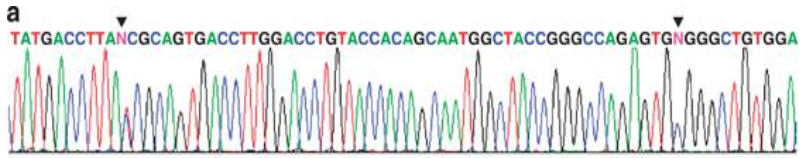
Data mining

Geert Vandeweyer
Wim Wuyts

Universiteit Antwerpen

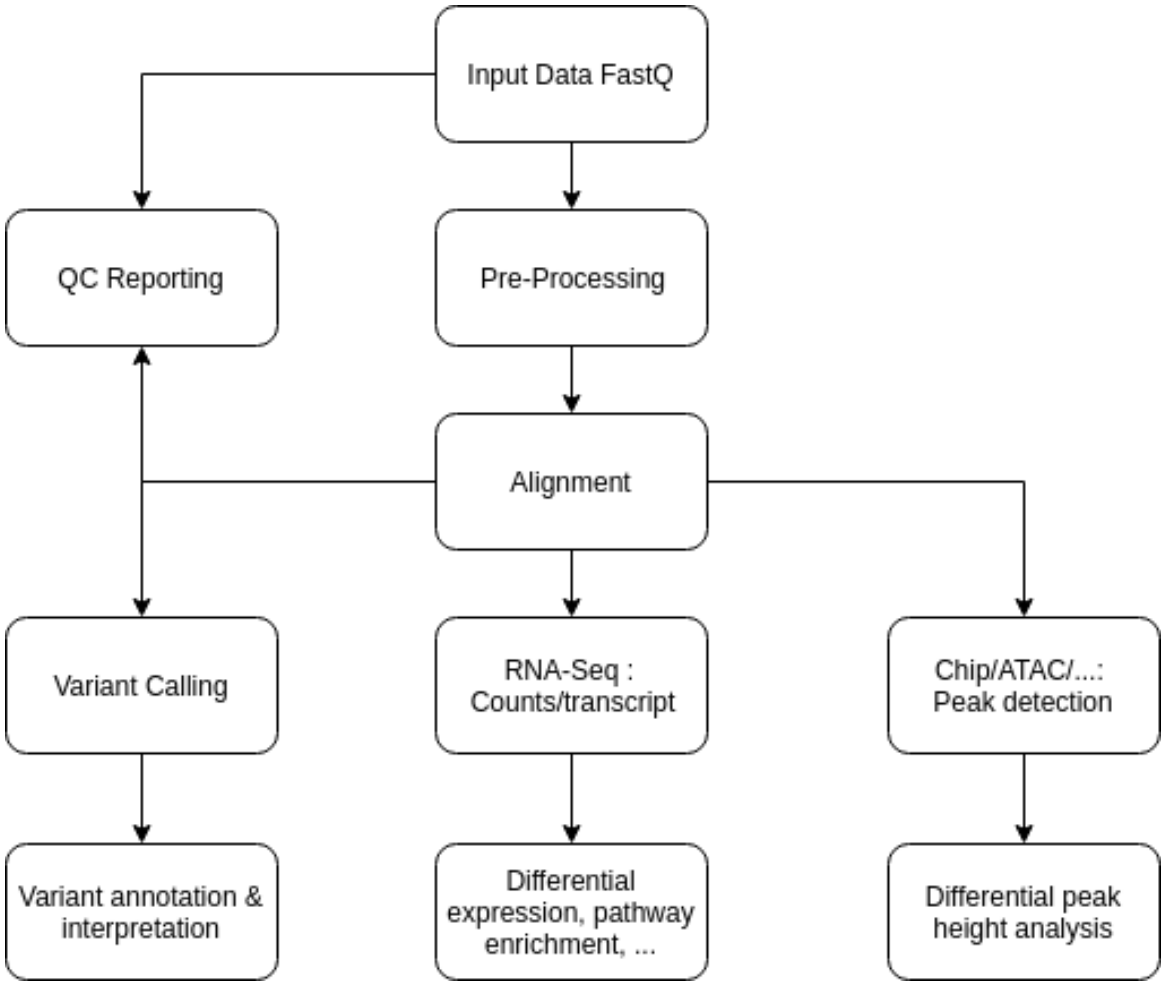
Scaling up Medical Genetics

High-Throughput Clinical Genomics

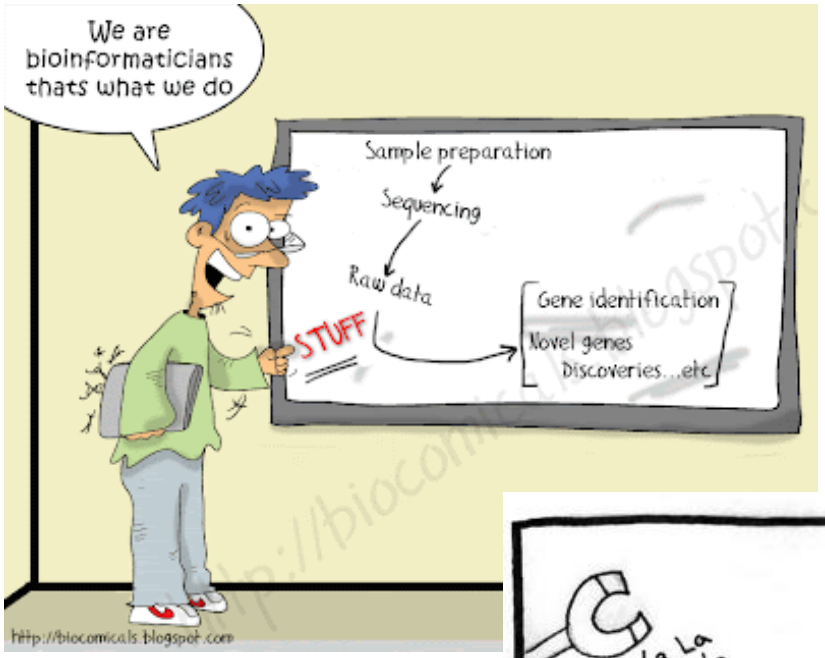


Goal 1 : Understand the data
Goal 2 : Interpret the data

NGS in Medical Genetics



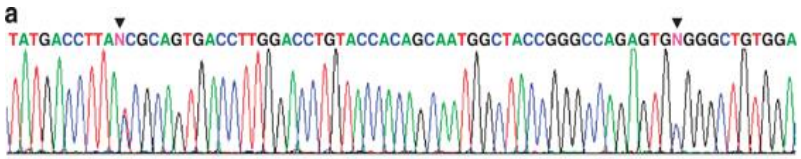
Generating Variant Data



Understand the data !

Generating Variant Data

- *Sanger Sequencing:*
  - 1 amplicon / reaction
  - 1 sequence / amplicon (or 2)
  - Visual inspection for overlapping peaks



- *Next-Generation Sequencing:*
  - Massive Parallel sequencing
    - *small* panel : few hundred targets
    - *exome* panel: > 200.000 targets
  - Multiple fragments / target
    - *optimal design:* > 40 unique fragments covering *every* nucleotide in targets.

Generating Variant Data

- Data format : FASTQ
  - FASTA :

```
>Sequence_Name
AACTACTAGATACTGATAGTATATCTCTCTTAATCGA
GCTCTAGATCGATCTATACCGAT
```

  - Add Quality (fasta-Q => FASTQ)

```
@Read_Name
 AACTACTAGATACTGATAGTATATCTCTCTTAATCGA
+
BCEECEEFFECGECGECFGFF@?<<=??<>53@##
```

=> *Phred Score :* correlates with the chance on error

Sanger Format : Quality = phred + 33, ascii-encoded
=> *Example:* Quality "B" = Phred-score "33"

Generating Variant Data

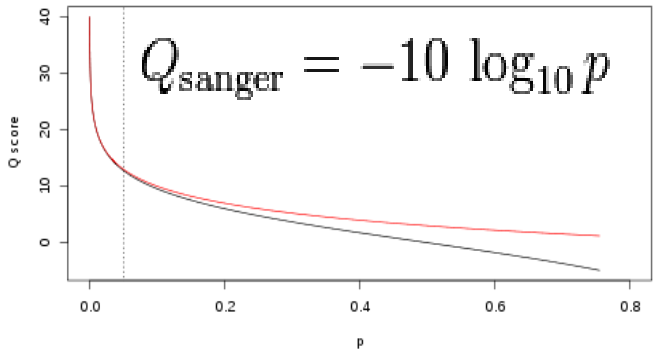
- Data format : FASTQ
  - FASTA :

```
>Sequence_Name
AACTACTAGATACTGATAGTATATCTCTCTTAATCGA
GCTCTAGATCGATCTATACCGAT
```

  - Add Quality (fasta-Q => FASTQ)

```
@Read_Name
 AACTACTAGATACTGATAGTATATCTCTCTTAATCGA
+
BCEECEEFFECGECGECFGFF@?<<=??<>53@##
```

=> *Phred Score :* correlates with the chance on error



=> *Example:*

Q30 => 1 error / 1000 nt

Q10 => 1 error / 10 nt

Generating Variant Data

Issue: artificial sequences

```
PE Adapter1:
5' -------------------- -----ACACTCTTTCCCTAC ACGACGCTCTTCCGATCT (-) -------------------- -------------------- -------------------- - 3'
3' -------------------- -----TGTGAGAAAGGGATG TGCTGCGAGAAGGCTAGp (-) -------------------- -------------------- -------------------- - 5'
PE Adapter2:
5' -------------------- -------------------- -------------------- (-) pGATCGGAAGAGCGGTTCAG CAGGAATGCCGAG------- -------------------- - 3'
3' -------------------- -------------------- -------------------- (-) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTC------- -------------------- - 5'
PE PCR Primer1:
5' AATGATACGGCGACCACCGA GATCTACACTCTTTCCCTAC ACGACGCTCTTCCGATCT (-) -------------------- -------------------- -------------------- - 3'
3' -------------------- -------------------- -------------------- (-) -------------------- -------------------- -------------------- - 5'
PE PCR Primer2:
5' -------------------- -------------------- -------------------- (-) -------------------- -------------------- -------------------- - 3'
3' -------------------- -------------------- -------------------- (-) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTCTGGCTAG AGCATACGGCAGAAGACGAA C 5'
Result Library:
5' AATGATACGGCGACCACCGA GATCTACACTCTTTCCCTAC ACGACGCTCTTCCGATCT (N) AGATCGGAAGAGCGGTTCAG CAGGAATGCCGAGACCGATC TCGTATGCCGTCTTCTGCTT G 3'
3' TTACTATGCCGCTGGTGGCT CTAGATGTGAGAAAGGGATG TGCTGCGAGAAGGCTAGA (N) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTCTGGCTAG AGCATACGGCAGAAGACGAA C 5'
PE DNA Sequencing Primer1
5' -------------------- -----ACACTCTTTCCCTAC ACGACGCTCTTCCGATCT (-) -------------------- -------------------- -------------------- - 3'
3' -------------------- -------------------- -------------------- (-) -------------------- -------------------- -------------------- - 5'
PE DNA Sequencing Primer2
5' -------------------- -------------------- -------------------- (-) -------------------- -------------------- -------------------- - 3'
3' -------------------- -------------------- -------------------- (-) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTCTGGC--- -------------------- - 5'
```

→ Sequence Read 1 ← Sequence Read 2

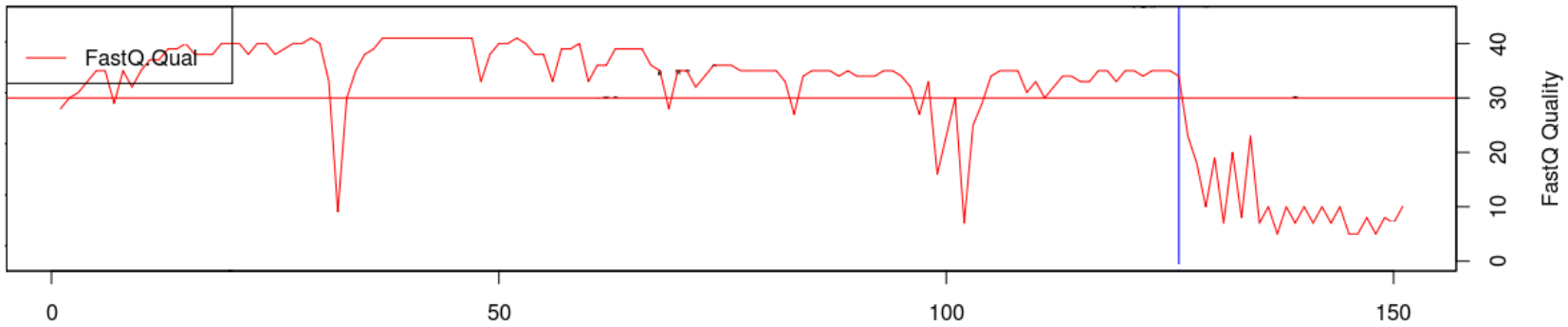
→ Sequence Barcode

Scan all reads for presence of artificial sequence & remove them from the reads

Note: Adapters are sequenced when length(Targeted fragment) < read_length

Generating Variant Data

Issue: low quality sequences



Low quality leads to high error rates (cfr Phred Score)

=> We want a limit of 1 error in 1000 positions

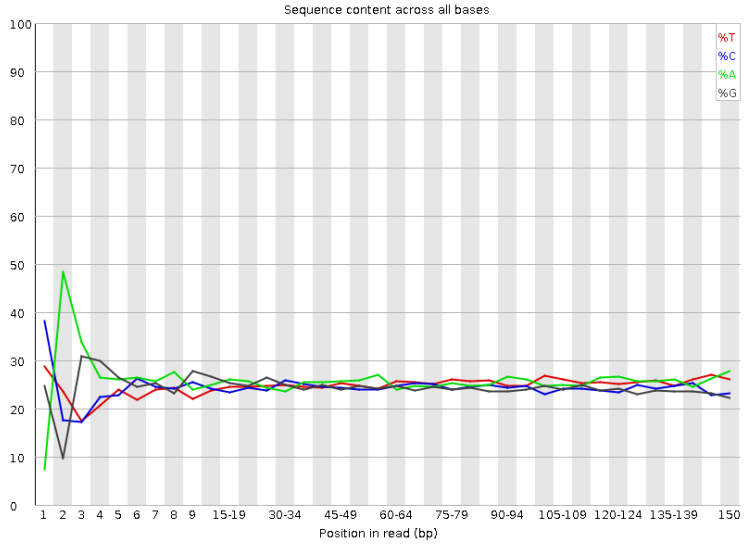
=> Due to chemical degradation, 3' ends are lower quality

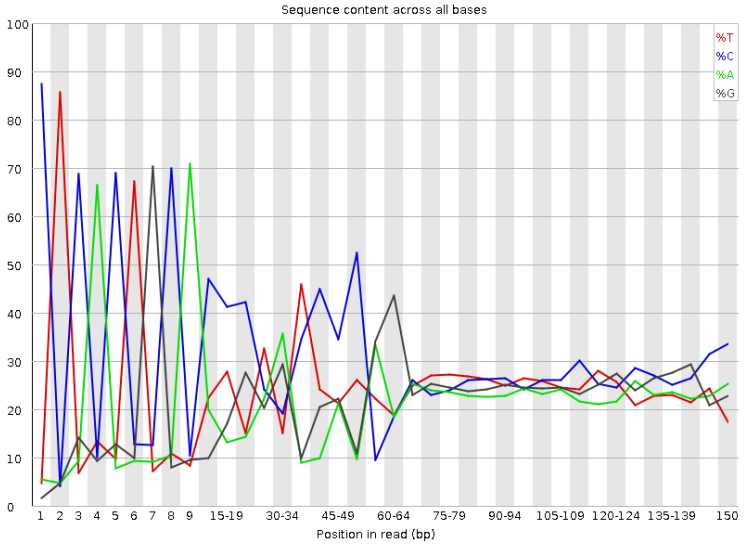
=> Trim everything on 3' end with quality < 30

Generating Variant Data

Issue: contamination ?

Base composition should be 25% for G,C,T,A

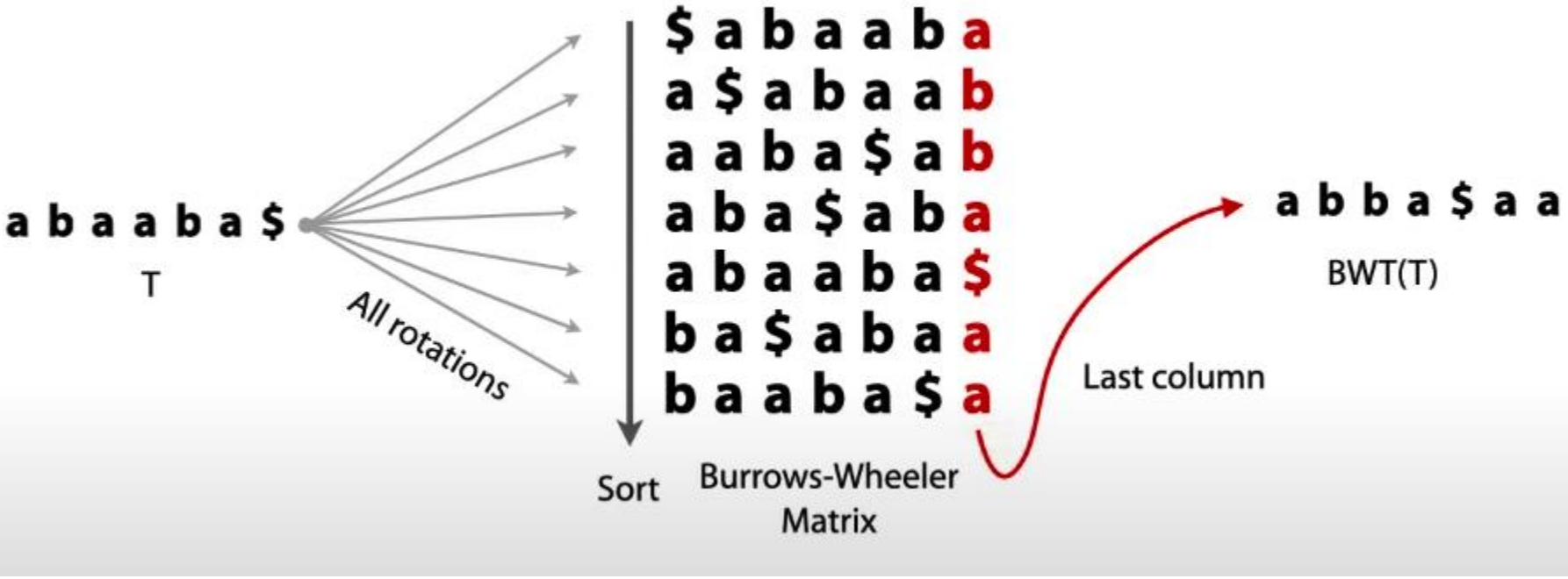




Generating Variant Data

Read Alignment

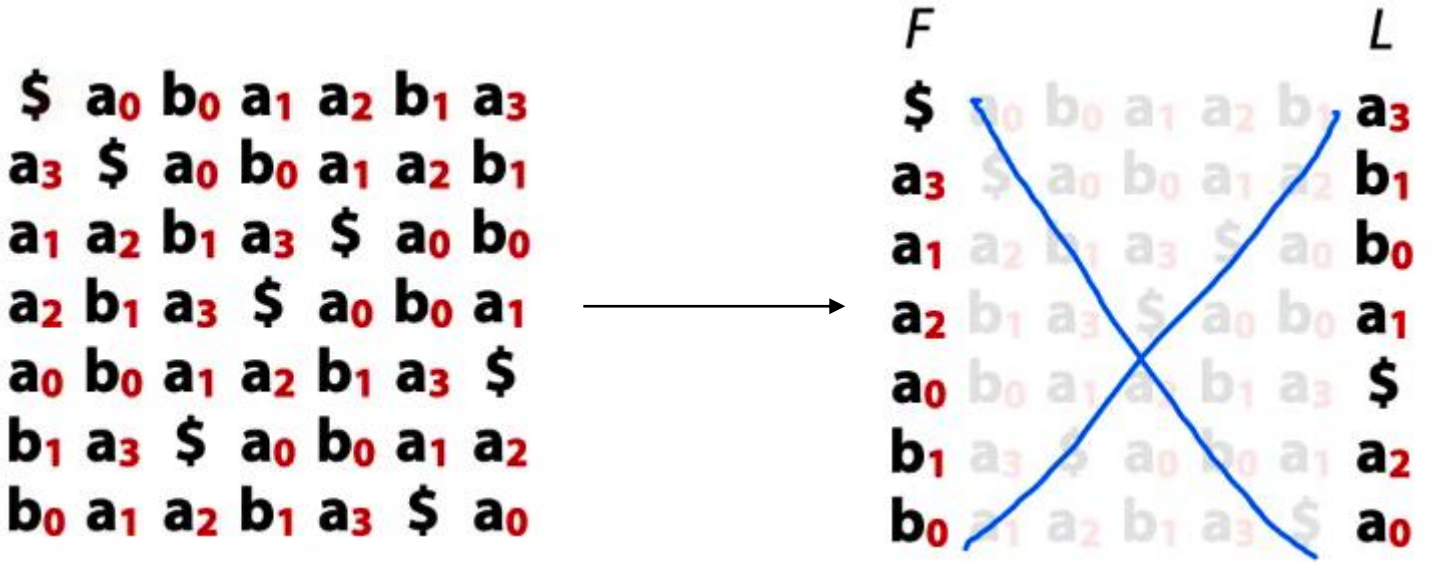
Burrows-Wheeler Transformation:



Generating Variant Data

Read Alignment

Burrows-Wheeler Transformation:

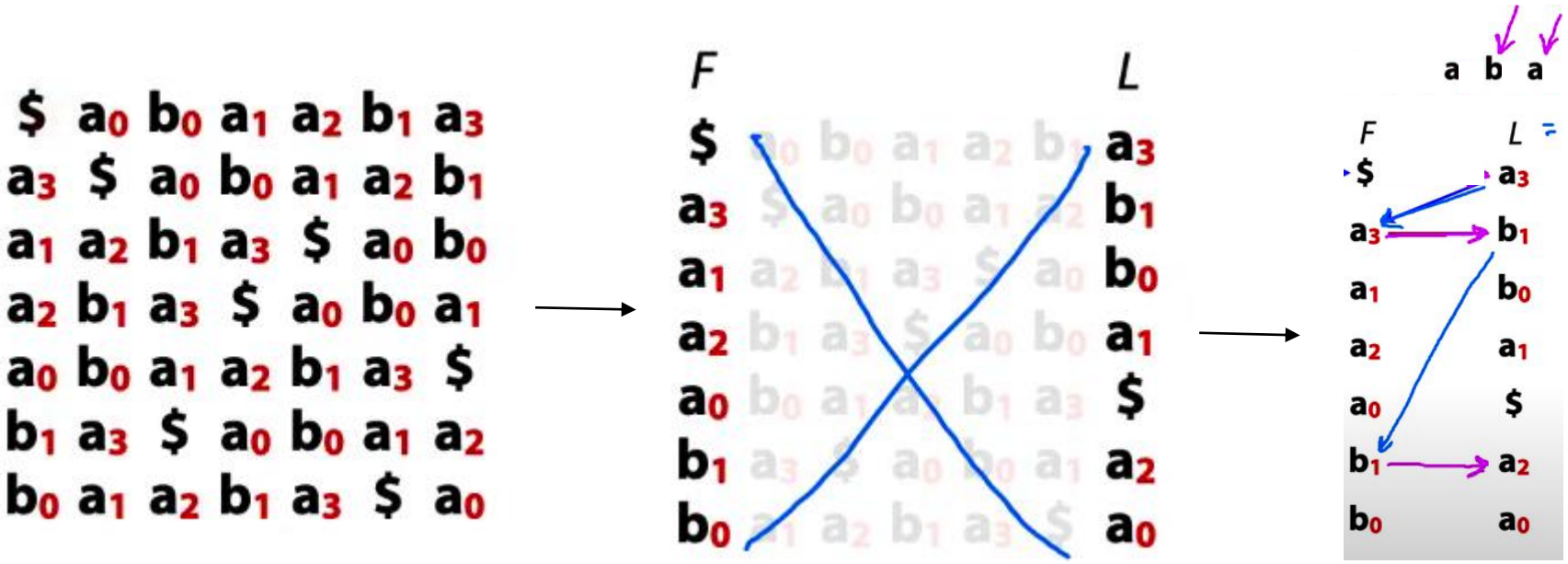


Generating Variant Data

Read Alignment

a b a a b a $

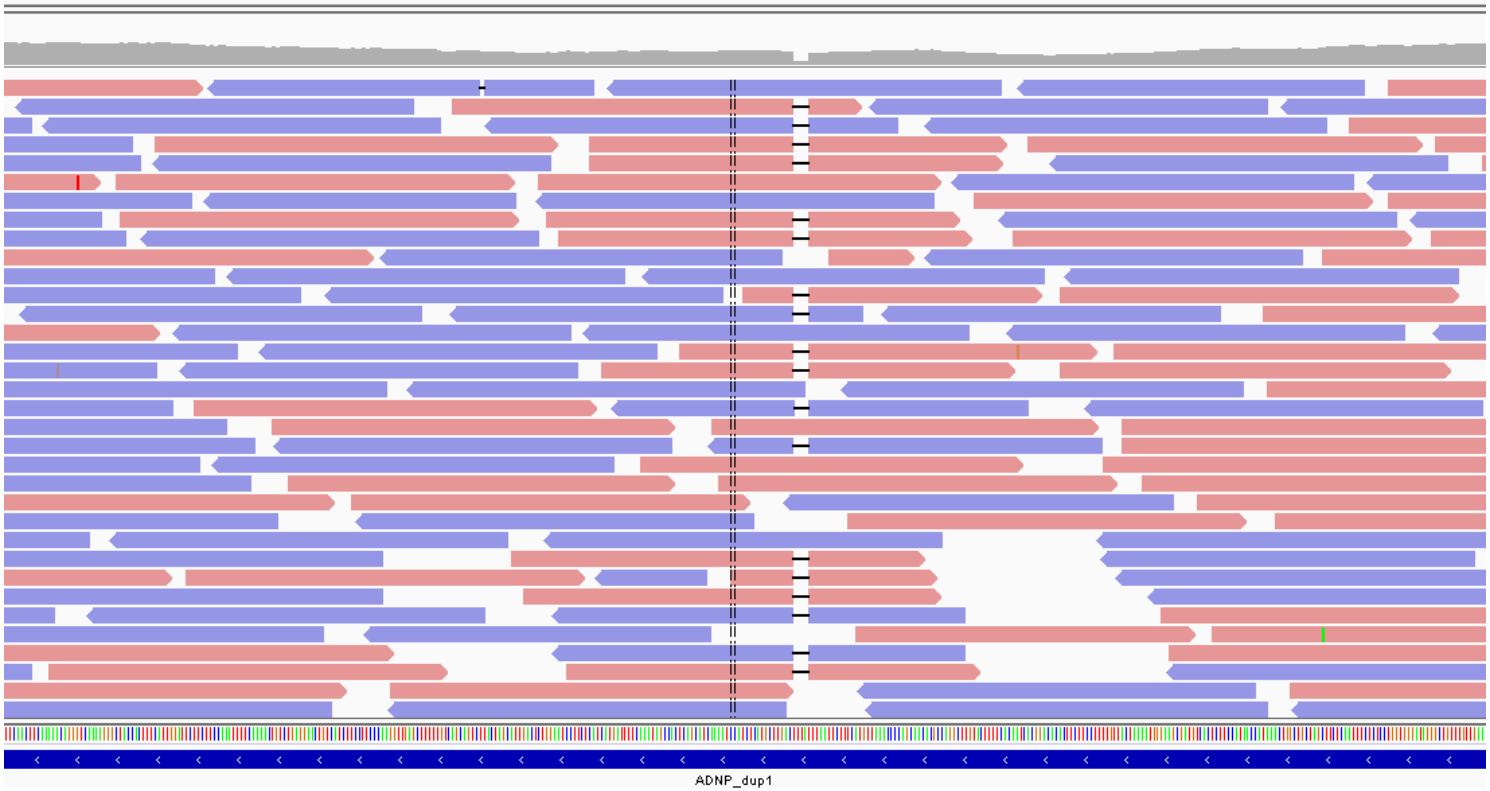
Burrows-Wheeler Transformation:



Alignment Works Back to Front !

