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To be or Not to Be" Variant of Uncertain Significance

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"To be or Not to Be"

Variant of Uncertain Significance

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GENE2INFO **Health Informatics, Turkey**

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FRASE DE SALVAMENTO

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MAT-CO-2202563

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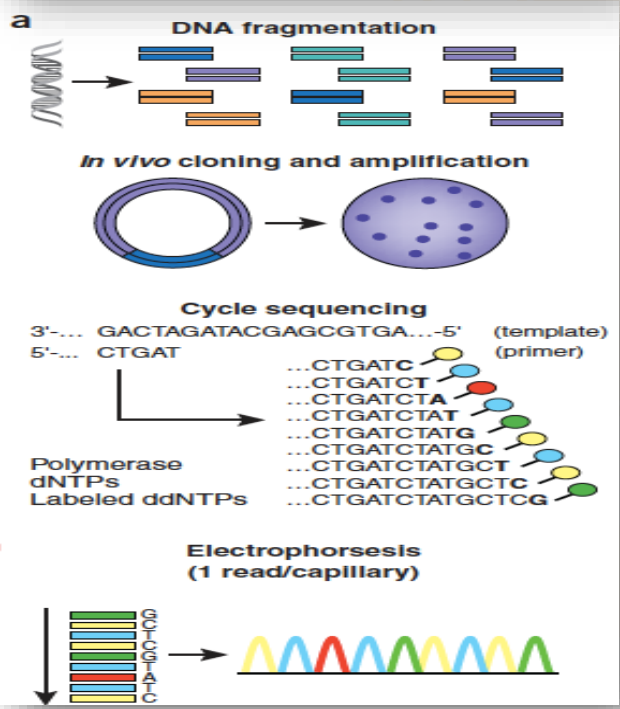
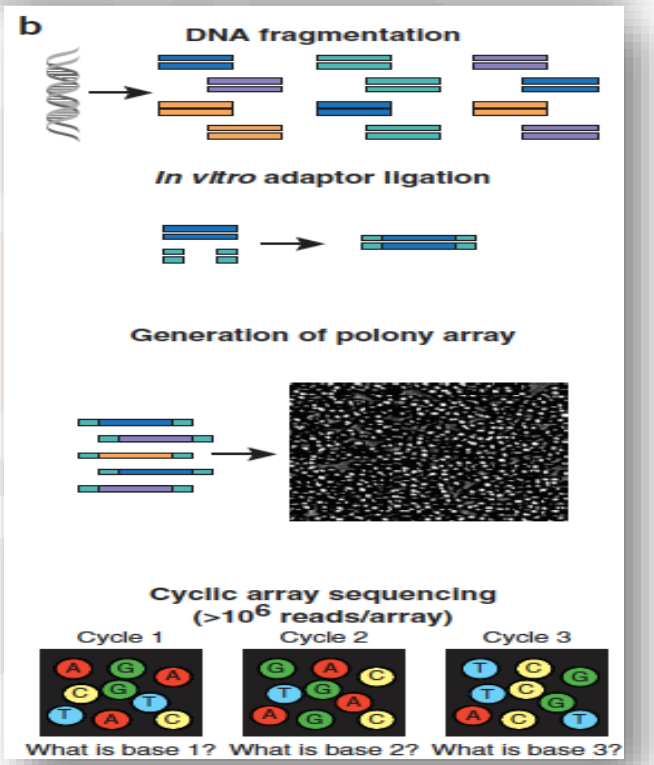
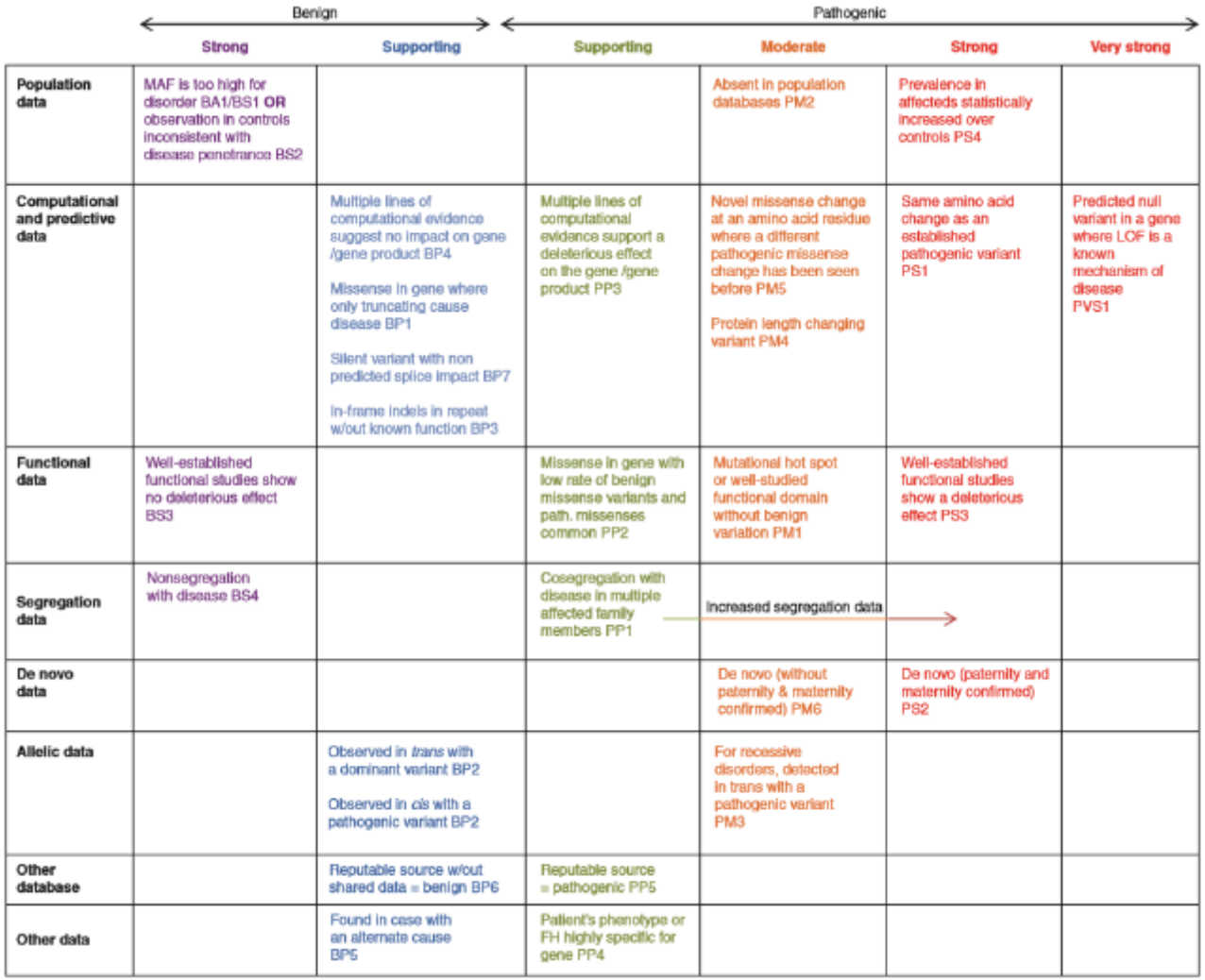
Sequencing





Thompson&Thompson, Genetics in Medicine, 2016

Classification of Mutations



	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 OR observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

- Pathogenic
- Likely pathogenic
- VUS
- Likely benign
- Benign

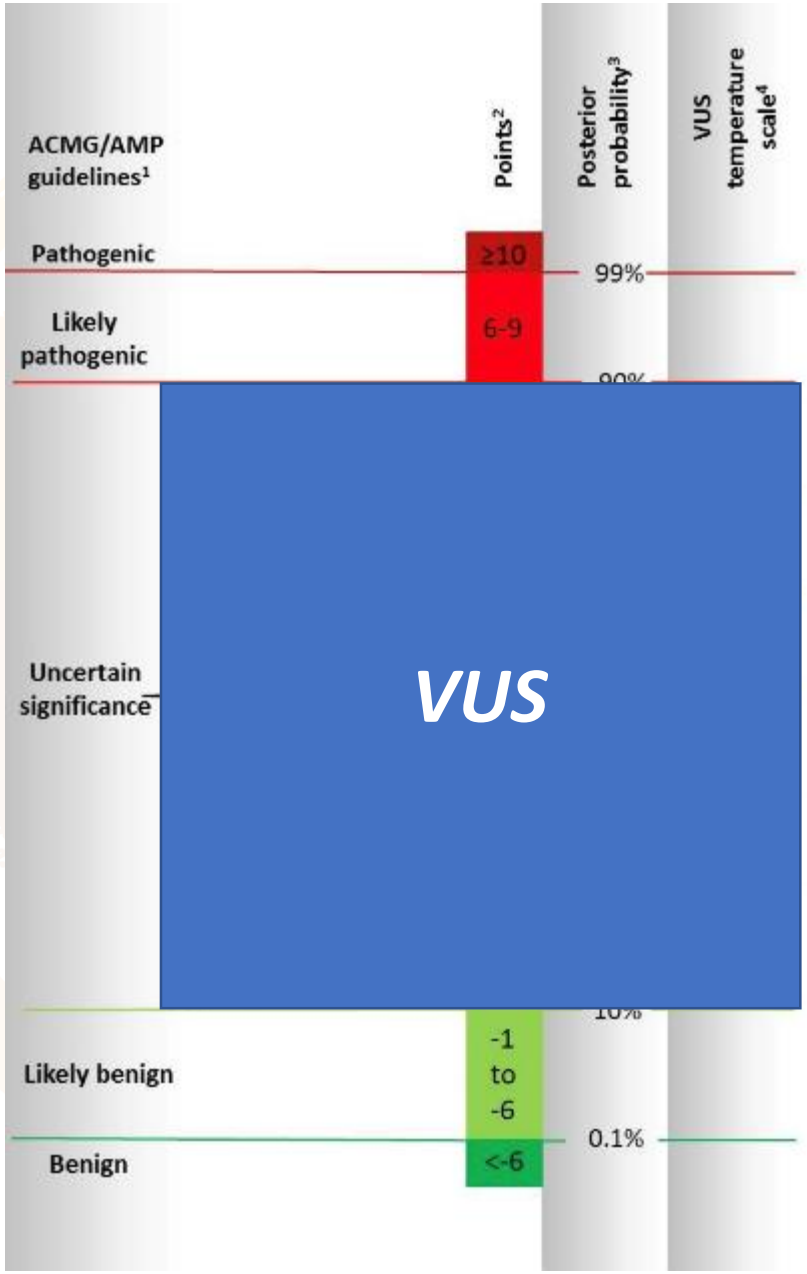
VUS: Variant of unknown significance.

