Nöroloji BD

İzmir Biyotıp ve Genom Enstitüsü Moleküler Biyoloji ve
Genetik BD

Next Generation Sequencing: CES-WES-WGS

- 1. **Kütüphane** hazırlığı: DNA eldesi / adaptörlerin eklenmesi / parçalanması / çoğaltılması (amplifikasyon) ve problemlerin hedefe (ekzonlar, genom vs) bağlanması
 - * Kalite kontrol
- 2. Sekanslama ile **"FASTQ file"**
 - Makinenin okuduğu ham harfler
 - Genomun neresinden bilmiyoruz
- 3. Referans insan genomu ile dizileme (alignment): **"BAM file"**
 - Hangi kromozomda, hangi pozisyonda
 - Kaç kez okunmuş (coverage) ve güvenilir mi?
- 4. Referanstan farklı neler var: **"VCF file"**
 - Variant calling: Varyant listesi;
Yeri, referans ve değişen baz, ht/hm, kalite, derinlik



VCF Data'nın Bize Verdikleri

- WGS 'de yaklaşık 3-5 milyon varyant
- WES 'de yaklaşık 30.000-50.000 varyant
 - Çoğu SNP, az kısmı küçük indel
 - Çoğu intronik kenar, sinonim, klinik önemsiz/ benign varyantlar
- Ön filtreler ile sayı 15.000-30.000'e düşer
 - Quality, depth, artefakt temizliği, tekrar bölgeleri...
- Populasyon frekansı (MAF < %1 veya %0.1): 1000-3000'e düşer
- Protein etkisi filtreleri ile 200-800'e düşer
 - Öncelik missense, nonsense, fs, splice site olanlara
 - Sinonimler, intronik derin bölgeler çıkarılır
- Fenotip ile hastanın kliniğine uymayan genler filtrelenir; 20-100 varyanta iner
- Kalıtım modeli; 10-50 aralığına iner
- Gerçek raporlanabilen aday varyantlar: literatür + veri tabanları + ACMG ile değerlendirilir
- Real life: 0-3 varyant raporlanır

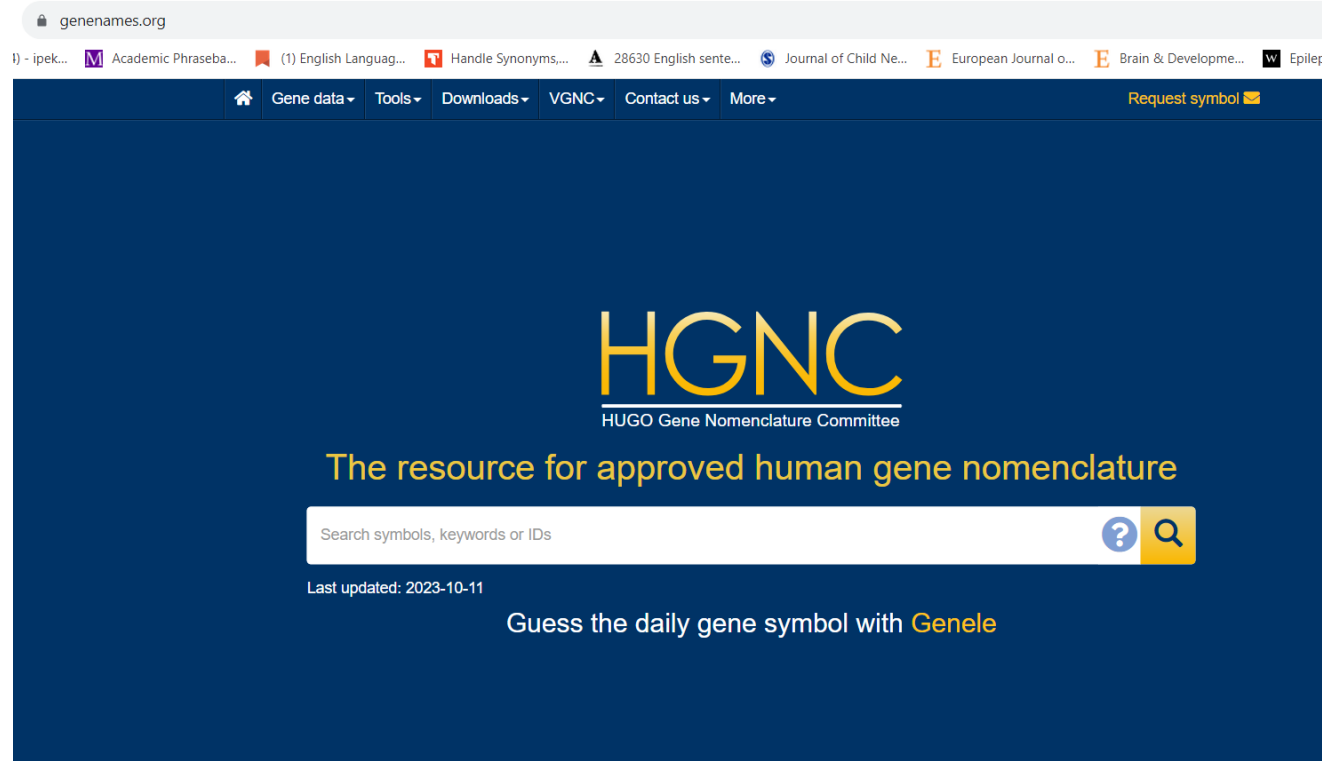


Genlerin isimlendirilmesi



Genlerin isimlendirilmesi

- İnsan genleri büyük harf ve italik yazılır (*RYR1*) (Ryr1: Mouse)





Search results

Filter by type

● Gene 1

Filter by gene entry status

Approved 1

Filter by gene locus type

Protein-coding gene 1

Filter by symbol report tag

Stable symbol 1

Download all results

TXT

JSON

20 items per page

Items: 1 to 1 of 1

RYR1: ryanodine receptor 1
Gene **HGNC ID** HGNC:10483 **Locus type** Gene with protein product **Status** Approved
Matches Gene symbol: **RYR1**

Items: 1 to 1 of 1

Search results

Filter by type

● Gene 1

Filter by gene entry status

Approved 1

Filter by gene locus type

Protein-coding gene 1

Download all results

TXT

JSON

20 items per page

Items: 1 to 1 of 1

PYROXD2: pyridine nucleotide-disulphide oxidoreductase domain 2
Gene **HGNC ID** HGNC:23517 **Locus type** Gene with protein product **Status** Approved
Matches Previous gene symbol: **C10orf33**

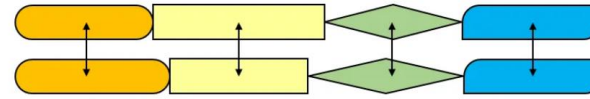
Items: 1 to 1 of 1

Referans genom nedir?



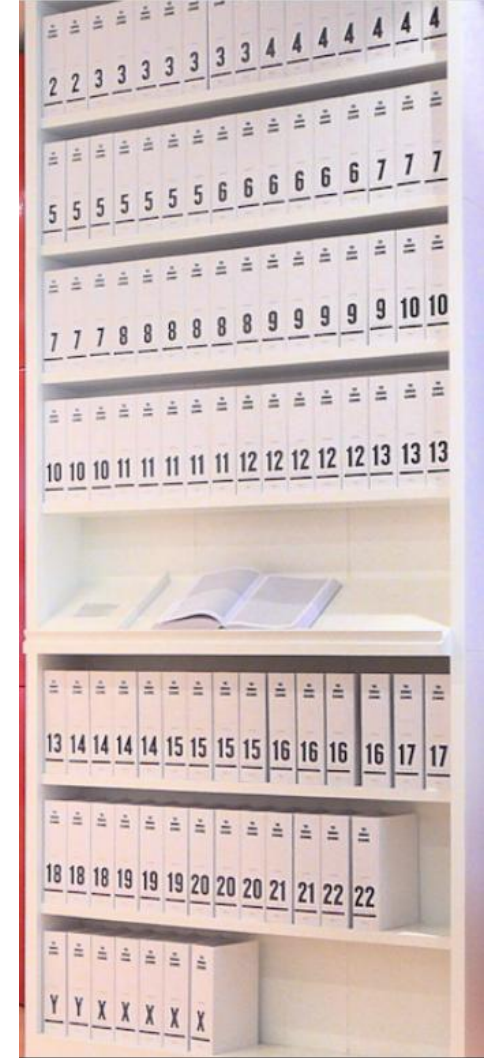
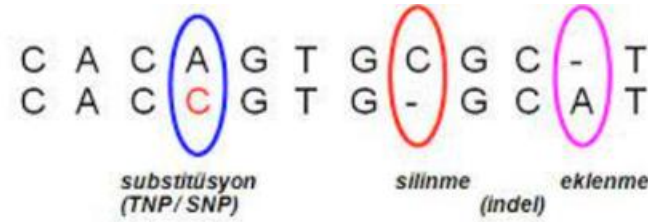
Referans genom

- Bir canlı türünün dizilenmiş ve biraraya getirilmiş temsili DNA dizisidir
- Bütün okumalar referans bir genomla hizalanarak gerçekleştirilir.



Global Alignment

referans:
birey:



İnsan referans genomu;
Wellcome Collection, Londra

“Genome Reference Consortium Human Reference 38”

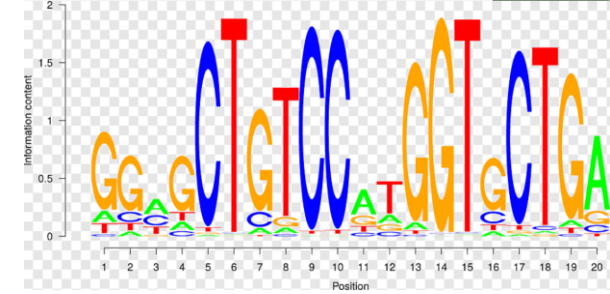
The Genome Reference Consortium consists of:



Release name	Date of release	Equivalent UCSC version
GRCh39	Indefinitely postponed ^[33]	-
T2T-CHM13	January 2022	-
GRCh38	Dec 2013	hg38
GRCh37	Feb 2009	hg19
NCBI Build 36.1	Mar 2006	hg18
NCBI Build 35	May 2004	hg17
NCBI Build 34	Jul 2003	hg16

GRCh38 (hg38) vs GRCh37 (hg19)

- hg19: tek tip hizalama
- hg38: alternatif sekanslar ve uç uca birleştirmeler ve mtDNA
- Koordinatlar farklı !!

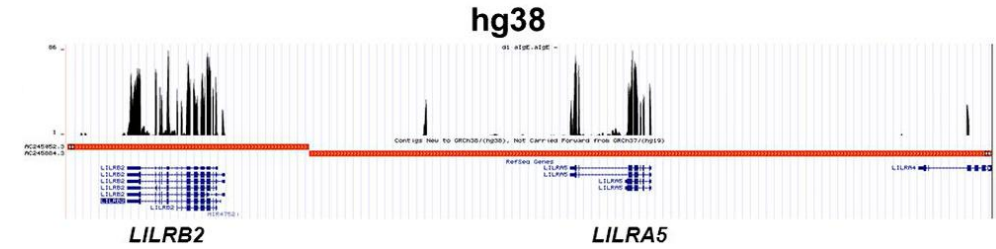
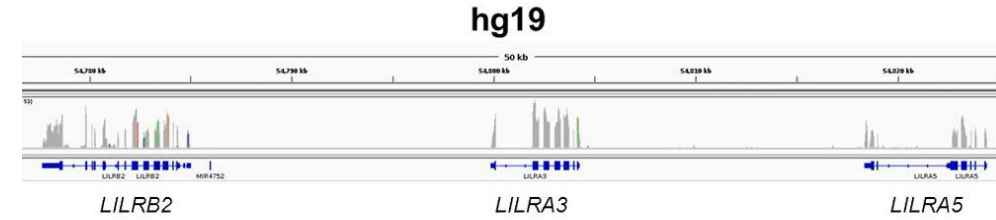


Genome assembly GRCh37.p13

Download	datasets	curl
See latest version: GCF_000001405.40		
		Actions
NCBI RefSeq assembly	GCF_000001405.25	
Submitted GenBank assembly	GCA_000001405.14	
Taxon	Homo sapiens (human)	
Synonym	hg19	
Assembly type	haploid with alt loci	
Submitter	Genome Reference Consortium	
Date	Jun 28, 2013	

Genome assembly GRCh38.p14 reference

Download	datasets	curl
NCBI RefSeq assembly	GCF_000001405.40	
Submitted GenBank assembly	GCA_000001405.29	
Taxon	Homo sapiens (human)	
Synonym	hg38	
Assembly type	haploid with alt loci	
Submitter	Genome Reference Consortium	
Date	Feb 3, 2022	



hg38 veya hg19

41572512

İşlem : Hastanın periferik kanından elde edilen DNA örneğinde, mitokondriyal hastalıklar ile ilişkili 13 gene ait varyasyonlar yeni nesil dizi analizi yöntemi ile araştırılmıştır. "BCS1L (ENST00000431802), DGUOK (ENST00000264093), MPV17 (ENST00000380044), NDUFS1 (ENST00000455934), NDUFS3 (ENST00000263774), NDUFV1 (ENST00000322776), NF1 (ENST00000358273), NF2 (ENST00000338641), POLG (ENST00000268124), SCO2 (ENST00000543927), SURF1 (ENST00000371974), TMEM70 (ENST00000312184) ve TRMU (ENST00000290846)" genlerinin kodlayıcı bölgelerinin (intronik, 5' ve 3' UTR hariç) %99'undan fazlası, en az 50X okuma derinliği ile incelenmiştir. Ortalama okuma derinliği 1413 okumadır. Ekzon-intron bağlantı noktaları (±10bp) analize dahil edilmiştir. Elde edilen verilerin patojenisite sınıflandırması "ACMG Guideline" a göre yapılmıştır. Genetik değişimlere ait kromozom pozisyonu bilgisi "hg19/GRCh37 Human Reference Genome" referans genomuna göre raporlanmıştır.

Kullanılan Kit : Mitochondrial DNA Depletion Syndrome Kit, Celeomics

Analiz Platformu : NextSeq Sequencing System, Illumina

Analiz Yazılımı : SEQ Analiz Platformu, Genomize

SONUÇ: Çalışmada hastanın kliniği ile ilişkilendirilebilecek, patojenik olduğu bildirilmiş bir değişim saptanmamıştır.

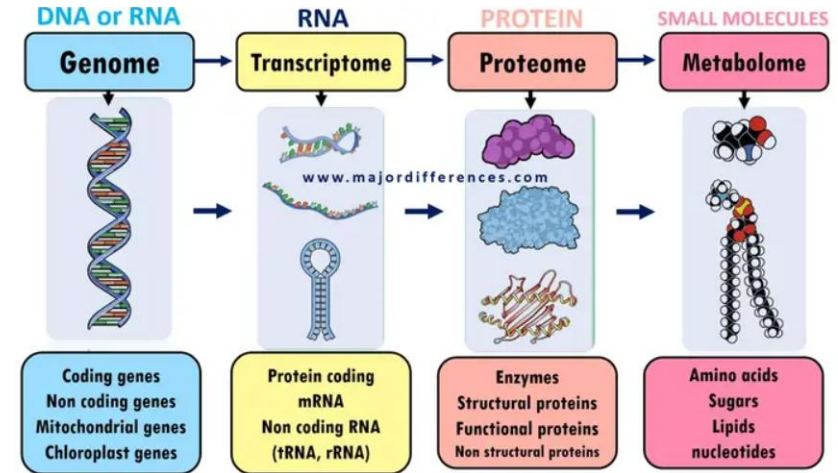
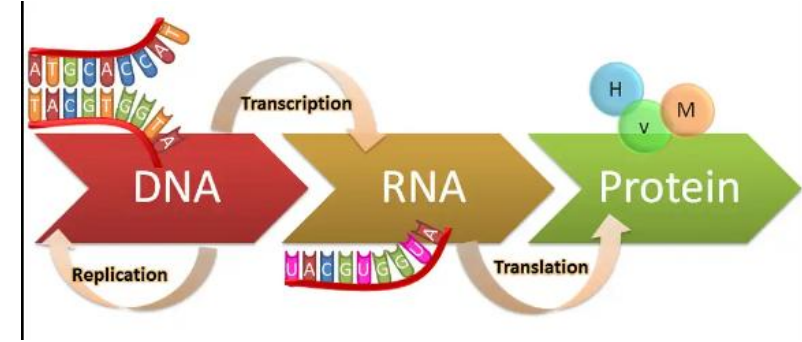
NDUFS1 geninin 3. ekzonunda klinik önemi bilinmeyen, heterozigot c.158A>G (chr2:207017180, p.Gln53Arg) değişimi saptanmıştır.

NOT: *SURF1* geni için kodlayıcı bölgeler kaplam oranı %94'tür. Bu gen için yapılan değerlendirme suboptimaldir. Hastanın klinik bulgularının adı geçen gen ile uyumlu olduğu düşünülüyorsa farklı bir moleküler yöntemle araştırma önerilir. Bu test, primerler dışında kalan bölgelerdeki mutasyonları, geniş delesyon/duplikasyonları (kopya sayısı değişiklikleri), epigenetik değişiklikleri ve mozaikliği göstermez. Aminoasit değişimine yol açmayan ve polimorfizm olarak belirtilen değişimler rapor edilmemiştir. Sonuçlar çok nadir olarak hastadaki durumu göstermeyebilir. Hastanın test sonucuna yönelik genetik danışma alması önerilir. *PMID: 25741868. Sonuçlar bölümümüzün izni olmadan kullanılamaz. Rapor tek sayfadır.

Raporlarda Varyant Nasıl İfade Edilir?

Varyantın İfadesi

- Varyantlar DNA, RNA veya Protein düzeyinde olabilir
- Öncelikle DNA düzeyinde verilmeli
- ‘en baştaki küçük harf’ sekansın tipini gösterir;
 - c. Kodlanan (coding) DNA
 - g. lineer genomik referans
 - m. mitokondriyal DNA
 - n. Kodlanmayan (noncoding) DNA
 - p. protein referans
 - r. RNA referans (transkript)



Örnek

Gen	Yeri	Varyant	Zigozite	Sınıflandırma	Hastalık OMIM#, Kalıtım
<i>FHL1</i> NM_001159699.2	İntron 5	c.736+8_736+9delAA	Hemizigot	Class 3 Klinik Önemi Bilinmeyen	<i>FHL1</i> ilişkili Hastalık OMIM:300717 X'e Bağlı Resesif

<i>UBA2</i> (ENST00000246548.4)	chr19:34959996 (Exon 17)	Missense Variant (p.S598L) c.1793C>T rs536680033	VUS	HETEROZİGOT	ACCES syndrome AD
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Bazı Biyolojik Veritabanları

- Veri tabanlarında birçok dizi birden fazla kez belirtilmiş ve gösterilmiştir.
- Sekans bilgileri için gereksiz fazlalığı olan gösterimleri engellemek ve bu belirtilimleri düzenlemek için **NCBI**, **RefSeq** ikincil alt veri tabanını oluşturmuştur.
- Genomik DNA, RNA ve protein dizi bilgileri için, geniş kapsamlı, düzenlenmiş ve gerekli olan sekans bilgilerini tekrar düzenlemiştir.
- Yani her bir DNA, RNA ve protein dizisi için doğruluğu kanıtlanmış ve kabul edilmiş sekans bilgilerini içerir.

RefSeq Erişim Numaraları

- RefSeq’de betimlenen diziye atanmış bir kimlik numarasıdır
- N ile başlayan 2 harf, alt çizgi ve ardından en az 6 rakamdan oluşur

NC_123456	Genomik	Bütünsel genomik molekülleri ifade eder (kromozomlar, organel DNA’sı, plasmidler)
NG_123456	Genomik	Analizi ve belirtimi tamamlanmamış genomik bölgeleri ifade eder.
NM_123456	mRNA	Genlerin transkript ürünlerini ifade etmektedir (haberci RNA). Veri tabanlarında bulunan, mRNA’lar, aslında ilgili RNA’ların cDNA’ya çevrilmiş hallerini belirtmektedir.
NP_123456	Protein	Protein dizilerini ifade eder.

RefSeq Veritabanında Neler Araştırabilirim?



Gen	Yeri	Varyant	Zigozite	Sınıflandırma	Hastalık OMIM#, Kalıtım
FHL1 NM_001159699.2	Intron 5	c.736+8_736+9delAA	Hemizigot	Class 3 Klinik Önemi Bilinmeyen	<i>FHL1</i> ilişkili Hastalık OMIM:300717 X'e Bağlı Resesif

An official website of the United States government [Here's how you know](#)

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National Center for Biotechnology Information

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RefSeq RefSeq NM_001159699.2 Search

RefSeq: NCBI Reference Sequence Database

A comprehensive, integrated, non-redundant, well-annotated set of reference sequences including genomic, transcript, and protein.

Using RefSeq

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- [Prokaryotic RefSeq Genomes](#)
- [FAQ](#)
- [NCBI Handbook](#)
- [Factsheet](#)

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- [RefSeq FTP](#)
- [RefSeq genomes FTP](#)
- [New RefSeq genomic \(last 30 days\)](#)
- [New RefSeq transcripts \(last 30 days\)](#)
- [New RefSeq proteins \(last 30 days\)](#)
- [Searching for RefSeq records \(Queries\)](#)

RefSeq projects

- [Consensus CDS \(CCDS\)](#)
- [RefSeq Functional Elements](#)
- [RefSeqGene](#)
- [Targeted Loci](#)
- [Virus Variation](#)
- [RefSeq Select](#)
- [MANE](#)

Announcements

September 11, 2023
RefSeq Release 220 is available for FTP
This release includes:

Related Links

- [Assembly](#)
- [Gene](#)

Feedback & Credits

- [Publications and Citing RefSeq](#)
- [Contact RefSeq Help Desk](#)

<https://www.ncbi.nlm.nih.gov/refseq/>



Nucleotide

Nucleotide

Advanced

GenBank

Send to:

Homo sapiens four and a half LIM domains 1 (FHL1), transcript variant 7, mRNA

NCBI Reference Sequence: NM_001159699.2

[FASTA](#) [Graphics](#)

Go to:

LOCUS NM_001159699 2286 bp mRNA linear PRI 26-JUN-2023
DEFINITION Homo sapiens four and a half LIM domains 1 (FHL1), transcript variant 7, mRNA.
ACCESSION NM_001159699
VERSION NM_001159699.2
KEYWORDS RefSeq; MANE Select.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 2286)
AUTHORS van Essen MF, Peereboom ETM, Schlagwein N, van Gijlswijk-Janssen DJ, Nelemans T, Joeloemsingh JV, van den Berg CW, Prins J, Clark SJ, Schmidt CQ, Trouw LA and van Kooten C.
TITLE Preferential production and secretion of the complement regulator factor H-like protein 1 (FHL-1) by human myeloid cells
JOURNAL Immunobiology 228 (3), 152364 (2023)
PUBMED [36881973](#)
REMARK GeneRIF: Preferential production and secretion of the complement

- Gen adı
- Fonksiyonu
- Pubmed yayınlarına erişim linki

PUBMED
COMMENT

(1993)
[20301609](#)

REVIEWED [REFSEQ](#): This record has been curated by NCBI staff. The reference sequence was derived from [DC373386.1](#), [BC088369.1](#) and [BM995585.1](#).

This sequence is a reference standard in the [RefSeqGene](#) project.

On Feb 20, 2019 this sequence version replaced [NM_001159699.1](#).