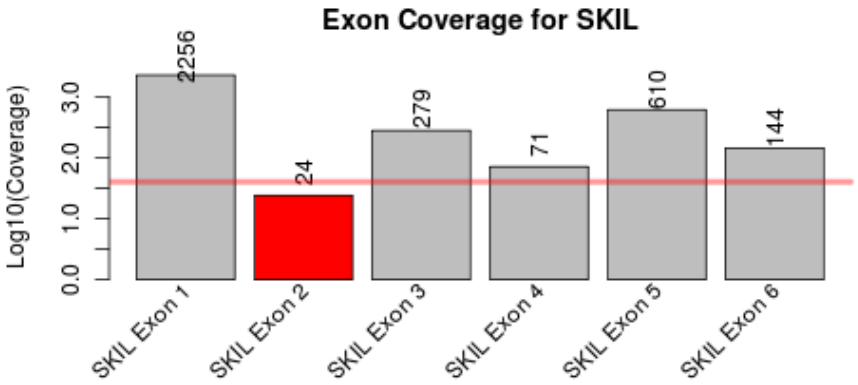
Generating Variant Data

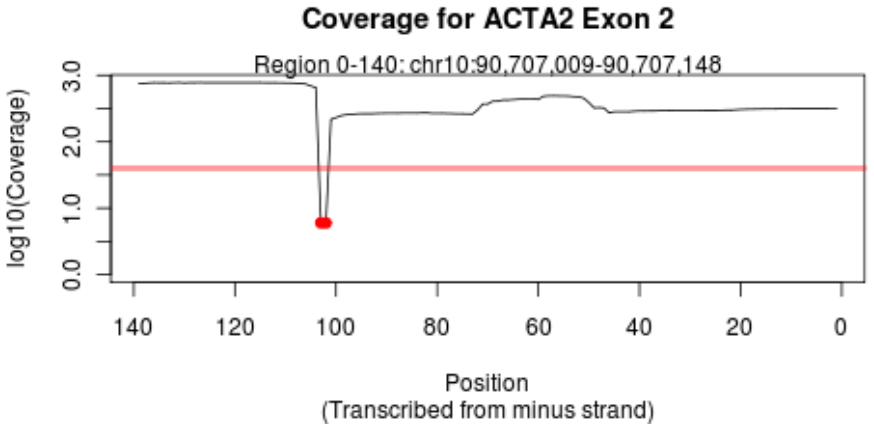
Read Alignment : Result: [BS]AM file



Generating Variant Data

Read Alignment : Quality Checks :

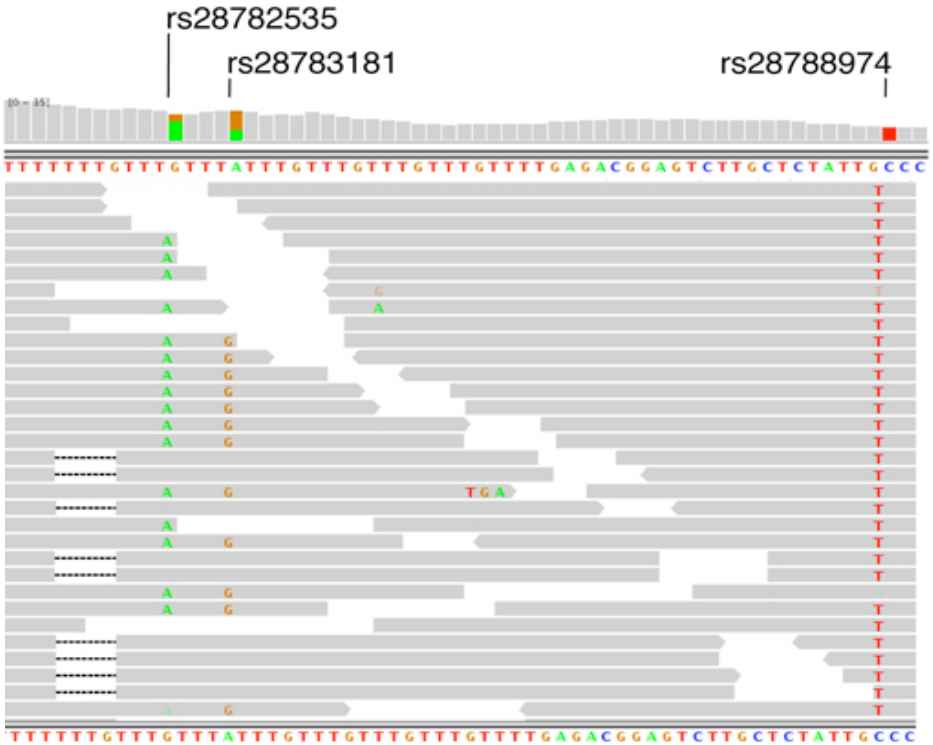


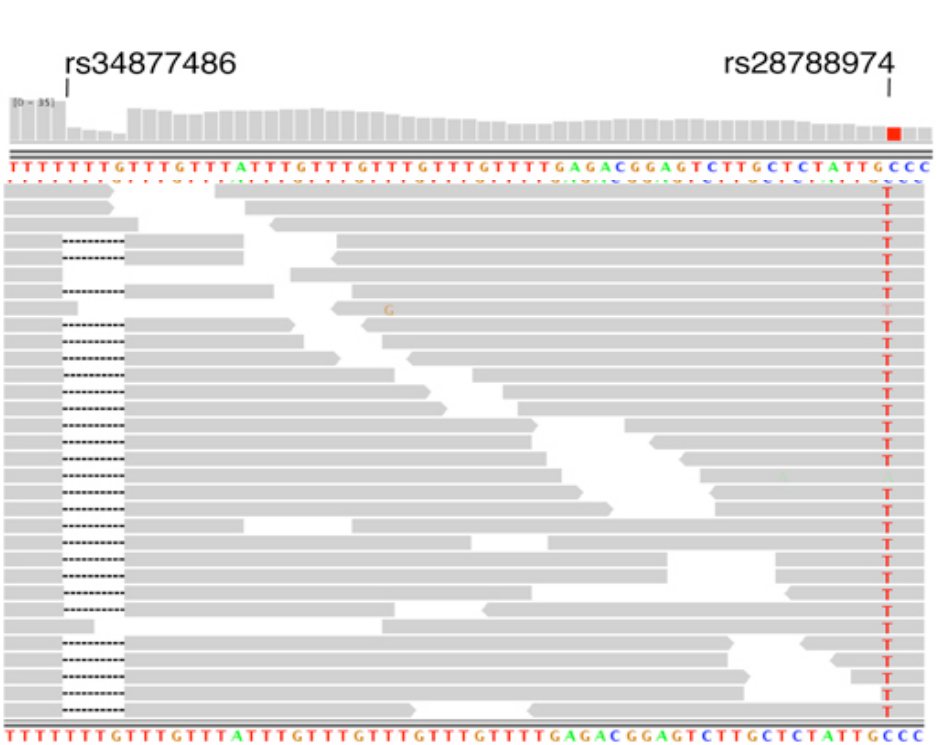


Generating Variant Data

Variant Calling: positions with statistically significant evidence for a non-reference nucleotide

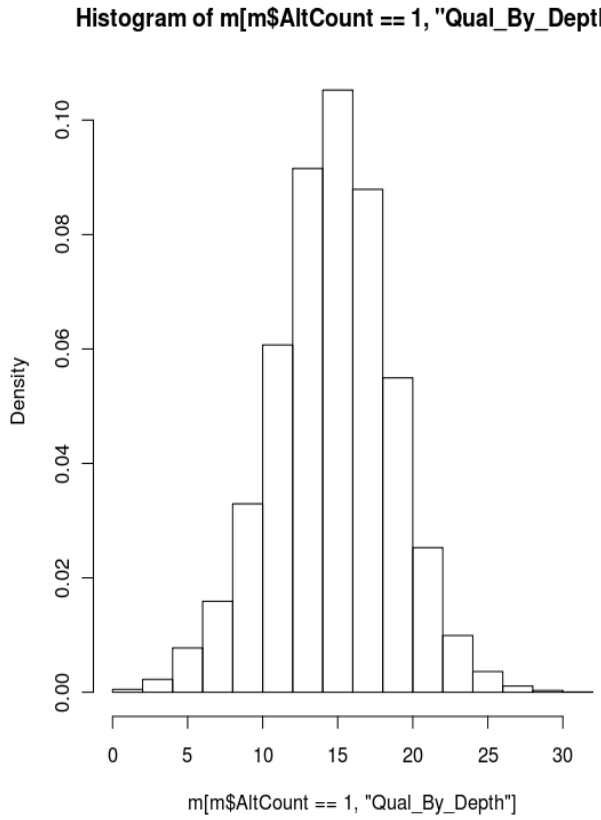
=> Visualize the "interesting" variants !

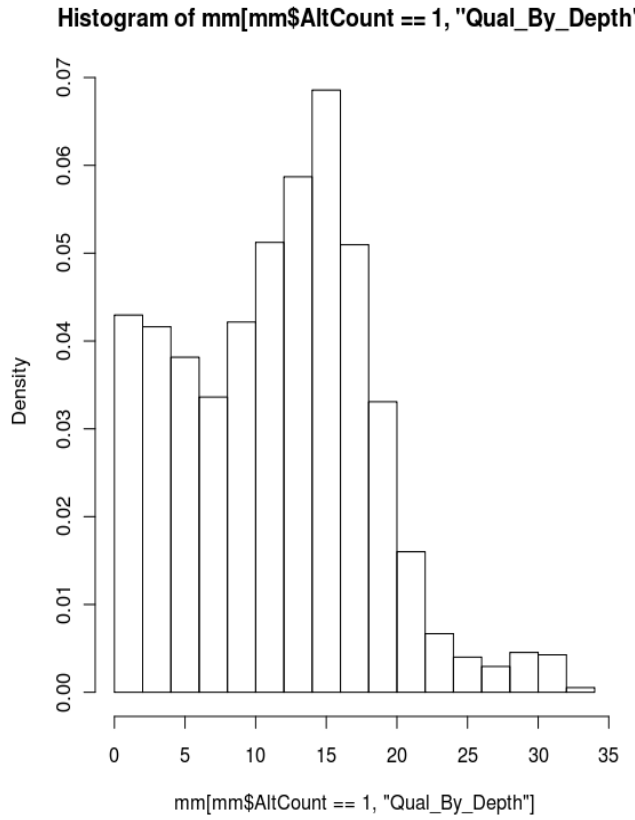




Generating Variant Data

Variant Calling: Quality Check : protocol-specific !





Variant interpretation

mut DB	In...	Gene	Transcript	Name	L...	Nuc Change	Coverage	A...	C.	Annotation	H.	web Ref.	c. HGVS	p. HGVS
☐	1	CACNA1D	NM_000720.4	CACNA1D-E07...	E7	G -> C (het)	46% (50) [47% (28) / 44% (22)]	A...	S.	missense, ...		rs1026156097 (dbSNP)	c.928G>C	p.(Ala310Pro)
☐	2	CD164	NM_006016.6	CD164-E01-NM	E1	G -> T (het)	47% (61) [49% (34) / 44% (27)]	5'...	S.	5' UTR, exon		rs1400159381 (dbSNP)	c.-66G>T	
☑	3	CDH23	NM_022124.6	CDH23-E24-NM	E24	G -> A (het)	51% (95) [50% (41) / 52% (54)]	P ...	S.	synonymou...		rs570110527 (ClinVar; ...	c.2712G>A	p.(Pro904=)
☐	4	CEP250	NM_007186.6	CEP250-E18	E18	G -> A (het)	44% (94) [41% (41) / 47% (53)]	V...	S.	missense, ...		rs754323656 (dbSNP; g...	c.2242G>A	p.(Val748Met)
☐	5	HARS2	NM_012208.4	HARS2-E07-NM	E7	G -> A (het)	38% (65) [42% (38) / 34% (27)]	R...	S.	missense, ...		rs780173856 (dbSNP; g...	c.644G>A	p.(Arg215Gln)
☑	6	MYH14	NM_0011458...	MYH14-E02-NM	E2	G -> T (het)	52% (119) [53% (64) / 51% (5...	G...	S.	synonymou...		rs181055215 (ClinVar; ...	c.192G>T	p.(Gly64=)
☑	7	OTOG	NM_0012772...	OTOG-E54-NM	E54	C -> T (het)	42% (87) [44% (47) / 41% (40)]	R...	S.	missense, ...		rs191662816 (ClinVar; ...	c.8512C>T	p.(Arg2838Cys)
☑	8	PI4KB	NM_002651.4	PI4KB-E03	E3	T -> C (ho...	100% (234) [100% (116) / 100...	D...	S.	synonymou...		rs1752379 (ExAC; dbSN...	c.603T>C	p.(Asp201=)
☑	9	PI4KB	NM_002651.4	PI4KB-E03	E3	C -> T (het)	49% (87) [47% (43) / 50% (44)]	D...	S.	synonymou...		rs1056847 (ExAC; dbSN...	c.822C>T	p.(Asp274=)
☐	10	PTPRQ	ENST000006...	PTPRQ-E41-2	E41	A (het)	16% (9) [17% (4) / 14% (5)]		S.	intron		rs770656462 (gnomAD)...	c.6453+12dup	
☑	11	TPRN	NM_0011282...	TPRN-E01-NM	E1	GCC (het)	17% (4) [18% (2) / 17% (2)]	P...	S.	inframe_del...		rs957768814 (dbSNP; g...	c.489_491del	p.(Pro164del)

☐ **20 Variants** in **20 Genes** were found

★ Knobloch syndrome 1 was found to have a **Very High** connection to the case

VUS **COL18A1** — Heterozygote — p.T60I | c.179C>T

FREQUENCY	INTERNAL	COMMUNITY
0.01%	0.00%	55
0 Hom	null Hom	1 Hom

Chr21:46875623-C-T | NM_130444.3 | Missense | Exon 1

★ Myopia 24, autosomal dominant (Autosomal Dominant) was found to have a

LP **SLC39A5** — Heterozygote — p.H377Tfs*26 | c.1128del

FREQUENCY	INTERNAL	COMMUNITY
N/A	0.00%	15
	null Hom	

Chr12:56630448-TG-T | NM_173596.3 | Fr...

★ Stickler syndrome, iia 6 was found to

VUS **COL9A3** — Heterozygote — p.R103W | c.307C>T

362	264736	CABP2	NM_016366.3	E2	51% (151) [48% (78) / 54% (73)]	c.117G>A	p.(Gly39=)
363	264736	CLRN1	NM_174878.3	E1	53% (107) [53% (49) / 53% (58)]	c.183G>T	p.(Met61Ile)
364	264736	ESRP1	NM_017697.4	E8	39% (32) [43% (17) / 36% (15)]	c.756-12T>A	
365	264736	GSDME	NM_004403.3	E5	55% (101) [56% (53) / 54% (48)]	c.630G>A	p.(Glu210=)
366	264736	LOXHD1	NM_144612.6	E32	52% (76) [54% (36) / 51% (40)]	c.5023C>T	p.(Arg1675Cys)
367	264736	MCM2	NM_004526.4	E2	51% (75) [54% (49) / 46% (26)]	c.15G>A	p.(Ser5=)
368	264736	MYO15A	NM_016239.4	E54	100% (106) [100% (50) / 100% (56)]	c.9229+1G>A	
369	264736	OTOA	NM_144672.3	E18	40% (51) [44% (26) / 37% (25)]	c.1998G>A	p.(Arg666=)
370	264736	OTOG	NM_001277269.2	E35	50% (88) [59% (46) / 43% (42)]	c.5146G>A	p.(Ala1716Thr)
371	264736	PDZD7	NM_001195263.2	E15	39% (82) [40% (44) / 39% (38)]	c.2411C>T	p.(Ala804Val)
372	264736	PI4KB	NM_002651.4	E3	100% (211) [99% (97) / 100% (114)]	c.603T>C	p.(Asp201=)
373	264736	PI4KB	NM_002651.4	E3	100% (151) [100% (78) / 100% (73)]	c.822C>T	p.(Asp274=)
374	264736	REST	NM_005612.5	E4	38% (54) [37% (28) / 39% (26)]	c.2855A>G	p.(Asp952Gly)
375	264736	TRIOBP	NM_001039141.3	E23	45% (64) [48% (34) / 43% (30)]	c.7059C>G	p.(Leu2353=)
376	264736	USH1G	NM_173477.5	E3	55% (70) [54% (30) / 56% (40)]	c.*49C>T	

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ACMG classification

	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 In-frame indels in repeat w/out known function BP3	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	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and 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			

ACMG classification

		BENIGN CRITERIA		PATHOGENIC CRITERIA			
Strength of evidence		Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Odds of Pathogenicity*		–18.7	–2.08	2.08	4.33	18.7	350.0
Evidence Category and Corresponding ACMG/AMP Codes	Population Data	*BA1*† BS1 BS2			PM2	PS4	
	Allelic Evidence & Cosegregation Data	BS4	BP2 BP5	PP1 →	PM3 PM6	PS2	
	Computation & Predictive Data		BP1 BP3 BP4 BP7	PP2 PP3	PM1 PM4 PM5	PS1	PVS1
	Functional Data	BS3				PS3	
	Other		BP6	PP4 PP5			

Variant classification

Variant classification categories and their probabilistic boundaries

Category	Posterior-Probability (PP) based boundaries
Pathogenic	PP > 0.99
Likely Pathogenic	0.99 ≥ PP > 0.90 †
Uncertain	0.10 ≤ PP ≤ 0.90
Likely Benign	0.001 ≤ PP < 0.10 †
Benign	PP < 0.001.

ACMG variant classification

Point values for ACMG/AMP strength of evidence categories

Evidence Strength	Point Scale Pathogenic	Benign
Indeterminate	0	0 §
Supporting	1	−1
Moderate	2	−2 †
Strong	4	−4
Very Strong	8	−8 †

Point based variant classification categories

Category	Point ranges
Pathogenic	≥ 10
Likely Pathogenic	6 – 9 ¥
Uncertain	0 – 5
Likely Benign	−1 – −6 ¥
Benign	≤ −7

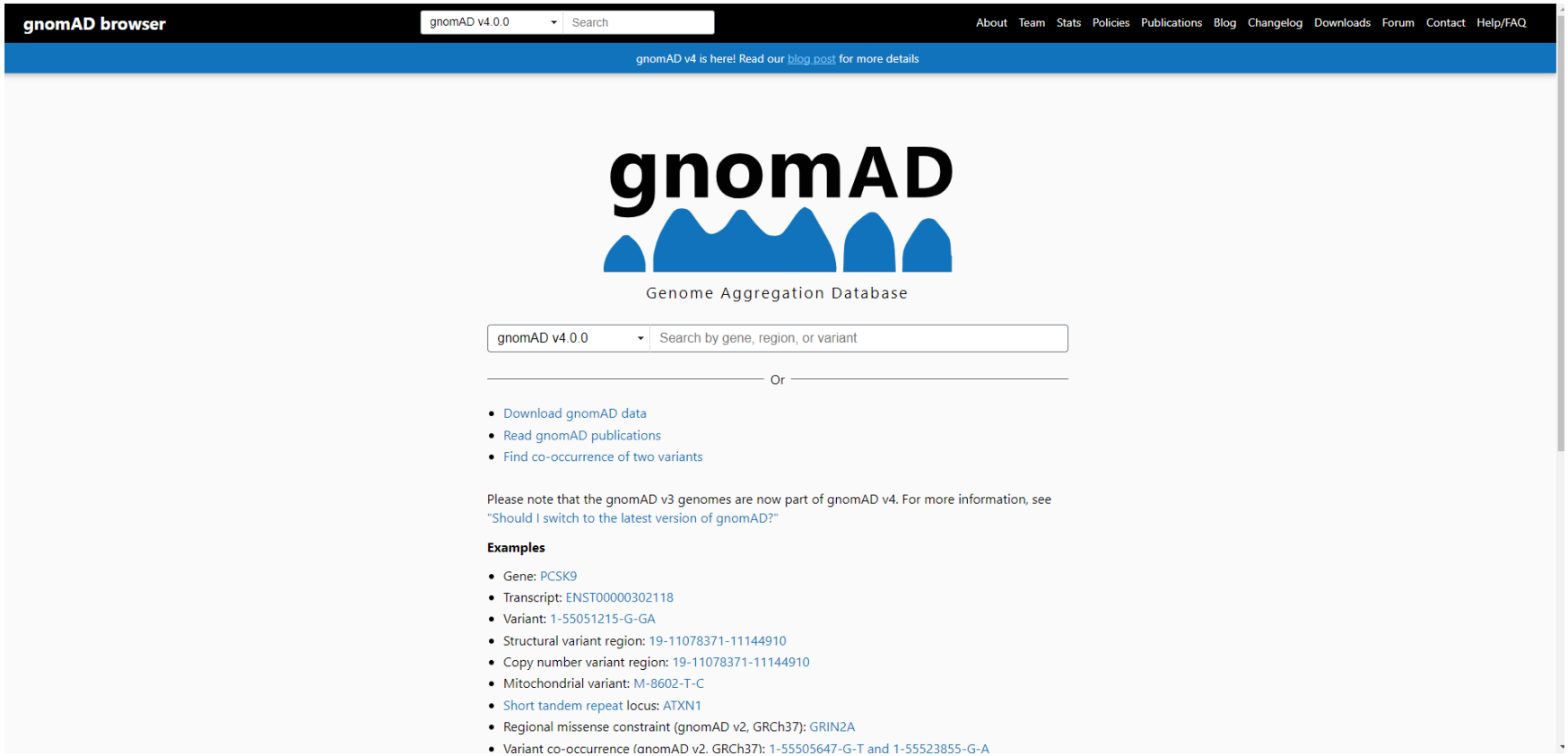
Population data

Exclude a variant as being pathogenic based on its population frequency (BA1/BS1)

- frequency
- inheritance model
- penetrance

Supporting for possible pathogenic effect (PM2)

https://gnomad.broadinstitute.org/

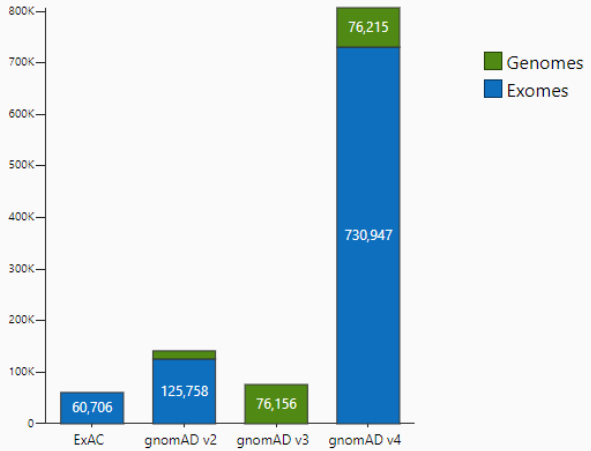


gnomAD

What's in gnomAD

gnomAD v4 includes 807,162 individuals

- 730,947 exomes
- 76,215 genomes



v4 variants

Short variants

- Total SNVs: 786,500,648
- Total InDels: 122,583,462
- Variant type* counts
  - Synonymous: 9,643,254
  - Missense: 16,412,219
  - Nonsense: 726,924
  - Frameshift: 1,186,588
  - Canonical splice site: 542,514

**This is only a subset of commonly asked for variant types from the dataset.*

Structural variants

- 1,199,117 genome SVs
  - 627,947 Deletions
  - 258,882 Duplications
  - 711 CNVs
  - 296,184 Insertions
  - 2,185 Inversersions
  - 13,116 Complex
  - 92 Canonical recriprocal translocations
- 66,903 rare (<1% site frequency (SF)) exome CNVs
  - 30,877 Deletions
  - 36,026 Duplications

gnomAD

Study Diseases in gnomAD

During the sample aggregation phase of v4 we began collecting study-disease of interest and case/control status at the individual level. This enabled us to provide a better sense of the phenotype breakdown in gnomAD (see table below). While we are provided high level study phenotype and case/control status for some exome samples, **we do not have comprehensive phenotype metadata for gnomAD samples** and many samples are now derived from large biobanks which can include individuals with disease.

