VUS Değerlendirmede Kullanılan Veritabanları ve Araçlar

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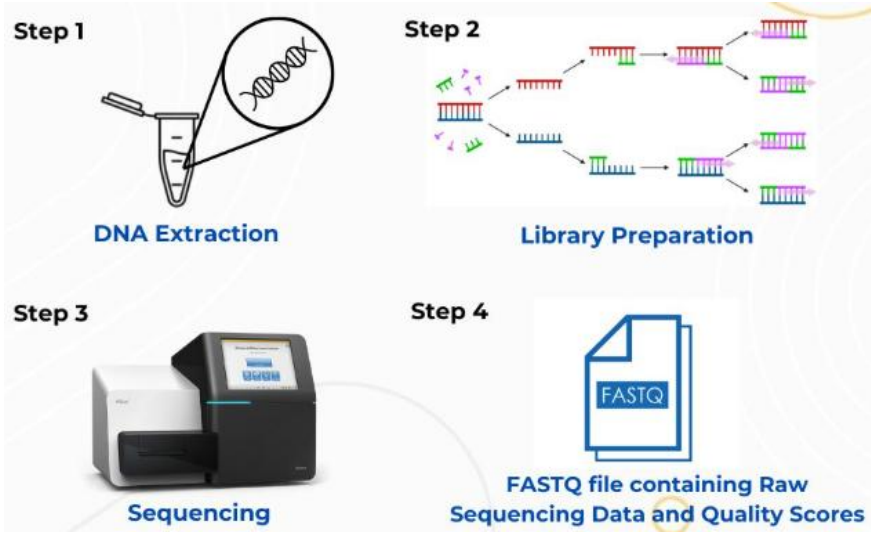
İzmir Biyotıp ve Genom Enstitusu Moleküler Biyoloji ve Genetik BD

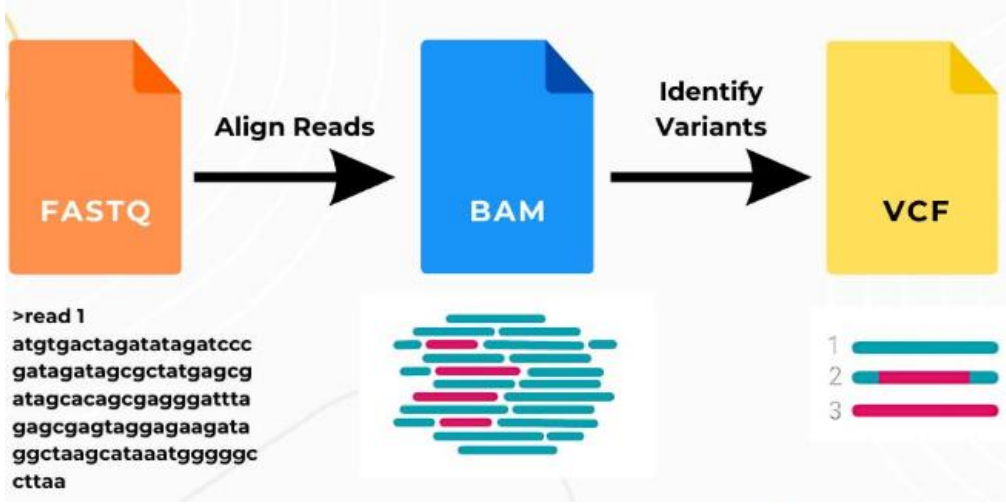
Next Generation Sequencing: CES-WES-WGS



- 1. **Kütüphane** hazırlığı: DNA eldesi / adaptörlerin eklenmesi / parçalanması / çoğaltılması (amplifikasyon) ve probların hedefe (ekzonlar, genom vs) bağlanması

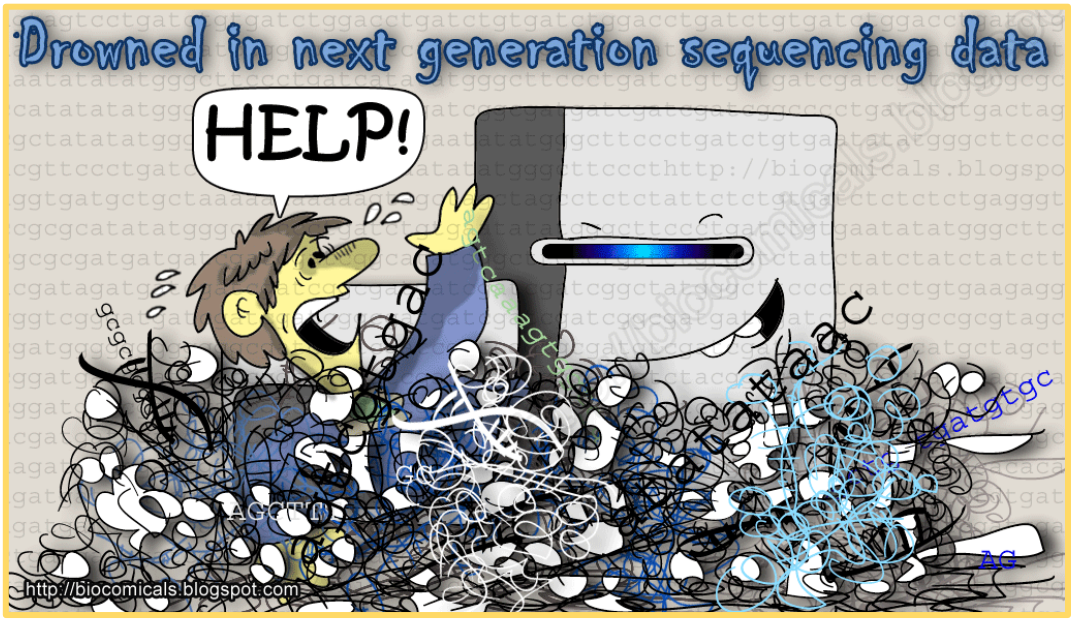
  * Kalite kontrol
- 2. Sekanslama ile ‘’**FASTQ file**’’
  - Makinenin okuduğu ham harfler
  - Genomun neresinden bilmiyoruz
- 3. Referans insan genomu ile dizileme (alignment): ‘’**BAM file**’’
  - Hangi kromozomda, hangi pozisyonda
  - Kaç kez okunmuş (covarage) ve güvenilir mi?
- 4. Referanstan farklı neler var: ‘’**VCF file**’’
  - Variant calling: Varyant listesi;

    Yeri, referans ve değişen baz, ht/hm, kalite, derinlik



VCF Data'nın Bize Verdikleri

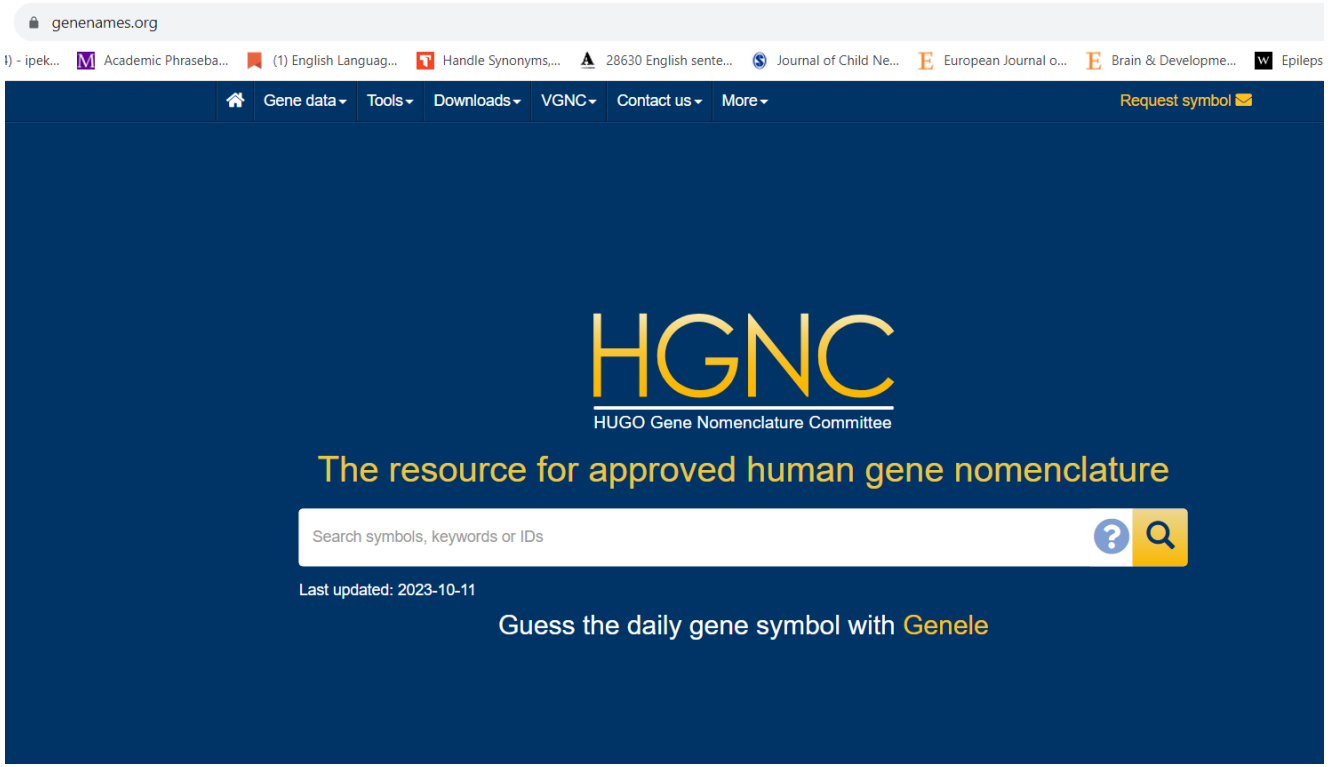
- WGS 'de yaklaşık 3-5 milyon varyant
- WES 'de yaklaşık 30.000-50.000 varyant
  - Çoğu SNP, az kısmı küçük indel
  - Çoğu intronik kenar, sinonim, klinik önemsiz/ benign varyantlar
- Ön filtreler ile sayı 15.000-30.000'e düşer
  - Quality, depth, artefakt temizliği, tekrar bölgeleri…
- Populasyon frekansı (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)



http://genenames.org

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

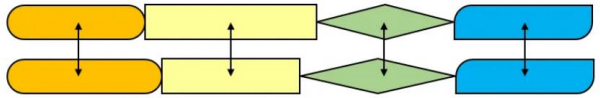
PYROXD2: pyridine nucleotide-disulphide oxidoreductase domain 2
Gene HGNC ID HGNC:23517 Locus type Gene with protein product Status Approved
Matches Previous gene symbol: C10orf33

Items: 1 to 1 of 1

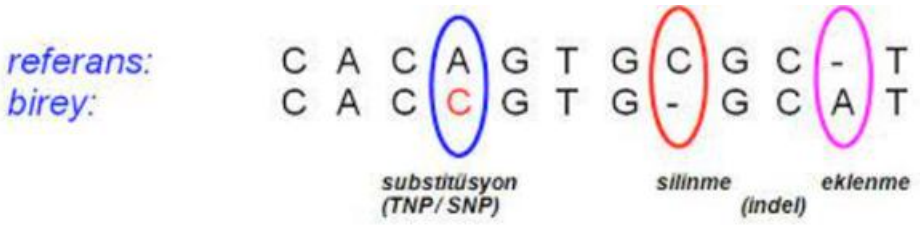
Referans genom nedir?

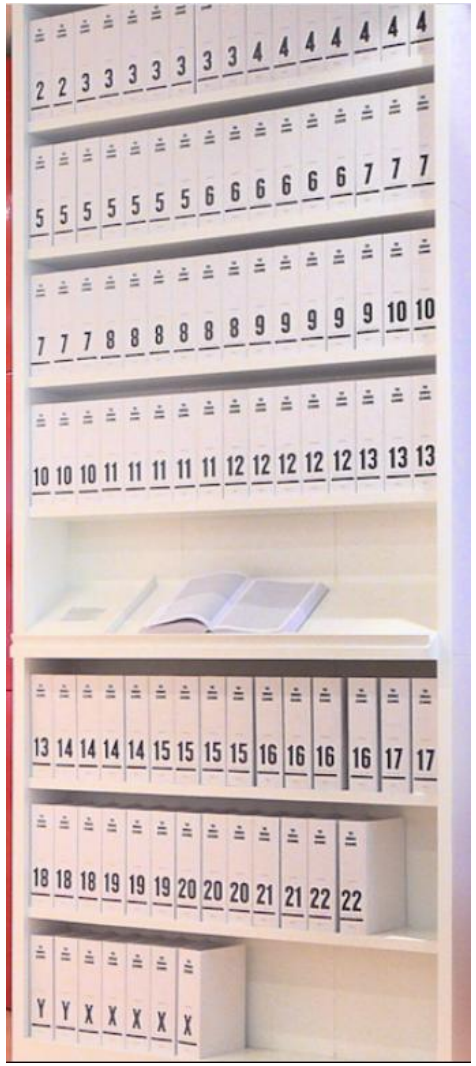
Referans genom

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



Global Alignment





İnsan referans genomu; Wellcome Collection, Londra

“Genome Reference Consortium Human Reference 38”

The Genome Reference Consortium consists of:

Wellcome Sanger Institute

The McDonnell Genome Institute at Washington University

The European Bioinformatics Institute

The National Center for Biotechnology Information

The Zebrafish Model Organism Database

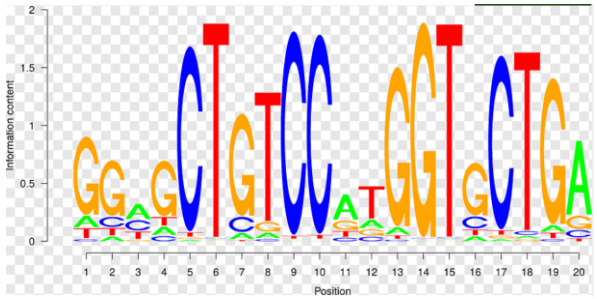
Rat Genome Database

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

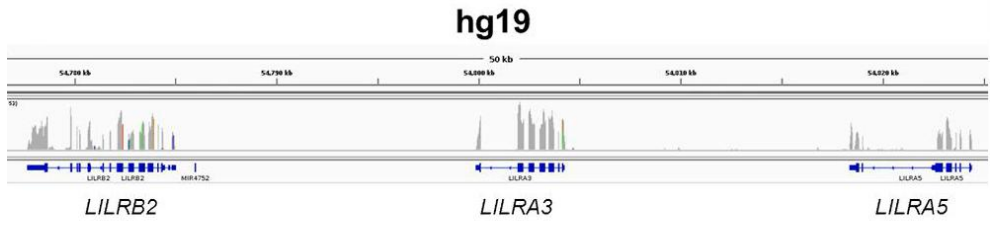
https://www.ncbi.nlm.nih.gov/datasets/genome/GCF_000001405.26/

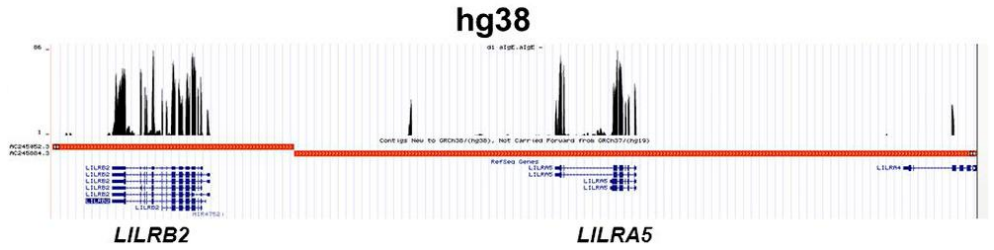
GRCh38 (hg38) vs GRCh37 (hg19)

- 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

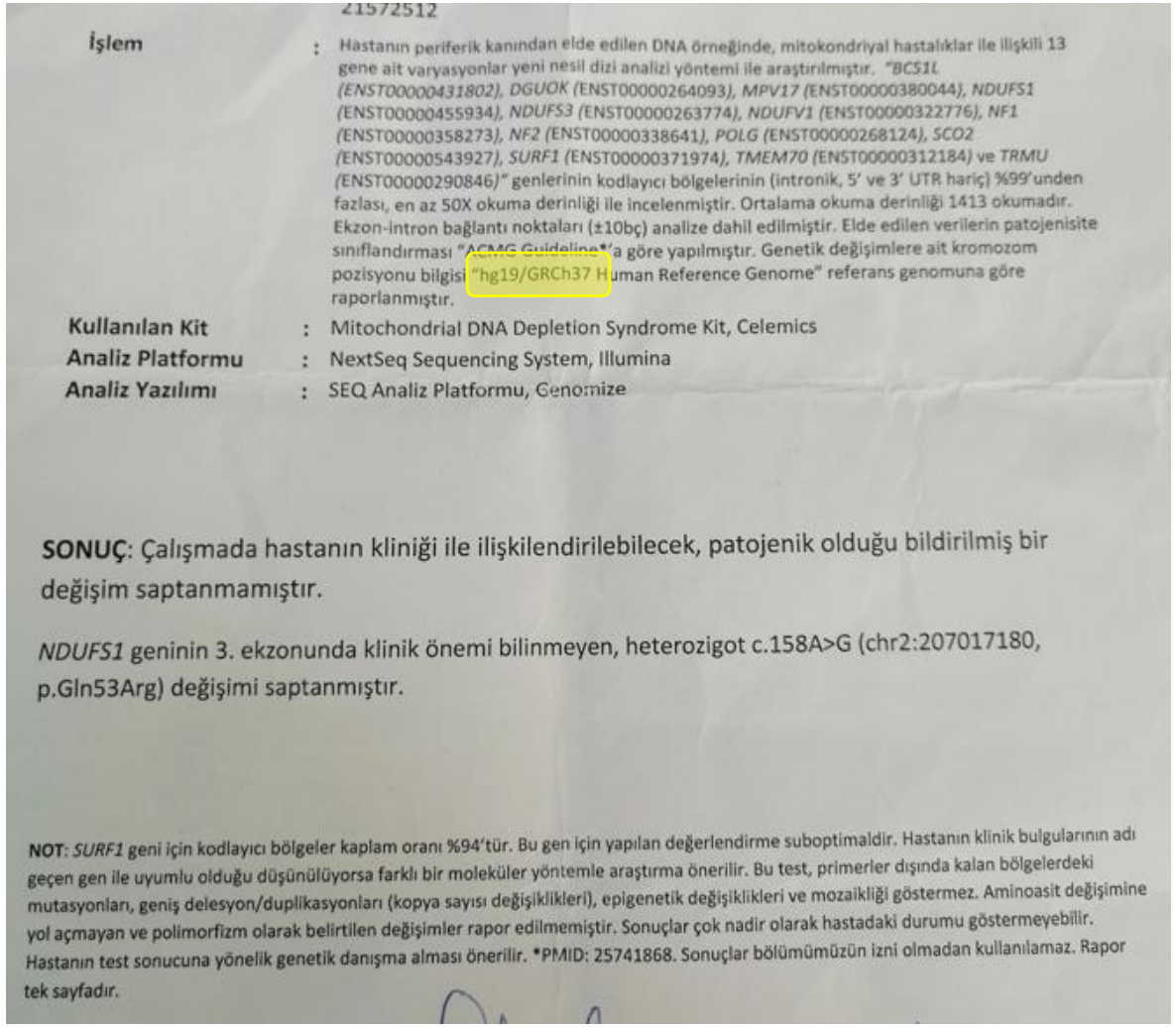
		Actions
NCBI RefSeq assembly	GCF_000001405.25	
Submitted GenBank assembly	GCA_000001405.14	
Taxon	*Homo sapiens* (human)	
Synonym	hg19	
Assembly type	haploid with alt loci	
Submitter	Genome Reference Consortium	
Date	Jun 28, 2013	

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



21572512

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'unden fazlası, en az 50X okuma derinliği ile incelenmiştir. Ortalama okuma derinliği 1413 okumadır. Ekzon-intron bağlantı noktaları (±10bç) 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, Celemics
Analiz Platformu : NextSeq Sequencing System, Illumina
Analiz Yazılımı : SEQ Analiz Platformu, Genomize

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

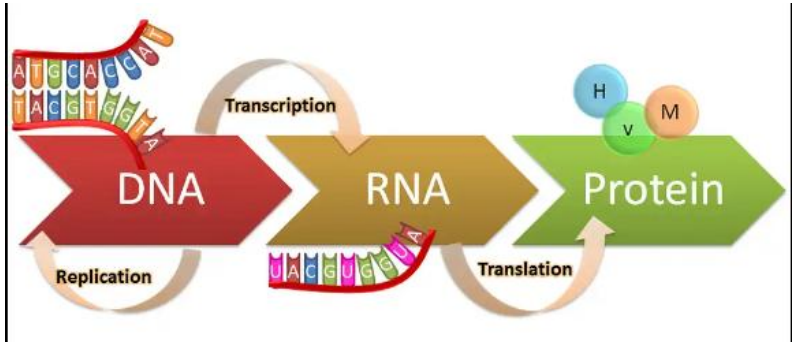
NDUFS1 geninin 3. ekzonunda klinik önemi bilinmeyen, heterozigot c.158A>G (chr2:207017180, p.Gln53Arg) değişimi saptanmıştır.

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.

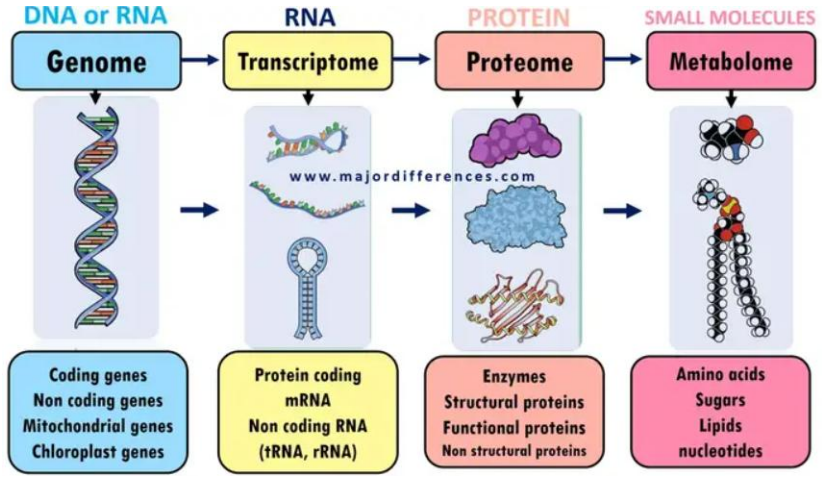
Raporlarda Varyant Nasıl İfade Edilir?

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)



https://varnomen.hgvs.org

Örnek

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

UBA2 (ENST00000246548.4)	chr19:34959996 (Exon 17)	Missense Variant (p.S598L) c.1793C>T rs536680033	VUS	HETEROZİGOT	ACCES syndrome | AD

Bazı Biyolojik Veritabanları

- Veri tabanlarında birçok dizi birden fazla kez belirtilmiş ve gösterilmiştir.
- Sekans bilgileri için gereksiz fazlalığı olan gösterimleri engellemek ve bu belirtimleri 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

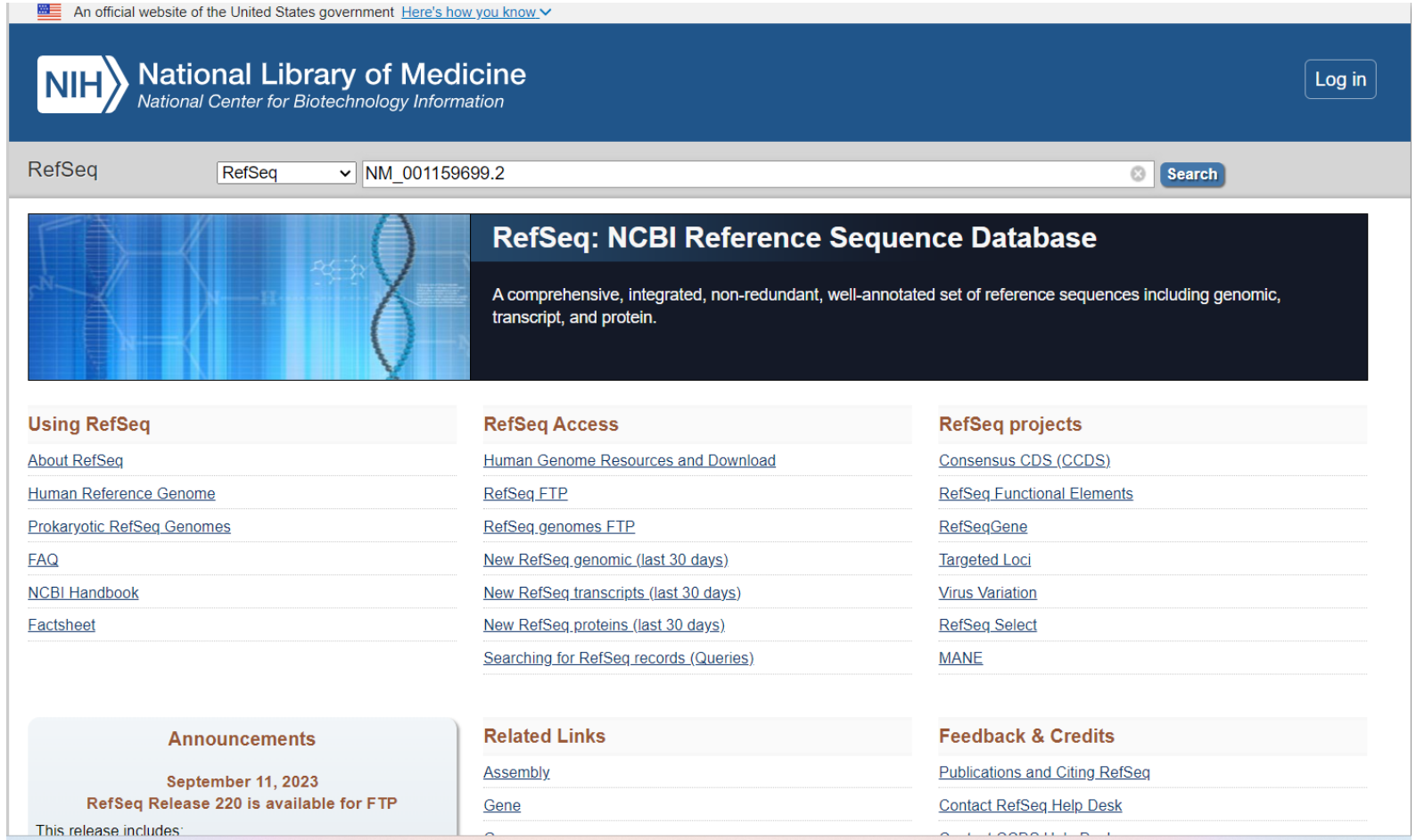
NC_123456	Genomik	Bütünsel genomik molekülleri ifade eder (kromozomlar, organel DNA'sı, plasmidler)
NG_123456	Genomik	Analizi ve belirtimi tamamlanmamış genomik bölgeleri ifade eder.
NM_123456	mRNA	Genlerin transkript ürünlerini ifade etmektedir (haberci RNA). **Veri tabanlarında bulunan, mRNA'lar, aslında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

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

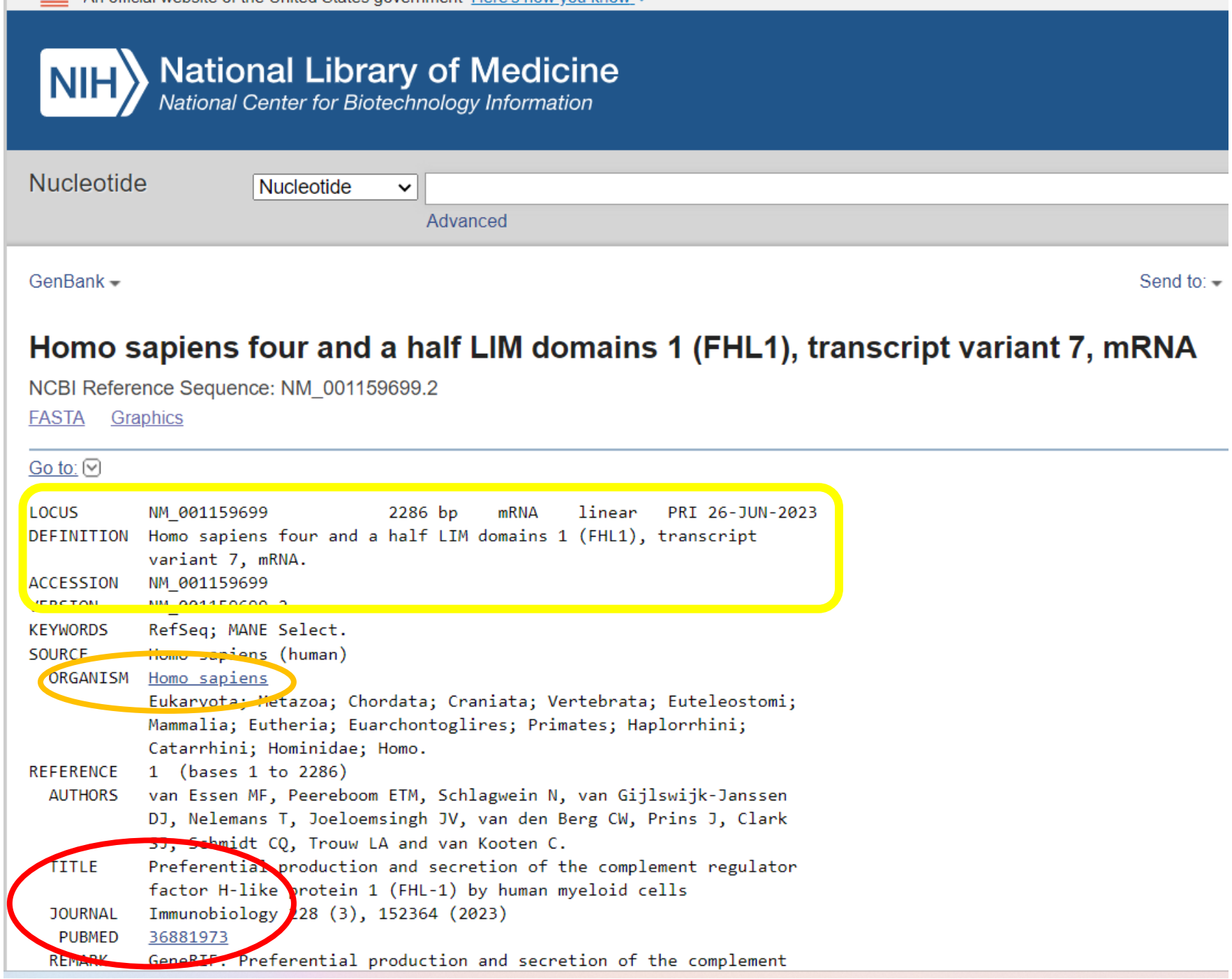
RefSeq Veritabanında Neler Araştırabilirim?

