



Data mining

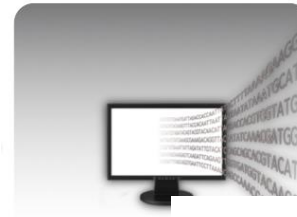
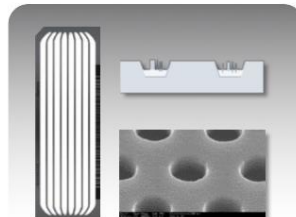
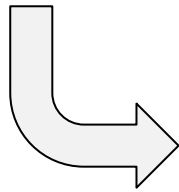
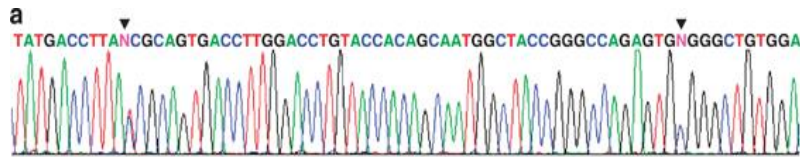


Geert Vandeweyer
Wim Wuyts

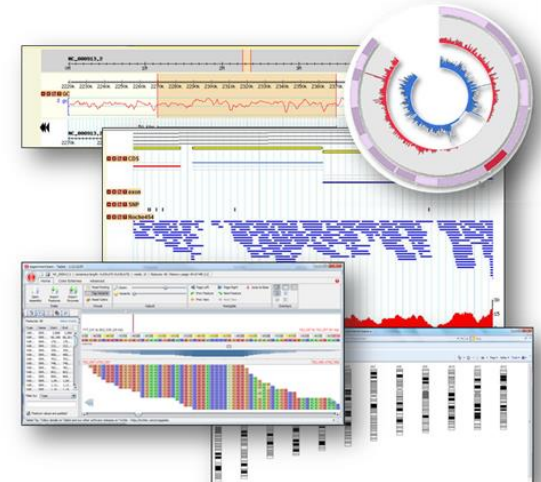
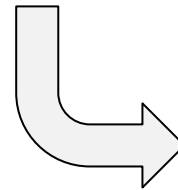


Scaling up Medical Genetics

High-Throughput Clinical Genomics

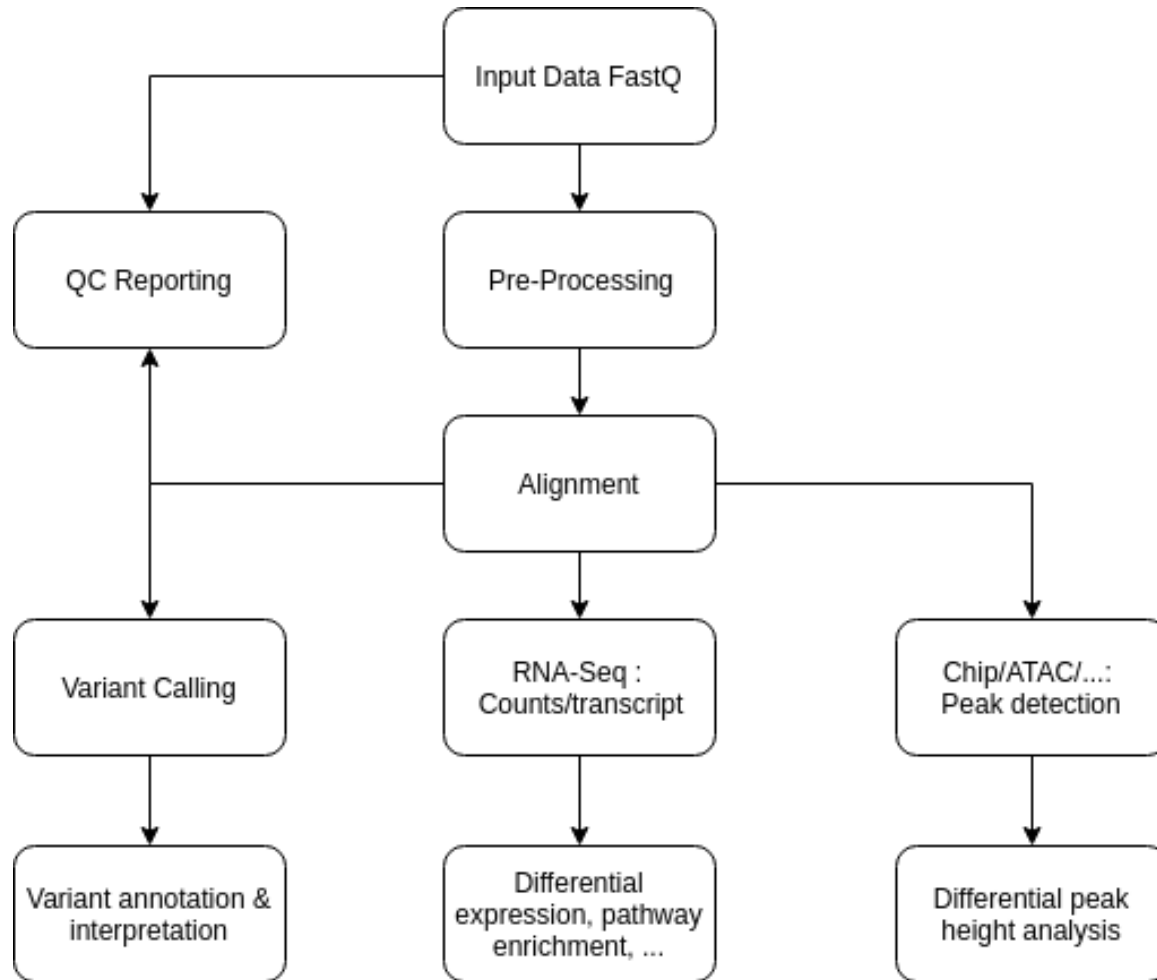


Goal 1 : Understand the data
Goal 2 : Interpret the data



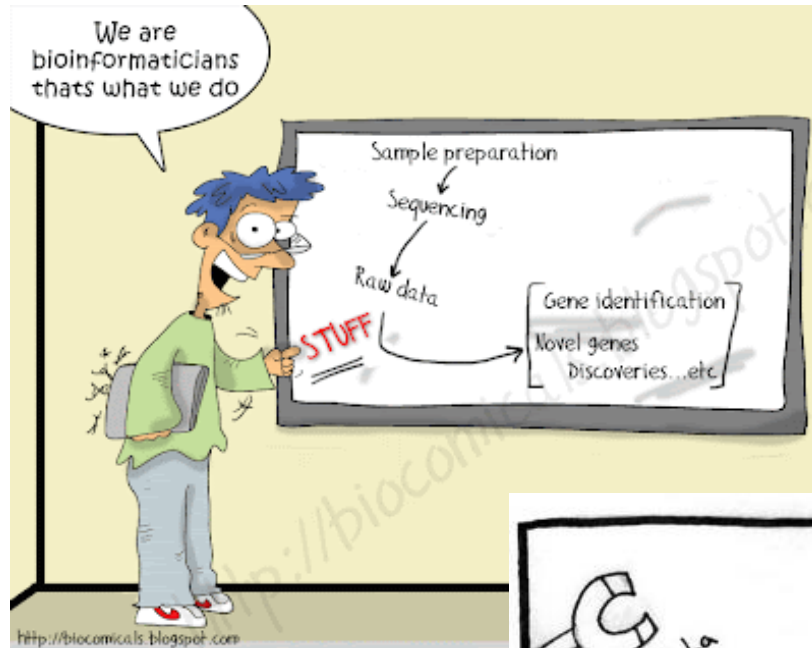


NGS in Medical Genetics

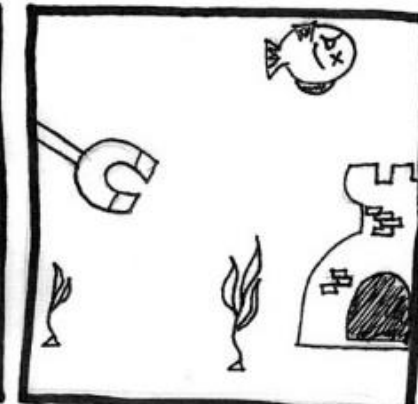
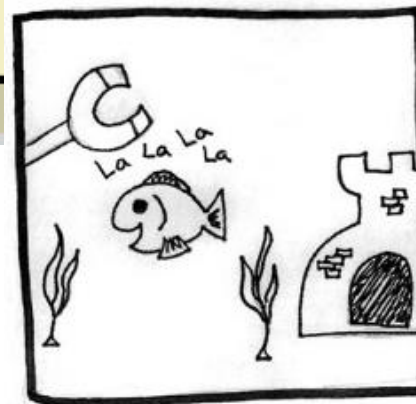




Generating Variant Data



Understand the data !



Let's see if the subject responds to magnetic stimuli... ADMINISTER THE MAGNET!

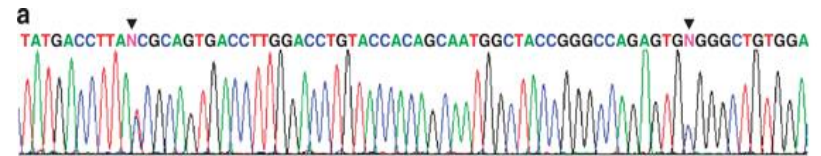
Interesting...there seems to be a significant decrease in heart rate. The fish must sense the magnetic field.



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  
GCTCTAGATCGATCTATAACCGAT
```

- 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

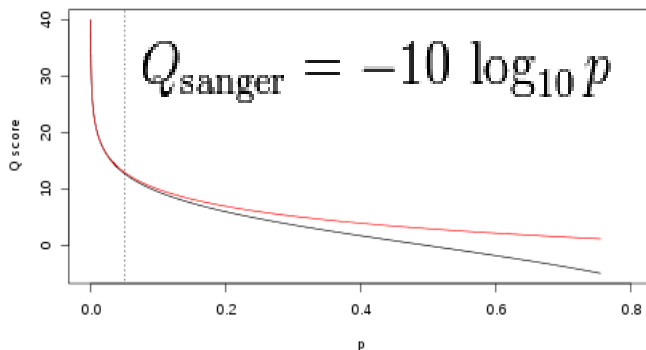
- FASTA :

```
>Sequence_Name  
AACTACTAGATACTGATAGTATATCTCTCTTAATCGA  
GCTCTAGATCGATCTATAACCGAT
```

- 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



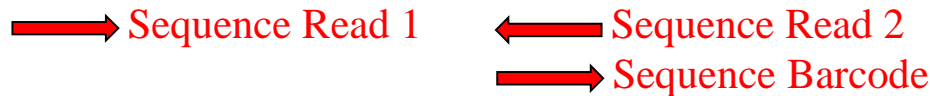
Generating Variant Data

Issue: artificial sequences