Summary: This gene encodes a member of the four-and-a-half-LIM-only protein family. Family members contain two highly conserved, tandemly arranged, zinc finger domains with four highly conserved cysteines binding a zinc atom in each zinc finger. Expression of these family members occurs in a cell- and tissue-specific mode and these proteins are involved in many cellular processes. Mutations in this gene have been found in patients with Emery-Dreifuss muscular dystrophy. Multiple alternately spliced transcript variants which encode different protein isoforms have been described.[provided by RefSeq, Nov 2009].

Transcript Variant: This variant (7) differs in the 5' UTR, 3' UTR, and 3' coding region and initiates translation at an alternate start codon, compared to variant 1. The encoded protein (isoform 5) has distinct N- and C-termini and is shorter than isoform 1.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Gene record to access additional publications.

##Evidence-Data-START##

Transcript exon combination :: SRR5189655.191858.1, BC088369.1
[ECO:0000332]

RNAseq introns :: single sample supports all introns
SAMEA1965299, SAMEA1966682
[ECO:0000348]

##Evidence-Data-END##

ORIGIN

```
1 agccttatca gctgggggtg aggggaagact ggtctagggt ctgctcctga acttggtctc
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2221 tgtcatatgc tattatcatc taacgtttca gtgtatcctt acagaaataa agcagcatat
2281 gaataa
```

- Fonksiyonu
- İyi korunmuş bölgeleri
- Domainleri
- İlişkili hastalıklar
- Transkriptin özellikleri
- Gen nükleotid dizimi

FEATURES

source

Location/Qualifiers

1..2286

/organism="Homo sapiens"

/mol_type="mRNA"

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/chromosome="X"

/map="Xq26.3"

gene

1..2286

/gene="FHL1"

/gene_synonym="FCMSU; FHL-1; FHL1A; FHL1B; FLH1A; KYOT;

RBMX1A; RBMX1B; SLIM; SLIM-1; SLIM1; SLIMMER; XMPMA"

/note="four and a half LIM domains 1"

/db_xref="GeneID:2273"

/db_xref="HGNC:HGNC:3702"

/db_xref="MIM:300163"

exon

1..88

/gene="FHL1"

/gene_synonym="FCMSU; FHL-1; FHL1A; FHL1B; FLH1A; KYOT;

RBMX1A; RBMX1B; SLIM; SLIM-1; SLIM1; SLIMMER; XMPMA"

/inference="alignment:Splign:2.1.0"

- GeneID
- OMIM linkleri

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Gene Advanced

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FHL1 four and a half LIM domains 1 [*Homo sapiens* (human)] Download Datasets

Gene ID: 2273, updated on 10-Oct-2023

Summary

Official Symbol FHL1 provided by HGNC

Official Full Name four and a half LIM domains 1 provided by HGNC

Primary source HGNC:HGNC:3702

See related Ensembl:ENSG0000022267 MIM:300163 AllianceGenome:HGNC:3702

Gene type protein coding

RefSeq status REVIEWED

Organism *Homo sapiens*

Lineage Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as KYOT; SLIM; FCMSU; FHL-1; FHL1A; FHL1B; FLH1A; SLIM1; XMPMA; RBMX1A; RBMX1B; SLIM-1; SLIMMER

Summary This gene encodes a member of the four-and-a-half-LIM-only protein family. Family members contain two highly conserved, tandemly arranged, zinc finger domains with four highly conserved cysteines binding a zinc atom in each zinc finger. Expression of these family members occurs in a cell- and tissue-specific mode and these proteins are involved in many cellular processes. Mutations in this gene have been found in patients with Emery-Dreifuss muscular dystrophy. Multiple alternately spliced transcript variants which encode different protein isoforms have been described [provided by RefSeq, Nov 2009]

Expression Broad expression in heart (RPKM 286.6), fat (RPKM 281.6) and 18 other tissues [See more](#)

Orthologs [mouse](#) [all](#)

[NEW](#) Try the new Gene table

<https://www.ncbi.nlm.nih.gov/gene>

GeneID Veritabanında Neler Araştırabilirim?

GeneID

NIH National Library of Medicine
National Center for Biotechnology Information

Gene

Full Report

FHL1 four and a half LIM domains 1 [*Homo sapiens* (human)]

Gene ID: 2273, updated on 10-Oct-2023

Summary

Official Symbol FHL1 provided by [HGNC](#)

Official Full Name four and a half LIM domains 1 provided by [HGNC](#)

Primary source [HGNC:HGNC:3702](#)

See related [Ensembl:ENSG00000022267](#) [MIM:300163](#) [AllianceGenome:HGNC:3702](#)

Gene type protein coding

RefSeq status REVIEWED

Organism [Homo sapiens](#)

Lineage Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as KYOT; SLIM; FCMSU; FHL-1; FHL1A; FHL1B; FLH1A; SLIM1; XMPMA; RBMX1A; RBMX1B; SLIM-1; SLIMMER

Summary This gene encodes a member of the four-and-a-half-LIM-only protein family. Family members contain two highly conserved, tandemly arranged, zinc finger domains with four highly conserved cysteines binding a zinc atom in each zinc finger. Expression of these family members occurs in a cell- and tissue-specific mode and these proteins are involved in many cellular processes. Mutations in this gene have been found in patients with Emery-Dreifuss muscular dystrophy. Multiple alternately spliced transcript variants which encode different protein isoforms have been described. [provided by RefSeq, Nov 2009]

Expression Broad expression in heart (RPKM 286.6), fat (RPKM 281.6) and 18 other tissues [See more](#)

Orthologs [mouse](#) [all](#)

NEW Try the new Gene table

- Gen isimleri
- Fonksiyonu
- Domainleri

<https://www.ncbi.nlm.nih.gov/gene/>

Expression

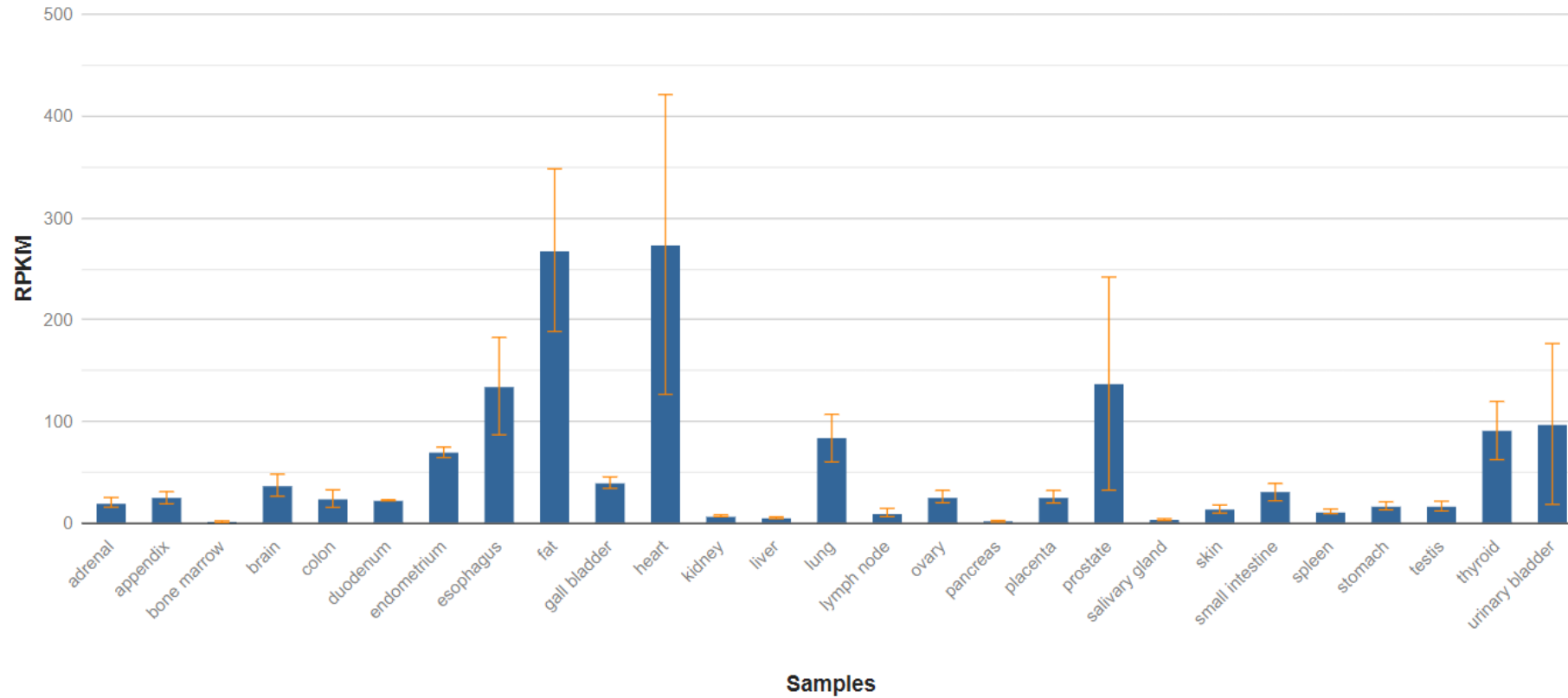


[See details](#)

HPA RNA-seq normal tissues

- Project title: HPA RNA-seq normal tissues
- Description: RNA-seq was performed of tissue samples from 95 human individuals representing 27 different tissues in order to determine tissue-specificity of all protein-coding genes
- BioProject: [PRJEB4337](#)
- Publication: [PMID 24309898](#)
- Analysis date: Wed Apr 4 07:08:55 2018

- Eksprese edildiği dokular



mRNA and Protein(s)

1. [NM_001159699.2](#) → [NP_001153171.1](#) four and a half LIM domains protein 1 isoform 5

[See identical proteins and their annotated locations for NP_001153171.1](#)

Status: REVIEWED

Description	Transcript Variant: This variant (7) differs in the 5' UTR, 3' UTR, and 3' coding region and initiates translation at an alternate start codon, compared to variant 1. The encoded protein (isoform 5) has distinct N- and C-termini and is shorter than isoform 1.
Source sequence(s)	BC088369_BM995585_DC373386
Consensus CDS	CCDS55506.1
UniProtKB/TrEMBL	Q53FI7
Related	ENSP00000359717.1 , ENST00000370683.6

Conserved Domains (5) [summary](#)

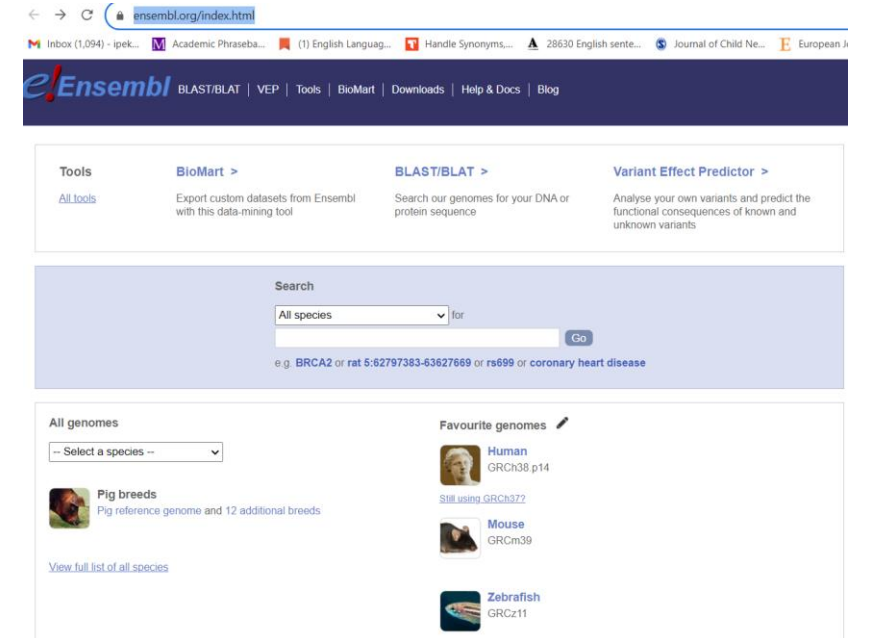
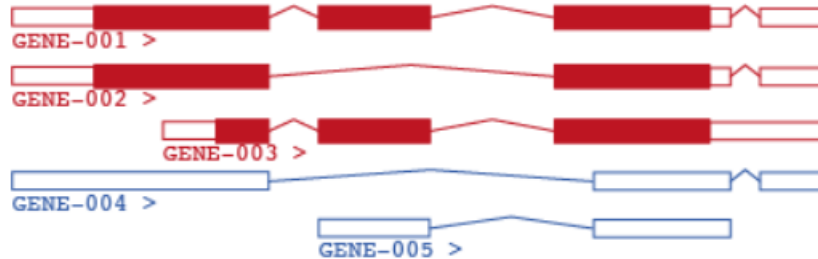
cd09344 Location:56 → 109	LIM1_FHL1; The first LIM domain of Four and a half LIM domains protein 1
cd09348 Location:233 → 296	LIM4_FHL1; The fourth LIM domain of Four and a half LIM domains protein 1 (FHL1)
cd09424 Location:117 → 174	LIM2_FHL1; The second LIM domain of Four and a half LIM domains protein 1 (FHL1)
cd09429 Location:178 → 230	LIM3_FHL1; The third LIM domain of Four and a half LIM domains protein 1 (FHL1)
cl02475 Location:21 → 49	LIM; LIM is a small protein-protein interaction domain, containing two zinc fingers

- Transkript özellikleri
- Protein düzeyinde domainler ve aminoasid lokalizasyonları

Bazı Biyolojik Veritabanları-2

- RefSeq'e benzer amaçlarla **Avrupa Biyoinformatik Enstitüsü; ENSEMBLE** Genom Veritabanı Projesi verilerini belirli erişim numaraları ile sunmaktadır.

ENSG00000198745.17 Gen
ENST00000357033.8 Transkript
ENSP00000354823.3 Protein



Matched Annotation from NCBI and EMBL-EBI (MANE)

<https://www.ensembl.org/index.html>

Ensembl Veritabanında Neler Araştırabilirim?

<https://www.ensembl.org/index.html>

Tools

[All tools](#)

BioMart >

Export custom datasets from Ensembl with this data-mining tool

BLAST/BLAT >

Search our genomes for your DNA or protein sequence

Variant Effect Predictor >

Analyse your own variants and predict the functional consequences of known and unknown variants

Search

Human for

FHL1

[Go](#)

e.g. [BRCA2](#) or [rat 5:62797383-63627669](#) or [rs699](#) or [coronary heart disease](#)

All genomes

-- Select a species --



Pig breeds

Pig reference genome and 12 additional breeds

[View full list of all species](#)

Favourite genomes



Human

GRCh38.p14

[Still using GRCh37?](#)



Mouse

GRCm39



Zebrafish

GRCz11

- İnsan, fare, zebra balığı gibi diğer organizmalar dahil

e!Ensembl BLAST/BLAT | VEP | Tools | BioMart | Downloads | Help & Docs | Blog Login/Reg

Human (GRCh38.p14) ▼ Search all species...

Location: X:136,146,702-136,211,359 **Gene: FHL1**

Gene-based displays

- Summary
 - Splice variants
 - Transcript comparison
 - Gene alleles
- Sequence
 - Secondary Structure
- Comparative Genomics
 - Genomic alignments
 - Gene tree
 - Gene gain/loss tree
 - Orthologues
 - Paralogues
- Ontologies
 - GO: Cellular component
 - GO: Biological process
 - GO: Molecular function
- Phenotypes
- Genetic Variation
 - Variant table
 - Variant image
 - Structural variants
- Gene expression
- Pathway
- Molecular interactions
- Regulation
- External references
- Supporting evidence
- ID History
 - Gene history

Gene: FHL1 ENSG00000022267

Description four and a half LIM domains 1 [Source:HGNC Symbol;Acc:[HGNC:3702](#)]

Gene Synonyms BA535K18.1, FHL1B, FLH1A, KYO-T, MGC111107, SLIM1, XMPMA

Location [Chromosome X: 136,146,702-136,211,359](#) forward strand.
GRCh38:CM000685.2

About this gene This gene has 36 transcripts ([splice variants](#)), [277 orthologues](#), [20 paralogues](#) and is associated with [12 phenotypes](#).

Transcripts [Show transcript table](#)

Summary

Name [FHL1](#) (HGNC Symbol)

MANE This gene contains MANE Select [ENST00000370683](#), [ENSP00000359717](#) and MANE Plus Clinical [ENST00000394155](#), [ENSP00000377710](#)

UniProtKB This gene has proteins that correspond to the following UniProtKB identifiers: [Q13642](#)

RefSeq This Ensembl/Gencode gene contains transcript(s) for which we have [selected identical RefSeq transcript\(s\)](#). If there are other RefSeq transcripts available they will be in the [External references](#) table

CCDS This gene is a member of the Human CCDS set: [CCDS14655.1](#), [CCDS55505.1](#), [CCDS55506.1](#), [CCDS55507.1](#), [CCDS76036.1](#), [CCDS83493.1](#)

LRG [LRG_739](#) provides a stable genomic reference framework for describing sequence variants for this gene

Ensembl version ENSG00000022267.19

Other assemblies This gene maps to [135,228,861-135,293,518](#) in GRCh37 coordinates.
View this locus in the GRCh37 archive: [ENSG00000022267](#)

Gene type Protein coding

Annotation method Annotation for this gene includes both automatic annotation from Ensembl and Havana manual curation, see [article](#).

[Go to Region in Detail](#) for more tracks and navigation options (e.g. zooming)

[Configure this page](#) [Custom tracks](#) [Export data](#)

- Transkriptleri
- Ortologlar
- İlişkili olduğu fenotipler
- Karşılaştırmalı genomik
- Bildirilen varyantlar
- Yolaklar
- Etkileşimde olduğu proteinler

MANE; Ensembl ve RefSeq veritabanlarını bağlar



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Human (GRCh38.p14) ▼

Location: X:136,146,702-136,211,359

Gene: FHL1

Gene-based displays

- Summary
 - Splice variants
 - Transcript comparison
 - Gene alleles
- Sequence
 - Secondary Structure
- Comparative Genomics
 - Genomic alignments
 - Gene tree
 - Gene gain/loss tree
 - Orthologues
 - Paralogues
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 - GO: Cellular component
 - GO: Biological process
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- Phenotypes
- Genetic Variation
 - Variant table
 - Variant image
 - Structural variants
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- Regulation
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 - Gene history

Gene: FHL1 ENSG00000022267

Description

four and a half LIM domains 1 [Source:HGNC Symbol;Acc:[HGNC:3702](#)]

Gene Synonyms

BA535K18.1, FHL1B, FLH1A, KYO-T, MGC111107, SLIM1, XMPMA

Location

[Chromosome X: 136,146,702-136,211,359](#) forward strand.

GRCh38:CM000685.2

About this gene

This gene has 36 transcripts ([splice variants](#)), [277 orthologues](#), [20 paralogues](#) and is associated with [12 phenotypes](#).

Transcripts

Show transcript table

Summary ?

Name

[FHL1](#) (HGNC Symbol)

MANE

This gene contains MANE Select [ENST00000370683](#), [ENSP00000359717](#) and MANE Plus Clinical [ENST00000394155](#), [ENSP00000377710](#)

UniProtKB

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RefSeq

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This gene is a member of the Human CCDS set: [CCDS14655.1](#), [CCDS55505.1](#), [CCDS55506.1](#), [CCDS55507.1](#), [CCDS76036.1](#), [CCDS83493.1](#)

LRG

[LRG_739](#) provides a stable genomic reference framework for describing sequence variants for this gene

Ensembl version

ENSG00000022267.19

Other assemblies

This gene maps to [135,228,861-135,293,518](#) in GRCh37 coordinates.

View this locus in the GRCh37 archive: [ENSG00000022267](#)

Gene type

Protein coding

Annotation method

Annotation for this gene includes both automatic annotation from Ensembl and Havana manual curation, see [article](#).



Go to Region in Detail for more tracks and navigation options (e.g. zooming)

Configure this page

Custom tracks

Export data

Gen	Yeri	Varyant	Zigozite	Sınıflandırma	Hastalık OMIM#, Kalıtım
<i>FHL1</i> NM_001159699.2	Intron 5	c.736+8_736+9delAA	Hemizigot	Class 3 Klinik Önemi Bilinmeyen	<i>FHL1</i> ilişkili Hastalık OMIM:300717 X'e Bağlı Resesif



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Human (GRCh38.p14) ▼

Location: X:136,146,702-136,211,359 Gene: **FHL1** Transcript: **FHL1-203**

Transcript-based displays

- Summary**
- Sequence
 - Exons
 - cDNA
 - Protein
- Protein Information
 - Protein summary
 - Domains & features
 - Variants
 - PDB 3D protein model
 - AlphaFold predicted model
- Genetic Variation
 - Variant table
 - Variant image
 - Haplotypes
 - Population comparison
 - Comparison image
- External References
 - General identifiers
 - Oligo probes
 - Supporting evidence
- ID History
 - Transcript history
 - Protein history

Transcript: ENST00000370683.6 FHL1-203

Description four and a half LIM domains 1 [Source:HGNC Symbol;Acc:HGNC:3702]

Gene Synonyms BA535K18.1, FHL1B, FLH1A, KYO-T, MGC111107, SLIM1, XMPMA

Location [Chromosome X: 136,197,047-136,211,354](#) forward strand.

About this transcript This transcript has 6 exons, is annotated with 36 domains and features, is associated with 3248 variant alleles and maps to 704 oligo probes.

Gene This transcript is a product of gene [ENSG00000022267.19](#) [Show transcript table](#)

Summary ?

Export image

FHL1-203 - ENST00000370683 > protein coding

Statistics Exons: 6, Coding exons: 6, Transcript length: 2,286 bps, Translation length: 296 residues

MANE This MANE Select transcript contains [ENSP00000359717](#) and matches to [NM_001159699.2](#) and [NP_001153171.1](#)

Uniprot This transcript corresponds to the following Uniprot identifiers: [Q13642](#)

CCDS This transcript is a member of the Human CCDS set: [CCDS55506](#)

Transcript Support Level (TSL) TSL:1

Version ENST00000370683.6

Type Protein coding

Annotation Method Transcript where the Ensembl genebuild transcript and the Havana manual annotation have the same sequence, for every base pair. See [article](#).

GENCODE basic gene This transcript is a member of the [Gencode basic](#) gene set.

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- Bildirilen varyantlar



Bazı Biyolojik Veritabanları-3

- dbSNP: Single Nucleotide Database
- rs ile başlayan SNP erişim numarasıdır

UBA2 (ENST00000246548.4)	chr19:34959996 (Exon 17)	Missense Variant (p.S598L) c.1793C>T rs536680033
---------------------------------	-----------------------------	---

NIH National Library of Medicine
National Center for Biotechnology Information

dbSNP
[Create alert](#) [Advanced](#)

Display Settings: ▾ Summary Send to: ▾

☐ rs536680033 [*Homo sapiens*]

1.

Variant type:	SNV
Alleles:	C>T [Show Flanks]
Chromosome:	19:34469091 (GRCh38) 19:34959996 (GRCh37)
Canonical SPDI:	NC_000019.10:34469090:C:T
Gene:	UBA2 (Varview)
Functional Consequence:	coding_sequence_variant,genic_downstream_transcript_variant,missense_variant
Validated:	by frequency,by alfa,by cluster
MAF:	T=0.000045/2 (ALFA) T=0.00003/8 (TOPMED) T=0.000036/5 (GnomAD)

[...more](#)

- hg19 ve hg38 koordinatları
- Varyant özellikleri
- Minör allel sıklığı

İdeal Varyant İfadesi

- NC_000023.11:g.32849790T>A
- NM_004006.3:c.124A>T r(124a>u) p.(Ser42Cys)
- DMD hemizigot

Varyantın Patojenik Olduğunu Nasıl Anlarız?