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

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



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



- Gen adı
- Fonksiyonu

- Pubmed yayınlarına erişim linki

(1993)

PUBMED 20301609

COMMENT 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

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     61 tgagccatgg cttcccatag acactcaggt ccctccagct acaaggtggg caccatggcg
    121 gagaagtttg actgccacta ctgcagggat cccttgcagg ggaagaagta tgtgcaaaag
    181 gatggccacc actgctgcct gaaatgcttt gacaagttct gtgccaacac ctgtgtggaa
    241 tgccgcaagc ccatcggtgc ggactccaag gaggtgcact ataagaaccg cttctggcat
    301 gacacctgct tccgctgtgc caagtgcctt cacccctgg ccaatgagac ctttgtggcc
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    481 cacaaagact gcttcacctg tagtaactgc aagcaagtca tcgggactgg aagcttcttc
    541 cctaaagggg aggacttcta ctgcgtgact tgccatgaga ccaagtttgc caagcattgc
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   1261 ccacttagtg atgtaagcaa gaagcatagg agataaaacc cccactgaga tgcctctcat
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   1441 cttcctcatc agaactctgc ccttccttct gttcttttgt gctttcaaat aactaacacg
   1501 aacttccaga aaattaacat ttgaacttag ctgtaattct aaactgacct ttccccgtac
   1561 taacgtttgg tttccccgtg tggcatgttt tctgagcgtt cctactttaa agcatggaac
   1621 atgcaggtga tttgggaagt gtagaaagac ctgagaaaac gagcctgttt cagaggaaca
   1681 tcgtcacaac gaatacttct ggaagcttaa caaaactaac cctgctgtcc tttttattgt
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   2041 gaggaaatct ggatttccac ctaccgctta cctgaaatgc aggatcacct acttactgta
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   2161 aatacatact aacattcttg taggagtggt tagagaagct gatgcctcat ttctacattc
   2221 tgtcattagc tattatcatc taacgtttca gtgtatcctt acagaaataa agcagcatat
   2281 gaataa
```

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

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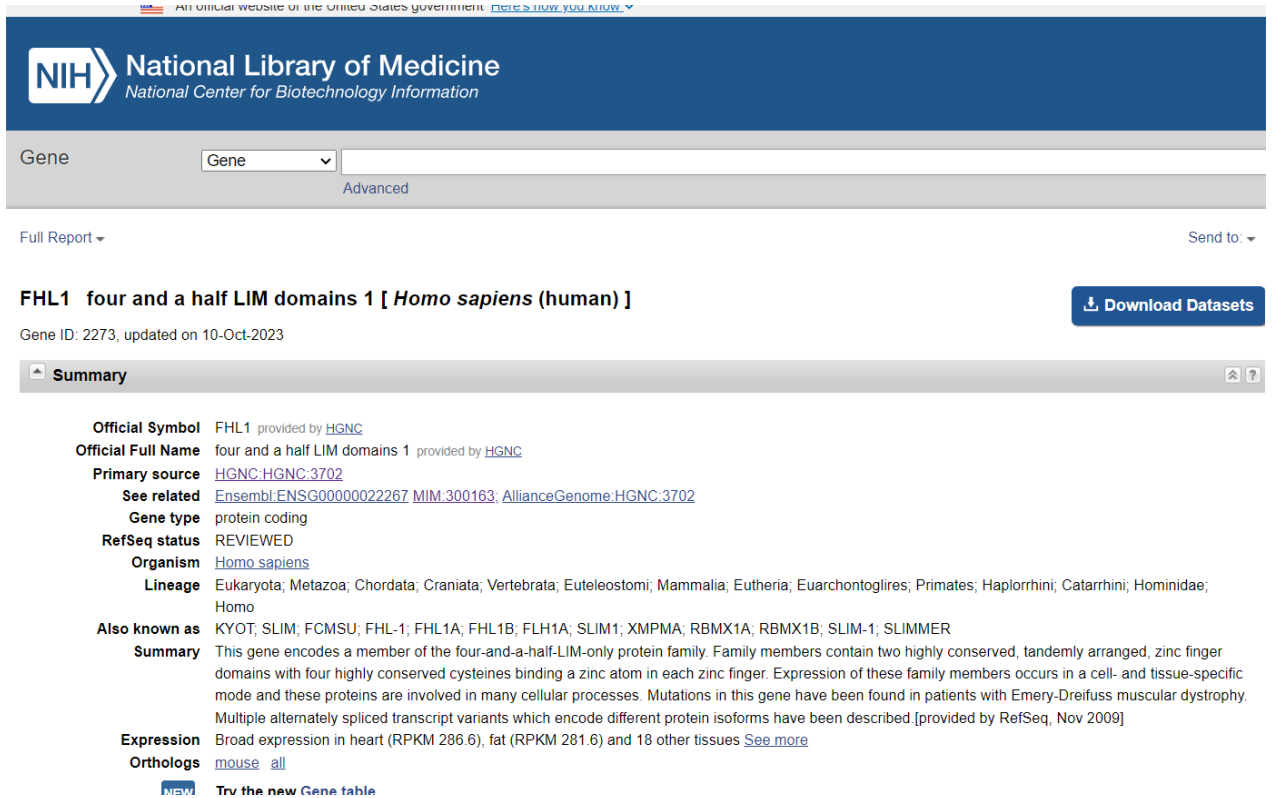
- GeneID
- OMİM linkleri



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

GeneID Veritabanında Neler Araştırabilirim?

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

GeneID

- Gen isimleri
- Fonksiyonu
- Domainleri

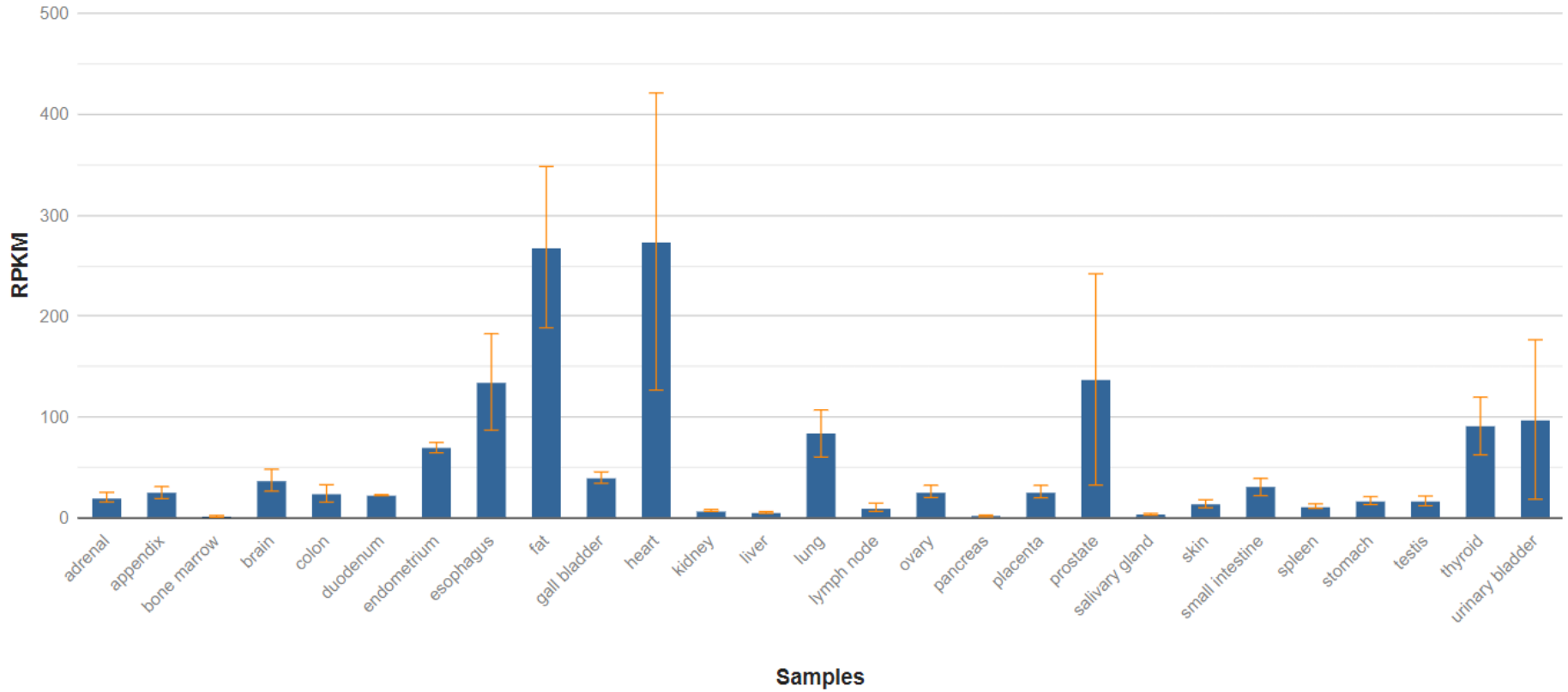
https://www.ncbi.nlm.nih.gov/gene/

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

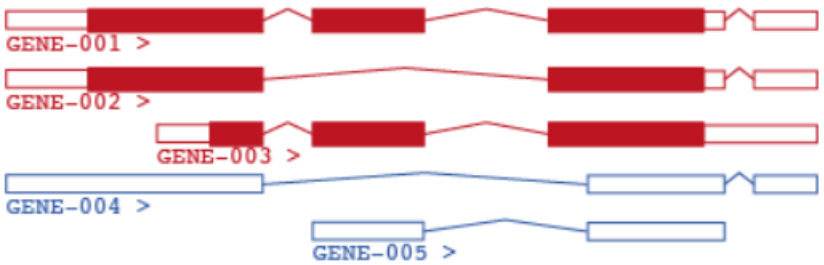
cd09344 Location:56 → 109	LIM1_FHL1; The first LIM domain of Four and a half LIM domains protein 1
cd09348 Location:233 → 296	LIM4_FHL1; The fourth LIM domain of Four and a half LIM domains protein 1 (FHL1)
cd09424 Location:117 → 174	LIM2_FHL1; The second LIM domain of Four and a half LIM domains protein 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

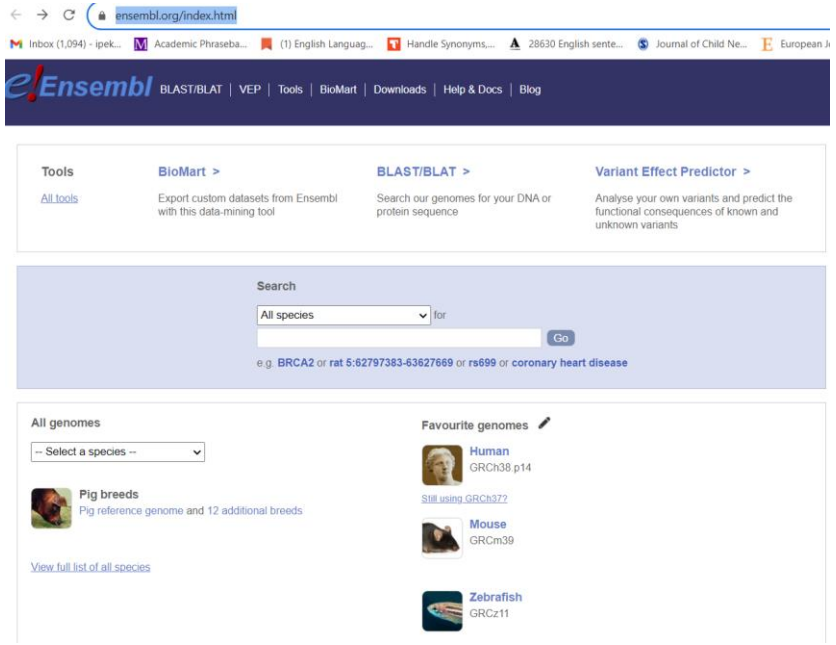
- Transkript özellikleri
- Protein düzeyinde domainler ve aminoasid lokalizasyonları

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



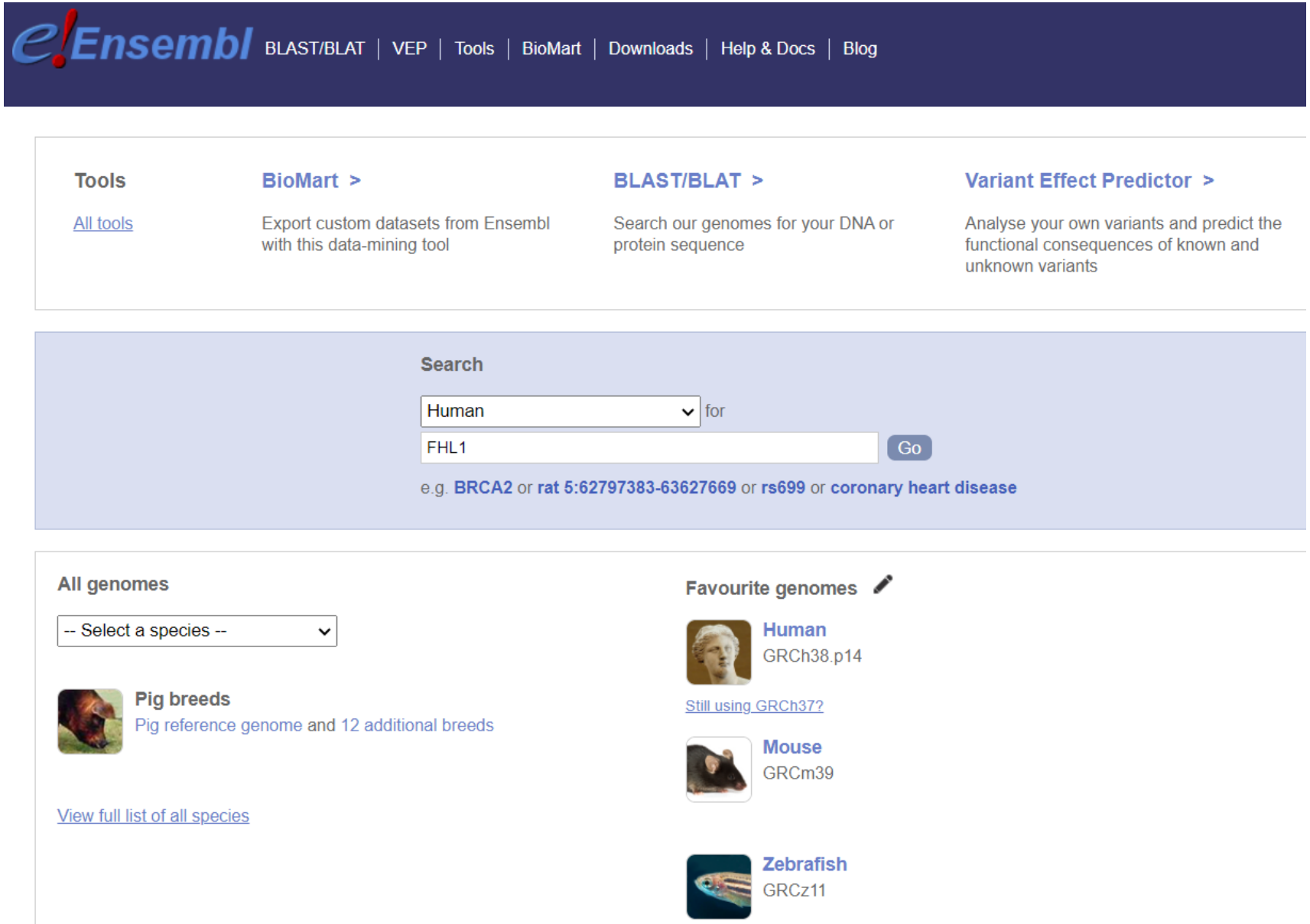


Matched Annotation from NCBI and EMBL-EBI (MANE)

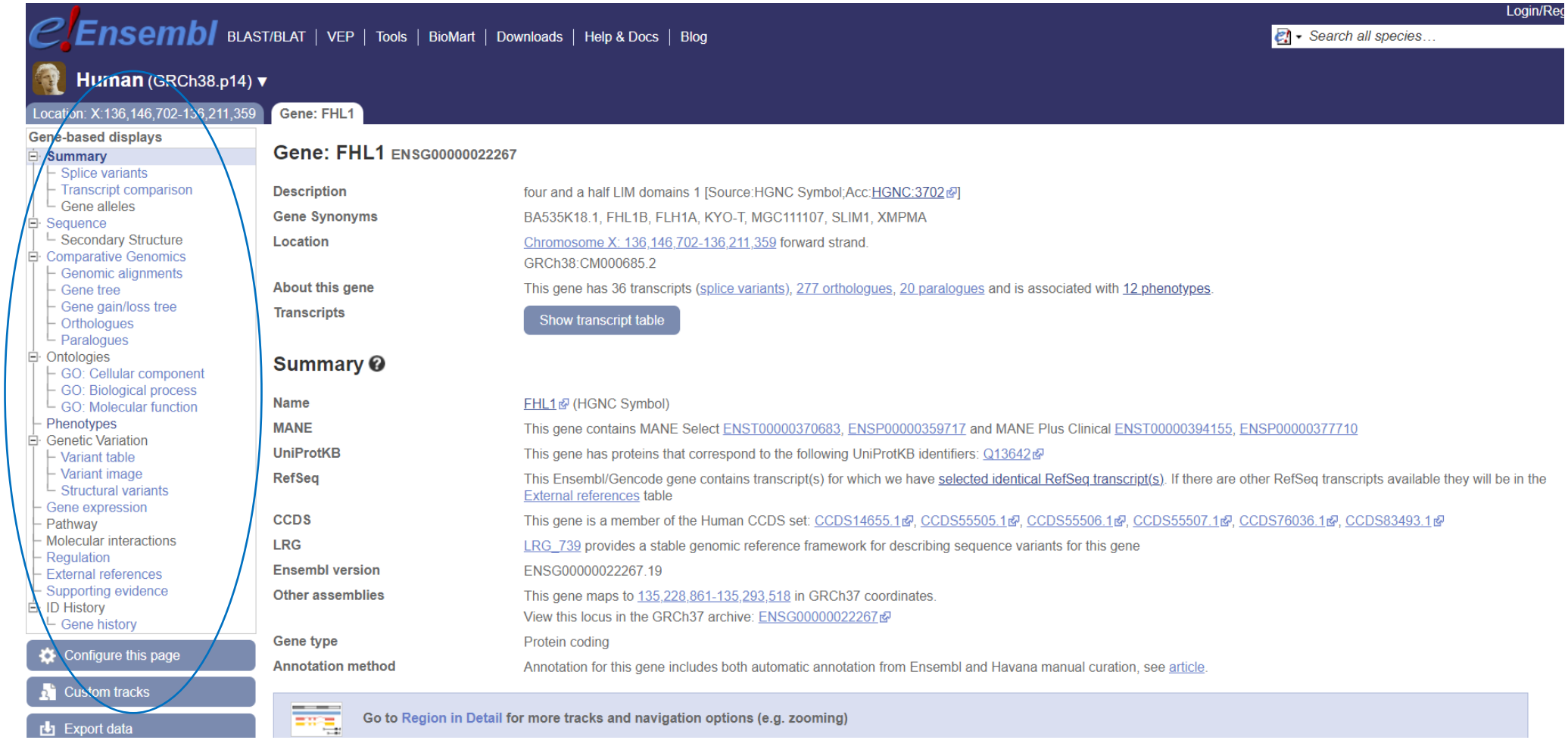
https://www.ensembl.org/index.html

Ensembl Veritabanında Neler Araştırabilirim?

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

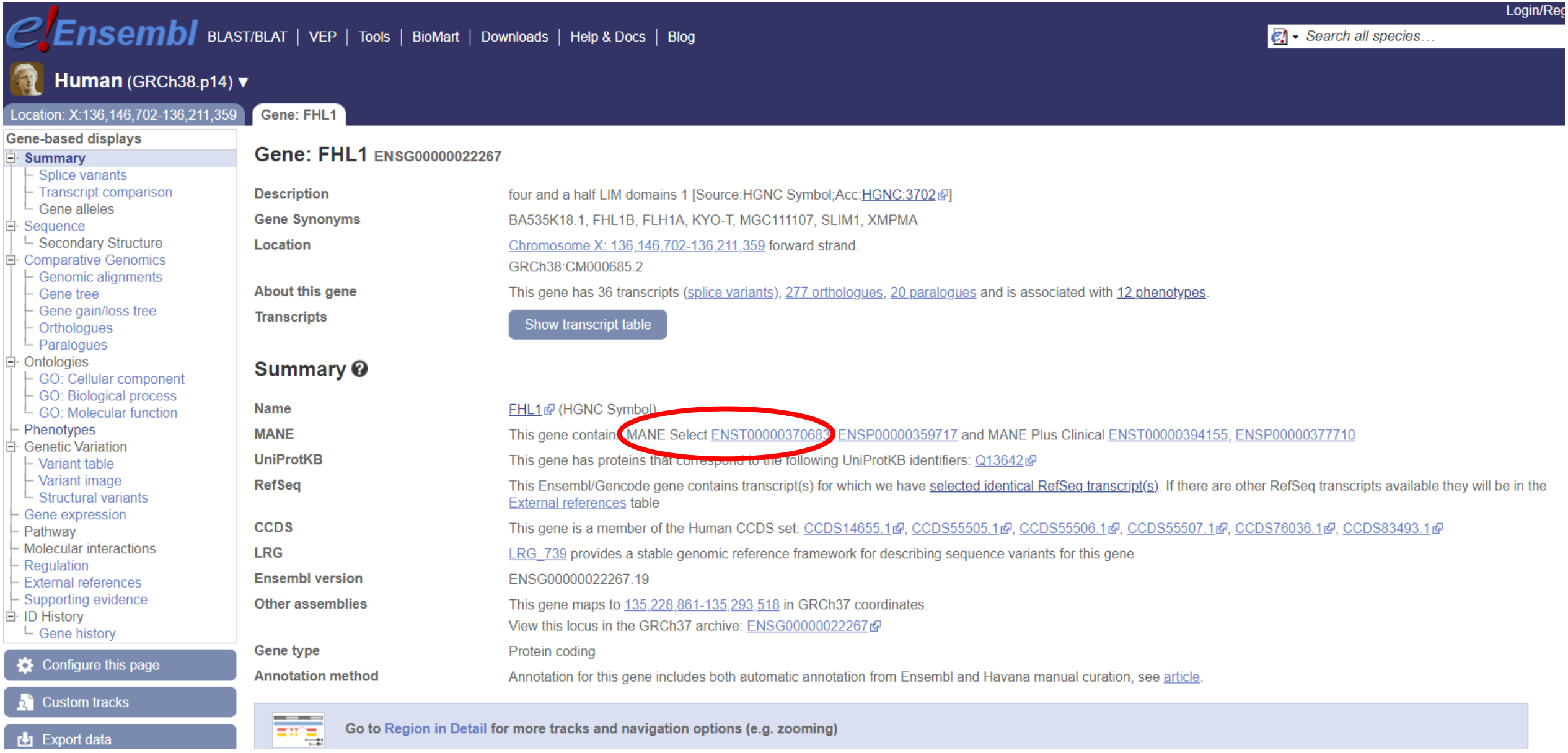


- İnsan, fare, zebra balığı gibi diğer organizmalar dahil

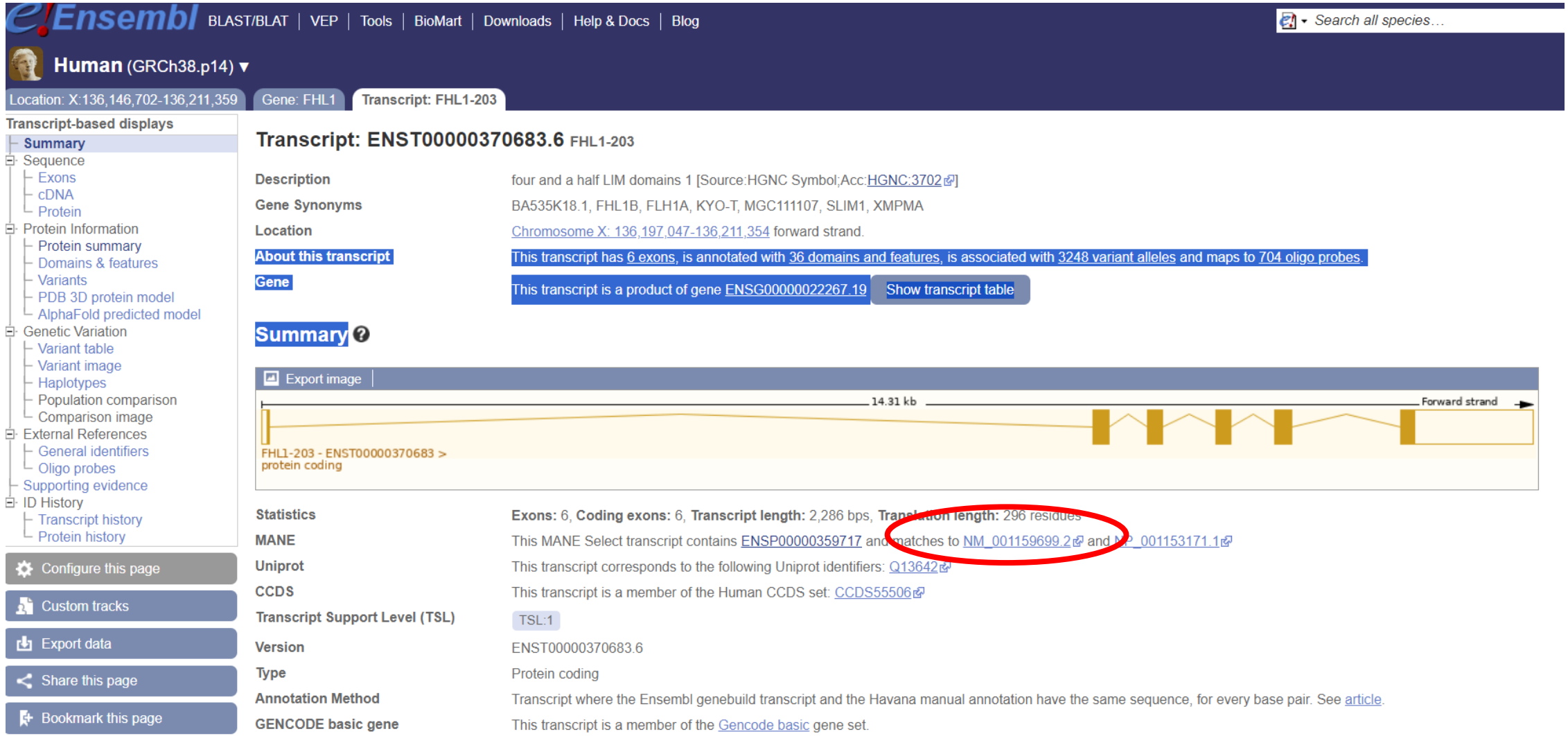


- Transkriptleri
- Ortologlar
- İlişkili olduğu fenotipler
- Karşılaştırmalı genomik
- Bildirilen varyantlar
- Yolaklar
- Etkileşimde olduğu proteinler

MANE; Ensembl ve RefSeq veritabanlarını bağlar



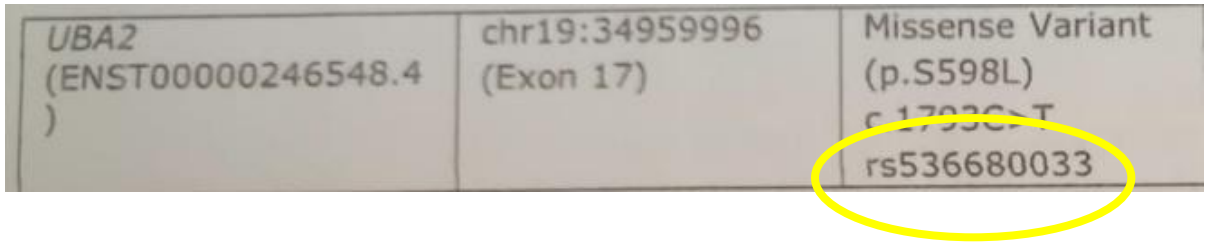
Gen	Yeri	Varyant	Zigozite	Sınıflandırma	Hastalık OMIM#, Kalıtım
FHL1 NM_001159699.2	İntron 5	c.736+8_736+9delAA	Hemizigot	Class 3 Klinik Önemi Bilinmeyen	*FHL1* İlişkili Hastalık OMIM:300717 X'e Bağlı Resesif



- Bildirilen varyantlar

Bazı Biyolojik Veritabanları-3

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



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

https://www.ncbi.nlm.nih.gov/snp

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 *

HHS Public Access
Author manuscript
Genet Med. Author manuscript; available in PMC 2015 November 01.

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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Human Genomics