```

PE Adapter1:
5' -----ACACTCTTCCCTAC ACGACGCTCTCCGATCT (-) ----- 3'
3' -----TGTGAGAAAGGGATG TGCTGCGAGAAGGCTAGp (-) ----- 5'
PE Adapter2:
5' ----- (-) pGATCGGAAGAGCGGTTCAG CAGGAATGCCGAG----- 3'
3' ----- (-) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTC----- 5'
PE PCR Primer1:
5' AATGATACGGCGAACCACCGA GATCTACACTCTTCCCTAC ACGACGCTCTCCGATCT (-) ----- 3'
3' ----- (-) ----- 5'
PE PCR Primer2:
5' ----- (-) ----- 3'
3' ----- (-) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTCTGGCTAG AGCATACGGCAGAGAAGACGAA C 5'
Result Library:
5' AATGATACGGCGAACCACCGA GATCTACACTCTTCCCTAC ACGACGCTCTCCGATCT (N) AGATCGGAAGAGCGGTTCAG CAGGAATGCCGAGACCGATC TCGTATGCCGCTCTTCTGCTT G 3'
3' TTACTATGCCGCTGGTGGCT CTAGATGTGAGAAAGGGATG TGCTGCGAGAAGGCTAGA (N) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTCTGGCTAG AGCATACGGCAGAGAAGACGAA C 5'
PE DNA Sequencing Primer1
5' -----ACACTCTTCCCTAC ACGACGCTCTCCGATCT (-) ----- 3'
3' ----- (-) ----- 5'
PE DNA Sequencing Primer2
5' ----- (-) ----- 3'
3' ----- (-) TCTAGCCTTCTCGCCAAGTC GTCCTTACGGCTCTGGC----- 5'

```



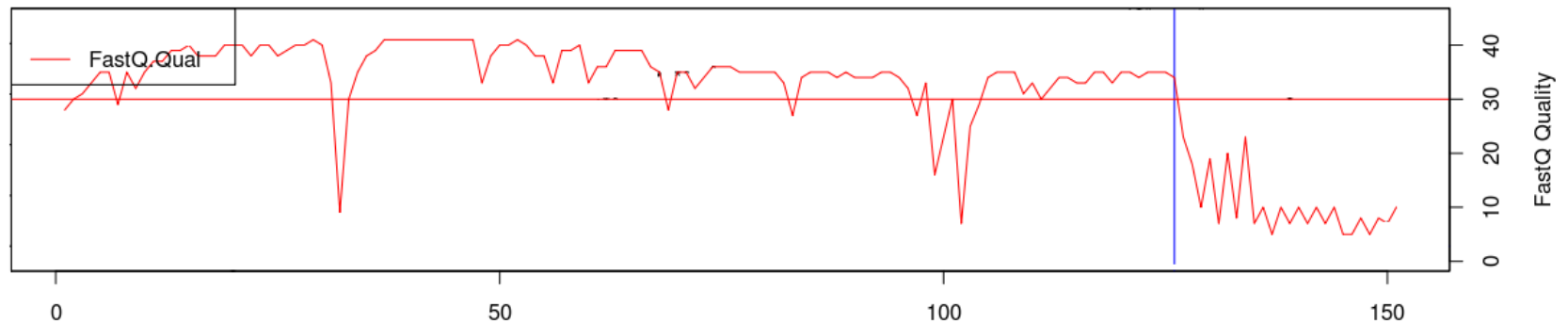
Scan all reads for presence of artificial sequence & remove them from the reads

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



Generating Variant Data

Issue: low quality sequences



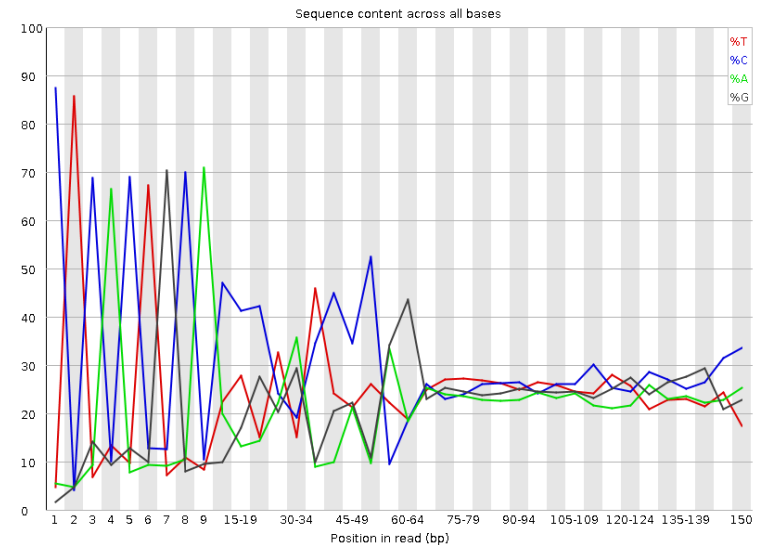
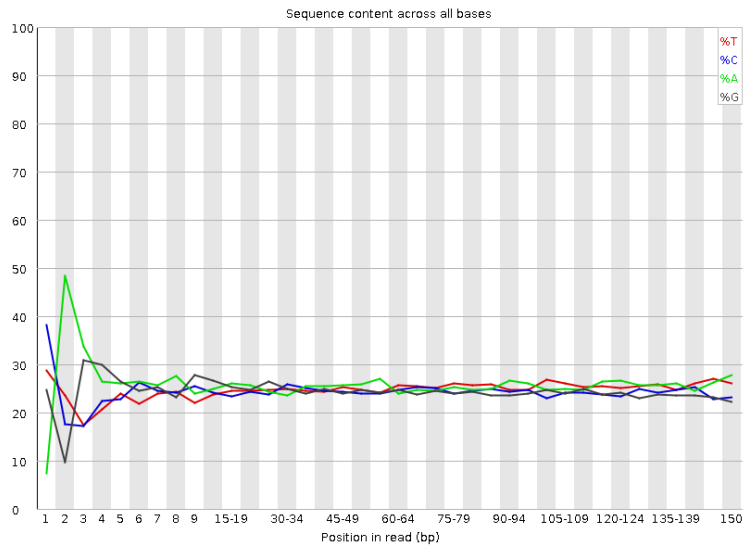
- Low quality leads to high error rates (cfr Phred Score)
 - => We want a limit of 1 error in 1000 positions
 - => Due to chemical degradation, 3' ends are lower quality
 - => Trim everything on 3' end with quality < 30



Generating Variant Data

Issue: contamination ?

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

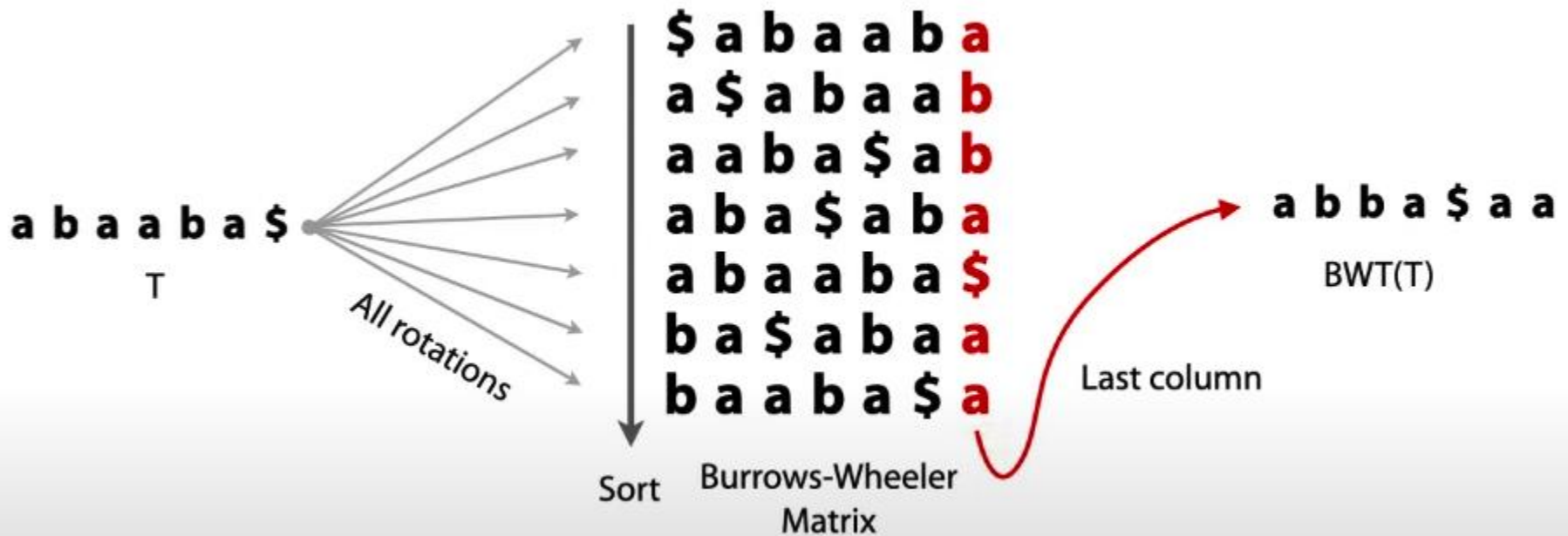




Generating Variant Data

Read Alignment

Burrows-Wheeler Transformation:





Generating Variant Data

Read Alignment

Burrows-Wheeler Transformation:

\$ a₀ b₀ a₁ a₂ b₁ a₃
a₃ \$ a₀ b₀ a₁ a₂ b₁
a₁ a₂ b₁ a₃ \$ a₀ b₀
a₂ b₁ a₃ \$ a₀ b₀ a₁
a₀ b₀ a₁ a₂ b₁ a₃ \$
b₁ a₃ \$ a₀ b₀ a₁ a₂
b₀ a₁ a₂ b₁ a₃ \$ a₀



F *L*

\$ **a₀** **b₀** **a₁** **a₂** **b₁** **a₃**
a₃ **\$** **a₀** **b₀** **a₁** **a₂** **b₁**
a₁ **a₂** **b₁** **a₃** **\$** **a₀** **b₀**
a₂ **b₁** **a₃** **\$** **a₀** **b₀** **a₁**
a₀ **b₀** **a₁** **a₂** **b₁** **a₃** **\$**
b₁ **a₃** **\$** **a₀** **b₀** **a₁** **a₂**
b₀ **a₁** **a₂** **b₁** **a₃** **\$** **a₀**



Generating Variant Data

Read Alignment

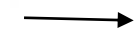
Burrows-Wheeler Transformation:

a b a a b a \$

\$	a ₀	b ₀	a ₁	a ₂	b ₁	a ₃
a ₃	\$	a ₀	b ₀	a ₁	a ₂	b ₁
a ₁	a ₂	b ₁	a ₃	\$	a ₀	b ₀
a ₂	b ₁	a ₃	\$	a ₀	b ₀	a ₁
a ₀	b ₀	a ₁	a ₂	b ₁	a ₃	\$
b ₁	a ₃	\$	a ₀	b ₀	a ₁	a ₂
b ₀	a ₁	a ₂	b ₁	a ₃	\$	a ₀



<i>F</i>								<i>L</i>
\$	a ₀	b ₀	a ₁	a ₂	b ₁	a ₃		a ₃
a ₃	\$	a ₀	b ₀	a ₁	a ₂	b ₁		b ₁
a ₁	a ₂	b ₁	a ₃	\$	a ₀	b ₀		b ₀
a ₂	b ₁	a ₃	\$	a ₀	b ₀	a ₁		a ₁
a ₀	b ₀	a ₁	a ₂	b ₁	a ₃	\$		\$
b ₁	a ₃	\$	a ₀	b ₀	a ₁	a ₂		a ₂
b ₀	a ₁	a ₂	b ₁	a ₃	\$	a ₀		a ₀



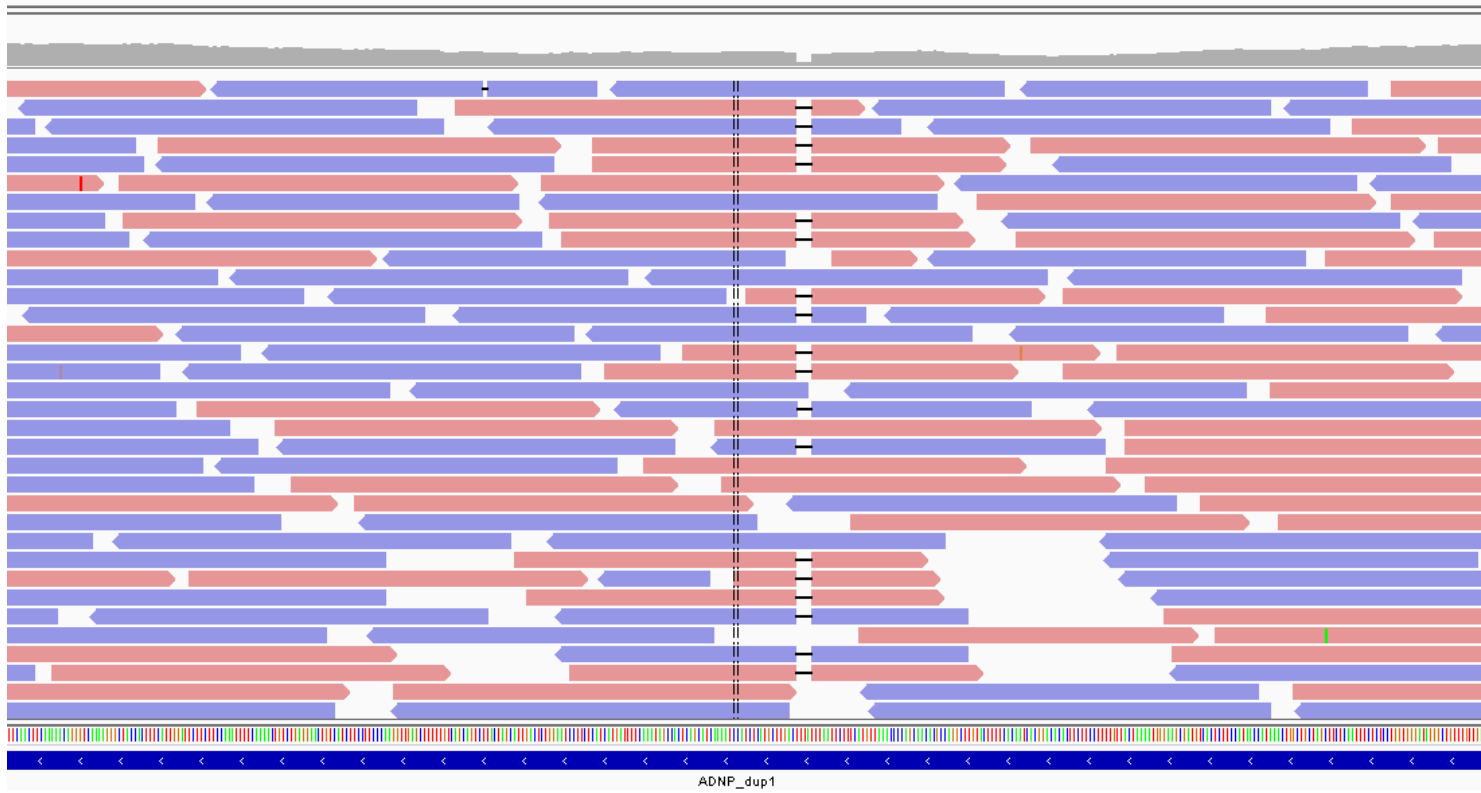
		a	b	a	
<i>F</i>					<i>L</i>
\$					a ₃
a ₃					b ₁
a ₁					b ₀
a ₂					a ₁
a ₀					\$
b ₁					a ₂
b ₀					a ₀

Alignment Works Back to Front !



Generating Variant Data

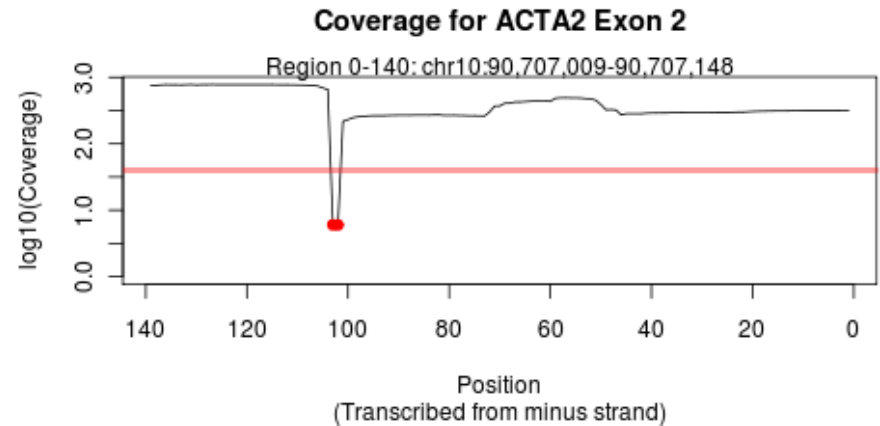
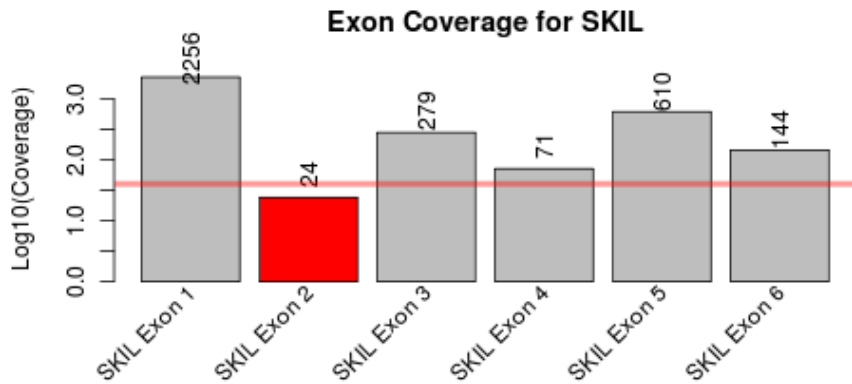
Read Alignment : Result: [BS]AM file





Generating Variant Data

Read Alignment : Quality Checks :

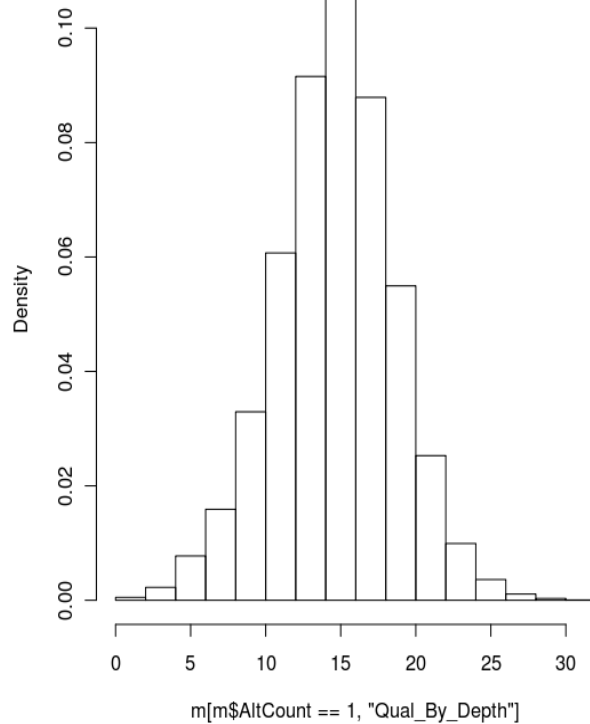




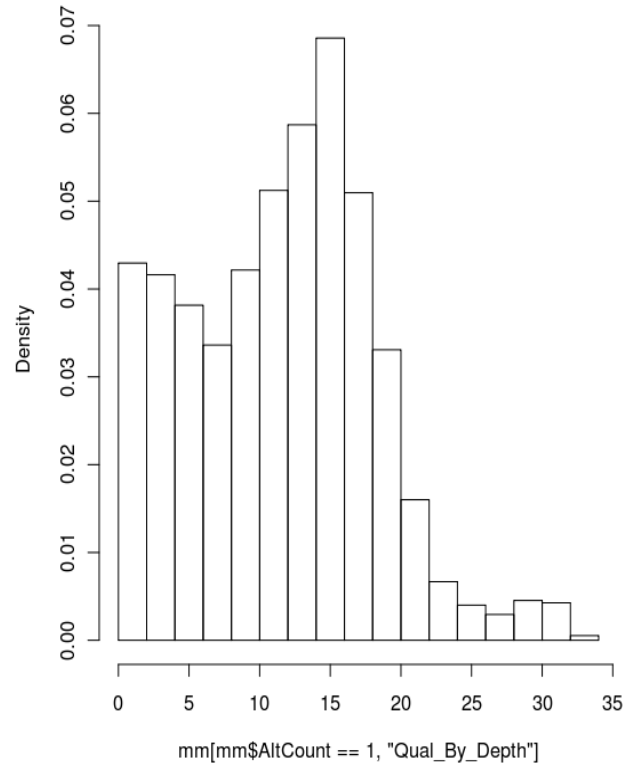
Generating Variant Data

Variant Calling: Quality Check : protocol-specific !

Histogram of `m[m$AltCount == 1, "Qual_By_Depth"]`



Histogram of `mm[mm$AltCount == 1, "Qual_By_Depth"]`





Variant interpretation

mut DB	In...	Gene	Transcript	Name	L...	Nuc Change	Coverage	A...	C.	Annotation	H.	web Ref.	c. HGVS	p. HGVS
<input type="checkbox"/>	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)
<input type="checkbox"/>	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	
<input checked="" type="checkbox"/>	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=)
<input type="checkbox"/>	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)
<input type="checkbox"/>	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)
<input checked="" type="checkbox"/>	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=)
<input checked="" type="checkbox"/>	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)
<input checked="" type="checkbox"/>	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=)
<input checked="" type="checkbox"/>	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=)
<input type="checkbox"/>	10	PTPRQ	ENST000006...	PTPRQ-E41-2	E41	A (het)	16% (9) [17% (4) / 14% (5)]		S.	intron		rs770656462 (gnomAD)...	c.6453+12dup	
<input checked="" type="checkbox"/>	11	TPRN	NM_0011282	TPRN-F01-NM	F1	GCC (het)	17% (4) [18% (2) / 17% (2)]	P	S.	inframe del		rs957768814 (dbSNP; n	c.489_491del	n (Pro164del)

20 Variants in 20 Genes were found

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

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

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

FREQUENCY	INTERNAL	COMMUNITY
N/A	0.00%	15
	null Hom	

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

★ Stickler syndrome, iia 6 was found to

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




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 <i>trans</i> with a dominant variant BP2 Observed in <i>cis</i> with a pathogenic variant BP2		For recessive disorders, detected in <i>trans</i> 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	$0.99 \geq PP > 0.90$ †
Uncertain	$0.10 \leq PP \leq 0.90$
Likely Benign	$0.001 \leq PP < 0.10$ †
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 browser gnomAD v4.0.0

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gnomAD v4 is here! [Read our blog post](#) for more details

gnomAD

Genome Aggregation Database

gnomAD v4.0.0

— Or —

- [Download gnomAD data](#)
- [Read gnomAD publications](#)
- [Find co-occurrence of two variants](#)

Please note that the gnomAD v3 genomes are now part of gnomAD v4. For more information, see ["Should I switch to the latest version of gnomAD?"](#)

Examples

- Gene: [PCSK9](#)
- Transcript: [ENST00000302118](#)
- Variant: [1-55051215-G-GA](#)
- Structural variant region: [19-11078371-11144910](#)
- Copy number variant region: [19-11078371-11144910](#)
- Mitochondrial variant: [M-8602-T-C](#)
- Short tandem repeat locus: [ATXN1](#)
- Regional missense constraint (gnomAD v2, GRCh37): [GRIN2A](#)
- Variant co-occurrence (gnomAD v2, GRCh37): [1-55505647-G-T](#) and [1-55523855-G-A](#)



gnomAD

What's in gnomAD

gnomAD v4 includes 807,162 individuals

- 730,947 exomes
- 76,215 genomes

v4 variants

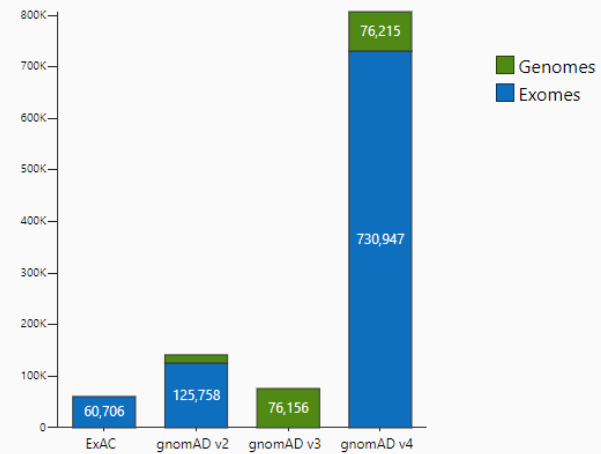
Short variants

- 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 Inversions
 - 13,116 Complex
 - 92 Canonical reciprocal translocations
- 66,903 rare (<1% site frequency (SF)) exome CNVs