***ACMG ***



Published in final edited form as:
Genet Med. 2015 May ; 17(5): 405–424. doi:10.1038/gim.2015.30.

Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

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<https://doi.org/10.1186/s40246-022-00407-x>

Human Genomics

RESEARCH

Open Access

Expanding ACMG variant classification guidelines into a general framework

Emmanuelle Masson^{1,2†}, Wen-Bin Zou^{3,4†}, Emmanuelle Génin¹, David N. Cooper⁵, Gerald Le Gac^{1,2}, Yann Fichou¹, Na Pu^{1,6}, Vinciane Rebours⁷, Claude Férec¹, Zhuan Liao^{3,4} and Jian-Min Chen^{1*}

Abstract

Background: The American College of Medical Genetics and Genomics (ACMG)-recommended five variant classification categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign) have been widely used in medical genetics. However, these guidelines are fundamentally constrained in practice owing to their focus upon Mendelian disease genes and their dichotomous classification of variants as being either causal or not. Herein, we attempt to expand the ACMG guidelines into a general variant classification framework that takes into account not only the continuum of clinical phenotypes, but also the continuum of the variants' genetic effects, and the different pathological roles of the implicated genes.

Main body: As a disease model, we employed chronic pancreatitis (CP), which manifests clinically as a spectrum from monogenic to multifactorial. Bearing in mind that any general conceptual proposal should be based upon sound data, we focused our analysis on the four most extensively studied CP genes, *PRSS1*, *CFTR*, *SPINK1* and *CTRC*. Based upon several cross-gene and cross-variant comparisons, we first assigned the different genes to two distinct categories in terms of disease causation: CP-causing (*PRSS1* and *SPINK1*) and CP-predisposing (*CFTR* and *CTRC*). We then employed two new classificatory categories, "predisposing" and "likely predisposing", to replace ACMG's "pathogenic" and "likely pathogenic" categories in the context of CP-predisposing genes, thereby classifying all pathologically relevant variants in these genes as "predisposing". In the case of CP-causing genes, the two new classificatory categories served to extend the five ACMG categories whilst two thresholds (allele frequency and functional) were introduced to discriminate "pathogenic" from "predisposing" variants.

Conclusion: Employing CP as a disease model, we expand ACMG guidelines into a five-category classification system (predisposing, likely predisposing, uncertain significance, likely benign, and benign) and a seven-category classification system (pathogenic, likely pathogenic, predisposing, likely predisposing, uncertain significance, likely benign, and benign) in the context of disease-predisposing and disease-causing genes, respectively. Taken together, the two systems constitute a general variant classification framework that, in principle, should span the entire spectrum of variants in any disease-related gene. The maximal compliance of our five-category and seven-category classification systems with the ACMG guidelines ought to facilitate their practical application.

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder <i>BA1/BS1</i> OR observation in controls inconsistent with disease penetrance <i>BS2</i>			Absent in population databases <i>PM2</i>	Prevalence in affecteds statistically increased over controls <i>PS4</i>	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product <i>BP4</i> Missense in gene where only truncating cause disease <i>BP1</i> Silent variant with non predicted splice impact <i>BP7</i>	Multiple lines of computational evidence support a deleterious effect on the gene /gene product <i>PP3</i>	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before <i>PM5</i> Protein length changing variant <i>PM4</i>	Same amino acid change as an established pathogenic variant <i>PS1</i>	Predicted null variant in a gene where LOF is a known mechanism of disease <i>PVS1</i>
Functional Data	Well-established functional studies show no deleterious effect <i>BS3</i>		Missense in gene with low rate of benign missense variants and path. missenses common <i>PP2</i>	Mutational hot spot or well-studied functional domain without benign variation <i>PM1</i>	Well-established functional studies show a deleterious effect <i>PS3</i>	
Segregation Data	Non-segregation with disease <i>BS4</i>		Co-segregation with disease in multiple affected family members <i>PP1</i>	Increased segregation data →		
De novo Data				<i>De novo</i> (without paternity & maternity confirmed) <i>PM6</i>	<i>De novo</i> (paternity & maternity confirmed) <i>PS2</i>	
Allelic Data		Observed in <i>trans</i> with a dominant variant <i>BP2</i> Observed in <i>cis</i> with a pathogenic variant <i>BP2</i>		For recessive disorders, detected in <i>trans</i> with a pathogenic variant <i>PM3</i>		
Other Database		Reputable source w/out shared data = benign <i>BP6</i>	Reputable source = pathogenic <i>PP5</i>			
Other Data		Found in case with an alternate cause <i>BPS</i>	Patient's phenotype or FH highly specific for gene <i>PP4</i>			

Pathogenic

- 1 Very Strong (PVS1) AND
 - ≥1 Strong (PS1–PS4) OR
 - ≥2 Moderate (PM1–PM6) OR
 - 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) OR
 - ≥2 Supporting (PP1–PP5)
- ≥2 Strong (PS1–PS4) OR
- 1 Strong (PS1–PS4) AND
 - ≥3 Moderate (PM1–PM6) OR
 - 2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR
 - 1 Moderate (PM1–PM6) AND ≥4 Supporting (PP1–PP5)

Likely Pathogenic

- 1 Very Strong (PVS1) AND 1 Moderate (PM1–PM6) OR
- 1 Strong (PS1–PS4) AND 1–2 Moderate (PM1–PM6) OR
- 1 Strong (PS1–PS4) AND ≥2 Supporting (PP1–PP5) OR
- ≥3 Moderate (PM1–PM6) OR
- 2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR
- 1 Moderate (PM1–PM6) AND ≥4 Supporting (PP1–PP5)

Benign

- 1 Stand-Alone (BA1) OR
- ≥2 Strong (BS1–BS4)

Likely Benign

- 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) OR
- ≥2 Supporting (BP1–BP7)

- BS benign strong, BP benign supporting
- PVS pathogenic very strong, PS pathogenic strong, PM pathogenic moderate, PP pathogenic supporting

- Benign veya patojenik skorlara göre kolay sınıflama



Seçilen Kanıt Kodları:

PS4,PM6

Sonuç:

Muhtemelen Patojenik

? Aile Segregasyonunu Düzenle (PP1):

Destekleyen (Öntanımlı) ▾

? Hepsi Çok Kuvvetli Patojenik Kuvvetli Patojenik Orta Patojenik Destekleyen Patojenik Tek Başına Benin Kuvvetli Benin Destekleyen Benin

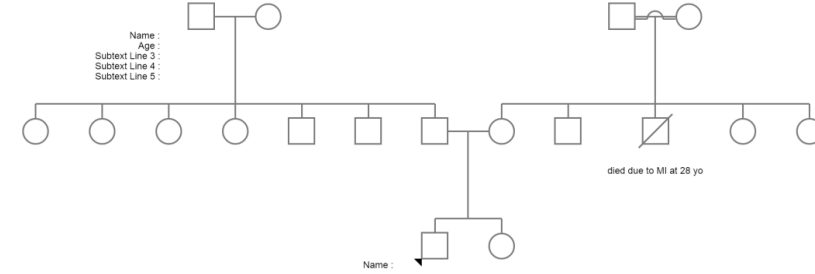
Arayın...

PP1 Ailedeki diğer hasta bireylerin varyasyonu taşıması	PVS1 Sıfır varyant (nonsense, frameshift, splice bölgesi, başlangıç kodonu, tekli veya çoklu ekzon delesyonu)	PS1 Daha önce patojenik olduğu belirlenen varyantla nükleotid değişiminden bağımsız olarak aynı amino asit değişimi	PS2 Hastada bulunup aile geçmişinde bulunmayan de novo vartantı. (Gen fenotip ile ilişkili olmalıdır.)
PS3 In vitro veya in vivo çalışmaları fonksiyona zarar verici etkiyi işaret ediyor	PS4 Varyantın hasta kişilerde görülme sıklığı sağlıklı kişilere göre çok daha fazla	PM1 Benin varyasyonların görülmediği mutasyon yoğun bölgelerde yer alması	PM2 Düşük alel frekansı (Exome Sequencing Project, 1000 Genomes Project, ya da Exome Aggregation Consortium)
PM3 Patojenik başka bir varyantla trans halinde bulunması (çekinik hastalıklar için)	PM4 Varyant sonucu protein uzunluğunun değişimi	PM5 Daha önce patojenik olduğu belirlenen bir missense varyasyonun olduğu amino asitte olan novel bir missense varyant	PM6 De Novo varyasyon (ebeveyn bilgisi olmadan)

https://seq.genomize.com/pathogenicity_calculator/

Örnek;

Fenotip	HSP
Bulgular	Motor gerilik Progresif süreç Prx ve distal güçsüzlük (AE) AE spastisite, hiperrefleksi, Babinski + Destekle yürüyor Kr-spinal MR normal CK normal-hafif artmış
Cinsiyet, yaş	E, 11yaş
Kalıtım paterni (olası)	X-e bağlı? De novo?
Testler	NM panel, WES
Sonuç	PLP1 c.636 G>A p.Trp212Ter (PM2, PVS1)



- Sıklıklar
- GnomAD veritabanında kullanmak için kromozom koordinatları



varsome **PLP1 c.636G>A** hg38 Search Editions About Community News Demo Sign in Join

chrX-103788450-G-A (PLP1:p.W212*) Submit to ClinVar Link publication Classify Share API Link Favorites

General Information SNV PLP1(ENST00000621218.5):c.636G>A (p.Trp212Ter)	PharmGKB No data available	Germline Classification Likely Pathogenic 9 points = 9 P - 0 B	Frequencies exomes: not found genomes: not found (cov: 24.2)	Conservation Scores phyloP100: 9.494	Structural Variants
Genes PLP1 (+2 more)	Transcripts ENST00000621218.5 - nonsense MANE Select	ClinVar No data available	MitoMap No data available	In-Silico Predictors 3 2 12	Beacon Network
Community Contributions	Region Browser	LOVD No data available	Deafness Variation Database No data available	ClinGen No data available	Protein Viewer No data available
Publications Variant: 0 Gene: 1788	Expression Data Top: brain_spinal_cord_cervical_c_1 Tissues: 54	Uniprot Variants No data available	OMIM No data available	GWAS No data available	

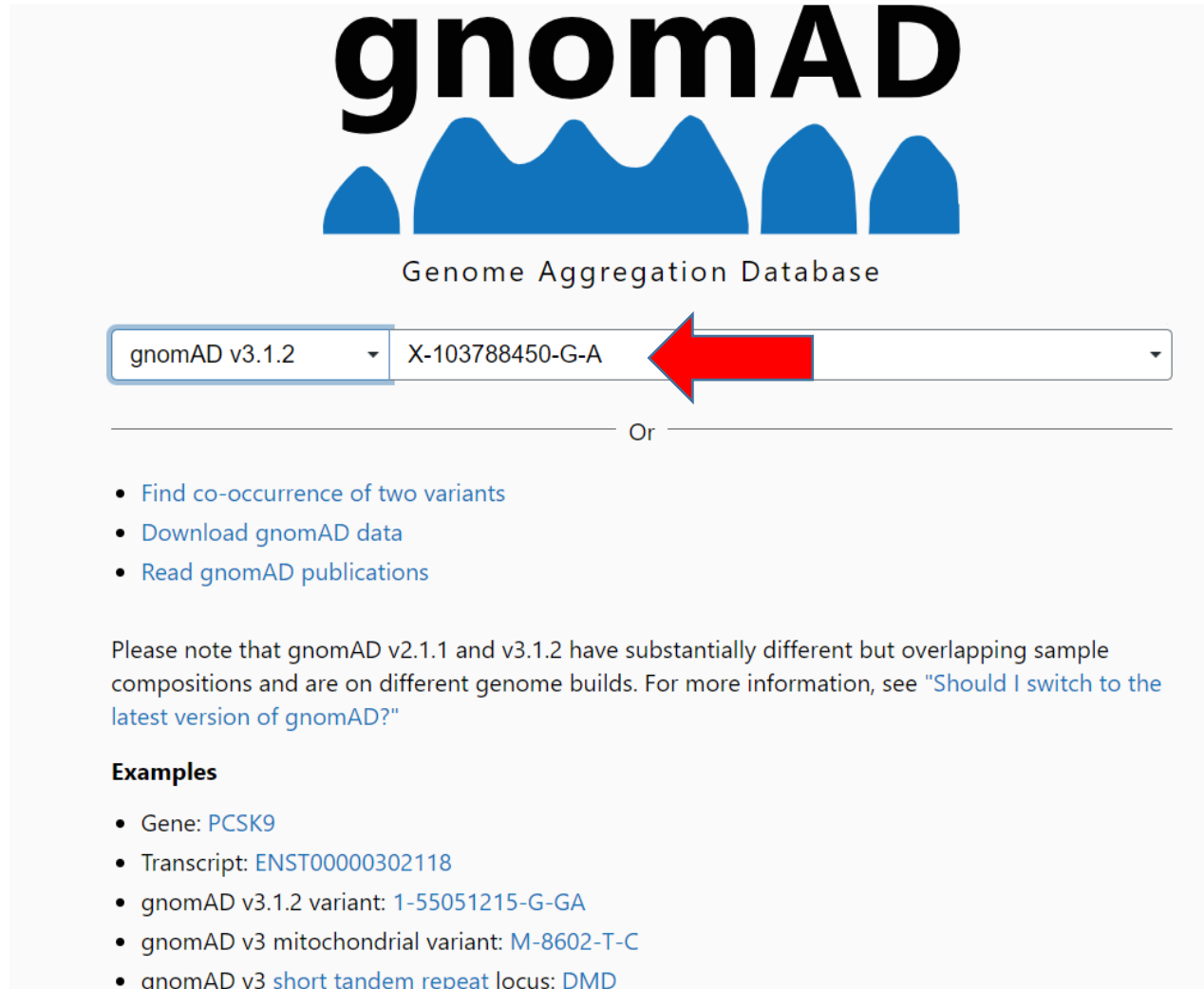
Variant Explain

Chromosome chrX	Position 103788450	REF Sequence G	ALT Sequence A	Variant type SNV	Cytoband Xq22.2	HGVS PLP1(ENST00000621218.5):c.636G>A (p.Trp212Ter)	Gene symbols PLP1 ENSG00000288597 RAB9B
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UCSC genome browser

This variant has been viewed 6 times on VarSome.

Genom Toplama Veritabanı (Genome Aggregation Database)



gnomAD
Genome Aggregation Database

gnomAD v3.1.2 X-103788450-G-A

Or

- Find co-occurrence of two variants
- Download gnomAD data
- Read gnomAD publications

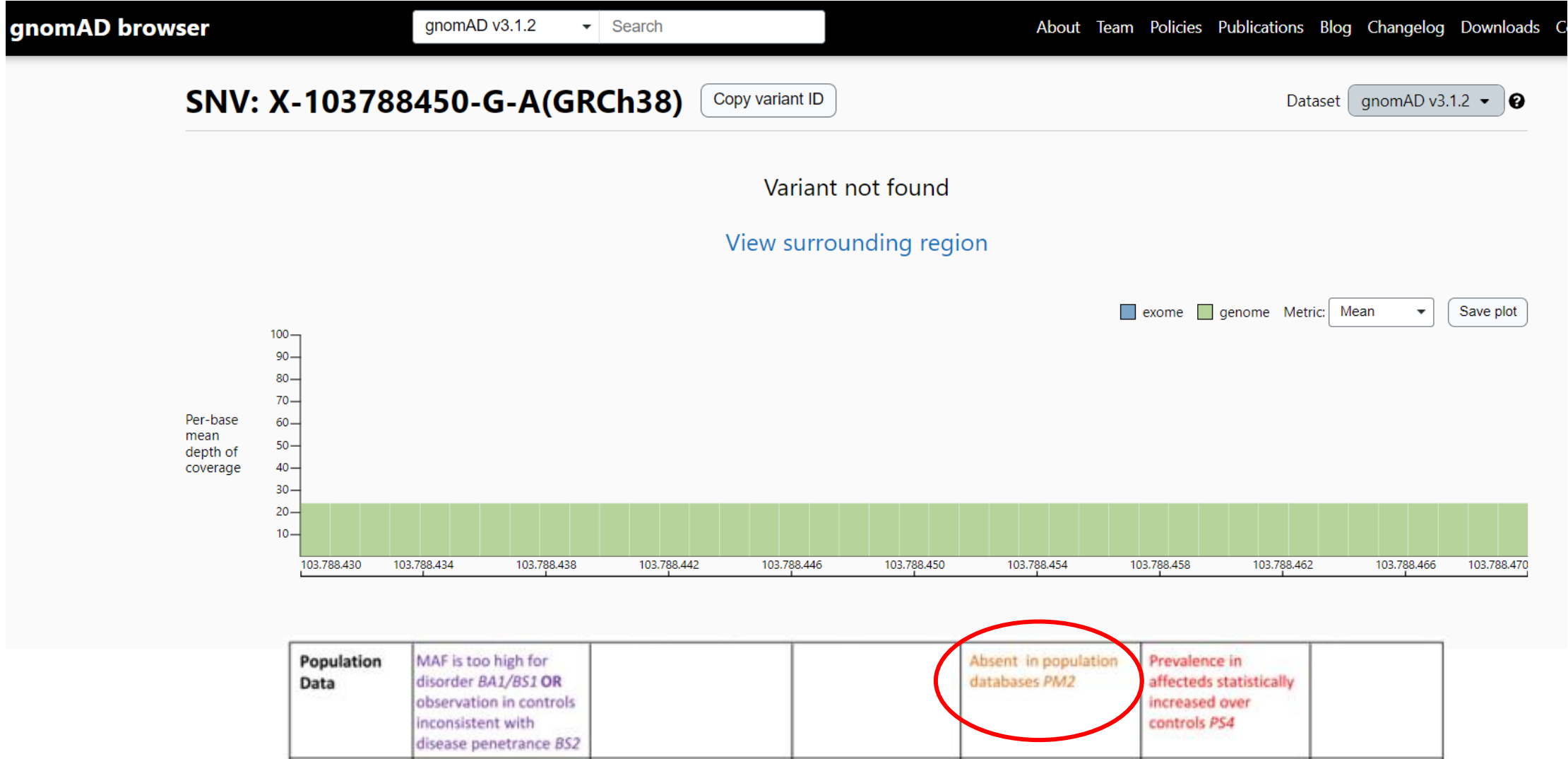
Please note that gnomAD v2.1.1 and v3.1.2 have substantially different but overlapping sample compositions and are on different genome builds. For more information, see "[Should I switch to the latest version of gnomAD?](#)"

Examples

- Gene: [PCSK9](#)
- Transcript: [ENST00000302118](#)
- gnomAD v3.1.2 variant: [1-55051215-G-GA](#)
- gnomAD v3 mitochondrial variant: [M-8602-T-C](#)
- gnomAD v3 short tandem repeat locus: [DMD](#)

<https://gnomad.broadinstitute.org/>

- GnomAD'de bu varyant bulunamadı
- Normal popülasyonda karşılaşılan bir varyant olmadığı için PM2



- Hastamızdaki c.636 pozisyonunun yakın çevresinde de bildirilen bir varyant yok

View surrounding region

gnomAD variants

gnomAD v3.1.2 variants (14)

Viewing in table

103.788.354 103.788.372 103.788.391 103.788.410 103.788.428 103.788.447 103.788.466 103.788.484 103.788.503 103.788.522 103.788.540

☒ pLoF only
 ☒ Missense / Inframe indel only
 ☒ Synonymous only
 ☒ Other only

 ?

☒ Exomes
 ☒ SNVs
 ☐ Filtered variants ?

☒ Genomes
 ☒ Indels
 ☒ Display neighboring variants

Search variant table

Variant ID	Source	Gene	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count	Allele Number	Allele Frequency
X-103788375-G-T	G	PLP1	c.623-62G>T	● intron				1	111993	8.
X-103788383-G-A	G	PLP1	c.623-54G>A	● intron				1	111901	8.
X-103788385-G-A	G	PLP1	c.623-52G>A	● intron				1	111794	8.
X-103788387-C-T	G	PLP1	c.623-50C>T	● intron				1	111858	8.
X-103788390-C-T	G	PLP1	c.623-47C>T	● intron				1	111792	8.
X-103788391-G-A	G	PLP1	c.623-46G>A	● intron				17	111837	1.
X-103788396-TC-T	G	PLP1	c.623-39del	● intron				5	111952	4.
X-103788410-C-T	G	PLP1	c.623-27C>T	● intron				2	111560	1.
X-103788424-G-T	G	PLP1	c.623-13G>T	● intron				3	111765	2.
X-103788451-A-T	G	PLP1	p.Asn213Tyr	● missense				1	111586	8.
X-103788480-C-T	G	PLP1	p.Ser222Ser	● synonymous		Benign		2	111882	1.
X-103788518-G-T	G	PLP1	c.696+8G>T	● splice region		Conflicting interpret...		1	111548	8.
X-103788531-A-G	G	PLP1	c.696+21A>G	● intron				4	111938	3.
X-103788537-C-T	G	PLP1	c.696+27C>T	● intron				1	112110	8.

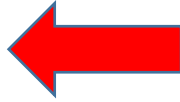
“Franklin Genoox’da” Populasyon Verileri

Franklin
by genoox

SEARCH KNOWLEDGE BASE MY CASES Learn More

The Future of Genomic Medicine

Examples: SNP CNV ROH

PLP1 c.636G>A 

REFERENCE hg38 TYPE Germline

Add your case details

What is the variant zygosity?