RESEARCH Open Access

Expanding ACMG variant classification guidelines into a general framework

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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 *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

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

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

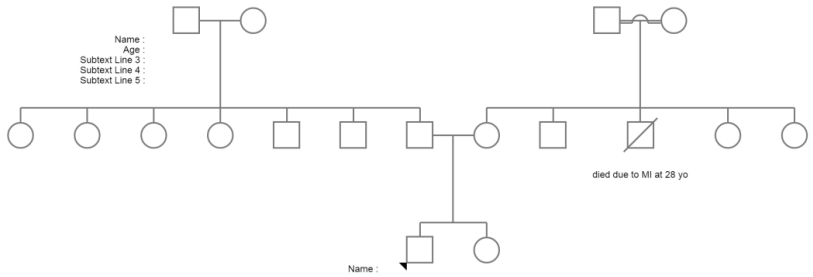
1. 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) *OR*
2. ≥2 Supporting (BP1–BP7)

- Benign veya patojenik skorlara göre kolay sınıflama

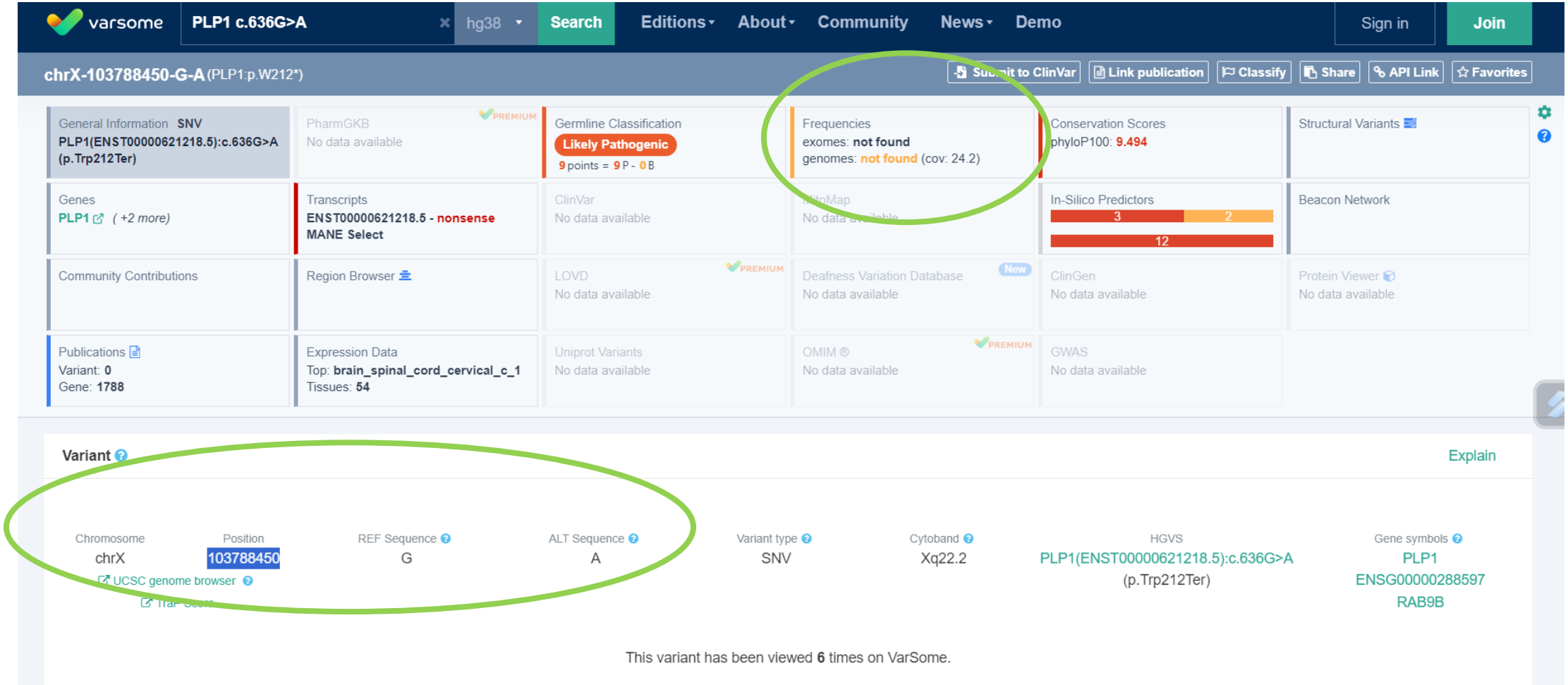
https://seq.genomize.com/pathogenicity_calculator/

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)**

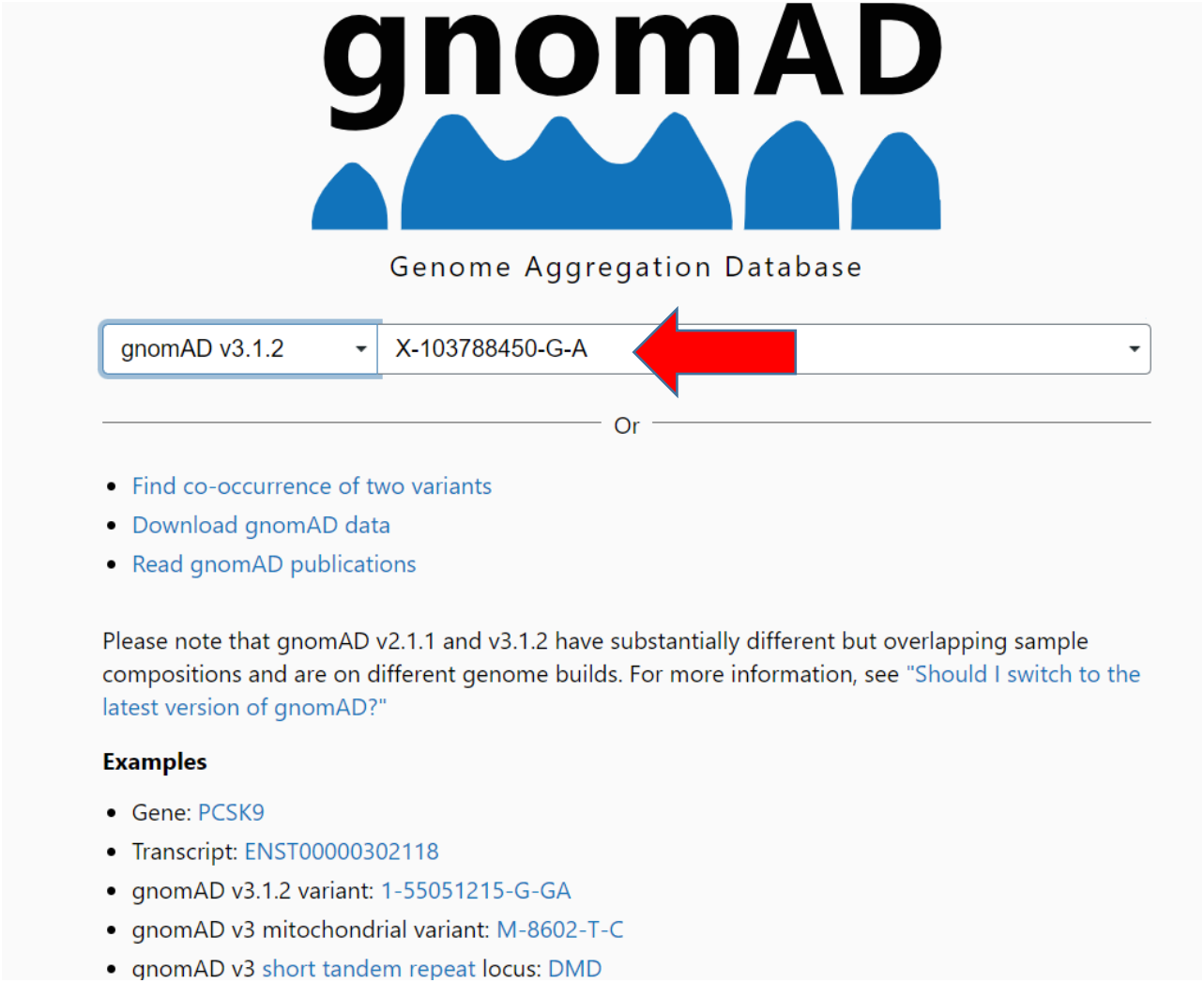


- Sıklıklar
- GnomAD veritabanında kullanmak için kromozom koordinatları



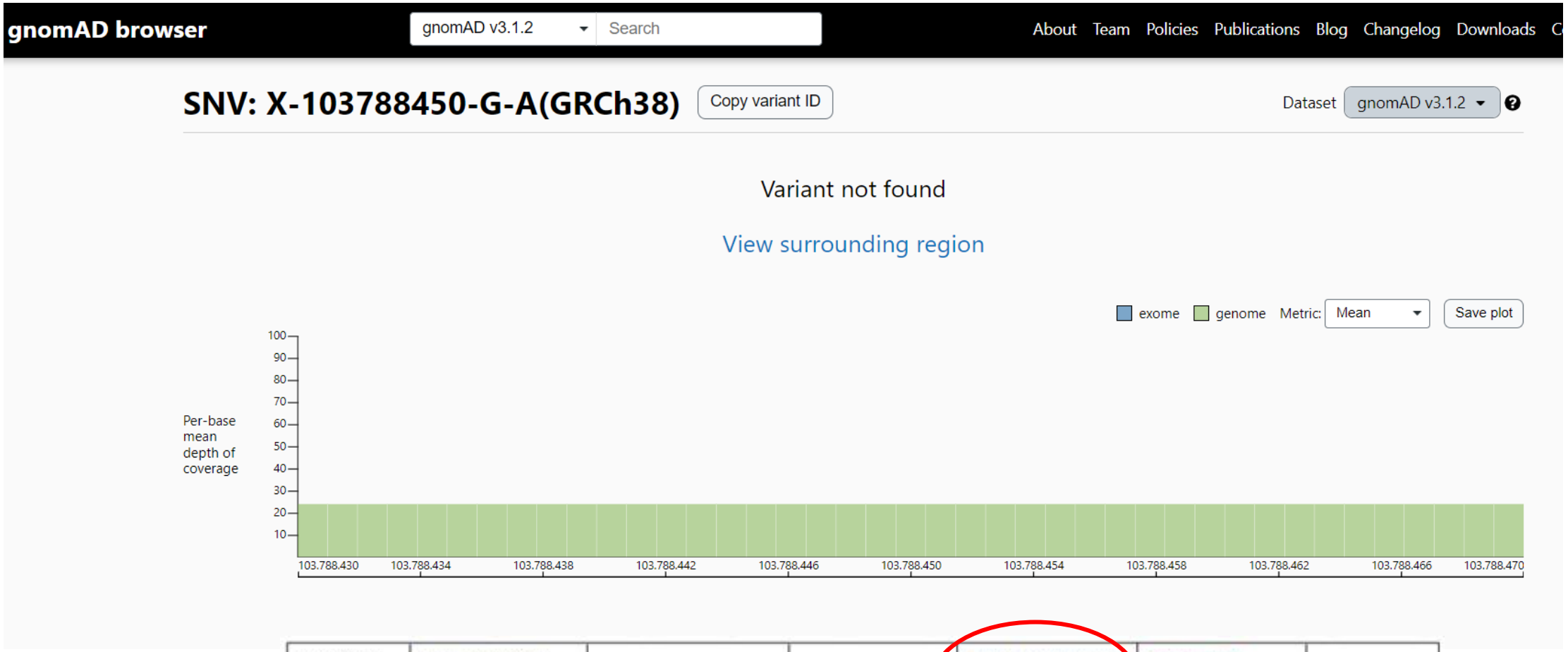
https://varsome.com/

Genom Toplama Veritabanı (Genome Aggregation Database)



https://gnomad.broadinstitute.org/

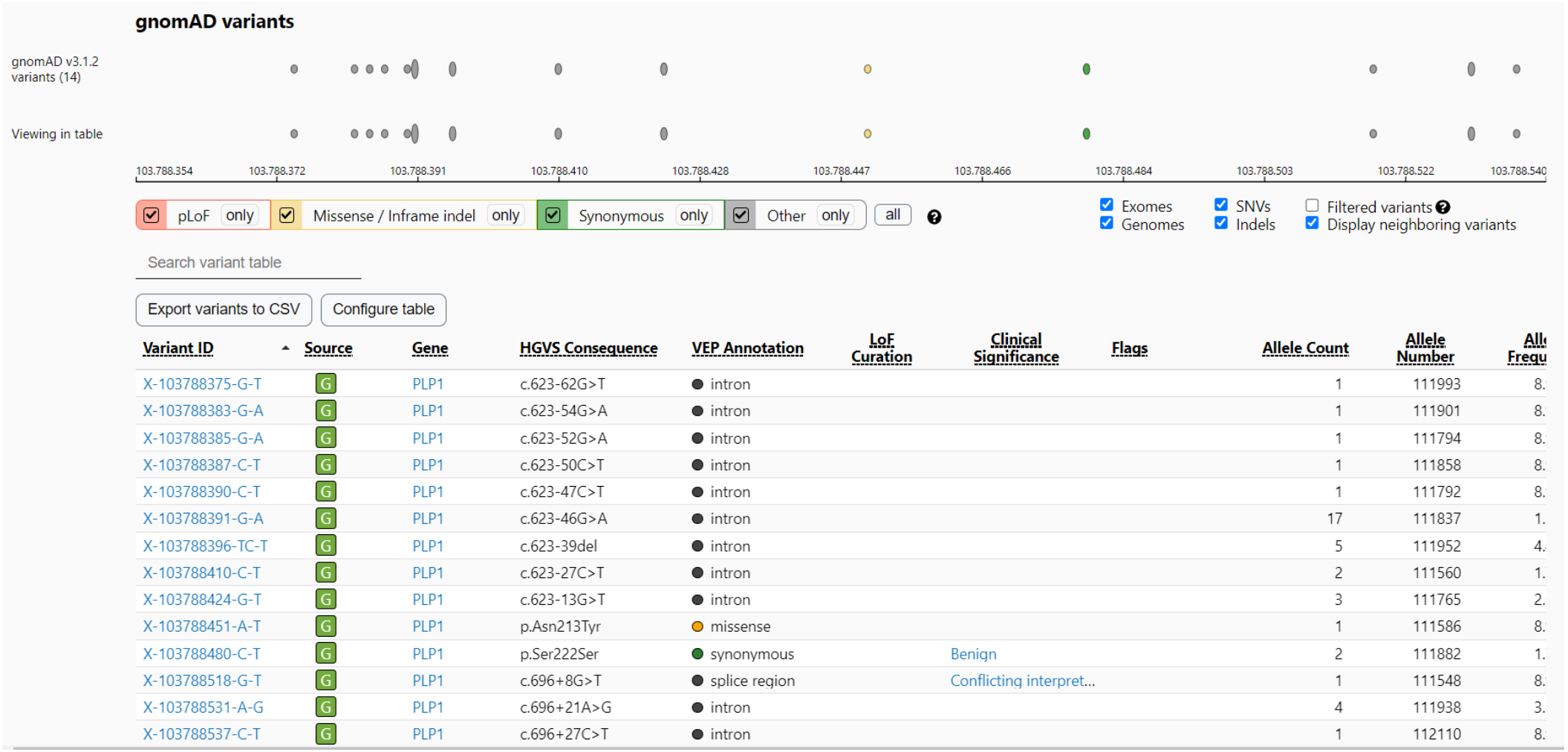
- GnomAD'de bu varyant bulunamadı
- Normal popülasyonda karşılaşılan bir varyant olmadığı için PM2



Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	

- 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 | all

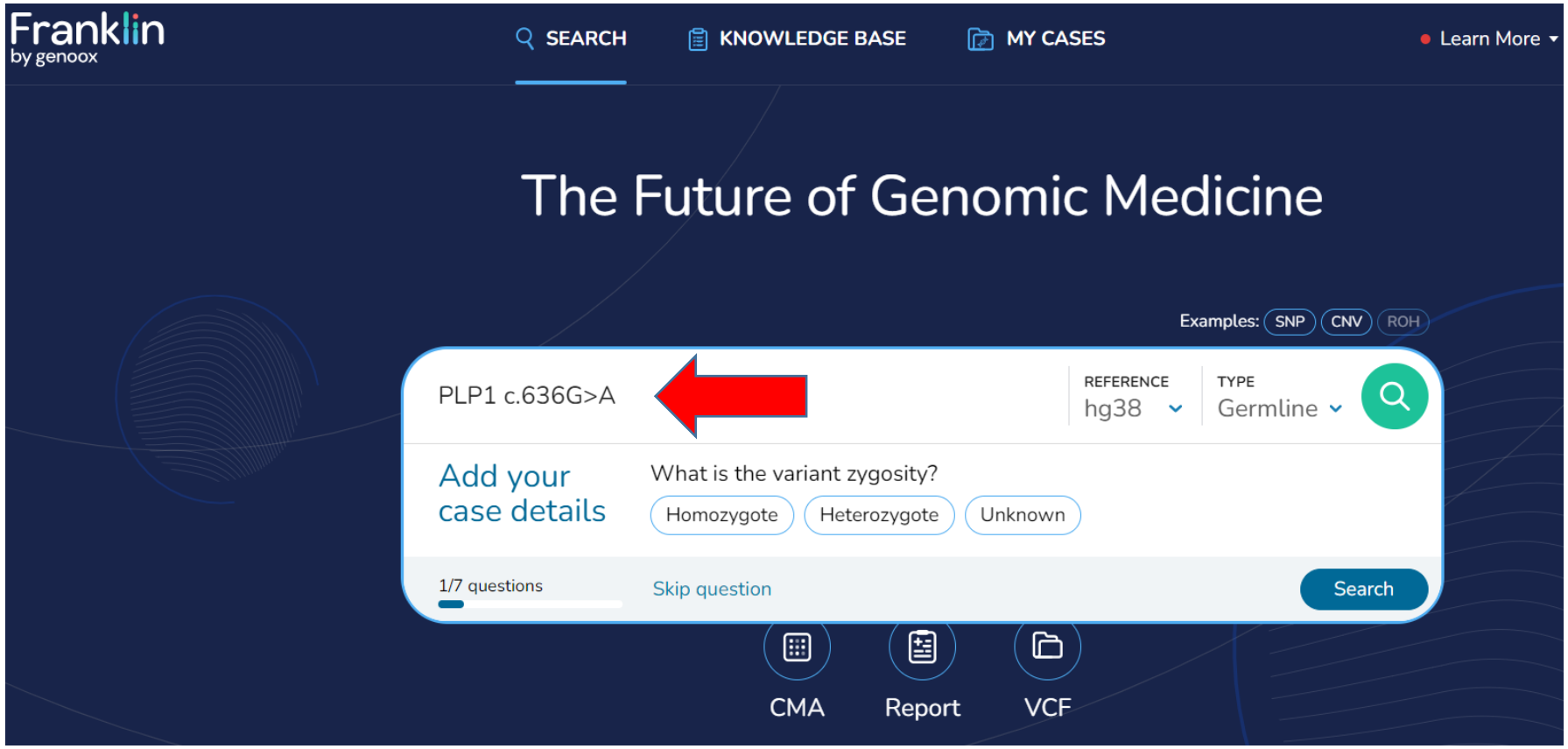
Exomes Genomes | SNVs Indels | Filtered variants Display neighboring variants

Search variant table

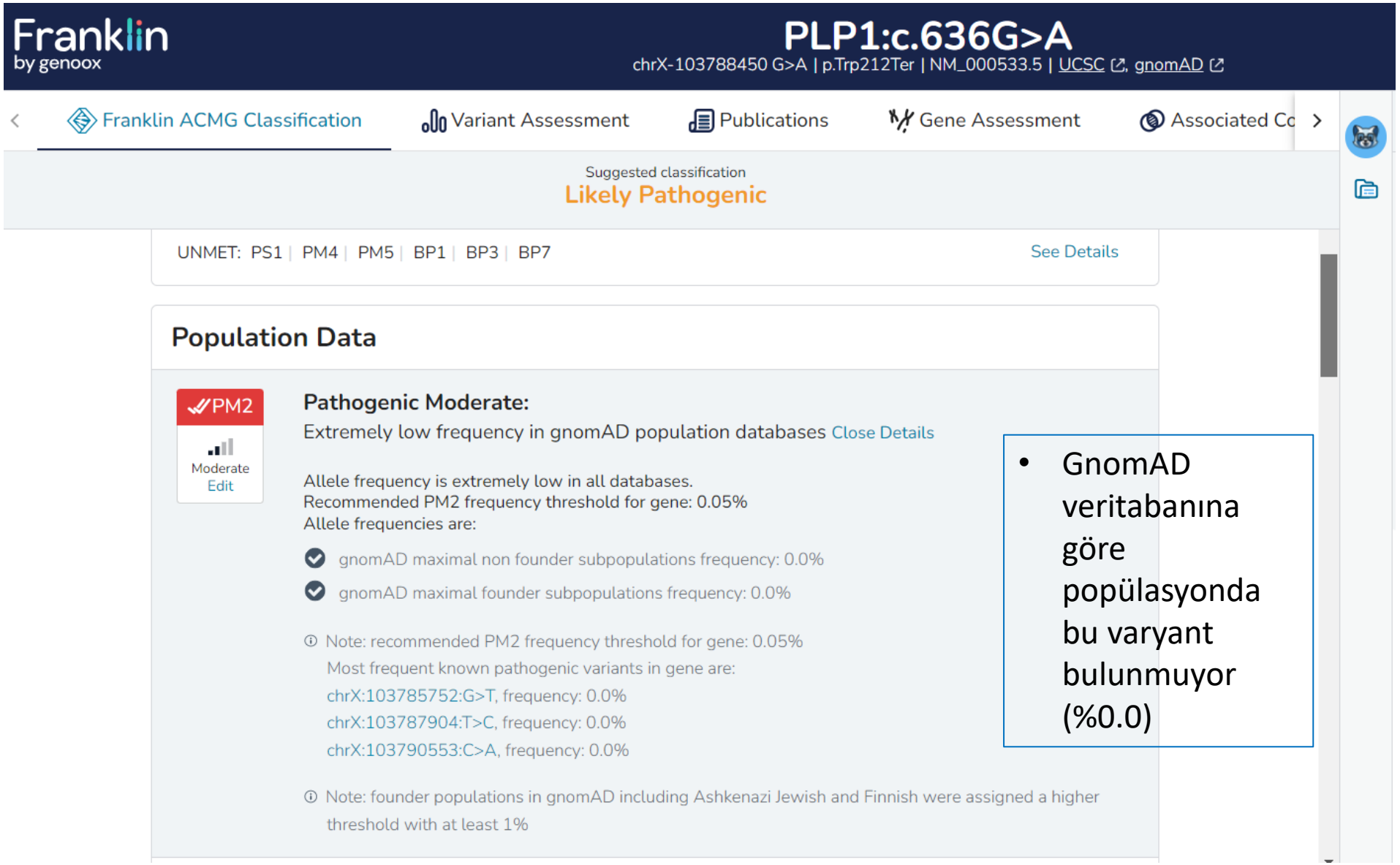
Export variants to CSV | Configure table

Variant ID	Source	Gene	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count	Allele Number	Allele Frequ
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

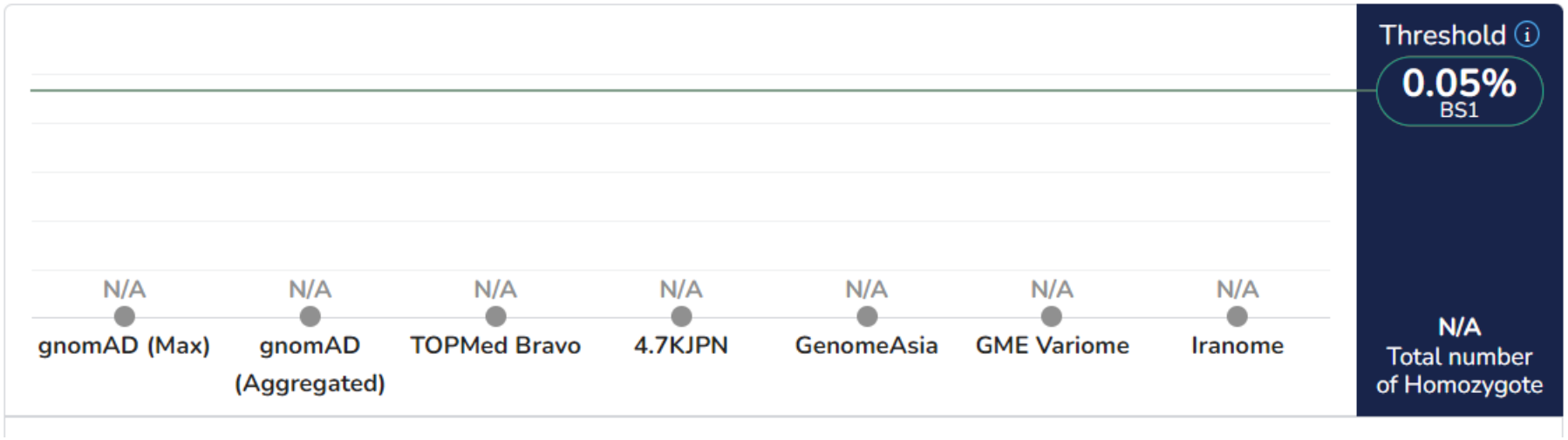


https://franklin.genoox.com/



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

Population Frequencies



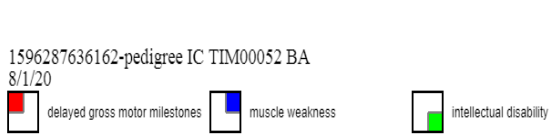
- Turkish variome dahil farklı veritabanları hakkında da bilgiye ulaşılabilir

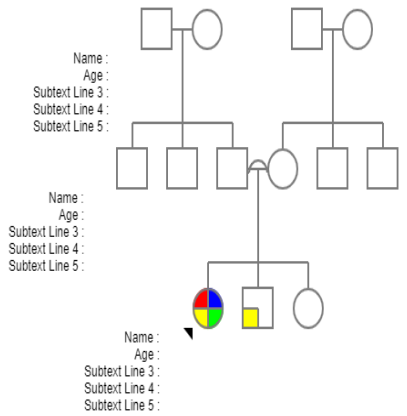
N/A	**4.7KJPN** **No Observation** for this variant in 4.7KJPN	N/A Alleles of N/A N/A homozygote N/A Individuals
N/A	**GenomeAsia** **No Observation** for this variant in GenomeAsia	N/A Alleles of N/A N/A homozygote N/A Individuals
N/A	**Mexican DB** **No Observation** for this variant in Mexican DB	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

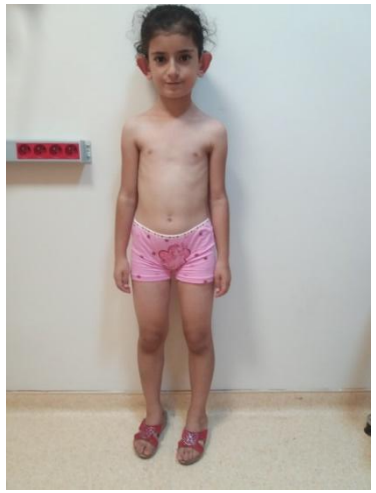
Minimize

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)







https://www.ncbi.nlm.nih.gov/clinvar
https://www.deciphergenomics.org/
https://lovd.nl

Pubmed

https://franklin.genoox.com/
https://varsome.com/

An official website of the United States government Here's how you know

National Library of Medicine
National Center for Biotechnology Information

Log in

ClinVar

ClinVar MICU1 Search

Advanced Help

Home About Access Help Submit 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!

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

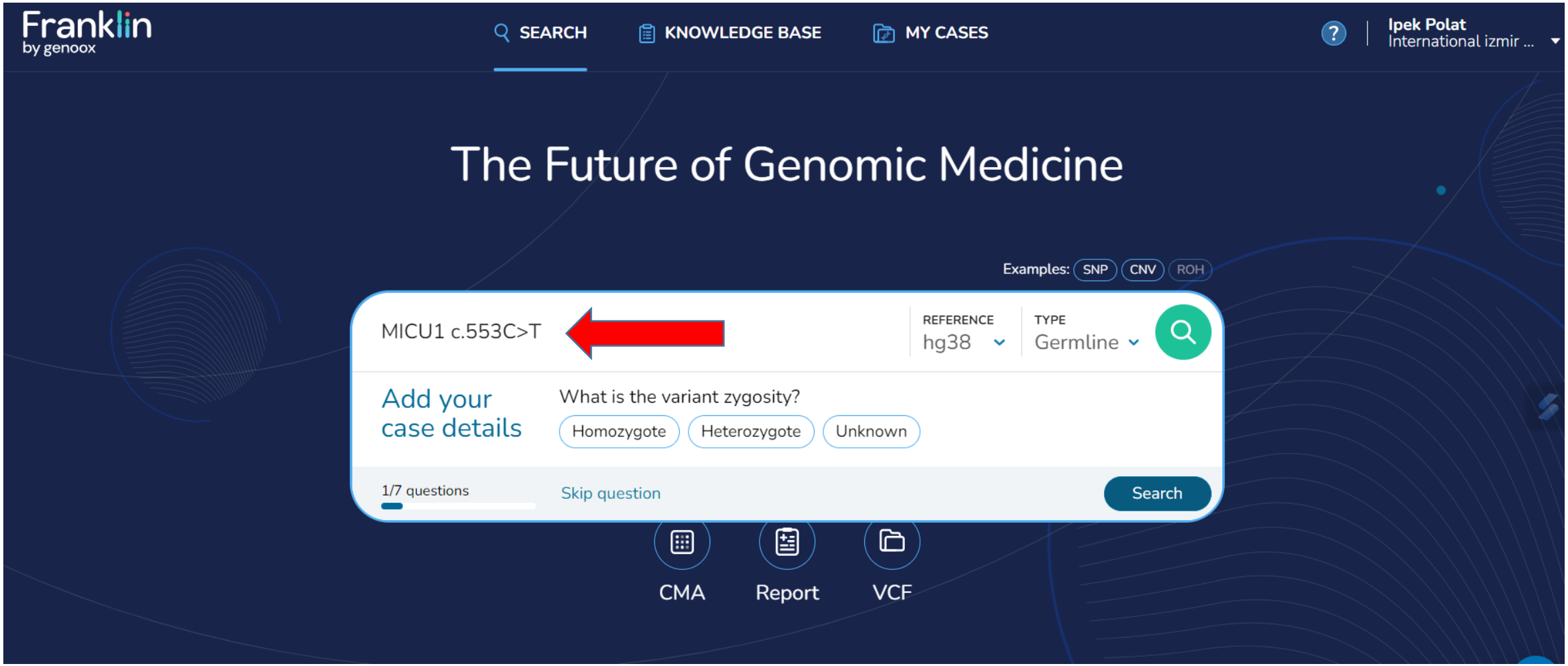
ClinGen

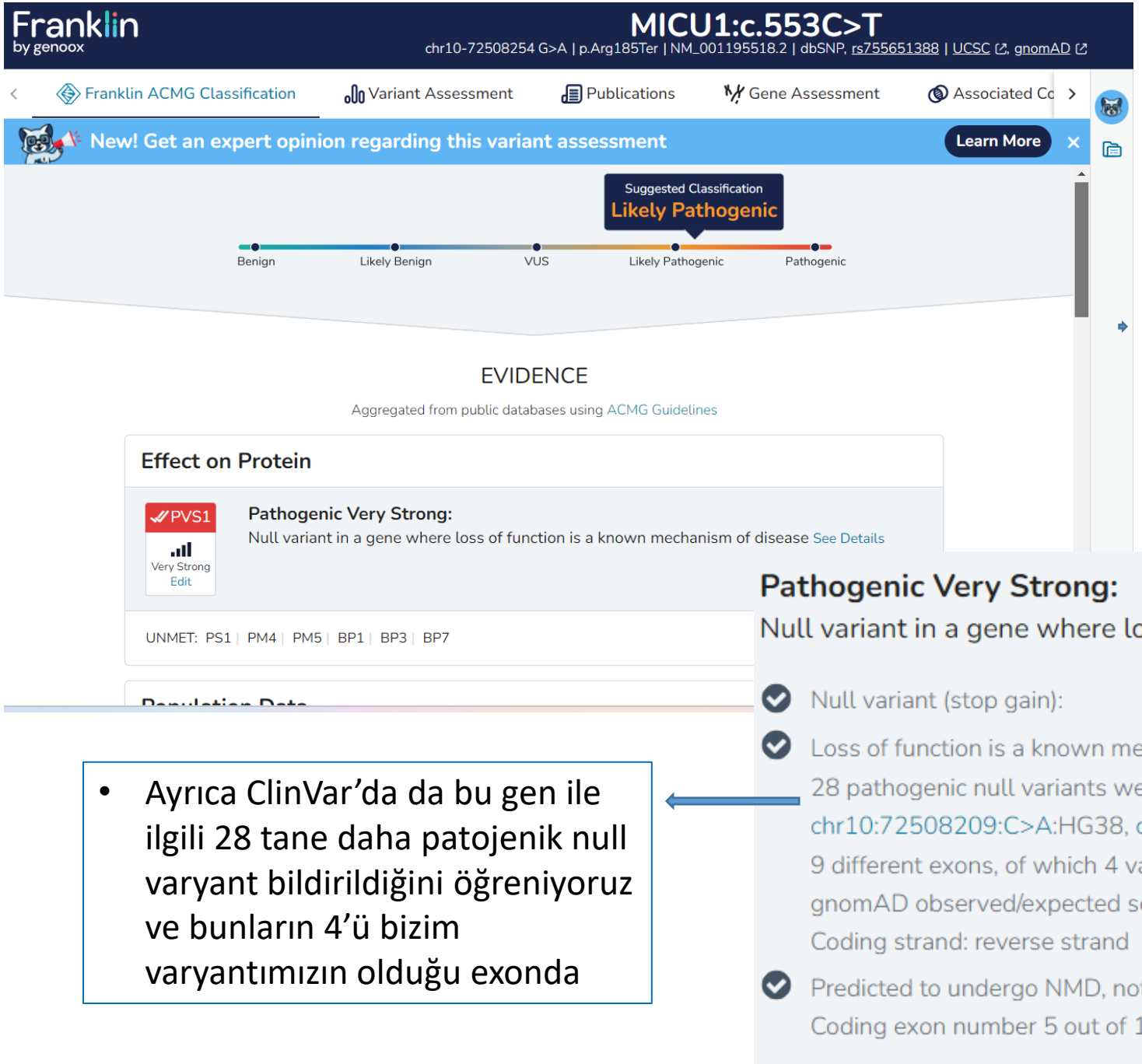
	Variation *Location*	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)	Review status
145.	NM_001195518.2(**MICU1**):c.603T>C (p.Cys201=) *GRCh37*: Chr10:74267962 *GRCh38*: Chr10:72508204	**MICU1**		not provided	Likely benign (Jul 5, 2022)	criteria provided, single submitter
146.	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*			provided, single submitter
147.	NM_001195518.2(**MICU1**):c.577A>G (p.Ser193Gly) *GRCh37*: Chr10:74267988 *GRCh38*: Chr10:72508230	**MICU1**	S193G, S199G, S195			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???


Franklin
by genoox
SEARCH
KNOWLEDGE BASE
MY CASES
Ipek Polat
International izmir ...
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



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

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)

- 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

PM2

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

ⓘ 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%

ⓘ 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)

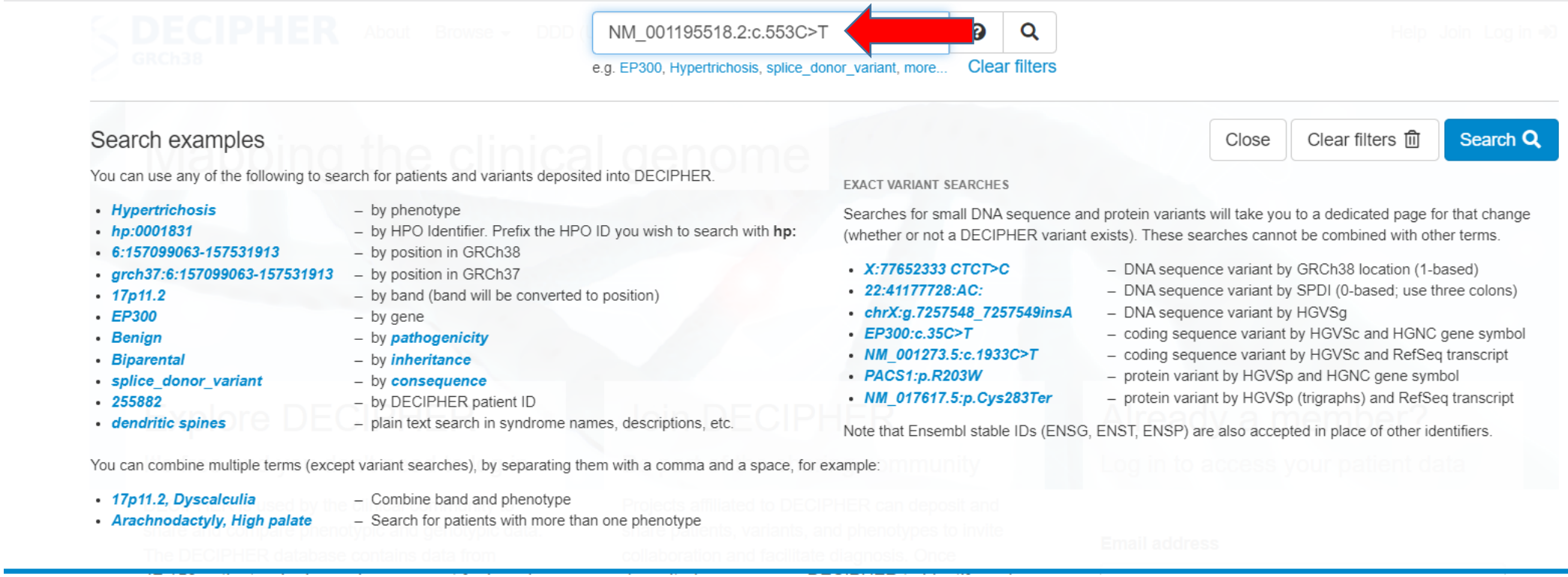
Benign

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?



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}