 - 30,877 Deletions
 - 36,026 Duplications



On average we see 2
SNVs every 3 basepairs

C G T
G T A



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



BRCA2 BRCA2 DNA repair associated

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](#)

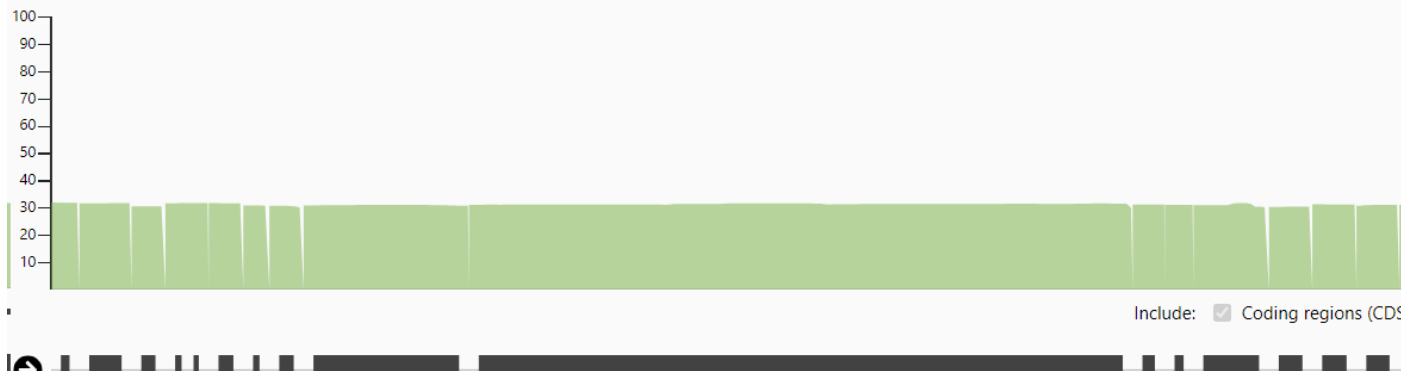
External resources [Ensembl](#), [UCSC Browser](#), and more

Constraint ?

Variant co-occurrence ?

Constraint not yet available for gnomAD v3.1.2.

ene. Zoom in



Dataset **gnomAD v3.1.2**

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

Include: Coding regions (CDS)



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

[Copy variant ID](#)[Gene page](#)Dataset [gnomAD v2.1.1](#)

Filters	Exomes	Genomes	Total
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/>

Criteria Specification (CSpec) Registry is intended to provide access to the Criteria Specifications used and applied by ClinGen Variant Curation Expert Panels and biocurators in the classification of variants.
For general information about the ClinGen Expert Panels and Variant Curation please visit: [Clinical Domain Working Groups](#). For specific inquiries regarding content correction or adding a new criteria specification refer to the [Help page](#).
Should you encounter any issues regarding the data displayed, lack of functionality or other problems, please let us know by contacting us via email.



Criteria Specification Registry

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Criteria Specifications

Show **25** entries

Search:

Title	Gene	Disease	CSpec Status	Version	
ABCA4 VCEP					
ClinGen ABCA4 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCA4 Version 1.0.0	ABCA4 (HGNC:34)	ABCA4-related retinopathy (MONDO:0800406) Autosomal recessive inheritance	Classification Rules Submitted	1.0.0	📄 🔍 📄
ACADVL VCEP					
ClinGen ACADVL Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1	ACADVL (HGNC:92)	very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)	Released	1.0.0	📄 🔍 📄
Amyotrophic Lateral Sclerosis Spectrum Disorders VCEP					
ClinGen Amyotrophic Lateral Sclerosis Spectrum Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for	SOD1 (HGNC:11179)		Classification Rules In Progress	1.0.0	📄 🔍 📄



<https://cspec.genome.network/cspect/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

Criteria Specification Registry Views ▾ More ▾ Contact Us

Criteria Specification

ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HNF1A Version 2.1.0 Monogenic Diabetes VCEP

Description : This version specified for the following genes: HNF1A
Version : 2.1.0
Release Notes :
Corrections to combining rules
Adding previously omitted PVS1 Decision Tree and PS2 Points Table
Indicated that gnomAD v.3.1.2 should be used for PM1_Supporting/BA1/BS1 frequency criteria for variants not covered in v2.1.1 exomes (consistent with recommendations of gnomAD based on sample sizes)

Released
8/11/2023
16.07.10

Rules for HNF1A

Gene: HNF1A (HGNC:11621) ↗	HGNC Name: HNF1 homeobox A
Transcripts: NM_000545.8	Disease: monogenic diabetes (MONDO:0015967) ↗
	Mode of Inheritance: Autosomal Dominant

Criteria & Strength 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 \geq 1:10,000 (\geq 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 \geq 1:30,000 (\geq 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%
	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	-			-
Hearing Loss (AD)	BA1	1:30	5% ^{L/A}	80%	0.001 (0.1%)
	BS1	1:150			0.0002 (0.02%)
	PM2	-			-
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



Computational 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



Computational 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



Computational data

Aggregated Prediction Uncertain (0.62)

Functional Coding

Revel Uncertain (0.55)

AlphaMissense Uncertain (0.582)

Eve (N/A)

Variety Benign (low) (0.24)

MUT Assessor 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

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Insights on variant analysis in silico tools for
pathogenicity prediction

 Felipe Antonio de Oliveira Garcia¹

 Edilene Santos de Andrade^{1†}

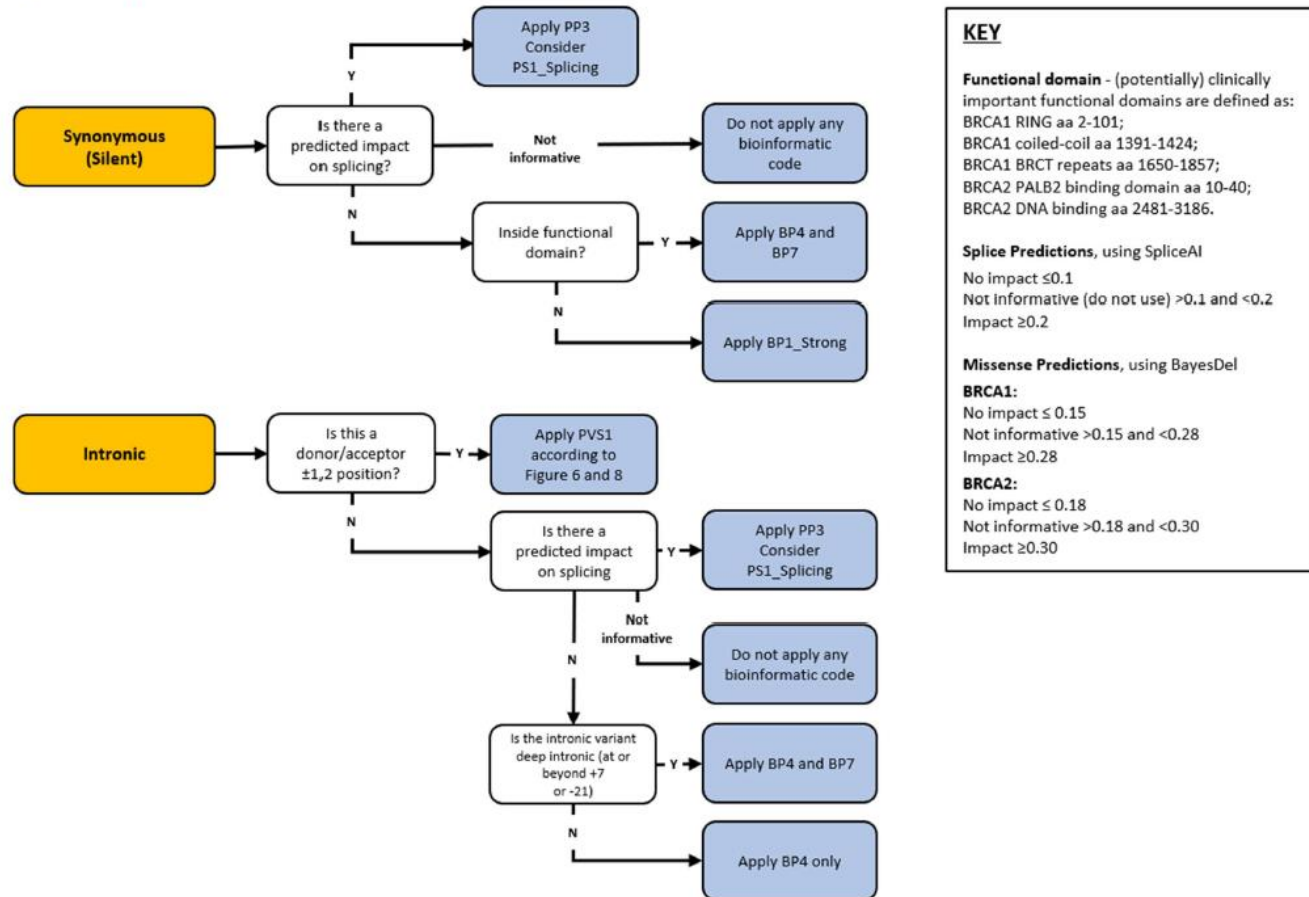
 Edenir Inez Palmero^{1,2*†}



VCEP specifications

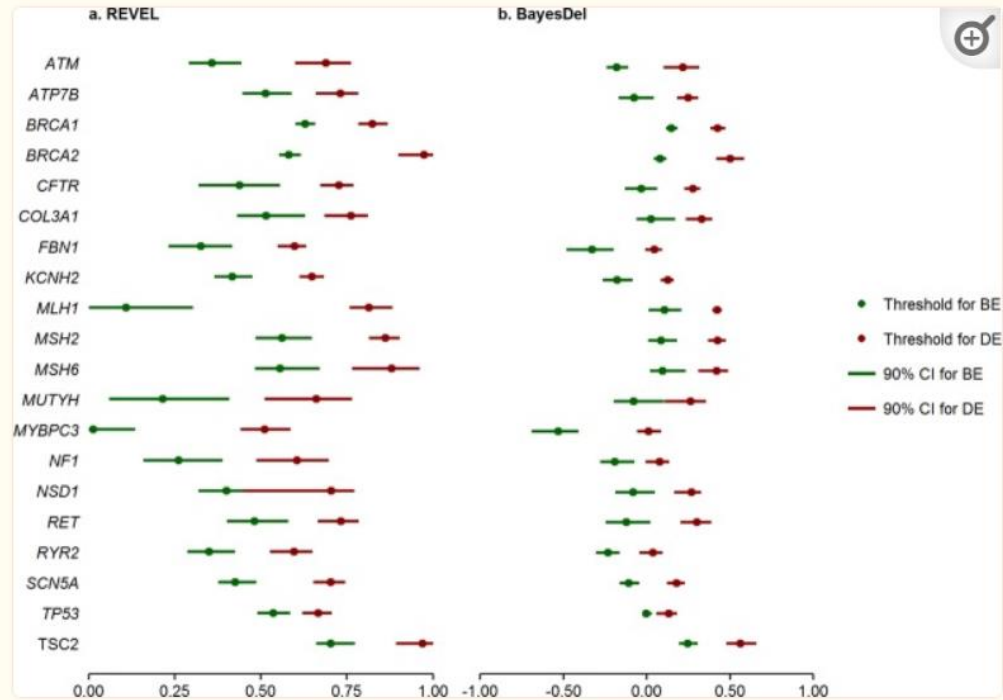
Figure 1: Application of bioinformatic codes and considerations for incorporating splicing and functional data depending on variant type and position.

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





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 ($\leq 40\%$ 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 less than 40% 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 immunofluorescence 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 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.



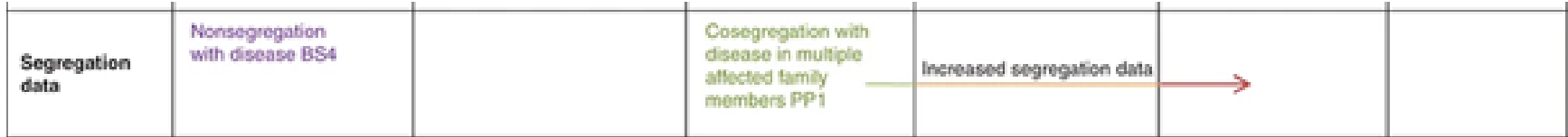
Functional data

Table 9: Summary of BRCA1 and BRCA2 functional assay results reviewed for application of PS3 and BS3 codes, following recommendations in Figure 1.

A	B	C	D	E	F	G	H	I	J	K
Gene	HGVSc Nucleotide	HGVSp Protein	Assigned Code	Code Weight	Standardised Text	Splice Result Published	Splicing Prediction	Predicted or Observed	# Publications	Res
BRCA1 or BRCA2	HGVSc nomenclature for variant or variant haplotype	HGVSp 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. Publications and additional details should be included in FV5/ or EPF 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 publications 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, 30765644)			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 pathogenic control variants (PMID:30209399) (BS3 met).		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 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.102T>C	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. 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.102T>G	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. 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>A	p.(Val135Ile)	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.(Val135Leu)	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 variants (PMID:30209399) (BS3 met).		0,01	N	one	Findlay 2018 (PMID:30209399)
BRCA1	c.103G>T	p.(Val135Phe)	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 variants (PMID:30209399) (BS3 met).		0,02	N	one	Findlay 2018 (PMID:30209399)
BRCA1	c.104T>A	p.(Val135Asp)	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.(Val135Ala)	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.(Val135Gly)	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 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.105C>G	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. 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.105C>T	p.(=)	BS3	Strong	Silent variant, functional data considered only from assays that measure effect via mRNA and protein. 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>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 calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		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 calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		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 calibrated study to exhibit protein function similar to benign control variants (PMID:30209399) (BS3 met).		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 Browning⁸

