Maintaining Accurate Information in Variant Databases

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PARTNERS HEALTHCARE

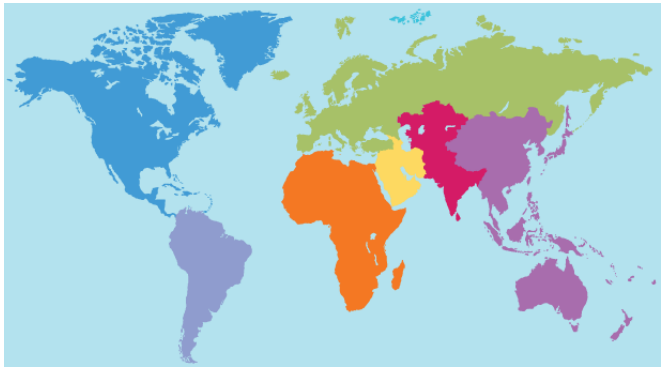
CENTER FOR PERSONALIZED GENETIC MEDICINE

HARVARD MEDICAL SCHOOL

Laboratory for Molecular Medicine at PCPGM

- CLIA accreditation in 2003
- LMM offers >150 tests in cardiovascular disease, cancer, hearing loss, pharmacogenetics and genetic syndromes

25% of testing is from Partners' patients
75% is from other US and International patients

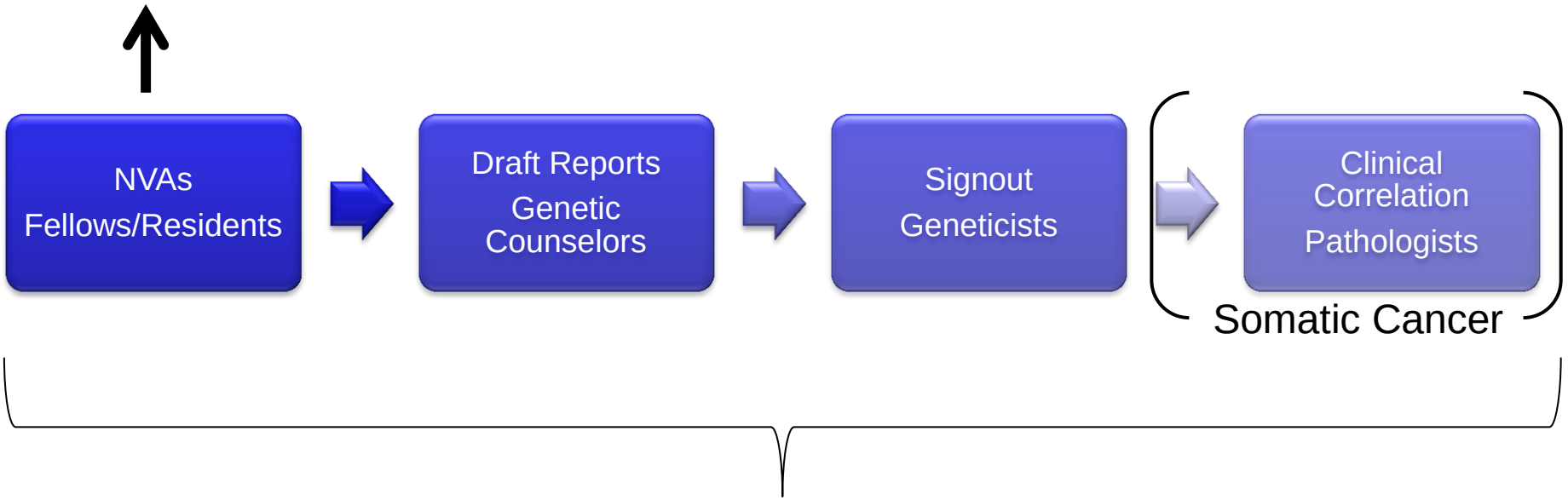


- Main focus of testing is large multi-gene panels using sequencing technologies (Sanger, chip-based, NGS)
- Other technologies include TaqMan, Luminex, allele-specific PCR, MLPA, PNAs, STRs, droplet PCR
- WGS interpretation service will launch in Oct 2012