MICU1 10:72367340-72626131

Gene/disease association

Gene2Phenotype

- Biallelic - Absent gene product: Myopathy with Extrapyramidal 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

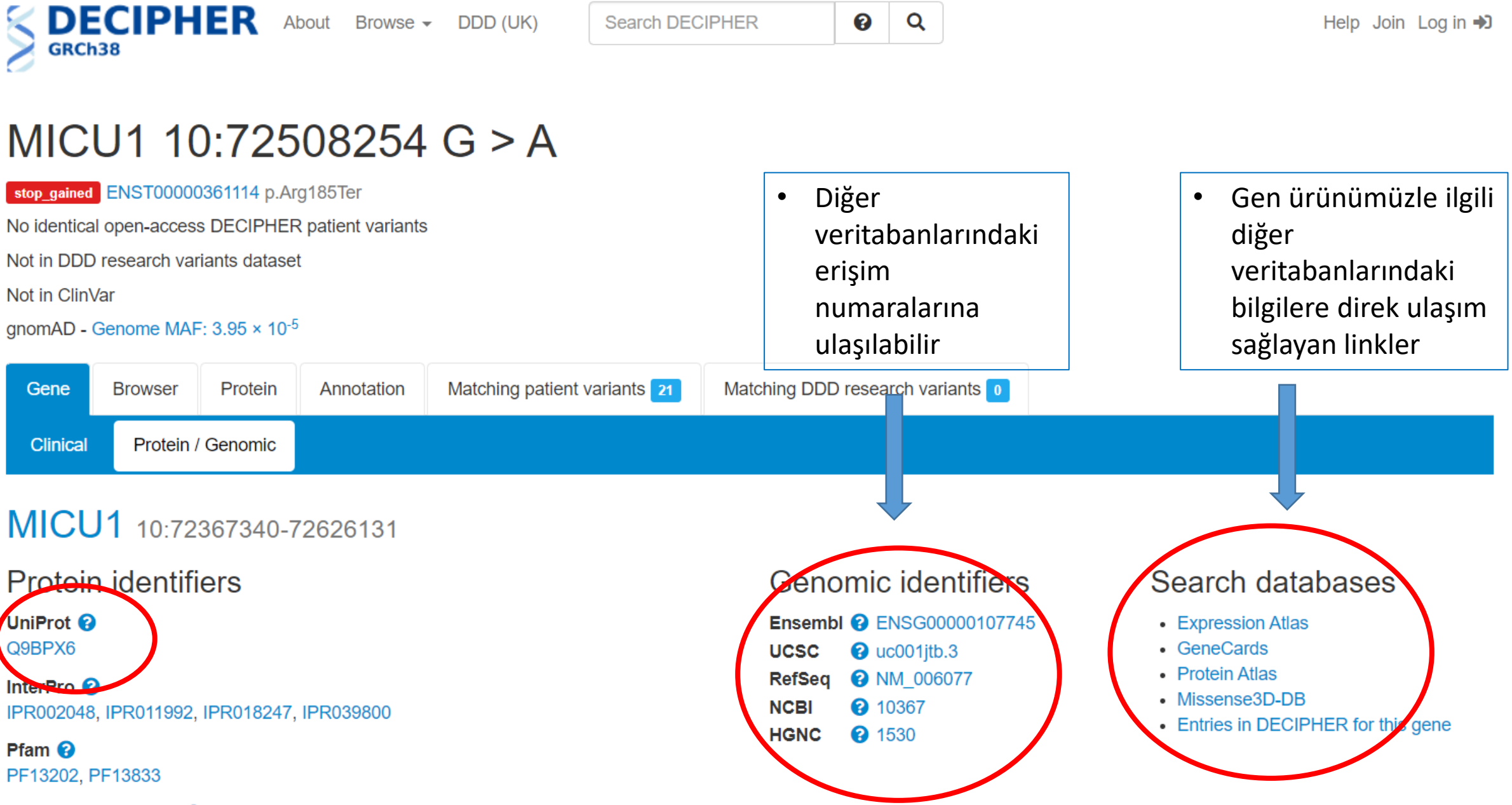
Search databases

- PubMed
- Gene Tests
- Genomics England PanelApp
- LSDB
- Entries in DECIPHER for this gene

Management resources

IEMbase

- Mitochondrial calcium uniporter 1 deficiency (Autosomal recessive)



- Diğer veritabanlarındaki erişim numaralarına ulaşılabilir

- Gen ürünümüzle ilgili diğer veritabanlarındaki bilgilere direk ulaşım sağlayan linkler

DECIPHER GRCh38 About Browse DDD (UK) Search DECIPHER Help Join Log in

MICU1 10:72508254 G > A

stop_gained ENST00000361114 p.Arg185Ter

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gnomAD - Genome MAF: 3.95×10^{-5}

- Diğer veritabanlarındaki erişim numaralarına ulaşılabilir

- Gen ürünümüzle ilgili diğer veritabanlarındaki bilgilere direk ulaşım sağlayan linkler

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

Clinical | Protein / Genomic

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

Gen ürünü proteinin;

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

DECIPHER GRCh38 About Browse DDD (UK) Search DECIPHER Help Join Log in

MICU1 10:72508254 G > A

stop_gained ENST00000361114 p.Arg185Ter

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Pfam
PF13202, PF13833

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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 datab

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

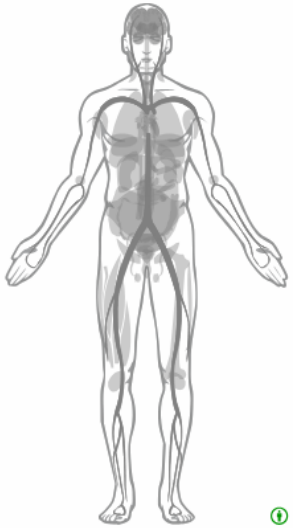
Expression Atlas

Gene expression across species and biological conditions

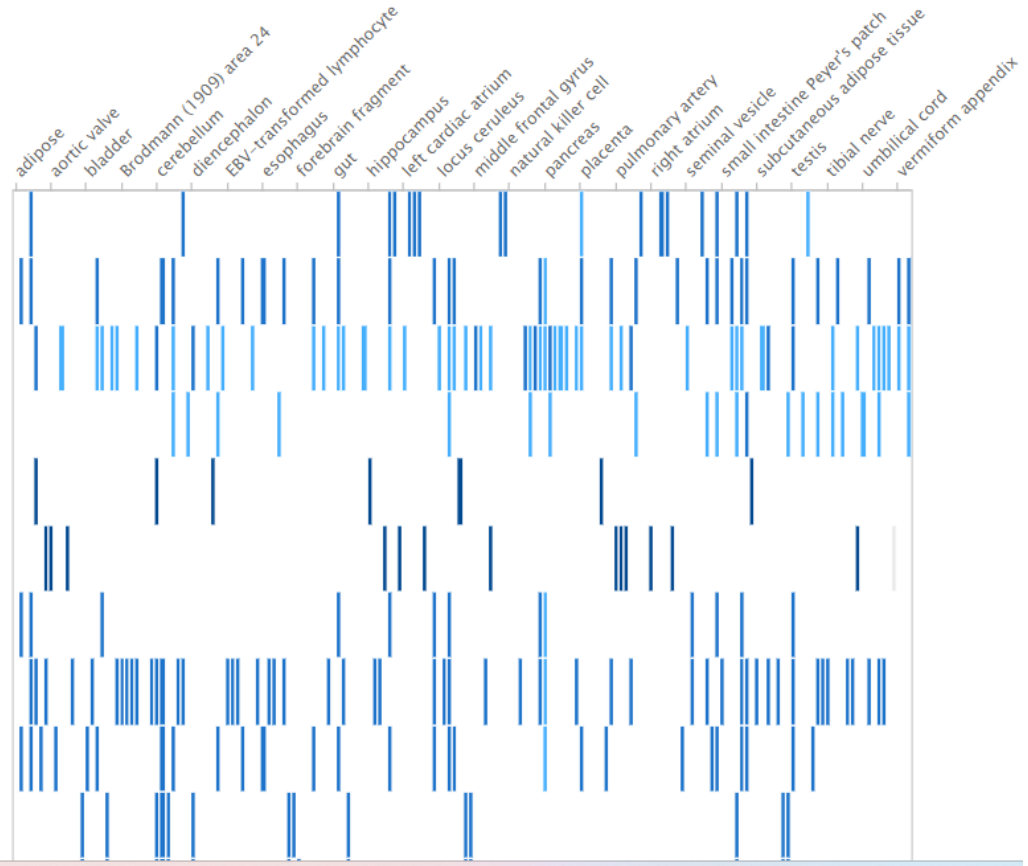
Home | Browse experiments | Download | Release notes | FAQ | Help | Licence | About | Support

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

Showing 67 experiments:



Alphabetical order | Filters | Download

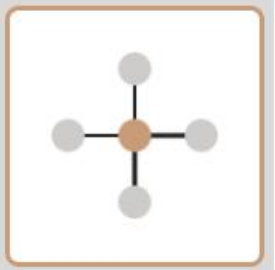


- 19 NIH Epigenomics Roadmap
- 32 Uhlen's Lab
- 68 FANTOM5 project – adult
- 68 FANTOM5 project – fetal
- brain regions
- Doll et al., 2017 – Organism part
- ENCODE (M. Snyder lab)
- GTEx
- Hallstrom et al., 2014 – Organism part
- HDBR developing brain – 10 post …

MICU1

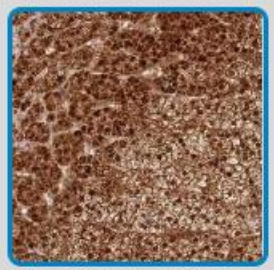
MICU1 INFORMATION

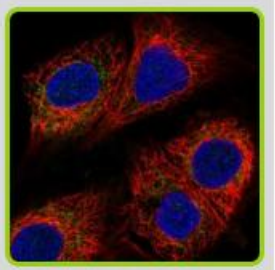
Protein[i]	Mitochondrial calcium uptake 1
Gene name[i]	MICU1 (CALC, CBARA1, EFHA3, FLJ12684)
Protein class[i]	Disease related genes Human disease related genes Potential drug targets Transporters
Protein evidence	Evidence at protein level (all genes)
Number of transcripts[i]	8
Protein interactions	Interacting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

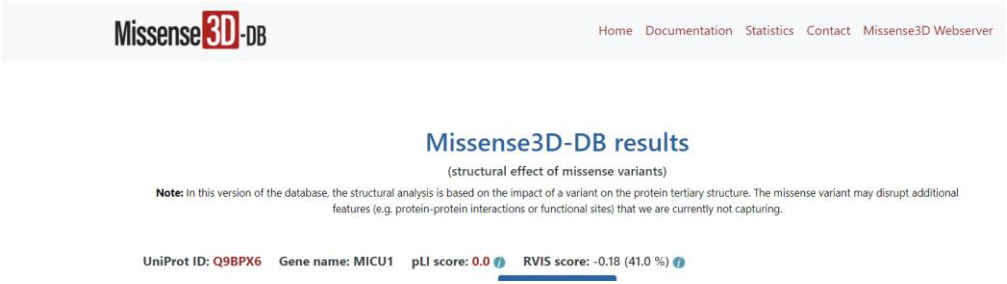


PROTEIN EXPRESSION AND LOCALIZATION

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







MICU1 pArg185* ClinVar gibi Missense 3D veritabanında da bildirilmemiş

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

DECIPHER GRCh38 About Browse DDD (UK) Search DECIPHER Help Join Log in

MICU1 10:72508254 G > A

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

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

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

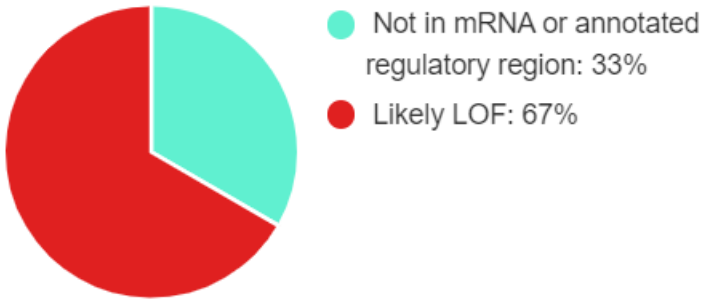
- Expression Atlas
- GeneCards
- Protein Atlas
- Missense3D-DB
- Entries in DECIPHER for this gene

Patients with sequence variants matching this variant or its genes

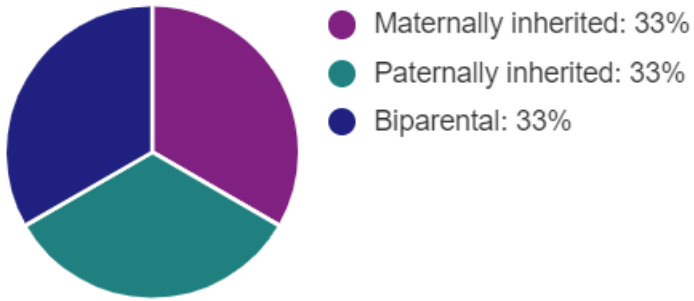
MICU1 c.553 C>T ClinVar gibi Decipher veritabanında da bildirilmemiş

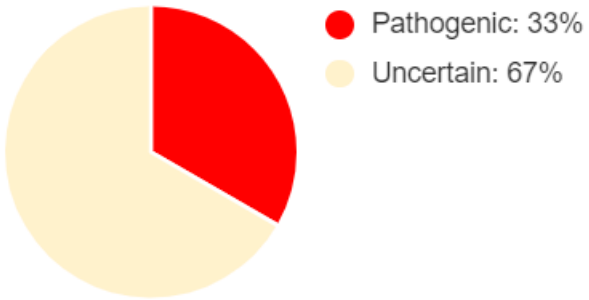
Filters: Sex ▾ | Consequence ▾ | Pathogenicity ▾ | Contribution ▾ | Inheritance ▾ | Genotype ▾ | Phenotype

Consequence



Inheritance





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?

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 the: Leiden Muscular Dystrophy pages© 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**

LOVD 3 Leiden Open Variation Database — THE HUMAN VARIOME PROJECT

Global Variome shared LOVD

MICU1 (mitochondrial calcium uptake 1)

LOVD v.3.0 Build 29 [Cur

Register as s

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