Homozygote Heterozygote Unknown

1/7 questions Skip question Search

CMA Report VCF



Suggested classification

Likely Pathogenic

UNMET: PS1 | PM4 | PM5 | BP1 | BP3 | BP7

[See Details](#)

Population Data



Moderate
[Edit](#)

Pathogenic Moderate:

Extremely low frequency in gnomAD population databases [Close Details](#)

Allele frequency is extremely low in all databases.
Recommended PM2 frequency threshold for gene: 0.05%
Allele frequencies are:

- ✓ gnomAD maximal non founder subpopulations frequency: 0.0%
- ✓ gnomAD maximal founder subpopulations frequency: 0.0%

① Note: recommended PM2 frequency threshold for gene: 0.05%

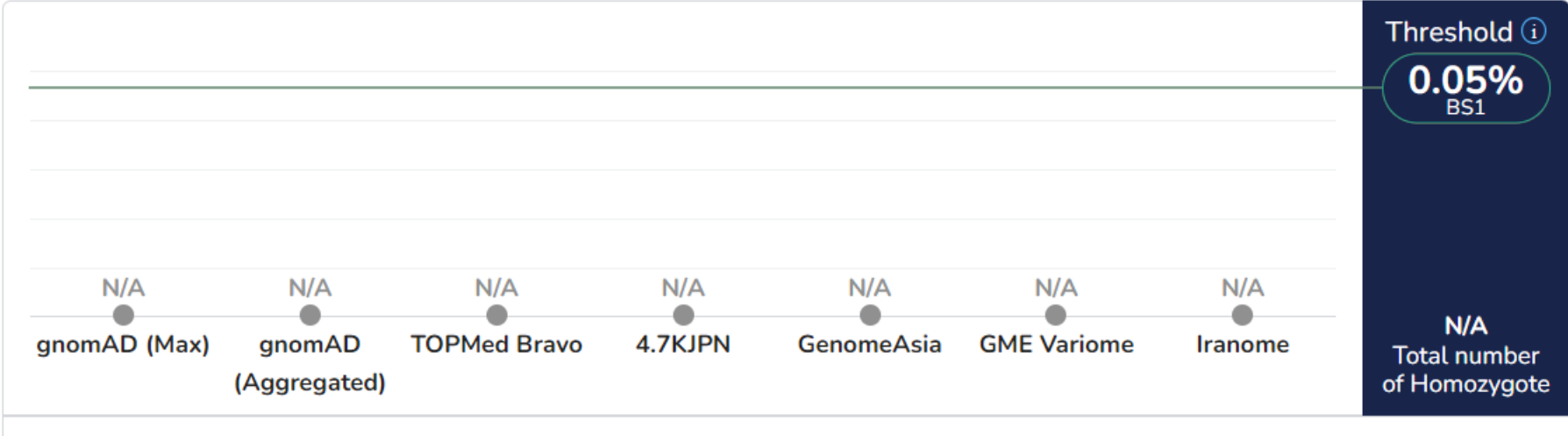
Most frequent known pathogenic variants in gene are:

chrX:103785752:G>T, frequency: 0.0%
chrX:103787904:T>C, frequency: 0.0%
chrX:103790553:C>A, frequency: 0.0%

① Note: founder populations in gnomAD including Ashkenazi Jewish and Finnish were assigned a higher threshold with at least 1%

- GnomAD veritabanına göre popülasyonda bu varyant bulunmuyor (%0.0)

Population Frequencies



- Turkish variome dahil farklı veritabanları hakkında da bilgiye ulaşılabilir

N/A	4.7KJPN No Observation for this variant in 4.7KJPN	N/A Alleles of N/A N/A homozygote N/A Individuals
N/A	GenomeAsia No Observation for this variant in GenomeAsia	N/A Alleles of N/A N/A homozygote N/A Individuals
N/A	Mexican DB No Observation for this variant in Mexican DB	N/A Alleles of N/A N/A homozygote N/A Individuals
N/A	India DB No Observation for this variant in India DB	N/A Alleles of N/A N/A homozygote N/A Individuals
N/A	Turkish Variome No Observation for this variant in Turkish Variome	N/A Alleles of N/A N/A homozygote N/A Individuals
Minimize		

Örnek;

Fenotip	Mitokondriyal
Bulgular	Infantil muskuler hipotoni Motor gerilik ,Dil alanında gerilik SNİK, ID AE/ÜE proksimal güçsüzlük Hareket bozuklukları CK 10000 U/L EMG miyopatik Kas bx: Mitokondriyal miyopati
Cinsiyet, yaş	K, 4 yaş
Kalıtım paterni (olası)	OR? Maternal?
Testler	NM panel, WES
Sonuç	MICU1 homozigot c.553 C>T, p.Arg185* (rs755651388)

1596287636162-pedigree IC TIM00052 BA
8/1/20



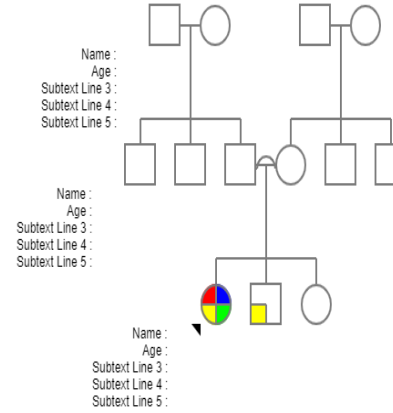
delayed gross motor milestones



muscle weakness



intellectual disability



<https://www.ncbi.nlm.nih.gov/clinvar>

<https://www.deciphergenomics.org/>

<https://lovd.nl>

Pubmed

<https://franklin.genoox.com/>

<https://varsome.com/>



ClinVar

ClinVar ▼

MICU1

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Statistics ▼

FTP ▼



Announcing changes to support somatic variant classifications

We anticipate changes to the ClinVar XML files and our submission spreadsheet templates in the fall of 2023 to improve support for classifications of somatic variants in ClinVar. To help our users and submitters prepare for this change, we are providing a preview of submission spreadsheet templates, updated XSDs, sample XMLs, and supporting documentation on [GitHub](#). Please share this information with your colleagues, including your bioinformatics team!

ACTGATGGTATGGGGCCAAGAGATATATCT
CAGGTACGGCTGTCATCACTTAGACCTCAC
CAGGGCTGGGCATAAAAGTCAGGGCAGAGC
CCATGGTGCATCTGACTCCTGAGGAGAAGT
GCAGGTTGGTATCAAGGTTACAAGACAGGT
GGCACTGACTCTCTCTGCCTATTGGTCTAT

ClinVar

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

Using ClinVar

[About ClinVar](#)

Tools

[ACMG Recommendations for Reporting of Secondary Findings](#)

Related Sites

[ClinGen](#)

	Variation Location	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)	Review status
☐ 145.	NM_001195518.2(MICU1):c.603T>C (p.Cys201=) GRCh37: Chr10:74267962 GRCh38: Chr10:72508204	MICU1		not provided	Likely benign (Jul 5, 2022)	criteria provided, single submitter
☐ 146.	NM_001195518.2(MICU1):c.598G>T (p.Glu200Ter) GRCh37: Chr10:74267967 GRCh38: Chr10:72508209	MICU1	E200*, E202*, E206*	not provided	Pathogenic (Oct 17, 2022)	criteria provided, single submitter
☐ 147.	NM_001195518.2(MICU1):c.577A>G (p.Ser193Gly) GRCh37: Chr10:74267988 GRCh38: Chr10:72508230	MICU1	S193G, S199G, S195G	not provided	Uncertain significance (Jun 27, 2022)	criteria provided, single submitter
☐ 148.	NM_001195518.2(MICU1):c.549G>A (p.Gln183=) GRCh37: Chr10:74268016 GRCh38: Chr10:72508258	MICU1		not provided	Likely benign (Jul 16, 2022)	criteria provided, single submitter
☐ 149.	NM_001195518.2(MICU1):c.547C>G (p.Gln183Glu) GRCh37: Chr10:74268018 GRCh38: Chr10:72508260	MICU1	Q183E, Q185E, Q189E	not provided	Uncertain significance (Apr 6, 2022)	criteria provided, single submitter
☐ 150.	NM_001195518.2(MICU1):c.547C>T (p.Gln183Ter) GRCh37: Chr10:74268018 GRCh38: Chr10:72508260	MICU1	Q185*, Q183*, Q189*	Proximal myopathy with extrapyramidal signs, not provided, Abnormality of the nervous system	Pathogenic (Oct 31, 2022)	criteria provided, multiple submitters, conflicts
☐ 151.	NM_001195518.2(MICU1):c.538-3T>C GRCh37: Chr10:74268030 GRCh38: Chr10:72508272	MICU1		not provided	Uncertain significance (Mar 1, 2022)	criteria provided, single submitter
☐ 152.	NM_001195518.2(MICU1):c.538-4A>G GRCh37: Chr10:74268031 GRCh38: Chr10:72508273	MICU1		Proximal myopathy with extrapyramidal signs, not provided	Benign (Nov 4, 2022)	criteria provided, multiple submitters, conflicts

	Variation Location	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)	Review status
☐ 145.	NM_001195518.2(MICU1):c.603T>C (p.Cys201=) GRCh37: Chr10:74267962 GRCh38: Chr10:72508204	MICU1		not provided	Likely benign (Jul 5, 2022)	criteria provided, single submitter
☐ 146.	NM_001195518.2(MICU1):c.598G>T (p.Glu200Ter) GRCh37: Chr10:74267967 GRCh38: Chr10:72508209	MICU1	E200*, E202*, E206*			criteria provided, single submitter
☐ 147.	NM_001195518.2(MICU1):c.577A>G (p.Ser193Gly) GRCh37: Chr10:74267988 GRCh38: Chr10:72508230	MICU1	S193G, S199G, S195*			criteria provided, single submitter
☐ 148.	NM_001195518.2(MICU1):c.549G>A (p.Gln183=) GRCh37: Chr10:74268016 GRCh38: Chr10:72508258	MICU1		not provided	Likely benign (Jul 16, 2022)	criteria provided, single submitter
☐ 149.	NM_001195518.2(MICU1):c.547C>G (p.Gln183Glu) GRCh37: Chr10:74268018 GRCh38: Chr10:72508260	MICU1	Q183E, Q185E, Q189E	not provided	Uncertain significance (Apr 6, 2022)	criteria provided, single submitter
☐ 150.	NM_001195518.2(MICU1):c.547C>T (p.Gln183Ter) GRCh37: Chr10:74268018 GRCh38: Chr10:72508260	MICU1	Q185*, Q183*, Q189*	Proximal myopathy with extrapyramidal signs, not provided, Abnormality of the nervous system	Pathogenic (Oct 31, 2022)	criteria provided, multiple submitters, conflicts
☐ 151.	NM_001195518.2(MICU1):c.538-3T>C GRCh37: Chr10:74268030 GRCh38: Chr10:72508272	MICU1		not provided	Uncertain significance (Mar 1, 2022)	criteria provided, single submitter
☐ 152.	NM_001195518.2(MICU1):c.538-4A>G GRCh37: Chr10:74268031 GRCh38: Chr10:72508273	MICU1		Proximal myopathy with extrapyramidal signs, not provided	Benign (Nov 4, 2022)	criteria provided, multiple submitters, conflicts

CliVar'da bu varyant (c.553C>T) bildirilmemiş

Novel varyant???



The Future of Genomic Medicine

Examples: **SNP** **CNV** **ROH**

MICU1 c.553C>T



REFERENCE
hg38

TYPE
Germline



Add your
case details

What is the variant zygosity?

Homozygote

Heterozygote

Unknown

1/7 questions

Skip question

Search



CMA

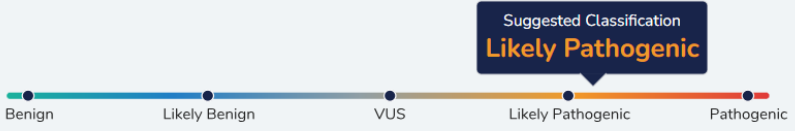


Report



VCF

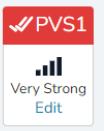
New! Get an expert opinion regarding this variant assessment [Learn More](#)



EVIDENCE

Aggregated from public databases using ACMG Guidelines

Effect on Protein



Pathogenic Very Strong:

Null variant in a gene where loss of function is a known mechanism of disease [See Details](#)

UNMET: PS1 | PM4 | PM5 | BP1 | BP3 | BP7

Population Data

Pathogenic Very Strong:

Null variant in a gene where loss of function is a known mechanism of disease [Close Details](#)

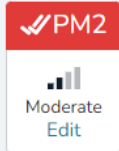
- ✓ Null variant (stop gain):
- ✓ Loss of function is a known mechanism of disease:
28 pathogenic null variants were reported in ClinVar for this gene (chr10:72508260:G>A:HG38, chr10:72508209:C>A:HG38, chr10:72508167:TTG>T:HG38, chr10:72508153:A>C:HG38...), across 9 different exons, of which 4 variants in this exon (6)
gnomAD observed/expected score 1.291
Coding strand: reverse strand
- ✓ Predicted to undergo NMD, not located in last exon or last 50bp of preliminary exon.
Coding exon number 5 out of 11 coding exons (6 out of total exons)

• Franklin Genoox'da stop kodon oluşturan "null varyant" olduğu bilgisine ulaşıyoruz ve PVS1 skorunu alıyor

• Ayrıca ClinVar'da da bu gen ile ilgili 28 tane daha patojenik null varyant bildirildiğini öğreniyoruz ve bunların 4'ü bizim varyantımızın olduğu exonda

MICU1: LP varyant

Population Data



Pathogenic Moderate:

Extremely low frequency in gnomAD population databases [Close Details](#)

Allele frequency is extremely low in all databases.
Recommended PM2 frequency threshold for gene: 0.05%
Allele frequencies are:

- ✓ gnomAD maximal non founder subpopulations frequency: 0.009%
- ✓ gnomAD maximal founder subpopulations frequency: 0.0%

① Note: recommended PM2 frequency threshold for gene: 0.05%
Most frequent known pathogenic variants in gene are:
chr10:72408038:C>G, frequency: 0.021%
chr10:72551178:C>T, frequency: 0.017%
chr10:72566753:GC>G, frequency: 0.012%

① Note: founder populations in gnomAD including Ashkenazi Jewish and Finnish were assigned a higher threshold with at least 1%



- Franklin Genoox'da gnomAD'de popülasyon sıklığının çok düşük olduğunu görüyoruz ve PVS1'e ek olarak PM2 skorunu alıyor

Pathogenic

- 1 1 Very Strong (PVS1) *AND*
 - a. ≥ 1 Strong (PS1–PS4) *OR*
 - b. ≥ 2 Moderate (PM1–PM6) *OR*
 - c. 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) *OR*
 - d. ≥ 2 Supporting (PP1–PP5)
- 2 ≥ 2 Strong (PS1–PS4) *OR*
- 3 1 Strong (PS1–PS4) *AND*
 - a. ≥ 3 Moderate (PM1–PM6) *OR*
 - b. 2 Moderate (PM1–PM6) *AND* ≥ 2 Supporting (PP1–PP5) *OR*
 - c. 1 Moderate (PM1–PM6) *AND* ≥ 4 Supporting (PP1–PP5)

Likely Pathogenic

- 1 1 Very Strong (PVS1) *AND* 1 Moderate (PM1–PM6) *OR*
- 2 1 Strong (PS1–PS4) *AND* 1–2 Moderate (PM1–PM6) *OR*
- 3 1 Strong (PS1–PS4) *AND* ≥ 2 Supporting (PP1–PP5) *OR*
- 4 ≥ 3 Moderate (PM1–PM6) *OR*
- 5 2 Moderate (PM1–PM6) *AND* ≥ 2 Supporting (PP1–PP5) *OR*
- 6 1 Moderate (PM1–PM6) *AND* ≥ 4 Supporting (PP1–PP5)

Benign

- 1 1 Stand-Alone (BA1) *OR*
- 2 ≥ 2 Strong (BS1–BS4)

Likely Benign

- 1 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) *OR*
- 2 ≥ 2 Supporting (BP1–BP7)

Decipher'de Neler Araştırabilirim?


[About](#)
[Browse](#)
[DDD](#)

?
Q
Help
Join
Log in

e.g. EP300, Hypertrichosis, splice_donor_variant, more...
Clear filters

Search examples

You can use any of the following to search for patients and variants deposited into DECIPHER.

- Hypertrichosis** – by phenotype
- hp:0001831** – by HPO Identifier. Prefix the HPO ID you wish to search with **hp:**
- 6:157099063-157531913** – by position in GRCh38
- grch37:6:157099063-157531913** – by position in GRCh37
- 17p11.2** – by band (band will be converted to position)
- EP300** – by gene
- Benign** – by **pathogenicity**
- Biparental** – by **inheritance**
- splice_donor_variant** – by **consequence**
- 255882** – by DECIPHER patient ID
- dendritic spines** – plain text search in syndrome names, descriptions, etc.

EXACT VARIANT SEARCHES

Searches for small DNA sequence and protein variants will take you to a dedicated page for that change (whether or not a DECIPHER variant exists). These searches cannot be combined with other terms.

- X:77652333 CTCT>C** – DNA sequence variant by GRCh38 location (1-based)
- 22:41177728:AC:** – DNA sequence variant by SPDI (0-based; use three colons)
- chrX:g.7257548_7257549insA** – DNA sequence variant by HGVSg
- EP300:c.35C>T** – coding sequence variant by HGVSg and HGNC gene symbol
- NM_001273.5:c.1933C>T** – coding sequence variant by HGVSg and RefSeq transcript
- PACS1:p.R203W** – protein variant by HGVSg and HGNC gene symbol
- NM_017617.5:p.Cys283Ter** – protein variant by HGVSg (trigraphs) and RefSeq transcript

Note that Ensembl stable IDs (ENSG, ENST, ENSP) are also accepted in place of other identifiers.

You can combine multiple terms (except variant searches), by separating them with a comma and a space, for example:

- 17p11.2, Dyscalculia** – Combine band and phenotype
- Arachnodactyly, High palate** – Search for patients with more than one phenotype

Close

Clear filters

Search

<https://www.deciphergenomics.org/>

MICU1 10:72508254 G > A

stop_gained ENST00000361114 p.Arg185Ter

No identical open-access DECIPHER patient variants

Not in DDD research variants dataset

Not in ClinVar

gnomAD - Genome MAF: 3.95×10^{-5}

[Gene](#)
[Browser](#)
[Protein](#)
[Annotation](#)
[Matching patient variants](#) 21

[Matching DDD research variants](#) 0

[Clinical](#)
[Protein / Genomic](#)

MICU1 10:72367340-72626131

Gene/disease association

Gene2Phenotype ?

- Biallelic - Absent gene product: Myopathy with Extrapyraxidal Signs **DD, Definitive**

OMIM ?

605084

Morbid ?

Myopathy with extrapyramidal signs (Autosomal recessive)

GeneReviews ?

-

ClinGen gene/disease ?

Predictive scores

pLI 0.00 ?

LOEUF 1.29 ?

sHet 0.005 ?

pHaplo 0.25 ?

pTriplo 0.62 ?

Management resources

IEMbase ?

- Mitochondrial calcium uniporter 1 deficiency (Autosomal recessive)

Search databases

- [PubMed](#)
- [Gene Tests](#)
- [Genomics England PanelApp ?](#)
- [LSDB](#)
- [Entries in DECIPHER for this gene](#)

MICU1 10:72508254 G > A

stop_gained ENST00000361114 p.Arg185Ter

No identical open-access DECIPHER patient variants

Not in DDD research variants dataset

Not in ClinVar

gnomAD - Genome MAF: 3.95×10^{-5}

Gene Browser Protein Annotation Matching patient variants **21** Matching DDD research variants **0**

Clinical Protein / Genomic

• Diğer veritabanlarındaki erişim numaralarına ulaşılabilir

• Gen ürünümüzle ilgili diğer veritabanlarındaki bilgilere direk ulaşım sağlayan linkler

MICU1 10:72367340-72626131

Protein identifiers

UniProt ?
Q9BPX6

InterPro ?
IPR002048, IPR011992, IPR018247, IPR039800

Pfam ?
PF13202, PF13833

3D Structures (PDB) ?
4NSC, 4NSD, 6K7Y, 6LB7, 6LB8, 6LE5, 6WDN, 6WDO, 6XJV, 6XJX, 6XQN, 6XQO

Genomic identifiers

Ensembl ? ENSG00000107745
UCSC ? uc001jtb.3
RefSeq ? NM_006077
NCBI ? 10367
HGNC ? 1530

Search databases

- Expression Atlas
- GeneCards
- Protein Atlas
- Missense3D-DB
- Entries in DECIPHER for this gene

MICU1 10:72508254 G > A

stop_gained ENST00000361114 p.Arg185Ter

No identical open-access DECIPHER patient variants

Not in DDD research variants dataset

Not in ClinVar

gnomAD - Genome MAF: 3.95×10^{-5}

[Gene](#)
[Browser](#)
[Protein](#)
[Annotation](#)
[Matching patient variants 21](#)
[Matching DDD research variants 0](#)

[Clinical](#)
[Protein / Genomic](#)

• Diğer veritabanlarındaki erişim numaralarına ulaşılabilir

• Gen ürünümüzle ilgili diğer veritabanlarındaki bilgilere direk ulaşım sağlayan linkler

MICU1 10:72367340-72626131

Protein identifiers

[UniProt](#) 
[Q9BPX6](#)

[InterPro](#) 
[IPR002048](#), [IPR011092](#), [IPR018247](#), [IPR039800](#)

[Pfam](#) 
[PF13202](#), [PF13833](#)

3D Structures (PDB)

[4NSC](#), [4NSD](#), [6K7Y](#), [6LB7](#), [6LB8](#), [6LE5](#), [6WDN](#), [6WDO](#), [6XJV](#), [6XJX](#), [6XQN](#), [6XQO](#)

Genomic identifiers

[Ensembl](#)  [ENSG00000107745](#)
[UCSC](#)  [uc001jtb.3](#)
[RefSeq](#)  [NM_006077](#)
[NCBI](#)  [10367](#)
[HGNC](#)  [1530](#)

Search databases

- [Expression Atlas](#)
- [GeneCards](#)
- [Protein Atlas](#)
- [Missense3D-DB](#)
- [Entries in DECIPHER for this gene](#)



BLAST Align Peptide search ID mapping SPARQL

UniProtKB

Advanced | List

Search



Function

Names & Taxonomy

Subcellular Location

Disease & Variants

PTM/Processing

Expression

Interaction

Structure

Family & Domains

Sequence & Isoforms

Similar Proteins

Q9BPX6 · MICU1_HUMAN

Proteinⁱ | Calcium uptake protein 1, mitochondrial

Geneⁱ | MICU1

Statusⁱ | UniProtKB reviewed (Swiss-Prot)

Organismⁱ | Homo sapiens (Human)

Amino acids | 476 (go to sequence)

Protein existenceⁱ | Evidence at protein level

Annotation scoreⁱ | 5/5

Entry Variant viewer Feature viewer Publications External links History

BLAST Align Download Add Add a publication Entry feedback

Functionⁱ

Key regulator of mitochondrial calcium uniporter (MCU) that senses calcium level via its EF-hand domains (PubMed:20693986, PubMed:23101630, PubMed:23747253, PubMed:24313810, PubMed:24332854, PubMed:24503055, PubMed:24560927, PubMed:26341627, PubMed:26903221, PubMed:27099988).

MICU1 and MICU2 form a disulfide-linked heterodimer that stimulates and inhibits MCU activity, depending on the concentration of calcium. MICU1 acts both as activator or inhibitor of mitochondrial calcium uptake (PubMed:26903221).

Acts as a gatekeeper of MCU at low concentration of calcium, preventing channel opening (PubMed:26903221).

Enhances MCU opening at high calcium concentration, allowing a rapid response of mitochondria to calcium signals generated in the cytoplasm (PubMed:2456092).