- Single Family : $\leq 1/32$ (5 meioses)
- >1 Family : $\leq 1/16$ (4 meioses)

Modification Type: General recommendation, Gene-specific

Moderate

Use thresholds suggested by Jarvik and Browning⁸

- Single Family : $\leq 1/16$ (4 meioses)
- >1 Family : $\leq 1/8$ (3 meioses)

Modification Type: General recommendation, Gene-specific

Supporting

Use thresholds suggested by Jarvik and Browning⁸

- Single Family : $\leq 1/8$ (3 meioses)
- >1 Family : $\leq 1/4$ (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) PM5	De novo (paternity and maternity confirmed) P52	
--------------	--	--	--	---	---	--

BEWARE: PHENOTYPE MUST FIT !!!



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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

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Nomenclature

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History

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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 ▾



▼ TEXT

ICD+

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► Protein

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EuroGentest
Gene Reviews
Genetic Alliance
GTR
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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Seattle (WA): [University of Washington, Seattle](#); 1993-2024.
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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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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.](#)

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Database Statistics

Patients and Variants

47,801

open-access patient records

194,099

phenotype observations in these patients

48,507

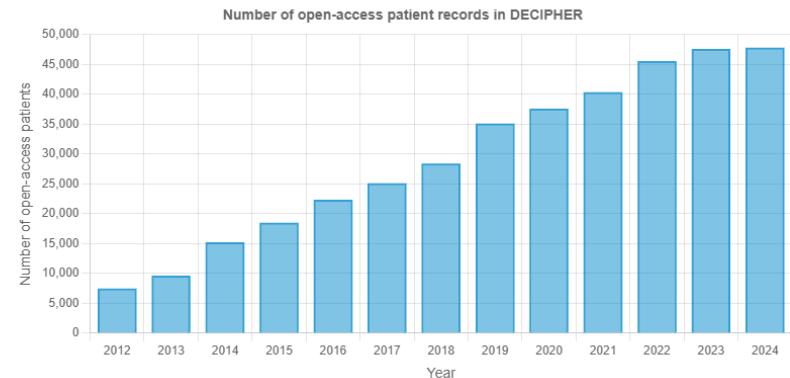
open-access copy-number variants

13,106

open-access sequence variants

Patient Records

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





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Patient: 486567

Overview **Genotype 1** Phenotypes 4 Assessments 0 Karyotype Citations 0 Contact

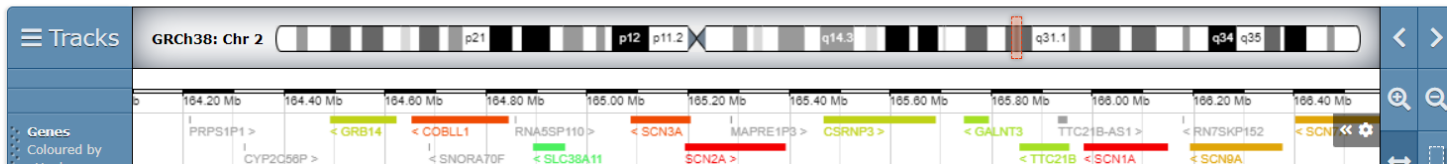
Variants: 1 to 1 of 1

Show: All Filter...

Location	Type	Genes	Size	Annotations	Inheritance / Genotype	Pathogenicity / Contribution	Links
2:164513206-166158786 GRCh38	Deletion	15	1.65 Mb	Dosage sensitivity score: 12.70 Sampling probability: < 1%	De novo (unconfirmed parentage) Heterozygous	Pathogenic Full	Show more ▾

Deletion 2:164513206-166158786

Browser Genes 15 Matching patient variants 218 Matching CNV syndromes 0 Pathogenicity evidence





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Patient: 486567

Overview Genotype **1** **Phenotypes 4** Assessments **0** Karyotype Citations **0** Contact

Patient 4 Mother **0** Father **0**

Patient phenotypes

Abnormality of the musculoskeletal system

Hypotonia



Abnormality of the nervous system

Delayed speech and language development

Seizure



Other / obsolete terms

obsolete Psychomotor retardation



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 <i>A strong consensus supporting a clinical diagnosis of the syndrome based on the features described.</i>	Functional evidence (e.g. biochemical, MRI, muscle biopsy)
Supporting	Sotos syndrome	<i>NSD1</i>	~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	<i>NSD1</i>	~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	<i>KMT2D</i> and <i>KDM6A</i>	55-80%	Facial gestalt and mild-moderate developmental delay/intellectual disability	N/A
Moderate	Kabuki syndrome	<i>KMT2D</i> and <i>KDM6A</i>	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)	<i>IDS</i>		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	<i>HNF1A/HNF4A</i>	N/A	Diabetes	Improved glycaemic response when treated with sulphonylurea tablets
Strong	Calpainopathy	<i>CAPN3</i>	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	<i>CASK</i>	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



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A screenshot of the PubMed website interface. The background is dark blue with a network of white nodes and lines. In the top left, the NIH logo is followed by the text 'National Library of Medicine' and 'National Center for Biotechnology Information'. In the top right, there is a 'Log in' button. The main heading is 'PubMed®'. Below it is a large white search input field with a green 'Search' button to its right. Under the search field, the word 'Advanced' is written. At the bottom, a paragraph of text describes the database: 'PubMed® comprises more than 36 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full text content from PubMed Central and publisher web sites.'



<https://www.ncbi.nlm.nih.gov/research/litvar2/>

LitVar² NIH NLM FAQ API

Search for variants in more than 35 million biomedical publications.

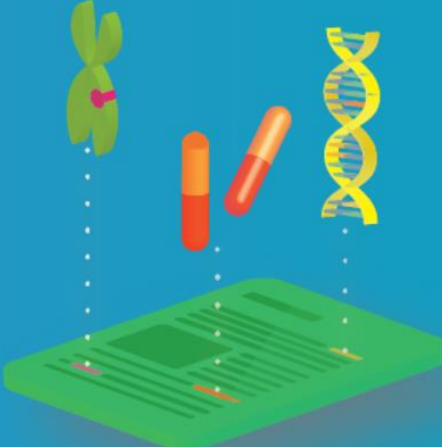
Variant (e.g. CFH R1210C)

Optional Text (e.g. AMD)

SEARCH

Try: KRAS A146T CFH R1210C rs121913527 CA123643

LitVar allows the search and retrieval of variant specific information from relevant studies in the literature, with related concept (e.g., diseases) annotations. By normalizing variant names, LitVar returns the same results regardless of which name of a variant (e.g. BRCA1 p.P871L or c.2612C>T) is used in the query. [Read more here.](#)





Litvar²

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TOP JOURNALS

-

PMID29410599 • PMC5788811 Jan 27, 2018

Geographic distribution of rare variants associated with age-related macular degeneration.

Geerlings MJ, Kersten E ... den Hollander AI • Mol Vis

ABSTRACT

Methods: We explored the occurrence of seven rare variants independently associated with AMD (CFH **rs121913059** (**p.Arg1210Cys**), CFI rs141853578 (p.Gly119Arg), C3 rs147859257 (p.Lys155Gln), and C9 rs34882957 (p.Pro167Ser)) and three non-coding variants in or near the CFH gene (rs148553336, rs35292876, and rs191281603) in 24 AMD case-control studies.

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PMID24036949 • PMC3812337 Nov 1, 2013

Identification of a rare coding variant in complement 3 associated with age-related macular degeneration.

Zhan X, Larson DE ... Abecasis GR • Nat Genet

ABSTRACT

VARIANT

p.R1210C rs121913059

CFH

likely-benign pathogenic uncertain-significance

ALFA TOTAL MAF T=0.001091/121

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CLINGEN IDENTIFIERS

Q CA128563

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BIOCONCEPTS