Average Time to Assess a Novel Variant

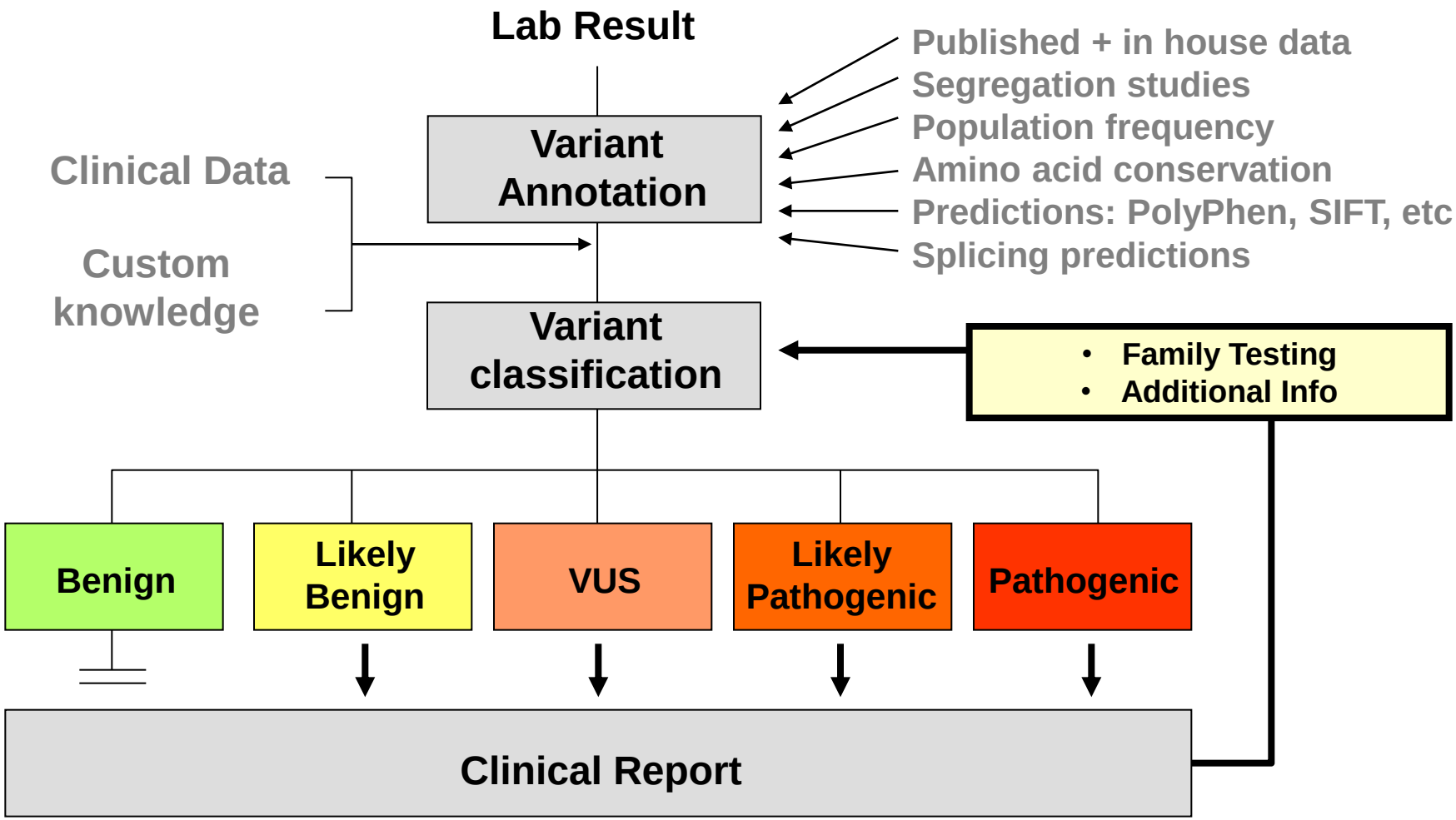
Variant Assessment Type	Average
Variant with no data	22 min
Variant with dbSNP/ESP data only	25 min
Varant with publications	120 min

~300 NVAs/month



~25,000 variants curated to date

Clinical Grade Variant Assessment



Courtesy of Birgit Funke

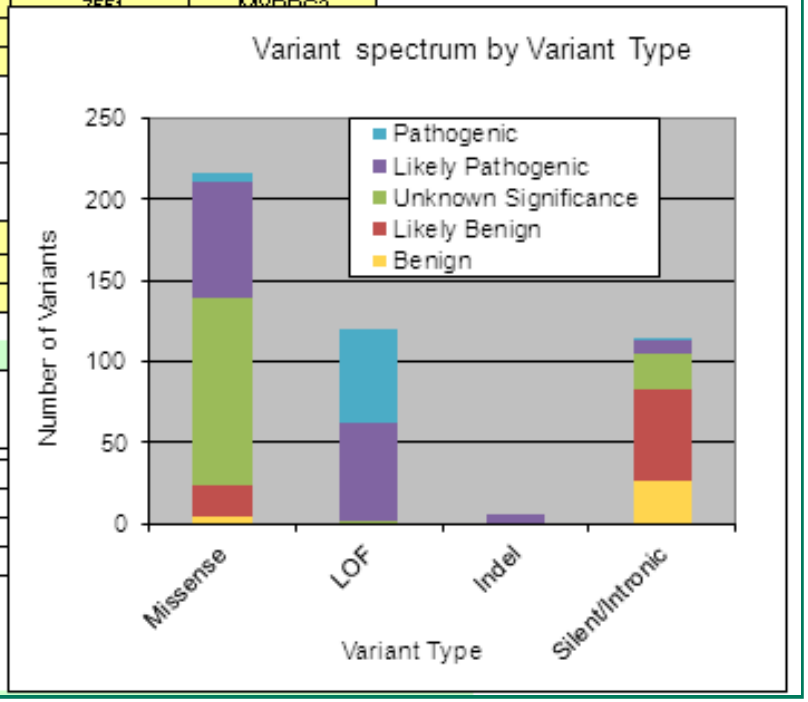
NVA: Gene Characteristics and Variant Spectrum