Richard S, *et al*. Genetics in Medicine, (2015).

Submission significance	Variants	Genes
Uncertain significance	266,759	13,346
Likely benign	203,141	9515
Benign	128,364	14,810
Pathogenic	91,322	9998
Likely pathogenic	41,404	4198
Not provided	17,066	1594
Other	2134	109

Data available on the ClinVar Miner website: https://clinvarminer.genetics.utah.edu/

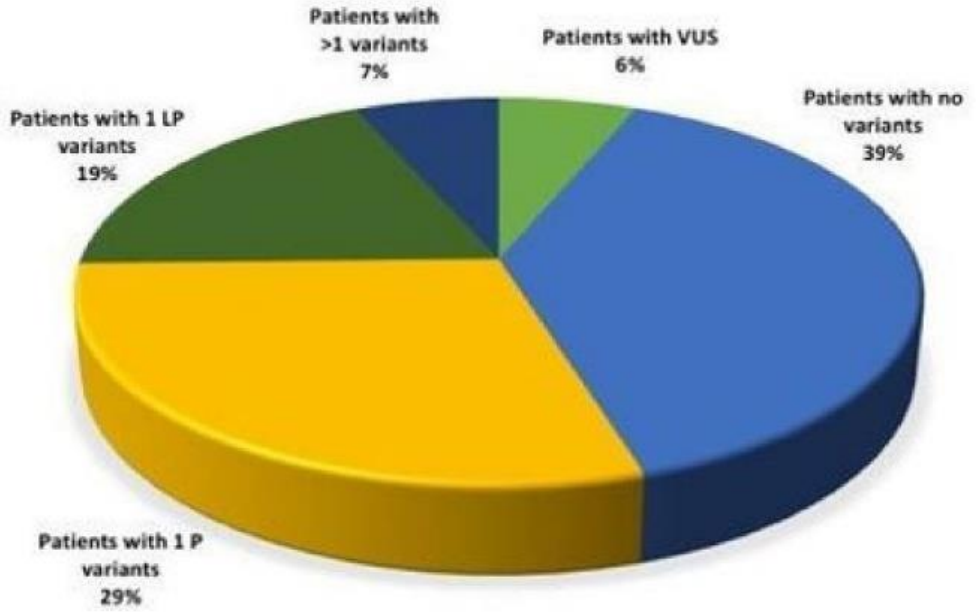
Federici and Soddu Journal of Experimental & Clinical Cancer Research, 2020



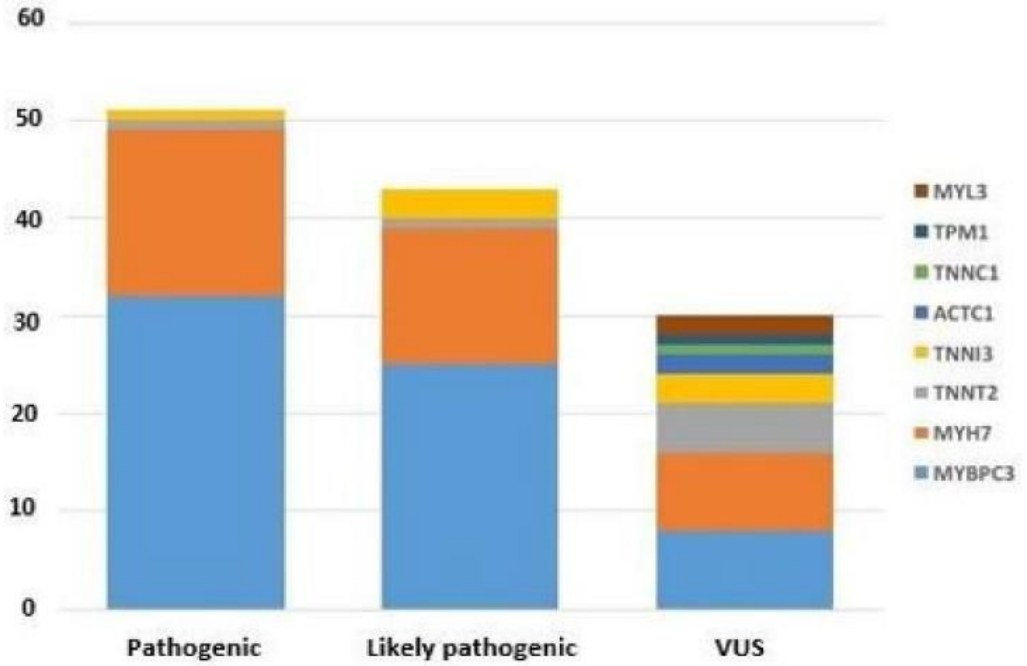
Ellard S et al. ACGS, 2020

HCM-VUS

GENETIC TESTING ANALYSIS (n= 371 pts)



TYPE OF SARCOMERIC UNIQUE VARIANTS (n= 124 pts)



Magri D et al., J. Clin. Med. 2020

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MYH7-Varsome

Total classified variants (UniProt, ClinVar, VarSome & PubMed)
2511

Pathogenic
535

Uncertain significance
1474

Benign
502

Coding impact	Pathogenic	Likely Pathogenic	Uncertain Significance	Likely Benign	Benign	Total
Synonymous	1	1	97	339	70	508
Missense	313	180	1187	7	10	1697
Nonsense	1	2	39	0	0	42
Start loss	0	0	1	0	0	1
Stoploss	0	0	1	0	0	1
Frameshift	2	3	21	0	0	26
Inframe Indel	5	15	27	0	0	47
Splice junction loss	5	6	27	0	0	38
Non-coding	1	0	74	69	7	151
Total	328	207	1474	415	87	2511

MYH7-Varsome

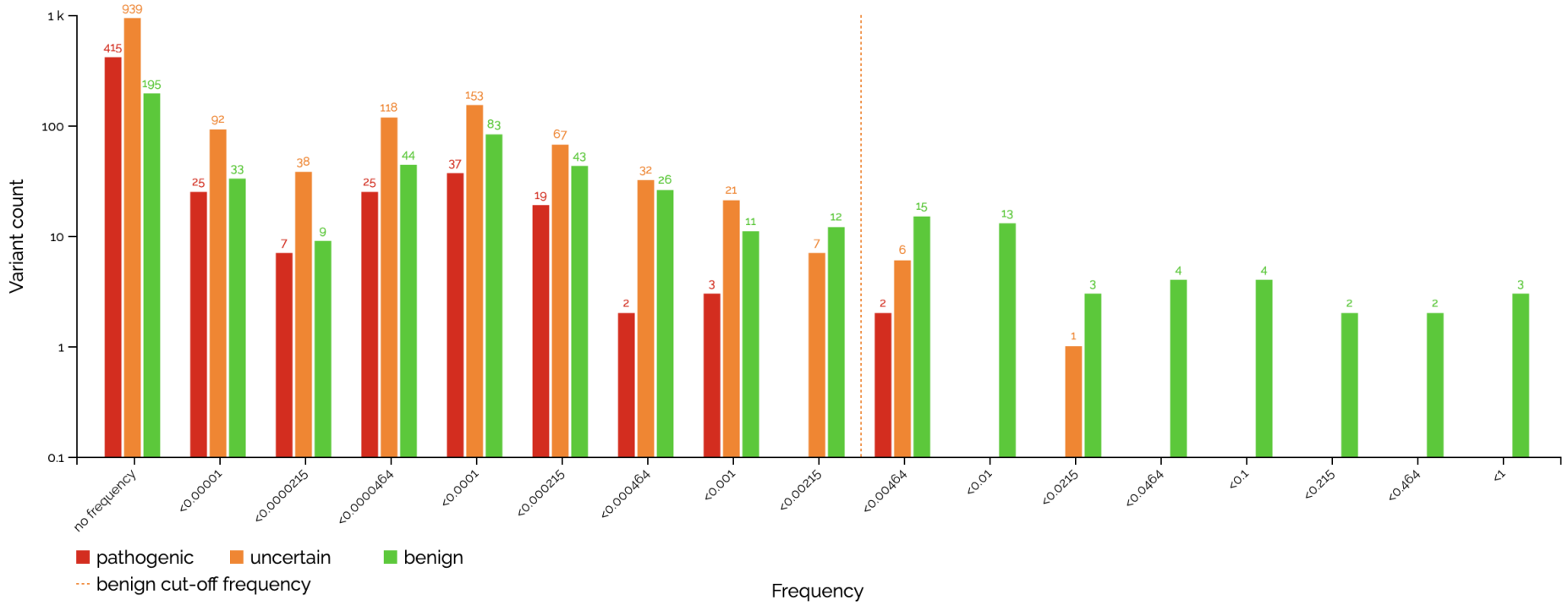
Total classified variants (UniProt, ClinVar, VarSome & PubMed)
2511

Pathogenic	Uncertain significance	Benign
535	1474	502

Coding impact	Pathogenic	Likely Pathogenic	Uncertain Significance	Likely Benign	Benign	Total
Synonymous	0.2%	0.2%	19.1%	66.7%	13.8%	508
Missense	18.4%	10.6%	69.9%	0.4%	0.6%	1697
Nonsense	2.4%	4.8%	92.9%	0%	0%	42
Start loss	0%	0%	100%	0%	0%	1
Stoploss	0%	0%	100%	0%	0%	1
Frameshift	7.7%	11.5%	80.8%	0%	0%	26
Inframe Indel	10.6%	31.9%	57.4%	0%	0%	47
Splice junction loss	13.2%	15.8%	71.1%	0%	0%	38
Non-coding	0.7%	0%	49.0%	45.7%	4.6%	151
Total	13.1%	8.2%	58.7%	16.5%	3.5%	2511

☑ Display percentages

MYH7-Varsome



The recommended benign frequency cut-off for rule BS1 is **0.0025**, derived from the 2511 clinical known variants observed in gene MYH7, of which 535 pathogenic, 1474 uncertain and 502 benign.

The pathogenic variant with the highest allele frequency is: chr14-23898249-G-A, with East Asian frequency = 0.002555 .