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	2	c.1A>G	r.(?)	p.0?	-		C
?/.	1	2	c.53G>A	r.(?)	p.(Gln18Arg)	-		T
?/.	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.537+9898A>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	g.74234860C>A

JIMD Reports
DOI 10.1007/8904_2018_107

RESEARCH REPORT

A Middle Eastern Founder Mutation Expands the Genotypic and Phenotypic Spectrum of Mitochondrial *MICU1* Deficiency: A Report of 13 Patients

Sara Musa · Wafaa Eyaid · Kimberli Kamer · Rehab Ali · Mariam Al-Mureikhi · Noora Shahbeck · Fatma Al Mesaifri · Nawal Makhseed · Zakkiriah Mohamed · Wafaa Ali AlShehhi · Vamsi K. Mootha · Jane Juusola · Tawfeg Ben-Omran

ClinVar'da bu varyant bildirilmemiş

Ama Pubmed'de bir yayında bildirilmiş !!

Received: 05 September 2017 / Revised: 27 March 2018 / Accepted: 29 March 2018 / Published online: 03 May 2018
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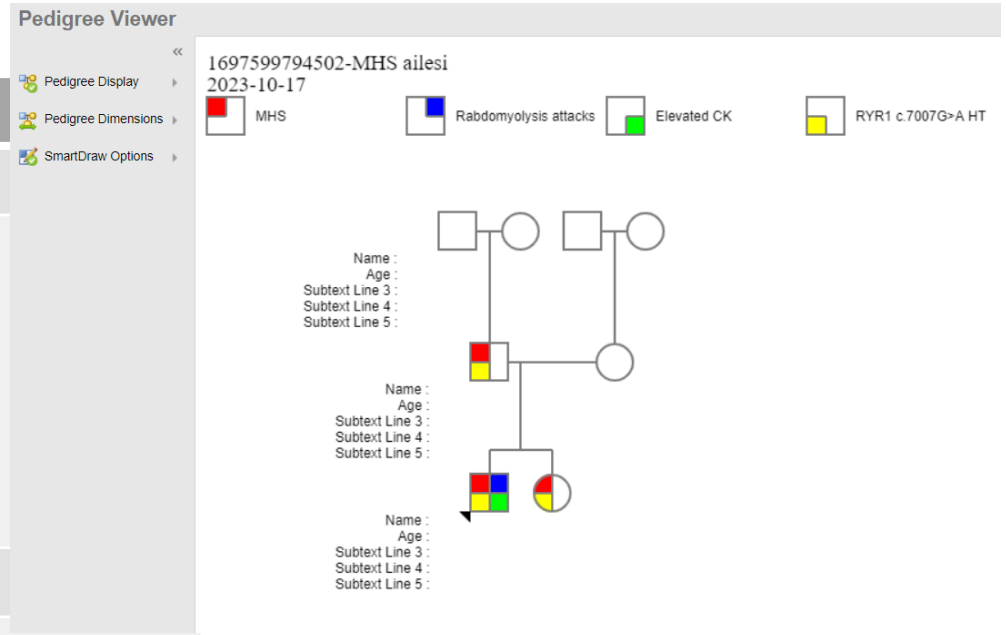
Abstract *MICU1* encodes a Ca^{2+} sensing, regulatory subunit of the mitochondrial uniporter, a selective calcium channel within the organelle's inner membrane. Ca^{2+} entry into mitochondria helps to buffer cytosolic Ca^{2+} transients and also activates ATP production within the organelle. Mutations in *MICU1* have previously been reported in 17 children from nine families with muscle weakness, fatigue, normal lactate, and persistently elevated creatine kinase, 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

Communicated by: John Christodoulou, MB BS PhD FRACP FRCPA (Communicating Editor)

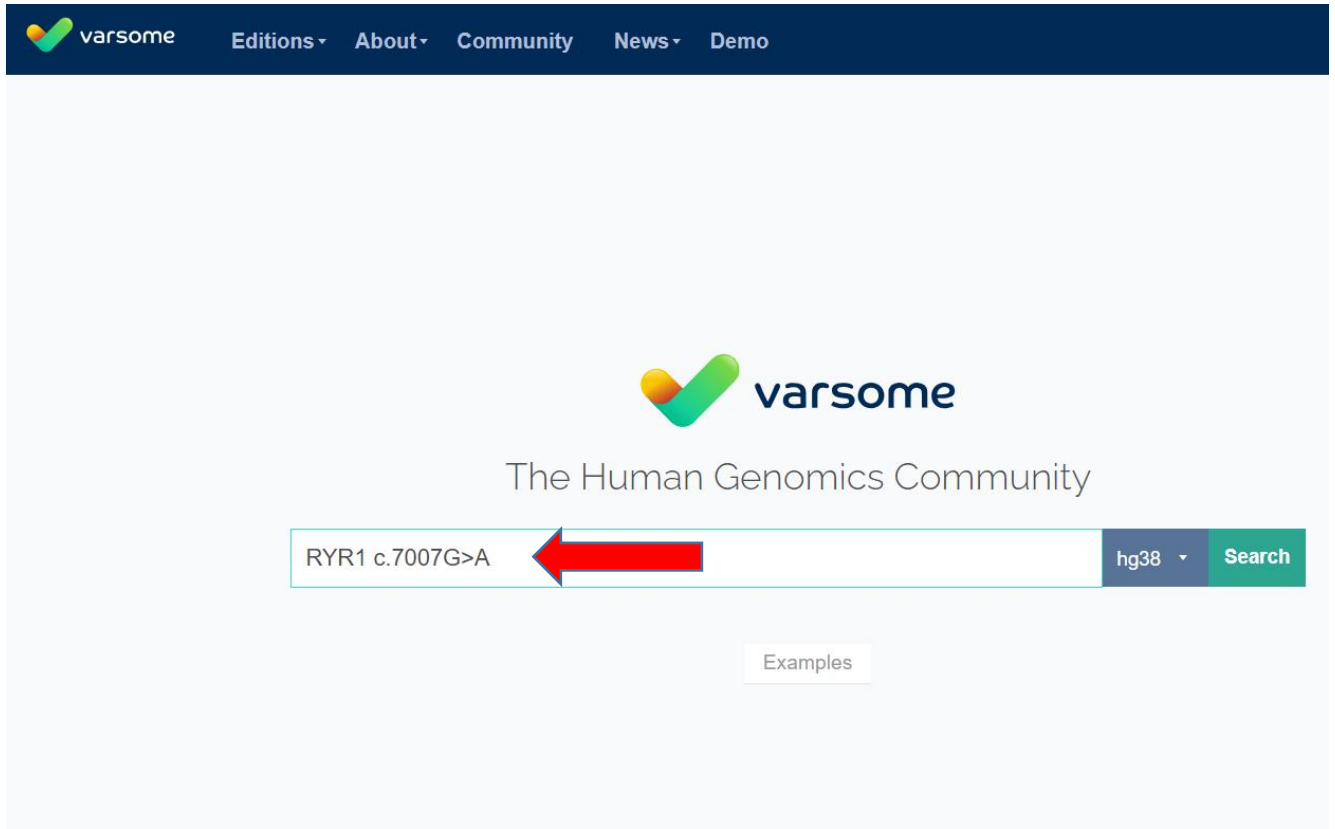
S. Musa · R. Ali · M. Al-Mureikhi · N. Shahbeck · F. Al Mesaifri · T. Ben-Omran (✉)
Section of Clinical and Metabolic Genetics, Department of Pediatrics,

Örnek;

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



Varsome'da Neler Araştırabilirim ve Prediktif Datayı Nasıl Değerlendirebilirim?



https://varsome.com/

varsome | RYR1 c.7007G>A | hg38 | Search | Editions | About | Community | News | Demo | Sign in | Join

chr19-38499223-G-A (RYR1:p.R2336H) | Submit to ClinVar | Link publication | Classify | Share | 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** ★★★☆ 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
Publications Variant: **59** Gene: **1169**	Expression Data Top: **muscle_skeletal** Tissues: **38**	Uniprot Variants **Pathogenic**	OMIM ® No data available	GWAS No data available	

Variant

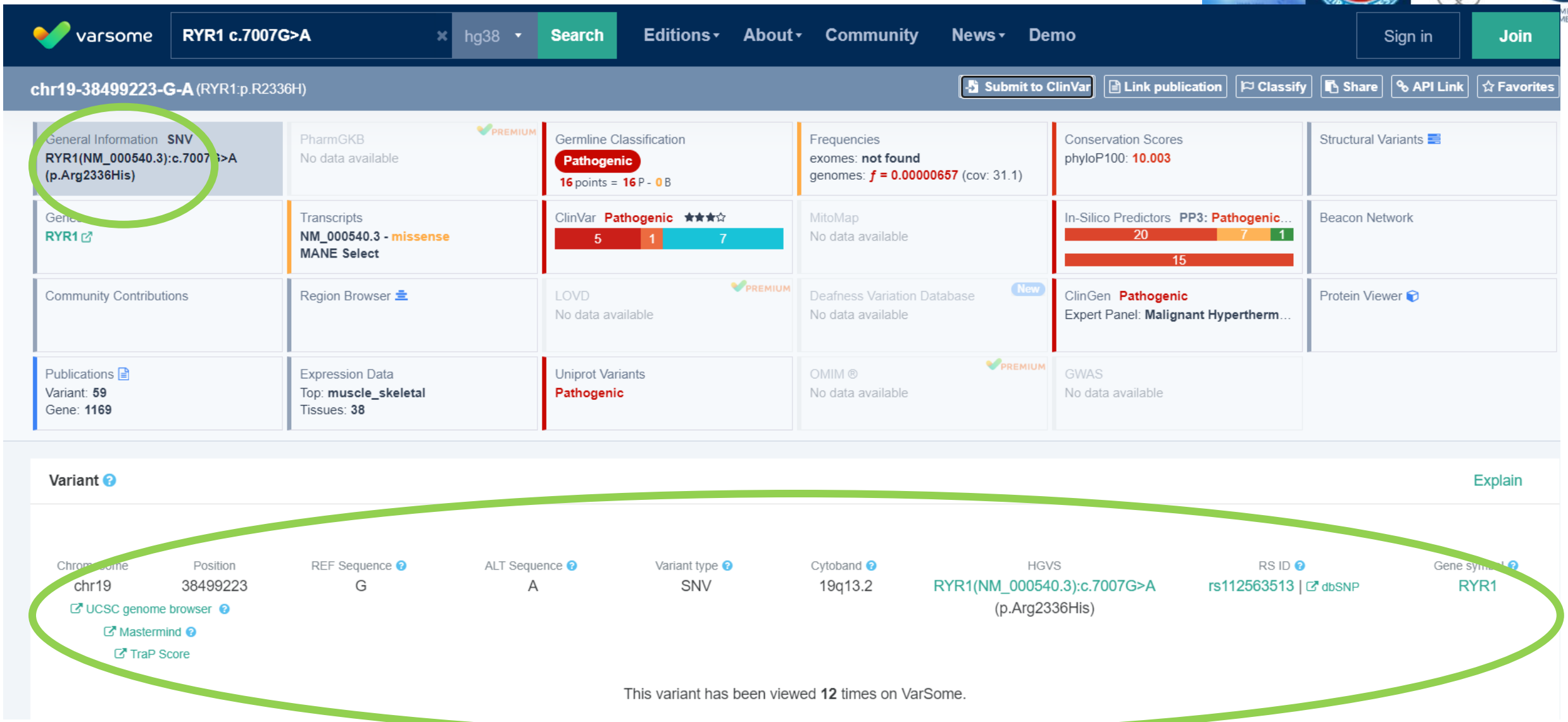
Explain

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/



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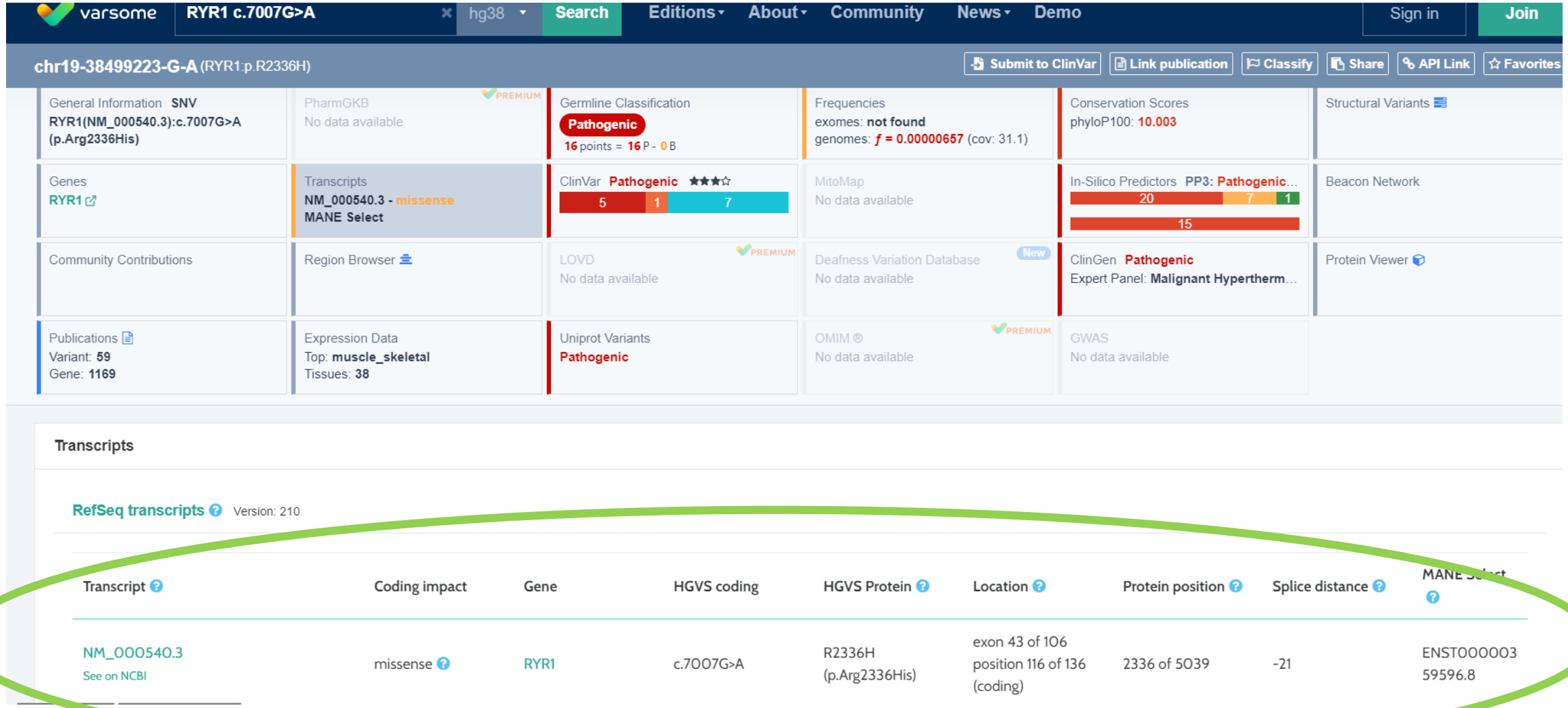
varsome
RYR1 c.7007G>A
hg38
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Demo
Sign in
Join
chr19-38499223-G-A (RYR1:p.R2336H)
Submit to ClinVar
Link publication
Classify
Share
API Link
Favorites
General Information SNV
RYR1(NM_000540.3):c.7007G>A
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PharmGKB
No data available
PREMIUM
Germline Classification
Pathogenic
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Frequencies
exomes: not found
genomes: f = 0.00000657 (cov: 31.1)
Conservation Scores
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Structural Variants
Genes
RYR1
Transcripts
NM_000540.3 - missense
MANE Select
ClinVar Pathogenic ★★★☆
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MitoMap
No data available
In-Silico Predictors PP3: Pathogenic...
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Beacon Network
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Uniprot Variants
Pathogenic
OMIM ®
No data available
PREMIUM
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
ENST00000359596.8

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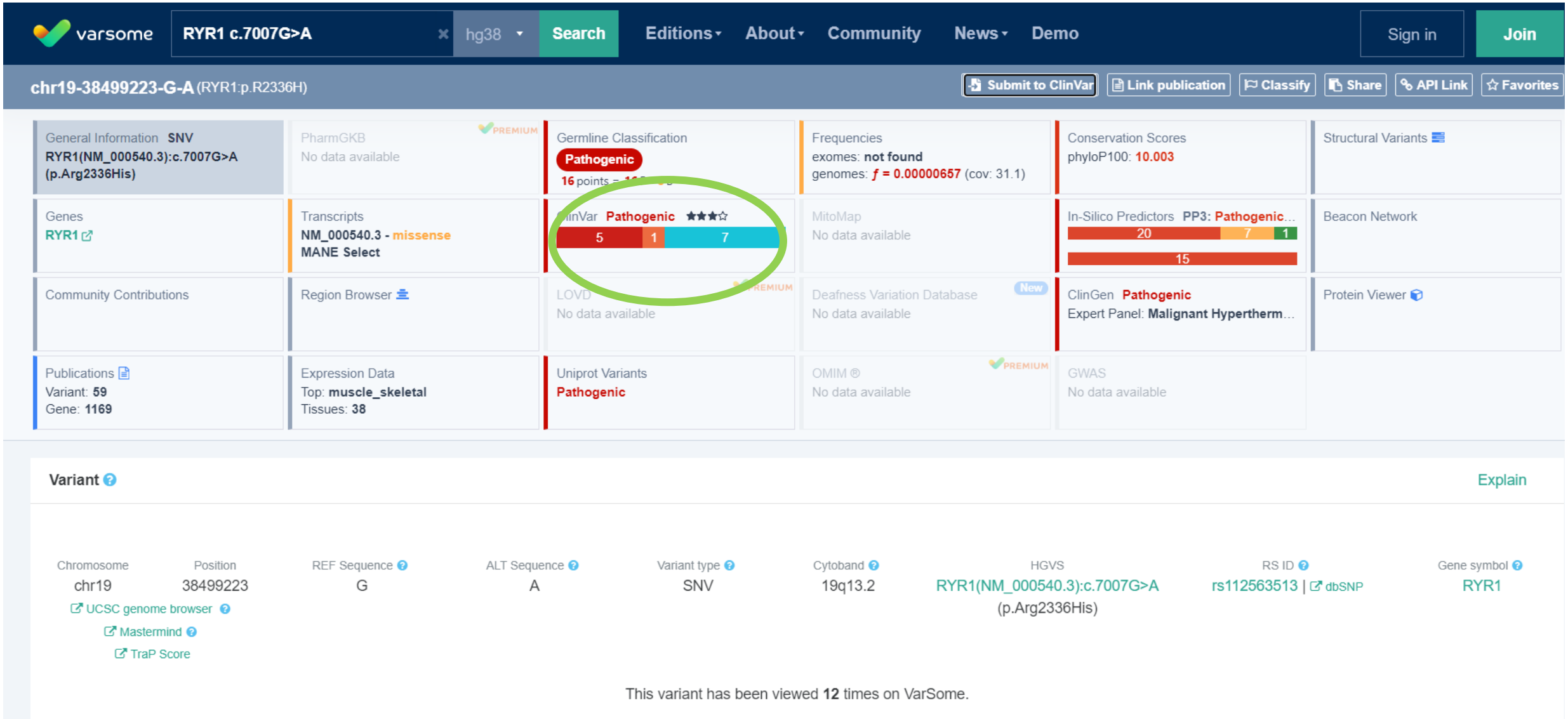

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UCSC genome browser | Mastermind | TraP Score

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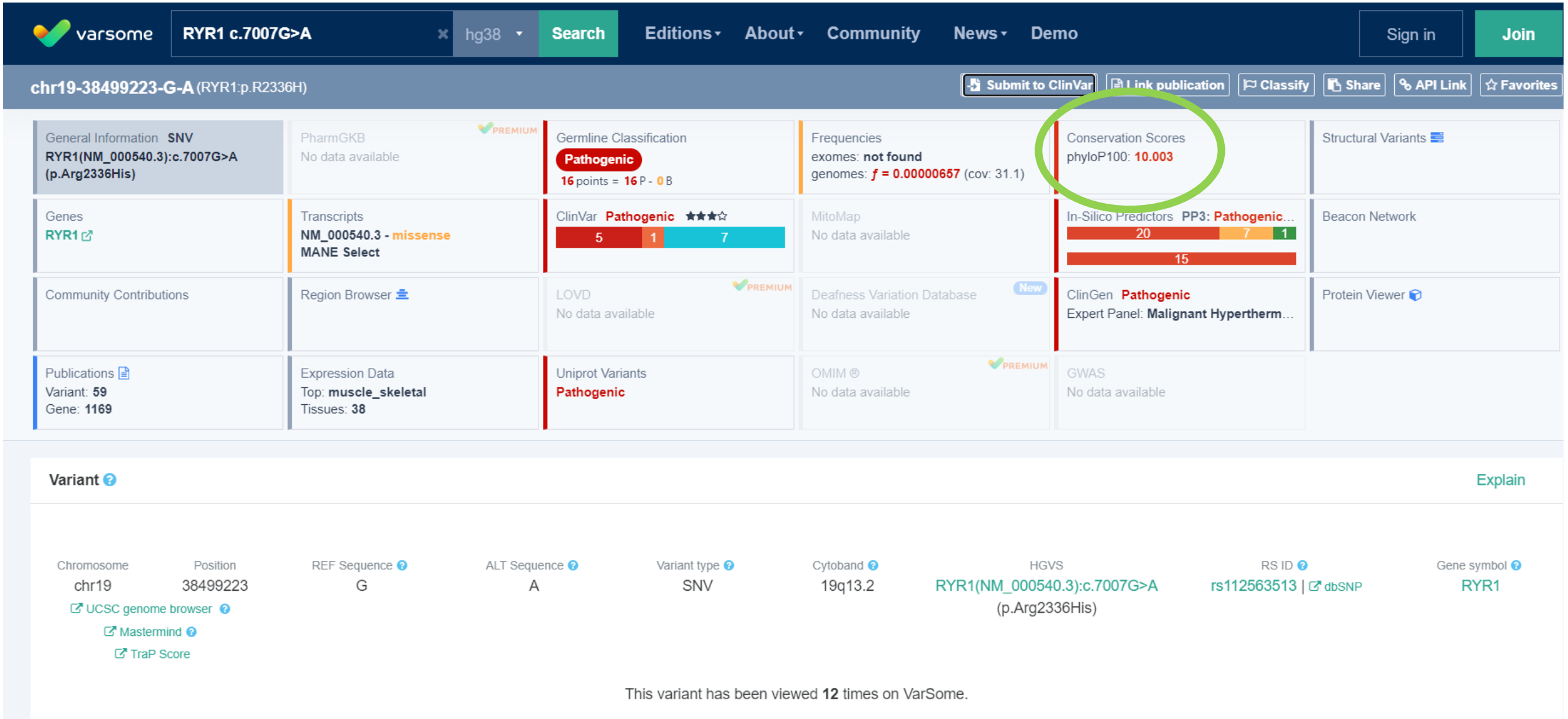
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RYR1 c.7007G>A
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TraP Score
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38499223
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ALT Sequence