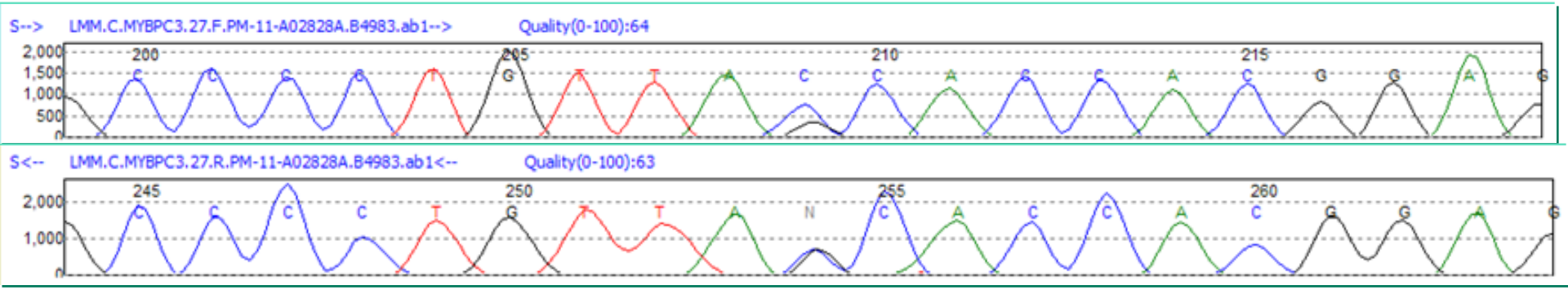
VARIANT INFO — Variant Folders link | Alamut link | Link to NVA form

		Transcript	Protein	HGNC ID	GI Name
Gene	MYBPC3	NM_000256.3	NP_000247	[illegible]	[illegible]
Genome build, coordinates	GRCh37	chr11:47356628-47356628			
Exon/Intron	27	of 33 total exons			
Zygosity	Het				
Nucleotide Change	2870C>G	Wildtype AA	Position		
Amino Acid change	Thr957Ser	T	957		
Variant Type	Missense				
Distance from exon/intron junction	36				
Protein Domains	Fibronectin, type III, Fibronectin, type III-like fold				
Gene-specific warning	None				
Exon-specific warning & link	None				