GLA-Varsome

Total classified variants (UniProt, ClinVar, VarSome & PubMed)
1107

Pathogenic
681

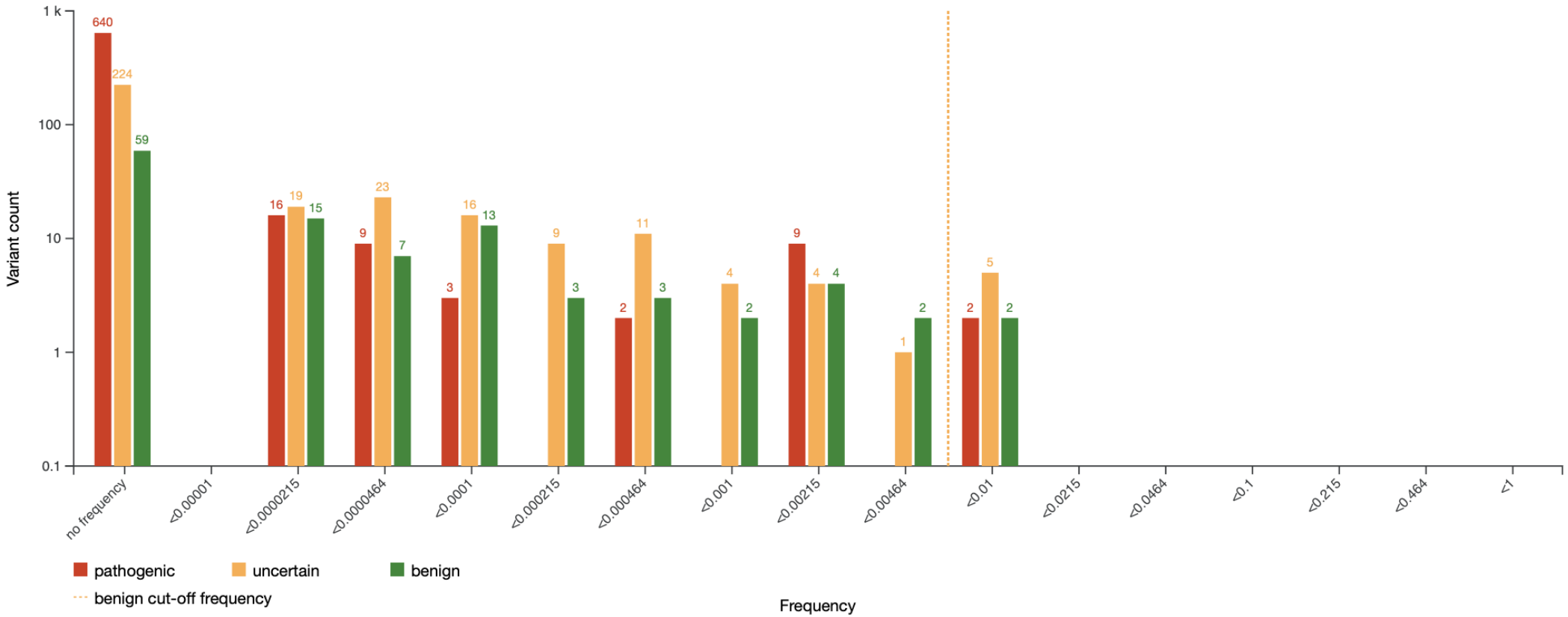
Uncertain significance
316

Benign
110

Coding impact	Pathogenic	Likely Pathogenic	Uncertain Significance	Likely Benign	Benign	Total
Synonymous	0%	2.2%	7.5%	87.1%	3.2%	93
Missense	46.9%	15.5%	35.9%	1.0%	0.7%	767
Nonsense	85.5%	11.3%	3.2%	0%	0%	62
Start loss	83.3%	16.7%	0%	0%	0%	6
Frameshift	63.9%	22.2%	12.9%	0%	0.9%	108
Inframe Indel	26.7%	40%	33.3%	0%	0%	15
Splice junction loss	67.7%	25.8%	6.5%	0%	0%	31
Non-coding	4%	4%	44%	44%	4%	25
Total	46.3%	15.2%	28.5%	9.0%	0.9%	1107

☑ Display percentages

GLA-Varsome


1 k
100
10
1
0.1
Variant count
640
224
59
16
19
15
9
23
7
3
16
13
9
3
2
11
3
4
2
9
4
4
1
2
2
5
2
no frequency
<0.00001
<0.0000215
<0.0000464
<0.0001
<0.000215
<0.000464
<0.001
<0.00215
<0.00464
<0.01
<0.0215
<0.0464
<0.1
<0.215
<0.464
<1
pathogenic
uncertain
benign
benign cut-off frequency
Frequency

VUS are difficult to classify

- Lack of sufficient population-based statistical evidence
- Scarcity of functional evidence
- Different evaluations by clinicians and researchers

Federici and Soddu Journal of Experimental & Clinical Cancer Research, 2020

PgmNr 26: Comprehensive functional classification of Lynch syndrome missense variants.

Authors:
Jia [1]; B. Burugula [1]; V. Chen [1]; M. Maksutova [1]; S. Jayakody [1]; J. Kitzman [1,2]

View Session Add to Schedule

Affiliations:
1) Department of Human Genetics,; 2) Department of Computational Medicine and Bioinformatics, Univ MICHIGAN, Ann Arbor, Michigan.

The rapid expansion of clinical genetic testing has shifted the bottleneck in human genetics from data acquisition to variant interpretation. For many clinically actionable genes, there is a large burden of individually rare variants of uncertain significance (VUS), particularly missense variants for which the impact upon the encoded protein remains undetermined and can vary from loss of function to entirely benign. We selected one such gene, *MSH2*, which is frequently mutated in Lynch Syndrome, the highest prevalence inherited cancer risk syndrome (1:279 individuals). We systematically classified variant function by synthesizing and introducing into human cells a library containing every possible single-codon variant of *MSH2* full-length cDNA (N=58,842). Targeted deep sequencing of *MSH2* from the resulting cellular population indicated that >95% of all possible variants were stably integrated, representing the largest human gene subjected to full saturation mutagenesis and deep mutational scanning to date in a mammalian cellular model. We performed mismatch repair activity-dependent screening to measure the molecular function of each *MSH2* mutation in cells, using as a read-out ultra-deep sequencing of the mutant *MSH2* library before and after drug selection. After stringent data quality control and filtering, we arrived at loss-of-function scores for 16,588 (~93.5%) single amino-acid substitution missense variants of *MSH2*. These scores were bimodally distributed, and indicated that most missense alleles of *MSH2* (88.7%) retain mismatch repair function, while a small minority (11.3%) are functionally impaired. These functional scores showed near-perfect concordance with published biochemical characterization of individual variants. Additionally, these high-throughput measurements show strong agreement with the expert-panel reviewed classification of *MSH2* missense variants in ClinVar. This dataset will enable greatly improved interpretation of clinically observed variants of *MSH2*, towards prospective, genotype-guided early detection and intervention for inherited colorectal cancer.

Databases/Online Tools for Reclassifying VUSs

- Population frequency
  - Varsome, Alamut, dbSNP, gnomAD
- Mutation/Polymorphism
  - HGMD, ClinVar, dbFGP
- Novel/Published
  - HGMD, ClinVar, dbFGP
- Pathogenic/Benign
  - Varsome, Franklin, PolyPhen, SIFT, MutationTaster, CADD,
- Related to a specific disorder/incidental
  - HGMD, ClinVar, OMIM

HGMD

HGMD® Professional 2020.1 Trial version

Gene Mutation Phenotype Reference Batch Advanced | Statistics Information Su

Gene Symbol	Location	Gene description	cDNA sequence
GLA XLD (Aliases: GALA)	Xq22	Galactosidase alpha (Aliases: Agalsidase alfa; Alpha-D-galactosidase A; Alpha-D-galactoside galactohydrolase 1; Alpha-gal A; Melibiase)	NM_000169.2

Mutation type	Total number of mutations	
Missense/nonsense	695	
Splicing substitutions	49	
Regulatory substitutions	6	
Small deletions	142	
Small insertions/duplications	45	
Small indels	16	
Gross deletions	39	
Gross insertions/duplications	8	
Complex rearrangements	7	
Repeat variations	0	
TOTAL	1007	

Variant class	Number of mutations	
DM	945	
DM?	57	
FP	4	
DFP	1	

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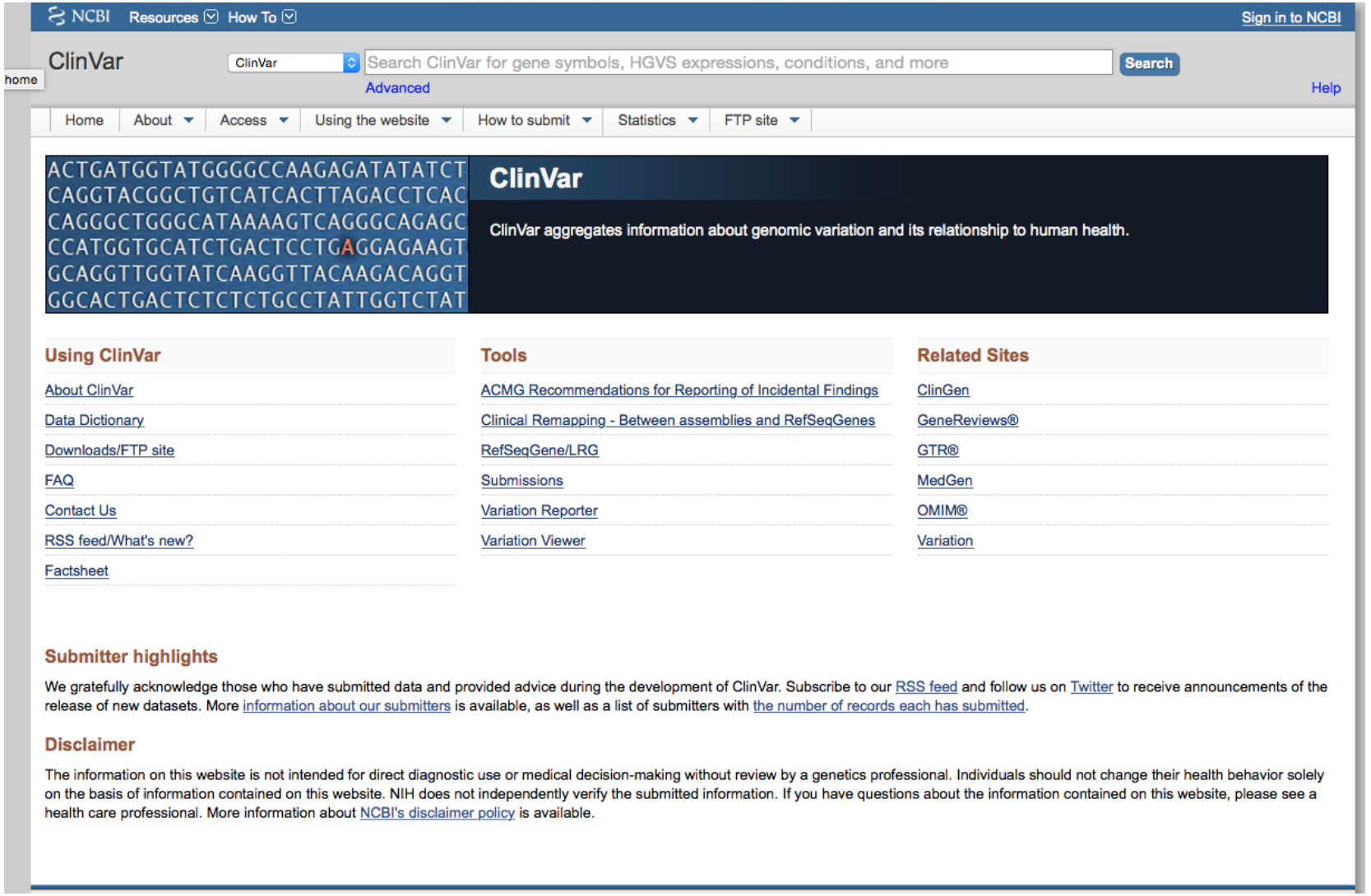
http://dbfgp.org/dbFgp/fabry/Mutation.html