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Variant type
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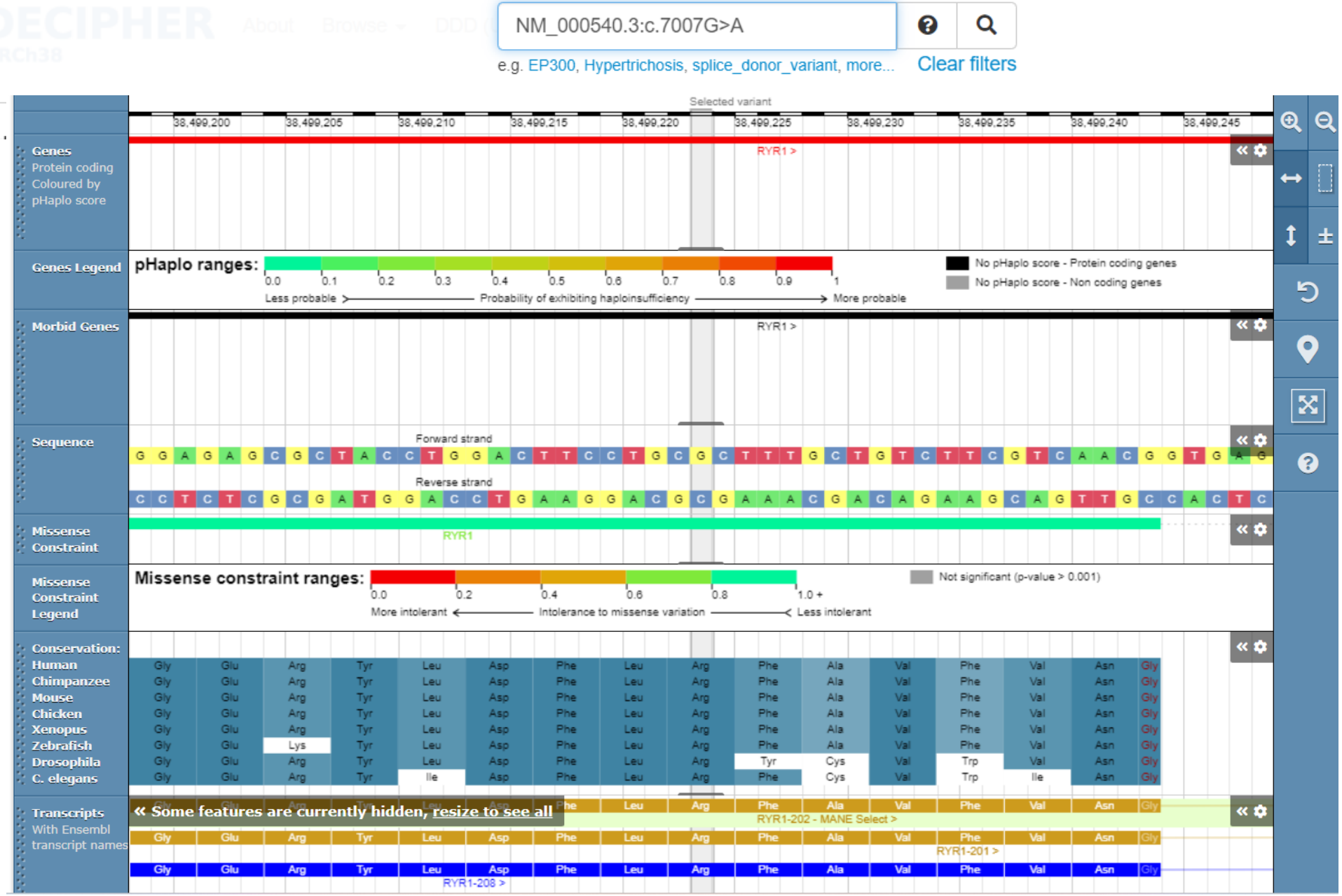
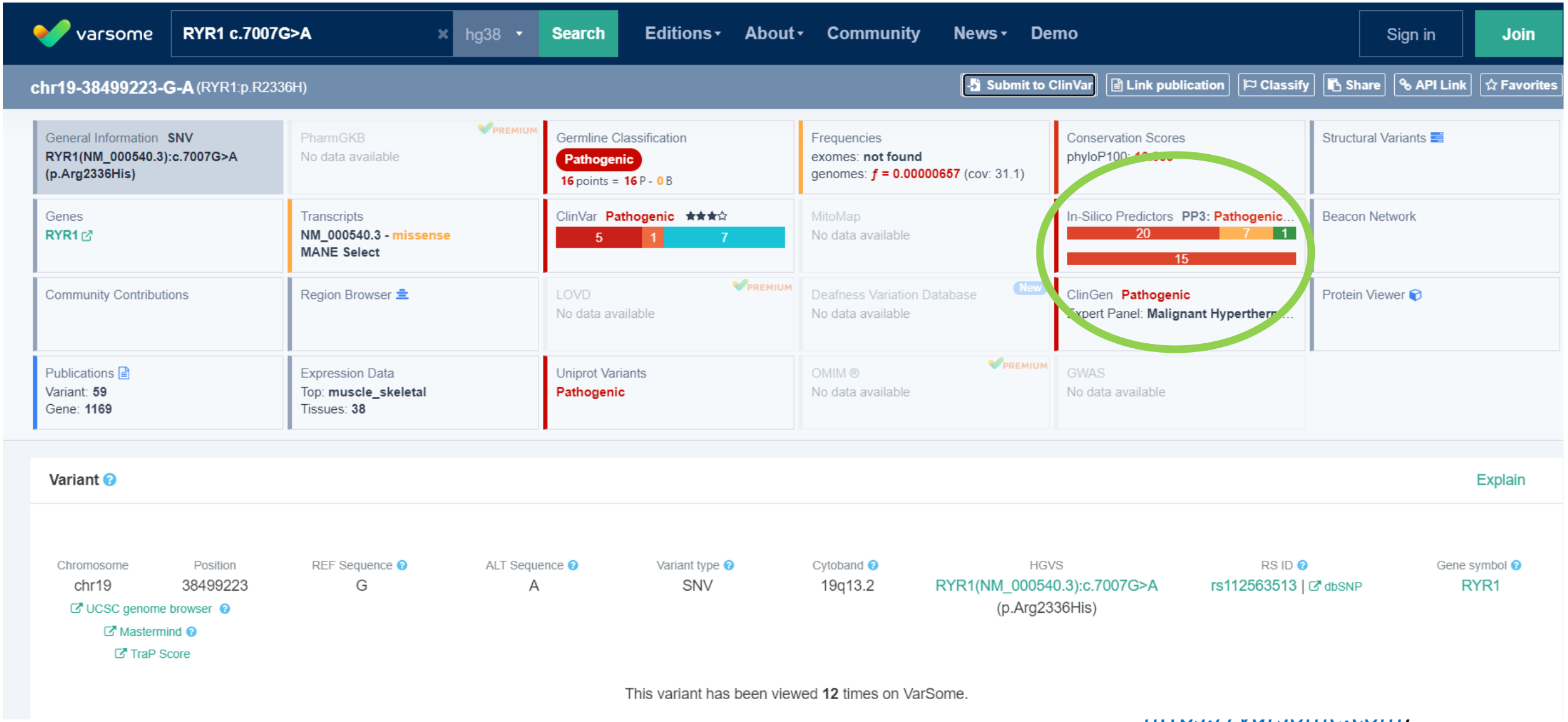


https://www.deciphergenomics.org/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UCSC genome browser
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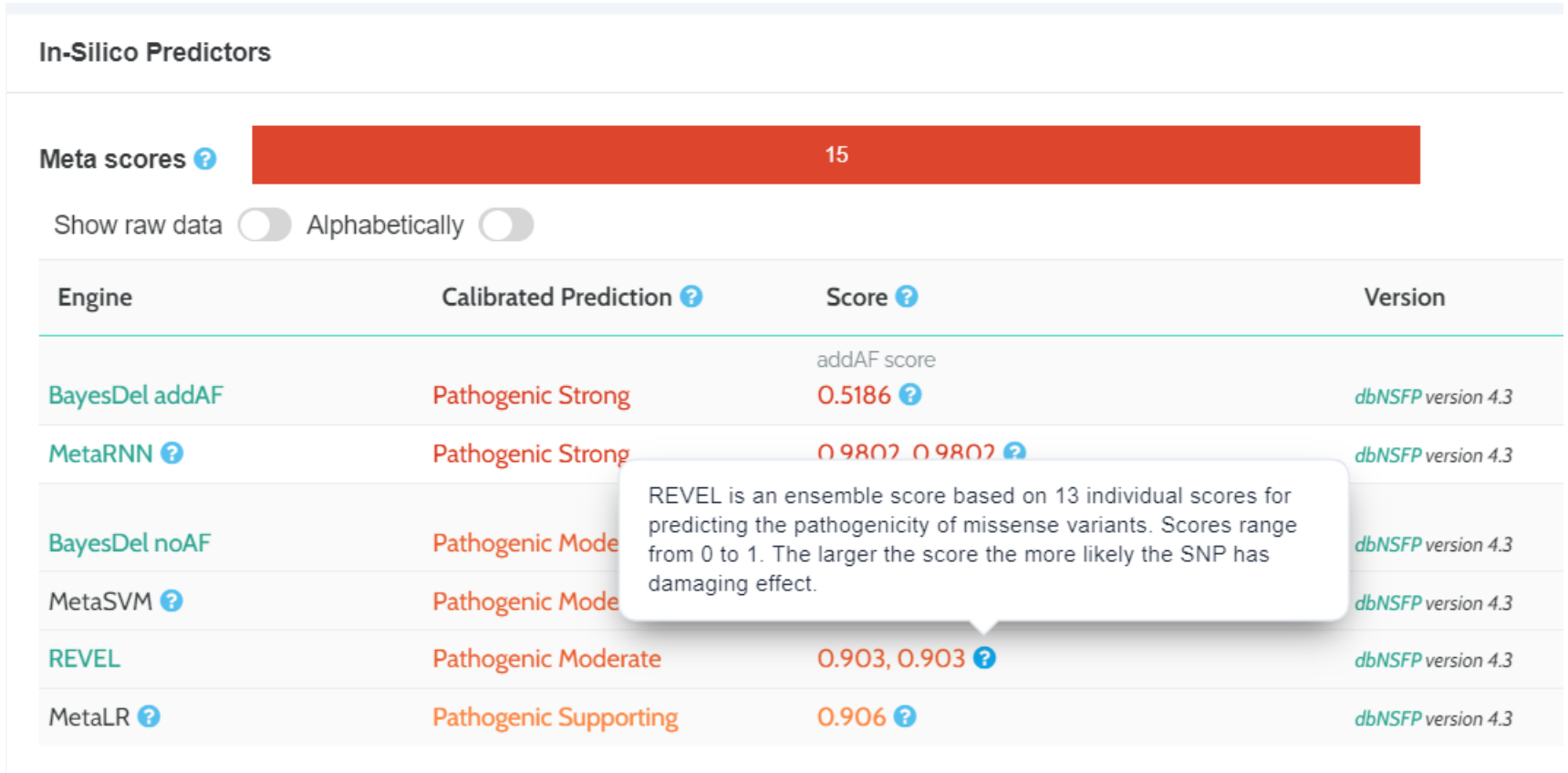
Revel

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



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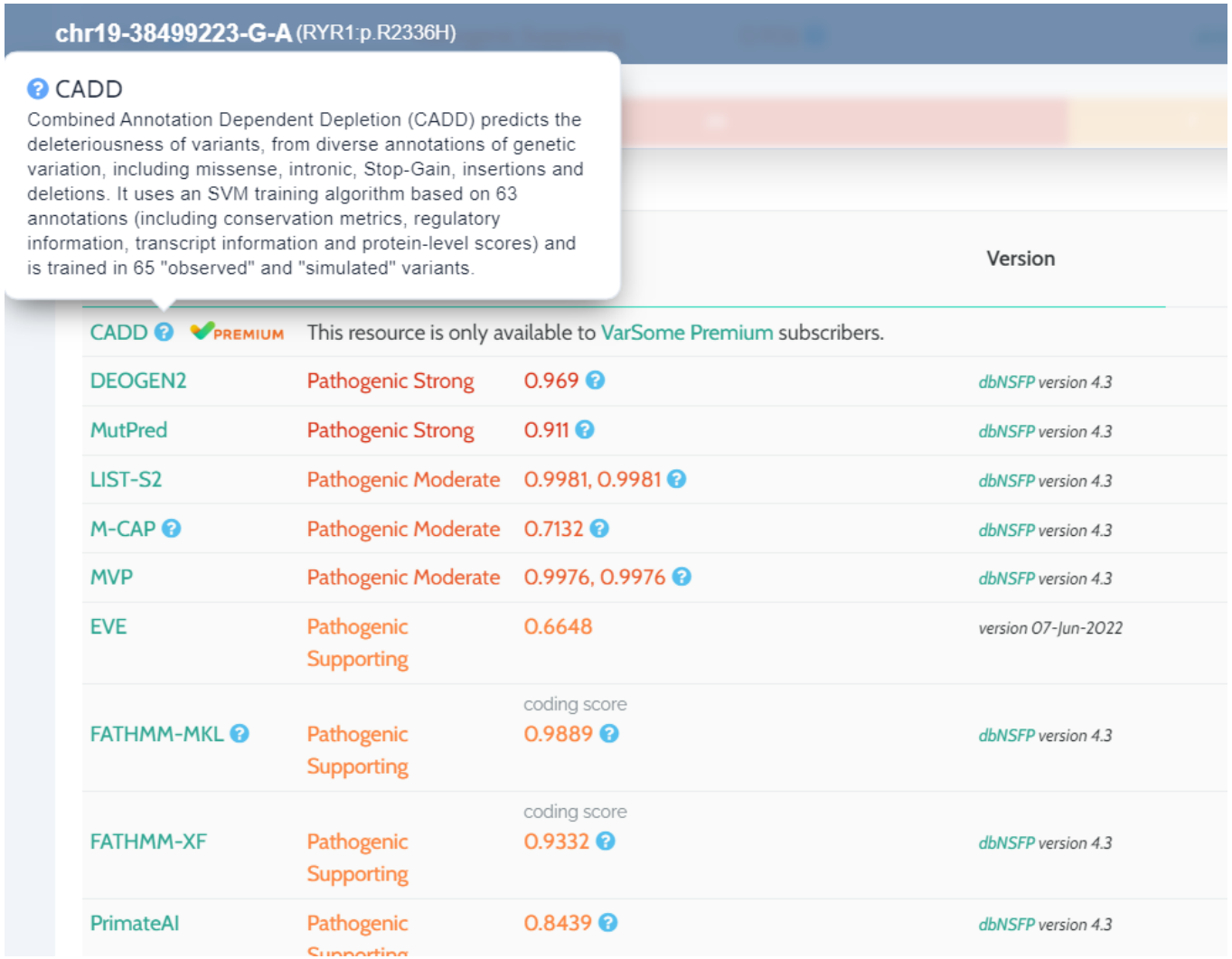
CADD

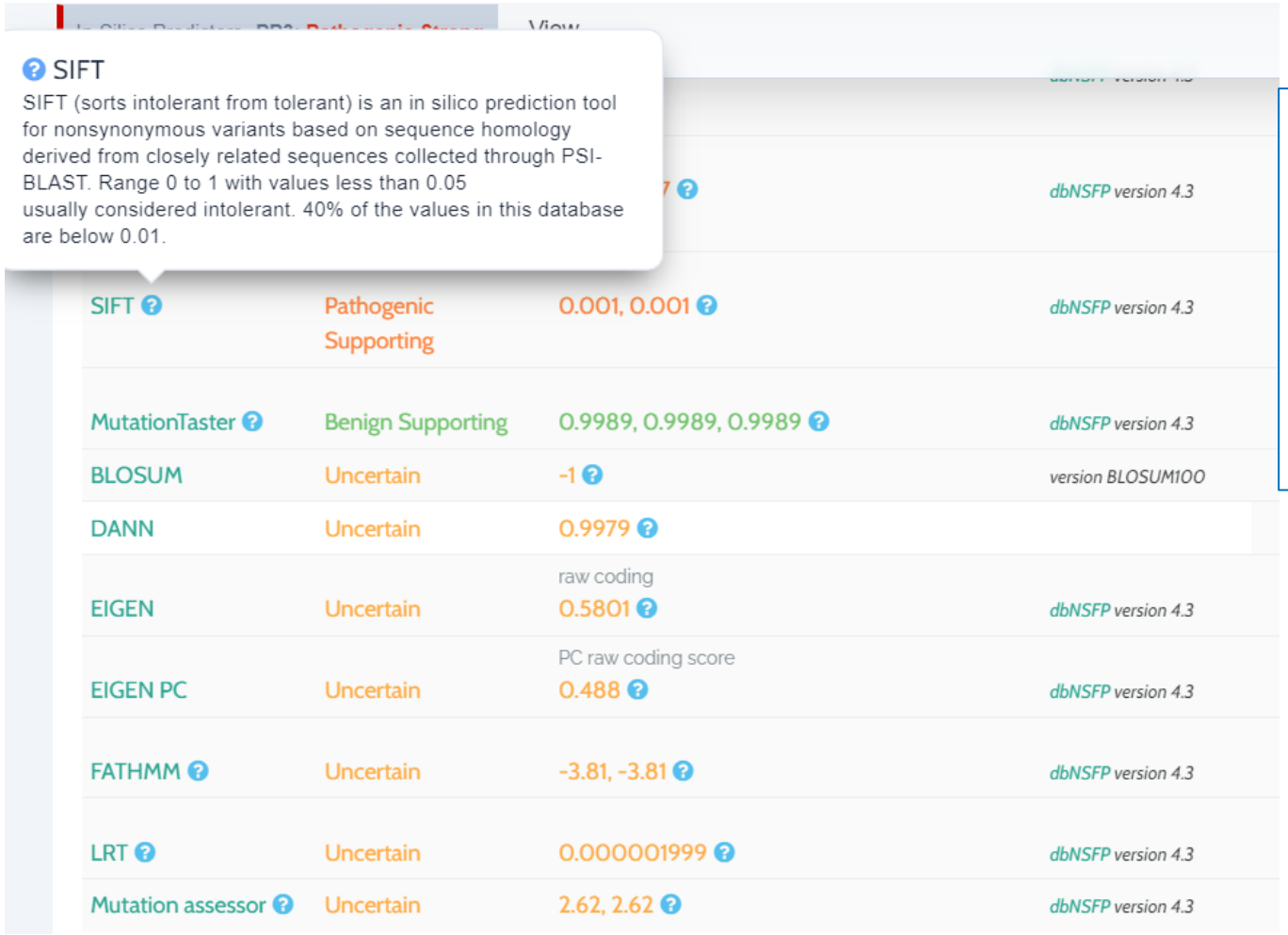


- Varyantın patojenitesi hakkında bilgi verir
- >20 olan skorlar protein üzerinde yıkıcı etki

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

SIFT

Sorting Intolerant From Tolerant



- 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:

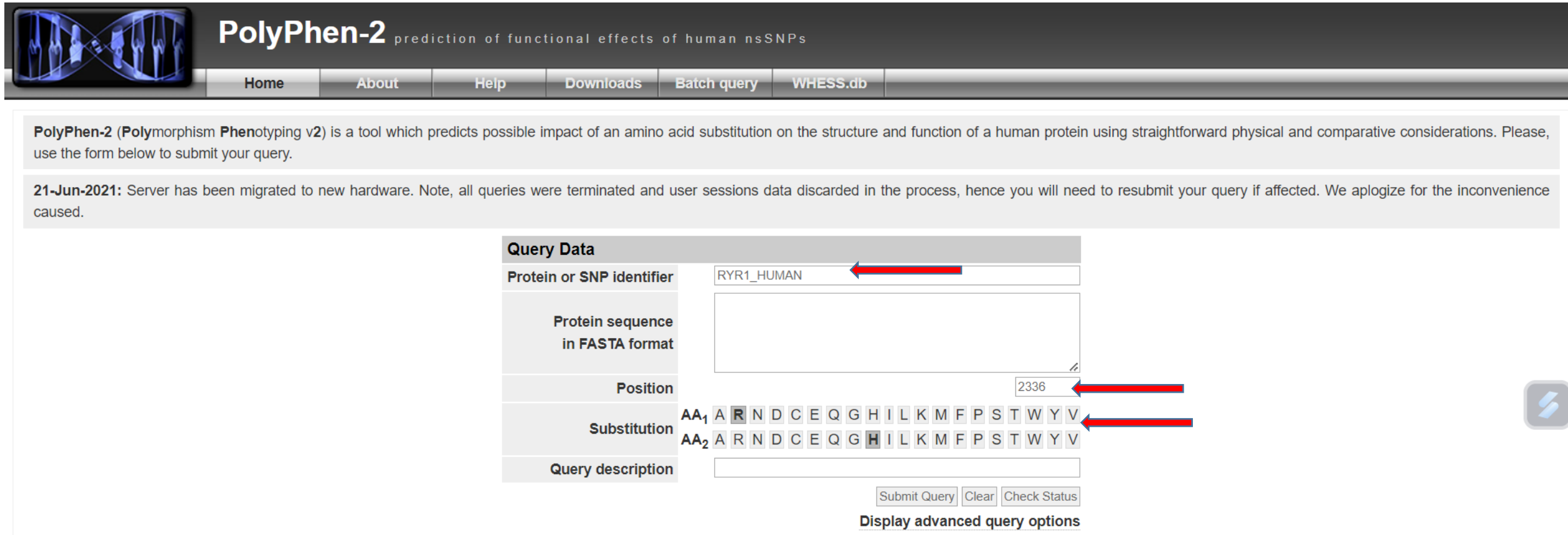
- 0.0 to 0.15 -- Variants with scores in this range are predicted to be benign.
- 0.15 to 1.0 -- Variants with scores in this range are possibly damaging.
- 0.85 to 1.0 -- Variants with scores in this range are more confidently predicted to be damaging.

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



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

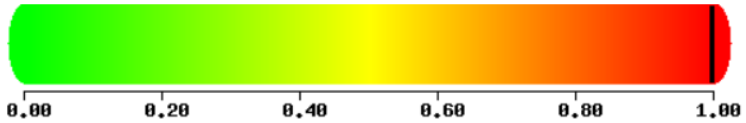
Protein Acc	Position	AA_1	AA_2	Description
P21817	2336	R	H	Canonical; RecName: Full=Ryanodine receptor 1; Short=RYR-1; Short=RyR1; AltName: Full=Skeletal muscle calcium release channel; AltName: Full=Skeletal muscle-type ryanodine receptor; Length: 5038

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 RYR1 HGNC gene symbol, NCBI Gene ID, Ensembl gene ID show available transcripts clear input

Transcript ENST00000359596 Ensembl transcript ID

Position / snippet refers to ○ coding sequence (ORF) ◉ transcript (cDNA sequence) ○ gene (genomic sequence)

Alteration

all types by sequence

enter a few bases around your alteration

Format:

ACTGTC[A/*T*] GTGTF	A substituted by *T*
ACTGTC[AG/*T*] GTGTF	AG substituted by *T*
ACTGTC[ACGT/-] GTGTF	ACGT deleted
ACTGTC[-/*AA*] GTGTF	*AA* inserted

options

☐ show nucleotide alignment

single base exchange by position

enter **position** 7007

and **new base** A

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

hyperlink

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

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	PhyloP PhastCons (flanking) 1.535 1 5.812 1 (flanking) 1.396 1 explain score(s) and/or inspect your position(s) in in UCSC Genome Browser

distance from splice site	15
Kozak consensus sequence altered?	N/A

conservation
protein level for non-synonymous changes

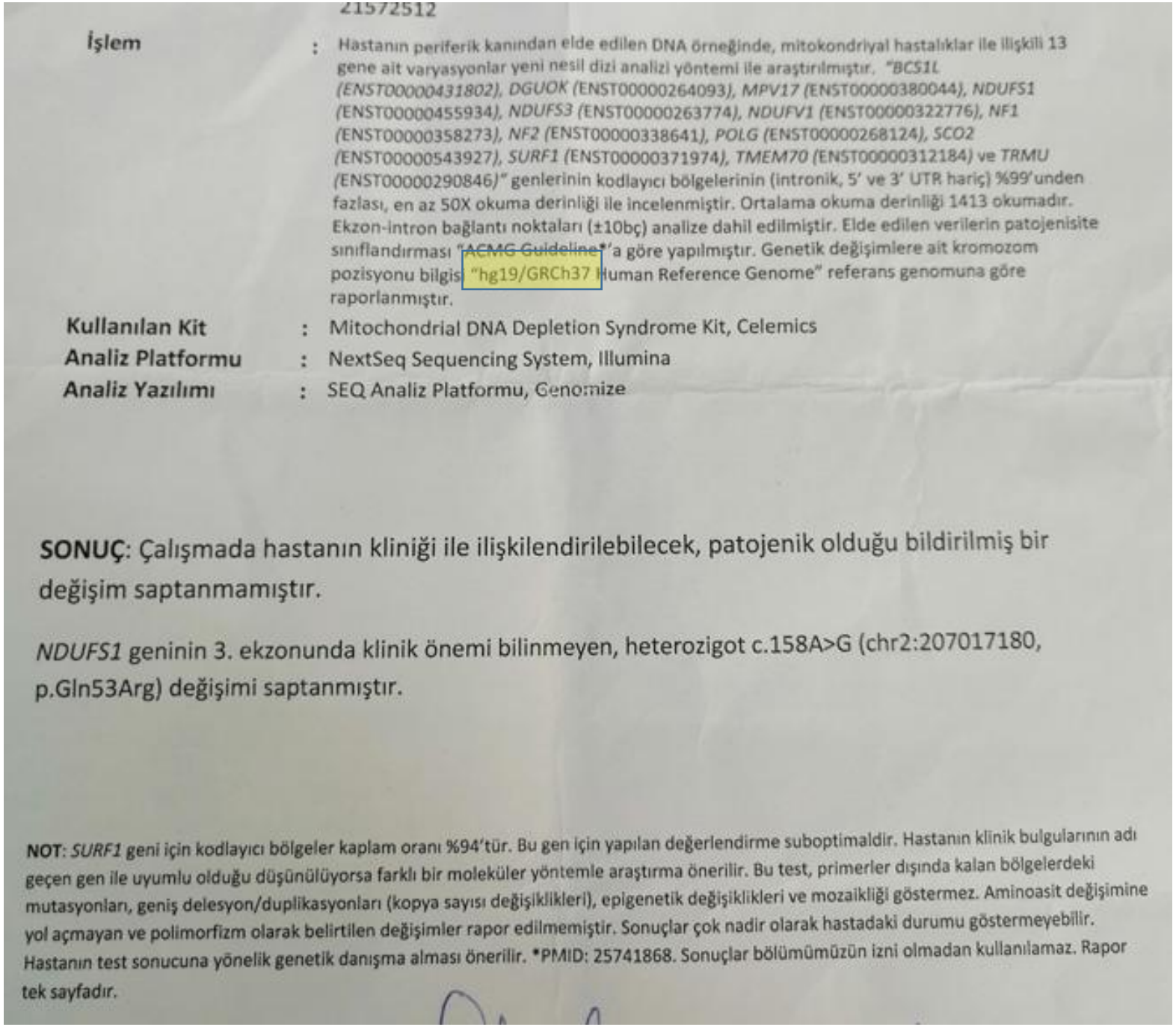
species	match	gene	aa	alignment
Human			2293	D N N E L A L A L Q E Q D L E K V V S Y L A G C
mutated	all conserved		2293	D N N E L A L A L Q E K D L E K V V S Y L A G
Ptroglodytes	all identical	ENSPTRG00000010931	2294	D N N E L A L A L Q E Q D L E K V V S Y L A G
Mmulatta	no alignment	ENSMMUG00000028770	n/a	
Fcatus	all identical	ENSFCAG00000000828	2290	D N N E L A L A L Q E Q D L E K
Mmusculus	all identical	ENSMUSG00000030592	2294	D N N E L A L A L Q E Q D L E K V V S Y L A G
Ggallus	no homologue			
Trubripes	no homologue			
Drerio	no alignment	ENSDARG00000003706	n/a	
Dmelanogaster	no homologue			
Celegans	no homologue			
Xtropicalis	all identical	ENSXETG00000002823	2211	N E L A L A L Q E Q D L E K V V S Y L A G

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. *"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'unden fazlası, en az 50X okuma derinliği ile incelenmiştir. Ortalama okuma derinliği 1413 okumadır. Ekzon-intron bağlantı noktaları (±10bç) 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, Celemics

Analiz Platformu : NextSeq Sequencing System, Illumina

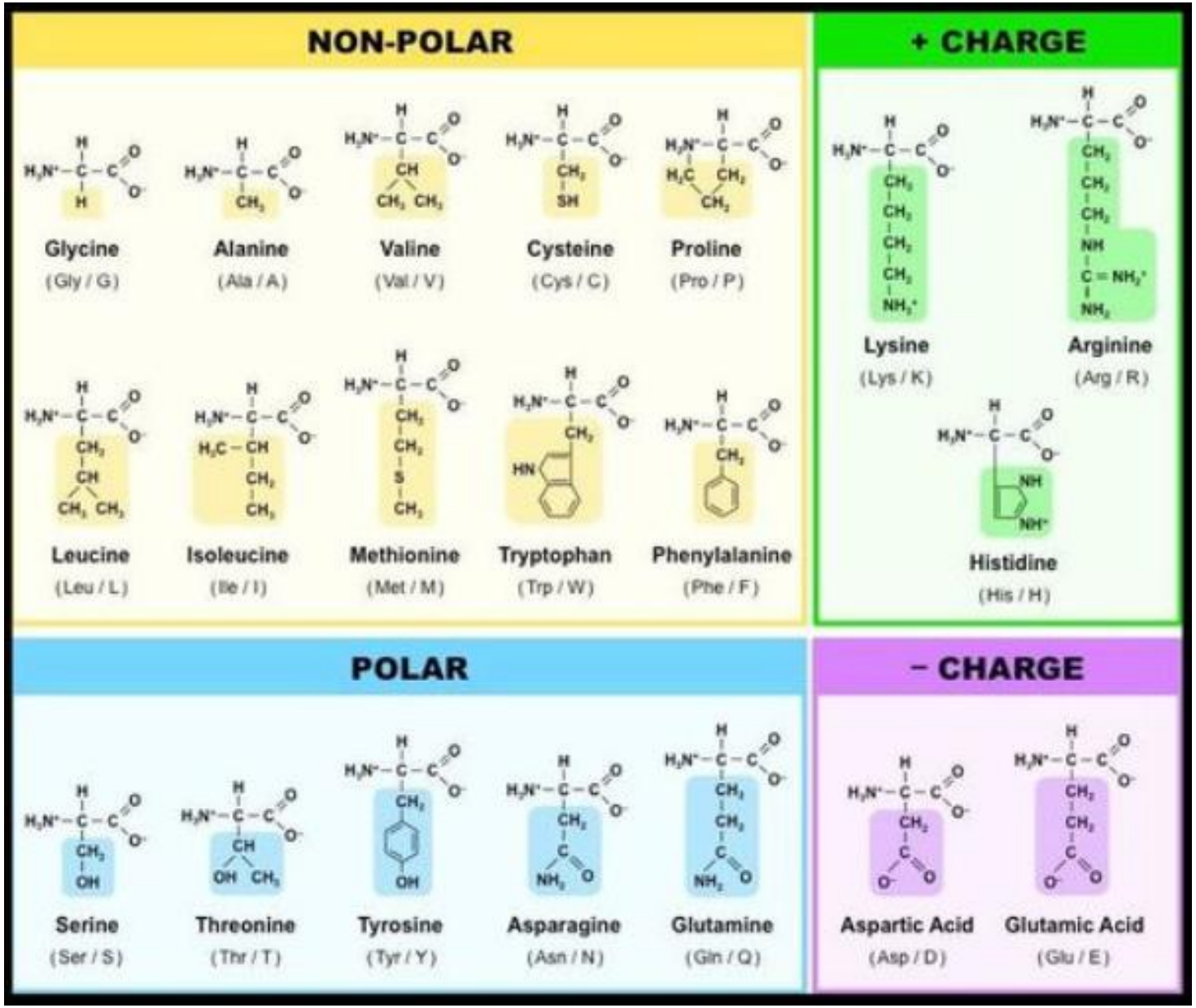
Analiz Yazılımı : SEQ Analiz Platformu, Genomize

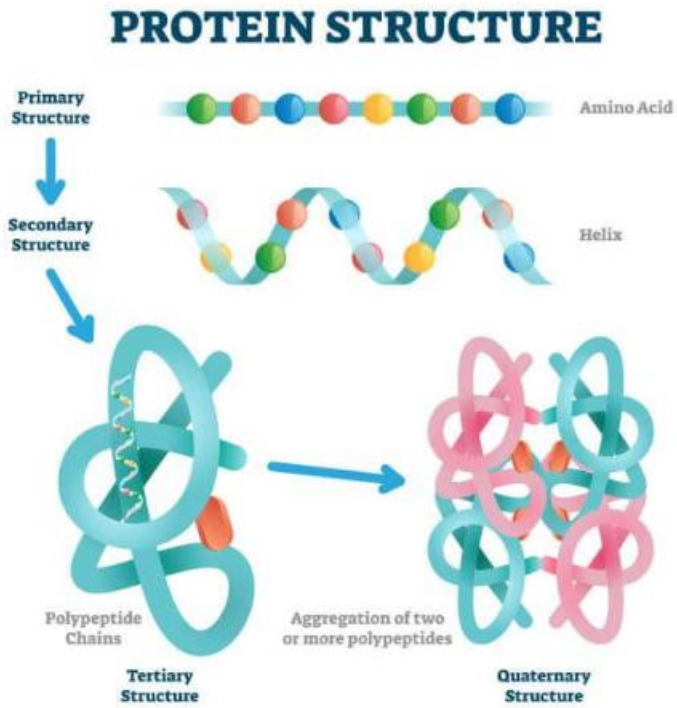
SONUÇ: Çalışmada hastanın kliniği ile ilişkilendirilebilecek, patojenik olduğu bildirilmiş bir değişim saptanmamıştır.

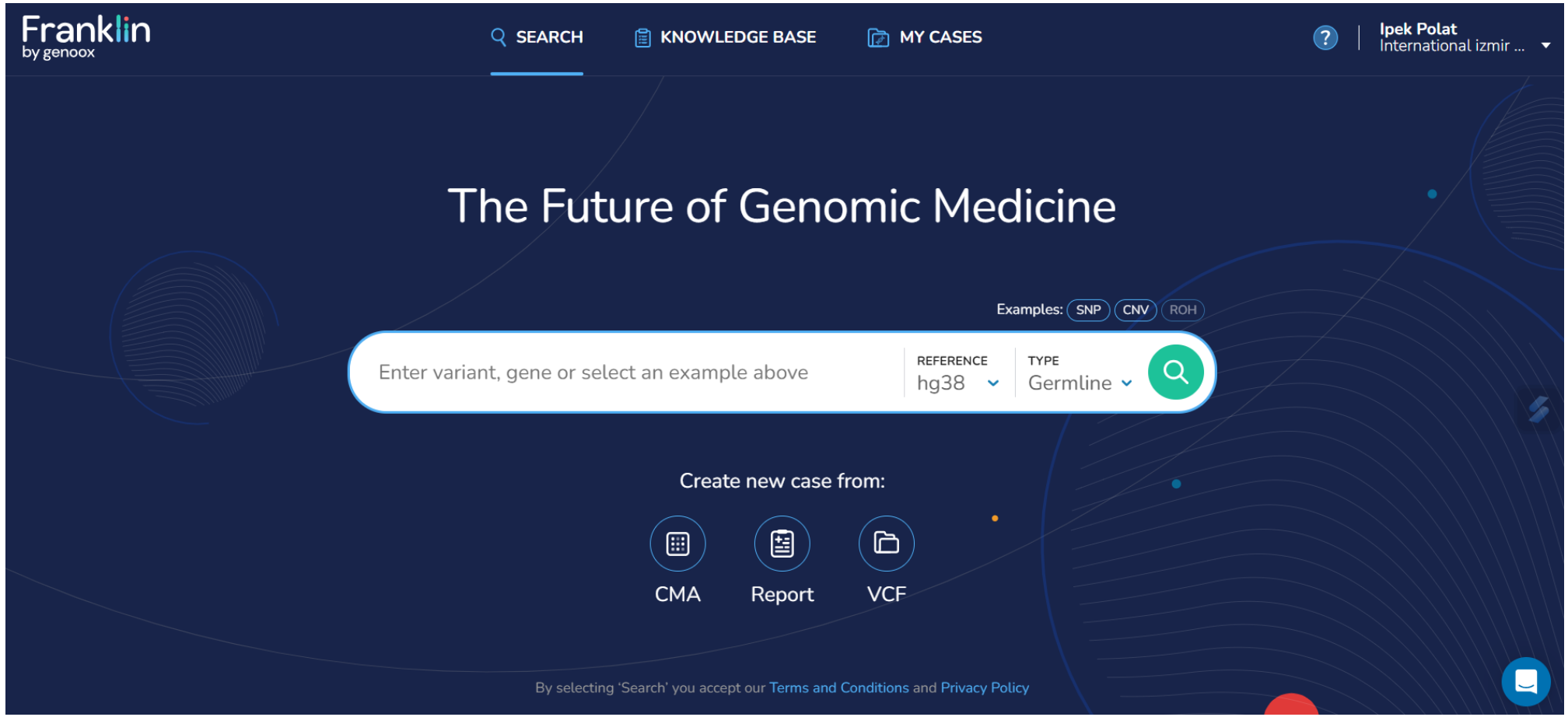
NDUFS1 geninin 3. ekzonunda klinik önemi bilinmeyen, heterozigot c.158A>G (chr2:207017180, p.Gln53Arg) değişimi saptanmıştır.

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.