Gen ürünü proteinin;

- Fonksiyonu,
- Bu veritabanında bildirilen varyantları,
- Farklı dokularda ekspresyon oranları
- Diğer proteinler ile etkileşimleri
- Domainleri
- Izoformları

MICU1 10:72508254 G > A

stop_gained ENST00000361114 p.Arg185Ter

No identical open-access DECIPHER patient variants

Not in DDD research variants dataset

Not in ClinVar

gnomAD - Genome MAF: 3.95×10^{-5}

Gene

Browser

Protein

Annotation

Matching patient variants 21

Matching DDD research variants 0

Clinical

Protein / Genomic

- Diğer veritabanlarındaki erişim numaralarına ulaşılabilir

- Gen ürünümüzle ilgili diğer veritabanlarındaki bilgilere direk ulaşım sağlayan linkler

MICU1 10:72367340-72626131

Protein identifiers

UniProt ?
Q9BPX6

InterPro ?
IPR002048, IPR011992, IPR018247, IPR039800

Pfam ?
PF13202, PF13833

3D Structures (PDB) ?
4NSC, 4NSD, 6K7Y, 6LB7, 6LB8, 6LE5, 6WDN, 6WDO, 6XJV, 6XJX, 6XQN, 6XQO

Genomic identifiers

Ensembl ? ENSG00000107745
UCSC ? uc001jtb.3
RefSeq ? NM_006077
NCBI ? 10367
HGNC ? 1530

Search data

- Expression Atlas
- GeneCards
- Protein Atlas
- Missense3D-DB
- Entries in DECIPHER for this gene



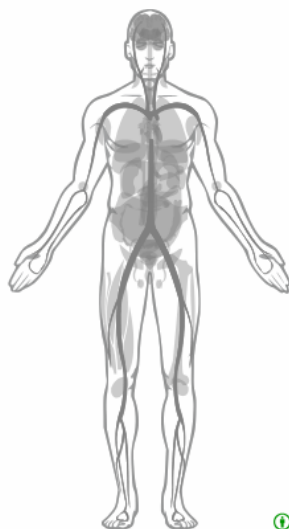
Expression Atlas

Gene expression across species and biological conditions

[Home](#) [Browse experiments](#) [Download](#) [Release notes](#) [FAQ](#) [Help](#) [Licence](#) [About](#) [Support](#)

ENSG00000107745 (MICU1) *Homo sapiens* mitochondrial calcium uptake 1

Showing 67 experiments:



T 19 NIH Epigenomics Roadmap

T 32 Uhlen's Lab

T 68 FANTOM5 project – adult

T 68 FANTOM5 project – fetal

P brain regions

P Doll et al., 2017 – Organism part

T ENCODE (M. Snyder lab)

T GTEx

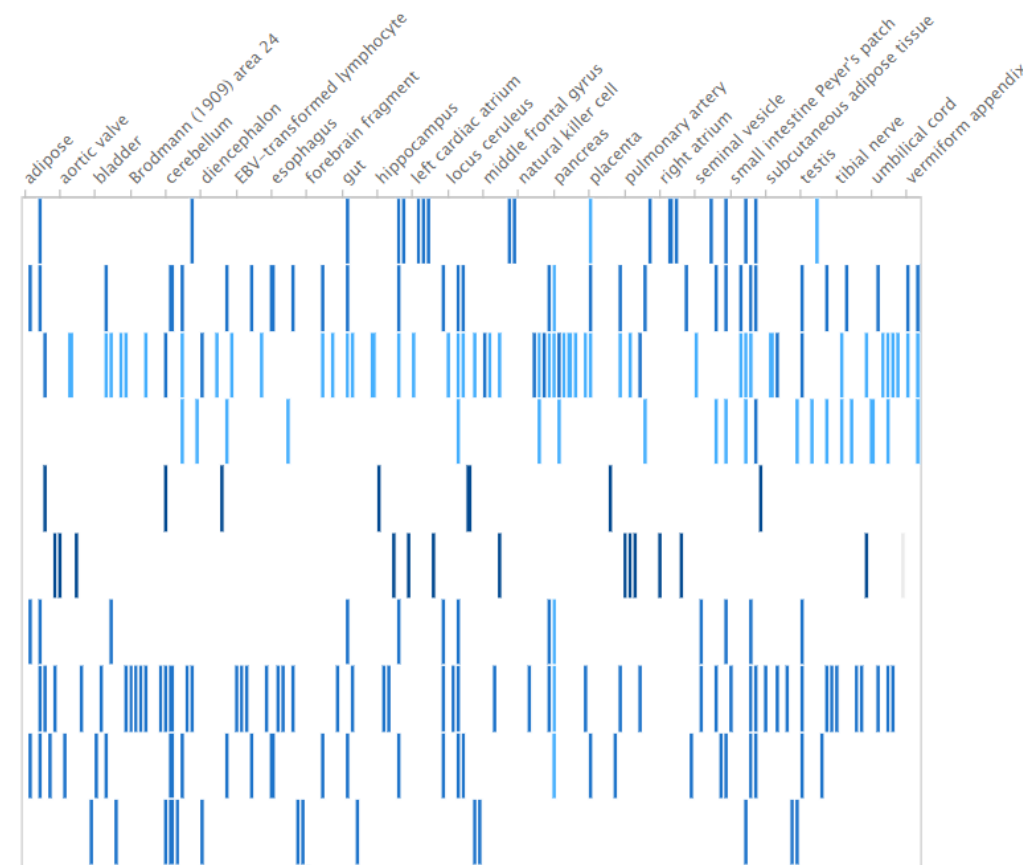
T Hallstrom et al., 2014 – Organism part

T HDBR developing brain – 10 post ...

Alphabetical order ▼

Filters

Download ▼



Search [Fields »](#)

Search result (1 genes): PYROXD2

MICU1



TISSUE



BRAIN



SINGLE CELL



TISSUE CELL



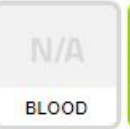
PATHOLOGY



DISEASE



IMMUNE



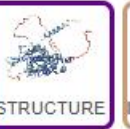
BLOOD



SUBCELL



CELL LINE



STRUCTURE



INTERACTION

PROTEIN SUMMARY

SECTION OVERVIEW

GENE INFORMATION

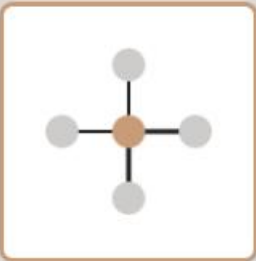
RNA DATA

ANTIBODY DATA



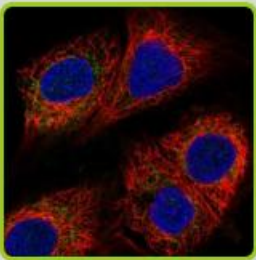
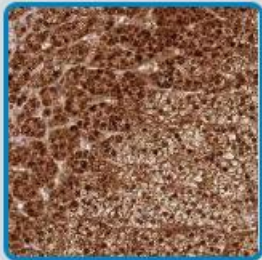
MICU1 INFORMATION

Protein ⁱ	Mitochondrial calcium uptake 1
Gene name ⁱ	MICU1 (CALC, CBARA1, EFHA3, FLJ12684)
Protein class ⁱ	Disease related genes Human disease related genes Potential drug targets Transporters
Protein evidence	Evidence at protein level (all genes)
Number of transcripts ⁱ	8
Protein interactions	Interacting with 4 proteins



PROTEIN EXPRESSION AND LOCALIZATION

Tissue profile ⁱ	Mainly cytoplasmic expression in most tissues.
Subcellular location ⁱ	Localized to the Mitochondria
Predicted location ⁱ	Intracellular



Missense3D-DB results

(structural effect of missense variants)

Note: In this version of the database, the structural analysis is based on the impact of a variant on the protein tertiary structure. The missense variant may disrupt additional features (e.g. protein-protein interactions or functional sites) that we are currently not capturing.

UniProt ID: **Q9BPX6** Gene name: MICU1 pLI score: **0.0** RVIS score: **-0.18** (41.0 %)

Download Report	Uniprot Position	PDB/Model Position	Residue Wildtype	Residue Mutant	Missense3D Prediction	Structural damage predicted
	178	178	GLY	GLU	Neutral	none predicted
	181	181	ILE	THR	Neutral	none predicted
	182	182	SER	ALA	Neutral	none predicted
	184	184	GLU	ASP	Neutral	none predicted
	187	187	LYS	GLU	Neutral	none predicted
	188	188	PHE	LEU	Neutral	none predicted
	189	189	ALA	VAL	Neutral	none predicted
	191	191	GLU	ASP	Neutral	none predicted
	192	192	GLY	SER	Damaging	Gly in a bend
	192	192	GLY	VAL	Damaging	Gly in a bend
	193	193	SER	GLY	Neutral	none predicted
	193	193	SER	CYS	Neutral	none predicted

MICU1 pArg185* ClinVar gibi
Missense 3D veritabanında da
bildirilmemiş

MICU1 10:72508254 G > A

stop_gained ENST00000361114 p.Arg185Ter

No identical open-access DECIPHER patient variants

Not in DDD research variants dataset

Not in ClinVar

gnomAD - [Genome MAF: \$3.95 \times 10^{-5}\$](#)

Gene

Browser

Protein

Annotation

Matching patient variants 21

Matching DDD research variants 0

Clinical

Protein / Genomic

- Decipher veritabanında bildirilen diğer varyantlara ve varyantı taşıyan olguların fenotipi hakkında bilgilere ulaşılabilir

MICU1 10:72367340-72626131

Protein identifiers

UniProt ?

Q9BPX6

InterPro ?

IPR002048, IPR011992, IPR018247, IPR039800

Pfam ?

PF13202, PF13833

3D Structures (PDB) ?

4NSC, 4NSD, 6K7Y, 6LB7, 6LB8, 6LE5, 6WDN, 6WDO, 6XJV, 6XJX, 6XQN, 6XQO

Genomic identifiers

Ensembl ? ENSG00000107745

UCSC ? uc001jtb.3

RefSeq ? NM_006077

NCBI ? 10367

HGNC ? 1530

Search databases

- [Expression Atlas](#)
- [GeneCards](#)
- [Protein Atlas](#)
- [Missense3D-DB](#)
- [Entries in DECIPHER for this gene](#)

Patients with sequence variants matching this variant or its genes

Filters:

Sex

Consequence

Pathogenicity

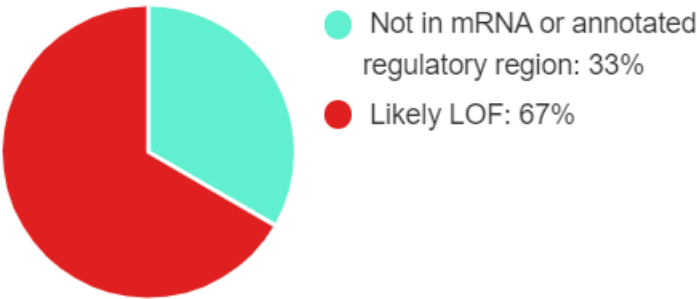
Contribution

Inheritance

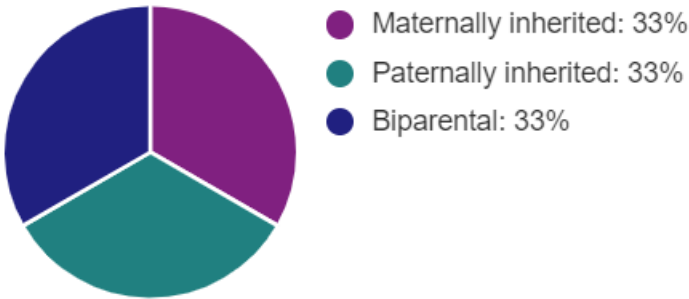
Genotype

Phenotype

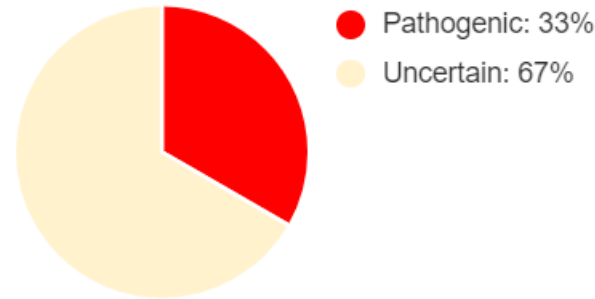
Consequence



Inheritance



MICU1 c.553 C>T ClinVar gibi Decipher veritabanında da bildirilmemiş



Phenotypes present in multiple matching patients

- 2 Intracranial cystic lesion
- 2 Limbal dermoid
- 2 Microcephaly
- 2 Severe postnatal growth retardation

Patient	Sex	Transcript / Location (GRCh38)	Consequence	Pathogenicity / Contribution	Inheritance / Genotype	Phenotypes
264616	46XY	ENST00000361114.10 c.1072-1G>C 10:72408038	splice_acceptor_variant	Pathogenic Full	Biparental Homozygous	Abnormal facial shape; Autism; Elevated circulating creatine kinase concentration; Excessive wrinkling of palmar skin; Generalized hypotonia; Global developmental delay; Ichthyosis; Specific learning disability
282187	46XY	ENST00000361114.10	intron_variant	Uncertain	Paternally inherited	Intracranial cystic lesion; Limbal dermoid;

LOVD'de Neler Araştırabilirim?

**LOVD v.3.0 - Leiden Open Variation Database**
Online gene-centered collection and display of DNA variants



LOVD is the software powering the largest network of curated gene variant databases in the world.

Main database:


Global Variome shared LOVD

**The LOVD software**
Frequently Asked Questions (FAQ), documentation, download the software, see all installations, contact us...

 **Search all LOVDs for a variant**

See all databases for a certain gene:

 **MICU1.LOVD.NL**
Examples: DMD.lovd.nl, BRCA1.lovd.nl.
See also our [full list of LSDBs](#), or the [list of registered LOVD installations](#).

LOVD is supported by:



LOVD is recommended by HVP and IRDIRC

<http://lovd.nl>

The MICU1 gene homepage

This database is one of the gene variant databases from the ["Leiden Muscular Dystrophy pages" \(LMDp\)](#).

General information	
Gene symbol	MICU1
Gene name	mitochondrial calcium uptake 1
Chromosome	10
Chromosomal band	q22.1
Imprinted	Unknown
Genomic reference	NG_033179.1
Transcript reference	NM_006077.3
Exon/intron information	NM_006077.3 exon/intron table
Associated with diseases	ID , MPXPS
Citation reference(s)	-
Refseq URL	Genomic reference sequence
Curators (1)	Johan den Dunnen
Total number of public variants reported	46
Unique public DNA variants reported	27
Individuals with public variants	31
Hidden variants	1
Download all this gene's data	Download all data
Notes	This database is one of the gene variant databases from Leiden Muscular Dystrophy pages[©] the: The link between MICU1 and disease could be established when (pre-publication) Marjolein Kriek reported MICU1 variants using LOVD's VIP option, asking others to contact her when similar variant/phenotype associations were observed. The request was successful and lead to the definite association as published by Logan et al. (2014).
Date created	January 23, 2013
Date last updated	April 16, 2023
Version	MICU1:230416

26 entries on 1 page. Showing entries 1 - 26.

100 per page  [Legend](#) [How to query](#)

Effect 	Reported 	Exon 	DNA change (cDNA) 	RNA change 	Protein 	Classific 	genomic) (hg1
+/. ?/.	1 1	2 2	c.1A>G c.53G>A	r.(? r.(?	p.0? p.(Gln18Arg)	- -	
?/.	1	2	c.77C>G	r.(?	p.(Pro26Arg)	-	VUS g.74326475G>C
?/.	1	2	c.83A>G	r.(?	p.(Gln83Arg)	-	VUS g.74326469T>C
?/.	1	2	c.114C>G	r.(?	p.(Phe38Leu)	-	VUS g.74326438G>C
?/.	1	-	c.119G>A	r.(?	p.(Gly40Glu)	-	VUS g.74326433C>T
-?/.	1	-	c.143C>T	r.(?	p.(Thr48Ile)	-	likely benign g.74326409G>A
?/.	1	2	c.160A>G	r.(?	p.(Arg54Gly)	-	VUS g.74326392T>C
+?/.	1	2i	c.161+1G>A	r.spl	p.?	-	likely pathogenic g.74326390C>T
-?/.	1	-	c.161+3G>A	r.spl?	p.?	-	likely benign g.74326388C>T
?/.	1	3	c.211G>C	r.(?	p.(Gly71Arg)	-	VUS g.74322772C>G
-?/.	1	-	c.307C>T	r.(?	p.(Arg103Cys)	-	likely benign g.74322676G>A
?/.	1	-	c.355C>G	r.(?	p.(Arg119Gly)	-	VUS g.74311075G>C
+?/.	1	4	c.385C>T	r.(?	p.(Arg129*)	-	likely pathogenic g.74311045G>A
+/.	1	4	c.386G>C	r.(?	p.(Arg129Pro)	-	pathogenic g.74311044C>G
+?/.	1	4i	c.493+1G>A	r.spl	p.?	-	likely pathogenic g.74310936C>T
-?/.	1	-	c.527+2888A>G	r.(=)	p.(=)	-	likely benign g.74283606T>C
+/.	1	-	c.553C>T	r.(?	p.(Gln185*)	ACMG	pathogenic (recessive) g.74268018G>A
-?/.	1	-	c.565A>G	r.(?	p.(Lys189Glu)	-	likely benign g.74268006T>C
+/.	1	-	c.614_615dup	r.(?	p.(Ile206SerfsTer30)	-	pathogenic g.74267957_74267958dup
+?/.	1	7	c.644_645del	r.spl	p.fs*	-	likely pathogenic g.74267928_74267929del
+/. , +?/., ?/.	11	8i	c.741+1G>A	r.741_742insains741+2_741+155, r.spl, r.spl?	p.?, p.Val248Thrfs*9	ACMG	likely pathogenic, pathogenic, pathogenic (recessive), VUS g.74236931C>T
-?/.	1	-	c.891C>T	r.(?	p.(Asn297=)	-	likely benign g.74234906G>A
+/.	1	-	c.937G>T	r.(?	p.(Glu313*)	-	pathogenic q.74234860C>A

MICU1 c.553 C>T
ClinVar ve Decipher'da HENÜZ
bildirilmemiş
Ama LOVD 'de bildirilmiş

Ama Pubmed'de bir yayında bildirilmiş !!

Received: 05 September 2017 / Revised: 27 March 2018 / Accepted: 29 March 2018 / Published online: 03 May 2018
© Society for the Study of Inborn Errors of Metabolism (SSIEM) 2018

as well as variable features that include progressive extrapyramidal signs, learning disabilities, nystagmus, and cataracts. In this study, we report the clinical features of an additional 13 patients from consanguineous Middle Eastern families with recessive mutations in *MICU1*. Of these patients, 12/13 are homozygous for a novel founder mutation c.553C>T (p.Q185*) that is predicted to lead to a complete loss of function of *MICU1*, while one patient is compound heterozygous for this mutation and an intragenic duplication of exons 9 and 10. The founder mutation occurs with a minor allele frequency of 1:60,000 in the ExAC database, but in ~1:500 individual in the Middle East. All 13 of these patients presented with developmental delay, learning disability, muscle weakness and easy fatigability, and failure to thrive, as well as additional variable features

S. Musa · R. Ali · M. Al-Mureikhi · N. Shahbeck · F. Al Mesaifri · T. Ben-Omran (✉)
Section of Clinical and Metabolic Genetics, Department of Pediatrics,
Shuaib Medical College, Baghdad, Iraq

Örnek;

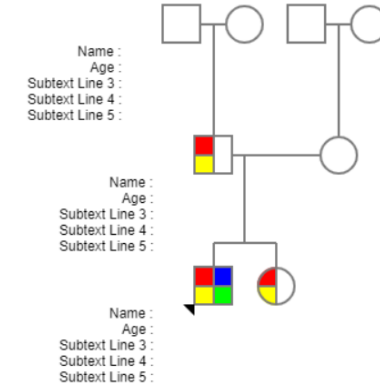
Fenotip	CM, MHS
Bulgular	Myalji atakları Rabdomiyoliz MHS İlımlı CK yüksekliği EMG miyopatik MUPlar Kas bx miyopatik degisiklikler
Cinsiyet, yaş	E, 5 yaş
Kalıtım paterni (olası)	OD? De novo?
Testler	NM panel, WES
Sonuç	<i>RYR1 (ENST00000359596.3) HT c.7007 G>A, p.Arg2336His</i>

Pedigree Viewer

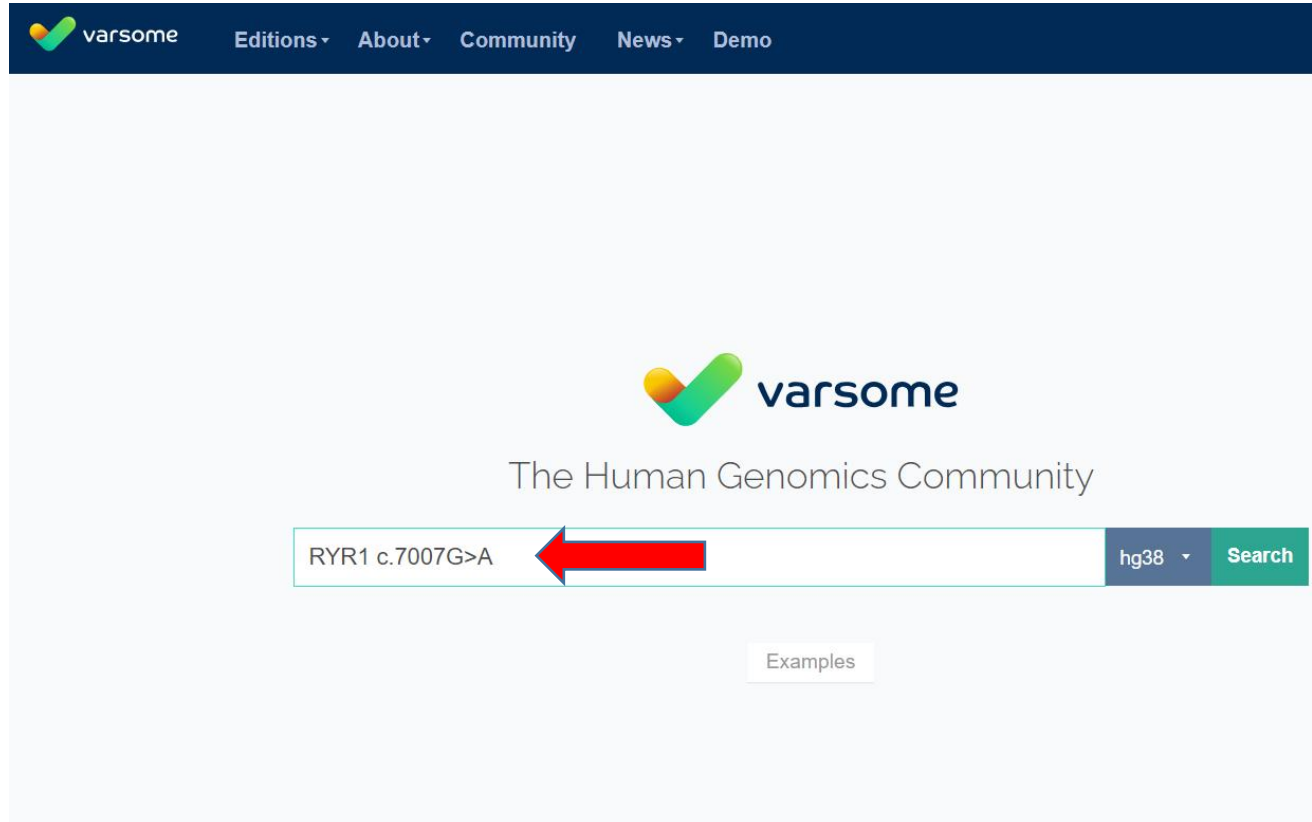
- Pedigree Display
- Pedigree Dimensions
- SmartDraw Options

1697599794502-MHS ailesi
2023-10-17

☒ MHS
 ☒ Rabdomiyoliz attacks
 ☒ Elevated CK
 ☒ RYR1 c.7007G>A HT



Varsome'da Neler Araştırabilirim ve Prediktif Datayı Nasıl Değerlendirebilirim?



The screenshot shows the Varsome website interface. At the top, there is a dark blue navigation bar with the Varsome logo and links for Editions, About, Community, News, and Demo. Below the navigation bar, the Varsome logo and the text "The Human Genomics Community" are displayed. A search bar is present with the text "RYR1 c.7007G>A" entered. A red arrow points to the search bar. To the right of the search bar, there is a dropdown menu showing "hg38" and a "Search" button. Below the search bar, there is a link labeled "Examples".