- GENE DISEASE
- CHEMICAL VARIANT
- SPECIES CELLLINE

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GENE: BRCA1 AND VARIANT: BRCA1:p.E1535X Filter Categories Full-text and Supplemental Share PRO Explore Associations PRO View Evidence

VARIANT INFO ClinVar Related

Select ClinVar Record: NM_007294.4:c.4603G>T (p.Glu1535Ter) INFO

PATHOGENIC
Last Evaluated 2/4/24

- DESCRIPTION: single nucleotide variant
- REVIEW STATUS: ★★☆☆ reviewed by expert panel
- SUBMISSIONS: 14
- MOST RECENT: 12/21/23

[View in ClinVar](#)

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JOURNAL	DATE	TITLE	MATCHES
Front Pharmacol	2022 Jun 28	Functional Restoration of BRCA1 Nonsense Mutations by Aminoglycoside-Induced Readthrough.	BRCA1 .E1535X
BMC Cancer	2015 Jul 17	Spectrum and frequencies of BRCA1/2 mutations in Bulgarian high risk breast cancer patients.	
Hum Mutat	2019 Jul 26	The spectrum of BRCA1 and BRCA2 pathogenic sequence variants in Middle Eastern, North African, and South European countries.	
Fam Cancer	2020 Oct 21	Frequency and spectrum of mutations across 94 cancer predisposition genes in African American women with invasive breast cancer.	
Biol Res	2012 Jan 1	BRCA1 and BRCA2 mutations in breast cancer patients from Venezuela.	
Gynecol Oncol	2018 Mar 2	Characteristics of African American women at high-risk for ovarian cancer in the southeast: Results from a Gynecologic Cancer Risk Assessment Clinic.	
Breast Cancer Res Treat	2017 May 13	Contribution of germline mutations in cancer predisposition genes to tumor etiology in young women diagnosed with invasive breast cancer.	
Breast Cancer Res Treat	2012 Nov 29	Evaluation of BRCA1 mutations in an unselected patient population with triple-negative breast cancer.	
Hered Cancer Clin Pract	2017 Jan 21	Hereditary cancer syndromes in Latino populations: genetic characterization and surveillance guidelines.	
Hum Mutat	1999 Jan 1	Mutation in the coding region of the BRCA1 gene leads to aberrant splicing of the transcript.	



http://scholar.google.be

The screenshot shows a Microsoft Internet Explorer browser window displaying the Google Scholar search results for the query 'P51S'. The browser's address bar shows the URL: http://scholar.google.be/scholar?hl=en&q=P51S&as_sdt=0%2C5&as_ylo=&as_vis=0. The search results are displayed in a list format, with each entry including a title, author information, publication details, and a brief abstract. The results are sorted by relevance, and the first result is 'A common ancestor for COCH related cochleovestibular (DFNA9) patients in Belgium and The Netherlands bearing the P51S mutation' by E Fransen, M VERSTREKEN, and SJH BOM, published in the Journal of Medical Genetics in 2001. Other results include 'Vestibular deterioration precedes hearing deterioration in the P51S COCH mutation (DFNA9): an analysis in 74 mutation carriers', 'Direct coronary stenting without predilatation', 'High prevalence of symptoms of Meniere's disease in three families with a mutation in the COCH gene', 'Unity of Command--Countering Aircraft and Missile Threats', and 'Phenotype description of a novel DFNA9/COCH mutation, I109T'.

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[A common ancestor for COCH related cochleovestibular \(DFNA9\) patients in Belgium and The Netherlands bearing the P51S mutation](#) [\[HTML\] from bmj.com](#)
E Fransen, M VERSTREKEN, SJH BOM... - Journal of medical ..., 2001 - jmg.bmj.com
Editor—Hearing impairment is extremely heterogeneous, both phenotypically and genetically. It is the most frequent form of sensory impairment in the western world, affecting approximately 1/1000 newborns and approximately half of the people above the age of 80 ...
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[Vestibular deterioration precedes hearing deterioration in the P51S COCH mutation \(DFNA9\): an analysis in 74 mutation carriers](#)
AML Bischoff, PLM Huygen... - Otology & ..., 2005 - journals.lww.com
Objectives: To analyze cochleovestibular impairment features in P51S COCH mutation carriers (n= 22) in a new, large Dutch family and to compare the results to those obtained in previously identified similar mutation carriers (n= 52). To evaluate age-related features ...
[Cited by 11](#) - [Related articles](#) - [BL Direct](#) - [All 7 versions](#)

[Direct coronary stenting without predilatation](#) [\[HTML\] from onlinejacc.org](#)
C Briguori, I Sheiban, J De Gregorio... - Journal of the American ..., 1999 - Elsevier
[Cited by 133](#) - [Related articles](#) - [BL Direct](#) - [All 11 versions](#)


[High prevalence of symptoms of Meniere's disease in three families with a mutation in the COCH gene](#) [\[HTML\] from oxfordjournals.org](#)
E Fransen, M Verstreken... - Human molecular ..., 1999 - Oxford Univ Press
... The age of the living family members is indicated. Family members that are heterozygous for the P51S mutation are marked by a + sign. ... Figure 2 Confirmation of the P51S mutation by restriction analysis. The P51S mutation destroys a BglI restriction site. ...
[Cited by 130](#) - [Related articles](#) - [BL Direct](#) - [All 9 versions](#)

[Unity of Command--Countering Aircraft and Missile Threats](#) [\[PDF\] from dtic.mil](#)
VP DiFronzo - 1996 - DTIC Document
... myriad aircraft and missile threats must be neutralized to attain air superiority P-51s escorting bombers during World War II. ... Spaatz realized that an all out ef- fort, including P-51s and medium bombers under Leigh-Mallory's control, would be needed to de- feat the Luftwaffe. ...
[Cited by 9](#) - [Related articles](#) - [All 6 versions](#)

[Phenotype description of a novel DFNA9/COCH mutation, I109T](#)
RJ Pauw, PL Huygen, RW Collin... - The Annals of otology, ..., 2007 - ukpmc.ac.uk
... family. Pure tone thresholds, phoneme recognition scores, and vestibular responses of the I109T mutation carriers were essentially similar to those previously established in P51S, G87W, and G88E mutation carriers. Deterioration ...



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

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National Center for Biotechnology Information Log in

ClinVar Search ClinVar by gene symbols, location, HGVS expressions, c-dot, p-dot, conditions, and more Search Help
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i **Announcing changes to support somatic variant classifications**
We have delayed changes to the ClinVar XML files and our submission spreadsheet templates until January 2024; these changes will improve support for classifications of somatic variants in ClinVar. To help our users and submitters prepare for this change, we are providing a preview of submission spreadsheet templates, updated XSDs, sample XMLs, and supporting documentation on [GitHub](#). Please share this information with your colleagues, including your bioinformatics team!