Phenotypes	Case	Control	Unknown	Total	% of cases out of all v4 exomes
Alzheimer's disease	2,594	665	1,632	4,890	0.35%
Atrial Fibrillation	4,398	3,546	38,289	46,233	0.60%
Biobank or control dataset*	-	24,016	447,750	471,766	N/A
Bipolar disorder	19,284	16,383	80	35,747	2.64%
Cardiac arrhythmia	458	-	-	458	0.06%
Coronary heart disease	1,557	-	-	1,557	0.21%
Inflammatory bowel disease spectrum and related disorders^	35,008	11,928	280	47,217	4.79%
Myocardial infarction	11,900	369	-	12,269	1.63%
Neurodevelopmental**	-	132	-	143	N/A
Non-specific cardiovascular disease	1,888	11,376	15,000	28,264	0.26%
Schizophrenia spectrum and related disorders	30,278	17,689	39	47,994	4.14%
Type 2 Diabetes	17,506	13,096	3,807	34,409	2.39%
Grand Total	**124,871**	**99,200**	**506,877**	**730,947**	**17.08%**

* This category includes: GTEx, 1KG, UKBB, and the Qatar Genome Project, as well as the FinnGen and MGB biobank samples when no phenotype was specified
^ includes diseases like Crohn's disease, irritable bowel syndrome, interstitial cystitis, ulcerative colitis
** Neurodevelopmental controls are unaffected parents of children with confirmed or suspected de novo cause of their neurodevelopmental disorder

gnomAD


BRCA2 BRCA2 DNA repair associated
Dataset gnomAD v3.1.2
Genome build GRCh38 / hg38
Ensembl gene ID ENSG00000139618.17
MANE Select transcript ENST00000380152.8 / NM_000059.4
Ensembl canonical transcript ENST00000380152.8
Other transcripts ENST00000470094.1, ENST00000528762.1, and 7 more
Region 13:32315086-32400268
External resources Ensembl, UCSC Browser, and more
Constraint
Variant co-occurrence
Constraint not yet available for gnomAD v3.1.2.
Zoom in
100
90
80
70
60
50
40
30
20
10
Include:
Coding regions (CDS
GRCh38
gnomAD v4.0.0
807,162 samples
gnomAD v3.1.2
76,156 samples
gnomAD v3.1.2 (non-cancer)
74,023 samples
gnomAD v3.1.2 (non-neuro)
67,442 samples
gnomAD v3.1.2 (non-v2)
57,344 samples
gnomAD v3.1.2 (non-TOPMed)
40,433 samples
gnomAD v3.1.2 (controls/biobanks)
16,465 samples
GRCh37
gnomAD v2.1.1
141,456 samples
gnomAD v2.1.1 (non-TOPMed)
135,743 samples
gnomAD v2.1.1 (non-cancer)
134,187 samples
gnomAD v2.1.1 (non-neuro)
114,704 samples
gnomAD v2.1.1 (controls)
60,146 samples
ExAC v1.0
60,706 samples

gnomAD

SNV: 16-49670211-G-A(GRCh37)

Copy variant ID | Gene page | Dataset: gnomAD v2.1.1

	Exomes	Genomes	Total
Filters	Pass	Pass	
Allele Count	77	14	91
Allele Number	249876	31376	281252
Allele Frequency	0.0003082	0.0004462	0.0003236
Grpmax Filtering AF (95% confidence)	0.0004720	0.0004487	
Number of homozygotes	0	0	0
Mean depth of coverage	78.0	32.1	

External Resources

- dbSNP (rs200057861)
- UCSC
- ClinVar (836139)
- ClinGen Allele Registry (CA8046416)

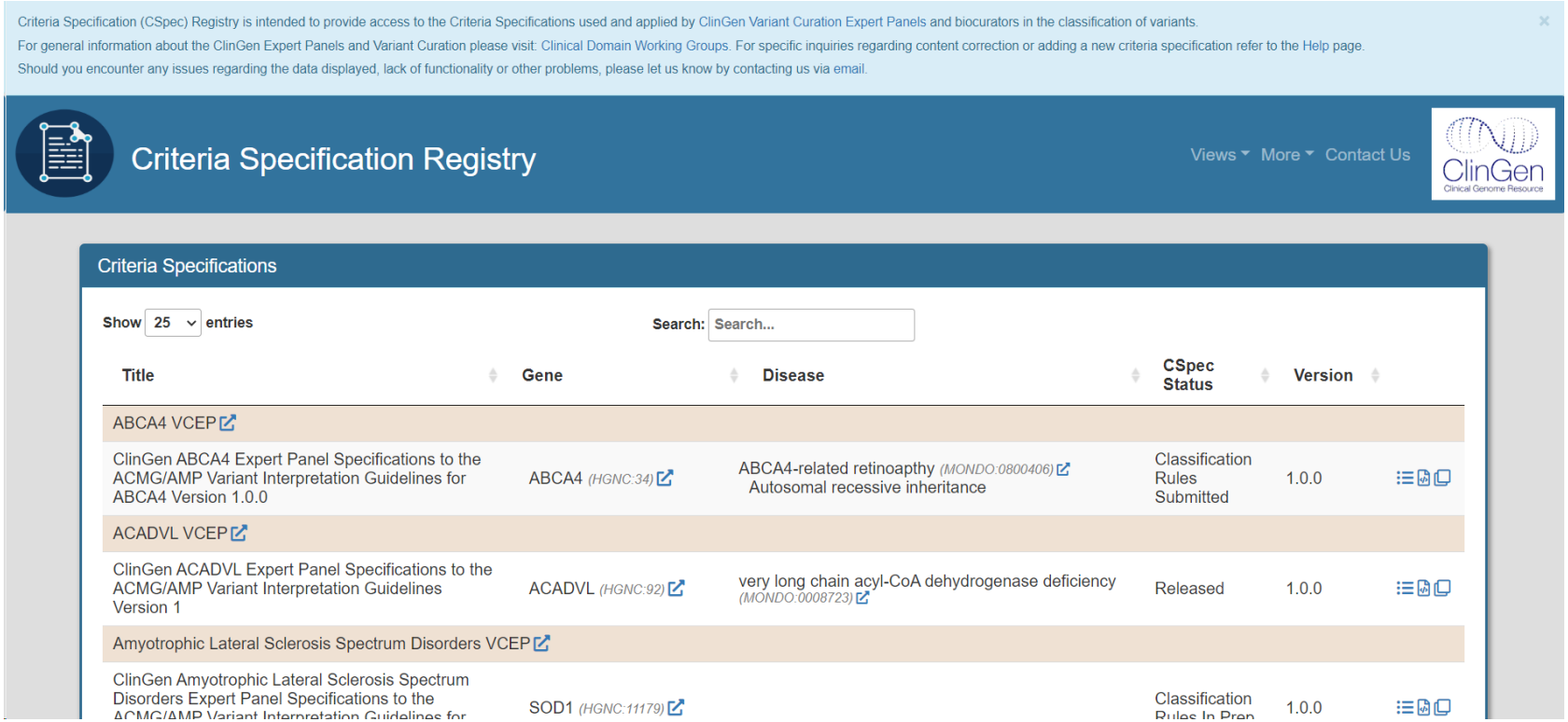
Feedback

Report an issue with this variant

Genetic Ancestry Group Frequencies

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (non-Finnish)	78	128152	0	0.0006087
Admixed American	7	35414	0	0.0001977
African/African American	4	24816	0	0.0001612
Remaining individuals	1	7206	0	0.0001388
South Asian	1	30614	0	0.00003266
Ashkenazi Jewish	0	10336	0	0.000
East Asian	0	19936	0	0.000
European (Finnish)	0	24778	0	0.000
XX	39	128348	0	0.0003039
XY	52	152904	0	0.0003401
Total	**91**	**281252**	**0**	**0.0003236**

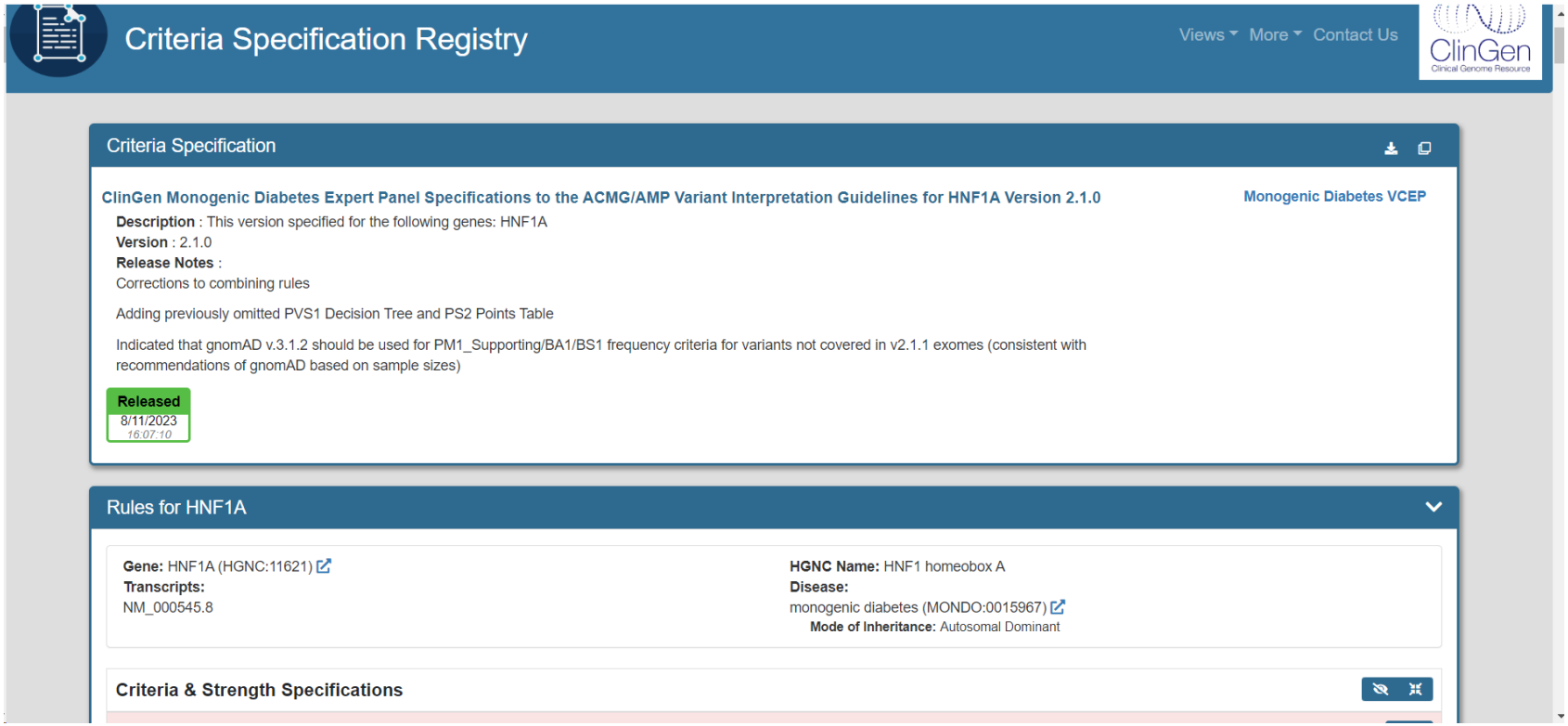
https://cspec.genome.network/cspec/ui/svi/



https://cspec.genome.network/cspec/ui/svi/

Cardiomyopathy VCEP					
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1	MYH7 *(HGNC:7577)*		Released	1.0.0	
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MYBPC3 Version 1.0.0	MYBPC3 *(HGNC:7551)*	hypertrophic cardiomyopathy *(MONDO:0005045)* Autosomal dominant inheritance	Pilot Rules In Prep	1.0.0	
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TNNI3 Version 1.0.0	TNNI3 *(HGNC:11947)*	hypertrophic cardiomyopathy *(MONDO:0005045)* Autosomal dominant inheritance	Pilot Rules In Prep	1.0.0	
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TNNT2 Version 1.0.0	TNNT2 *(HGNC:11949)*	dilated cardiomyopathy *(MONDO:0005021)* Autosomal dominant inheritance hypertrophic cardiomyopathy *(MONDO:0005045)* Autosomal dominant inheritance	Pilot Rules In Prep	1.0.0	
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TPM1 Version 1.0.0	TPM1 *(HGNC:12010)*	hypertrophic cardiomyopathy *(MONDO:0005045)* Autosomal dominant inheritance	Pilot Rules In Prep	1.0.0	
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ACTC1 Version 1.0.0	ACTC1 *(HGNC:143)*	hypertrophic cardiomyopathy *(MONDO:0005045)* Autosomal dominant inheritance	Pilot Rules In Prep	1.0.0	
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MYL2 Version 1.0.0	MYL2 *(HGNC:7583)*	hypertrophic cardiomyopathy *(MONDO:0005045)* Autosomal dominant inheritance	Pilot Rules In Prep	1.0.0	
ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MYL3 Version 1.0.0	MYL3 *(HGNC:7584)*	hypertrophic cardiomyopathy *(MONDO:0005045)* Autosomal dominant inheritance	Pilot Rules In Prep	1.0.0	

VCEP specifications



VCEP specifications

BA1

Original ACMG Summary

Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes or Exome Aggregation Consortium.

Stand Alone

MAF ≥ 1:10,000 (≥ 0.01% or 0.0001) in gnomAD 2.1.1* Popmax Filtering AF.

*Use gnomAD 2.1.1 exome data unless the region is not covered in the exome, in which case gnomAD 3.1.2 genome data should be used.

Modification Type: Gene-specific

BS1

Original ACMG Summary

Allele frequency is greater than expected for disorder.

Strong

MAF ≥ 1:30,000 (≥0.0033% or 0.000033) in gnomAD 2.1.1* Popmax Filtering AF.

*Use gnomAD 2.1.1 exome data unless the region is not covered in the exome, in which case gnomAD 3.1.2 genome data should be used.

Modification Type: Gene-specific

BS2

Original ACMG Summary

Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age.

Strong

Apply to normoglycemic individuals age 70 or older (i.e., genotype positive, phenotype negative)

VCEP specifications

Comparison of population frequency thresholds from ClinGen Variant Curation Expert Panels.

	Criteria	Prevalence	Heterogeneity	Penetrance	Threshold
Cardiomyopathy (AD)	**BA1**	1:200	10.60% [L]	30%	0.001 (0.1%)
	BS1		2% [A]		0.0002 (0.02%)
	PM2	1:500		50%	<0.00004 (0.004%)
RASopathy (AD)	**BA1**	1:2500	100%	40%	0.0005 (0.05%)
	BS1		50% [L]		0.00025 (0.025%)
	PM2	-	-	-	Absent [R]
***CDH1* (AD)**	**BA1**	1:800	100%	30%	0.002 (0.2%)
	BS1	1:1250			0.001 (0.1%)
	PM2	-	-	-	<0.00001 (0.001%) [R]
Hearing Loss (AD)	**BA1**	1:30	5% [L/A]	80%	0.001 (0.1%)
	BS1	1:150			0.0002 (0.02%)
	PM2	-	-	-	<0.00002 (0.002%) [M]
Hearing Loss (AR)	**BA1**	1:200	7.2% [A]	100%	0.005 (0.5%)
	BS1		4.4% [A]		0.003 (0.3%)
	PM2	-	-	-	<0.00007 (0.007%) [M]
***PAH* (AR)**	**BA1**	1:5000	90% [L]	80%	0.015 (1.5%)
	BS1		2% [A]		0.002 (0.2%)
	PM2	-	-	-	<0.0002 (0.02%) [M]
***PTEN*[*] (AD)**	**BA1**	-	-	-	0.01 (1%)
	BS1	-	-	-	0.001 (0.1%)
	PM2	-	-	-	<0.00001 (0.001%) [R]

Computional and predictive data

Loss of function (if LoF is disease mechanism!) (PVS1)

Strong

Use HNF1A PVS1 decision tree.

- Variants generating PTCs 3' of c.1714 of NM_000545.8, which includes the last 55 nucleotides of exon 9 and all of exon 10, are not expected to cause NMD (PMID: 24274751). The transactivation domain (TAD) of the protein overlaps with this region. The last 55 nucleotides of exon 9 (c.1714-1768) is enriched for disease-causing variants and loss-of function variants in this region have been found in patients/families with a MODY phenotype. Therefore, a "very strong" level of evidence will be used for loss-of-function variants 5' of c.1768 regardless of where the premature termination codon occurs.
  - PVS1_Strong will be applied to nonsense variants at c.1803 (p.601) and 5' and frameshift variants at c.1854 (p.618) and 5'. The distinction of nonsense and frameshift variants was made following a careful review of the phenotypes of individuals with loss-of-function variants in exon 10, which lead to our prediction that the addition of new amino acids from a frameshift will disrupt the TAD and cause a MODY phenotype more so than the deletion of a small part of the end of the TAD. Moderate phenotypic evidence was applied to the c.1802del (p.601Ter) variant, but the individual with the next nonsense variant (p.Gln625Ter) was unaffected. Frameshift variants at p.Ile618 and 5' have been identified in patients with a phenotype consistent with MODY.
- "Exon skipping or use of a cryptic splice site that preserves reading frame" and "Single to multi-exon deletion that preserves reading frame"
  - Deletions of exon 1 would lead at least to loss of the initiation codon (see below for recommendations for initiation codon variants). Deletions of single exons 2, 3, 4, 5, 6, 8 or 9 all cause frameshift, and thus PVS1 would be used. In HNF1A, only exon 7 (LRG_522t1) is surrounded by introns of the same phase. Skipping or deletion of exon 7 would remove 64 amino acids in the TAD, which is >10% of the protein and 18% of the TAD. Given the significance of the TAD, we support still using PVS1 instead of PVS1_Strong in this situation. A deletion of exon 10 would remove part of the TAD but less than 10% of the protein. Since the TAD is critical to protein function, and variants that disrupt all of exon 10 have been found in patients with a MODY phenotype, we will use PVS1_Strong for deletions of exon 10 and splicing variants that would predict the skipping of exon 10. This specification is in accordance with Tayoun's recommendation to use PVS1_Strong in cases in which the truncated region is critical to protein function.
- Apply PVS1 to initiation codon variants. Four initiation codon variants have been identified in patients with a MODY phenotype. The closest potential in-frame start codon is p.Met118. Starting the protein at p.Met118 would remove 18% of the protein, including the entire dimerization domain. There are many P/LP variants upstream of p.Met118.
- Per recommendations from the SVI, when RNA analysis demonstrates abnormal splicing from non-canonical splice site variants, apply PS3 instead of PVS1.

Clingen specific criteria

Computional and predictive data

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 In-frame indels in repeat w/out known function BP3	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

Theoretical prediction programs:
- single program
- aggregated score
- gene specific recommendations

Computional data

Aggregated Prediction Uncertain (0.62)

Functional Coding
Revel Uncertain (0.55)
AlphaMissense Uncertain (0.582)
Eve (N/A)
Varity Benign (low) (0.24)
MUT Assesor Lo (1.69)
SIFT Uncertain (0.051)
Polyphen2 Deleterious (Supporting) (1)
MT Deleterious (1)
FATHMM Uncertain (2.08)
DANN Deleterious (1)
MetaLR Benign (0.1)
PrimateAI Deleterious (Moderate) (0.88)
BayesDel Uncertain (-0.08)
CardioBoost ARM (N/A)
CardioBoost CM (N/A)

Splice Altering
SpliceAI Benign (0)
dbscSNV Ada (N/A)
dbscSNV RF (N/A)

Conservation
GERP Uncertain (4.81)

Functional Whole Genome
GenoCanyon N/A (1)
fitCons Deleterious (0.71)

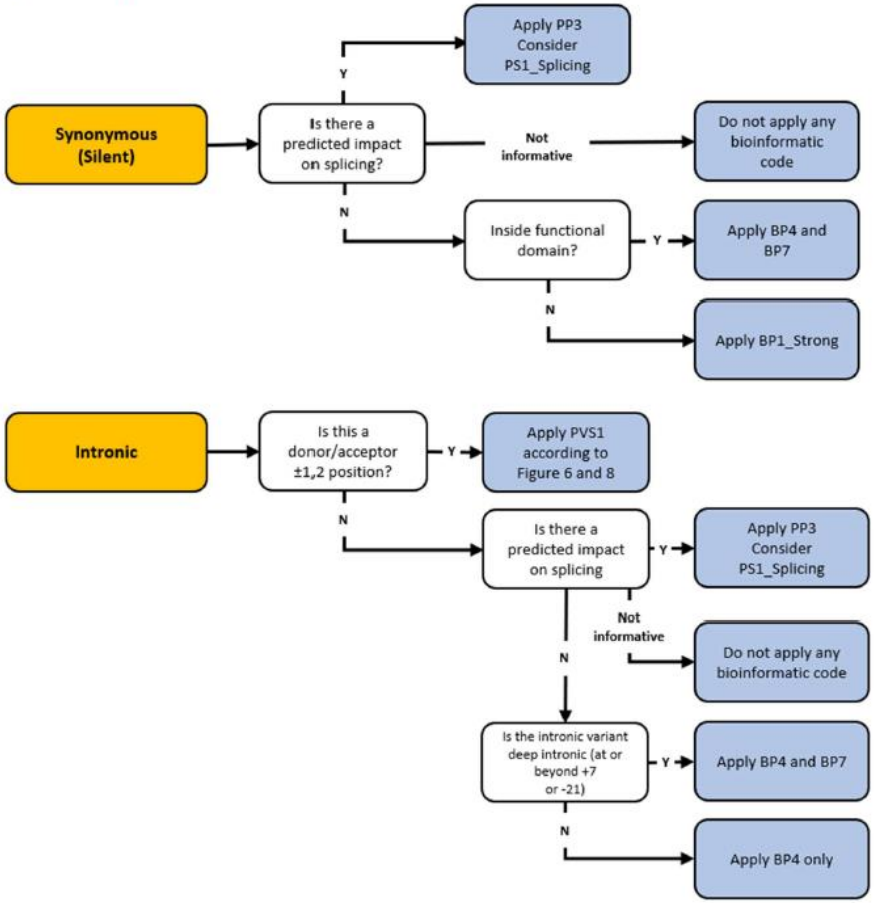
Mitochondrial
MitoTip (N/A)
APOGEE (N/A)


REVIEW article
Front. Genet., 29 November 2022
Sec. Computational Genomics
Volume 13 - 2022 |
https://doi.org/10.3389/fgene.2022.1010327
This article is part of the Research Topic
Using Big Data Approaches to Understand Metabolic Syndrome
View all 4 articles >
Insights on variant analysis in silico tools for pathogenicity prediction
Felipe Antonio de Oliveira Garcia[1]
Edilene Santos de Andrade[1†]
Edenir Inez Palmero[1,2*†]

VCEP specifications

Figure 1: Application of bioinformatic codes and considerations for incorporating splicing and functional data depending on variant type and position.

Figure 1A: Application of bioinformatic codes based on variant type and location.



KEY

Functional domain - (potentially) clinically important functional domains are defined as:
BRCA1 RING aa 2-101;
BRCA1 coiled-coil aa 1391-1424;
BRCA1 BRCT repeats aa 1650-1857;
BRCA2 PALB2 binding domain aa 10-40;
BRCA2 DNA binding aa 2481-3186.

Splice Predictions, using SpliceAI
No impact ≤0.1
Not informative (do not use) >0.1 and <0.2
Impact ≥0.2

Missense Predictions, using BayesDel
BRCA1:
No impact ≤ 0.15
Not informative >0.15 and <0.28
Impact ≥0.28
BRCA2:
No impact ≤ 0.18
Not informative >0.18 and <0.30
Impact ≥0.30

Gene specific thresholds

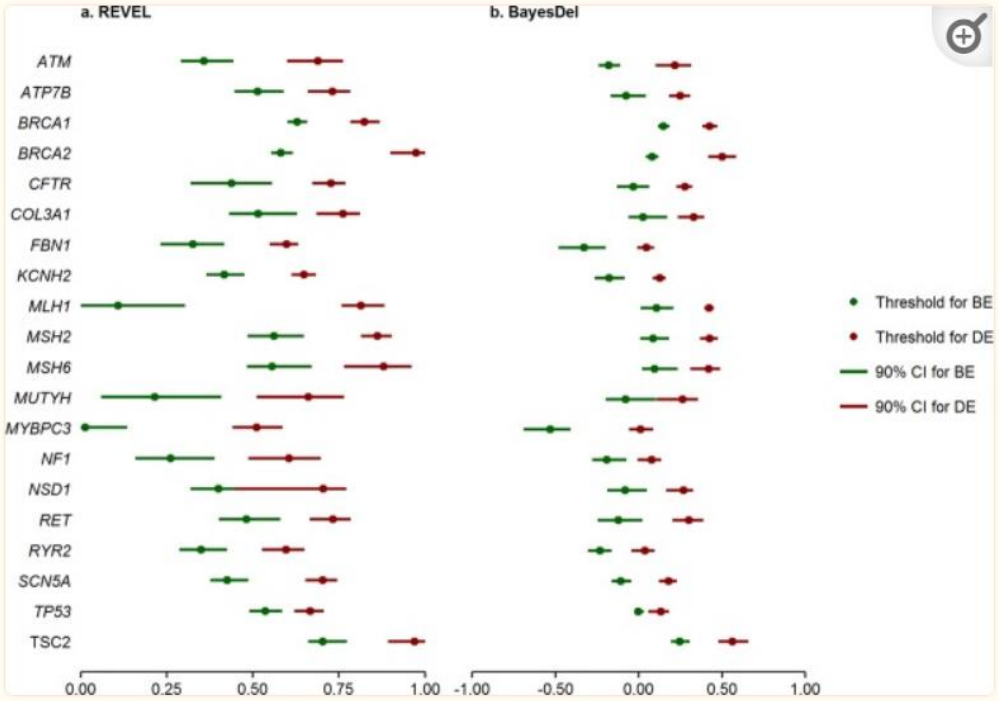


Figure 2

Variation in thresholds for assigning benign and deleterious *in silico* evidence across 20 genes. (**a**) Gene-level 2-sided thresholds and their 90% confidence intervals (CI) for REVEL. (**b**) Gene-level 2-sided thresholds and their 90% confidence intervals (CI) for BayesDel. Thresholds for BE and DE were represented by green and red dots, respectively. BE, benign evidence; DE, deleterious evidence.

Tian et al 2019 PMID: 31484976

Functional data

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	

VCEP specifications

PS3

Original ACMG Summary

Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.
Note: Functional studies that have been validated and shown to be reproducible and robust in a clinical diagnostic laboratory setting are considered the most well-established.

Strong

Applicable to non-canonical splice site variants that have RNA and in silico evidence of aberrant splicing.

Modification Type: Gene-specific,Strength

Moderate

Applicable for variants with luciferase assay data (evidence of decreased transactivation (<=40% of wild type) by the Gloyn/Oxford group (Althari et al 2020 https://pubmed.ncbi.nlm.nih.gov/32910913/)

Modification Type: Gene-specific,Strength

Supporting

See list of approved functional studies and guidelines for interpretation of data (below). (1) Luciferase assays for transactivation - "Decreased function" is defined as activity less than 40% of wildtype. Assays should include controls for WT, T2DM-risk, and known MODY variants. For additional specifications and recommendations, please see the HNF1A rules. (2) EMSA for DNA binding - "Decreased function" is defined as activity lesss than 405 of wildtype. We recommend that at least two of the following variants be used as positive controls for reduced DNA binding activity: c.335C>T (p.Pro112Leu), c.608G>A (p.Arg203His), c.787C>T (p.Arg263Cys) and c.686G>A (p.Arg229Gln) (PMID: 11162430, 12574234, 24915262). For additional specifications and recommendations, please see the HNF1A rules. (3) Western blotting and indirect immunoflorescence for protein expression and localization - Determining appropriate thresholds for protein expression is more difficult due to variability in results between experimental protocols. Altered protein expression can be indirectly captured through the read-out frame from transactivation assay, and reduced protein expression can provide an explanation for reduced transactivation. When exploring protein mis-localization, we recommend that the c.589_615del (p.Lys197_Lys205del) variant is included as a positive control for impaired nuclear localization (cytosolic retention).