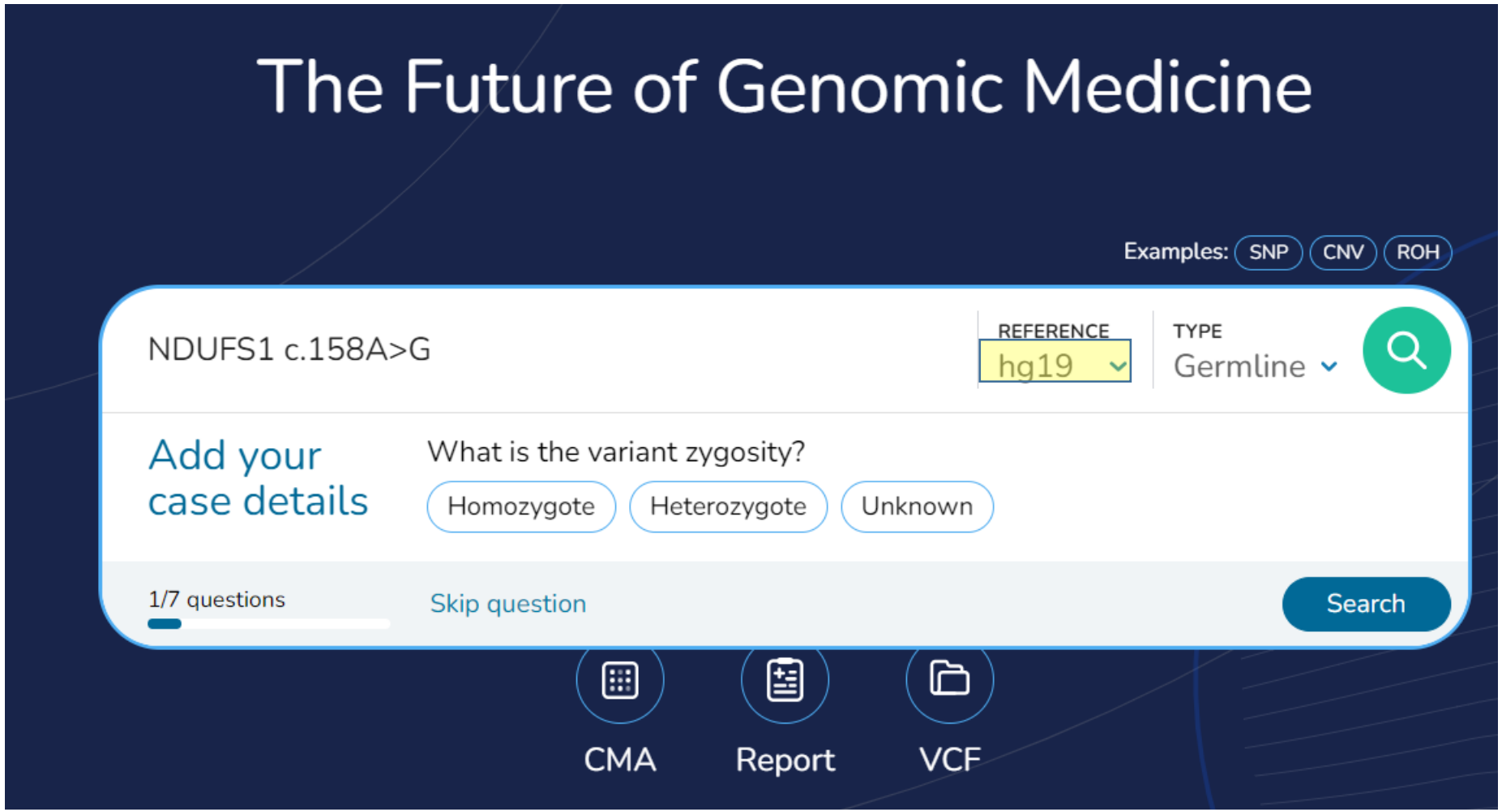
- NDUFS1
- 0/1
- c.158A>G
- p.Gln53Arg

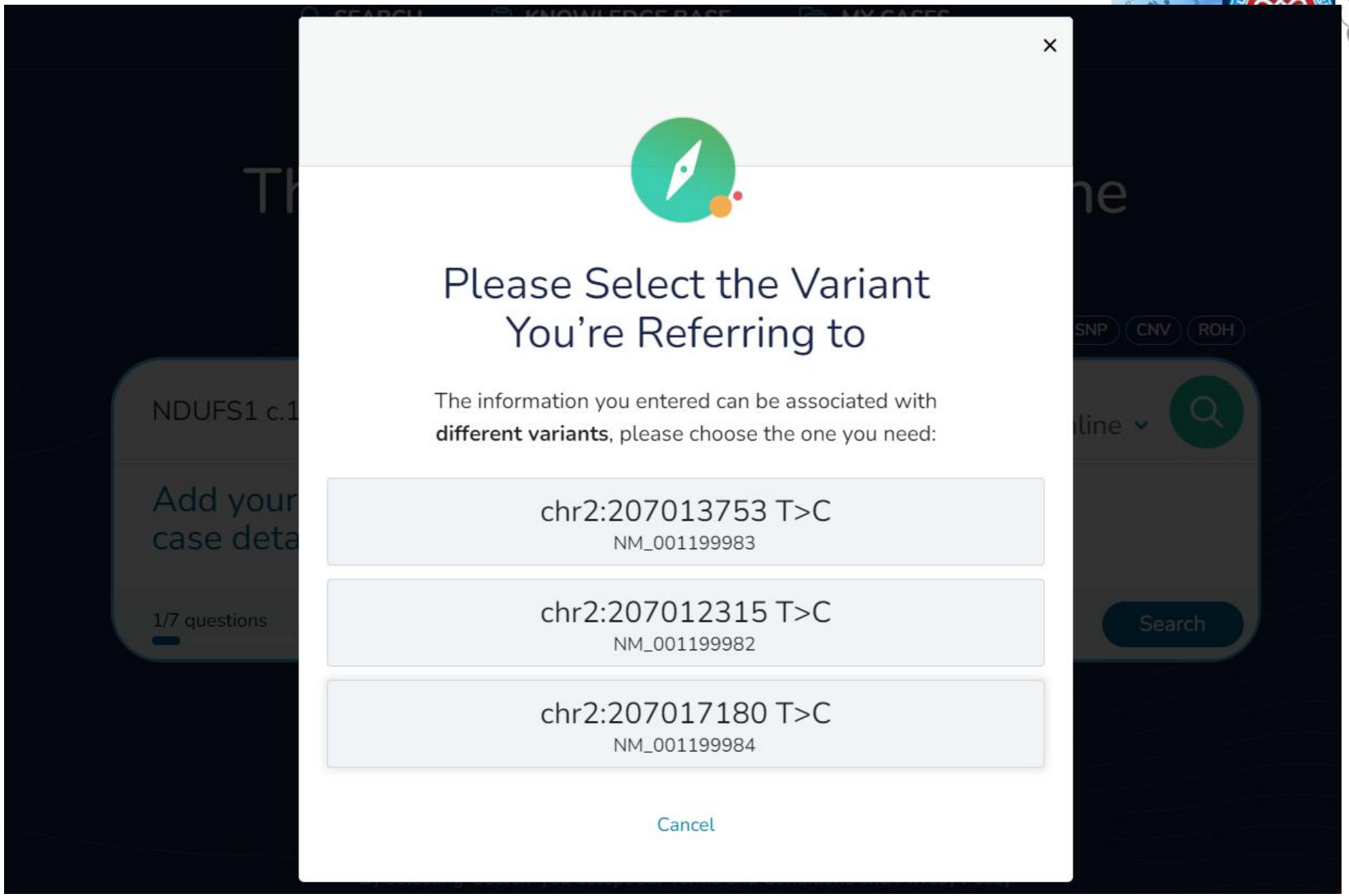

NON-POLAR
Glycine
(Gly / G)
Alanine
(Ala / A)
Valine
(Val / V)
Cysteine
(Cys / C)
Proline
(Pro / P)
Leucine
(Leu / L)
Isoleucine
(Ile / I)
Methionine
(Met / M)
Tryptophan
(Trp / W)
Phenylalanine
(Phe / F)
+ CHARGE
Lysine
(Lys / K)
Arginine
(Arg / R)
Histidine
(His / H)
POLAR
Serine
(Ser / S)
Threonine
(Thr / T)
Tyrosine
(Tyr / Y)
Asparagine
(Asn / N)
Glutamine
(Gln / Q)
– CHARGE
Aspartic Acid
(Asp / D)
Glutamic Acid
(Glu / E)

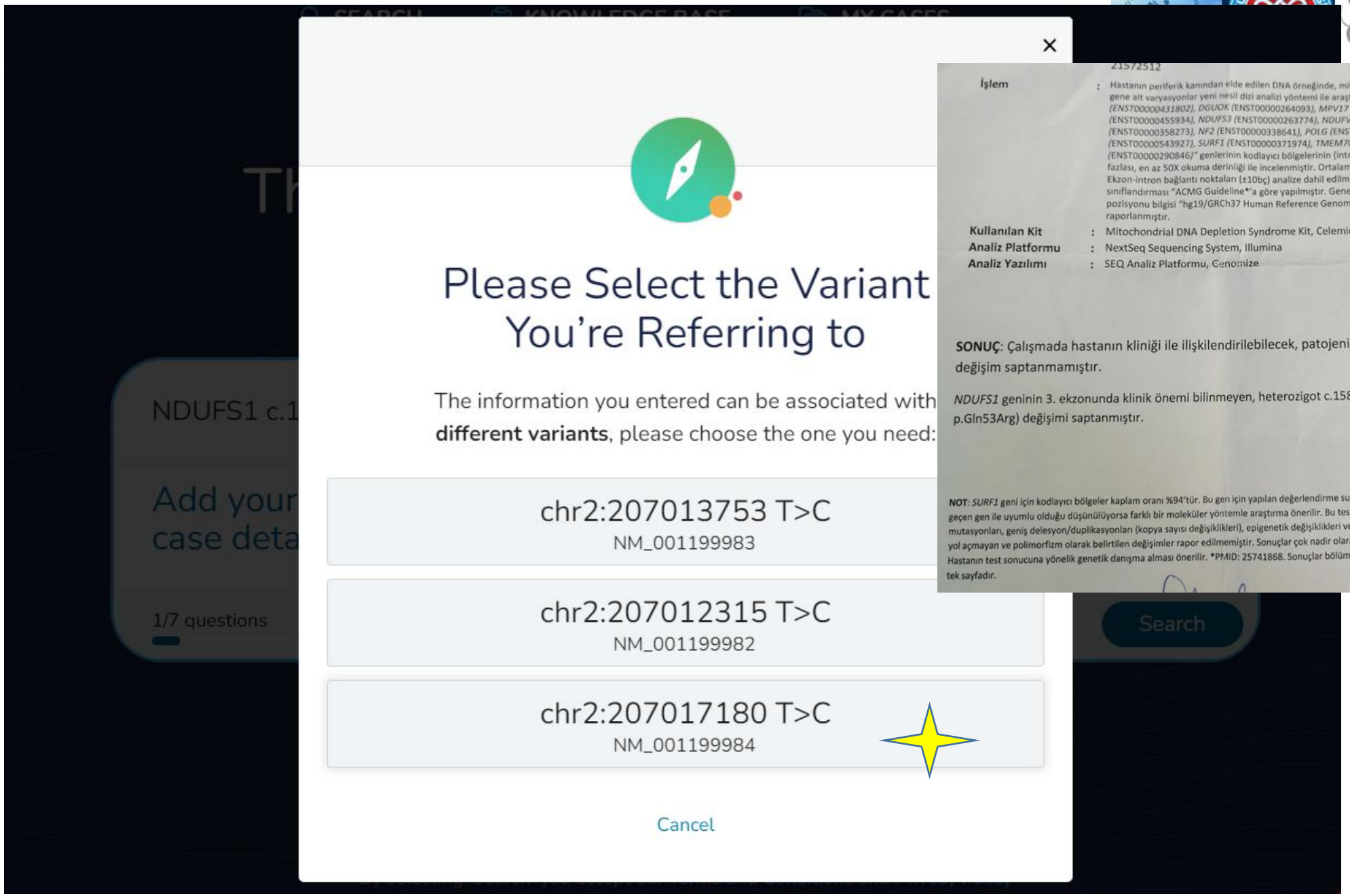

PROTEIN STRUCTURE
Primary Structure
Amino Acid
Secondary Structure
Helix
Polypeptide Chains
Tertiary Structure
Aggregation of two or more polypeptides
Quaternary Structure

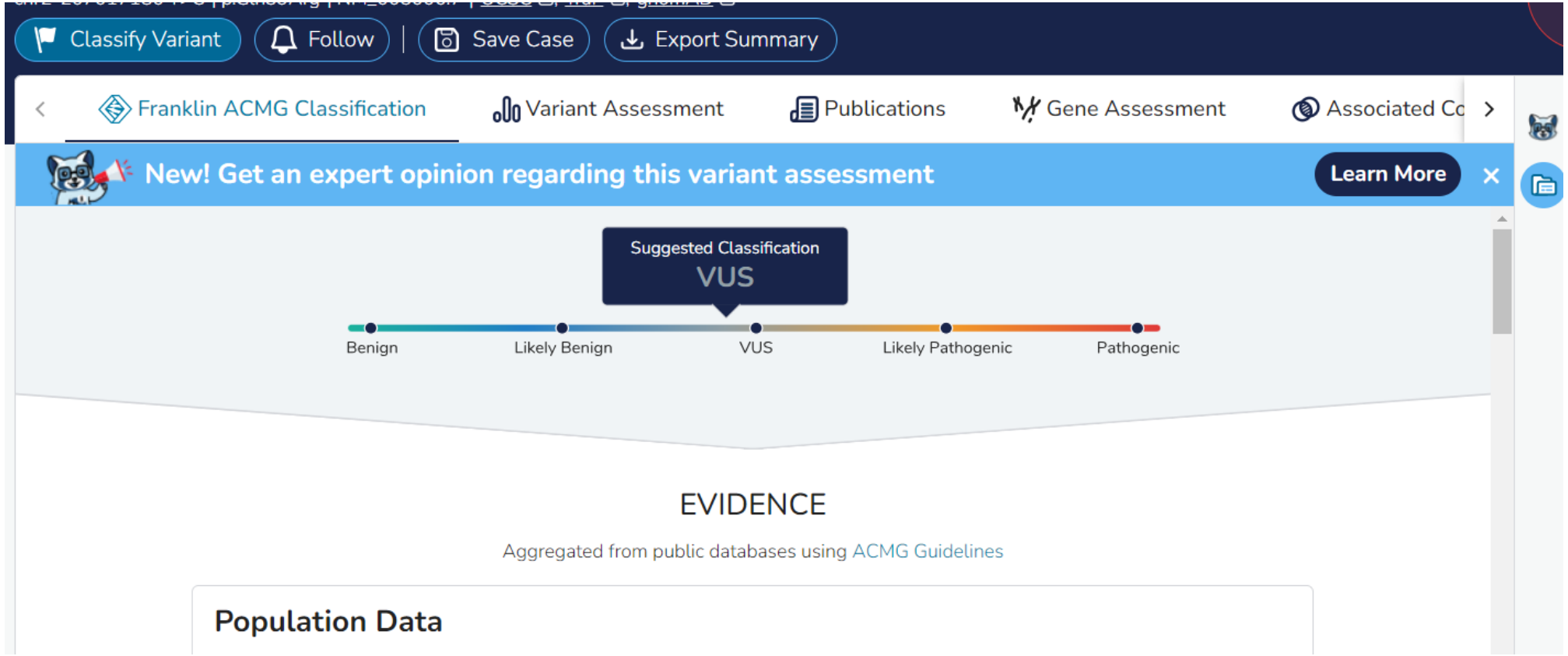


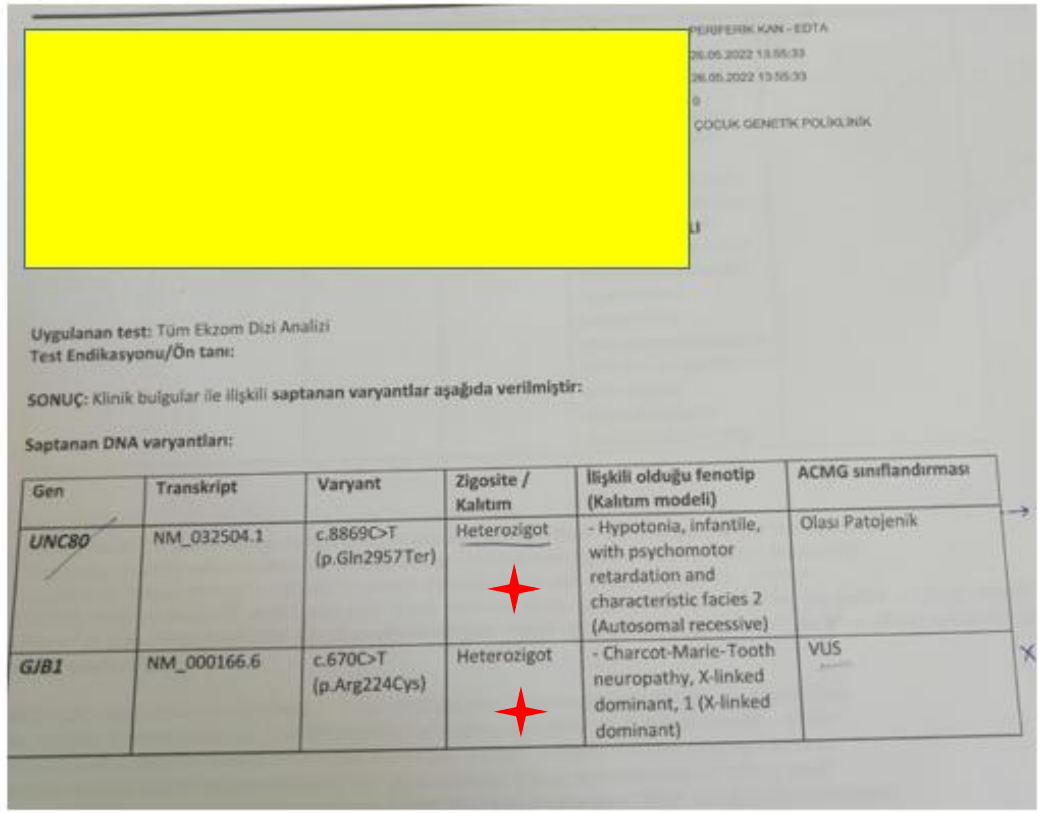
https://franklin.genoox.com/clinical-db/home


The Future of Genomic Medicine
Examples: SNP CNV ROH
NDUFS1 c.158A>G
REFERENCE
hg19
TYPE
Germline
Add your case details
What is the variant zygosity?
Homozygote
Heterozygote
Unknown
1/7 questions
Skip question
Search
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
NDUFS1 c.1
Add your case deta
1/7 questions
SNP
CNV
ROH
Search


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
NDUFS1 c.1
Add your case deta
1/7 questions
Search
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'unden fazlası, en az 50X okuma derinliği ile incelenmiştir. Ortalama okuma derinliği 1413 okumadır. Ekzon-intron bağlantı noktaları (±10bç) 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, Celemics
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
New! Get an expert opinion regarding this variant assessment
Learn More
Suggested Classification
VUS
Benign
Likely Benign
VUS
Likely Pathogenic
Pathogenic
EVIDENCE
Aggregated from public databases using ACMG Guidelines
Population Data



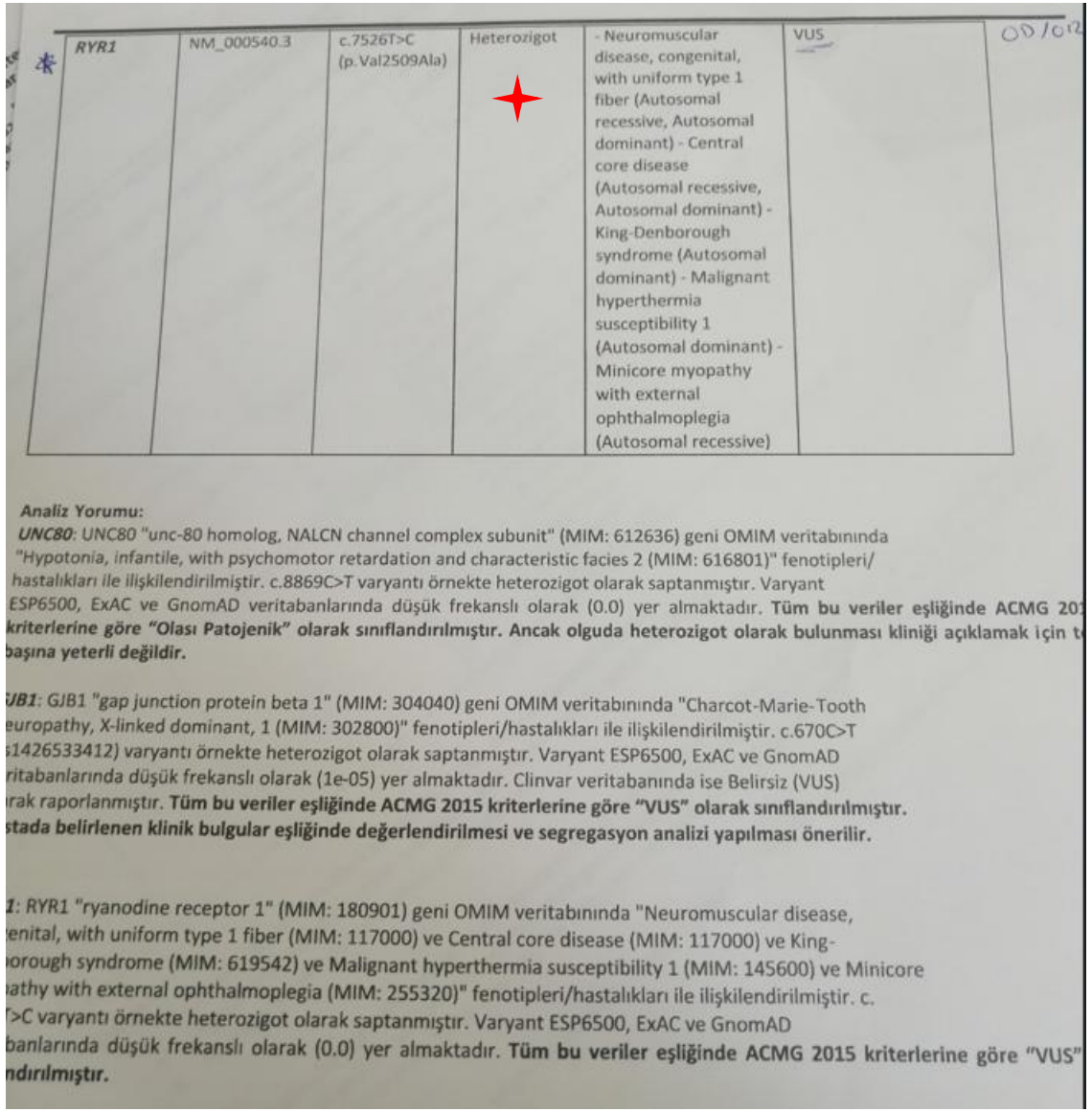
PERİFERİK KAN - EDTA
26.05.2022 13:55:33
26.05.2022 13:55:33
0
ÇOCUK GENETİK POLİKLİNİK

Uygulanan test: Tüm Ekzom Dizi 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



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:

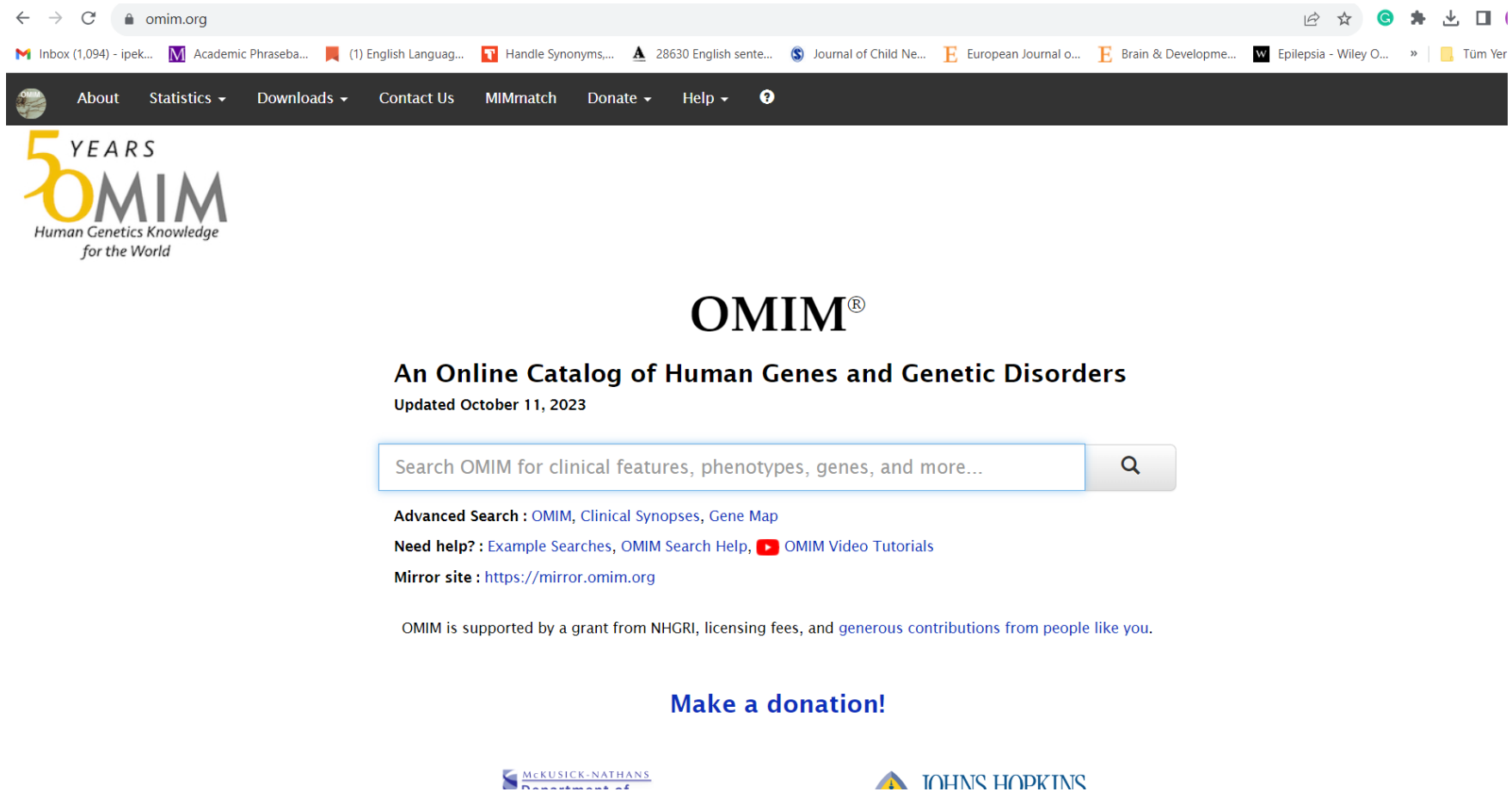
UNC80: UNC80 "unc-80 homolog, NALCN channel complex subunit" (MIM: 612636) geni OMIM veritabınında "Hypotonia, infantile, with psychomotor retardation and characteristic facies 2 (MIM: 616801)" fenotipleri/ hastalıkları ile ilişkilendirilmiştir. c.8869C>T varyantı örnekte heterozigot olarak saptanmıştır. Varyant ESP6500, ExAC ve GnomAD veritabanlarında düşük frekanslı olarak (0.0) yer almaktadır. **Tüm bu veriler eşliğinde ACMG 201 kriterlerine göre "Olası Patojenik" olarak sınıflandırılmıştır. Ancak olguda heterozigot olarak bulunması kliniği açıklamak için t başına yeterli değildir.**

GJB1: GJB1 "gap junction protein beta 1" (MIM: 304040) geni OMIM veritabınında "Charcot-Marie-Tooth neuropathy, X-linked dominant, 1 (MIM: 302800)" fenotipleri/hastalıkları ile ilişkilendirilmiştir. c.670C>T (rs1426533412) 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. Ancak olguda belirlenen klinik bulgular eşliğinde değerlendirilmesi ve segregasyon analizi yapılması önerilir.**

RYR1: RYR1 "ryanodine receptor 1" (MIM: 180901) geni OMIM veritabınında "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.**

Yürümede güçlük
Sık takılıp düşme

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



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)

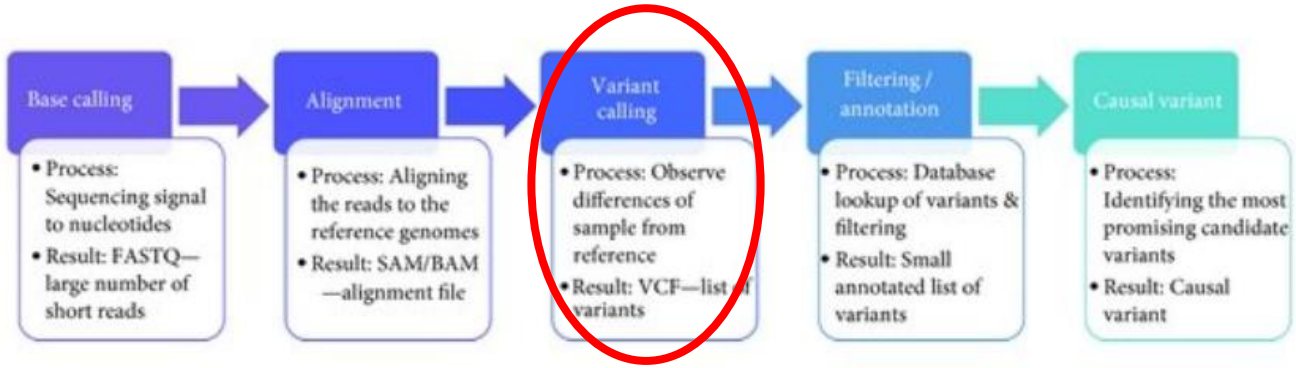
Gene-Phenotype Relationships

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

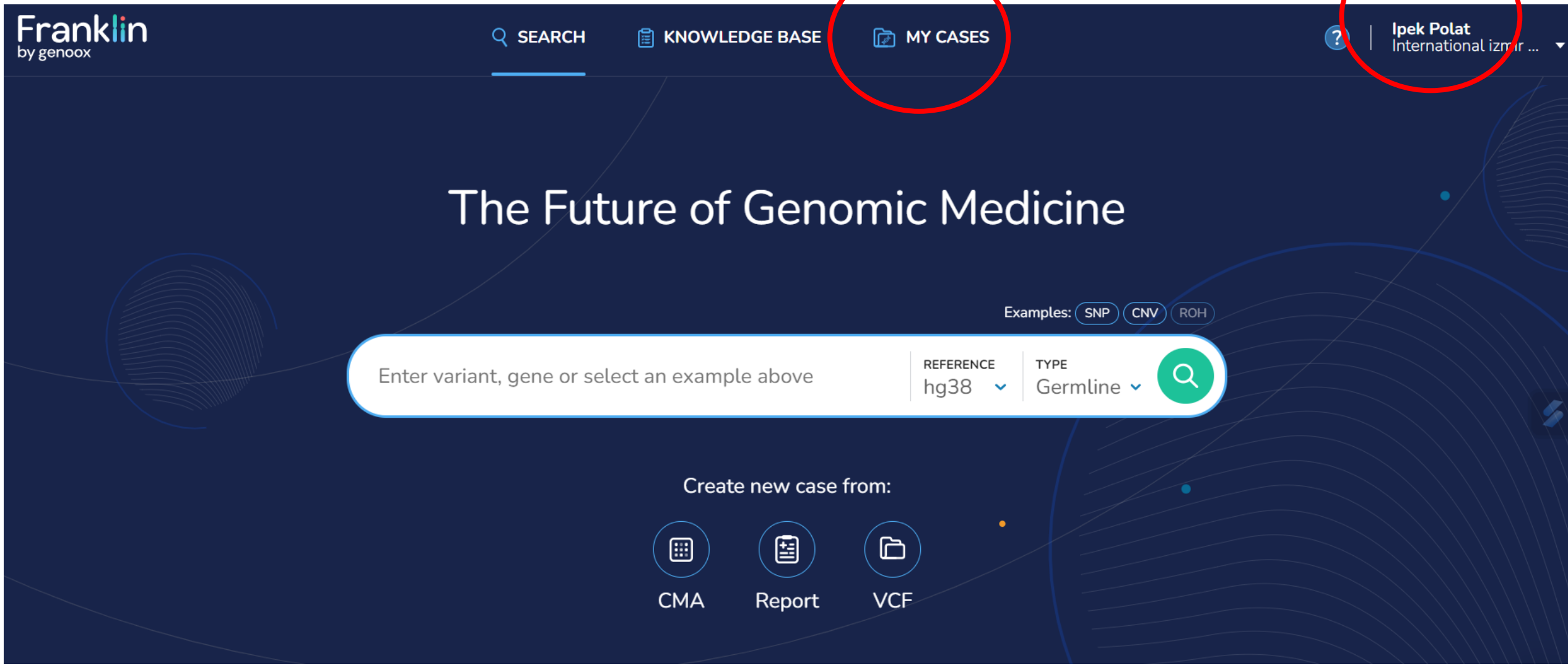
Derin fenotipleme;

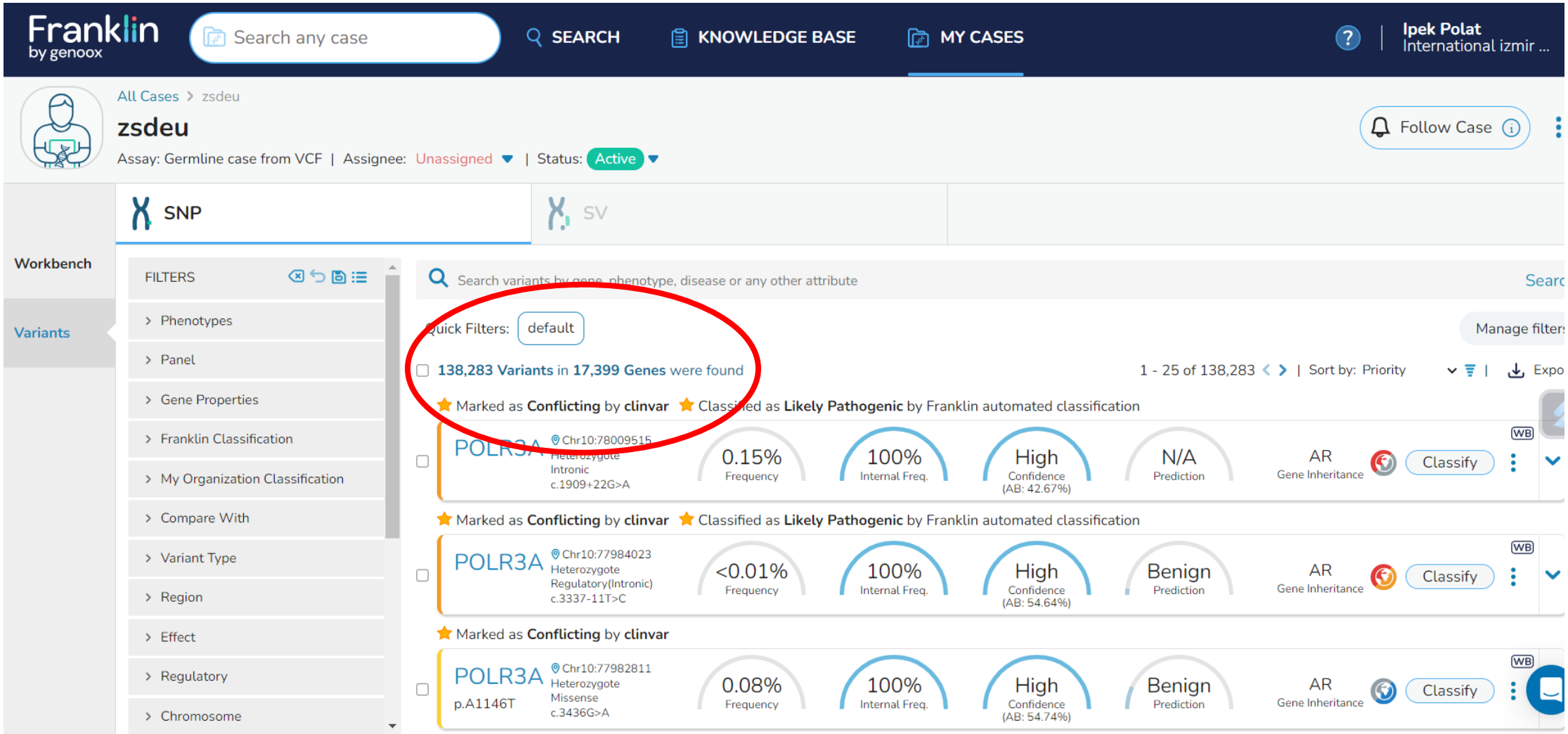
- NCS-EMG
- Kas bx
- Kas görüntüleme

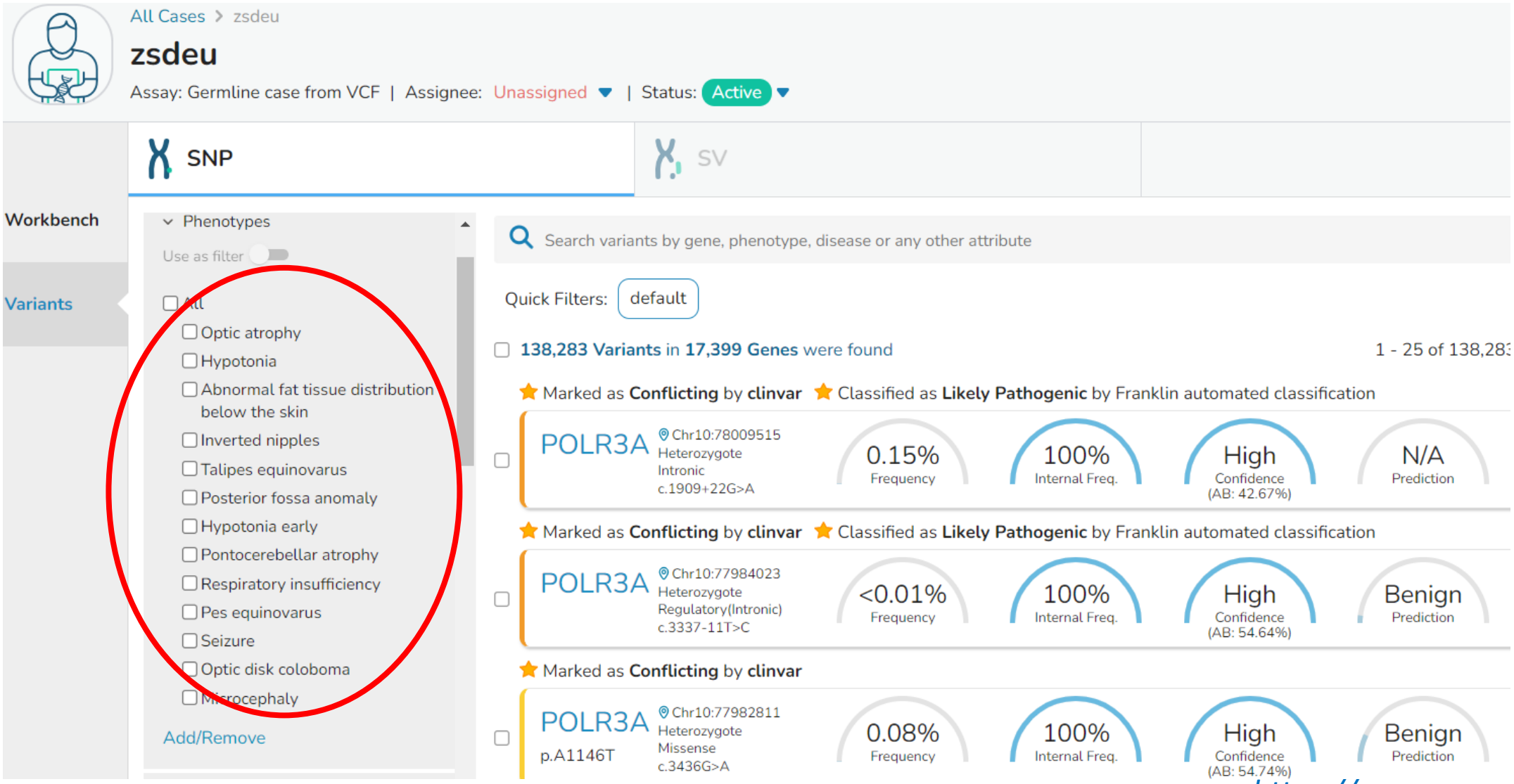
Vcf Datasını Kendim Değerlendirebilir miyim?



Rapor

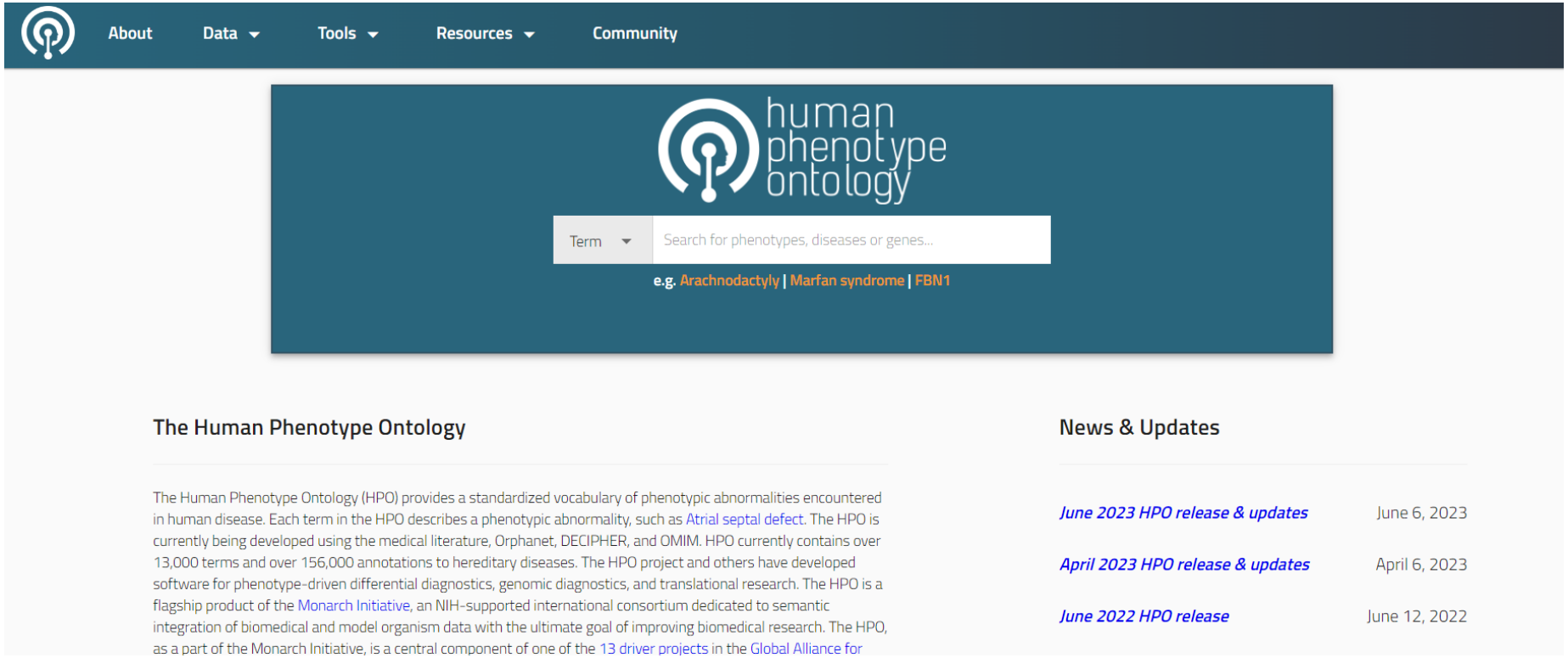

Franklin
by genoox
SEARCH
KNOWLEDGE BASE
MY CASES
Ipek Polat
International izmir ...
The Future of Genomic Medicine
Examples: SNP CNV ROH
Enter variant, gene or select an example above
REFERENCE
hg38
TYPE
Germline
Create new case from:
CMA
Report
VCF


Franklin
by genoox
Search any case
SEARCH
KNOWLEDGE BASE
MY CASES
Ipek Polat
International izmir ...