```
ACTGATGGTATGGGGCCAAGAGATATATCT
CAGGTACGGCTGTCATCACTTAGACCTCAC
CAGGGCTGGGCATAAAAAGTCAGGGCAGAGC
CCATGGTGCATCTGACTCCTGAGGAGAAGT
GCAGGTTGGTATCAAGGTTACAAGACAGGT
GGCACTGACTCTCTGCCTATTGGTCTAT
```

ClinVar

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

Using ClinVar
[About ClinVar](#)
[Data Dictionary](#)
[Downloads/FTP site](#)
[FAQ](#)
[Contact Us](#)

Tools
[ACMG Recommendations for Reporting of Secondary Findings](#)
[ClinVar Submission Portal](#)
[Submissions](#)
[Variation Viewer](#)
[RefSeqGene/LRG](#)

Related Sites
[ClinGen](#)
[GeneReviews @](#)
[GTR @](#)
[MedGen](#)
[OMIM @](#)



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



NM_000162.5(GCK):c.1175G>T (p.Arg392Leu)

Cite

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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



Clinvar

ClinVar Genomic variation as it relates to human health

Search by gene symbols, location, HGVS expressions, c-dot, p-dot, conditions, i

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Advanced search

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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](#).

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)



Citations for germline classification of this variant



Title	Author	Journal	Year	Link
Clinical implications of the glucokinase impaired function - GCK MODY today.	Hulín J <i>et al.</i>	Physiological research	2020	PMID: 33129248
MODY2 in Asia: analysis of GCK mutations and clinical characteristics.	Zhou Y <i>et al.</i>	Endocrine connections	2020	PMID: 32375122
Association of a homozygous GCK missense mutation with mild diabetes.	Marucci A <i>et al.</i>	Molecular genetics & genomic medicine	2019	PMID: 31197960
Insights into pathogenesis of five novel GCK mutations identified in Chinese MODY patients.	Liu L <i>et al.</i>	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 <i>et al.</i>	BMC pediatrics	2018	PMID: 29510678
GCK mutations in Chinese MODY2 patients: a family pedigree report and review of Chinese literature.	Ping Xiao Y <i>et al.</i>	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





<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](https://pubmed.ncbi.nlm.nih.gov/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](https://pubmed.ncbi.nlm.nih.gov/25684268/).

See the [Frequently Asked Questions \(FAQs\)](#) for Additional information.

Use of GeneMatcher is governed by the [End User License Agreement \(EULA\)](#).



GeneMatcher

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Gene Search

Gene symbol :

Submissions must match all gene symbols

Genomic coordinate :

Submissions must match all genomic coordinates

Assembly :

GRCh37 (default) ▾

Search

Note that this searches across your submissions **only**, you cannot search for other submitters' entries ([See FAQ 3](#) to see why).



<https://variantmatcher.org>

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About VariantMatcher

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

VariantMatcher is designed to enable connections between patients, their families, clinicians and researchers from around the world who share an interest in the same variant or variants. The principal goal for making VariantMatcher 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 genomic coordinate of interest and will connect these individuals to participants of the BHCMG with interest in a variant in the same position. Users create an account and submit genomic coordinate(s) of interest. The match is done automatically. When a match occurs, the submitters and the BHCMG participant will receive an email notification. Follow-up is at the discretion of both parties.

If a match is not identified at the time of submission, the genomic coordinate(s) of interest will not continue to be queried as the information is not stored in the database.

VariantMatcher adheres to strict safety and privacy protocols. Users must register and be approved to use the site. The database is not searchable and does not collect identifiable data. Users may not access the full database.

See the [Frequently Asked Questions \(FAQs\)](#) for Additional information.

Use of VariantMatcher is governed by the [End User License Agreement \(EULA\)](#).



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Search

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Search

Variants :

The variant search format is as follows:

`chr:coord_refAllele>altAllele`

For example :

`1:100100 A>T`

Allele can be one of `ATCG`, both reference and alternate alleles are required.