Modification Type: Gene-specific,Strength

Instructions: See list of approved functional studies and guidelines for interpretation of data.

Functional data

A	B	C	D	E	F	G	H	I	J	
Table 9: Summary of BRCA1 and BRCA2 functional assay results reviewed for application of PS3 and BS3 codes, following recommendations in Figure 1.										
Gene	HGVS Nucleotide	HGVS Protein	Assigned Cod	Code Weigh	Standardised Text	Splice Result Published	Splicing Predictio	Predicted or Observed	# Pub	Res
BRCA1 or BRCA2	*HGVS c. nomenclature for variant or variant haplotype*	*HGVS p. nomenclature for variant or variant haplotype*	*Code to be applied for the (subset of) functional assay data considered relevant for code assessment*	*Strength of the code to be applied*	*PS3 or BS3 related text to be included in a variant summary. Provides rationale of exclusion/inclusion of assay data from specific publications (based on variant type, predicted/observed splicing), and the final interpretation of the remaining functional assay evidence considered relevant for classification*	*Short summary text of published splicing results. Publication/s and additional details should be included in PVS1 or BP7 descriptions*	*Highest of four scores output by SpliceAI (10k window); score ≥ (0.2 coded as 'Y= predicted to alter splicing.*	*Summarizes combination of predicted splicing (column H) and observed splicing (column G).*	*Number of publicatio ns with calibrated assay results.*	*First source and*
BRCA1	c.[5359T>A;5363G>A]	p.([Cys1787Asp;Gly1788Asp])	PS3	Strong	Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:32546644, 307656(			N	two	Bouwman 2020 (PMID:32546644
BRCA1	c.100C>A	p.(Pro34Thr)	None	N/A	Reported by one calibrated study to exhibit a partial impact on protein function, between what was observed for benign and path		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.100C>G	p.(Pro34Ala)	BS3	Strong	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		0,02	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.100C>T	p.(Pro34Ser)	PS3	Strong	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.101C>A	p.(Pro34His)	PS3	Strong	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.101C>G	p.(Pro34Arg)	PS3	Strong	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.101C>T	p.(Pro34Leu)	PS3	Strong	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.102T>A	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.102T>C	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.102T>G	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.103G>A	p.(Val35Ile)	BS3	Strong	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.103G>C	p.(Val35Leu)	None	N/A	Reported by one calibrated study to exhibit a partial impact on protein function, between what was observed for benign and pathogenic control varian		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.103G>T	p.(Val35Phe)	None	N/A	Reported by one calibrated study to exhibit a partial impact on protein function, between what was observed for benign and path		0,02	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.104T>A	p.(Val35Asp)	PS3	Strong	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.104T>C	p.(Val35Ala)	PS3	Strong	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).		0	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.104T>G	p.(Val35Gly)	PS3	Strong	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).		0	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.105C>A	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.105C>G	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.105C>T	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.106T>A	p.(Ser36Thr)	BS3	Strong	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.106T>G	p.(Ser36Ala)	BS3	Strong	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.109A>C	p.(Thr37Pro)	BS3	Strong	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		0,02	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.109A>G	p.(Thr37Ala)	BS3	Strong	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.109A>T	p.(Thr37Ser)	BS3	Strong	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.-10A>C		BS3	Strong	5'UTR variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,06	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.-10A>G		BS3	Strong	5'UTR variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,03	N	one	Findlay 2018 (PMID:30209399) -
BRCA1	c.-10A>T		BS3	Strong	5'UTR variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrate		0,07	N	one	Findlay 2018 (PMID:30209399) -

Seggregation data

PP1

Original ACMG Summary

Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease.
Note: May be used as stronger evidence with increasing segregation data.

Strong

Use thresholds suggested by Jarvik and Browning[8]

- Single Family : ≤ 1/32 (5 meioses)
- >1 Family : ≤ 1/16 (4 meioses)

Modification Type: General recommendation,Gene-specific

Moderate

Use thresholds suggested by Jarvik and Browning[8]

- Single Family : ≤ 1/16 (4 meioses)
- >1 Family : ≤ 1/8 (3 meioses)

Modification Type: General recommendation,Gene-specific

Supporting

Use thresholds suggested by Jarvik and Browning[8]

- Single Family : ≤ 1/8 (3 meioses)
- >1 Family : ≤ ¼ (2 meioses)

Modification Type: General recommendation,Gene-specific

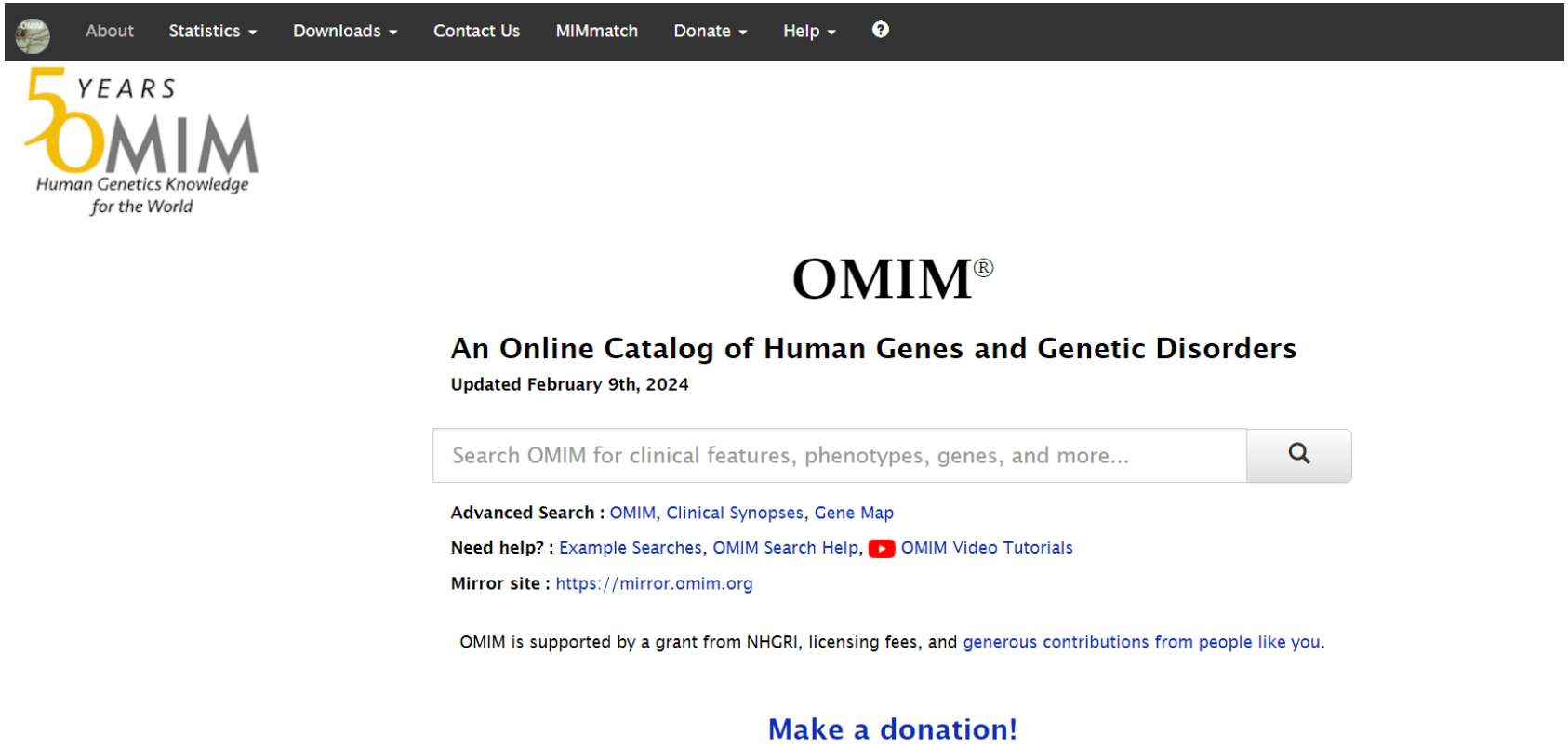
Instructions: Variable penetrance and phenocopies complicate co-segregation studies. The presence of type 1 and type 2 diabetes phenocopies and significance of variants in unaffected individuals as defined above will need to be considered. We expect to see hyperglycemia at birth in an individual with GCK-MODY and therefore consider

de novo data

De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	

BEWARE: PHENOTYPE MUST FIT !!!

https://www.omim.org/



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OMIM Entry Statistics

Number of Entries in OMIM (Updated February 9th, 2024) :

MIM Number Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Gene description *	16,352	769	51	37	17,209
Gene and phenotype, combined +	21	0	0	0	21
Phenotype description, molecular basis known #	6,368	386	5	34	6,793
Phenotype description or locus, molecular basis unknown %	1,390	110	4	0	1,504
Other, mainly phenotypes with suspected mendelian basis	1,639	100	3	0	1,742
Totals	25,770	1,365	63	71	27,269

Phenotypical data

#163950
Table of Contents

ICD+

163950

NOONAN SYNDROME 1; NS1

Alternative titles; symbols

NOONAN SYNDROME
MALE TURNER SYNDROME
FEMALE PSEUDO-TURNER SYNDROME
TURNER PHENOTYPE WITH NORMAL KARYOTYPE

Other entities represented in this entry:

PTERYGIUM COLLI SYNDROME, INCLUDED

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
12q24.13	Noonan syndrome 1	163950	AD	3	PTPN11	176876

Clinical Synopsis | Phenotypic Series | PheneGene Graphics

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  - GARD
  - OrphaNet
  - POSSUM
- ▶ Animal Models
- ▶ Cell Lines

Phenotypical data

163950
NOONAN SYNDROME 1; NS1

INHERITANCE
- Autosomal dominant
GROWTH
Height
- Short stature (postnatal onset)
Other
- Failure to thrive in infancy
- Specific growth curves are available
HEAD & NECK
Face
- Triangular face (with age)
- Micrognathia
Ears
- Low-set posteriorly rotated ears
- Hearing loss, sensorineural
Eyes
- Ptosis
- Hypertelorism
- Downslanting palpebral fissures
- Epicanthal folds
- Myopia
- Blue-green irides
Mouth
- Deeply grooved philtrum
- High peaks of upper lip vermilion border
- High arched palate
Teeth
- Dental malocclusion
Neck
- Short neck
- Webbed neck
- Cystic hygroma
CARDIOVASCULAR
Heart
- Congenital heart defect
- Hypertrophic obstructive cardiomyopathy
- Atrial septal defects
- Ventricular septal defects
- Pulmonic stenosis
Vascular
- Patent ductus arteriosus
- Aortic coarctation
CHEST
Ribs Sternum Clavicles & Scapulae
- Shield chest
- Pectus carinatum superiorly
- Pectus excavatum inferiorly
GENITOURINARY
Internal Genitalia (Male)
- Cryptorchidism
- Occasional hypogonadism
- Male infertility (in individuals with bilateral cryptorchidism)
SKELETAL
Spine
- Vertebral abnormalities
- Kyphoscoliosis
Limbs
- Cubitus valgus
- Clinodactyly
- Brachydactyly
- Blunt fingertips
- Polyarticular villonodular synovitis (knees, ankles, wrists, elbows - in some patients)
SKIN, NAILS, & HAIR
Hair
- Woolly-like hair
- Low posterior hairline
MUSCLE, SOFT TISSUES
- Lymphedema
NEUROLOGIC
Central Nervous System
- Articulation difficulties
- Mental retardation (25%)
HEMATOLOGY
- Amegakaryocytic thrombocytopenia
- Von Willebrand disease
- Bleeding tendency
NEOPLASIA
- Malignant schwannoma
- Multiple giant cell granulomas (bones, joints, soft tissues)
LABORATORY ABNORMALITIES
- Partial deficiency of factor XI(C)
- Partial deficiency of factor XII(C)
- Partial deficiency of factor XIII(C)
- Thrombocytopenia
MISCELLANEOUS
- Genetic heterogeneity
- Allelic to LEOPARD syndrome (151100)
MOLECULAR BASIS
- Caused by mutation in the protein tyrosine phosphatase, nonreceptor-type, 11 gene (PTPN11, 176876.0001)

Contributors:Cassandra L. Kniffin - updated : 10/26/2010
Creation Date:John F. Jackson : 6/15/1995
Edit History:joanna : 09/29/2017

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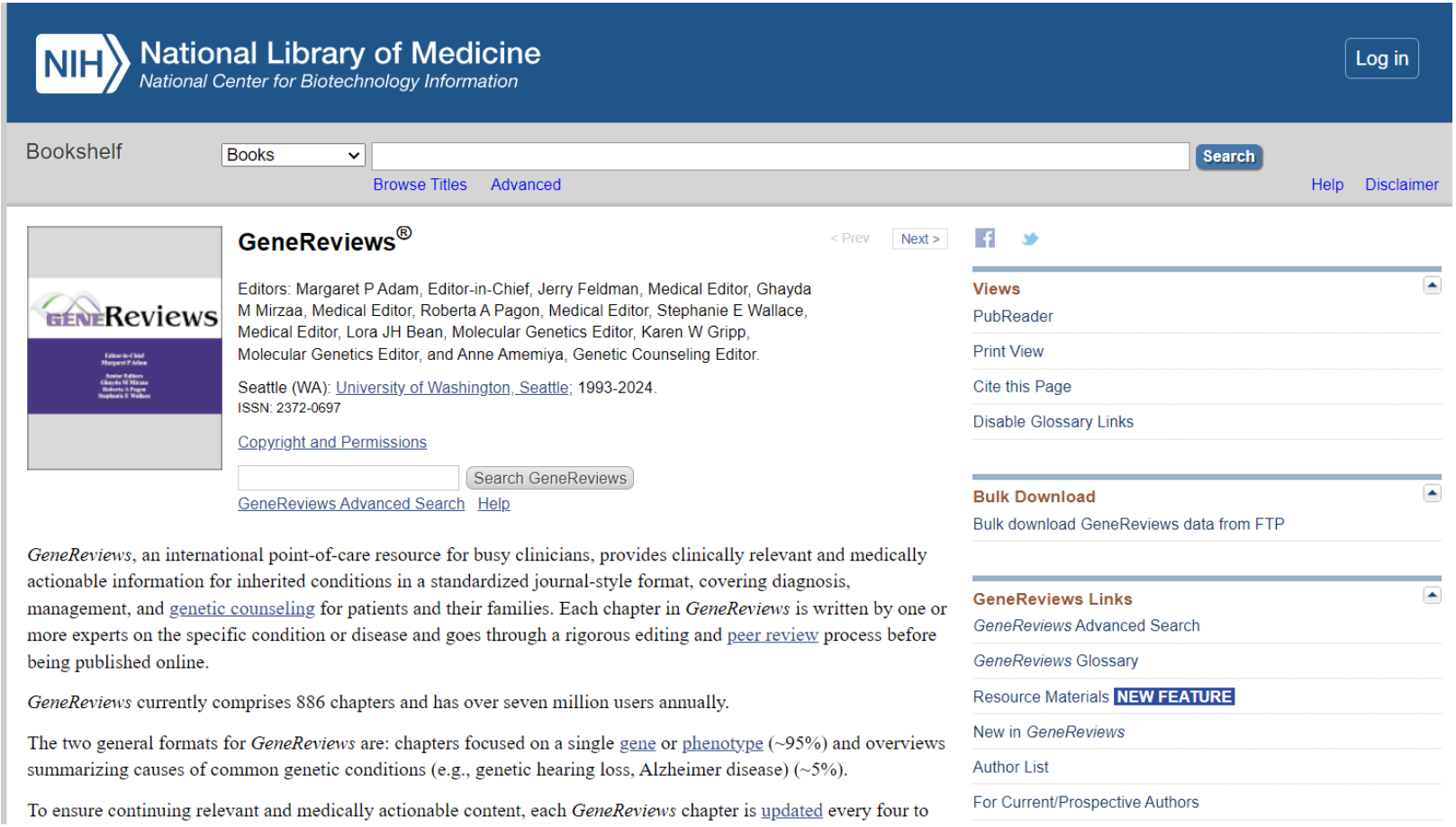

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Seattle (WA): University of Washington, Seattle; 1993-2024.
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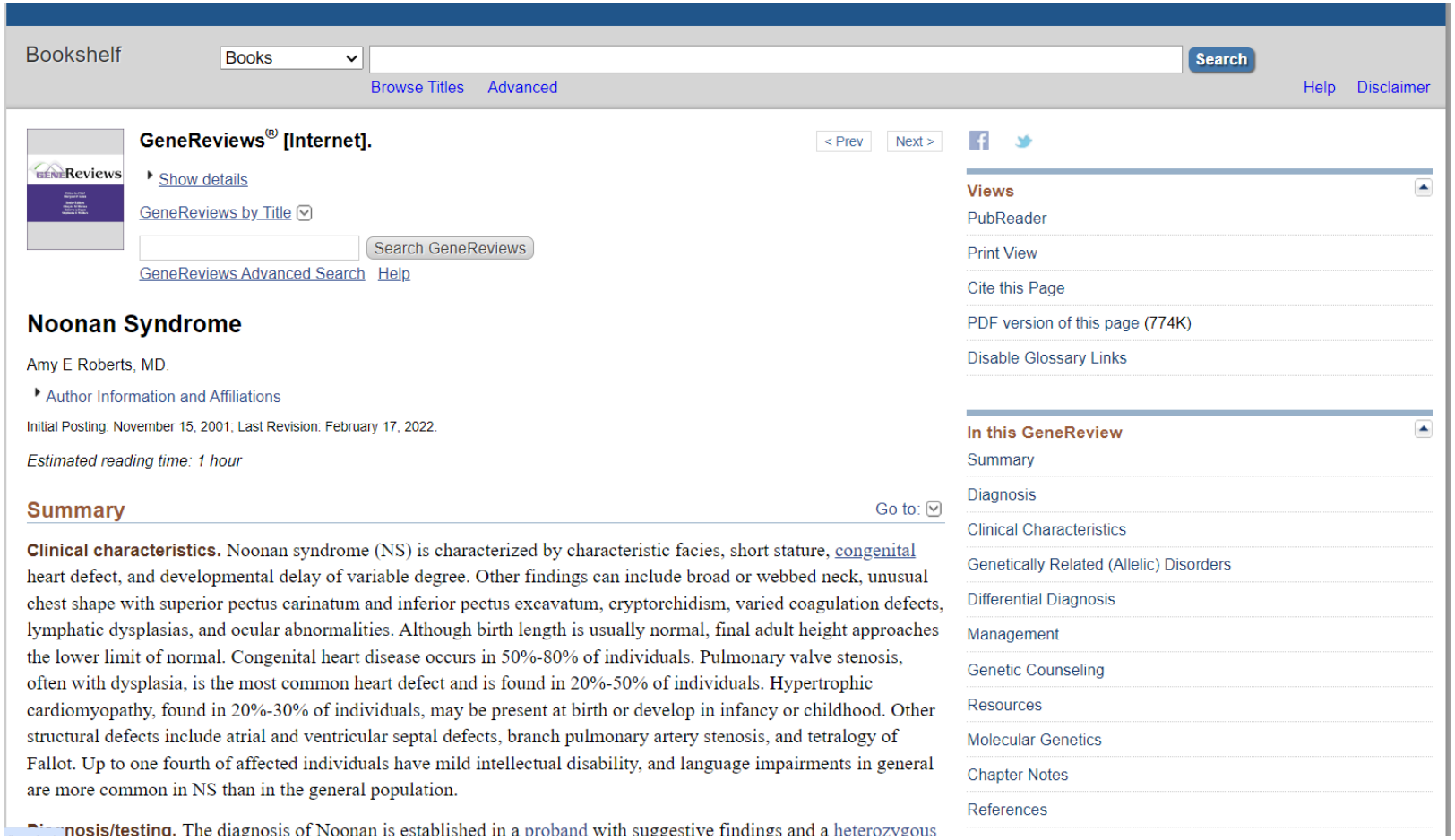

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Noonan Syndrome

Amy E Roberts, MD.

Author Information and Affiliations

Initial Posting: November 15, 2001; Last Revision: February 17, 2022.

Estimated reading time: 1 hour

Summary

Go to:

Clinical characteristics. Noonan syndrome (NS) is characterized by characteristic facies, short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one fourth of affected individuals have mild intellectual disability, and language impairments in general are more common in NS than in the general population.

Diagnosis/testing. The diagnosis of Noonan is established in a proband with suggestive findings and a heterozygous

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Genetically Related (Allelic) Disorders

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Management

Genetic Counseling

Resources

Molecular Genetics

Chapter Notes

References

https://www.deciphergenomics.org/

Explore DECIPHER

It's free and you don't need to log in

DECIPHER is used by the clinical community to share and compare phenotypic and genotypic data. The DECIPHER database contains data from 47,801 patients who have given consent for broad data-sharing; DECIPHER also supports more limited sharing via consortia. Have a look at the numbers.

Anyone can browse publicly-available patient data on DECIPHER and request to be put in contact with the responsible clinician. Why? Because sharing benefits everyone.

- Explore DECIPHER's genome browser
- Delve into the Human Phenotype Ontology
- Search all open-access DECIPHER data

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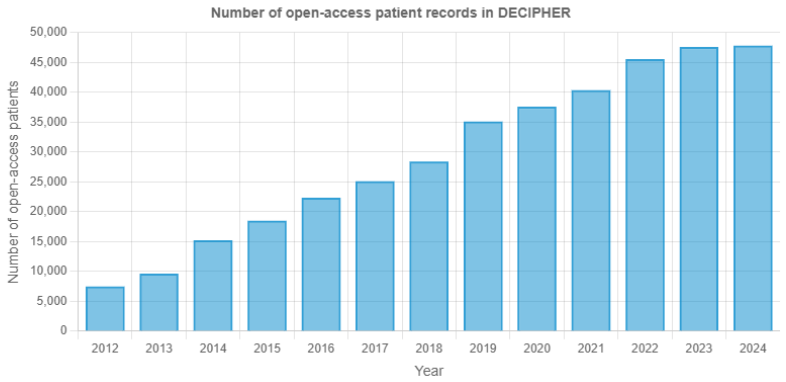
Database Statistics

Patients and Variants

47,801	194,099	48,507	13,106
open-access patient records	phenotype observations in these patients	open-access copy-number variants	open-access sequence variants

Patient Records

Right: Open-access patient records in DECIPHER by year.



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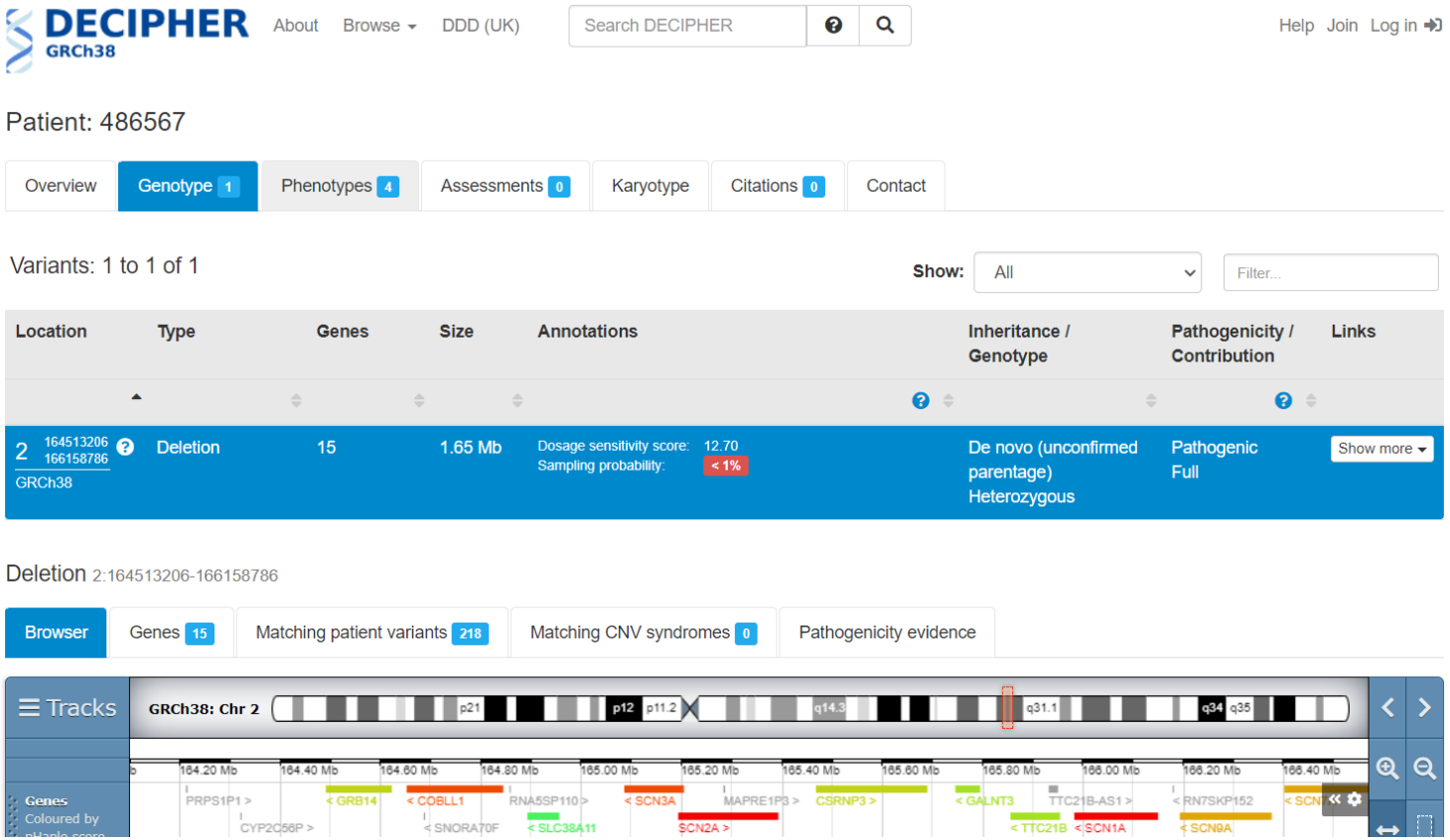