<https://varsome.com/>

chr19-38499223-G-A (RYY1:p.R2336H)

Submit to ClinVar

Link publication

Classify

Share

API Link

Favorites

General Information SNV RYY1(NM_000540.3):c.7007G>A (p.Arg2336His)	PharmGKB No data available	Germline Classification Pathogenic 16 points = 16 P - 0 B	Frequencies exomes: not found genomes: f = 0.00000657 (cov: 31.1)	Conservation Scores phyloP100: 10.003	Structural Variants
Genes RYY1	Transcripts NM_000540.3 - missense MANE Select	ClinVar Pathogenic ★★☆☆ 5 1 7	MitoMap No data available	In-Silico Predictors PP3: Pathogenic... 20 7 1 15	Beacon Network
Community Contributions	Region Browser	LOVD No data available	Deafness Variation Database New No data available	ClinGen Pathogenic Expert Panel: Malignant Hypertherm...	Protein Viewer
Publications Variant: 59 Gene: 1169	Expression Data Top: muscle_skeletal Tissues: 38	Uniprot Variants Pathogenic	OMIM No data available	GWAS No data available	

Variant

Explain

Chromosome	Position	REF Sequence	ALT Sequence	Variant type	Cytoband	HGVS	RS ID	Gene symbol
chr19	38499223	G	A	SNV	19q13.2	RYY1(NM_000540.3):c.7007G>A (p.Arg2336His)	rs112563513 dbSNP	RYY1
UCSC genome browser Mastermind TraP Score								

This variant has been viewed 12 times on VarSome.

chr19-38499223-G-A (RYR1:p.R2336H)

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Link publication

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Favorites

General Information **SNV**
RYR1(NM_000540.3):c.7007G>A
(p.Arg2336His)

PharmGKB
No data available

PREMIUM

Germline Classification

Pathogenic

16 points = 16 P - 0 B

Frequencies

exomes: not found

genomes: $f = 0.00000657$ (cov: 31.1)

Conservation Scores

phyloP100: 10.003

Structural Variants

Genes
RYR1

Transcripts
NM_000540.3 - missense
MANE Select

ClinVar Pathogenic ★★★★★

5

1

7

MitoMap

No data available

In-Silico Predictors PP3: Pathogenic...

20

7

1

15

Beacon Network

Community Contributions

Region Browser

LOVD

No data available

PREMIUM

Deafness Variation Database

No data available

New

ClinGen Pathogenic

Expert Panel: Malignant Hypertherm...

Protein Viewer

Publications

Variant: 59

Gene: 1169

Expression Data

Top: muscle_skeletal

Tissues: 38

Uniprot Variants

Pathogenic

PREMIUM

OMIM

No data available

GWAS

No data available

Variant

Explain

Chromosome	Position	REF Sequence	ALT Sequence	Variant type	Cytoband	HGVS	RS ID	Gene symbol
chr19	38499223	G	A	SNV	19q13.2	RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	rs112563513 dbSNP	RYR1

[UCSC genome browser](#)
[Mastermind](#)
[TraP Score](#)

This variant has been viewed 12 times on VarSome.



RYR1 c.7007G>A

hg38

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chr19-38499223-G-A (RYR1:p.R2336H)

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[Link publication](#)

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[API Link](#)

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General Information SNV RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	PharmGKB No data available	Germline Classification Pathogenic 16 points = 16 P - 0 B	Frequencies exomes: not found genomes: f = 0.00000657 (cov: 31.1)	Conservation Scores phyloP100: 10.003	Structural Variants
Genes RYR1	Transcripts NM_000540.3 - missense MANE Select	ClinVar Pathogenic ★★☆☆ 5 1 7	MitoMap No data available	In-Silico Predictors PP3: Pathogenic... 20 7 1 15	Beacon Network
Community Contributions	Region	LOVD No data available	Deafness Variation Database New No data available	ClinGen Pathogenic Expert Panel: Malignant Hypertherm...	Protein Viewer
Publications Variant: 59 Gene: 1169	Expression Data Top: muscle_skeletal Tissues: 38	Uniprot Variants Pathogenic	OMIM © No data available	GWAS No data available	

Variant ?

[Explain](#)

Chromosome	Position	REF Sequence ?	ALT Sequence ?	Variant type ?	Cytoband ?	HGVS	RS ID ?	Gene symbol ?
chr19	38499223	G	A	SNV	19q13.2	RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	rs112563513 dbSNP	RYR1
UCSC genome browser ? Mastermind ? TraP Score								

This variant has been viewed 12 times on VarSome.

<https://varsome.com/>

 varsome

RYR1 c.7007G>A

hg38

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chr19-38499223-G-A (RYR1:p.R2336H)

Submit to ClinVar

Link publication

Classify

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API Link

Favorites

General Information SNV RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	PharmGKB No data available	Germline Classification Pathogenic 16 points = 16 P - 0 B	Frequencies exomes: not found genomes: f = 0.00000657 (cov: 31.1)	Conservation Scores phyloP100: 10.003	Structural Variants
Genes RYR1	Transcripts NM_000540.3 - missense MANE Select	ClinVar Pathogenic ★★☆☆ 517	MitoMap No data available	In-Silico Predictors PP3: Pathogenic... 2071 15	Beacon Network
Community Contributions	Region Browser	LOVD No data available	Deafness Variation Database No data available	ClinGen Pathogenic Expert Panel: Malignant Hypertherm...	Protein Viewer
Publications Variant: 59 Gene: 1169	Expression Data Top: muscle_skeletal Tissues: 38	Uniprot Variants Pathogenic	OMIM No data available	GWAS No data available	

Transcripts

RefSeq transcripts Version: 210

Transcript	Coding impact	Gene	HGVS coding	HGVS Protein	Location	Protein position	Splice distance	MANE Select
NM_000540.3 See on NCBI	missense	RYR1	c.7007G>A	R2336H (p.Arg2336His)	exon 43 of 106 position 116 of 136 (coding)	2336 of 5039	-21	ENST000003 59596.8



RYR1 c.7007G>A

hg38

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chr19-38499223-G-A (RYR1:p.R2336H)

Submit to ClinVar

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General Information SNV RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	PharmGKB No data available	Germline Classification Pathogenic 16 points = 16 P - 0 B	Frequencies exomes: not found genomes: f = 0.00000657 (cov: 31.1)	Conservation Scores phyloP100: 10.003	Structural Variants
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UCSC genome browser Mastermind TraP Score								

This variant has been viewed 12 times on VarSome.

https://varsome.com/

General Information SNV RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	PharmGKB No data available	Germline Classification Pathogenic 16 points = 100%	Frequencies exomes: not found genomes: f = 0.00000657 (cov: 31.1)	Conservation Scores phyloP100: 10.003	Structural Variants
Genes RYR1	Transcripts NM_000540.3 - missense MANE Select	ClinVar Pathogenic ★★☆☆ 5 1 7	MitoMap No data available	In-Silico Predictors PP3: Pathogenic... 20 7 1 15	Beacon Network
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Variant

[Explain](#)

Chromosome	Position	REF Sequence	ALT Sequence	Variant type	Cytoband	HGVS	RS ID	Gene symbol
chr19	38499223	G	A	SNV	19q13.2	RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	rs112563513 dbSNP	RYR1

[UCSC genome browser](#)
[Mastermind](#)
[TraP Score](#)

This variant has been viewed 12 times on VarSome.

General Information SNV RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	PharmGKB No data available	Germline Classification Pathogenic 16 points = 16 P - 0 B	Frequencies exomes: not found genomes: f = 0.00000657 (cov: 31.1)	Conservation Scores phyloP100: 10.003	Structural Variants
Genes RYR1	Transcripts NM_000540.3 - missense MANE Select	ClinVar Pathogenic ★★☆☆ 5 1 7	MitoMap No data available	In-Silico Predictors PP3: Pathogenic... 20 7 1 15	Beacon Network
Community Contributions	Region Browser	LOVD No data available	Deafness Variation Database New No data available	ClinGen Pathogenic Expert Panel: Malignant Hypertherm...	Protein Viewer
Publications Variant: 59 Gene: 1169	Expression Data Top: muscle_skeletal Tissues: 38	Uniprot Variants Pathogenic	OMIM © No data available	GWAS No data available	

Variant ? Explain

Chromosome	Position	REF Sequence ?	ALT Sequence ?	Variant type ?	Cytoband ?	HGVS	RS ID ?	Gene symbol ?
chr19	38499223	G	A	SNV	19q13.2	RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	rs112563513 dbSNP	RYR1

[UCSC genome browser ?](#)
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Variant

[Explain](#)

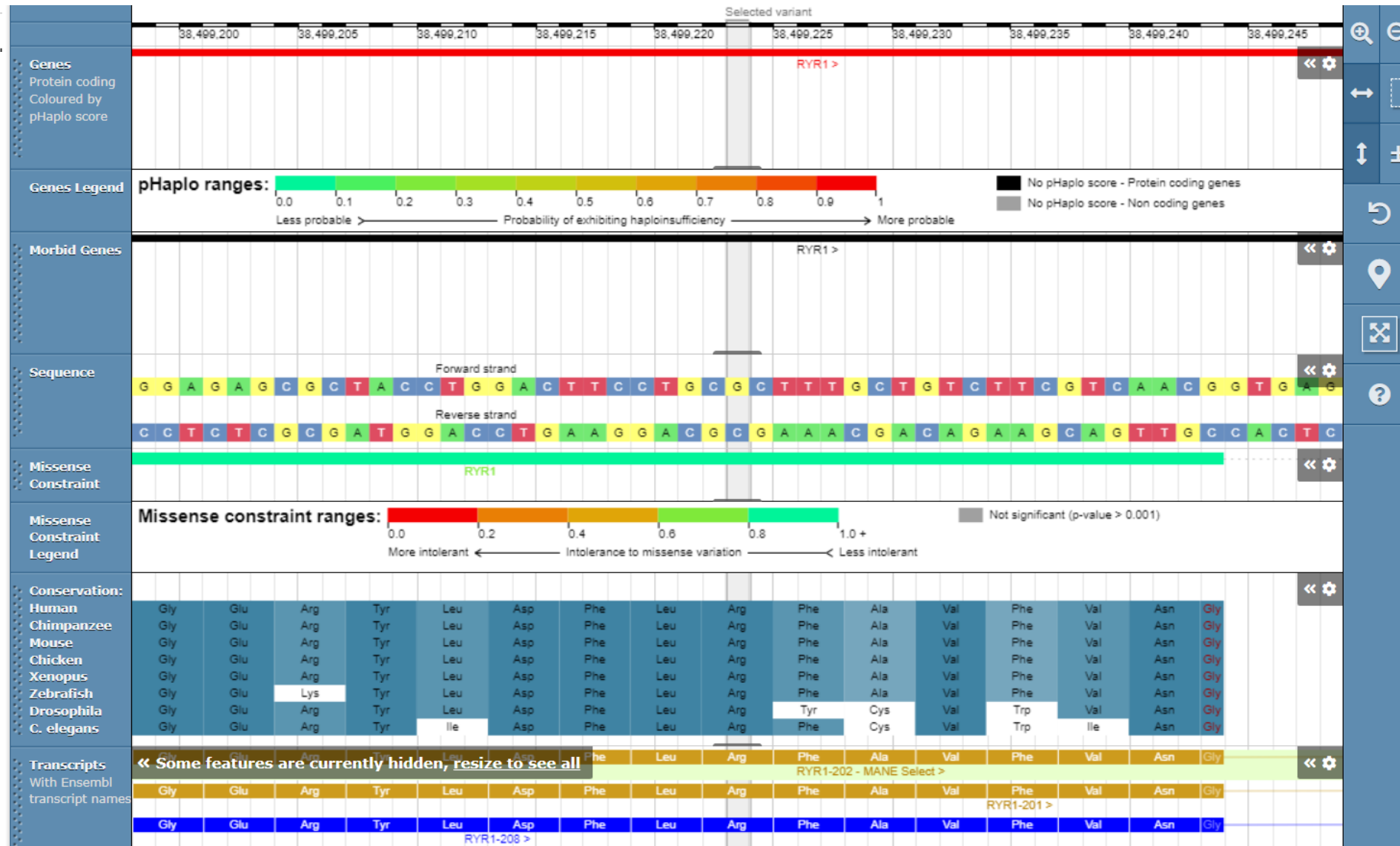
Chromosome	Position	REF Sequence	ALT Sequence	Variant type	Cytoband	HGVS	RS ID	Gene symbol
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[UCSC genome browser](#)

[Mastermind](#)

[TraP Score](#)

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General Information SNV RYR1(NM_000540.3):c.7007G>A (p.Arg2336His)	PharmGKB No data available	Germline Classification Pathogenic 16 points = 16 P - 0 B	Frequencies exomes: not found genomes: f = 0.00000657 (cov: 31.1)	Conservation Scores phyloP100: 18.800	Structural Variants
Genes RYR1	Transcripts NM_000540.3 - missense MANE Select	ClinVar Pathogenic ★★☆☆ 5 1 7	MitoMap No data available	In-Silico Predictors PP3: Pathogenic... 20 7 1 15	Beacon Network
Community Contributions	Region Browser	LOVD No data available	Deafness Variation Database No data available	ClinGen Pathogenic Expert Panel: Malignant Hypertherm...	Protein Viewer
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Variant

[Explain](#)

Chromosome	Position	REF Sequence	ALT Sequence	Variant type	Cytoband	HGVS	RS ID	Gene symbol
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[UCSC genome browser](#)
[Mastermind](#)
[TraP Score](#)

This variant has been viewed 12 times on VarSome.

Revel

- Varyantın patojenitesi hakkında bilgi verir
- 0-1 arası skor
- 1'e ne kadar yakın o kadar protein üzerinde yıkıcı etki

In-Silico Predictors

Meta scores ? 15

Show raw data ☐ Alphabetically ☐

Engine	Calibrated Prediction ?	Score ?	Version
BayesDel addAF	Pathogenic Strong	addAF score 0.5186 ?	dbNSFP version 4.3
MetaRNN ?	Pathogenic Strong	0.9802, 0.9802 ?	dbNSFP version 4.3
BayesDel noAF	Pathogenic Moderate		dbNSFP version 4.3
MetaSVM ?	Pathogenic Moderate		dbNSFP version 4.3
REVEL	Pathogenic Moderate	0.903, 0.903 ?	dbNSFP version 4.3
MetaLR ?	Pathogenic Supporting	0.906 ?	dbNSFP version 4.3

REVEL is an ensemble score based on 13 individual scores for predicting the pathogenicity of missense variants. Scores range from 0 to 1. The larger the score the more likely the SNP has damaging effect.

CADD



chr19-38499223-G-A (RYR1:p.R2336H)				Version
? CADD Combined Annotation Dependent Depletion (CADD) predicts the deleteriousness of variants, from diverse annotations of genetic variation, including missense, intronic, Stop-Gain, insertions and deletions. It uses an SVM training algorithm based on 63 annotations (including conservation metrics, regulatory information, transcript information and protein-level scores) and is trained in 65 "observed" and "simulated" variants.				
CADD ?	PREMIUM	This resource is only available to VarSome Premium subscribers.		
DEOGEN2	Pathogenic Strong	0.969 ?	dbNSFP version 4.3	
MutPred	Pathogenic Strong	0.911 ?	dbNSFP version 4.3	
LIST-S2	Pathogenic Moderate	0.9981, 0.9981 ?	dbNSFP version 4.3	
M-CAP ?	Pathogenic Moderate	0.7132 ?	dbNSFP version 4.3	
MVP	Pathogenic Moderate	0.9976, 0.9976 ?	dbNSFP version 4.3	
EVE	Pathogenic Supporting	0.6648	version 07-Jun-2022	
FATHMM-MKL ?	Pathogenic Supporting	coding score 0.9889 ?	dbNSFP version 4.3	
FATHMM-XF	Pathogenic Supporting	coding score 0.9332 ?	dbNSFP version 4.3	
PrimateAI	Pathogenic Supporting	0.8439 ?	dbNSFP version 4.3	

- Varyantın patojenitesi hakkında bilgi verir
- >20 olan skorlar protein üzerinde yıkıcı etki

<https://varsome.com/>
<https://cadd.gs.washington.edu/>

SIFT



Sorting Intolerant From Tolerant



? SIFT

SIFT (sorts intolerant from tolerant) is an in silico prediction tool for nonsynonymous variants based on sequence homology derived from closely related sequences collected through PSI-BLAST. Range 0 to 1 with values less than 0.05 usually considered intolerant. 40% of the values in this database are below 0.01.

SIFT ?

Pathogenic
Supporting

0.001, 0.001 ?

dbNSFP version 4.3

MutationTaster ?

Benign Supporting

0.9989, 0.9989, 0.9989 ?

dbNSFP version 4.3

BLOSUM

Uncertain

-1 ?

version BLOSUM100

DANN

Uncertain

0.9979 ?

EIGEN

Uncertain

raw coding
0.5801 ?

dbNSFP version 4.3

EIGEN PC

Uncertain

PC raw coding score
0.488 ?

dbNSFP version 4.3

FATHMM ?

Uncertain

-3.81, -3.81 ?

dbNSFP version 4.3

LRT ?

Uncertain

0.000001999 ?

dbNSFP version 4.3

Mutation assessor ?

Uncertain

2.62, 2.62 ?

dbNSFP version 4.3

- Varyantın patojenitesi hakkında bilgi verir
- 0-1 arası skor
- < 0.05 intolerans
- 0 'a ne kadar yakın skor o kadar protein üzerinde yıkıcı etki

<https://varsome.com/>
<https://sift.bii.a-star.edu.sg/>

PolyPhen

PolyPhen-2 score

The PolyPhen-2 score predicts the possible impact of an amino acid substitution on the structure and function of a human protein. This score represents the probability that a substitution is damaging. Ion Reporter™ Software reports the pph2-prob PolyPhen-2 score.

The PolyPhen-2 score ranges from 0.0 (tolerated) to 1.0 (deleterious). Variants with scores of 0.0 are predicted to be benign. Values closer to 1.0 are more confidently predicted to be deleterious. The score can be interpreted as follows:

- 0.0 to 0.15 -- Variants with scores in this range are predicted to be benign.
- 0.15 to 1.0 -- Variants with scores in this range are possibly damaging.
- 0.85 to 1.0 -- Variants with scores in this range are more confidently predicted to be damaging.

PolyPhen-2 and SIFT scores use the same range, 0.0 to 1.0, but with opposite meanings. A variant with a PolyPhen-2 score of 0.0 is predicted to be benign. A variant with a SIFT score of 1.0 is predicted to be benign.

- Varyantın patojenitesi hakkında bilgi verir
- 0-1 arası skor
- < 0.15 benign
- 1'e ne kadar yakın skor o kadar protein üzerinde yıkıcı etki

<https://varsome.com/>

<http://genetics.bwh.harvard.edu/pph2/index.shtml>

PolyPhen



PolyPhen-2 prediction of functional effects of human nsSNPs

[Home](#)[About](#)[Help](#)[Downloads](#)[Batch query](#)[WHESS.db](#)

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.

21-Jun-2021: Server has been migrated to new hardware. Note, all queries were terminated and user sessions data discarded in the process, hence you will need to resubmit your query if affected. We apologize for the inconvenience caused.

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](#)

<http://genetics.bwh.harvard.edu/pph2/index.shtml>

PolyPhen





PolyPhen-2

prediction of functional effects of human nsSNPs

[Home](#)[About](#)[Help](#)[Downloads](#)[Batch query](#)[WHESS.db](#)

PolyPhen-2 report for P21817 R2336H

Query

Protein Acc	Position	AA ₁	AA ₂	Description
P21817	2336	R	H	Canonical; RecName: Full=Ryanodine receptor 1; Short=RYP-1; Short=RyR1; AltName: Full=Skeletal muscle calcium release channel; AltName: Full=Skeletal muscle-type ryanodine receptor; Length: 5038

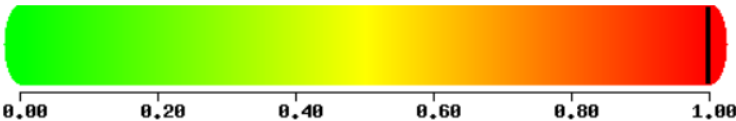
Results

☐ Prediction/Confidence

PolyPhen-2 v2.2.3r406

HumDiv

This mutation is predicted to be **PROBABLY DAMAGING** with a score of **0.997** (sensitivity: **0.41**; specificity: **0.98**)



☐ HumVar

Details

☐ Multiple sequence alignment

UniProtKB/UniRef100 Release 2011_12 (14-Dec-2011)

☐ 3D Visualization

PDB/DSSP Snapshot 25-May-2021 (178229 Structures)

<http://genetics.bwh.harvard.edu/pph2/index.shtml>
https://faculty.washington.edu/wjs18/GS561/cSNPs_lab.html



mutation t@sting

[MutationTaster2021](#) has been released! See [changes](#).

Gene
Transcript
Position / snippet refers to
Alteration

RYR1 NCBI gene symbol, NCBI Gene ID, Ensembl gene ID [show available transcripts](#)

ENST00000359596 Ensembl transcript ID

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

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
...**last wild type base** before alteration
...**first wild type base** after alteration
and the **inserted bases**
(if applicable)

<https://www.mutationtaster.org/>

Prediction

disease causing

Model: *simple_aae*, prob: 0.999761459451408

Summary

- amino acid sequence changed
- protein features (might be) affected

[hyperlink](#)

analysed issue

analysis result

name of alteration	no title												
alteration (phys. location)	chr19:38987580C>AN/A show variant in all transcripts IGV												
HGNC symbol	RYR1												
Ensembl transcript ID	ENST00000359596												
Genbank transcript ID	NM_000540												
UniProt peptide	P21817												
alteration type	single base exchange												
alteration region	CDS												
DNA changes	c.6877C>A cDNA.7007C>A g.63241C>A												
AA changes	Q2293K Score: 53 explain score(s)												
position(s) of altered AA if AA alteration in CDS	2293												
frameshift	no												
known variant	Variant was neither found in ExAC nor 1000G. Search ExAC.												
regulatory features	H3K27me3, Histone, Histone 3 Lysine 27 Tri-Methylation H3K36me3, Histone, Histone 3 Lysine 36 Tri-Methylation												
phyloP / phastCons	<table><thead><tr><th></th><th>PhyloP</th><th>PhastCons</th></tr></thead><tbody><tr><td>(flanking)</td><td>1.535</td><td>1</td></tr><tr><td></td><td>5.812</td><td>1</td></tr><tr><td>(flanking)</td><td>1.396</td><td>1</td></tr></tbody></table> explain score(s) and/or inspect your position(s) in in UCSC Genome Browser		PhyloP	PhastCons	(flanking)	1.535	1		5.812	1	(flanking)	1.396	1
	PhyloP	PhastCons											
(flanking)	1.535	1											
	5.812	1											
(flanking)	1.396	1											

distance from splice site	15
Kozak consensus sequence altered?	N/A
conservation	species match gene aa alignment
protein level for non-synonymous changes	Human 2293 DNNELALALQE QDLEKVVSYLAG C
	mutated all conserved 2293 DNNELALALQE K DLEKVVSYLAG
	Ptroglydotes all identical ENSPTRG00000010931 2294 DNNELALALQE Q DLEKVVSYLAG
	Mmulatta no alignment ENSMUG00000028770 n/a
	Fcatus all identical ENSFCAG00000000828 2290 DNNELALALQE Q DLEK
	Mmusculus all identical ENSMUSG00000030592 2294 DNNELALALQE Q DLEKVVSYLAG
	Ggallus no homologue
	Trubripes no homologue
	Drerio no alignment ENSDARG00000003706 n/a
	Dmelanogaster no homologue
	Celegans no homologue
	Xtropicalis all identical ENSXETG00000002823 2211 NELALALQE Q DLEKVVSYLAG
protein features	start (aa) end (aa) feature details
	1 4326 TOPO_DOM Cytoplasmic (Potential). lost
	841 2959 REGION 6 X approximate repeats. lost
length of protein	normal
AA sequence altered	yes

Örnek Raporlar



21572512

İşlem

: Hastanın periferik kanından elde edilen DNA örneğinde, mitokondriyal hastalıklar ile ilişkili 13 gene ait varyasyonlar yeni nesil dizi analizi yöntemi ile araştırılmıştır. "BC51L (ENST00000431802), DGUOK (ENST00000264093), MPV17 (ENST00000380044), NDUFS1 (ENST00000455934), NDUFS3 (ENST00000263774), NDUFV1 (ENST00000322776), NF1 (ENST00000358273), NF2 (ENST00000338641), POLG (ENST00000268124), SCO2 (ENST00000543927), SURF1 (ENST00000371974), TMEM70 (ENST00000312184) ve TRMU (ENST00000290846)" genlerinin kodlayıcı bölgelerinin (intronik, 5' ve 3' UTR hariç) %99'undan fazlası, en az 50X okuma derinliği ile incelenmiştir. Ortalama okuma derinliği 1413 okumadır. Ekzon-intron bağlantı noktaları (± 10 bp) analize dahil edilmiştir. Elde edilen verilerin patojenisite sınıflandırması "ACMG Guideline" a göre yapılmıştır. Genetik değişimlere ait kromozom pozisyonu bilgis "hg19/GRCh37 Human Reference Genome" referans genomuna göre raporlanmıştır.