http://dbfgp.org/dbFgp/fabry/Mutation.html

NCBI-ClinVar



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

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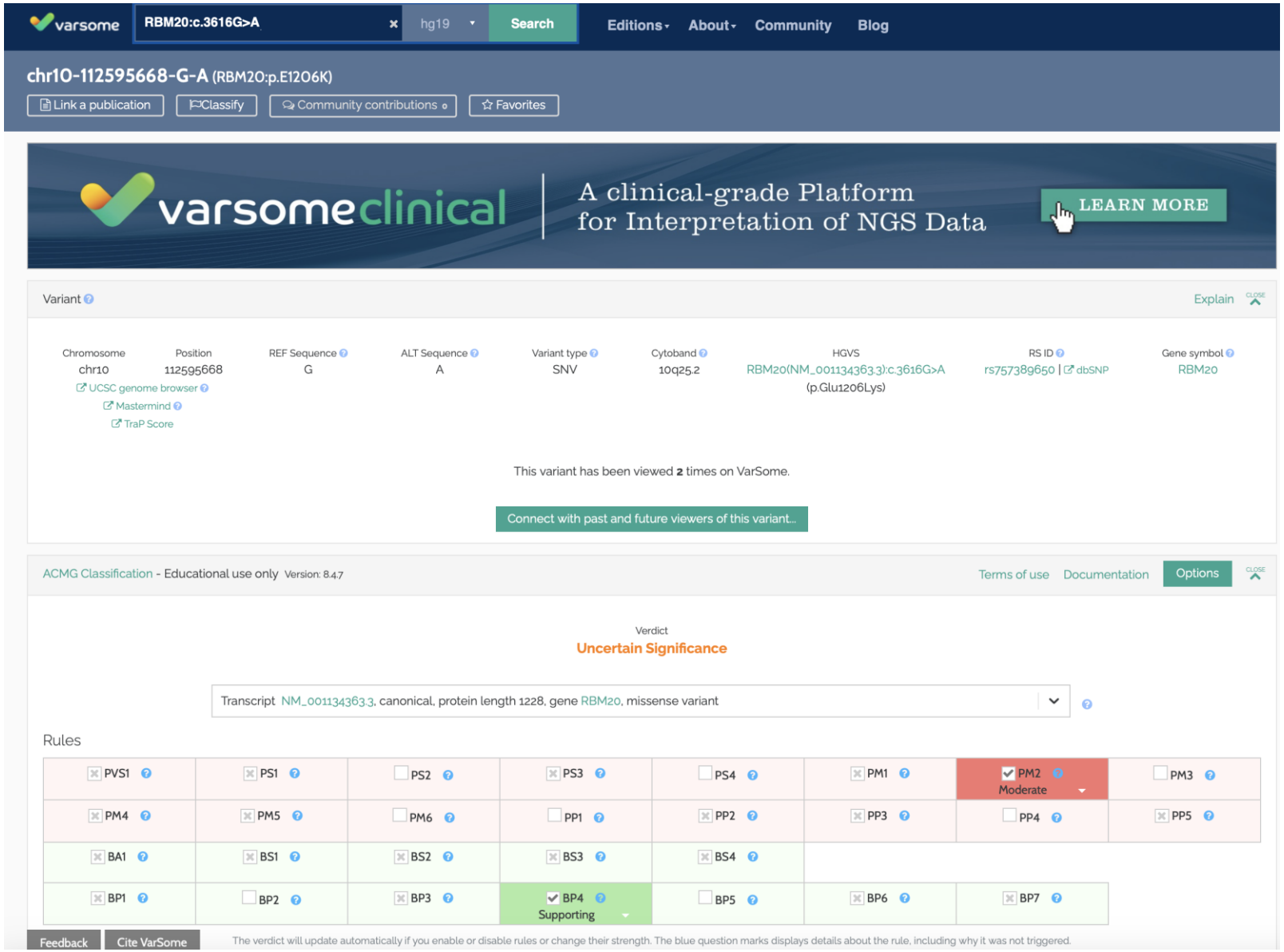
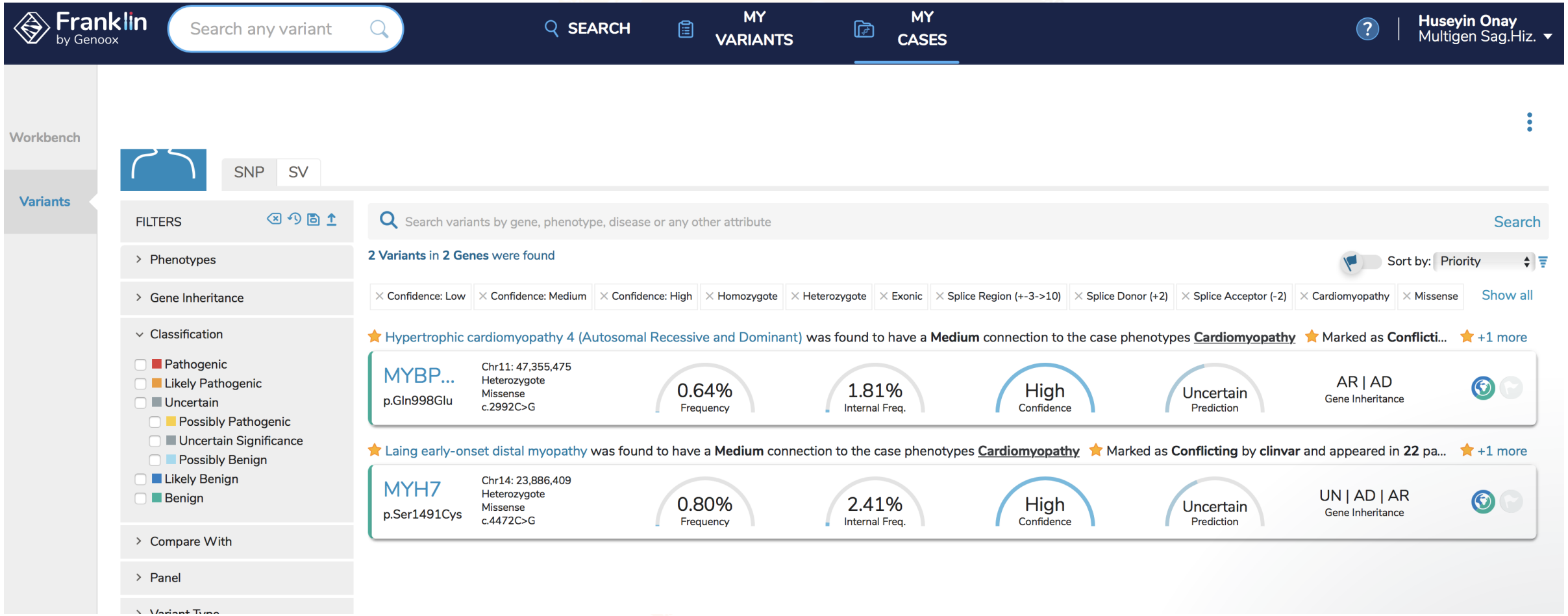
Varsome


varsome
RBM20:c.3616G>A
hg19
Search
Editions
About
Community
Blog
chr10-112595668-G-A (RBM20:p.E1206K)
Link a publication
Classify
Community contributions 0
Favorites
varsomeclinical
A clinical-grade Platform for Interpretation of NGS Data
LEARN MORE
Variant
Explain
Chromosome
chr10
Position
112595668
REF Sequence
G
ALT Sequence
A
Variant type
SNV
Cytoband
10q25.2
HGVS
RBM20(NM_001134363.3):c.3616G>A
(p.Glu1206Lys)
RS ID
rs757389650 | dbSNP
Gene symbol
RBM20
UCSC genome browser
Mastermind
TraP Score
This variant has been viewed 2 times on VarSome.
Connect with past and future viewers of this variant...
ACMG Classification - Educational use only Version: 8.4.7
Terms of use
Documentation
Options
Verdict
Uncertain Significance
Transcript NM_001134363.3, canonical, protein length 1228, gene RBM20, missense variant
Rules
PVS1
PS1
PS2
PS3
PS4
PM1
PM2
Moderate
PM3
PM4
PM5
PM6
PP1
PP2
PP3
PP4
PP5
BA1
BS1
BS2
BS3
BS4
BP1
BP2
BP3
BP4
Supporting
BP5
BP6
BP7
Feedback
Cite VarSome
The verdict will update automatically if you enable or disable rules or change their strength. The blue question marks displays details about the rule, including why it was not triggered.