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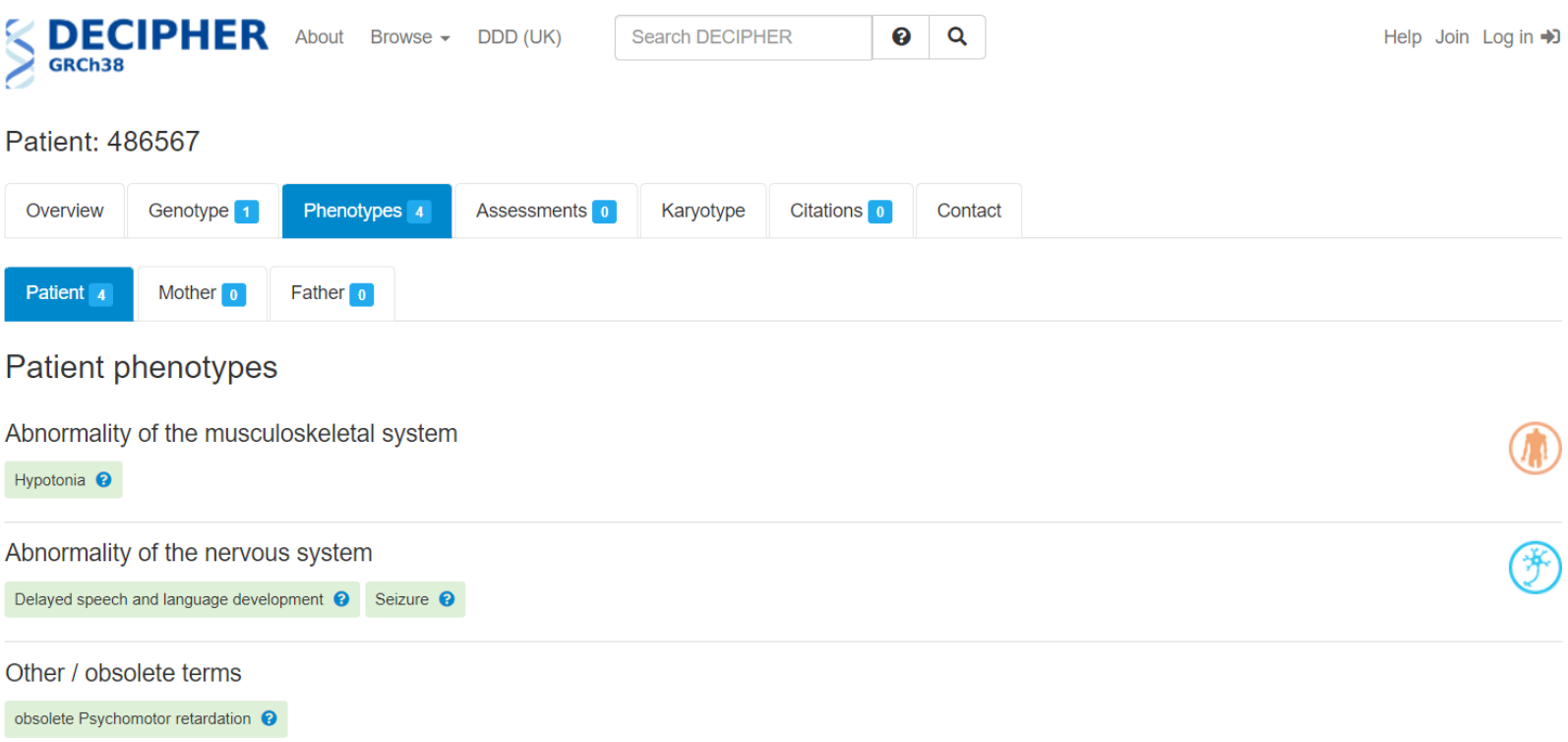


Phenotypical data

Table 2: Examples of using phenotype specificity as evidence for PP4.
*Data from GeneReviews (https://ghr.nlm.nih.gov/) accessed 01/04/2019. **Moog *et al* J Med Genet 2011

Evidence Level	Genetic aetiology	Gene(s)	Percentage of cases explained by variants in this gene or gene panel*	Phenotype *A strong consensus supporting a clinical diagnosis of the syndrome based on the features described.*	Functional evidence (e.g. biochemical, MRI, muscle biopsy)
Supporting	Sotos syndrome	*NSD1*	~90%	Facial gestalt and developmental delay/ intellectual disability or childhood overgrowth (height and/or head circumference ≥2 SD above the mean)	N/A
Moderate	Sotos syndrome	*NSD1*	~90%	Facial gestalt and developmental delay/intellectual disability **and childhood overgrowth** (height and/or head circumference ≥2 SD above the mean)	N/A
Supporting	Kabuki syndrome	*KMT2D* and *KDM6A*	55-80%	Facial gestalt and mild-moderate developmental delay/intellectual disability	N/A
Moderate	Kabuki syndrome	*KMT2D* and *KDM6A*	55-80%	Facial gestalt, mild-moderate developmental delay/intellectual disability **and one of the following**; characteristic skeletal anomalies, fetal fingertip pads, postnatal growth deficiency, hyperinsulinism	N/A
Strong	Hunter syndrome (MPS II)	*IDS*		Clinical and radiological features consistent with MPS II	Deficient iduronate 2-sulfatase (I2S) enzyme activity in white cells, fibroblasts, or plasma in the presence of normal activity of at least one other sulfatase.
Supporting	HNF1A/4A MODY	*HNF1A/ HNF4A*	N/A	Diabetes	Improved glycaemic response when treated with sulphonylurea tablets
Strong	Calpainopathy	*CAPN3*	84% for cases with severe calpain-3 protein deficiency	Clinical findings consistent with calpainopathy limb girdle muscular dystrophy and raised CK	Consistent muscle biopsy findings and immunoblot analysis identifying calpain-3 protein as absent or severely reduced
Moderate	CASK – related pontocerebellar hypoplasia (PCH) in an affected female	*CASK*	N/A	PCH, moderate-severe intellectual disability, progressive microcephaly	Classical *CASK* neuroimaging findings of PCH differentiating this from other cause of PCH**

Allelic data

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 data/databases

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			

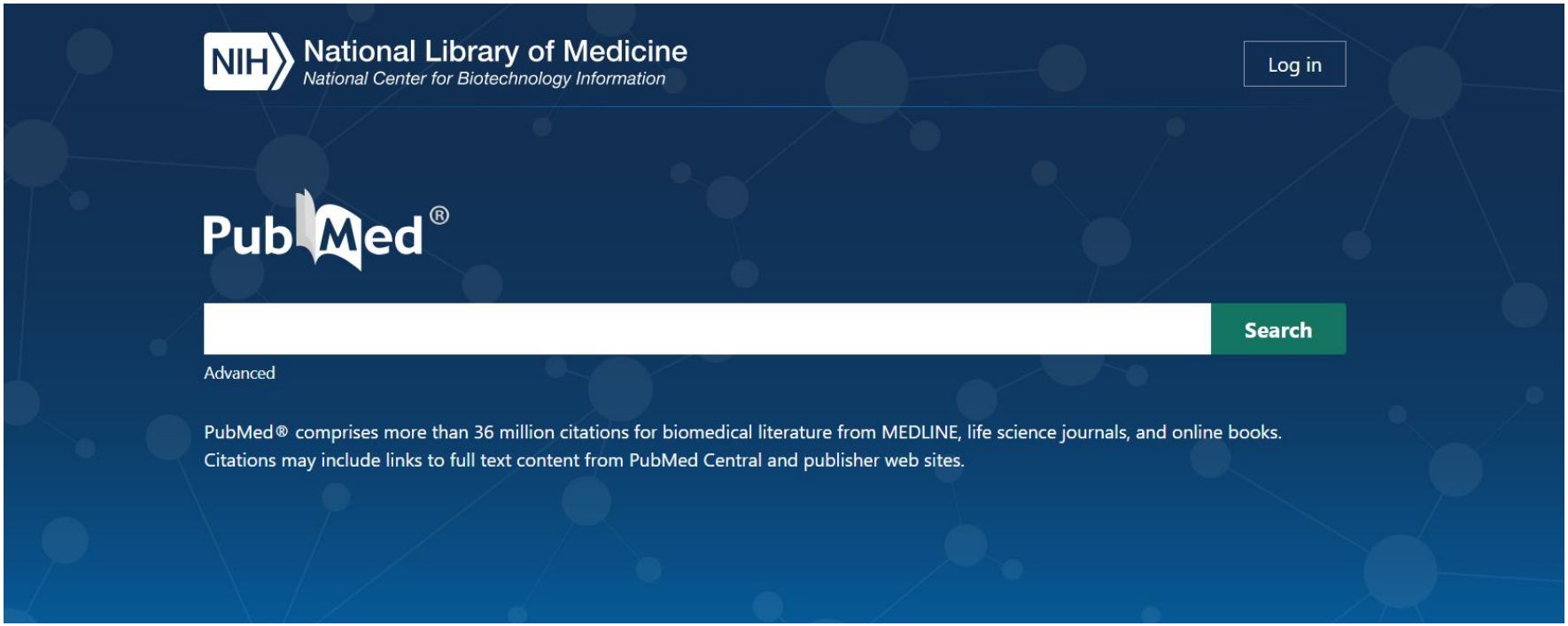
Other data/databases

Reputable source

- pathogenic

- benign

https://pubmed.ncbi.nlm.nih.gov/



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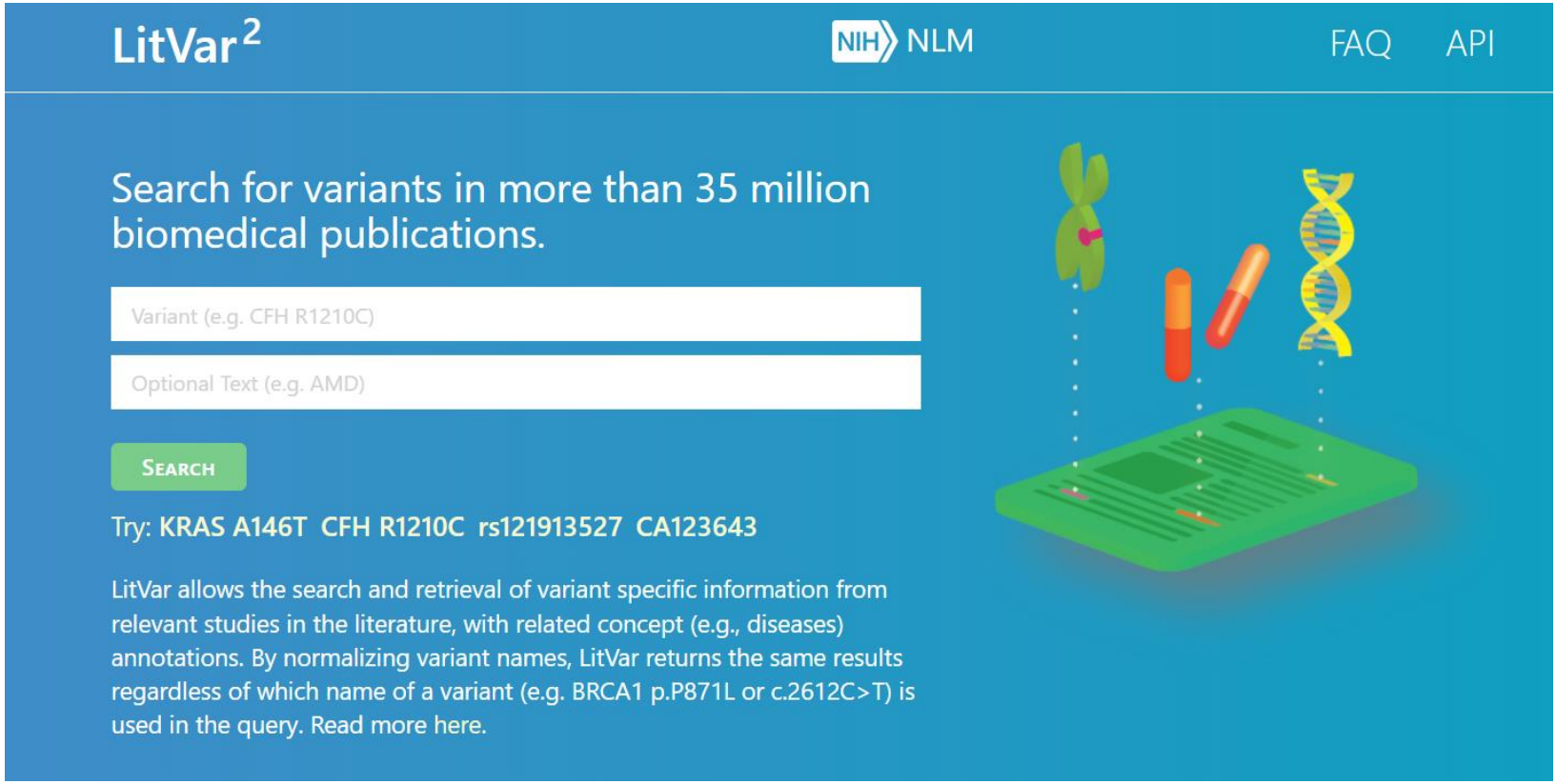
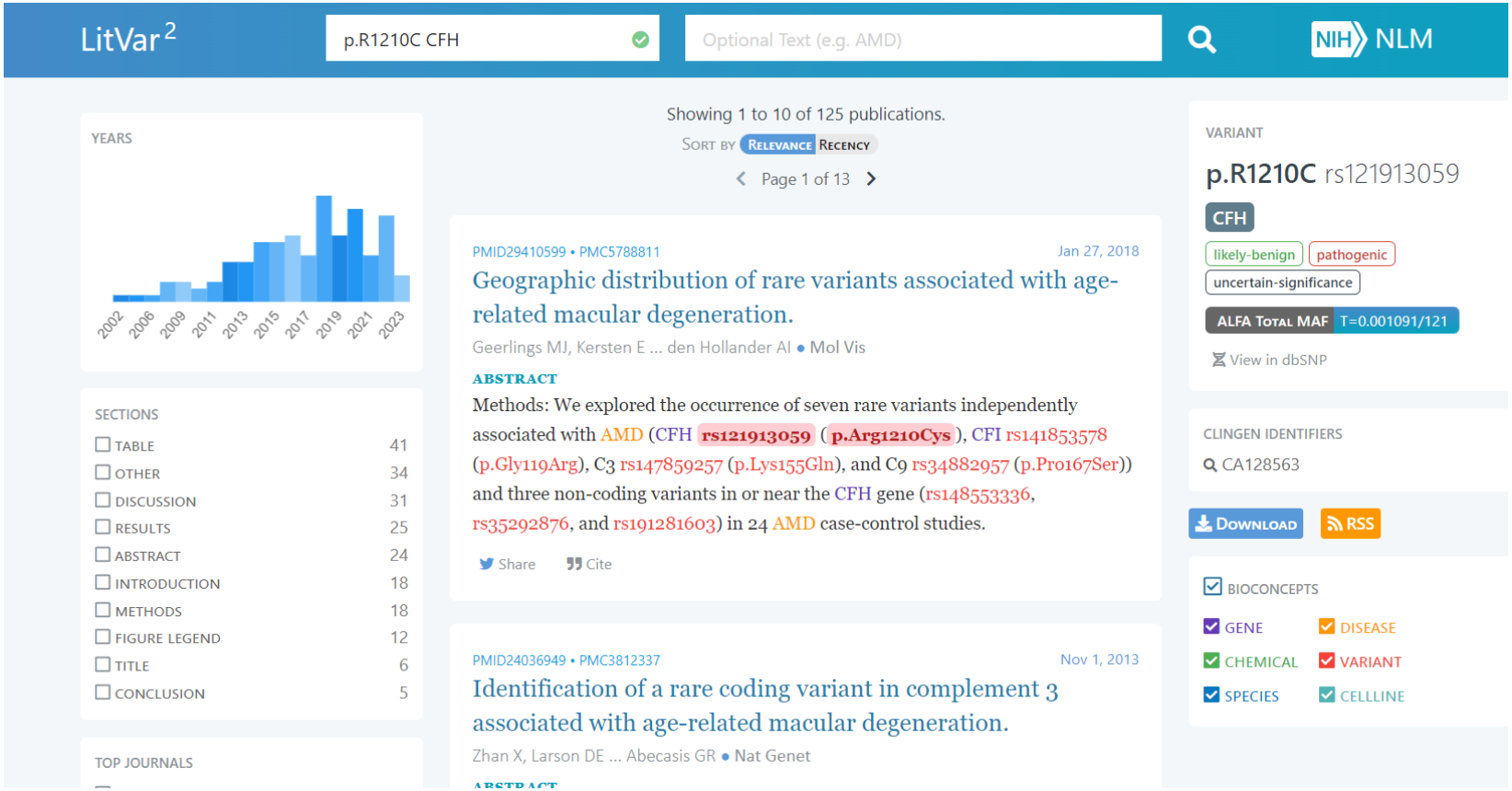


Litvar²



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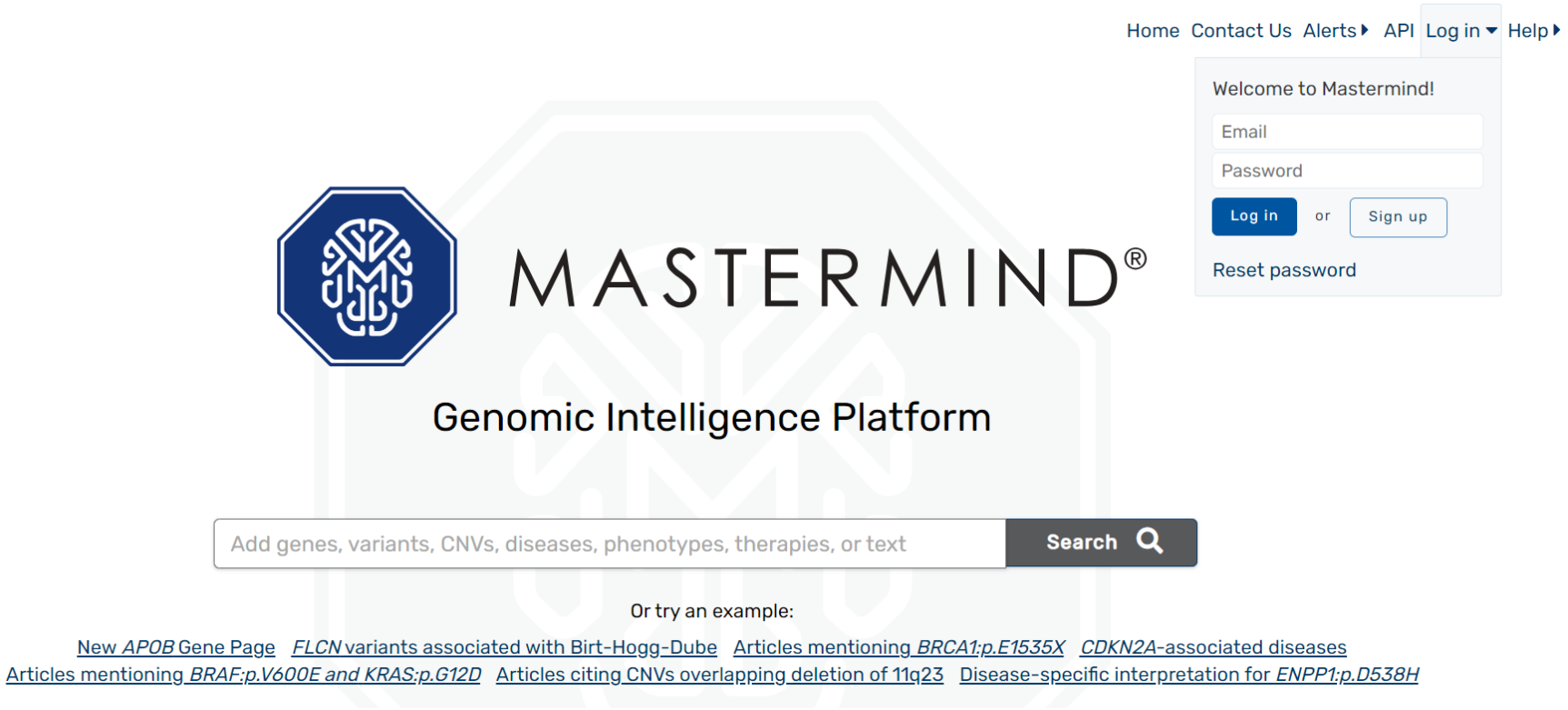

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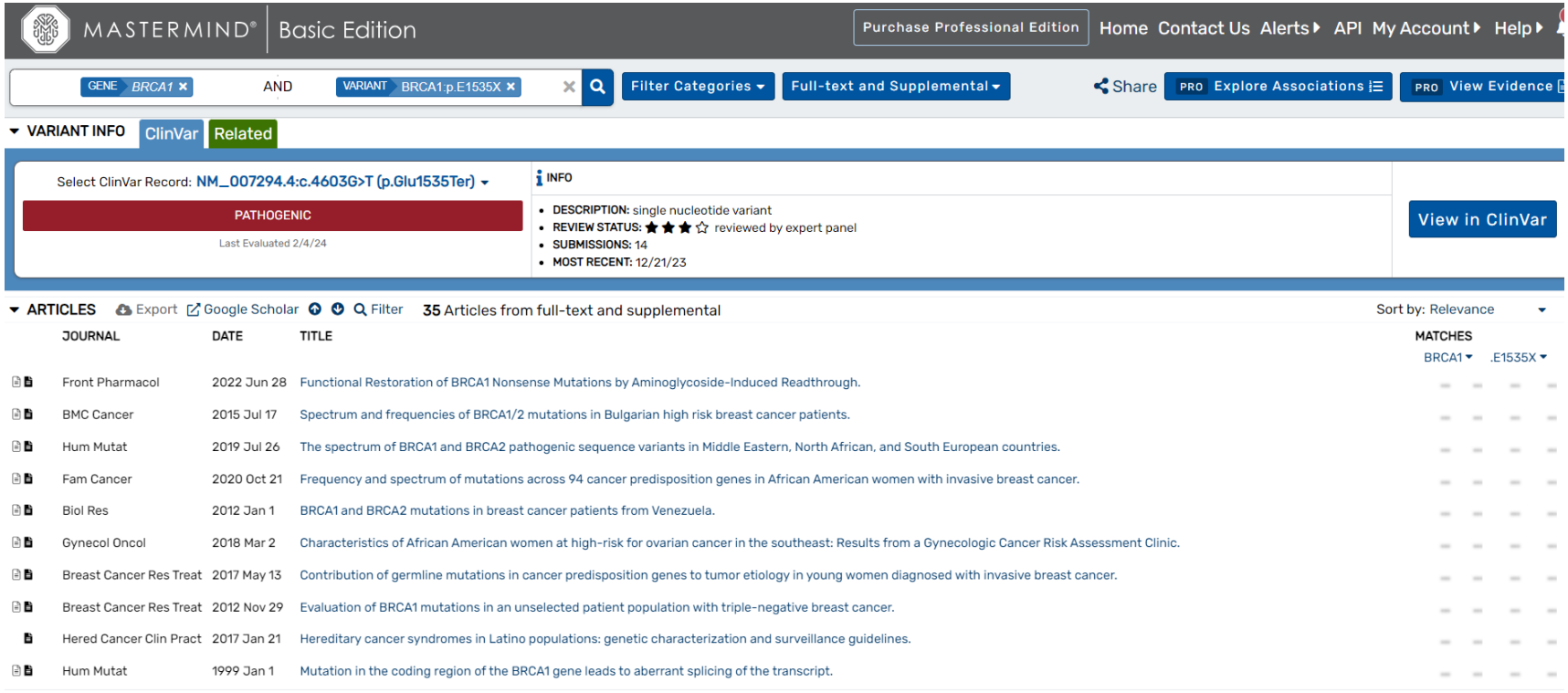

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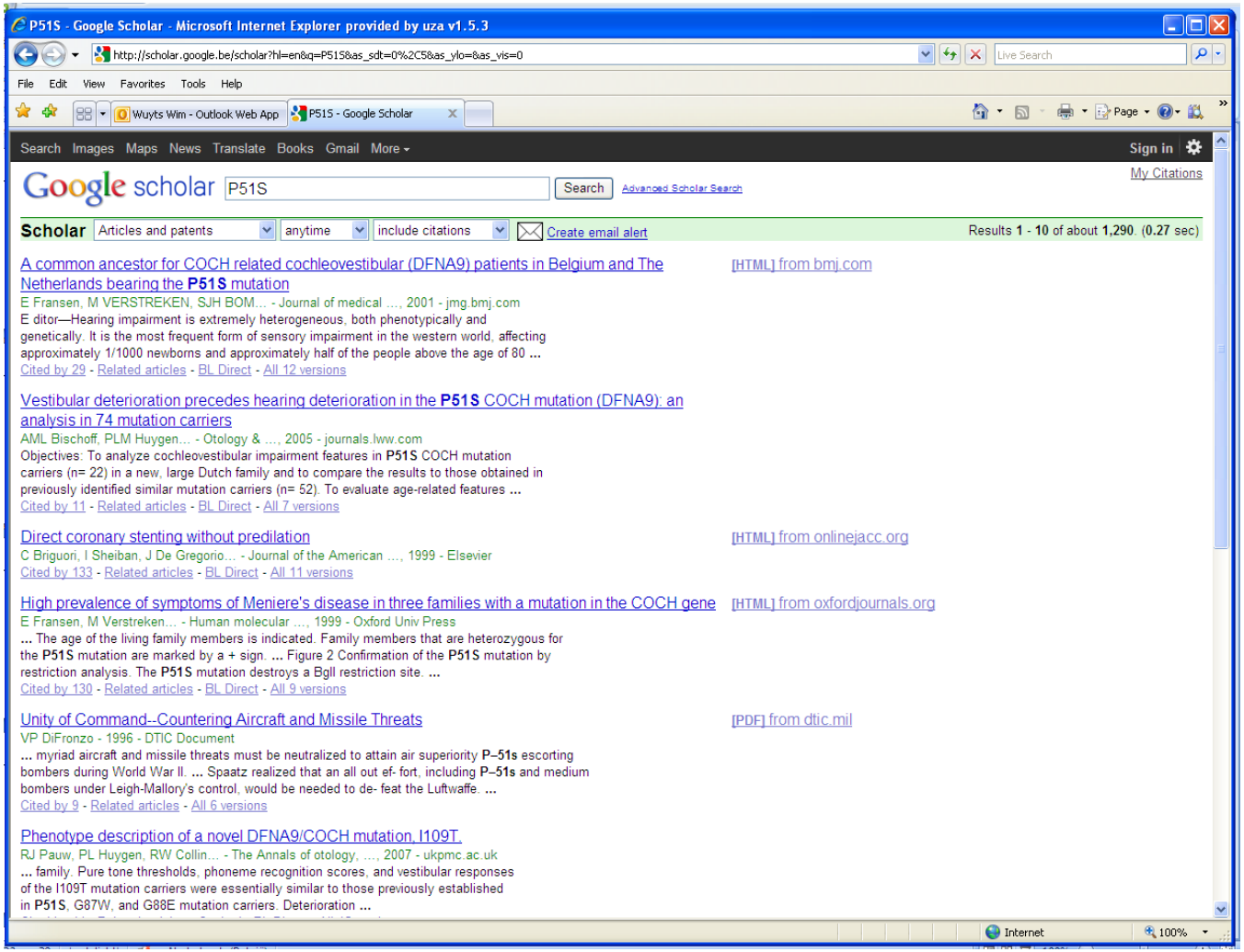