You may use `?` as a wildcard to represent any alleles, for example.

`1:100100 A>?`

You can search up to 10 variants per day.

Features :

Features entered here will be shared with submitters if there is a match, and submission features will be shared with you. This is optional, at least three need to be entered to be shared, up to six can be specified.

Save Search : Save this search to be automatically re-run monthly

Match against Matchmaker Exchange repositories:

Franklin by Genoox



Variant evaluation

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



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

The screenshot displays the Franklin by genoox interface for a variant analysis. At the top, there is a search bar and navigation links for 'SEARCH', 'KNOWLEDGE BASE', and 'MY CASES'. The main header shows the variant 'HSPG2:c.11072C>T' with its coordinates and a 'Classify Variant' button. Below this, a horizontal scale indicates the 'Suggested Classification' as 'Benign', with other categories like 'Likely Benign', 'VUS', 'Likely Pathogenic', and 'Pathogenic' also shown. A blue banner offers an expert opinion. The 'EVIDENCE' section is partially visible, showing 'Functional Data' with a 'PP2' (Pathogenic Supporting) indicator and a description of the variant's impact.



https://franklin.genoox.com/

Franklin
by genoox

HSPG2:c.11072C>T
chr1-22159784 G>A | p.Thr3691Ile | NM_005529.7 | dbSNP, rs149159881 | UCSC | TraP | gnomAD

Franklin ACMG Classification | Variant Assessment | Publications | Gene Assessment | Associated Co

Summary

- Region Viewer
- Franklin Community Frequency
- Internal Frequency
- Clinical evidence
- Predictions
- Population Frequencies
- Transcripts

Benign
PP2 BP6 BS1 BS2
See Details

My Organization Classification
No classification
Classify Variant

Clinical Evidence
Conflict
See Details

Silverman-Handmaker Type Dyssegmental Dysp... AR
OMIM | Monarch | Orphanet | GENCC | Decipher | CLINGEN

Schwartz-Jampel Syndrome Type 1 AR
OMIM | CLINGEN | Decipher | GENCC

Schwartz-Jampel Syndrome AR
Monarch | Orphanet | GENCC | Decipher

1 More Conditions

Population Freq
PM2
0.11%
0% 1% 100%
See all

Relevant Articles
201
Gene scope articles
See all

Prediction
Revel: Uncertain
MetaLR: Benign (Low)
Splice AI: Benign
See all Predictions

Region Viewer



https://gtexportal.org/home/

2022-03-23
GTEx implements GA4GH's RNAget API
The GTEx Portal RNAget API provides the ability to retrieve GTEx RNA-seq data using the GA4GH standard RNAget API. This API current...

Resource Overview

Current Release (V8)

- [Tissue & Sample Statistics](#)
- [Tissue Sampling Info \(Anatomogram\)](#)
- [Access & Download Data](#)
- [Release History](#)
- [How to cite GTEx?](#)

The Genotype-Tissue Expression (GTEx) project is an ongoing effort to build a comprehensive public resource to study tissue-specific gene expression and regulation. Samples were collected from 54 non-diseased tissue sites across nearly 1000 individuals, primarily for molecular assays including WGS, WES, and RNA-Seq. Remaining samples are available from the GTEx Biobank. The GTEx Portal provides open access to data including gene expression, QTLs, and histology images.

Developmental GTEx

Explore GTEx



Browse

Browse and search all data by gene

Browse and search all data by variant

[By Tissue](#)

Browse and search all data by tissue

[Histology Viewer](#)

Browse and search GTEx histology images



Single Cell

[Data Overview](#)

Learn more about available single cell data

[Multi-Gene Single Cell Query](#)

Browse and search single cell expression by gene and tissue



Expression

[Multi-Gene Query](#)

Browse and search expression by gene and tissue



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

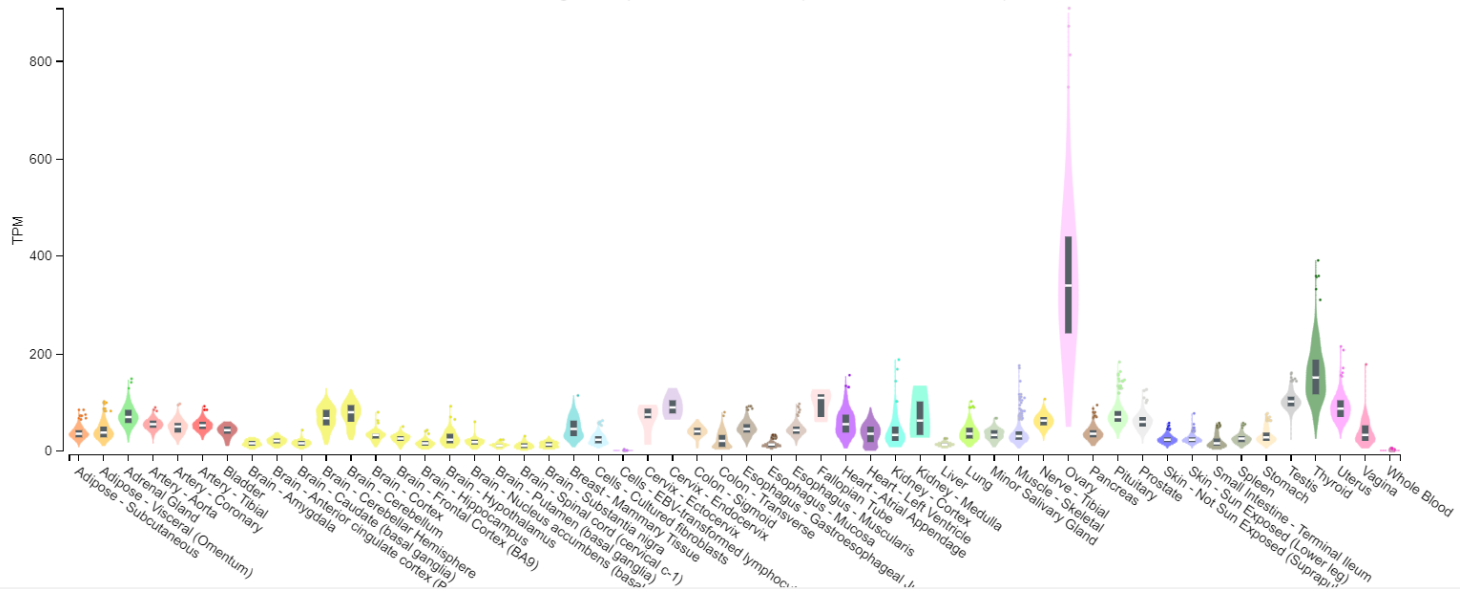
Single-Tissue sQTLs

Single-Tissue ieQTLs

Single-Tissue isQTLs

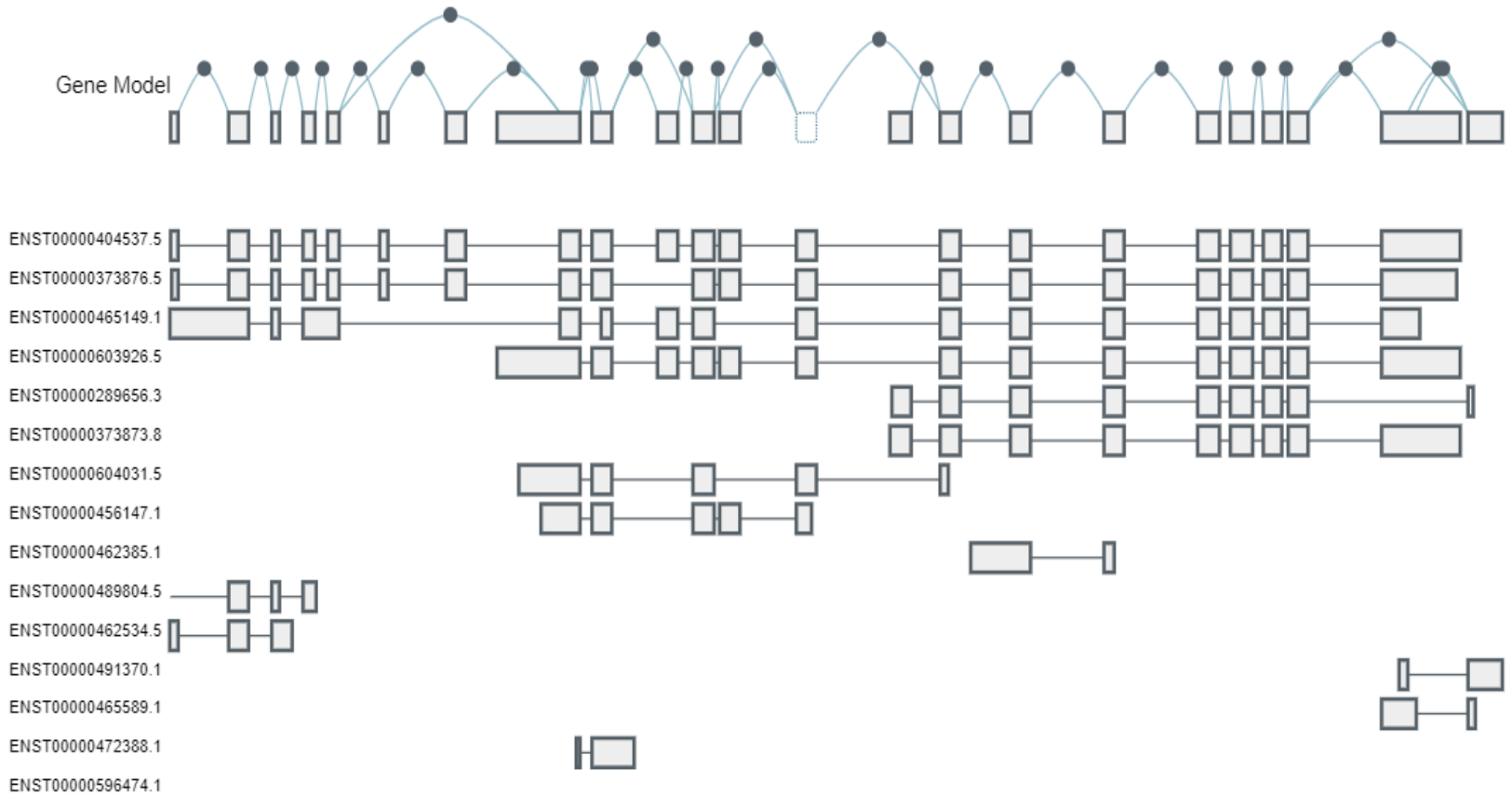
Download icon | Filter icon | SUBSET: None | Sex | SCALE: Log | Linear | TISSUE SORT: ▲ ▼ | MEDIAN SORT: ▲ ▼ | OUTLIERS: On | Off

Bulk tissue gene expression for OBSL1 (ENSG00000124006.14)



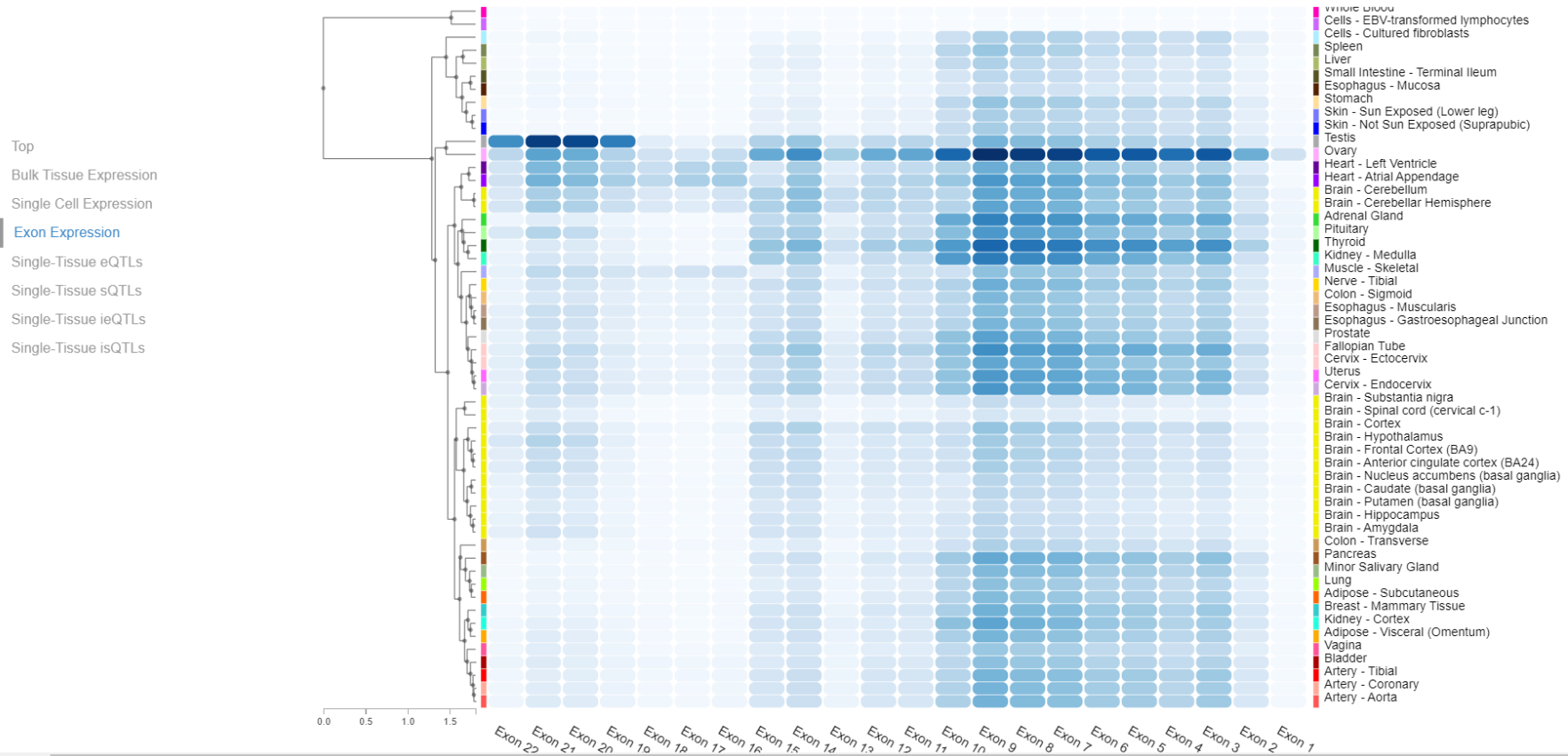


Exon expression OBSL1



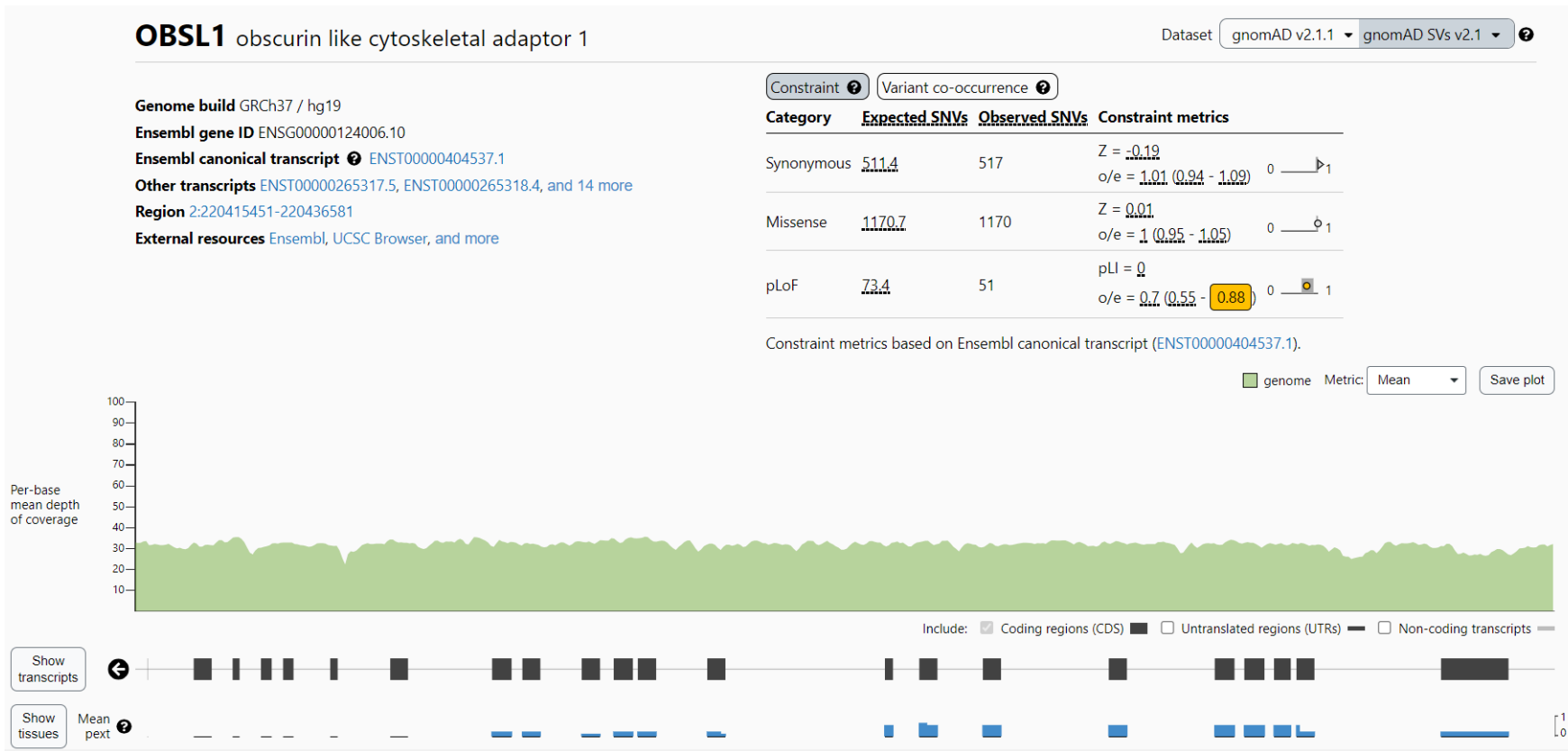


Exon expression OBSL1



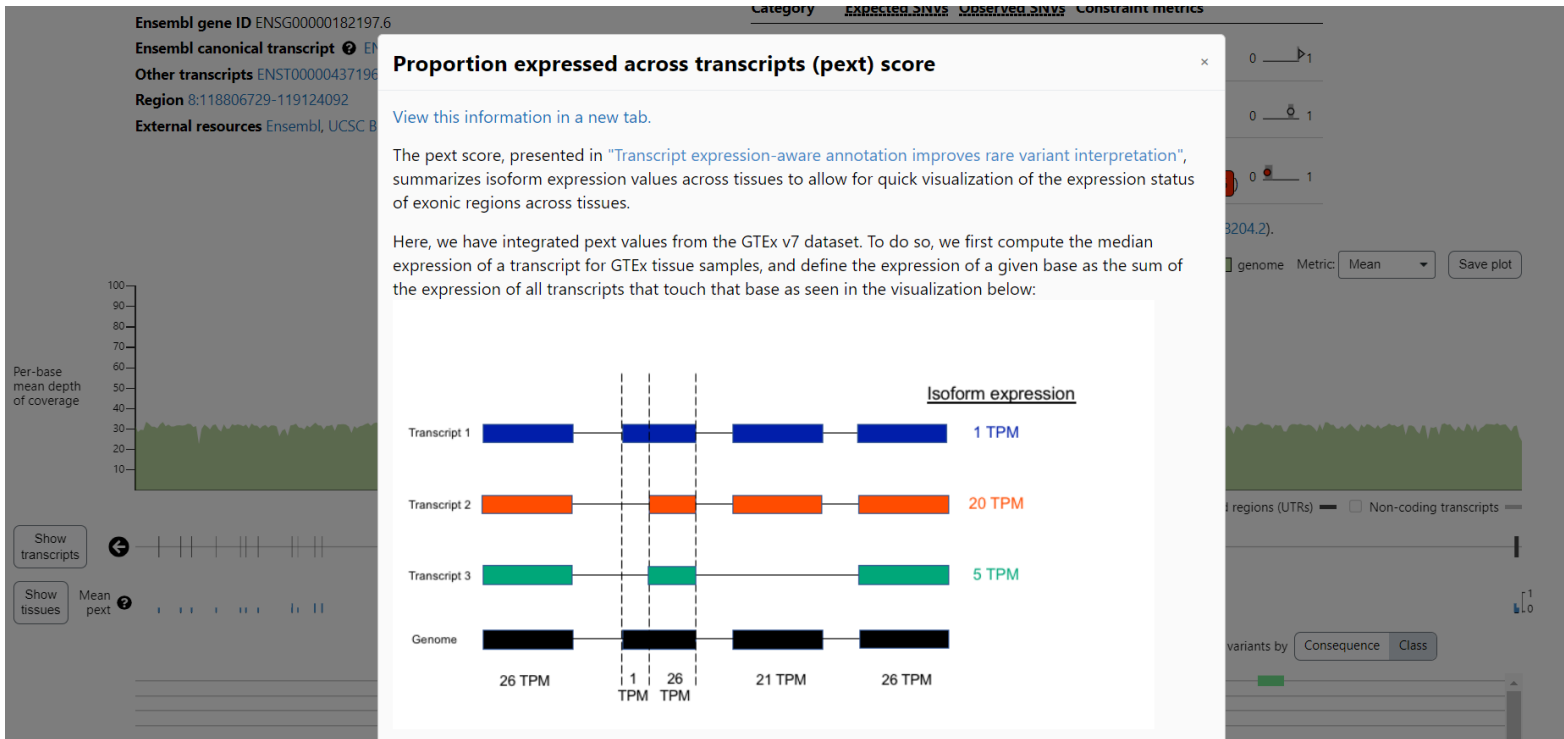


Exon expression in GnomAD





Exon expression in GnomAD





Exon expression in GnomAD





MANE

Matched Annotation from NCBI and EMBL-EBI (MANE)

- [What is MANE?](#)
- [Citing MANE](#)
- [Rationale](#)
- [MANE Select](#)
- [MANE Select Methodology](#)
 - [Choosing the transcript](#)