Kullanılan Kit

: Mitochondrial DNA Depletion Syndrome Kit, Celeomics

Analiz Platformu

: NextSeq Sequencing System, Illumina

Analiz Yazılımı

: SEQ Analiz Platformu, Genomize

SONUÇ: Çalışmada hastanın kliniği ile ilişkilendirilebilecek, patojenik olduğu bildirilmiş bir değişim saptanmamıştır.

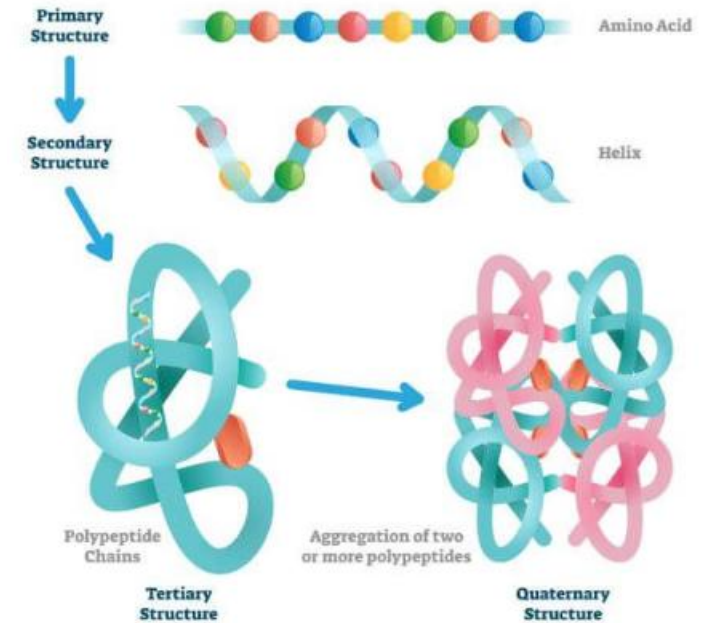
NDUFS1 geninin 3. ekzonunda klinik önemi bilinmeyen, heterozigot c.158A>G (chr2:207017180, p.Gln53Arg) değişimi saptanmıştır.

NOT: *SURF1* geni için kodlayıcı bölgeler kaplam oranı %94'tür. Bu gen için yapılan değerlendirme suboptimaldir. Hastanın klinik bulgularının adı geçen gen ile uyumlu olduğu düşünülüyorsa farklı bir moleküler yöntemle araştırma önerilir. Bu test, primerler dışında kalan bölgelerdeki mutasyonları, geniş delesyon/duplikasyonları (kopya sayısı değişiklikleri), epigenetik değişiklikleri ve mozaikliği göstermez. Aminoasit değişimine yol açmayan ve polimorfizm olarak belirtilen değişimler rapor edilmemiştir. Sonuçlar çok nadir olarak hastadaki durumu göstermeyebilir. Hastanın test sonucuna yönelik genetik danışma alması önerilir. *PMID: 25741868. Sonuçlar bölümümüzün izni olmadan kullanılamaz. Rapor tek sayfadır.

- NDUFS1
- 0/1
- c.158A>G
- p.Gln53Arg

NON-POLAR					+ CHARGE	
$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{H} \end{array}$ Glycine (Gly / G)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_3 \end{array}$ Alanine (Ala / A)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH} \\ \quad \\ \text{CH}_3 \text{ CH}_3 \end{array}$ Valine (Val / V)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{SH} \end{array}$ Cysteine (Cys / C)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{H}_2\text{C} \quad \text{CH}_2 \\ \quad \\ \text{CH}_2 \end{array}$ Proline (Pro / P)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{NH} \\ \\ \text{C}=\text{NH}_2^+ \\ \\ \text{NH}_2 \end{array}$ Lysine (Lys / K)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{NH} \\ \\ \text{C}=\text{NH}_2^+ \\ \\ \text{NH}_2 \end{array}$ Arginine (Arg / R)
$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{CH} \\ \quad \\ \text{CH}_3 \text{ CH}_3 \end{array}$ Leucine (Leu / L)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{H}_2\text{C}-\text{CH} \\ \quad \\ \text{CH}_2 \text{ CH}_2 \\ \\ \text{CH}_3 \end{array}$ Isoleucine (Ile / I)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{S} \\ \\ \text{CH}_3 \end{array}$ Methionine (Met / M)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{HN} \\ \\ \text{Indole Ring} \end{array}$ Tryptophan (Trp / W)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{Phenyl Ring} \end{array}$ Phenylalanine (Phe / F)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{NH} \\ \\ \text{NH}^+ \end{array}$ Histidine (His / H)	
POLAR					- CHARGE	
$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{OH} \end{array}$ Serine (Ser / S)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH} \\ \quad \\ \text{OH} \text{ CH}_3 \end{array}$ Threonine (Thr / T)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{Phenyl Ring} \\ \\ \text{OH} \end{array}$ Tyrosine (Tyr / Y)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{C}=\text{O} \\ \\ \text{NH}_2 \end{array}$ Asparagine (Asn / N)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{C}=\text{O} \\ \\ \text{NH}_2 \end{array}$ Glutamine (Gln / Q)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{C}=\text{O} \\ \\ \text{O}^- \end{array}$ Aspartic Acid (Asp / D)	$\begin{array}{c} \text{H} \\ \\ \text{H}_3\text{N}^+-\text{C}-\text{C}(=\text{O})\text{O}^- \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{C}=\text{O} \\ \\ \text{O}^- \end{array}$ Glutamic Acid (Glu / E)

PROTEIN STRUCTURE



Franklin
by genoox

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? Ipek Polat
International izmir ...

The Future of Genomic Medicine

Examples: SNP CNV ROH

Enter variant, gene or select an example above

REFERENCE
hg38

TYPE
Germline

Create new case from:

CMA Report VCF

By selecting 'Search' you accept our [Terms and Conditions](#) and [Privacy Policy](#)

<https://franklin.genoox.com/clinical-db/home>

The Future of Genomic Medicine

Examples:

NDUFS1 c.158A>G

REFERENCE

hg19

TYPE

Germline



Add your
case details

What is the variant zygosity?

1/7 questions

[Skip question](#)



CMA



Report



VCF



Please Select the Variant You're Referring to

The information you entered can be associated with
different variants, please choose the one you need:

chr2:207013753 T>C
NM_001199983

chr2:207012315 T>C
NM_001199982

chr2:207017180 T>C
NM_001199984

Cancel



Please Select the Variant You're Referring to

The information you entered can be associated with
different variants, please choose the one you need:

chr2:207013753 T>C
NM_001199983

chr2:207012315 T>C
NM_001199982

chr2:207017180 T>C
NM_001199984



Cancel

İşlem

: Hastanın periferik kanından elde edilen DNA örneğinde, mitokondriyal hastalıklar ile ilişkili 13 gene ait varyasyonlar yeni nesil dizi analizi yöntemi ile araştırılmıştır. "BCS1L (ENST00000431802), DGUOK (ENST00000264093), MPV17 (ENST00000380044), NDUFS1 (ENST00000455934), NDUFS3 (ENST00000263774), NDUFV1 (ENST00000322776), NF1 (ENST00000358273), NF2 (ENST00000338641), POLG (ENST00000268124), SCO2 (ENST00000543927), SURF1 (ENST00000371974), TMEM70 (ENST00000312184) ve TRMU (ENST00000290846)" genlerinin kodlayıcı bölgelerinin (intronik, 5' ve 3' UTR hariç) %99'ünden fazlası, en az 50X okuma derinliği ile incelenmiştir. Ortalama okuma derinliği 1413 okumadır. Ekzon-intron bağlantı noktaları (±10bp) analize dahil edilmiştir. Elde edilen verilerin patojenisite sınıflandırması "ACMG Guideline"a göre yapılmıştır. Genetik değişimlere ait kromozom pozisyonu bilgisi "hg19/GRCh37 Human Reference Genome" referans genomuna göre raporlanmıştır.

Kullanılan Kit : Mitochondrial DNA Depletion Syndrome Kit, Celomics
Analiz Platformu : NextSeq Sequencing System, Illumina
Analiz Yazılımı : SEQ Analiz Platformu, Genomize

SONUÇ: Çalışmada hastanın kliniği ile ilişkilendirilebilecek, patojenik olduğu bildirilmiş bir değişim saptanmamıştır.

NDUFS1 geninin 3. ekzonunda klinik önemi bilinmeyen, heterozigot c.158A>G (chr2:207017180, p.Gln53Arg) değişimi saptanmıştır.

NOT: *SURF1* geni için kodlayıcı bölgeler kaplam oranı %94'tür. Bu gen için yapılan değerlendirme suboptimaldir. Hastanın klinik bulgularının adı geçen gen ile uyumlu olduğu düşünülüyorsa farklı bir moleküler yöntemle araştırma önerilir. Bu test, primerler dışında kalan bölgelerdeki mutasyonları, geniş delesyon/duplikasyonları (kopya sayısı değişiklikleri), epigenetik değişiklikleri ve mozaikliği göstermez. Aminoasit değişimine yol açmayan ve polimorfizm olarak belirtilen değişimler rapor edilmemiştir. Sonuçlar çok nadir olarak hastadaki durumu göstermeyebilir. Hastanın test sonucuna yönelik genetik danışma alması önerilir. *PMID: 25741868. Sonuçlar bölümümüzün izni olmadan kullanılamaz. Rapor tek sayfadır.

[Classify Variant](#) | [Follow](#) | [Save Case](#) | [Export Summary](#)

[Franklin ACMG Classification](#) | [Variant Assessment](#) | [Publications](#) | [Gene Assessment](#) | [Associated Co](#)

 [Learn More](#) × 

Suggested Classification

VUS

Benign Likely Benign VUS Likely Pathogenic Pathogenic

EVIDENCE

Aggregated from public databases using [ACMG Guidelines](#)

Population Data

Uygulanan test: Tüm Ekzom Dizisi Analizi
Test Endikasyonu/Ön tanı:

SONUÇ: Klinik bulgular ile ilişkili saptanan varyantlar aşağıda verilmiştir:

Saptanan DNA varyantları:

Gen	Transkript	Varyant	Zigosite / Kalıtım	İlişkili olduğu fenotip (Kalıtım modeli)	ACMG sınıflandırması
UNC80	NM_032504.1	c.8869C>T (p.Gln2957Ter)	Heterozigot	- Hypotonia, infantile, with psychomotor retardation and characteristic facies 2 (Autosomal recessive)	Olası Patojenik
GJB1	NM_000166.6	c.670C>T (p.Arg224Cys)	Heterozigot	- Charcot-Marie-Tooth neuropathy, X-linked dominant, 1 (X-linked dominant)	VUS

Yürümede güçlük
Sık takılıp düşme

DTR hipoaktif
CK: 230 U/L
Kr-spinal MR Normal

RYR1	NM_000540.3	c.7526T>C (p.Val2509Ala)	Heterozigot	- Neuromuscular disease, congenital, with uniform type 1 fiber (Autosomal recessive, Autosomal dominant) - Central core disease (Autosomal recessive, Autosomal dominant) - King-Denborough syndrome (Autosomal dominant) - Malignant hyperthermia susceptibility 1 (Autosomal dominant) - Minicore myopathy with external ophthalmoplegia (Autosomal recessive)	VUS
------	-------------	-----------------------------	-------------	--	-----

Analiz Yorumu:

UNC80: UNC80 "unc-80 homolog, NALCN channel complex subunit" (MIM: 612636) geni OMIM veritabanında "Hypotonia, infantile, with psychomotor retardation and characteristic facies 2 (MIM: 616801)" fenotipleri/hastalıkları ile ilişkilendirilmiştir. c.8869C>T varyantı örnekte heterozigot olarak saptanmıştır. Varyant ESP6500, ExAC ve GnomAD veritabanlarında düşük frekanslı olarak (0.0) yer almaktadır. Tüm bu veriler eşliğinde ACMG 2015 kriterlerine göre "Olası Patojenik" olarak sınıflandırılmıştır. Ancak olguda heterozigot olarak bulunması kliniği açıklamak için tıbbi olarak yeterli değildir.

GJB1: GJB1 "gap junction protein beta 1" (MIM: 304040) geni OMIM veritabanında "Charcot-Marie-Tooth neuropathy, X-linked dominant, 1 (MIM: 302800)" fenotipleri/hastalıkları ile ilişkilendirilmiştir. c.670C>T varyantı örnekte heterozigot olarak saptanmıştır. Varyant ESP6500, ExAC ve GnomAD veritabanlarında düşük frekanslı olarak (1e-05) yer almaktadır. Clinvar veritabanında ise Belirsiz (VUS) olarak raporlanmıştır. Tüm bu veriler eşliğinde ACMG 2015 kriterlerine göre "VUS" olarak sınıflandırılmıştır. Olguda belirlenen klinik bulgular eşliğinde değerlendirilmesi ve segregasyon analizi yapılması önerilir.

RYR1: RYR1 "ryanodine receptor 1" (MIM: 180901) geni OMIM veritabanında "Neuromuscular disease, congenital, with uniform type 1 fiber (MIM: 117000) ve Central core disease (MIM: 117000) ve King-Denborough syndrome (MIM: 619542) ve Malignant hyperthermia susceptibility 1 (MIM: 145600) ve Minicore myopathy with external ophthalmoplegia (MIM: 255320)" fenotipleri/hastalıkları ile ilişkilendirilmiştir. c.7526T>C varyantı örnekte heterozigot olarak saptanmıştır. Varyant ESP6500, ExAC ve GnomAD veritabanlarında düşük frekanslı olarak (0.0) yer almaktadır. Tüm bu veriler eşliğinde ACMG 2015 kriterlerine göre "VUS" olarak sınıflandırılmıştır.



OMIM®

An Online Catalog of Human Genes and Genetic Disorders

Updated October 11, 2023



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Make a donation!



<https://www.omim.org>

* 612636

UNC80 HOMOLOG, NALCN CHANNEL COMPLEX SUBUNIT;
UNC80

Alternative titles; symbols

UNC80, C. ELEGANS, HOMOLOG OF
CHROMOSOME 2 OPEN READING FRAME 21; C2ORF21
KIAA1843



HGNC Approved Gene Symbol: **UNC80**

Cytogenetic location: **2q34** Genomic coordinates (GRCh38): **2:209,771,832-209,999,296** (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
2q34	Hypotonia, infantile, with psychomotor retardation and characteristic facies 2	616801	AR	3

* 180901

RYANODINE RECEPTOR 1; RYR1

Alternative titles; symbols

RYANODINE RECEPTOR, SKELETAL MUSCLE; RYDR
SKELETAL MUSCLE RYANODINE RECEPTOR; SKRR
SARCOPLASMIC RETICULUM CALCIUM RELEASE CHANNEL

HGNC Approved Gene Symbol: **RYR1**

Cytogenetic location: **19q13.2** Genomic coordinates (GRCh38): **19:38,433,691-38,587,564** (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	View Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
19q13.2	[Malignant hyperthermia susceptibility 1]		145600	AD	3
	Congenital myopathy 1A, autosomal dominant, with susceptibility to malignant hyperthermia		117000	AD	3
	Congenital myopathy 1B, autosomal recessive		255320	AR	3
	King-Denborough syndrome		619542	AD	3

* 304040

GAP JUNCTION PROTEIN, BETA-1; GJB1

Alternative titles; symbols

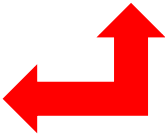
GAP JUNCTION PROTEIN, 32-KD
CONNEXIN 32; CX32
LIVER CONNEXIN

HGNC Approved Gene Symbol: **GJB1**

Cytogenetic location: **Xq13.1** Genomic coordinates (GRCh38): **X:71,215,239-71,225,516** (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
Xq13.1	Charcot-Marie-Tooth neuropathy, X-linked dominant, 1	302800	XLD	3

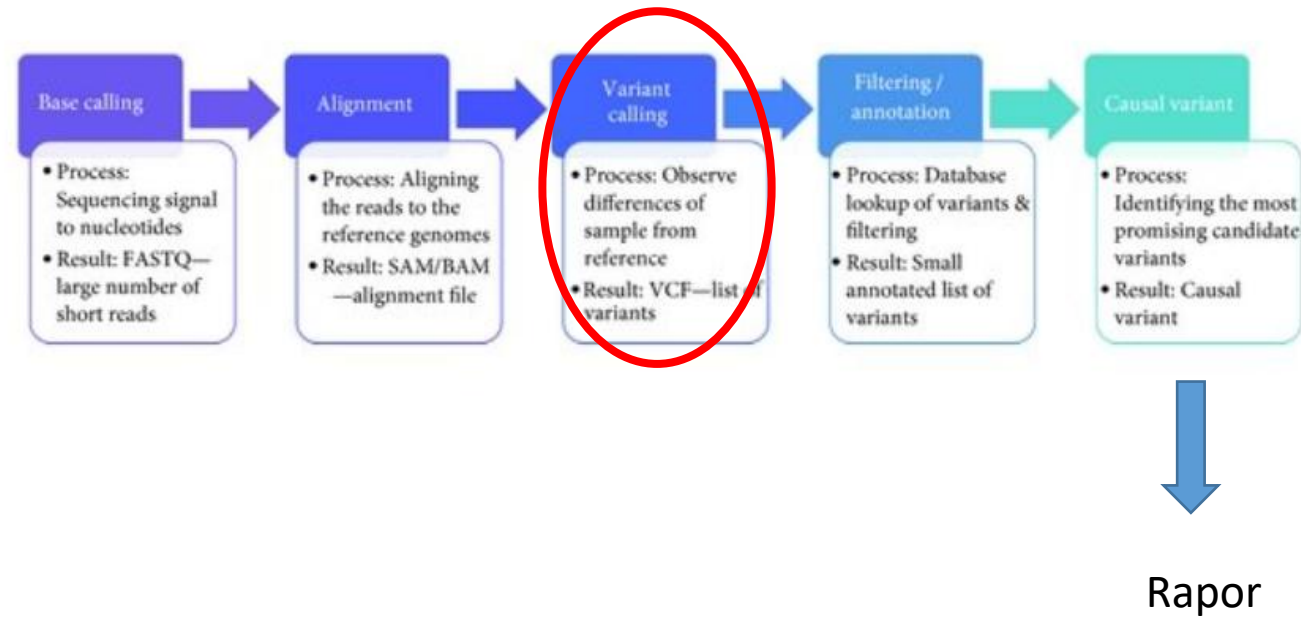


Derin fenotipleme;

- NCS-EMG
- Kas bx
- Kas görüntüleme



Vcf Datasını Kendim Değerlendirebilir miyim?



The Future of Genomic Medicine

Examples: **SNP** **CNV** **ROH**

Enter variant, gene or select an example above

REFERENCE
hg38

TYPE
Germline



Create new case from:



CMA



Report



VCF



All Cases > zsdeu

zsdeu

Assay: Germline case from VCF | Assignee: Unassigned | Status: Active



SNP



SV

Workbench

Variants

Phenotypes

Use as filter ☐

- ☐ All
- ☐ Optic atrophy
- ☐ Hypotonia
- ☐ Abnormal fat tissue distribution below the skin
- ☐ Inverted nipples
- ☐ Talipes equinovarus
- ☐ Posterior fossa anomaly
- ☐ Hypotonia early
- ☐ Pontocerebellar atrophy
- ☐ Respiratory insufficiency
- ☐ Pes equinovarus
- ☐ Seizure
- ☐ Optic disk coloboma
- ☐ Microcephaly

Add/Remove



Search variants by gene, phenotype, disease or any other attribute

Quick Filters: default

☐ 138,283 Variants in 17,399 Genes were found

1 - 25 of 138,283

★ Marked as **Conflicting** by **clinvar** ★ Classified as **Likely Pathogenic** by Franklin automated classification

☐

POLR3A

Chr10:78009515
 Heterozygote
 Intronic
 c.1909+22G>A

0.15%
 Frequency

100%
 Internal Freq.

High
 Confidence
 (AB: 42.67%)

N/A
 Prediction

★ Marked as **Conflicting** by **clinvar** ★ Classified as **Likely Pathogenic** by Franklin automated classification

☐

POLR3A

Chr10:77984023
 Heterozygote
 Regulatory(Intronic)
 c.3337-11T>C

<0.01%
 Frequency

100%
 Internal Freq.