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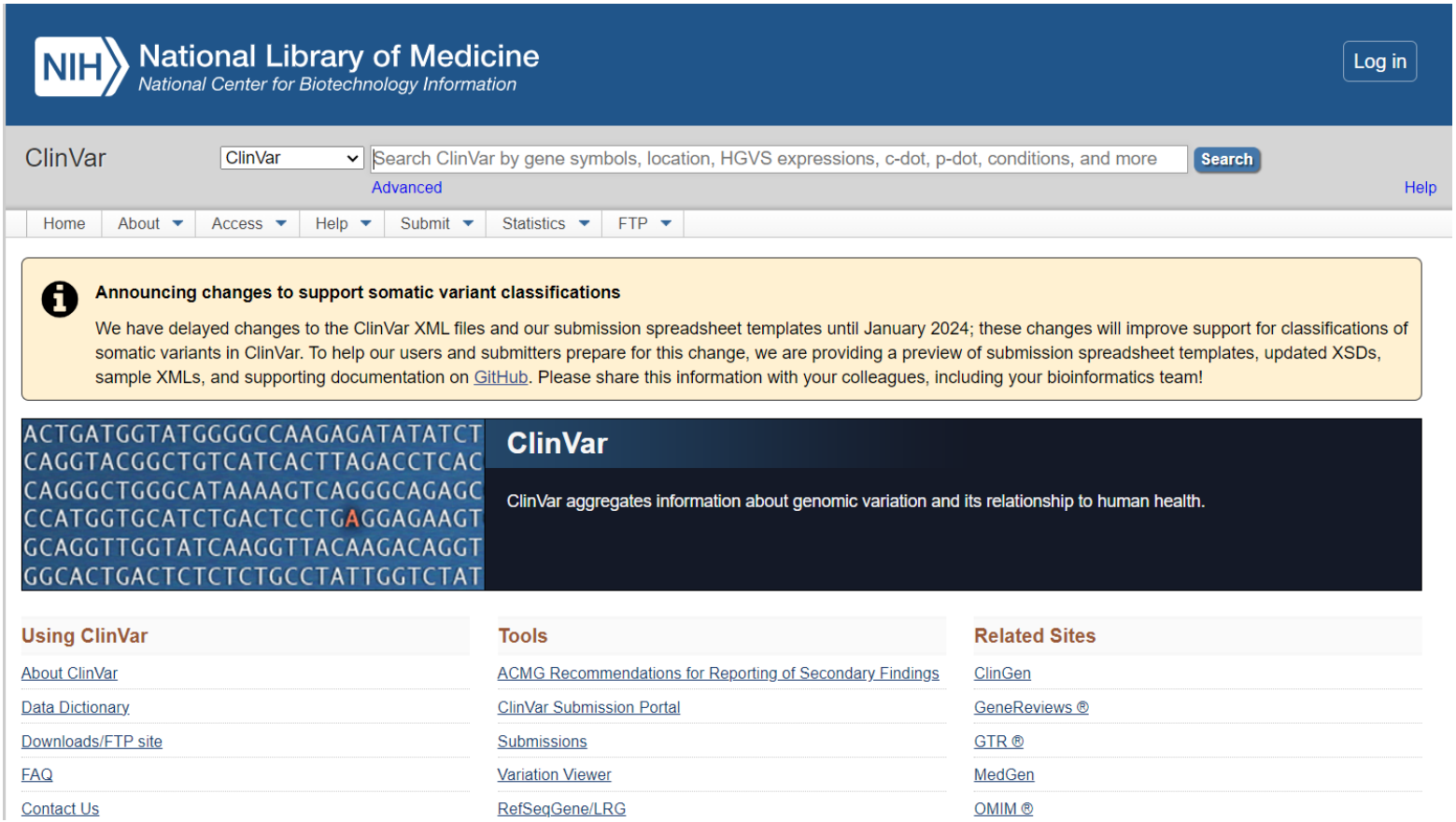

Clinvar

Classification on ClinVar aggregate records (VCV and RCV)

Overview

ClinVar calculates an aggregate classification for each of the three types of classifications – germline, somatic classification of clinical impact, and oncogenicity. ClinVar aggregates the values of each type of classification provided in submitted records (SCV) by the variant (VCV records) and by the variant/condition combination (RCV records).

Some classifications are given more weight in doing that aggregation, based on the review status of each submitted record represented in the VCV or RCV. Submitted records are used in this order of precedence of review statuses:

1. practice guideline (4 stars): The classification from the practice guideline record is used as the classification on the VCV and RCV records, no matter what other submitters may have reported.
2. Reviewed by expert panel (3 stars): The classification from the expert panel record is used as the classification on the VCV and RCV records, no matter what other submitters may have reported.
3. criteria provided, single submitter (1 star): The classification from all submitted records with this review status is used to calculate the aggregate classification on the VCV and RCV records.
    - For example, the classification on a single SCV record with review status "criteria provided, single submitter" supersedes classifications on multiple SCV records with lower review statuses.
4. no assertion criteria provided (0 stars): The classification from all submitted records with this review status is used to calculate the aggregate classification on the VCV and RCV records, if there is no record with higher precedence.

When there is a submission from an expert panel or a practice guideline, only the classification from that group is reported as the aggregate classification even if other submissions provide different classifications. The classifications on the SCV records from other submitters are not changed, but they do not contribute to the aggregate classification.

Conflicts in the aggregate classification are calculated for germline and oncogenicity classifications; see the following sections for more details. Conflicts on aggregate records are reported in the XML files, the VCF files, the tab-delimited variant_summary.txt file, and on VCV and RCV web pages

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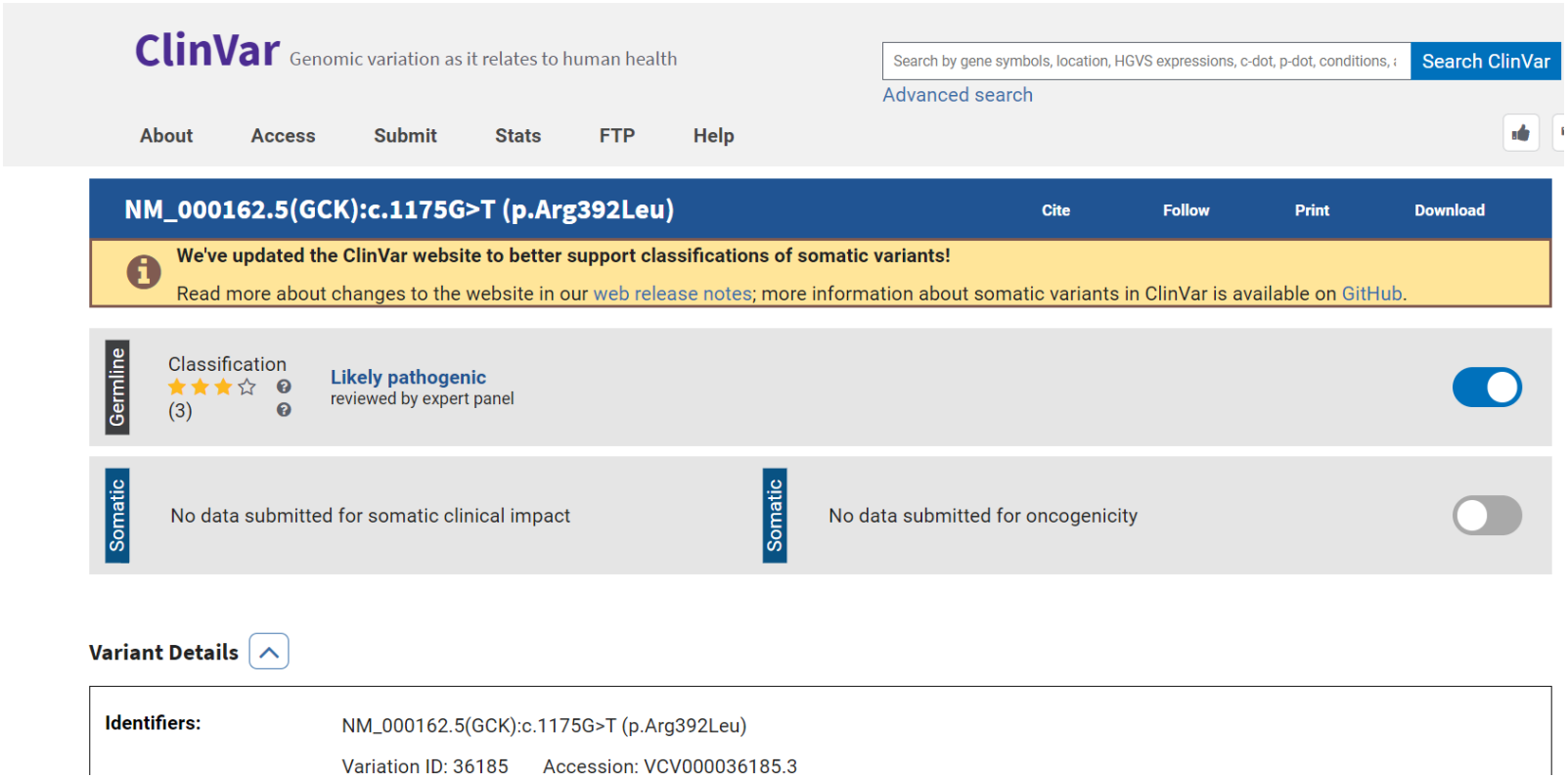
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NM_000162.5(GCK):c.1175G>T (p.Arg392Leu)
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We've updated the ClinVar website to better support classifications of somatic variants!
Read more about changes to the website in our web release notes; more information about somatic variants in ClinVar is available on GitHub.
Germline
Classification
(3)
Likely pathogenic
reviewed by expert panel
Somatic
No data submitted for somatic clinical impact
Somatic
No data submitted for oncogenicity
Variant Details
Identifiers:
NM_000162.5(GCK):c.1175G>T (p.Arg392Leu)
Variation ID: 36185
Accession: VCV000036185.3

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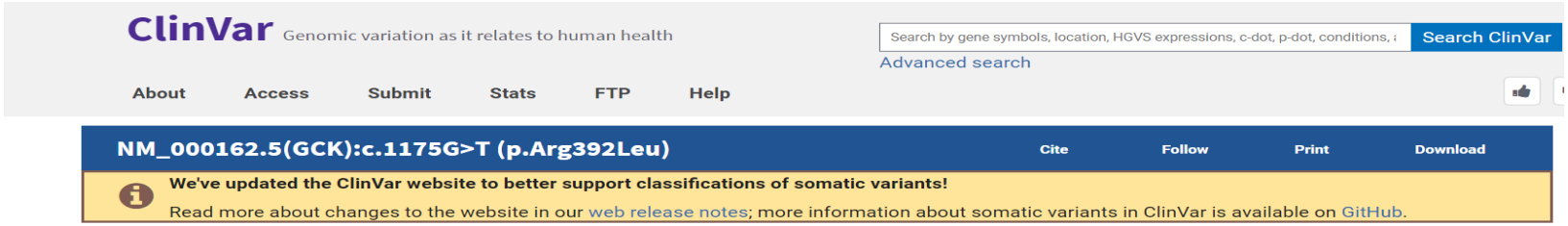


Submissions - Germline

Classification (Last evaluated)	Review status (Assertion criteria)	Condition	Submitter	More information
Likely pathogenic (Sep 20, 2023)	★★★☆ (ClinGen Monogenic Diabetes ACMG Specifications GCK V1.3.0) Method: curation	Monogenic diabetes (Semidominant inheritance) Affected status: unknown Allele origin: germline	ClinGen Monogenic Diabetes Variant Curation Expert Panel Accession: SCV004037471.1 First in ClinVar: Oct 07, 2023 Last updated: Oct 07, 2023	Other databases https://erepo.clinicalgenome.org... Comment: The c.1175G>T variant in the glucokinase gene, GCK, causes an amino acid change of Arg to Leu at codon 392 (p.(Arg392Leu)) of NM_000162.5. This variant ... (more)
likely pathogenic (Aug 18, 2011)	★☆☆☆ (LabCorp Variant Classification Summary - May 2015) Method: curation, clinical testing	MODY2 (autosomal unknown) Affected status: yes, unknown Allele origin: germline	Women's Health and Genetics/Laboratory Corporation of America, LabCorp Accession: SCV000052503.2 First in ClinVar: Apr 04, 2013 Last updated: Mar 28, 2022	Comment: Converted during submission to Likely pathogenic.
Likely risk allele (-)	★☆☆☆ (K & H Uppaluri Personalized Medicine Clinic Variant Classification & Assertion Criteria_Updated V.1) Method: research	Maturity onset diabetes mellitus in young (Autosomal dominant inheritance) Affected status: unknown Allele origin: unknown	Clinical Genomics, Uppaluri K&H Personalized Medicine Clinic Accession: SCV002605080.1 First in ClinVar: Dec 11, 2022 Last updated: Dec 11, 2022	Publications: PubMed (6) Comment: Potent mutations in GCK gene is associated with poor secretion of insulin. Its associated with milder forms of diabetes, which can be controlled by diet ... (more)

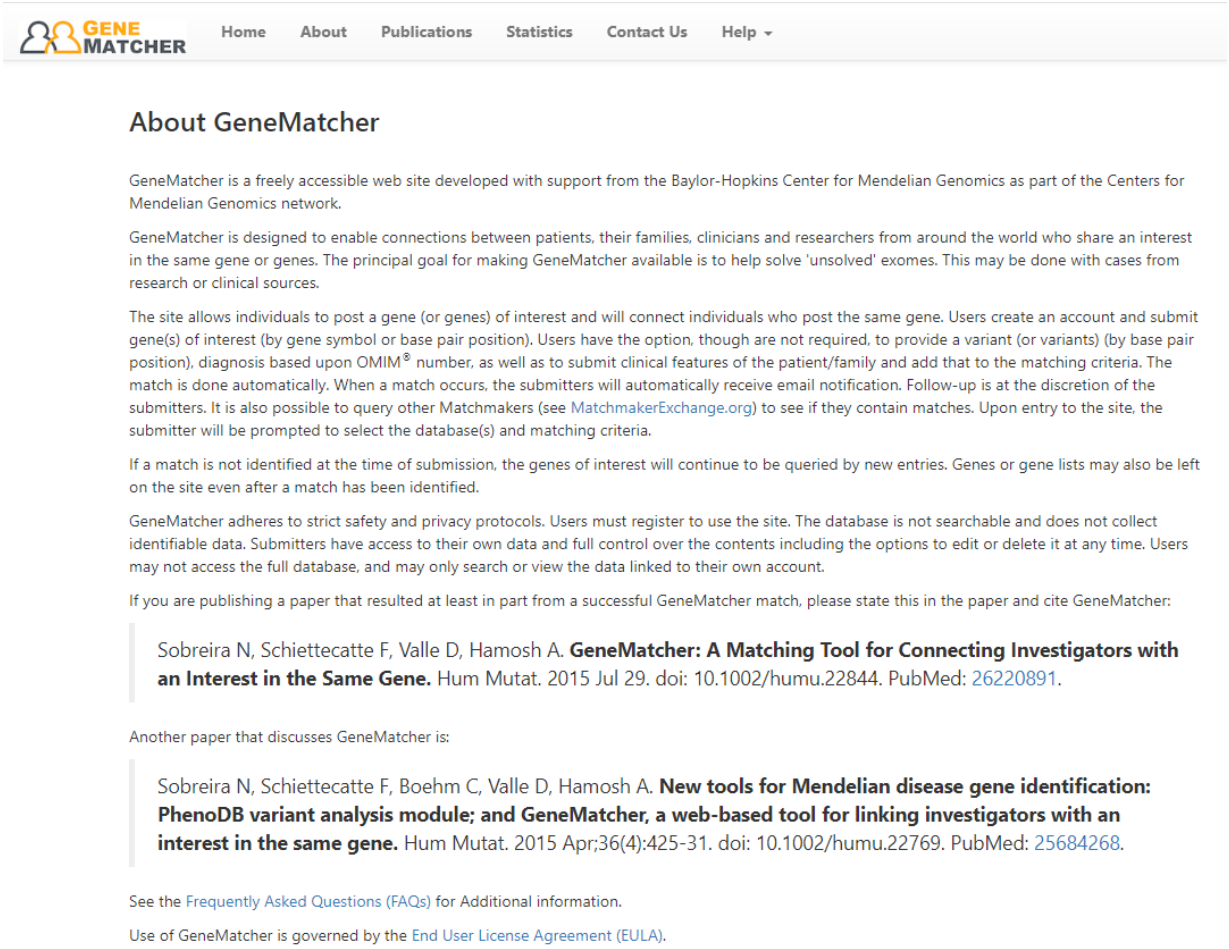
Clinvar

Citations for germline classification of this variant

Title	Author	Journal	Year	Link
Clinical implications of the glucokinase impaired function - GCK MODY today.	Hulín J *et al.*	Physiological research	2020	PMID: 33129248
MODY2 in Asia: analysis of GCK mutations and clinical characteristics.	Zhou Y *et al.*	Endocrine connections	2020	PMID: 32375122
Association of a homozygous GCK missense mutation with mild diabetes.	Marucci A *et al.*	Molecular genetics & genomic medicine	2019	PMID: 31197960
Insights into pathogenesis of five novel GCK mutations identified in Chinese MODY patients.	Liu L *et al.*	Metabolism: clinical and experimental	2018	PMID: 30257192
Genetic and clinical characteristics of Chinese children with Glucokinase-maturity-onset diabetes of the young (GCK-MODY).	Li X *et al.*	BMC pediatrics	2018	PMID: 29510678
GCK mutations in Chinese MODY2 patients: a family pedigree report and review of Chinese literature.	Ping Xiao Y *et al.*	Journal of pediatric endocrinology & metabolism : JPEM	2016	PMID: 27269892
https://erepo.clinicalgenome.org/evrepo/ui/interpretation/073547fa-68db-4acb-940d-76d74c6084d7	-	-	-	-

Text-mined citations for rs193922269 LitVar 2

https://genematcher.org/



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About GeneMatcher

GeneMatcher is a freely accessible web site developed with support from the Baylor-Hopkins Center for Mendelian Genomics as part of the Centers for Mendelian Genomics network.

GeneMatcher is designed to enable connections between patients, their families, clinicians and researchers from around the world who share an interest in the same gene or genes. The principal goal for making GeneMatcher available is to help solve 'unsolved' exomes. This may be done with cases from research or clinical sources.

The site allows individuals to post a gene (or genes) of interest and will connect individuals who post the same gene. Users create an account and submit gene(s) of interest (by gene symbol or base pair position). Users have the option, though are not required, to provide a variant (or variants) (by base pair position), diagnosis based upon OMIM® number, as well as to submit clinical features of the patient/family and add that to the matching criteria. The match is done automatically. When a match occurs, the submitters will automatically receive email notification. Follow-up is at the discretion of the submitters. It is also possible to query other Matchmakers (see MatchmakerExchange.org) to see if they contain matches. Upon entry to the site, the submitter will be prompted to select the database(s) and matching criteria.

If a match is not identified at the time of submission, the genes of interest will continue to be queried by new entries. Genes or gene lists may also be left on the site even after a match has been identified.

GeneMatcher adheres to strict safety and privacy protocols. Users must register to use the site. The database is not searchable and does not collect identifiable data. Submitters have access to their own data and full control over the contents including the options to edit or delete it at any time. Users may not access the full database, and may only search or view the data linked to their own account.

If you are publishing a paper that resulted at least in part from a successful GeneMatcher match, please state this in the paper and cite GeneMatcher:

> Sobreira N, Schiettecatte F, Valle D, Hamosh A. **GeneMatcher: A Matching Tool for Connecting Investigators with an Interest in the Same Gene.** Hum Mutat. 2015 Jul 29. doi: 10.1002/humu.22844. PubMed: 26220891.

Another paper that discusses GeneMatcher is:

> Sobreira N, Schiettecatte F, Boehm C, Valle D, Hamosh A. **New tools for Mendelian disease gene identification: PhenoDB variant analysis module; and GeneMatcher, a web-based tool for linking investigators with an interest in the same gene.** Hum Mutat. 2015 Apr;36(4):425-31. doi: 10.1002/humu.22769. PubMed: 25684268.

See the Frequently Asked Questions (FAQs) for Additional information.

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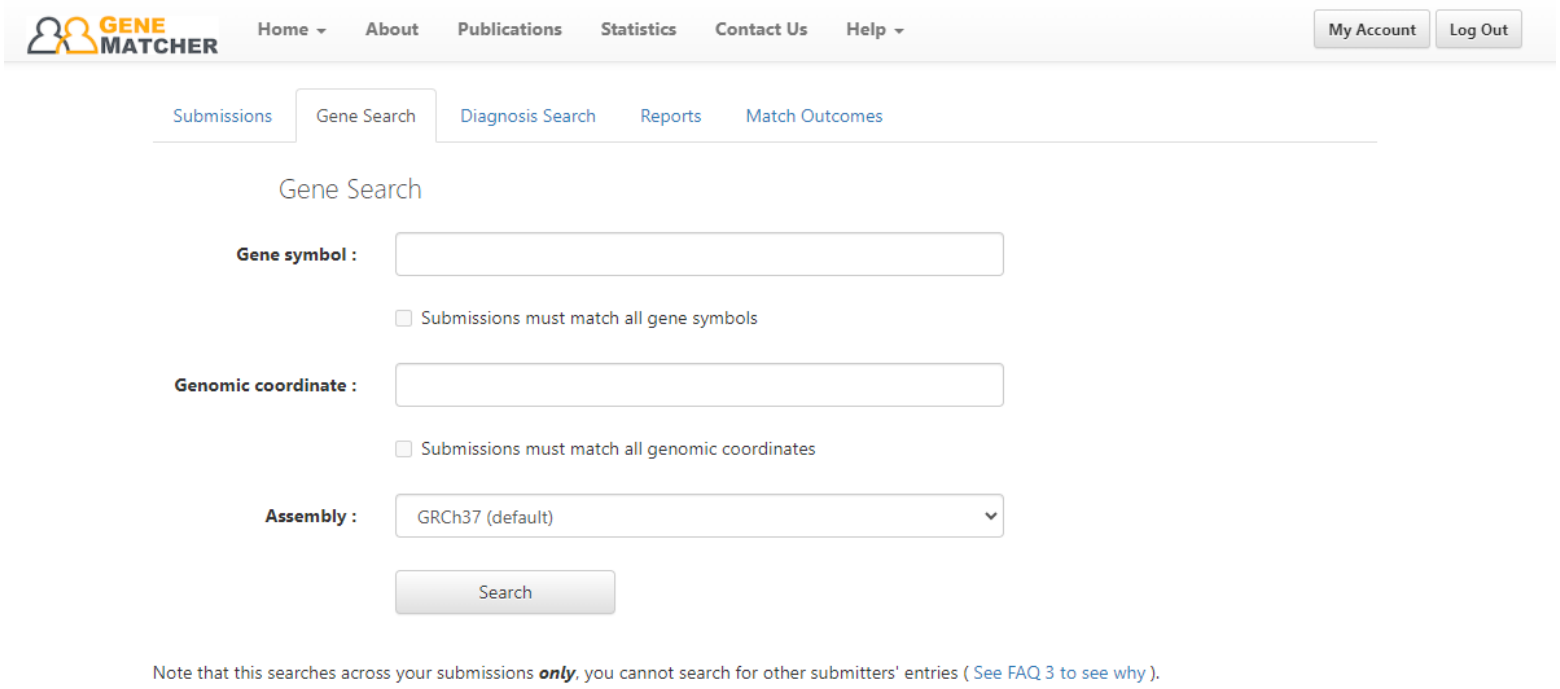
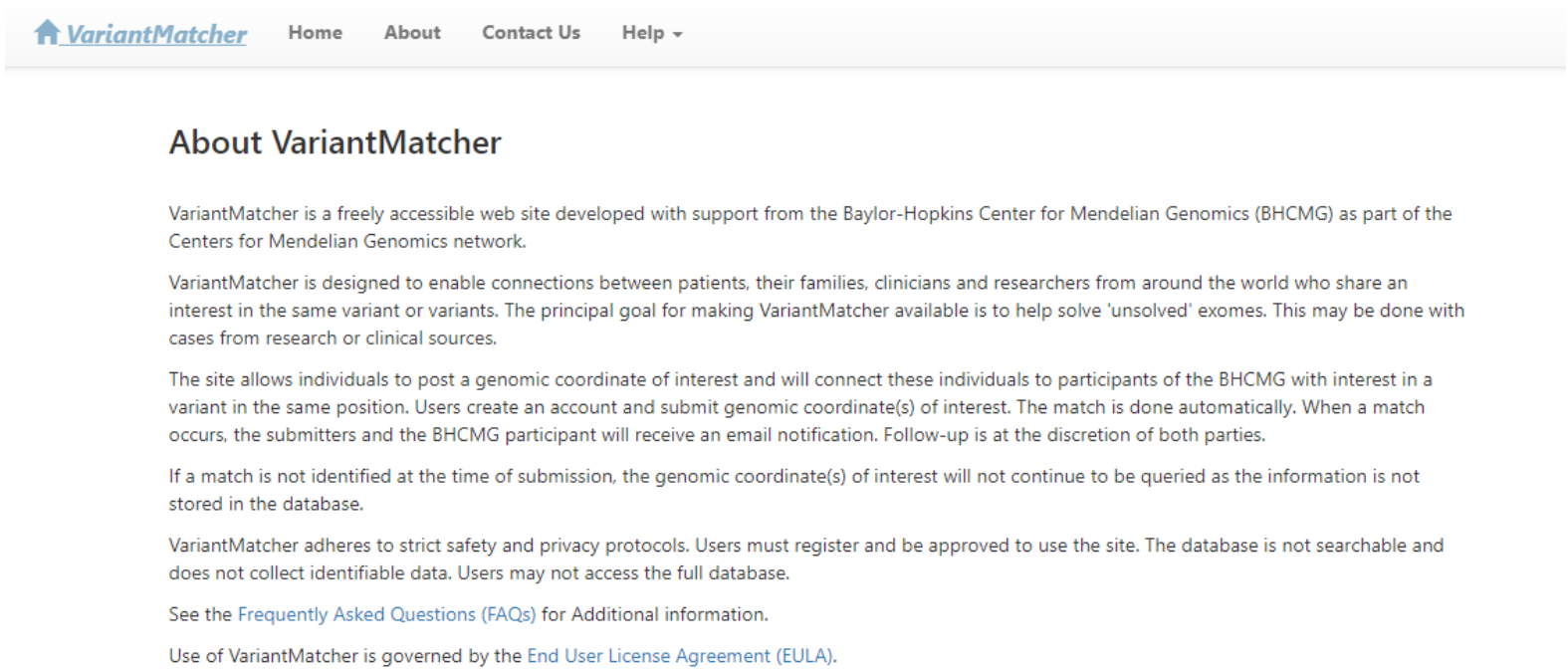
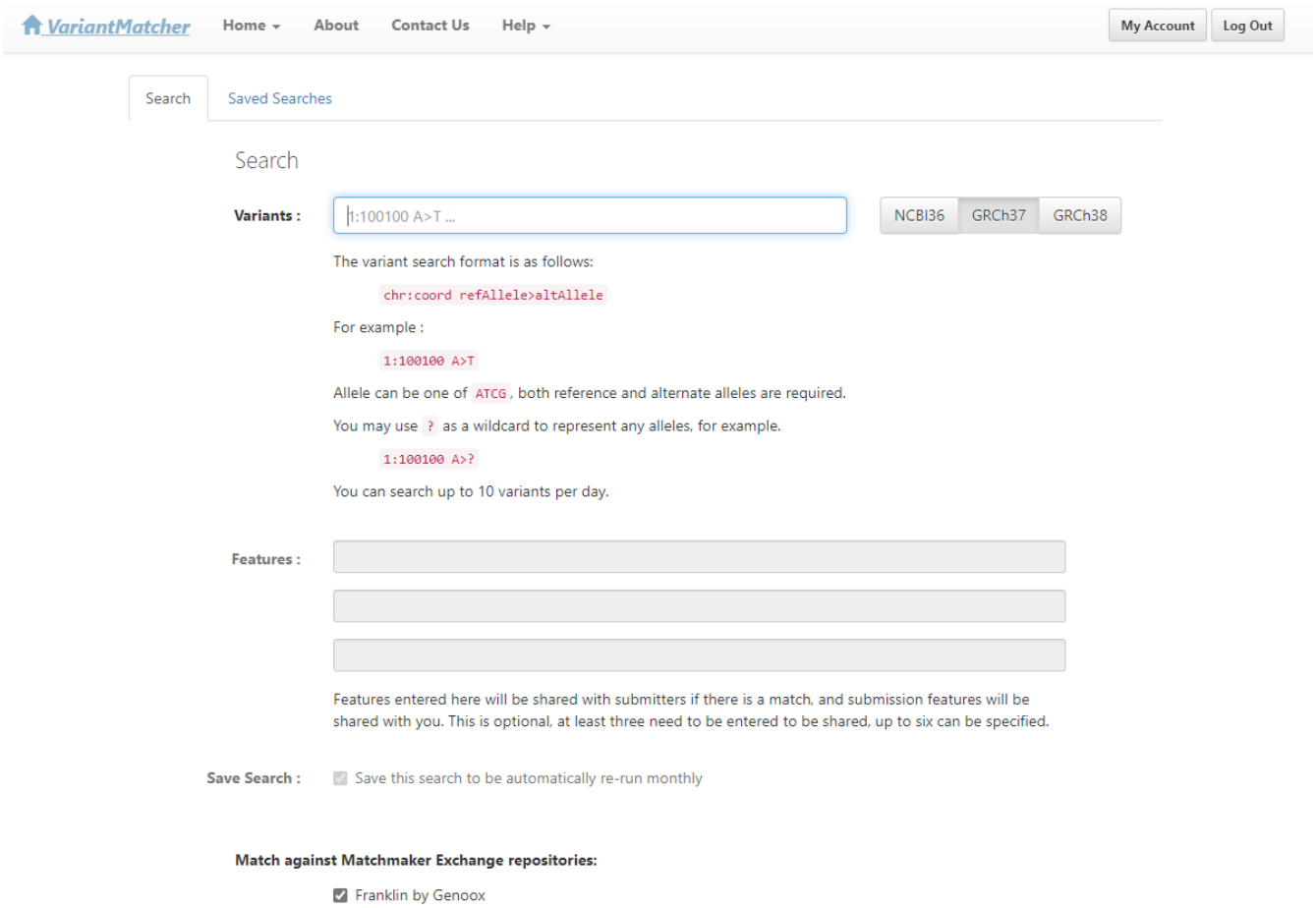
GeneMatcher