All Cases > zsdeu
zsdeu
Assay: Germline case from VCF | Assignee: Unassigned | Status: Active
Follow Case
SNP
SV
Workbench
Variants
FILTERS
Phenotypes
Panel
Gene Properties
Franklin Classification
My Organization Classification
Compare With
Variant Type
Region
Effect
Regulatory
Chromosome
Search variants by gene, phenotype, disease or any other attribute
Quick Filters: default
Manage filters
138,283 Variants in 17,399 Genes were found
1 - 25 of 138,283 | Sort by: Priority
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
AR Gene Inheritance
Classify
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
AR Gene Inheritance
Classify
Marked as Conflicting by clinvar
POLR3A p.A1146T Chr10:77982811 Heterozygote Missense c.3436G>A
0.08% Frequency
100% Internal Freq.
High Confidence (AB: 54.74%)
Benign Prediction
AR Gene Inheritance
Classify



https://varsome.com/

HPO Terimleri



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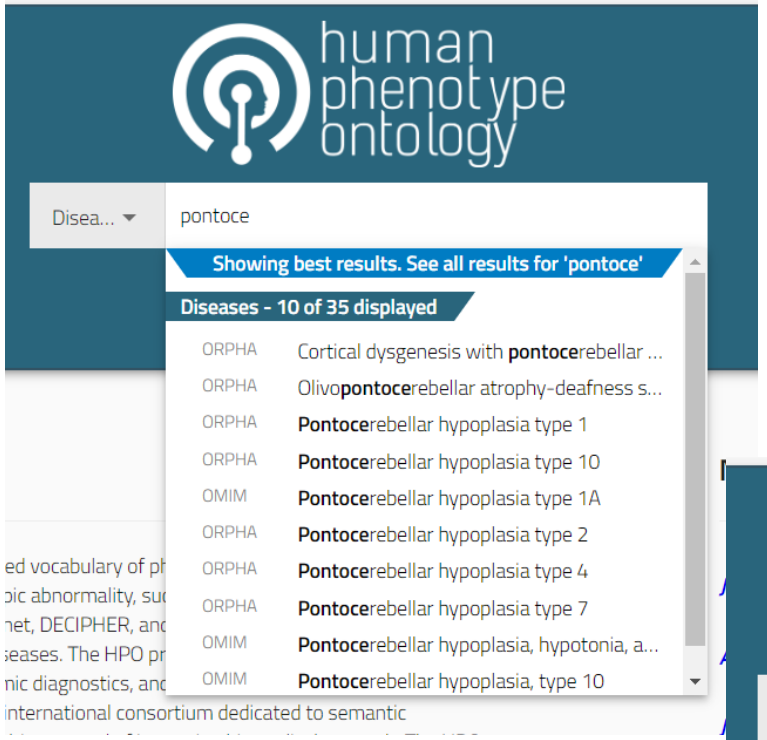
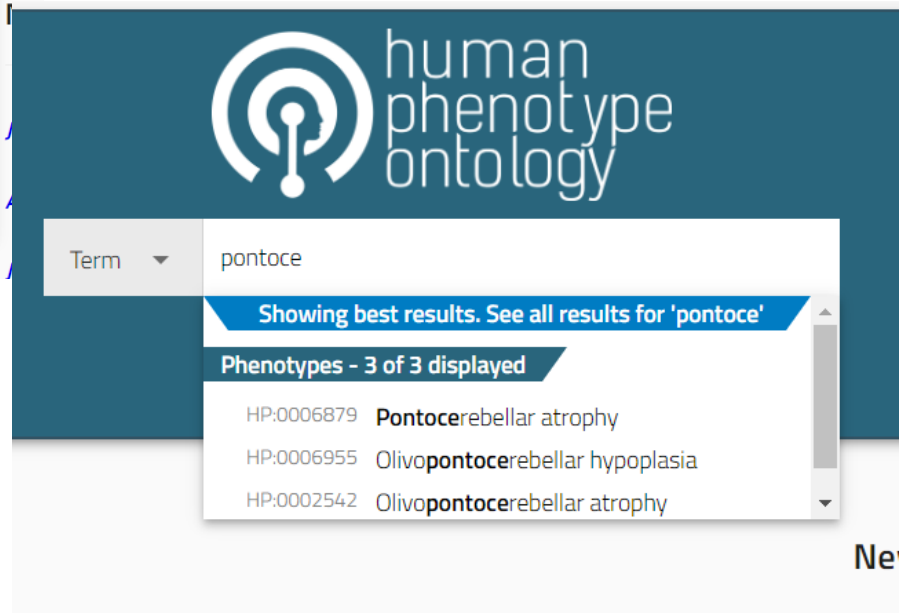
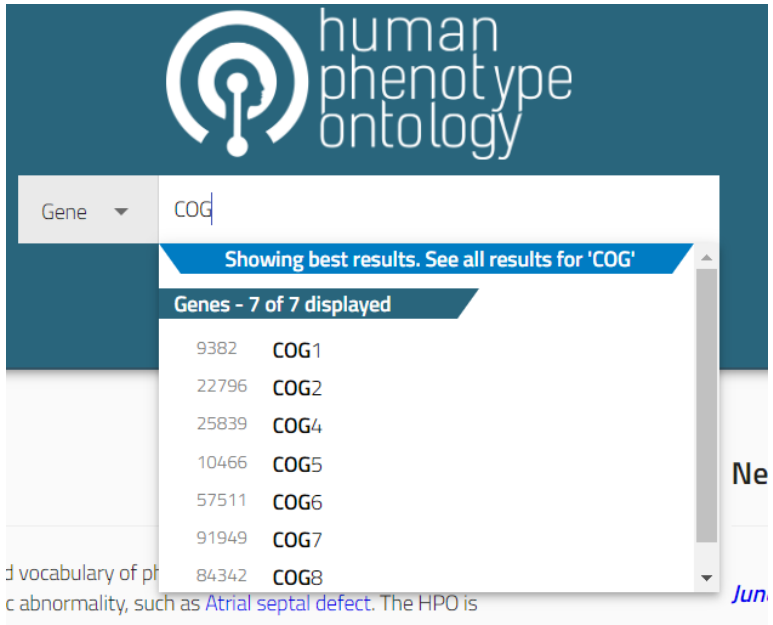
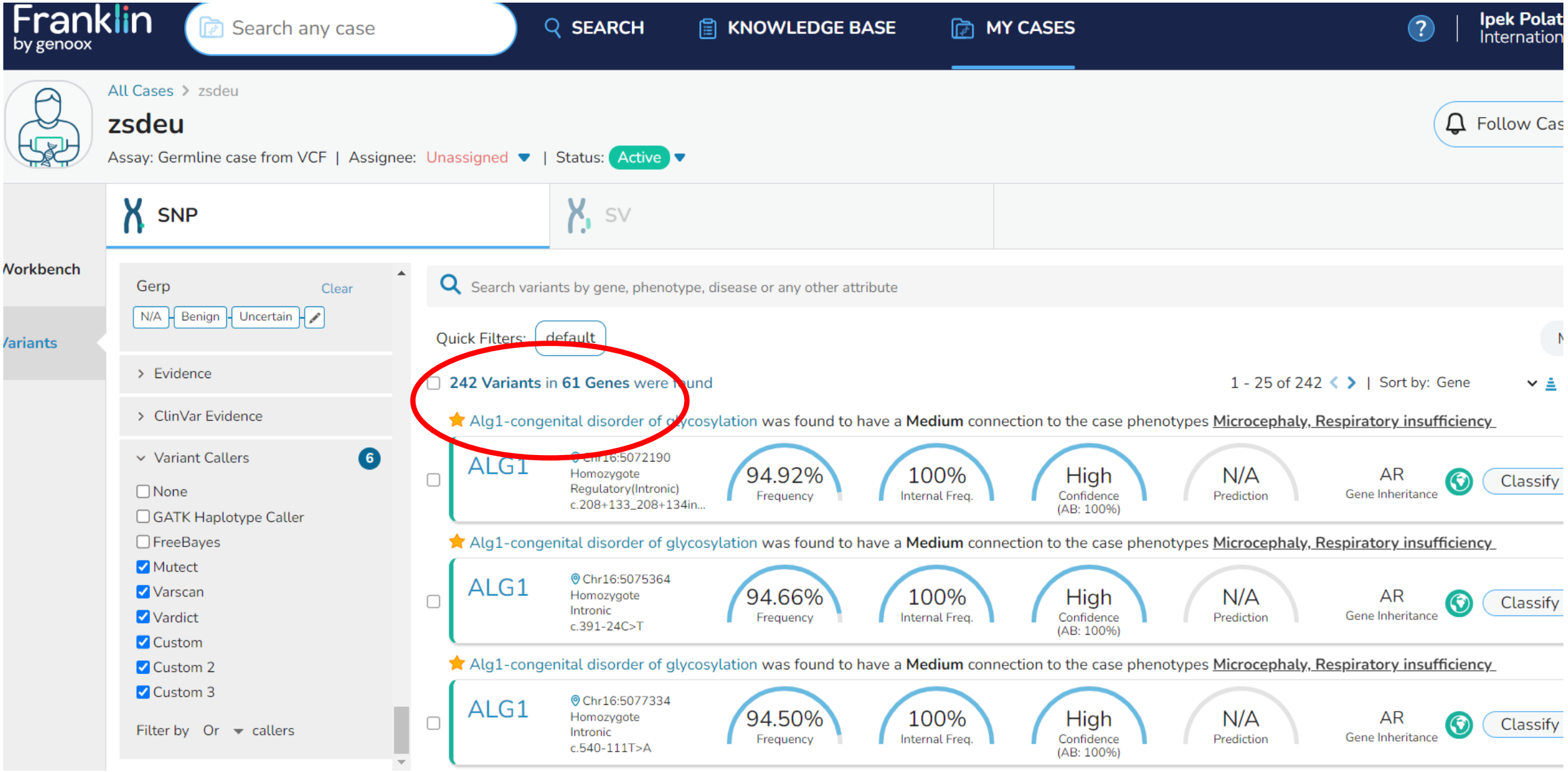

human phenotype ontology
Disea...
pontoce
Showing best results. See all results for 'pontoce'
Diseases - 10 of 35 displayed
ORPHA Cortical dysgenesis with pontocerebellar ...
ORPHA Olivopontocerebellar atrophy-deafness s...
ORPHA Pontocerebellar hypoplasia type 1
ORPHA Pontocerebellar hypoplasia type 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


human phenotype ontology
Term
pontoce
Showing best results. See all results for 'pontoce'
Phenotypes - 3 of 3 displayed
HP:0006879 Pontocerebellar atrophy
HP:0006955 Olivopontocerebellar hypoplasia
HP:0002542 Olivopontocerebellar atrophy


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


Franklin
by genoox
Search any case
SEARCH
KNOWLEDGE BASE
MY CASES
Ipek Polat
Internation
All Cases > zsdeu
zsdeu
Assay: Germline case from VCF | Assignee: Unassigned | Status: Active
Follow Cas
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 ilşkili 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 Gencode 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 üzerindenTüm 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 bazları 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

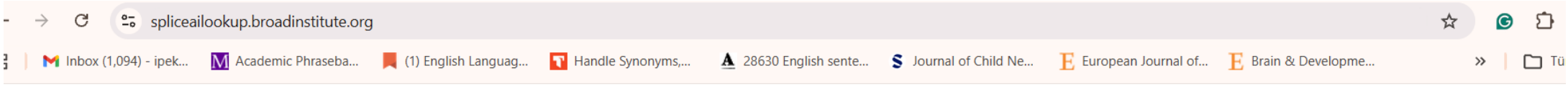
Compare two panels

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	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**
Green	VMA21	4 reviews 2 green	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**
Amber	ASCC1	2 reviews 2 green	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: 500 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: 500 masked scores REF & ALT scores

Submit

SpliceAI scores:

Variant	Gene	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	

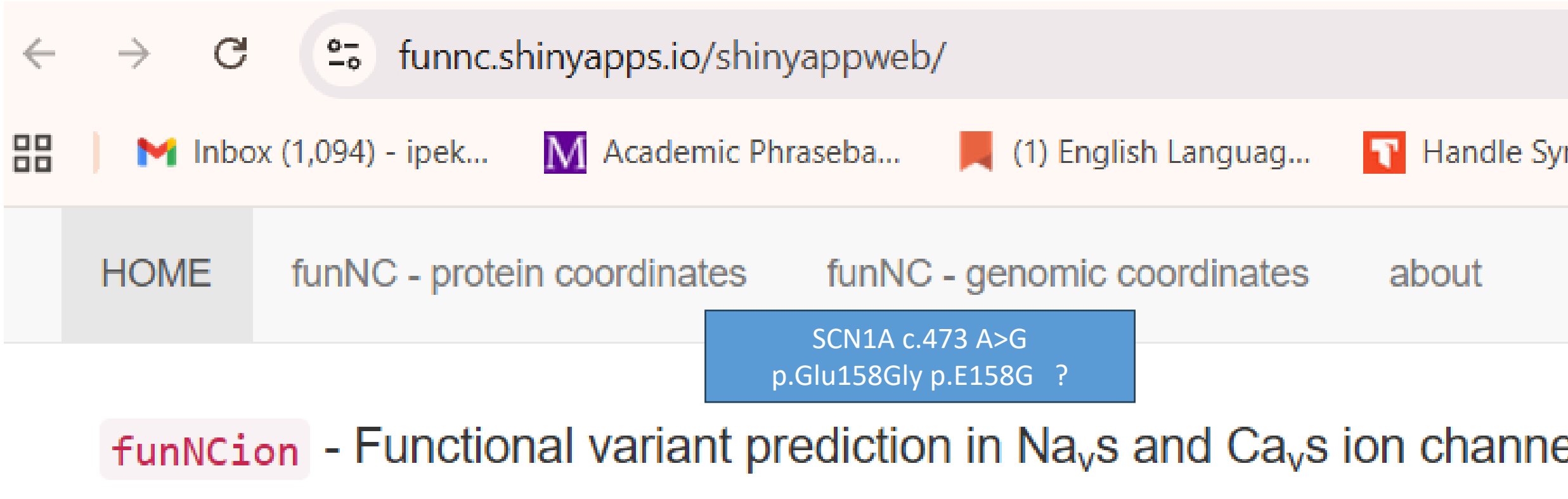
= MANE Select transcript = non-coding transcript

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)	Splice Gain	0.00	92 bp
UCSC, gnomAD	OMIM, GTEx, gnomAD, ClinGen, Ensembl, Decipher, GeneCards			

Gof-Lof ?


funnc.shinyapps.io/shinyappweb/
Inbox (1,094) - ipek...
Academic Phraseba...
(1) English Languag...
Handle Sy
HOME
funNC - protein coordinates
funNC - genomic coordinates
about
SCN1A c.473 A>G
p.Glu158Gly p.E158G ?
funNCion - Functional variant prediction in Na$_v$s and Ca$_v$s ion channe

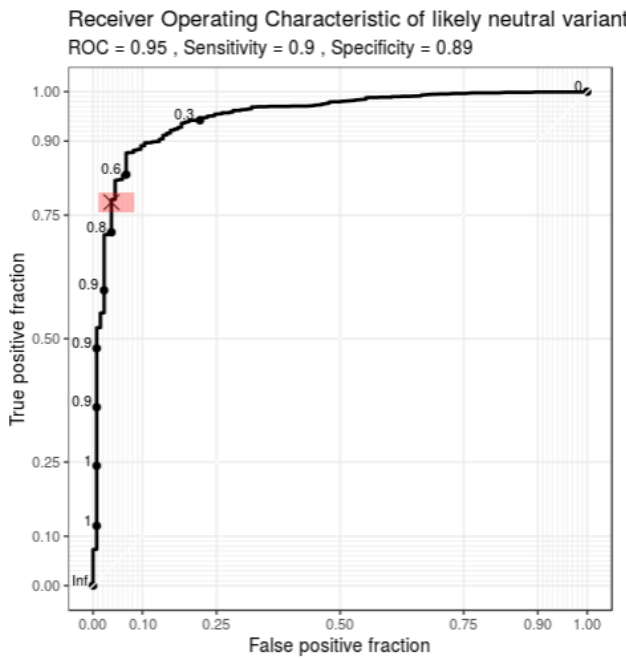
gene

SCN1A

alternative amino acid

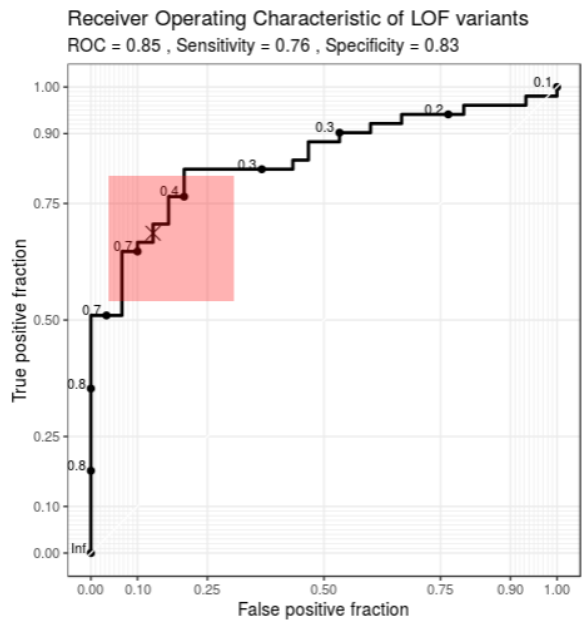
G

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) .



scn-viewer.broadinstitute.org

Inbox (1,094) - ipek... | Academic Phraseba... | (1) English Languag... | Handle Synonyms,... | 28630 English sente... | Journal of Child Ne... | European Journal of... | Brain & Developme...

SCN viewer

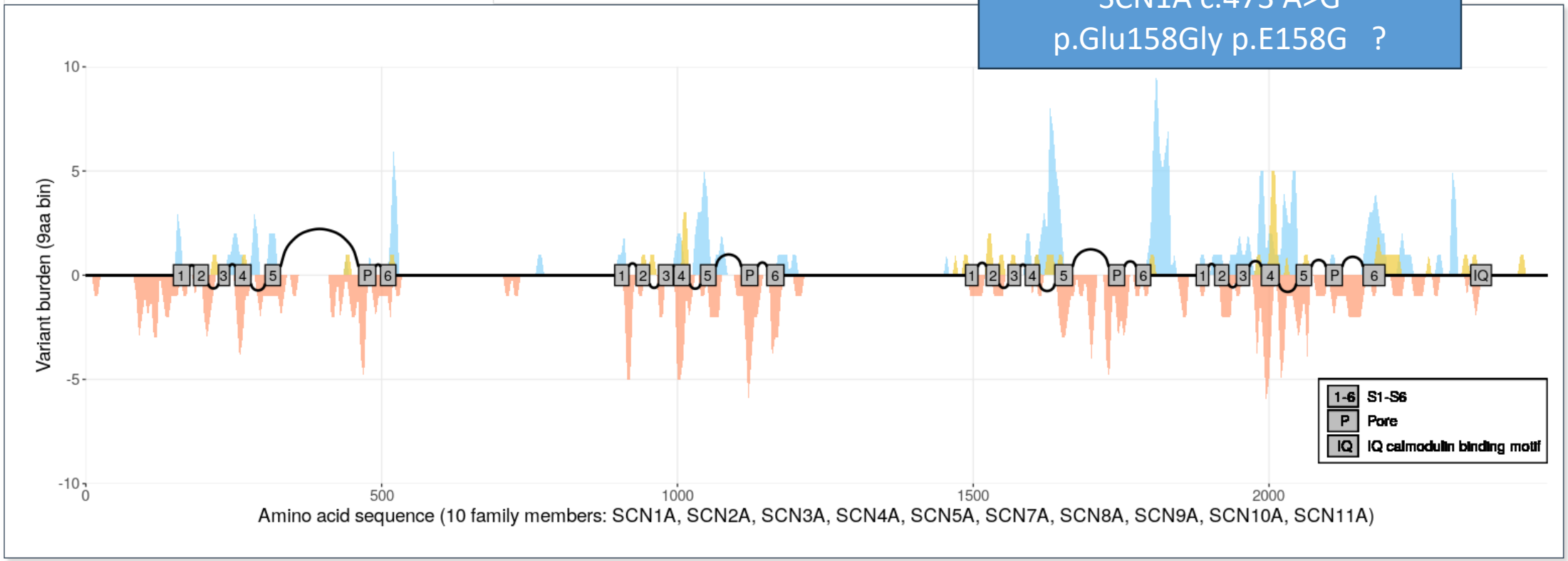
Main | About

Show variant distribution:

Gain of Function (GoF) | Loss of Function (LoF) | Mixed effects | General Population | Pathogenic/Likely Pathogenic

Voltage-Gated Sodium (SCN) gene-family alignment

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



Browse variant's fuctional effects across the aligment

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…

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