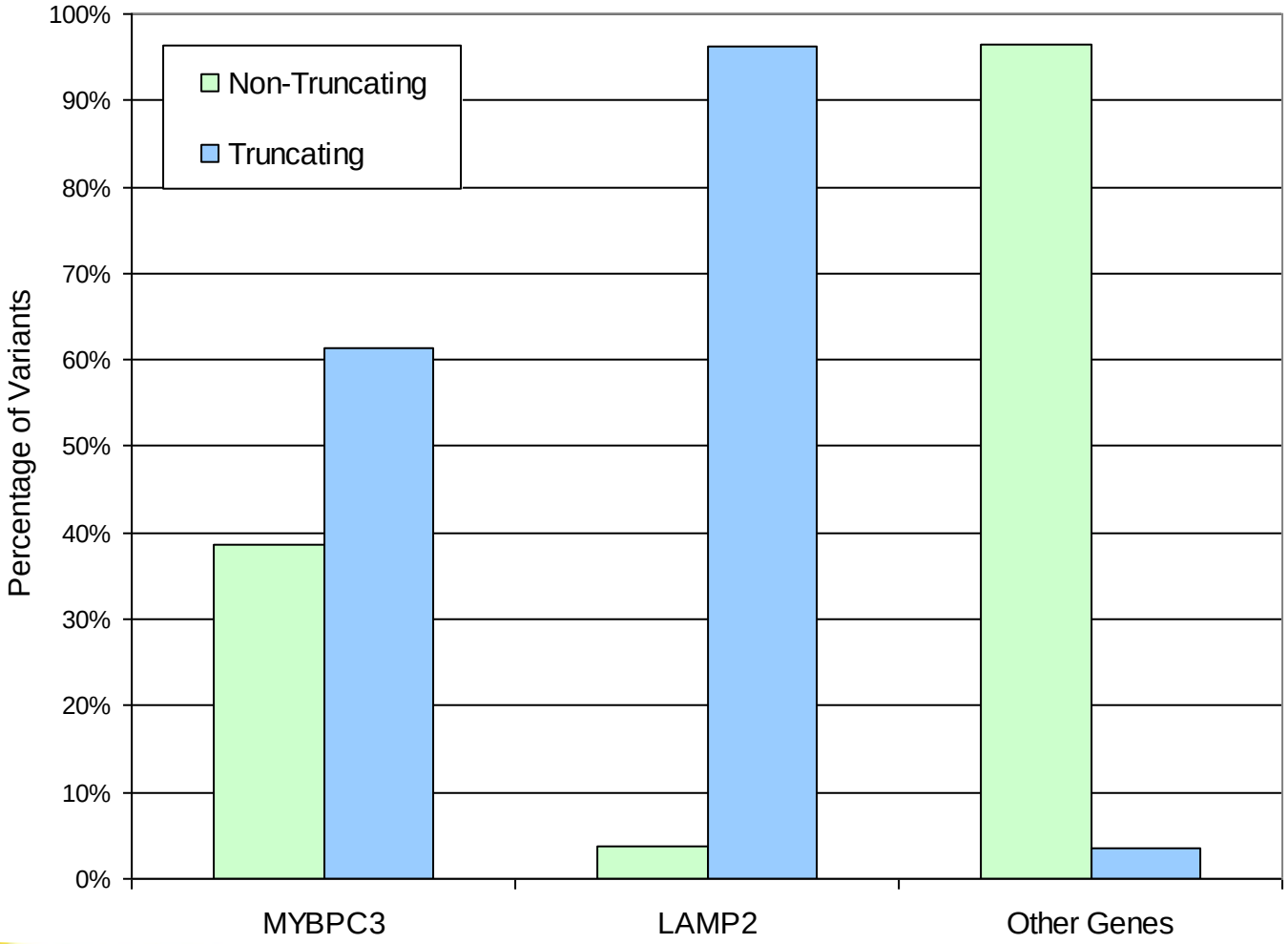
VARIANT SPECTRUM & ALTERNATE VARIANTS

LMM Variant Classifications	Mis	Missense	LOF (FS, Nonsense, +/-1,2 splice)
Total	217	217	120
% of type that are pathogenic or likely path.	36%	36%	99%
% of type that are VUS	53%	53%	1%
% of all pathogenic or likely pathogenic	37%	37%	56%
Variant type pathogenic in this gene?	Y	GeneReviews	Cardio Guide link
Same aa change from different variant?	N	GeneInsight link	
Different aa change at this codon?	N		





Gene-specific distribution of mutation types in HCM

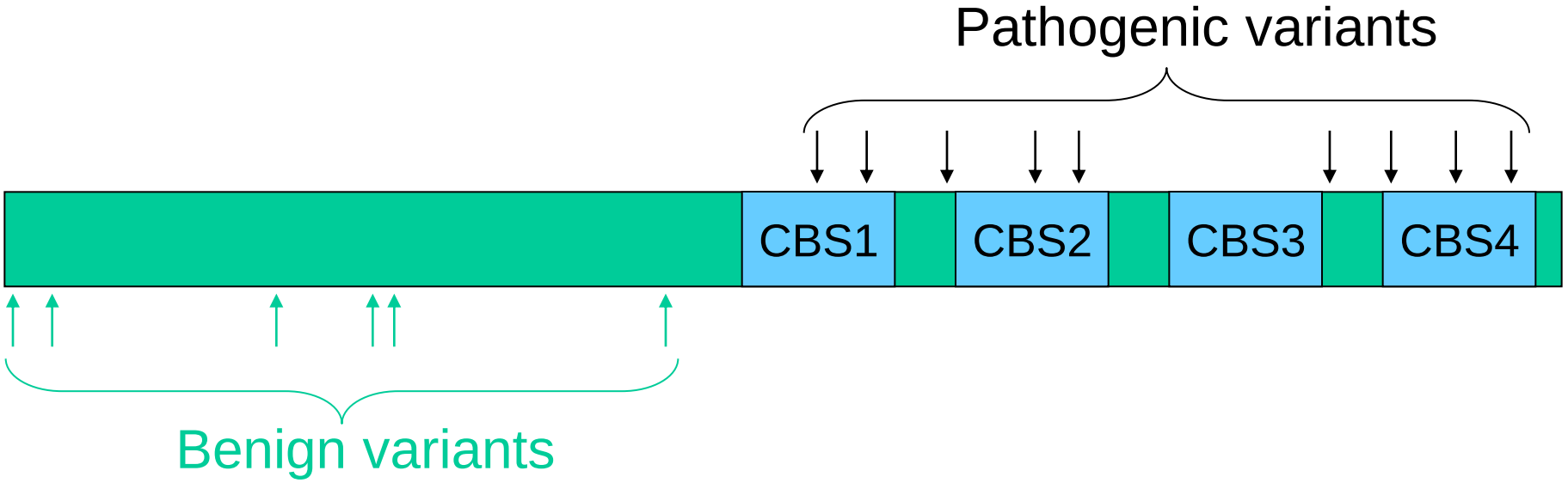


Silent and intronic variants are largely assumed benign for genes in which no truncating mutations have been observed or reported.

The Importance of Domain Location

PRKAG2 – AMP-activated protein kinase

All pathogenic mutations are missense and occur in or very close to the CBS domains.
All benign missense variants occur outside the CBS domain region.



NVA Form: Google, PubMed and LSDB Searches

Disease Gene	dbSNP locus ID	GeneInsight	HGMD	GET-Evidence	PubMed	Google (IE) (non-IE)	UMD	Cardio Genomics	Interm Fil. DB	Leiden Muscular Dystrophy	Barth	Inherited Arrhythmias DB	ARVC DB	Cardio genomics SNPs	TTR database	PTPN11-Base	RAS-MAPK Syndromes	LMM Noonan-CS-CFC DB	COSMIC	IARC TP53 DB	MUTp53LOAD	LMM Germline p53 DB	MutDB	MMR DB	MMRUV DB	InSiGHT Colon Cancer DB	Zhejiang Colon Cancer DB	TCA Cycle Gene Mut DB	ARUP MEN2 DB	LMM Usher DB	LOVD	Connexin-deafness	MitoMap	mtDB	Pendred-BOR DB	LMM Ohio Deafness DB
LOCUS SPECIFIC AND OTHER DATABASES																																				
JUP	3728																																			
LAMA4	3910																																			
LAMP2	3920																																			
LDB3	11155																																			
LMNA	4000																																			
MAP2K1	5604																																			
MAP2K2	5605																																			
MYBPC3	4607	Y	Y	N	Y	Y		N																												
MYH6	4624																																			
MYH7	4625																																			
MYL2	4633																																			
MYL3	4634																																			
MYLK2	85366																																			
MYOZ2	51778																																			
NEXN	91624																																			
NKX2-5	1482																																			
PKP2	5318																																			
HEARING LOSS																																				
CDH23	64072																																			
CLRN1	7401																																			
COCH	1690																																			
DFNB31	25861																																			
DFNB59	494513																																			
EYA1	2138																																			
GJB2	2706																																			
GJB6	10804																																			
GPR98	84059																																			
MTRNR1	4549																																			
MTTS	4574																																			
MYO6	4646																																			
MYO7A	4647																																			
OTOF	9381																																			
PCDH15	65217																																			
POU3F4	5456																																			
SLC26A4	5172																																			
TMC1	117531																																			
TMIE	259236																																			
TMPRSS3	64699																																			