Franklin


Franklin by Genoox
Search any variant
SEARCH
MY VARIANTS
MY CASES
Huseyin Onay
Multigen Sag.Hiz.
Workbench
Variants
SNP
SV
FILTERS
Search variants by gene, phenotype, disease or any other attribute
Search
Phenotypes
Gene Inheritance
Classification
Pathogenic
Likely Pathogenic
Uncertain
Possibly Pathogenic
Uncertain Significance
Possibly Benign
Likely Benign
Benign
Compare With
Panel
2 Variants in 2 Genes were found
Sort by: Priority
Confidence: Low
Confidence: Medium
Confidence: High
Homozygote
Heterozygote
Exonic
Splice Region (+-3->10)
Splice Donor (+2)
Splice Acceptor (-2)
Cardiomyopathy
Missense
Show all
Hypertrophic cardiomyopathy 4 (Autosomal Recessive and Dominant) was found to have a Medium connection to the case phenotypes Cardiomyopathy
Marked as Conflicti...
+1 more
MYBP...
p.Gln998Glu
Chr11: 47,355,475
Heterozygote
Missense
c.2992C>G
0.64%
Frequency
1.81%
Internal Freq.
High
Confidence
Uncertain
Prediction
AR | AD
Gene Inheritance
Laing early-onset distal myopathy was found to have a Medium connection to the case phenotypes Cardiomyopathy
Marked as Conflicting by clinvar and appeared in 22 pa...
+1 more
MYH7
p.Ser1491Cys
Chr14: 23,886,409
Heterozygote
Missense
c.4472C>G
0.80%
Frequency
2.41%
Internal Freq.
High
Confidence
Uncertain
Prediction
UN | AD | AR
Gene Inheritance

Franklin

RBM20
p.Glu1206Lys

Chr10: 112,595,668
Heterozygote
Missense
c.3616G>A

<0.01% Frequency | 1.20% Internal Freq. | High Confidence | Uncertain Prediction | AD Gene Inheritance

NM_001134363.3 | Exon 14 | dbSNP rs757389650 | See All Transcripts >

Frequency

+ 1K Genome:	N/A
+ ESP 6500:	N/A
+ ExAC:	0.01%%
+ UK10K (Control):	N/A
+ gnomAD (Exome):	<0.01%%
+ gnomAD (Genome):	<0.01%%
Internal:	2 (1.20%)
Community cases:	N/A | N/A

See Frequencies Details >

Suspected compound

Pathogenic	N/A
Likely Pathogenic	N/A
VUS	N/A

See all suspected compound variants >

Confidence

Variant Quality:	2656.6
Quality by Depth:	15.45
Genotype	
Quality:	99
Likelihoods:	2,664|0|1,811
Depth	
Total:	172
G:	75
A:	97
Allele balance:	
Strand bias:	
Fisher strand bias:	0
Alignment bias:	
ReadPosRankSum:	-0.884
Mapping Quality:	60
MQRankSum:	0

Found by all variant callers

Prediction

Aggregated:	Uncertain (0.59)
Functional Coding	
REVEL:	Uncertain (0.50)
MetaLR:	Uncertain (0.67)
MT:	Polymorph (<0.01)
MA:	Medium (2.10)
FATHMM:	Damaging (-3.12)
SIFT:	Damaging (<0.01)
POLYPHEN2:	Benign (0.01)
Splice Altering	
dbscSNV Ada:	N/A
Splice AI:	Benign (<0.01)
Conservation	
GERP:	4.99
Functionl Whole Genome	
GenoCanyon:	Deleterious (1.00)
fitCons:	Deleterious (0.55)
ncER:	N/A

See All Transcript Predictions >

Clinical information

Associated conditions

Dilated Cardiomyopathy 1Dd	OMIM |	AD
Dcm-...		
Familial Isolated Dilated Cardiomyopathy		

See All Conditions >

Curated Variant Submissions

Uniprot:	N/A
− Clinvar:	
Uncertain Significance	2

See All Clinical Evidence >

Publications

Variant:	3
Gene:	105

See Related Publications >

Possibly Pathogenic why this classification?

https://franklin.genoox.com/analysis-tool/analysis

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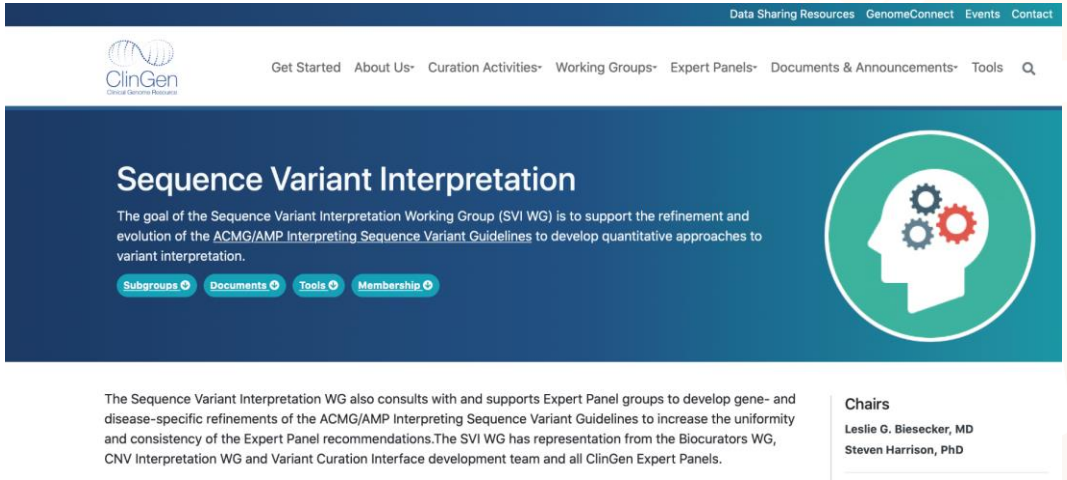


https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/

ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1

This version specified for the following genes: *MYH7*

Expert Panel Page: https://www.clinicalgenome.org/affiliation/50002

SUMMARY OF CLASSIFICATION CRITERIA

Pathogenic Criteria				Combination of Criteria Needed to Meet Classification								
	Rule	Modification Type	Rule Description	Pathogenic				Likely Pathogenic				
VS	PVS1	RE	Null variant in gene with established LOF as disease mechanism									
STRONG	PS1	NC	Different nucleotide change (same amino acid) as a previously established pathogenic variant	2	1	1	1	1	1			
STRONG	PS2	DG	*De novo* (paternity confirmed) in a patient with disease and no family history									
STRONG	PS3	DG	Functional studies of mammalian knock-in models supportive of a damaging effect on the gene or gene product									
STRONG	PS4	DG	Prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls -OR- Variant identified in ≥15 probands with consistent phenotypes									
STRONG	PP1_Strong	MS	Variant segregates with ≥7 meioses									
MODERATE	PM1	DG	Hotspot/est. functional domain (amino acids 181-937) without benign variation		3	2	1	1		3	2	1
MODERATE	PM2	DG	Absent/extremely rare (<0.004%) from large population studies									
MODERATE	PM3	RE	Detected in trans with a pathogenic variant (recessive)									
MODERATE	PM4	DG	Protein length changes due to in-frame deletions/insertions of any size in a non-repeat region or stop-loss variants									
MODERATE	PM5	NC	Missense change at an amino acid residue where a different missense change previously established as pathogenic									
MODERATE	PM6	DG	Confirmed *de novo* without confirmation of paternity									
MODERATE	PVS1_Moderate	MS	Null variant in gene with evidence supporting LOF as disease mechanism									
MODERATE	PS4_Moderate	MS	Variant identified in ≥6 probands with consistent phenotypes									
MODERATE	PP1_Moderate	MS	Variant segregates in ≥5 meioses									
SUPPORTING	PP1	DG	Variant segregates in ≥3 meioses			2	4		2		2	4
SUPPORTING	PP2	RE	Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease									
SUPPORTING	PP3	NC	Multiple lines of computational evidence support a deleterious effect on the gene or gene product									
SUPPORTING	PP4	RE	Phenotype specific for disease with single genetic etiology									
SUPPORTING	PP5	RE	Reputable source reports as pathogenic									
SUPPORTING	PS4_Supporting	MS	Variant identified in ≥2 probands with consistent phenotypes									

ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1

This version specified for the following genes: *MYH7*

Expert Panel Page: https://www.clinicalgenome.org/affiliation/50002

Benign Criteria				Combination of Criteria Needed to Meet Classification			
Rule		Modification Type	Rule Description	Benign		Likely Benign	
SA	BA1	DG	Allele frequency is ≥0.1% based on the filtering allele frequency (FAF) in ExAC	1			
STRONG	BS1	DG	Allele frequency is ≥0.02% based on the filtering allele frequency (FAF) in ExAC provided there is no conflicting information		2	1	
	BS2	RE	Observed in healthy adult with full penetrance expected at an early age				
	BS3	NC	Functional studies of mammalian knock-in models supportive of no damaging effect on protein function or splicing				
	BS4	DG	Non-segregation in affected members of a family				
SUPPORTING	BP1	RE	Missense variant in gene where only LOF causes disease				2
	BP2	DG	Observed as comp het (in trans) or double het in genes with overlapping function (e.g. sarcomere genes) without increased disease severity -OR- Observed in cis with a pathogenic variant in any inheritance pattern				
	BP3	RE	In-frame deletions/insertions in a repetitive region without a known function				
	BP4	NC	Multiple lines of computational evidence suggest no impact on gene or gene product				
	BP5	DG	Variant found in a case with an alternate molecular basis for disease				
	BP6	RE	Reputable source reports as benign				
	BP7	NC	A silent variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site -AND- the nucleotide is not highly conserved				

RULES FOR COMBINING CRITERIA

PATHOGENIC

1. 1 Very Strong AND
   a. ≥1 Strong OR
   b. ≥2 Moderate OR
   c. 1 Moderate and 1 Supporting OR
   d. ≥2 Supporting
2. ≥2 Strong OR
3. 1 Strong AND
   a. ≥3 Moderate OR
   b. 2 Moderate AND ≥2 Supporting OR
   c. 1 Moderate AND ≥4 Supporting

LIKELY PATHOGENIC

1. 1 Very Strong AND 1 Moderate OR
2. 1 Strong AND 1-2 Moderate OR
3. 1 Strong AND ≥2 Supporting OR
4. ≥3 Moderate OR
5. 2 Moderate AND ≥2 Supporting OR
6. 1 Moderate AND ≥4 Supporting