https://variantmatcher.org



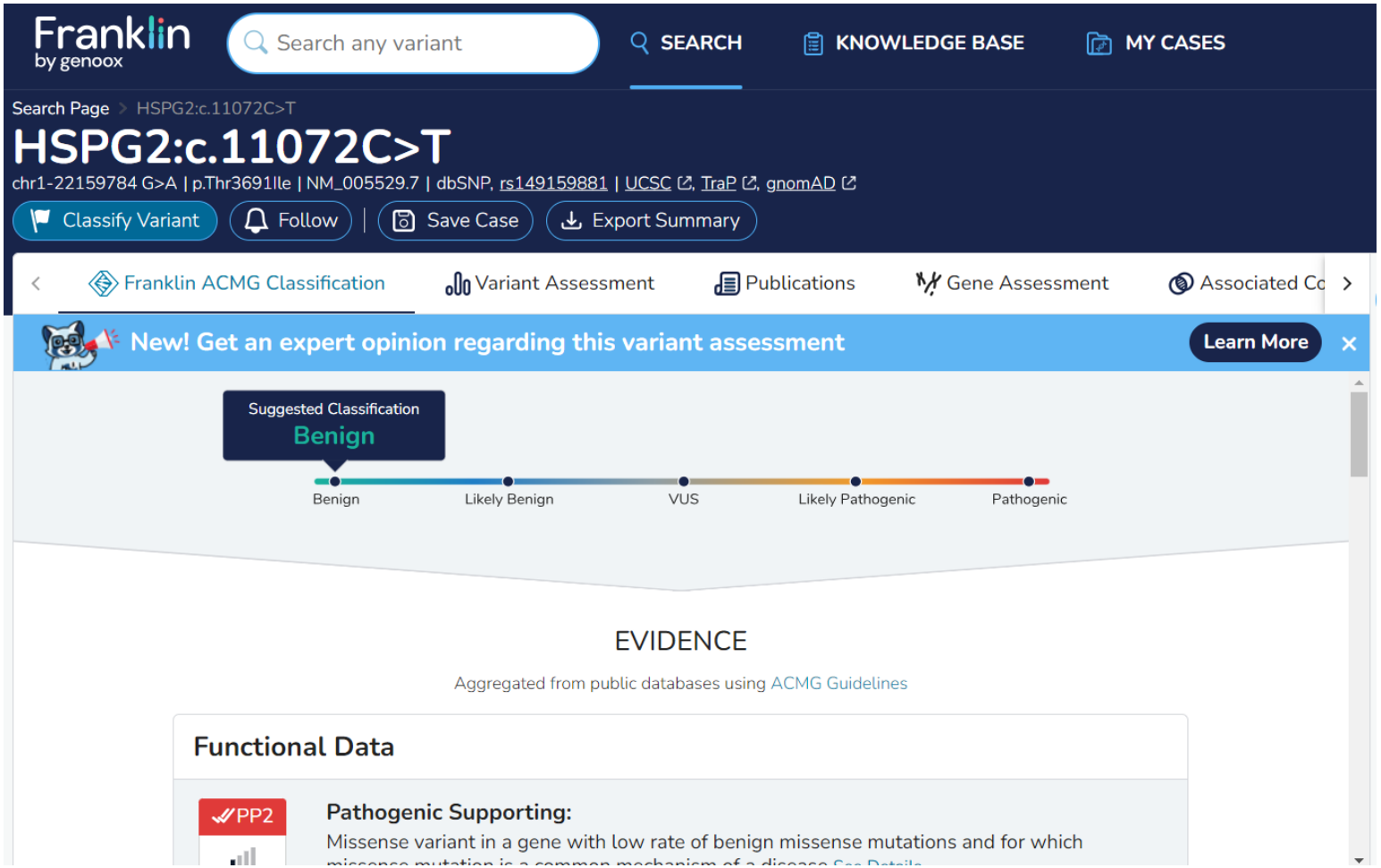
VariantMatcher



Variant evaluation

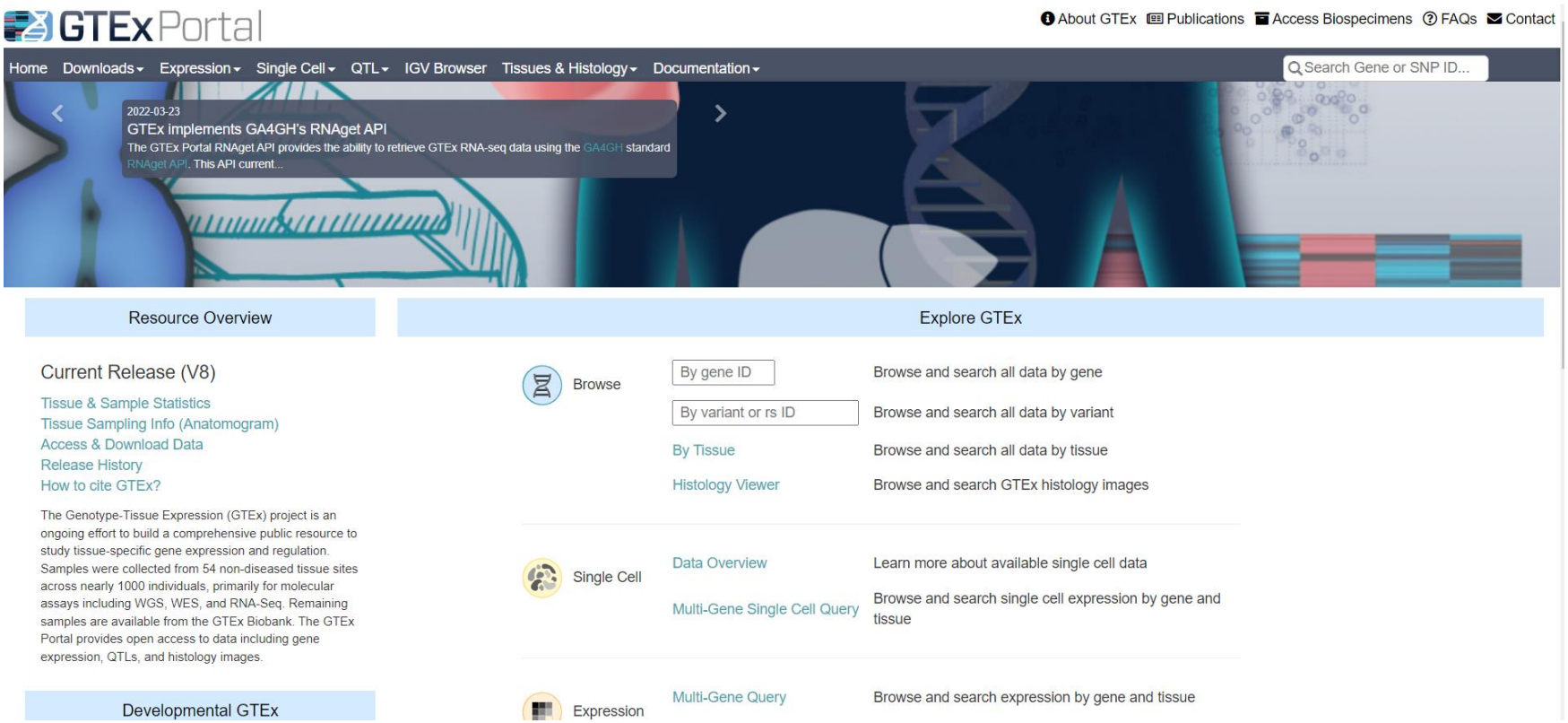
- individual search
- in-house pipelines (API)
- free/commercial portals

https://franklin.genoox.com/



https://franklin.genoox.com/

https://gtexportal.org/home/



Expression OBSL1

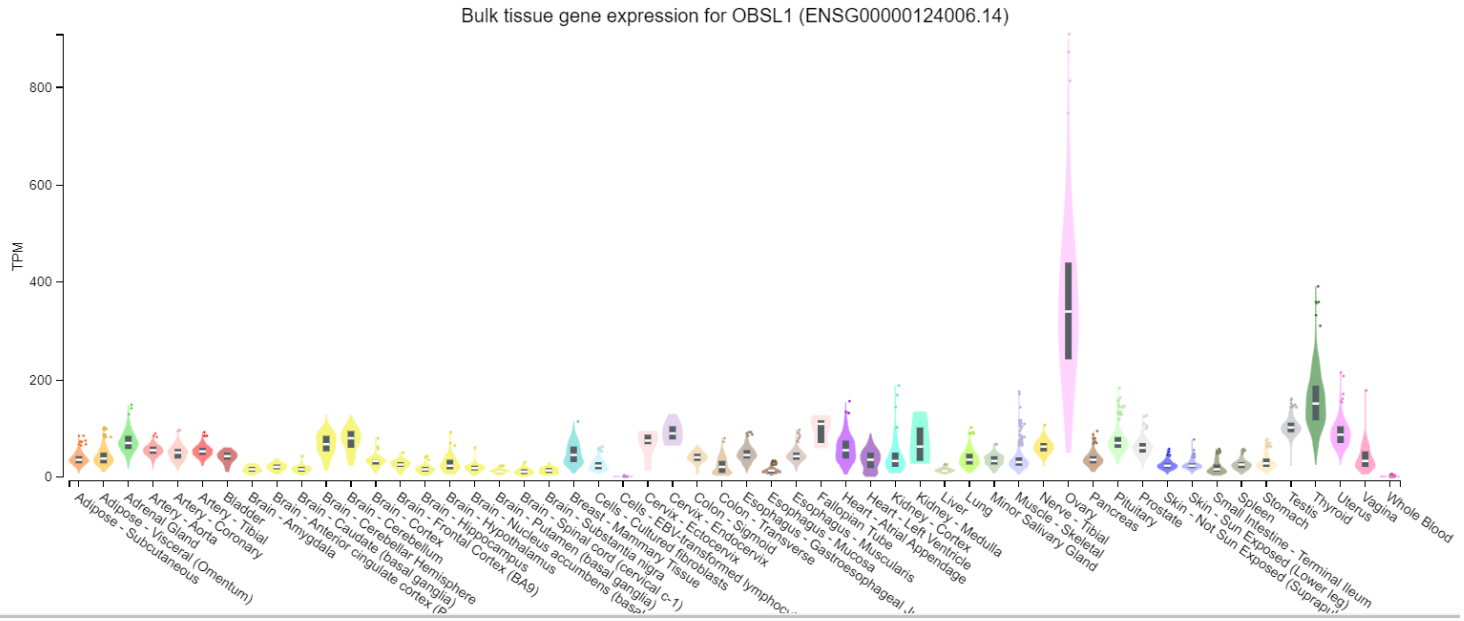
Bulk tissue gene expression for OBSL1 (ENSG00000124006.14)

Data Source: GTEx Analysis Release V8 (dbGaP Accession phs000424.v8.p2)

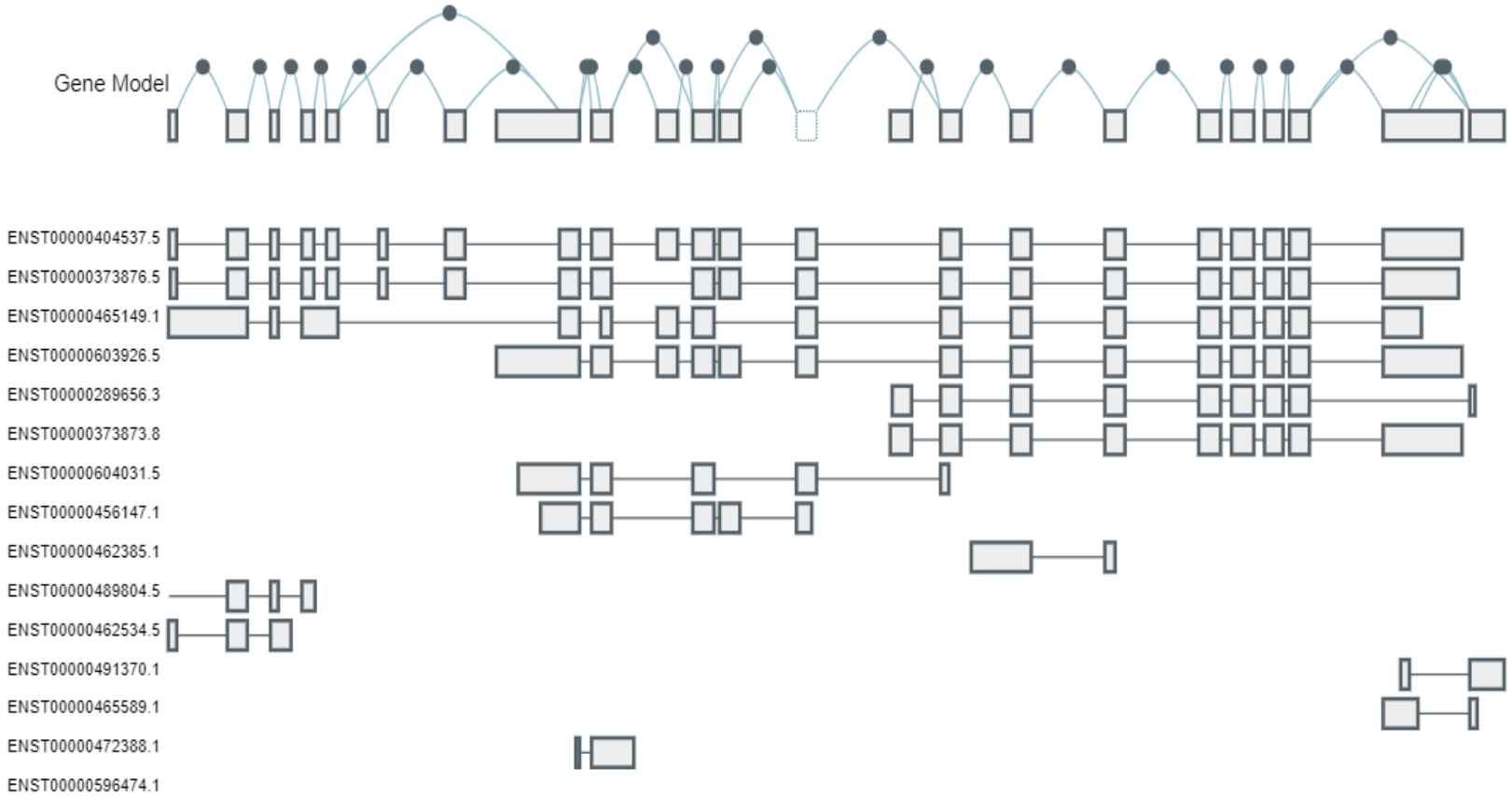
Data processing and normalization

Top
Bulk Tissue Expression
Single Cell Expression
Exon Expression
Single-Tissue eQTLs
Single-Tissue sQTLs
Single-Tissue ieQTLs
Single-Tissue isQTLs

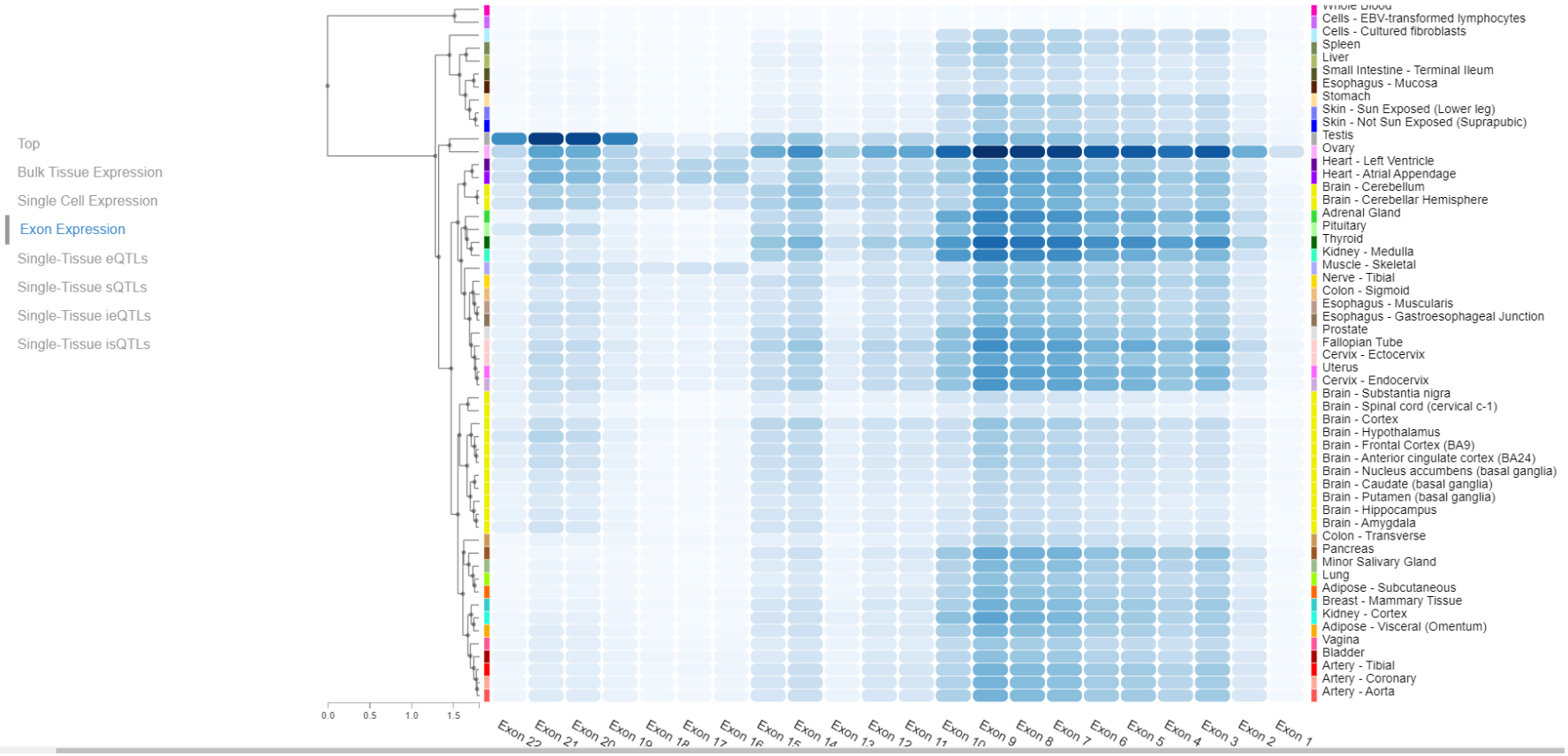
SUBSET None Sex SCALE Log Linear TISSUE SORT MEDIAN SORT OUTLIERS On Off



Exon expression OBSL1

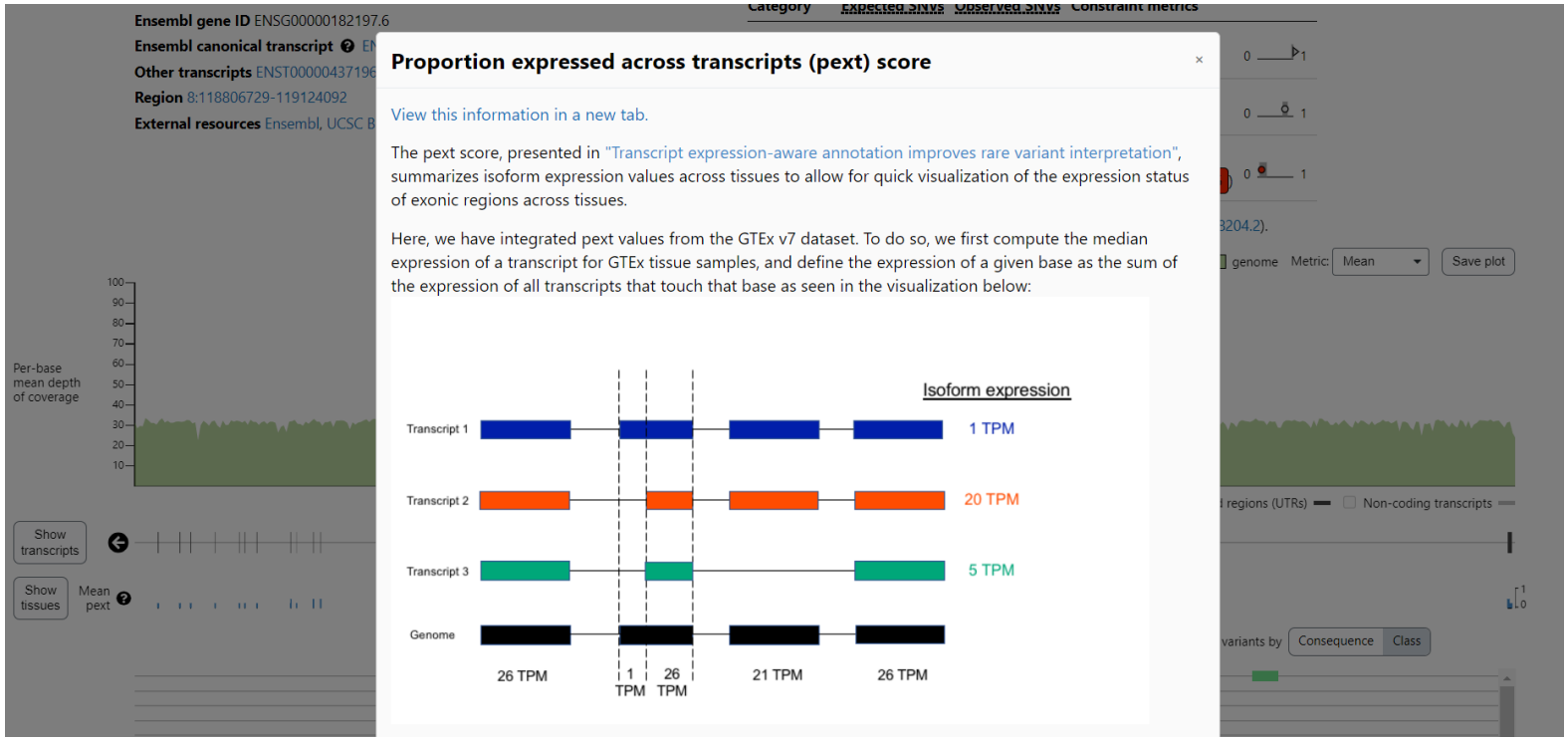


Exon expression OBSL1



Exon expression in GnomAD

Exon expression in GnomAD



Exon expression in GnomAD

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

MANE

Matched Annotation from NCBI and EMBL-EBI (MANE)

What is MANE?