NVA: Case/Control Data from Literature and Databases

	A	B	C	D	E	F–I	J	K	L	M–P	Q	R
8	**Gene**	MYBPC3		Manual LMM Proband Chr			8/4006			Segregation	0	
9	**Exon**	27		Automated LMM Proband Chr			7/4006			Non-Segregation	0	
10	**DNA**	2870C>G								Coupound/Double Hets	5	
11	**Protein**	Thr957Ser		Manual Lit Proband Chr			2/576			De novo variants	0	
12	Link to current variant folder			Automated Lit Proband Chr			2/576			Seen in different diseases?	Y	

				PROBANDS									SEGREG		CONTROL DATA				
16	**LMM data or Literature Reference**	**PMID**	**Family History?**	**# proband tested**	**# proband chrom tested**	**# positive HET probands**	**# positive HOM probands**	**positive proband phenotype(s)**	**Race matches case?**	**Allele frequency**	**# comp/double hets**	**# de novo variants**	**# informative meioses**	**# non-segregations**	**# control chrom tested**	**# positive control chrom**	**Control race matches case?**	**Allele frequency**	**Com (population details, fa e**
17	American Indian or Alaska			16	32				N										
19	Asian			193	386				N										
20	Black or African American			279	558				N										
21	Hispanic or Latino			106	212				N										
23	Native Hawaiian or Other Pacific			6	12				N										
26	White and Caucasian			2003	4006	7	0	HCM/	Y	0.002	4	0	0	0	0	0	0		The compound/double h
27	**LMM race matched**			2003	4006	7	0			0.002	4	0	0	0	0	0			
28	**LMM all races**			3297	6594	8	0			0.001	5	0	0	0	0	0			
29	Ehlermann, 2008	18957093	N	158	316	1	0	HCM	Unkno	0.003	0	0	0	0	860	0	Unkn own	0.000	Variant listed as novel a further information is giv proband.
30	Rodriguez-Garcia, 2010	20433692		130	260	1	0	HCM	Unkno	0.004	0	0	0	0	400	0	Unkn own	0.000	The pathogenicity of thi uncertain and no furthe
31	**Lit. race matched**			0	0	0	0				0	0	0	0	0	0			
32	**Literature all races**			288	576	2	0			0.003	0	0	0	0	1260	0		0.000	
33																			
34	**TOTAL CHROM race matched**			2003	4006	7	0			0.002	4	0	0	0	0	0			
35	**TOTAL CHROM all races**			3585	7170	10	0			0.001	5	0	0	0	1260	0		0.000	
36	GraphPad Fisher's Exact Test link																		

Variant | DB | Publ+LMM_data | LMM_Family | Control_Freq | Conserv_Biochem | Splicing | COSMIC(cancer_only) | Summary | One-liner | CLASSIFICATION RULES_052611