BENIGN

1. 1 Stand-Alone OR
2. ≥2 Strong

LIKELY BENIGN

1. 1 Strong* OR
2. ≥2 Supporting

https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/

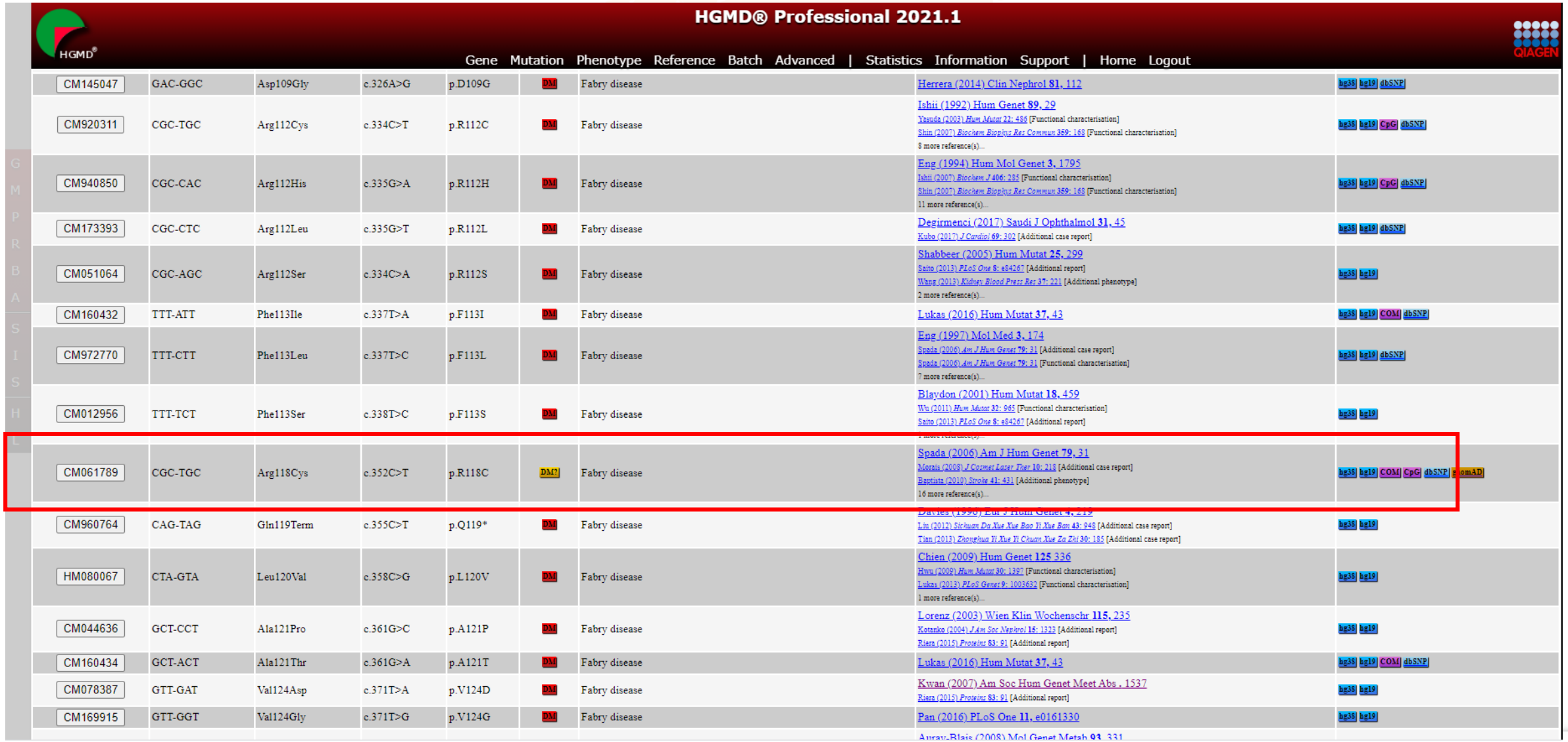
Classification	Variant included in report?	Result summary for genetic laboratory report	Explanatory Notes
VUS *where further testing or investigations could be considered as the results have the potential to change the classification to likely pathogenic*	***YES***	***Inconclusive result – consider further action*** *Clearly describe in the report the action required that could change the classification to likely pathogenic*	***Further testing or investigations*** ***a)testing parents to determine whether de novo (PS2/PM6)*** ***b) mRNA analysis for variants predicted to affect normal splicing (PS3)*** ***c) testing affected relatives to show co-segregation (PP1)*** ***d) biochemical testing (PP4)*** ***e) trial of a treatment that is specific for the genetic aetiology (PP4)***
VUS **hot/warm/tepid VUS where no further evidence can be obtained*	***Not Usually***	***A genetic cause for the patient's disorder has not been identified***	*These variants should only be reported in exceptional circumstances following MDT discussion*
VUS **cool/cold/ice cold VUS*	***NO***	***A genetic cause for the patient's disorder has not been identified***	*These variants are almost invariably unlikely to be disease-causing and are potentially confusing if included in the report.*

Ellard S et al. ACGS, 2020

Algorithm for Reclassifying VUSs

- Re-analyze the reported variant for prediction of pathogenicity and frequency
  - Varsome
  - Franklin
- Family screening
- Detecting frequency of the variant in healthy population
- Functional analysis
  - RNA sequencing
  - Model organism
- Annually re-evaluate VUSs using databases and publications

HGMD-GLA



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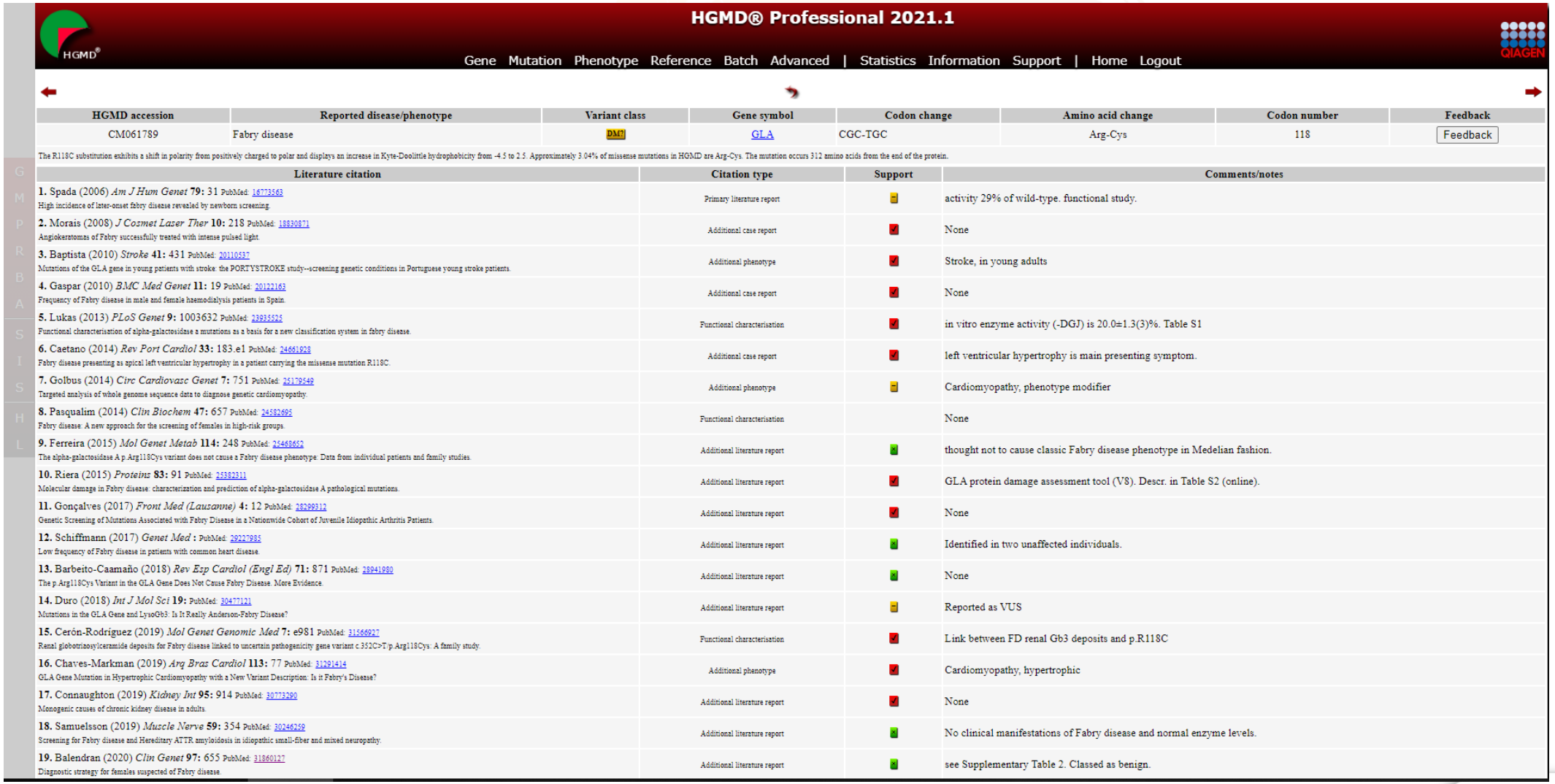
Gene Mutation Phenotype Reference Batch Advanced | Statistics Information Support | Home Logout