 - [Matching transcript ends](#)
- [Salient features of MANE Select transcripts](#)
- [Manual curation of MANE data](#)
- [Accessing MANE Select data](#)
- [Contact information](#)

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		F8VX12	-			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 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)	<input type="checkbox"/> 1A. Contains protein-coding or other known functionally important elements	0 (Continue Evaluation)	0	
	<input type="checkbox"/> 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)

<input type="checkbox"/> 2A. Complete overlap of an established HI gene/genomic region	1	1		Assigned points: 0
<input type="checkbox"/> 2B. Partial overlap of an established HI genomic region <ul style="list-style-type: none"> • 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/

UNIVERSITY OF CALIFORNIA
SANTA CRUZ
Genomics
Institute



Genome Browser



Genomes

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Search

Tools



hg38



hg19



mm39

- **Genome Browser** - Interactively visualize genomic data
- **BLAT** - Rapidly align sequences to the genome
- **In-Silico PCR** - Rapidly align PCR primer pairs to the genome
- **Table Browser** - Download and filter data from the Genome Browser
- **LiftOver** - Convert genome coordinates between assemblies
- **REST API** - Returns data requested in JSON format
- **Variant Annotation Integrator** - Annotate genomic variants
- **More tools...**

News

- Feb. 08, 2024 - **CRISPR Targets for human (T2T CHM13v2.0/hs1) now available**
- Jan. 24, 2024 - **AVADA variants track available for human (hg38)**
- Jan. 22, 2024 - **New hg38 HPRC track group and data**
- Dec. 7, 2023 - **VISTA Enhancers for human and mouse**
- Nov. 30, 2023 - **Support for previous RefSeq transcripts while searching on hg38**
- Nov. 22, 2023 - **CRISPR Targets for Zebrafish (danRer10/danRer11)**

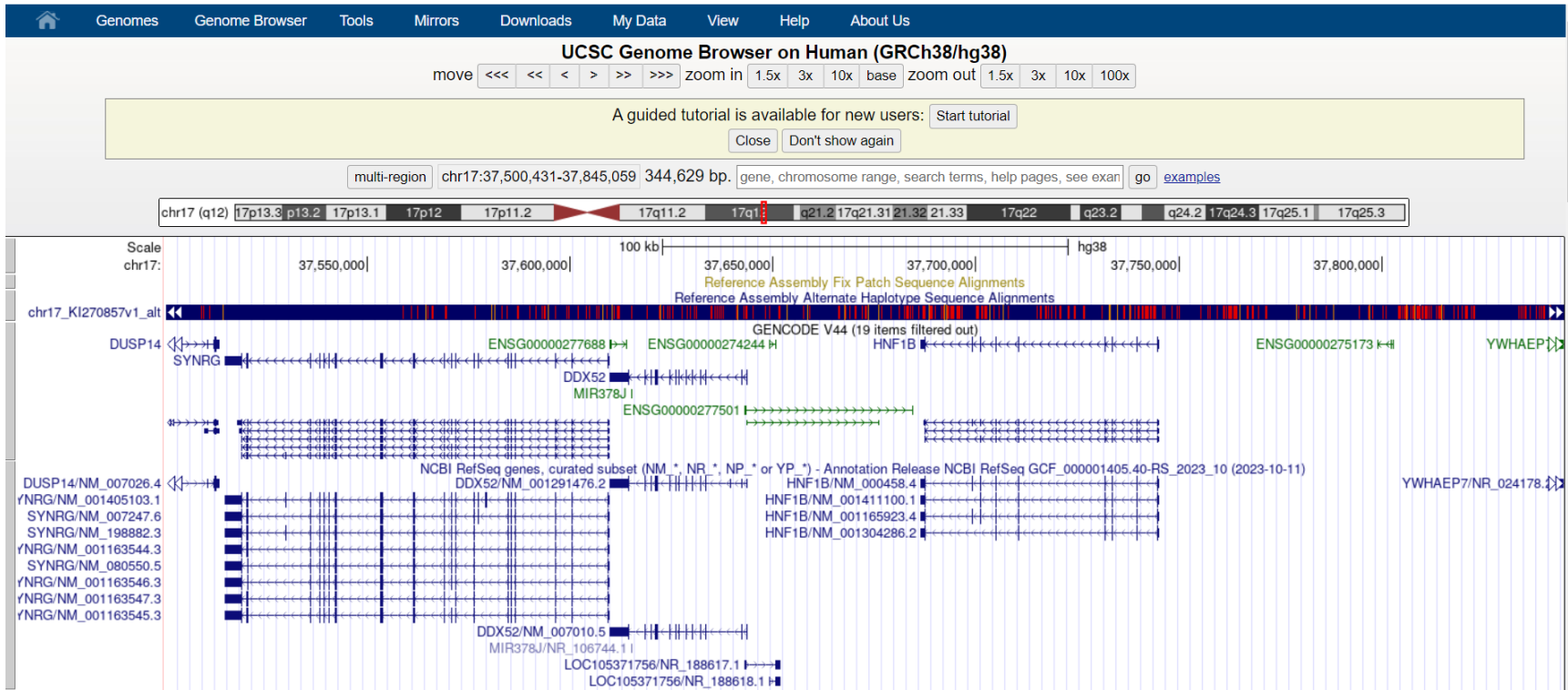
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Del chr17:37,500,431-37,845,059





Assembly converter

Lift Genome Annotations - Windows Internet Explorer provided by UZA

http://genome-euro.ucsc.edu/cgi-bin/hgl/LiftOver?hgid=196491628

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Wuyts Wim - Outlook Web App Lift Genome Annotations

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Lift Genome Annotations

This tool converts genome coordinates and genome annotation files between assemblies. The input data can be pasted into the text box, or uploaded from a file. If a pair of assemblies cannot be selected from the pull-down menus, a direct lift between them is unavailable. However, a sequential lift may be possible. Example: lift from Mouse, May 2004, to Mouse, Feb. 2006, and then from Mouse, Feb. 2006 to Mouse, July 2007 to achieve a lift from mm5 to mm9.

Original Genome: Original Assembly: New Genome: New Assembly:

Minimum ratio of bases that must remap:

BED 4 to BED 6 Options

Allow multiple output regions:

Minimum hit size in query:

Minimum chain size in target:

BED 12 Options

Min ratio of alignment blocks or exons that must map:

If thickStart/thickEnd is not mapped, use the closest mapped base:

Paste in data ([BED](#) or chrN:start-end formats):

```
chr7 127473530 | 127474697
```

Or upload data from a file ([BED](#) or chrN:start-end in plain text format):

Command Line Tool

To lift genome annotations locally on Linux systems, download the *liftOver* executable and the appropriate *chain* file. Run *liftOver* with no arguments to see the usage message.

start UZAWNET My Applications UZA - Z15 Ziekenh... UZA - Z15 Ziekenh... Lift Genome Annotati... UCSC Genome Bioinfo... Microsoft PowerPoint ... Internet 100% 8:53



Human chr9:133252000-133252000

genome.ucsc.edu/cgi-bin/hgTracks?db=hg38&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=

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. expand all
Tracks with lots of items will automatically be displayed in more compact modes.

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 ▾
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Variation Viewer 1.5 adds facet toggling, updated backend data
04 Feb 2016
Variation Viewer 1.5 provides several new features, improvements and bug fixes.
February 17th webinar: "Five ways to submit next-gen sequencing data to NCBI's Sequence Read Archive (SRA)"
03 Feb 2016
Genome Workbench 2.10 now available
29 Jan 2016
Genome Workbench 2.10 includes a reworked RI AST tool and new features.
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