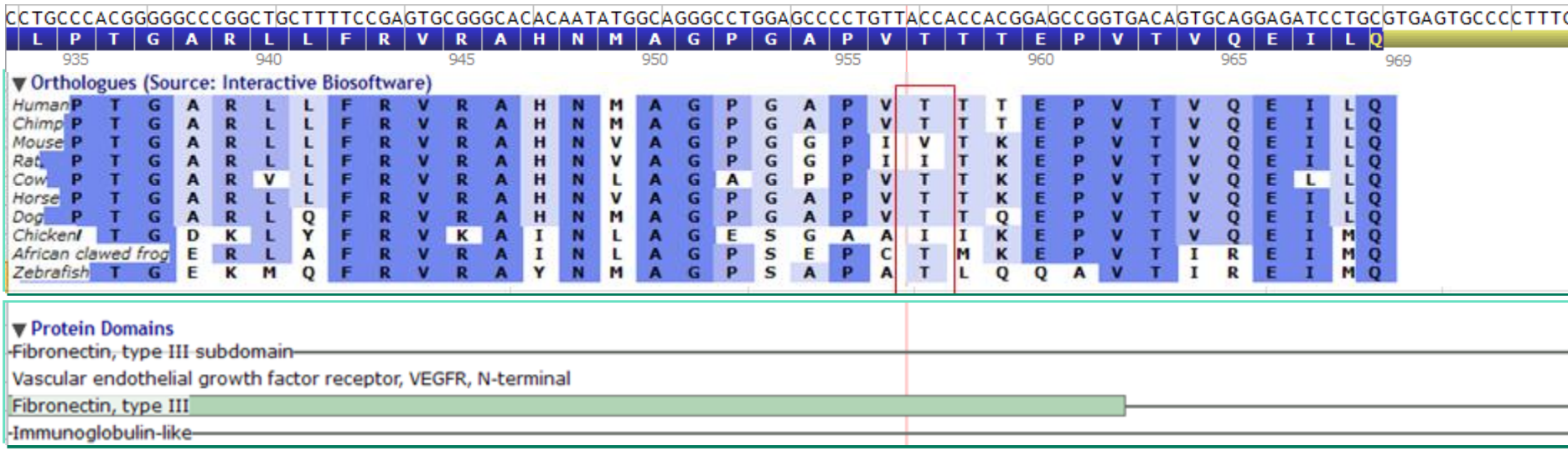
Control Frquency data

Variant in dbSNP?	N	dbSNP gene record link	HapMap link			
RS Number		dbSNP rs record link				
Clinically associated SNP?			**Allele 1**		**Allele 2**	
Validated?			C		G	
FREQUENCY INFORMATION	**Population**	**Chroms tested**	**Frequency**	**# identified**	**Frequency**	**# identified**
Population 1						
Population 2						
Population 3						
1000GENOMES						
ESP Project (EU)	[redacted]	6692.00	0.0013449	9	0.9986551	6683
ESP Project (AA)	[redacted]	3208.00	0	0	1	3208
Est. MAF in 200 Caucasian Exomes (Li 2010)	None					

Manual Control Frequency	9/6692	
Automated Control Frequency	9/6692	Rule: Take pop with hig
		Note, excel only allowe

NVA: *In Silico* Analysis

COMPUTATIONAL PATHOGENICITY PREDICTIONS							
	Prediction	**Score 1**	**Score 2**	**Score 1 & 2 descriptions**			
AlignGVGD	C0	89.28	57.75	(GV, GD) Prediction ranges from C0-benign to C65-pathogenic			
PolyPhen-2	Benign	Benign	0.002	(Class [*same as Prediction*], Probability of damaging)			
SIFT	Tolerated	0.08	3.93	(Weight, Median)			
SarcomerePolyPhen	Benign						
SNAP				(reliability, accuracy)			
Warnings:							
Comments							
BIOCHEMICAL PROPERTIES (AUTOLOOKUP)							
WT residue Cysteine?	N						
Amino Acid Similarity Matrices		Relatedness	**Amino Acid Biochemistry**	**Wildtype**	**Variant**		
BLOSUM45	2	distant	Composition	0.71	1.42	(0-2.75) ratio of carbon/non-carbon weig	
BLOSUM62	1	standard	Polarity	8.6	9.2	(4.9-13)	
BLOSUM80	1	close	Molecular volume	61	32	(3-170) measured in Angstroms	
PAM250	1	close	Grantham difference	58		(0-215)	
Substitutions >0 occur frequently (tolerated), <0 are rare (deleterious)			*Grantham difference ranges are: 0-50 Low, 50-150 Midrange, >150 High*				
EVOLUTIONARY CONSERVATION SUMMARY							
UCSC data added to Alamut.Orthologues?	Y	UCSC link					
PhastCons score	0.929		**Alamut.Orthologues Summary**	Conserved	Not conserved	Gapped alignment	
Conserved in mammals?	N		Mammals	6	3	0	
Conserved in birds, frogs, reptiles, fish?	N		Birds & Reptiles	0	1	0	
Conserved in invertebrates?	No data		Amphibians, Fish, Urchin	3	0	0	
Patient variant AA in other species?	N		Invertebrates & Fungi	0	0	0	
			Total	9	4	0	



NVA: Splicing Analysis

VARIANTS AFFECTING SPLICE CONSENSUS SEQUENCES

Alamut link

Distance from exon/intron junction	36
Splice site location	5' site exon
Alternate splice site created/removed?	N
Checked alternative splice site?	N

Difference in splice site score:	Wildtype	Variant	
SpliceSiteFinder-like	69.2378	69.2378	(0-100)
MaxEntScan	7.55301	7.55301	(0-12)
NNSPLICE	0.926597	0.926597	(0-1)
GeneSplicer	8.59212	8.94862	(0-15)
HumanSpliceFinder	80.99	80.99	(0-100)

Note: Alamut export scores are for nearest annotated exon splice site.
A difference of 10% of the respective scale is noted on the summary tab.