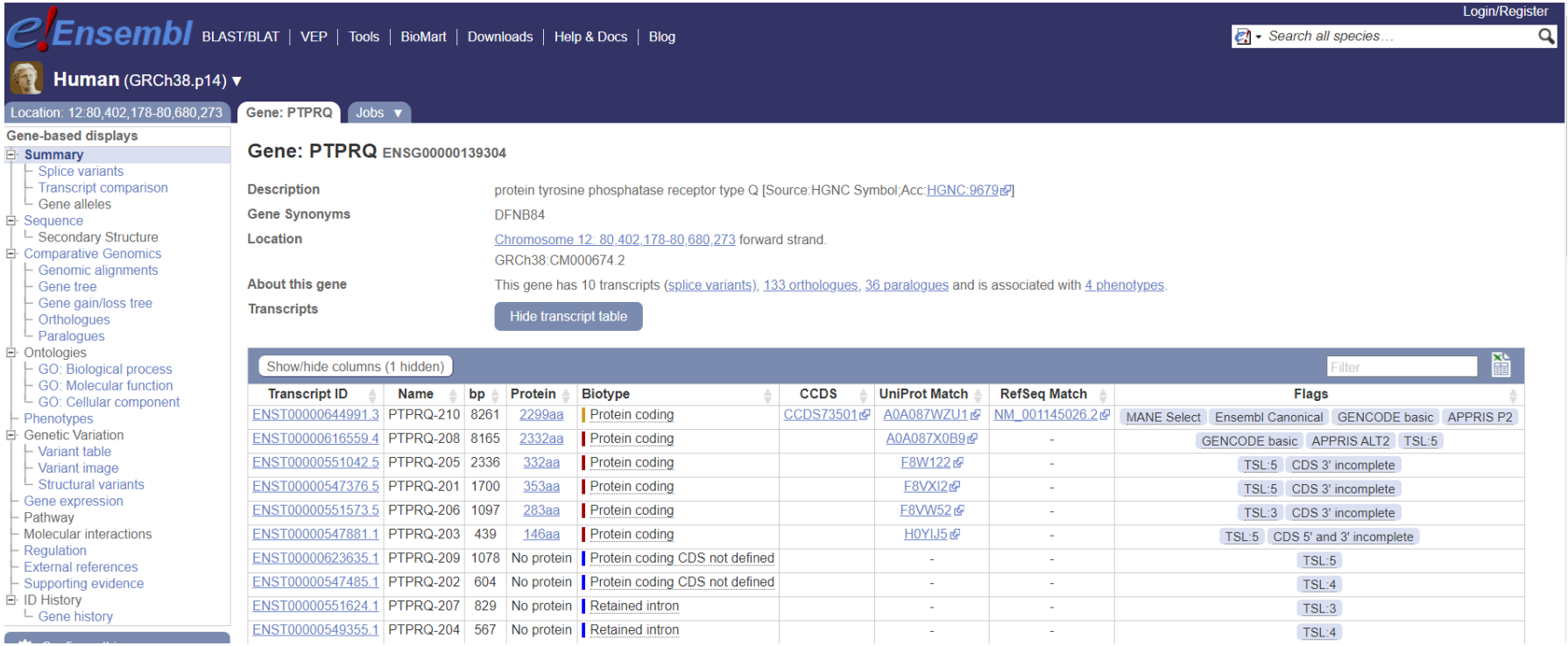
The MANE project - The Matched Annotation from the NCBI and EMBL-EBI (MANE) is a collaborative project that aims to converge on human gene and transcript annotation and to define a genome wide set of representative transcripts and corresponding proteins for human protein-coding genes. Each MANE transcript represents an exact match in exonic regions between a Refseq transcript and its counterpart in the Ensembl/GENCODE annotation such that the two identifiers can be used synonymously. Further, a MANE transcript matches GRCh38 reference genome assembly perfectly, and is chosen based on biologically relevant criteria such as transcript expression levels and conservation of coding regions. Currently, the deliverables of the project include:

MANE Select: The MANE Select set consists of one transcript at each protein-coding locus across the genome that is representative of biology at that locus. This set is useful as a universal standard for clinical reporting, as a default for display on browsers and key genomic resources, and as a starting point for comparative or evolutionary genomics. MANE Select transcripts are identified using computational methods complemented by manual review and discussion.

MANE Plus Clinical: The MANE Plus Clinical set includes additional transcripts for genes where MANE Select alone is not sufficient to report all "Pathogenic (P)" or "Likely Pathogenic (LP)" clinical variants available in public resources.

Watch the MANE webinar on YouTube!

Reference sequences



Ensembl BLAST/BLAT | VEP | Tools | BioMart | Downloads | Help & Docs | Blog

Login/Register

Search all species…

Human (GRCh38.p14) ▾

Location: 12:80,402,178-80,680,273 | Gene: PTPRQ | Jobs ▾

Gene-based displays

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

Gene: PTPRQ ENSG00000139304

Description protein tyrosine phosphatase receptor type Q [Source:HGNC Symbol;Acc:HGNC:9679]

Gene Synonyms DFNB84

Location Chromosome 12: 80,402,178-80,680,273 forward strand.
GRCh38:CM000674.2

About this gene This gene has 10 transcripts (splice variants), 133 orthologues, 36 paralogues and is associated with 4 phenotypes.

Transcripts Hide transcript table

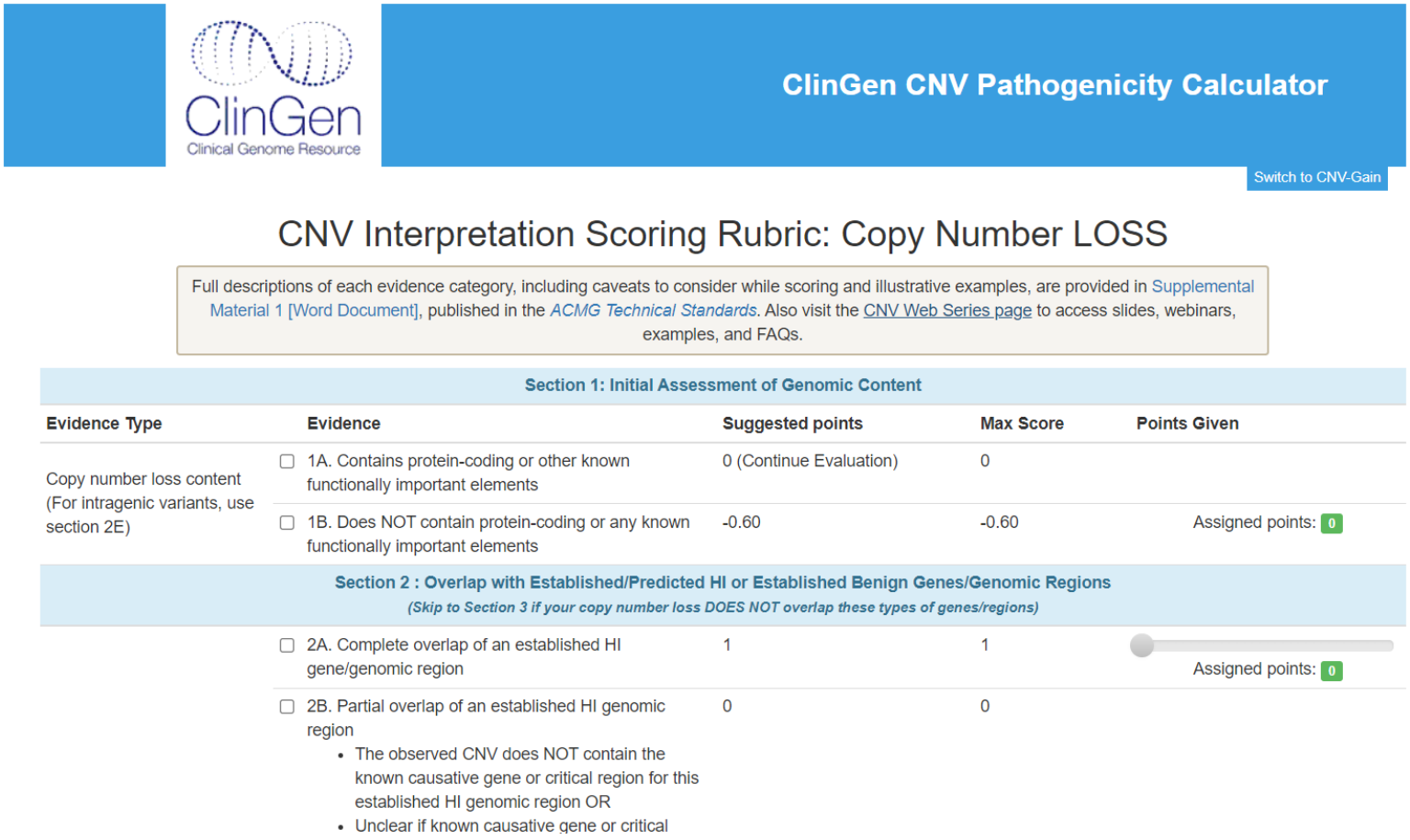
Show/hide columns (1 hidden) | Filter

Transcript ID	Name	bp	Protein	Biotype	CCDS	UniProt Match	RefSeq Match	Flags
ENST00000644991.3	PTPRQ-210	8261	2299aa	Protein coding	CCDS73501	A0A087WZU1	NM_001145026.2	MANE Select, Ensembl Canonical, GENCODE basic, APPRIS P2
ENST00000616559.4	PTPRQ-208	8165	2332aa	Protein coding		A0A087X0B9	-	GENCODE basic, APPRIS ALT2, TSL:5
ENST00000551042.5	PTPRQ-205	2336	332aa	Protein coding		F8W122	-	TSL:5, CDS 3' incomplete
ENST00000547376.5	PTPRQ-201	1700	353aa	Protein coding		F8VXI2	-	TSL:5, CDS 3' incomplete
ENST00000551573.5	PTPRQ-206	1097	283aa	Protein coding		F8VW52	-	TSL:3, CDS 3' incomplete
ENST00000547881.1	PTPRQ-203	439	146aa	Protein coding		H0YIJ5	-	TSL:5, CDS 5' and 3' incomplete
ENST00000623635.1	PTPRQ-209	1078	No protein	Protein coding CDS not defined		-	-	TSL:5
ENST00000547485.1	PTPRQ-202	604	No protein	Protein coding CDS not defined		-	-	TSL:4
ENST00000551624.1	PTPRQ-207	829	No protein	Retained intron		-	-	TSL:3
ENST00000549355.1	PTPRQ-204	567	No protein	Retained intron		-	-	TSL:4

Structural variants

" A heterozygous deletion was identified on chr17:37,500,431-37,845,059 (hg38)"

Structural variants



ClinGen Clinical Genome Resource

ClinGen CNV Pathogenicity Calculator

Switch to CNV-Gain

CNV Interpretation Scoring Rubric: Copy Number LOSS

Full descriptions of each evidence category, including caveats to consider while scoring and illustrative examples, are provided in Supplemental Material 1 [Word Document], published in the *ACMG Technical Standards*. Also visit the CNV Web Series page to access slides, webinars, examples, and FAQs.

Section 1: Initial Assessment of Genomic Content

Evidence Type	Evidence	Suggested points	Max Score	Points Given
Copy number loss content (For intragenic variants, use section 2E)	☐ 1A. Contains protein-coding or other known functionally important elements	0 (Continue Evaluation)	0	
	☐ 1B. Does NOT contain protein-coding or any known functionally important elements	-0.60	-0.60	Assigned points: 0

Section 2 : Overlap with Established/Predicted HI or Established Benign Genes/Genomic Regions

(Skip to Section 3 if your copy number loss DOES NOT overlap these types of genes/regions)

	☐ 2A. Complete overlap of an established HI gene/genomic region	1	1	Assigned points: 0
	☐ 2B. Partial overlap of an established HI genomic region • The observed CNV does NOT contain the known causative gene or critical region for this established HI genomic region OR • Unclear if known causative gene or critical	0	0	

Structural variants

Section 1: Initial Assessment of Genomic Content

Section 2 : Overlap with Established/Predicted HI or Established Benign Genes/Genomic Regions

(Skip to Section 3 if your copy number loss DOES NOT overlap these types of genes/regions)

Section 3: Evaluation of Gene Number

Section 4: Detailed Evaluation of Genomic Content Using Published Literature, Public Databases, and/or Internal Lab Data

(Skip to Section 5 if either your CNV overlapped with an established HI gene/region in Section 2, OR there have been no reports associating either the CNV or any genes within the CNV with human phenotypes caused by loss of function (LOF) or copy number loss)

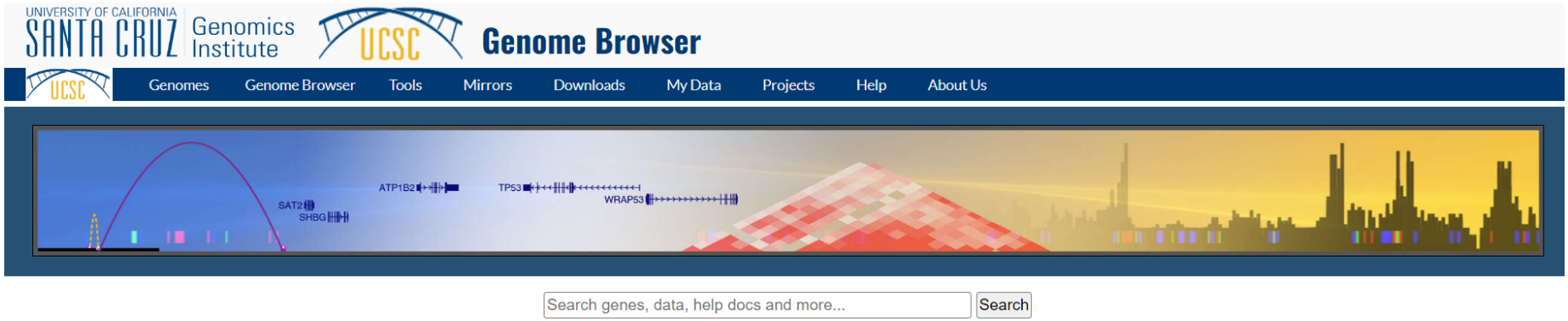
Section 5: Evaluation of Inheritance Pattern/Family History for Patient Being Studied

Genome browsers

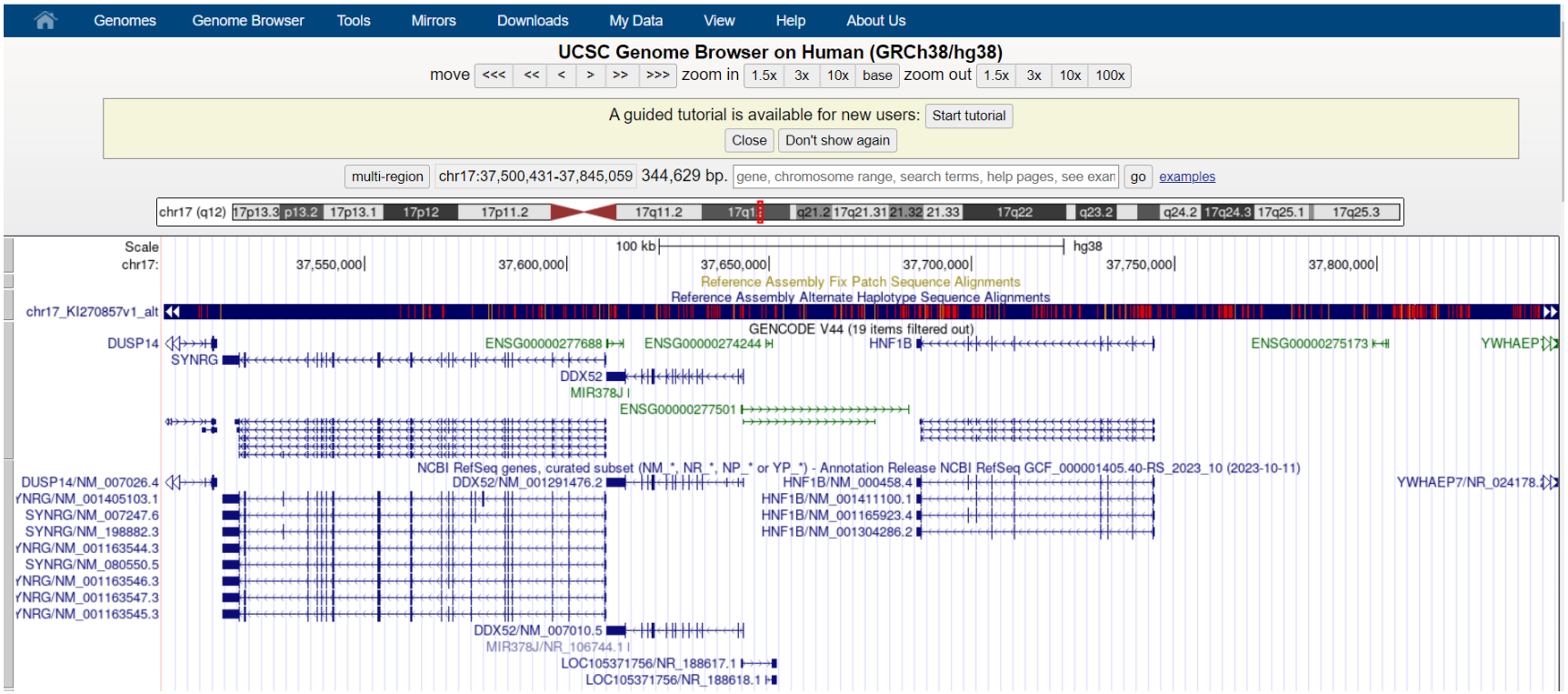
- ENSEMBL:
  http://www.ensembl.org/index.html

- UCSC :
  http://genome.ucsc.edu/

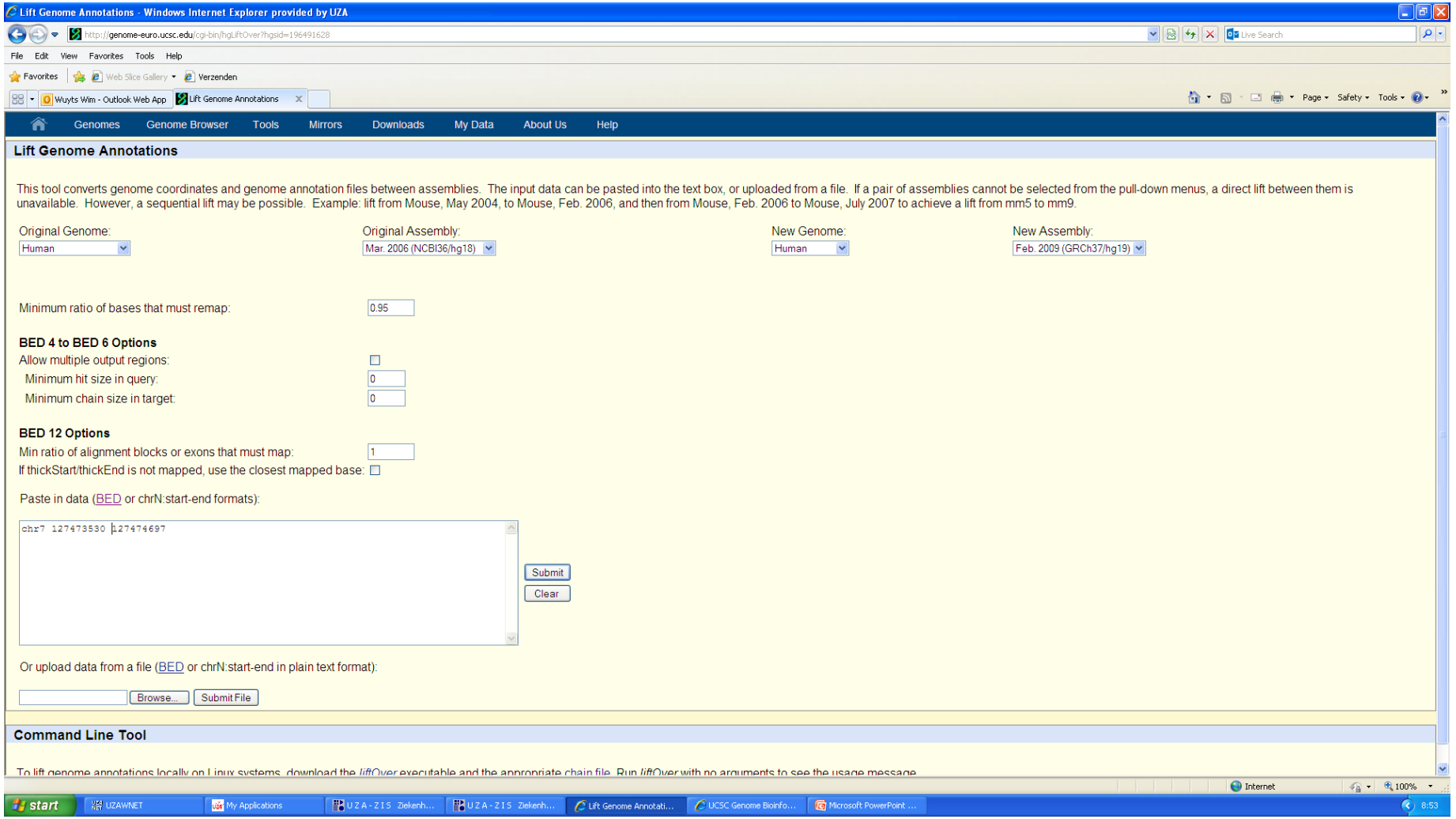
http://genome.ucsc.edu/

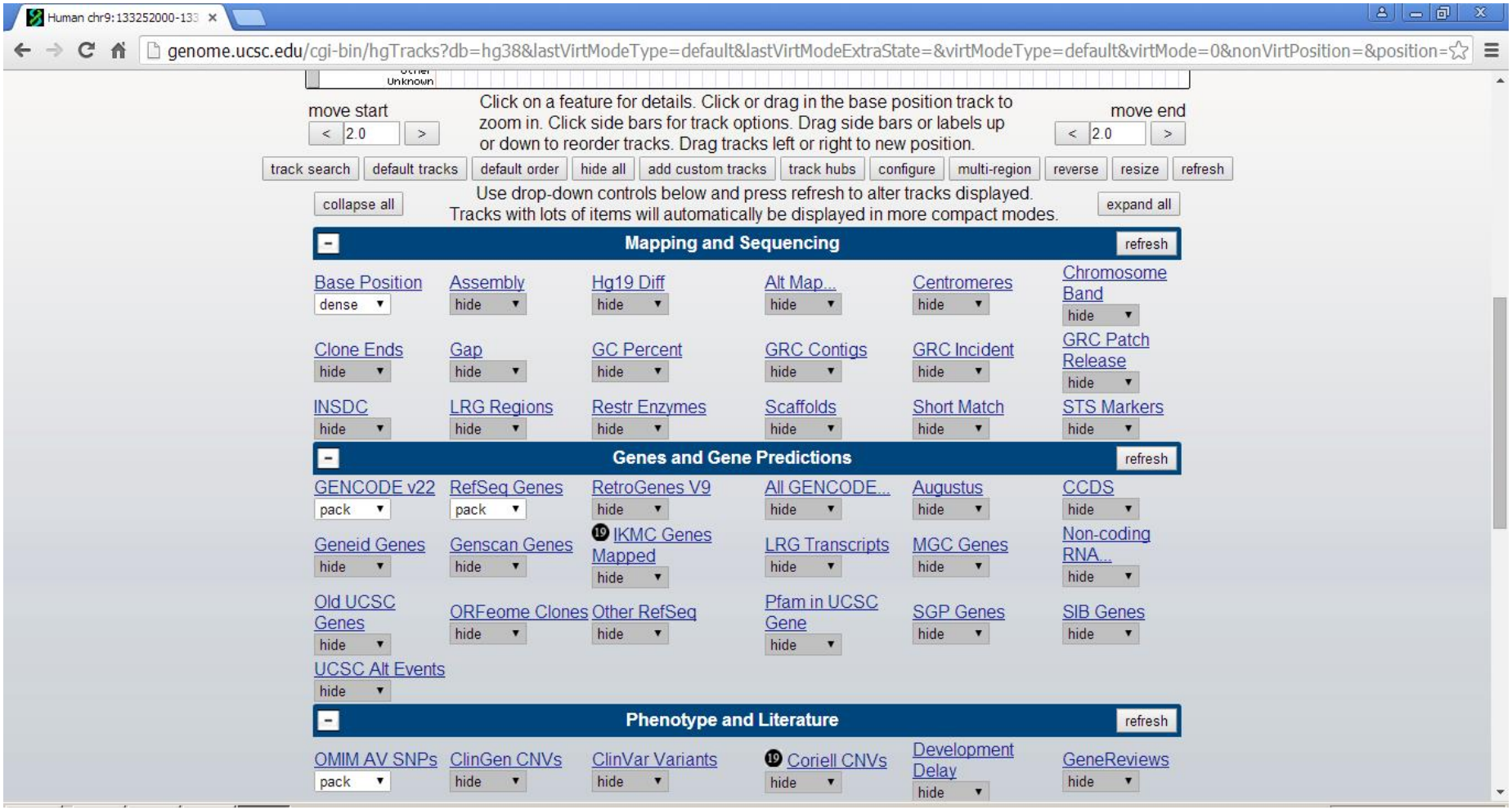


Del chr17:37,500,431-37,845,059



Assembly converter




Human chr9:133252000-133
genome.ucsc.edu/cgi-bin/hgTracks?db=hg38&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=
Unknown
move start
< 2.0 >
Click on a feature for details. Click or drag in the base position track to zoom in. Click side bars for track options. Drag side bars or labels up or down to reorder tracks. Drag tracks left or right to new position.
move end
< 2.0 >
track search
default tracks
default order
hide all
add custom tracks
track hubs
configure
multi-region
reverse
resize
refresh
collapse all
Use drop-down controls below and press refresh to alter tracks displayed.
Tracks with lots of items will automatically be displayed in more compact modes.
expand all
Mapping and Sequencing
refresh
Base Position
dense
Assembly
hide
Hg19 Diff
hide
Alt Map...
hide
Centromeres
hide
Chromosome Band
hide
Clone Ends
hide
Gap
hide
GC Percent
hide
GRC Contigs
hide
GRC Incident
hide
GRC Patch Release
hide
INSDC
hide
LRG Regions
hide
Restr Enzymes
hide
Scaffolds
hide
Short Match
hide
STS Markers
hide
Genes and Gene Predictions
refresh
GENCODE v22
pack
RefSeq Genes
pack
RetroGenes V9
hide
All GENCODE...
hide
Augustus
hide
CCDS
hide
Geneid Genes
hide
Genscan Genes
hide
IKMC Genes Mapped
hide
LRG Transcripts
hide
MGC Genes
hide
Non-coding RNA...
hide
Old UCSC Genes
hide
ORFeome Clones
hide
Other RefSeq
hide
Pfam in UCSC Gene
hide
SGP Genes
hide
SIB Genes
hide
UCSC Alt Events
hide
Phenotype and Literature
refresh
OMIM AV SNPs
pack
ClinGen CNVs
hide
ClinVar Variants
hide
Coriell CNVs
hide
Development Delay
hide
GeneReviews
hide

http://www.ncbi.nlm.nih.gov/