CM145047	GAC-GGC	Asp109Gly	c.326A>G	p.D109G	DM	Fabry disease	Herrera (2014) Clin Nephrol **81**, 112	hg38 hg19 dbSNP
CM920311	CGC-TGC	Arg112Cys	c.334C>T	p.R112C	DM	Fabry disease	Ishii (1992) Hum Genet **89**, 29 Yasuda (2003) *Hum Mutat* 22: 486 [Functional characterisation] Shin (2007) *Biochem Biophys Res Commun* 359: 168 [Functional characterisation] 8 more reference(s)...	hg38 hg19 CpG dbSNP
CM940850	CGC-CAC	Arg112His	c.335G>A	p.R112H	DM	Fabry disease	Eng (1994) Hum Mol Genet **3**, 1795 Ishii (2007) *Biochem J* 406: 285 [Functional characterisation] Shin (2007) *Biochem Biophys Res Commun* 359: 168 [Functional characterisation] 11 more reference(s)...	hg38 hg19 CpG dbSNP
CM173393	CGC-CTC	Arg112Leu	c.335G>T	p.R112L	DM	Fabry disease	Degirmenci (2017) Saudi J Ophthalmol **31**, 45 Kubo (2017) *J Cardiol* 69: 302 [Additional case report]	hg38 hg19 dbSNP
CM051064	CGC-AGC	Arg112Ser	c.334C>A	p.R112S	DM	Fabry disease	Shabbeer (2005) Hum Mutat **25**, 299 Saito (2013) *PLoS One* 8: e84267 [Additional report] Wang (2013) *Kidney Blood Press Res* 37: 221 [Additional phenotype] 2 more reference(s)...	hg38 hg19
CM160432	TTT-ATT	Phe113Ile	c.337T>A	p.F113I	DM	Fabry disease	Lukas (2016) Hum Mutat **37**, 43	hg38 hg19 COM dbSNP
CM972770	TTT-CTT	Phe113Leu	c.337T>C	p.F113L	DM	Fabry disease	Eng (1997) Mol Med **3**, 174 Spada (2006) *Am J Hum Genet* 79: 31 [Additional case report] Spada (2006) *Am J Hum Genet* 79: 31 [Functional characterisation] 7 more reference(s)...	hg38 hg19 dbSNP
CM012956	TTT-TCT	Phe113Ser	c.338T>C	p.F113S	DM	Fabry disease	Blaydon (2001) Hum Mutat **18**, 459 Wu (2011) *Hum Mutat* 32: 965 [Functional characterisation] Saito (2013) *PLoS One* 8: e84267 [Additional report]	hg38 hg19
CM061789	CGC-TGC	Arg118Cys	c.352C>T	p.R118C	DM?	Fabry disease	Spada (2006) Am J Hum Genet **79**, 31 Morais (2008) *J Cosmet Laser Ther* 10: 218 [Additional case report] Baptista (2010) *Stroke* 41: 431 [Additional phenotype] 16 more reference(s)...	hg38 hg19 COM CpG dbSNP gnomAD
CM960764	CAG-TAG	Gln119Term	c.355C>T	p.Q119*	DM	Fabry disease	Davies (1996) Eur J Hum Genet **4**, 219 Liu (2012) *Sichuan Da Xue Xue Bao Yi Xue Ban* 43: 948 [Additional case report] Tian (2013) *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 30: 185 [Additional case report]	hg38 hg19
HM080067	CTA-GTA	Leu120Val	c.358C>G	p.L120V	DM	Fabry disease	Chien (2009) Hum Genet **125** 336 Hwu (2009) *Hum Mutat* 30: 1397 [Functional characterisation] Lukas (2013) *PLoS Genet* 9: 1003632 [Functional characterisation] 1 more reference(s)...	hg38 hg19
CM044636	GCT-CCT	Ala121Pro	c.361G>C	p.A121P	DM	Fabry disease	Lorenz (2003) Wien Klin Wochenschr **115**, 235 Kotanko (2004) *J Am Soc Nephrol* 15: 1323 [Additional report] Riera (2015) *Proteins* 83: 91 [Additional report]	hg38 hg19
CM160434	GCT-ACT	Ala121Thr	c.361G>A	p.A121T	DM	Fabry disease	Lukas (2016) Hum Mutat **37**, 43	hg38 hg19 COM dbSNP
CM078387	GTT-GAT	Val124Asp	c.371T>A	p.V124D	DM	Fabry disease	Kwan (2007) Am Soc Hum Genet Meet Abs , 1537 Riera (2015) *Proteins* 83: 91 [Additional report]	hg38 hg19
CM169915	GTT-GGT	Val124Gly	c.371T>G	p.V124G	DM	Fabry disease	Pan (2016) PLoS One **11**, e0161330	hg38 hg19
							Auray-Blais (2008) Mol Genet Metab **93**, 331	

HGMD-GLA



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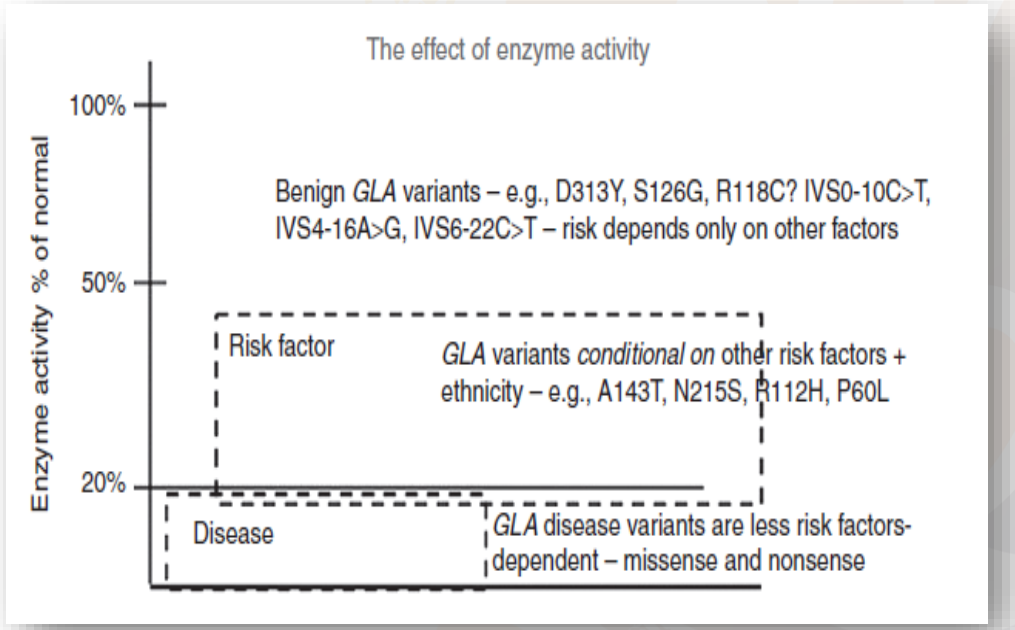
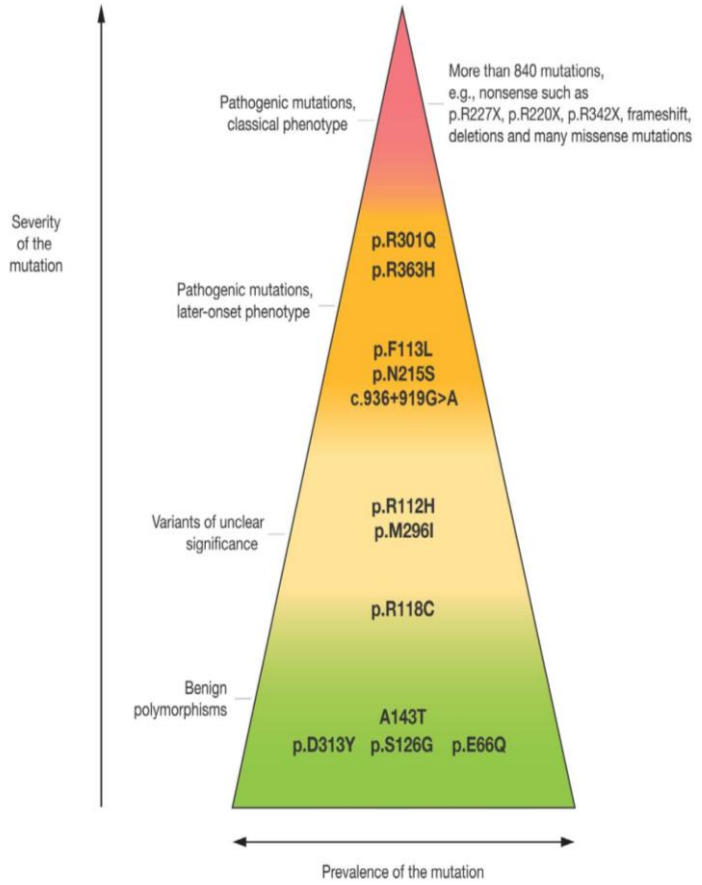
Gene Mutation Phenotype Reference Batch Advanced | Statistics Information Support | Home Logout

HGMD accession	Reported disease/phenotype	Variant class	Gene symbol	Codon change	Amino acid change	Codon number	Feedback
CM061789	Fabry disease	DM?	GLA	CGC-TGC	Arg-Cys	118	Feedback

The R118C substitution exhibits a shift in polarity from positively charged to polar and displays an increase in Kyte-Doolittle hydrophobicity from -4.5 to 2.5. Approximately 3.04% of missense mutations in HGMD are Arg-Cys. The mutation occurs 312 amino acids from the end of the protein.

Literature citation	Citation type	Support	Comments/notes
1. Spada (2006) *Am J Hum Genet* **79:** 31 PubMed: 16773563 High incidence of later-onset fabry disease revealed by newborn screening.	Primary literature report		activity 29% of wild-type. functional study.
2. Morais (2008) *J Cosmet Laser Ther* **10:** 218 PubMed: 18830871 Angiokeratomas of Fabry successfully treated with intense pulsed light.	Additional case report		None
3. Baptista (2010) *Stroke* **41:** 431 PubMed: 20110537 Mutations of the GLA gene in young patients with stroke: the PORTYSTROKE study--screening genetic conditions in Portuguese young stroke patients.	Additional phenotype		Stroke, in young adults
4. Gaspar (2010) *BMC Med Genet* **11:** 19 PubMed: 20122163 Frequency of Fabry disease in male and female haemodialysis patients in Spain.	Additional case report		None
5. Lukas (2013) *PLoS Genet* **9:** 1003632 PubMed: 23935525 Functional characterisation of alpha-galactosidase a mutations as a basis for a new classification system in fabry disease.	Functional characterisation		in vitro enzyme activity (-DGJ) is 20.0±1.3(3)%. Table S1
6. Caetano (2014) *Rev Port Cardiol* **33:** 183.e1 PubMed: 24661928 Fabry disease presenting as apical left ventricular hypertrophy in a patient carrying the missense mutation R118C.	Additional case report		left ventricular hypertrophy is main presenting symptom.
7. Golbus (2014) *Circ Cardiovasc Genet* **7:** 751 PubMed: 25179549 Targeted analysis of whole genome sequence data to diagnose genetic cardiomyopathy.	Additional phenotype		Cardiomyopathy, phenotype modifier
8. Pasqualim (2014) *Clin Biochem* **47:** 657 PubMed: 24582695 Fabry disease: A new approach for the screening of females in high-risk groups.	Functional characterisation		None
9. Ferreira (2015) *Mol Genet Metab* **114:** 248 PubMed: 25468652 The alpha-galactosidase A p.Arg118Cys variant does not cause a Fabry disease phenotype: Data from individual patients and family studies.	Additional literature report		thought not to cause classic Fabry disease phenotype in Medelian fashion.
10. Riera (2015) *Proteins* **83:** 91 PubMed: 25382311 Molecular damage in Fabry disease: characterization and prediction of alpha-galactosidase A pathological mutations.	Additional literature report		GLA protein damage assessment tool (V8). Descr. in Table S2 (online).
11. Gonçalves (2017) *Front Med (Lausanne)* **4:** 12 PubMed: 28299312 Genetic Screening of Mutations Associated with Fabry Disease in a Nationwide Cohort of Juvenile Idiopathic Arthritis Patients.	Additional literature report		None
12. Schiffmann (2017) *Genet Med* **:** PubMed: 29027985 Low frequency of Fabry disease in patients with common heart disease.	Additional literature report		Identified in two unaffected individuals.
13. Barbeito-Caamaño (2018) *Rev Esp Cardiol (Engl Ed)* **71:** 871 PubMed: 28941980 The p.Arg118Cys Variant in the GLA Gene Does Not Cause Fabry Disease. More Evidence.	Additional literature report		None
14. Duro (2018) *Int J Mol Sci* **19:** PubMed: 30477121 Mutations in the GLA Gene and LysoGb3: Is It Really Anderson-Fabry Disease?	Additional literature report		Reported as VUS
15. Cerón-Rodríguez (2019) *Mol Genet Genomic Med* **7:** e981 PubMed: 31566927 Renal globotriaosylceramide deposits for Fabry disease linked to uncertain pathogenicity gene variant c.352C>T/p.Arg118Cys: A family study.	Functional characterisation		Link between FD renal Gb3 deposits and p.R118C
16. Chaves-Markman (2019) *Arq Bras Cardiol* **113:** 77 PubMed: 31291414 GLA Gene Mutation in Hypertrophic Cardiomyopathy with a New Variant Description: Is it Fabry's Disease?	Additional phenotype		Cardiomyopathy, hypertrophic
17. Connaughton (2019) *Kidney Int* **95:** 914 PubMed: 30773290 Monogenic causes of chronic kidney disease in adults.	Additional literature report		None
18. Samuelsson (2019) *Muscle Nerve* **59:** 354 PubMed: 30246259 Screening for Fabry disease and Hereditary ATTR amyloidosis in idiopathic small-fiber and mixed neuropathy.	Additional literature report		No clinical manifestations of Fabry disease and normal enzyme levels.
19. Balendran (2020) *Clin Genet* **97:** 655 PubMed: 31860127 Diagnostic strategy for females suspected of Fabry disease.	Additional literature report		see Supplementary Table 2. Classed as benign.