For reference: conservation of splice site sequences

Major Class

Minor Class

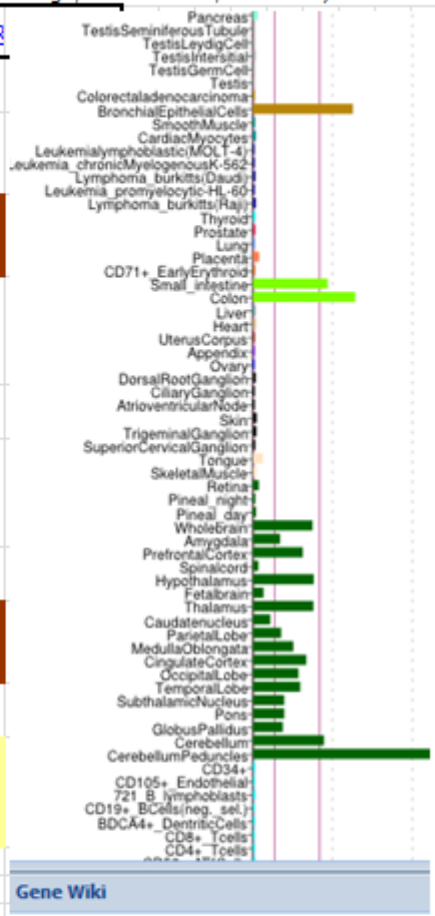
ALAMUT SPLICING MODULE SCREENSHOT

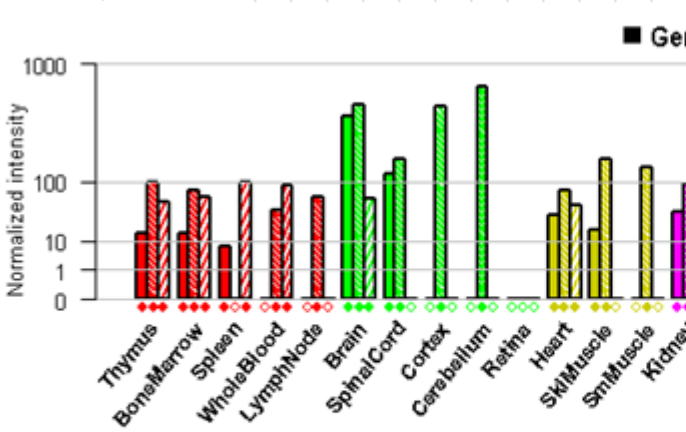
Manual Splice Prediction	Predicted Unlikely Impact
Automated Splice Prediction	Not assessed.

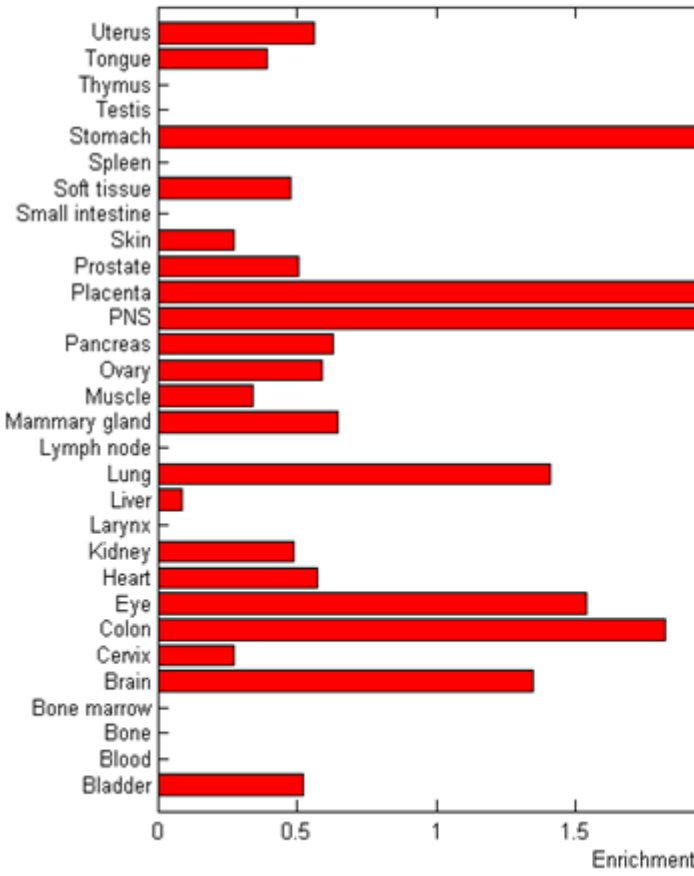
EXPRESSION

Instructions: For each organ system, indicate whether the gene is expressed (H for High, M for Medium, L for Low). If no data is available, leave blank

	BioGPS	Gene Expression Atla	GeneNote	TiGER
Auditory/Eye: inner, outer, and middle ear, eye				
Circulatory: heart, blood vessels, arteries, veins, blood, etc.			M	
Digestive: mouth, esophagus, stomach, intestines, liver, etc.	M	H		H
Endocrine: hypothalamus, pituitary, thyroid, pancreas, adrenals. etc.			M	
Excretory: kidney, uterus, bladder, urethra,			M	
Immune: bone marrow, lymph nodes and vessels, WBCs, T- and B-cells, etc.			M	
Muscular: skeletal and smooth muscle, etc.				
Nervous: brain, spinal cord, peripheral nerves, etc.	H	H	H	H
Respiratory: lungs, trachea, nasal, etc.	M			
Reproduction: ovaries, uterus, cervix, vagina, testes, seminal vesicles, penis, etc.			M	L







Is gene universally expressed?	N	
Is gene predominantly expressed in a certain tissue?	Y	**If yes, enter tissue(s):** Digestive, Nervous system
How many databases support tissue expression?	4	