High
 Confidence
 (AB: 54.64%)

Benign
 Prediction

★ Marked as **Conflicting** by **clinvar**

☐

POLR3A

Chr10:77982811
 Heterozygote
 Missense
 p.A1146T
 c.3436G>A

0.08%
 Frequency

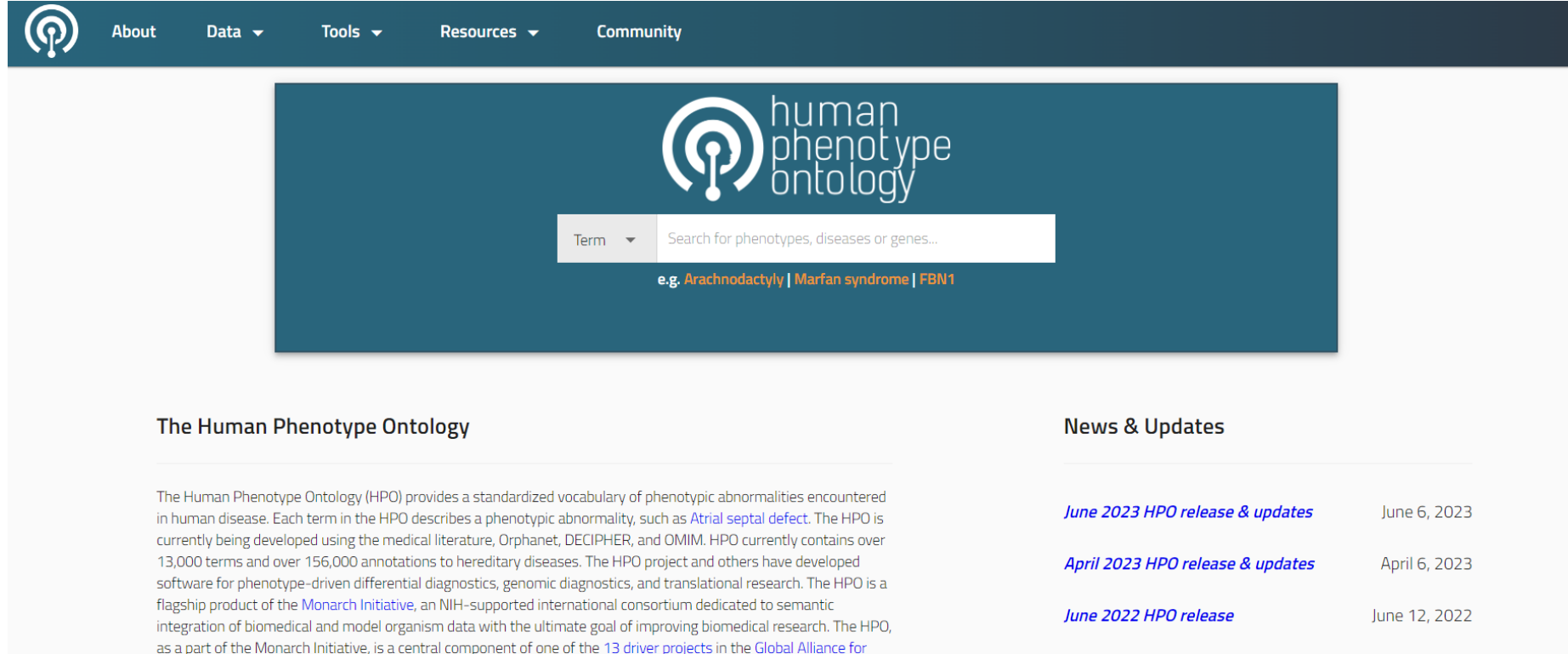
100%
 Internal Freq.

High
 Confidence
 (AB: 54.74%)

Benign
 Prediction

<https://varsome.com/>

HPO Terimleri



The screenshot shows the HPO website interface. At the top is a dark blue navigation bar with the HPO logo and links for About, Data, Tools, Resources, and Community. Below this is a large teal banner featuring the HPO logo and a search bar. The search bar has a dropdown menu labeled 'Term' and a search input field with the placeholder text 'Search for phenotypes, diseases or genes...'. Below the search bar, there are examples of search results: 'e.g. Arachnodactyly | Marfan syndrome | FBN1'. Below the banner, the page is divided into two columns. The left column is titled 'The Human Phenotype Ontology' and contains a paragraph describing the HPO project. The right column is titled 'News & Updates' and contains a list of recent releases and updates.

The Human Phenotype Ontology

The Human Phenotype Ontology (HPO) provides a standardized vocabulary of phenotypic abnormalities encountered in human disease. Each term in the HPO describes a phenotypic abnormality, such as [Atrial septal defect](#). The HPO is currently being developed using the medical literature, Orphanet, DECIPHER, and OMIM. HPO currently contains over 13,000 terms and over 156,000 annotations to hereditary diseases. The HPO project and others have developed software for phenotype-driven differential diagnostics, genomic diagnostics, and translational research. The HPO is a flagship product of the [Monarch Initiative](#), an NIH-supported international consortium dedicated to semantic integration of biomedical and model organism data with the ultimate goal of improving biomedical research. The HPO, as a part of the Monarch Initiative, is a central component of one of the [13 driver projects](#) in the [Global Alliance for](#)

News & Updates

June 2023 HPO release & updates	June 6, 2023
April 2023 HPO release & updates	April 6, 2023
June 2022 HPO release	June 12, 2022

<https://hpo.jax.org/app/>

human phenotype ontology

Disea... ▼ pontoce

Showing best results. See all results for 'pontoce'

Diseases - 10 of 35 displayed

ORPHA	Cortical dysgenesis with pontocerebellar ...
ORPHA	Olivop pontocerebellar atrophy-deafness s...
ORPHA	Pontocerebellar hypoplasia type 1
ORPHA	Pontocerebellar hypoplasia type 10
OMIM	Pontocerebellar hypoplasia type 1A
ORPHA	Pontocerebellar hypoplasia type 2
ORPHA	Pontocerebellar hypoplasia type 4
ORPHA	Pontocerebellar hypoplasia type 7
OMIM	Pontocerebellar hypoplasia, hypotonia, a...
OMIM	Pontocerebellar hypoplasia, type 10

ed vocabulary of ph
pic abnormality, suc
net, DECIPHER, and
seases. The HPO pr
nic diagnostics, and
international consortium dedicated to semantic

human phenotype ontology

Term ▼ pontoce

Showing best results. See all results for 'pontoce'

Phenotypes - 3 of 3 displayed

HP:0006879	Pontocerebellar atrophy
HP:0006955	Olivop pontocerebellar hypoplasia
HP:0002542	Olivop pontocerebellar atrophy

Ne

human phenotype ontology

Gene ▼ cog

Showing best results. See all results for 'COG'

Genes - 7 of 7 displayed

9382	COG1
22796	COG2
25839	COG4
10466	COG5
57511	COG6
91949	COG7
84342	COG8

d vocabulary of ph
c abnormality, such as [Atrial septal defect](#). The HPO is

Ne

Jun



All Cases > zsdeu

zsdeu

Assay: Germline case from VCF | Assignee: Unassigned | Status: Active

Follow Case

SNP

SV

Workbench

variants

Gerp

Clear

N/A Benign Uncertain

> Evidence

> ClinVar Evidence

Variant Callers

6

- ☐ None
- ☐ GATK Haplotype Caller
- ☐ FreeBayes
- ☒ Mutect
- ☒ VarScan
- ☒ Vardict
- ☒ Custom
- ☒ Custom 2
- ☒ Custom 3

Filter by Or callers

Search variants by gene, phenotype, disease or any other attribute

Quick Filters: default

242 Variants in 61 Genes were found

1 - 25 of 242 | Sort by: Gene

★ Alg1-congenital disorder of glycosylation was found to have a **Medium** connection to the case phenotypes Microcephaly, Respiratory insufficiency.

☐	ALG1	Chr16:5072190 Homozygote Regulatory(Intronic) c.208+133_208+134in...	94.92% Frequency	100% Internal Freq.	High Confidence (AB: 100%)	N/A Prediction	AR Gene Inheritance		Classify
--------------------------	-------------	---	---------------------	------------------------	----------------------------------	-------------------	------------------------	--	----------

★ Alg1-congenital disorder of glycosylation was found to have a **Medium** connection to the case phenotypes Microcephaly, Respiratory insufficiency.

☐	ALG1	Chr16:5075364 Homozygote Intronic c.391-24C>T	94.66% Frequency	100% Internal Freq.	High Confidence (AB: 100%)	N/A Prediction	AR Gene Inheritance		Classify
--------------------------	-------------	--	---------------------	------------------------	----------------------------------	-------------------	------------------------	--	----------

★ Alg1-congenital disorder of glycosylation was found to have a **Medium** connection to the case phenotypes Microcephaly, Respiratory insufficiency.

☐	ALG1	Chr16:5077334 Homozygote Intronic c.540-111T>A	94.50% Frequency	100% Internal Freq.	High Confidence (AB: 100%)	N/A Prediction	AR Gene Inheritance		Classify
--------------------------	-------------	---	---------------------	------------------------	----------------------------------	-------------------	------------------------	--	----------

Raporda Başka Nelere Dikkat Etmeliyim?

İşlem

: Hastanın periferik kanından elde edilen DNA örneğinde Limb Girdle kliniği ile ilişkili son sayfada belirtilen genler incelenmiştir. Dizileme Twist Biosciences teknolojisi kullanılarak gerçekleştirilmektedir. İlk olarak Konsensus Kodlama Sekanslarının (CCS) yaklaşık 36,5 Mb 'lık kısmı (insan genomundan elde edilen RefSeq ve Genocode v28 bölgelerinin >%98'ini hedef alan) fragmente edilmiş genomik DNA'dan Twist Exome 2.0 kiti ile çoğaltılır. Oluşturulan kütüphane, hedeflenen bazların >%98'i için en az 20x okuma derinliği elde etmek için MGI DNBSEQ-G400 NGS platformunda dizilenir. Dizileme sonucunda FASTQ formatında ham veri elde edilir. Franklin by Genoox programı kullanılarak FASTQ verisi üzerinden Tüm Ekzom Dizileme analizi yapılır. HGMD®, ClinVar ve CentoMD® veri bankalarında rapor edilen tüm hastalığa neden olan varyantların yanı sıra, gnomAD veritabanında %1'in altında minör allel frekansı (MAF) olan tüm varyantlar göz önünde bulundurulur. İlgili değişkenler için yapılan araştırma, kodlayıcı ekzonlara ve +/- 20 intronik bazıları çevrelemeye odaklanmıştır. Tüm potansiyel kalıtım kalıpları ele alınmıştır. Ek olarak, verilen aile öyküsü ve klinik bilgiler, patojeniteleri ve hastalıklara neden olmalarına göre tanımlanmış değişkenleri değerlendirmek için kullanılır ve Class 1 – 5 skorlamasında sınıflandırılır**. Benign veya muhtemel benign varyantlar hariç, hastanın fenotipiyle ilgili tüm değişkenler bildirilmiştir. Düşük kaliteli tek nükleotid varyantları ve tüm ilgili delesyon/insersiyon varyantları Sanger dizileme ile doğrulanır.

İçerdiği Genler Yeterli mi?



PanelApp Panels Genes and Entities Activity Log in Register

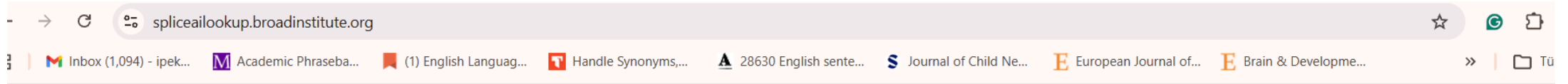
450 panels

Compare two panels

Panel ↓	Evaluated genes	Reviewers	Actions
congenital myo			1 panel
Congenital myopathy Level 3: Neuromuscular disorders Level 2: Neurology and neurodevelopmental disorders Relevant disorders: R81 Version 4.31 Panel Types: Rare Disease 100K, GMS Rare Disease, Component Of Super Panel, GMS signed-off, Latest signed off version: v4.0 (22 Mar 2023)	128 of 128 100% STRs: 2 Regions: 3	17 reviewers	Download
		Green TTN	5 reviews 2 green
		Green VMA21	4 reviews 2 green
		Amber ASCC1	2 reviews 2 green
			BIALLELIC, autosomal or pseudoautosomal
			Sources - Expert - Expert Review Green - Illumina TruGenome Clinical Sequencing Services - London South GLH - NHS GMS - Radboud University Medical Center, Nijmegen - UKGTN Phenotypes - Salih myopathy, OMIM:611705 Tags
			X-LINKED: hemizygous mutation in males, biallelic mutations in females
			Sources - Expert Review - Expert Review Green - London South GLH - NHS GMS Phenotypes - Myopathy, X-linked, with excessive autophagy, OMIM:310440 Tags
			BIALLELIC, autosomal or pseudoautosomal
			Sources - Expert Review Amber - Literature Phenotypes - Spinal muscular atrophy with congenital bone fractures 2, OMIM:616867

<https://panelapp.genomicsengland.co.uk/>

Splice AI



Enter a variant below to see its [SpliceAI](#) , [Pangolin](#) , [PromoterAI](#) , [PrimateAI-3D](#) , [\[more details\]](#) [AlphaMissense](#) and other scores:

Examples (on hg38):

NM_001089.3(ABCA3):c.875A>T (p.Glu292Val)

chr8-140300616-T-G

6 31740453 G T

[\[show more examples\]](#)

Enter a variant...

Genome version: ☐ hg19 ☒ hg38 Gencode: ☒ basic ☐ comprehensive ?

Max distance: ? ☐ masked scores ? ☐ REF & ALT scores ?

Submit

SCN1A c.602+1 G>A ??

[SpliceAI-lookup/issues](#): issues or feature requests for this website

December 14, 2025

- In the 'Other scores' section, only populate the 'Points' column for missense variants since the calibration was only done for missense

September 22, 2025

- updated to Gencode v49 (was previously on v47)
- added a new optional visualization track called **"genes used for precomputed scores"**. It shows the Gencode v24 transcript models originally used by the SpliceAI authors to generate the precomputed SpliceAI score tables available from Illumina. This track can help explain some of the differences in scores between SpliceAI-lookup and these precomputed tables.

[\[show older updates\]](#)

Related web tools:

[liftover](#): for variants/positions/intervals (hg19 <=> hg38 <=> T2T)

[TGG Viewer](#): igv.js-based web viewer for public reference tracks and private data in Google Storage buckets. Has custom track types for RNA-seq [splice junctions](#) and [gCNV](#) variants.



Enter a variant below to see its [SpliceAI](#) , [Pangolin](#) , [PromoterAI](#) , [PrimateAI-3D](#) , [\[more details\]](#) [AlphaMissense](#) and other scores:

Examples (on hg38):

NM_001089.3(ABCA3):c.875A>T (p.Glu292Val)

chr8-140300616-T-G

6 31740453 G T

[\[show more examples\]](#)

2 166054637 C T

Genome version: ☐ hg19 ☒ hg38 Gencode: ☒ basic ☐ comprehensive ?

Max distance: ? ☐ masked scores ? ☐ REF & ALT scores ?

Submit

SpliceAI scores: ?

Variant	Gene	☐ = MANE Select transcript	☐ = non-coding transcript	Δ type	Δ score ?	position ?
2 166054637 C T	SCN1A (ENSG00000144285.24 / ENST00000674923.1 / NM_001165963.4)			Acceptor Loss	0.93	129 bp
splice donor variant	protein coding MANE Select transcript (minus strand)			Donor Loss	0.99	1 bp
UCSC , gnomAD	OMIM , GTEx , gnomAD , ClinGen , Ensembl , Decipher , GeneCards			Acceptor Gain	0.00	
				Donor Gain	0.00	

MANE Select Transcript or All Transcripts

Pangolin scores: ?

Variant	Gene	Δ type	Δ score ?	position ?
2 166054637 C T	SCN1A (ENSG00000144285.24 / ENST00000674923.1 / NM_001165963.4)	Splice Loss	0.85	1 bp
splice donor variant	protein coding MANE Select transcript (minus strand)			
UCSC , gnomAD	OMIM , GTEx , gnomAD , ClinGen , Ensembl , Decipher , GeneCards	Splice Gain	0.00	92 bp

Gof-Lof ?

← → ↻ ☰ funnc.shinyapps.io/shinyappweb/

☰ |  Inbox (1,094) - ipek...  Academic Phraseba...  (1) English Languag...  Handle Syn

HOME funNC - protein coordinates funNC - genomic coordinates about

SCN1A c.473 A>G
p.Glu158Gly p.E158G ?

funNCion - Functional variant prediction in Na_vs and Ca_vs ion channels

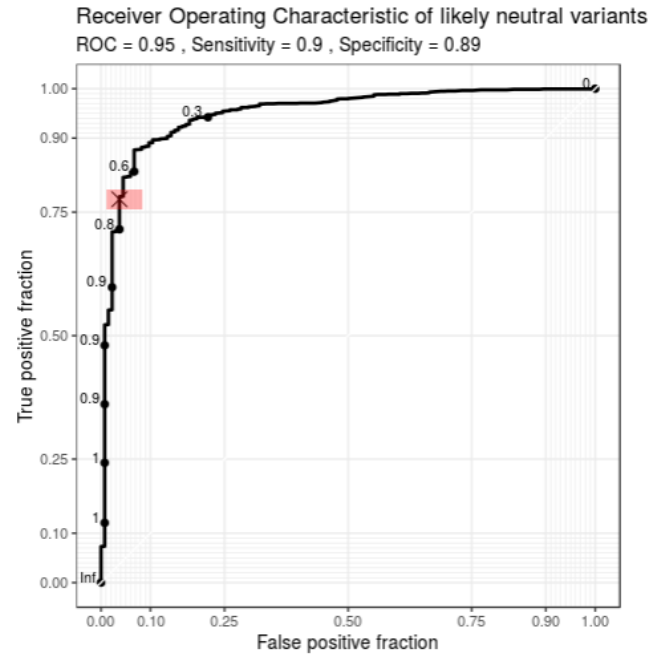
gene

SCN1A

alternative amino acid

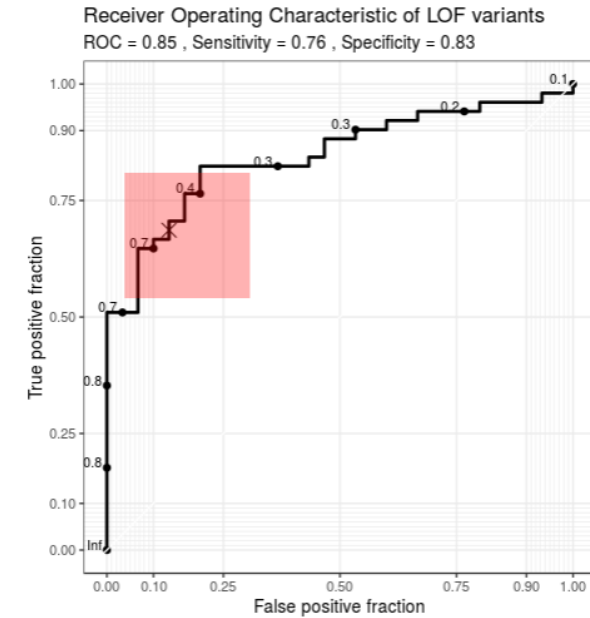
G

Other pathogenicity scores are CADD = 23.2 , MPC= 1 and PolyPhen= 0.13 . On the figure, you can see where your variant falls on the Receiver Operating Characteristic curve along with 95%-confidence intervals (red area).

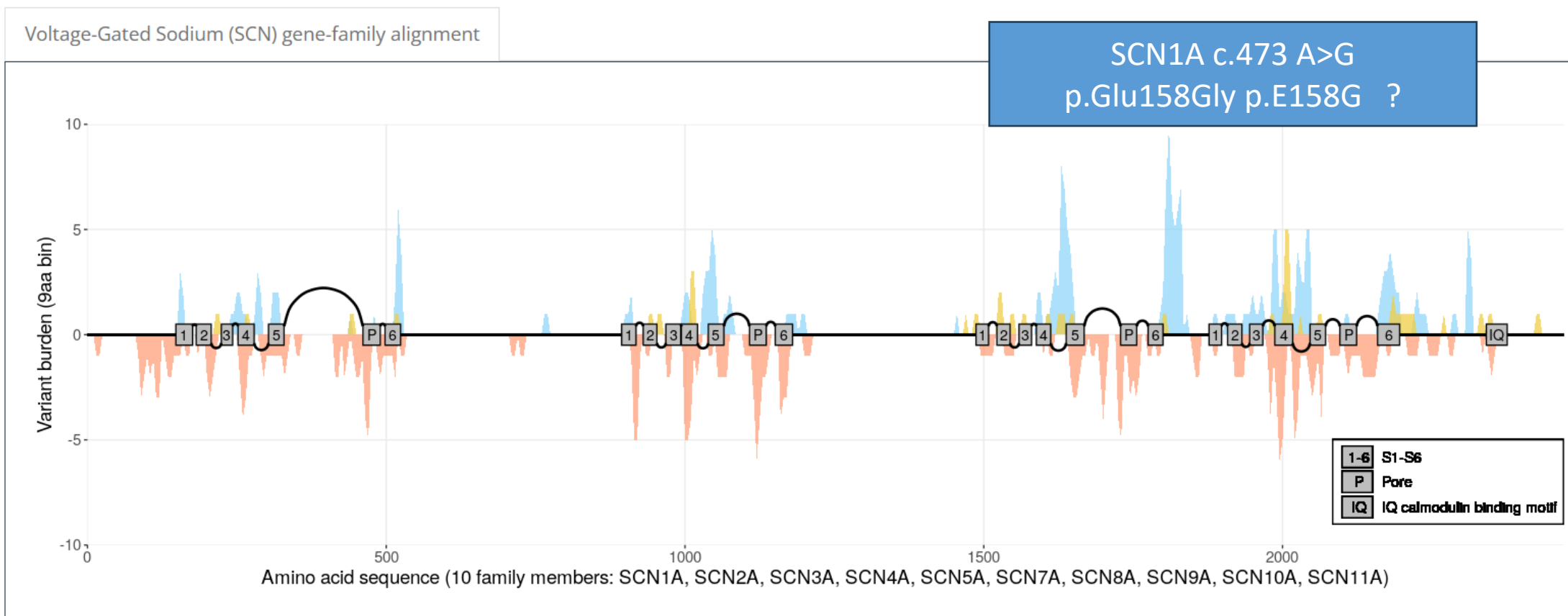
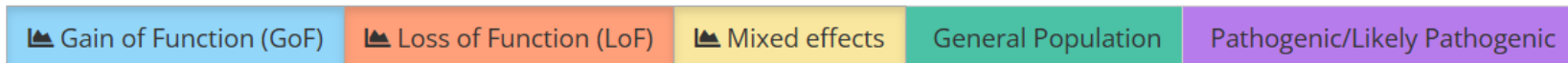


Functional prediction

The variant you selected is predicted to have no functional effect. Therefore, its functional prediction is unreliable (probability to be loss-of-function = 0.64) .



Show variant distribution:



Index	Functional_Effects	SCN1A	SCN2A	SCN3A	SCN4A	SCN5A	SCN7A	SCN8A	SCN9A	SCN10A	SCN11A	ClinVar phenotype reports
All	All	All	All	All	All	All	All	All	All	All	All	All
43		-	-	-	-	L_39	-	A_40	-	E_39	-	N/A
44		-	-	-	-	Q_40	-	D_41	-	K_40	-	N/A
45		-	-	-	-	E_41	-	G_42	-	-	-	N/A
46		-	-	-	-	-	-	S_43	-	-	-	N/A
51		-	E_44	-	-	L_46	-	-	-	K_45	T_44	N/A
97		-	-	-	-	-	N_78	-	-	-	-	N/A
155		-	-	-	-	-	-	-	-	-	A_147	N/A
156		-	-	-	-	-	-	-	-	-	T_148	N/A
157		-	-	-	-	-	-	-	-	-	G_149	N/A
158		-	-	-	-	-	-	-	-	-	P_150	N/A
224		-	-	-	-	-	-	-	-	-	I_216	N/A
308		-	F_295	Y_294	Y_295	-	-	-	-	-	-	N/A

Example: To evaluate missense variant "ENST00000357398.3(SCN2A):c.1149A>T (p.Gln383His)" search for "SCN2A" gene and then look for "Q_383" in its corresponding column

Özetle...

- Franklin genoox
- Varsome
- OMİM
- ClinVar, Decipher, LOVD, Pubmed
- PanelAPP
- SpliceAI
- Na-Ca kanal için bazı GOF_LOF veritabanları



- Prof. Dr. Semra Hız
- Prof. Dr. Uluç Yiş
- Prof. Dr. Adem Aydın
- Doç.Dr.A.İpek Polat



Teşekkür ederim...

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- Uzm.Dr. Mustafa Halk
- Uzm.Dr. Dilek Sönmezoğlu
- Uzm.Dr. Naz Kadem
- Uzm.Dr. Mine Sağlam Atmaca
- Uzm.Dr.Melike naz Akbaş