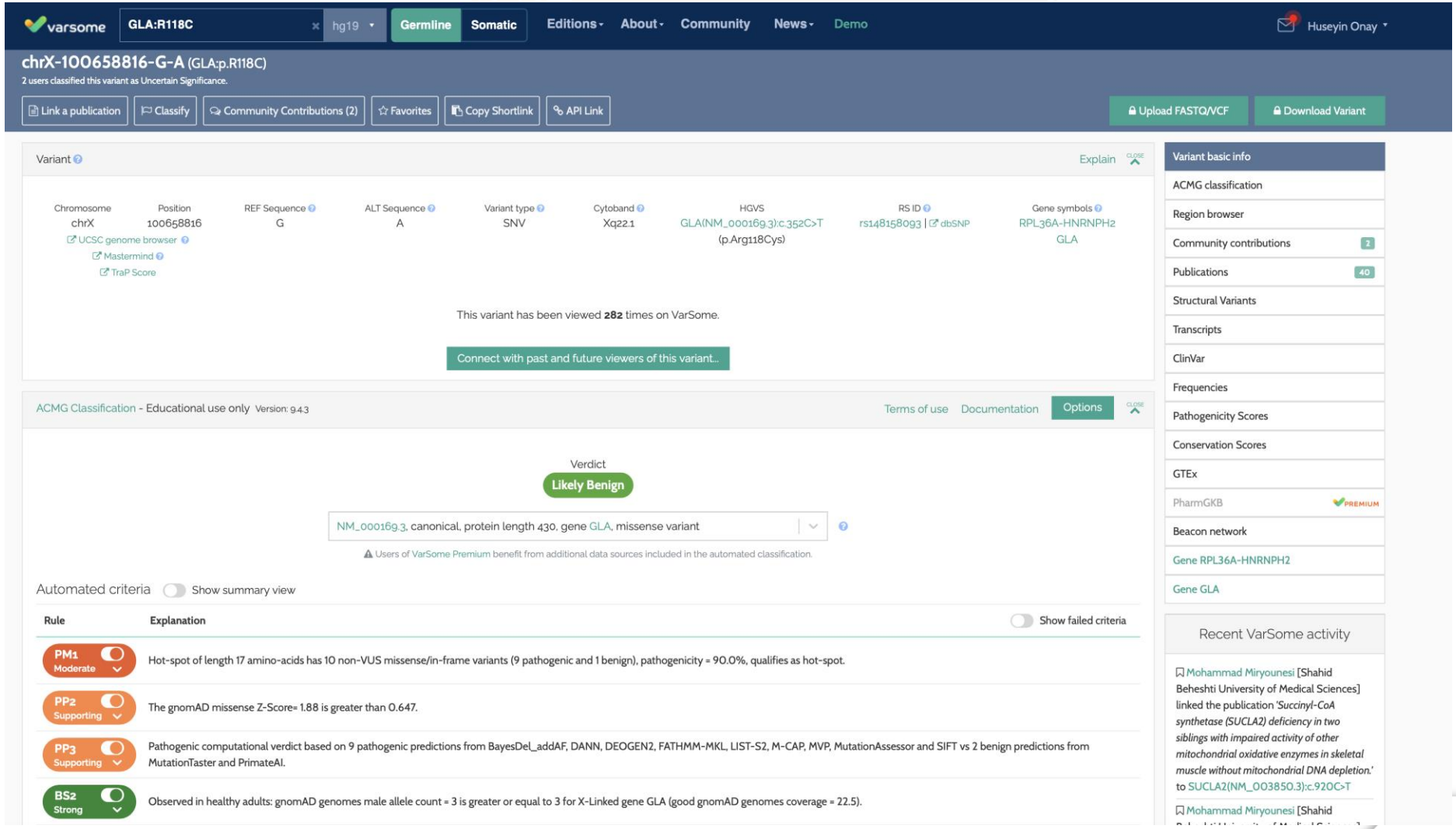




Schiffmann R ,et al. Genetics in Medicine (2016)

Ortiz A et al, Molecular Genetics and Metabolism, 2018

VARSOME-GLA_R118C



VARSOME-GLA_R118C

chrX-100658816-G-A (GLA:p.R118C)

Link a publication | Classify | Community Contributions (2) | Favorites | Copy Shortlink | API Link | Uplo

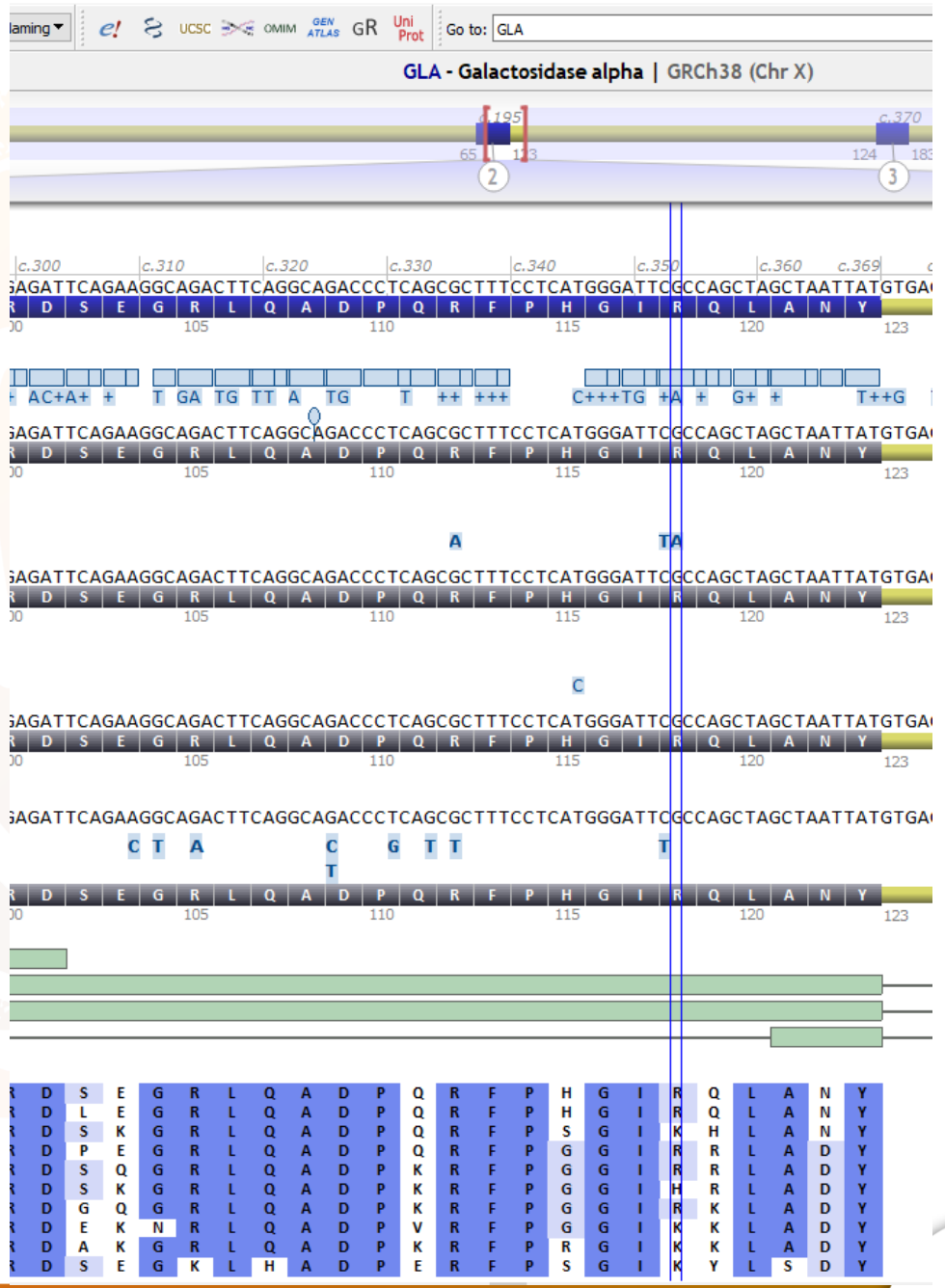
81.7	88	99.93%

gnomAD Genomes Version: 2.1.1 f = **0.000319** Explain View this on gnomAD Browser CLOSE

Population frequencies

Population	Allele Count	Allele Number	Homozygotes	Allele Frequency
African	-	5.900	-	-
Ashkenazi Jewish	-	182	-	-
East Asian	-	1.006	-	-
European (Finnish)	-	2.617	-	-
European (Non-Finnish)	6	10.805	-	0.000555
Latino	1	623	-	0.00161
Other	-	805	-	-
Total	**7**	**21.938**	-	~ 1 in 2675
Male	3	8.026	-	0.000374
Female	4	13.912	-	0.000288

Alamut-GLA_R118C



Conclusion

- Fabry variant is cold VUS/benign
  - No need to follow up

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