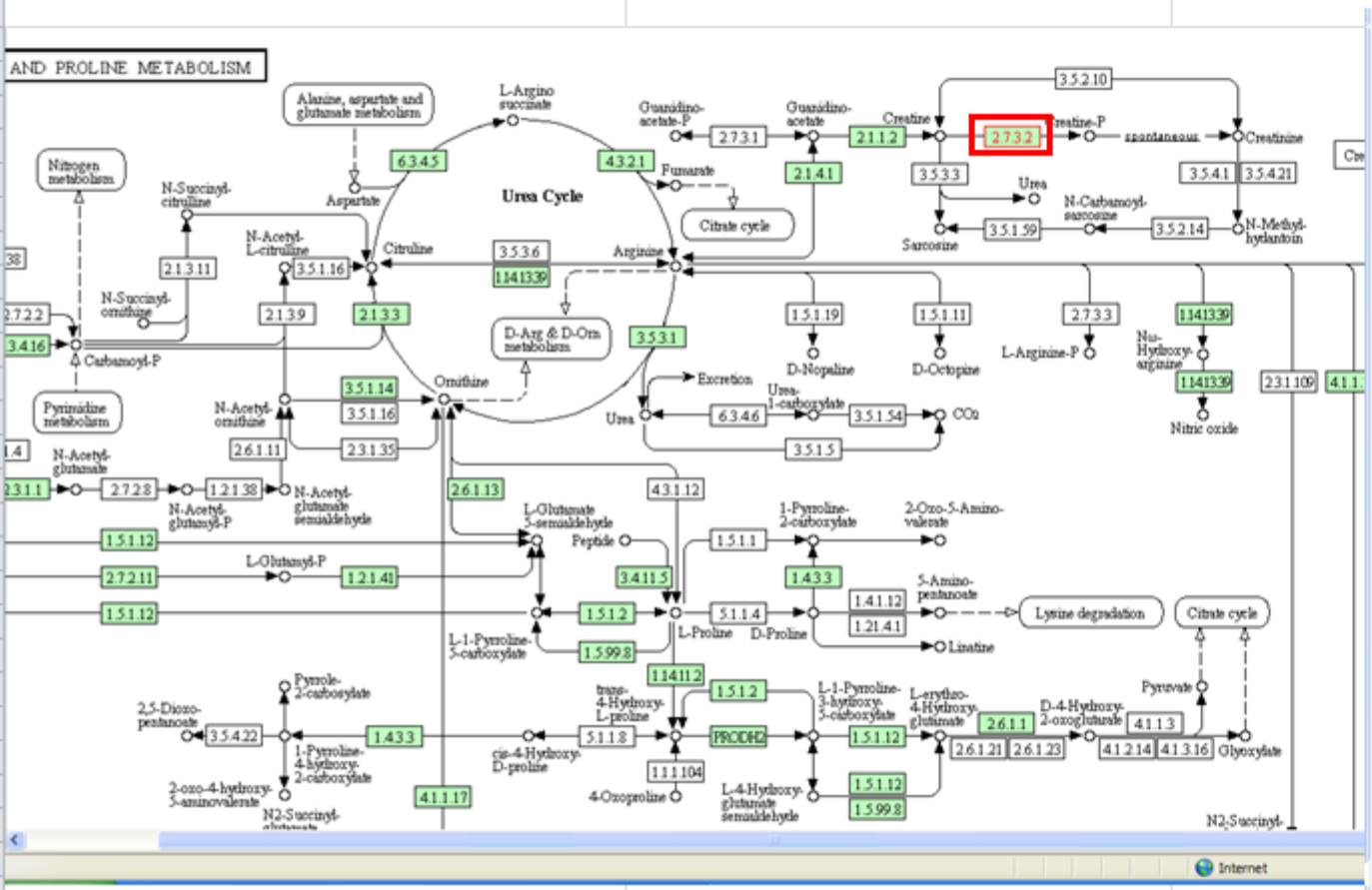
Key

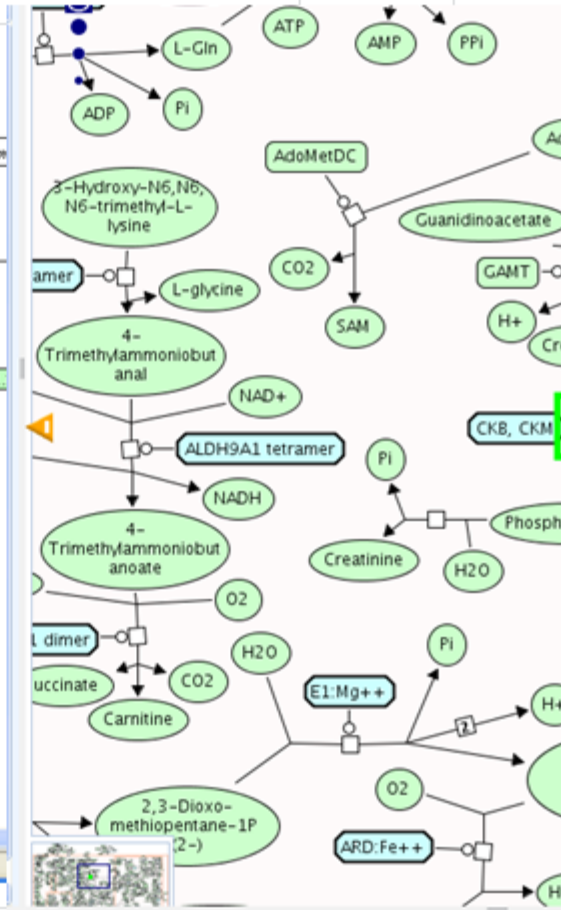
- **High**
- **Medium**
- **Low**

Paste Screenshots Below

PATHWAYS

	Pathway List	Pathways Relevant to Current Case	Comments
KEGG	Arginine and proline metabolism	N/A	
Biocarta			No entires
GO	ATP binding, kinase activity		
Pathway Interaction Database			No entires
Reactome	Creatine metabolism		
List of all pathways relevant to current case:	Creatine metabolism		
How many databases support these pathways?	3		





DISEASE ASSOCIATIONS

	Disease List	Diseases Common to Current Cas	Comments
KEGG			No entries
OMIM	None	N/A	
Genetic Association Database	None	N/A	
HuGE Navigator			No entries
Gene Atlas	None	N/A	
HGMD	None	N/A	

List of all diseases common to current case:

How many databases support these disease associations?

MODEL ORGANISMS

Mouse Genome Informatics Database

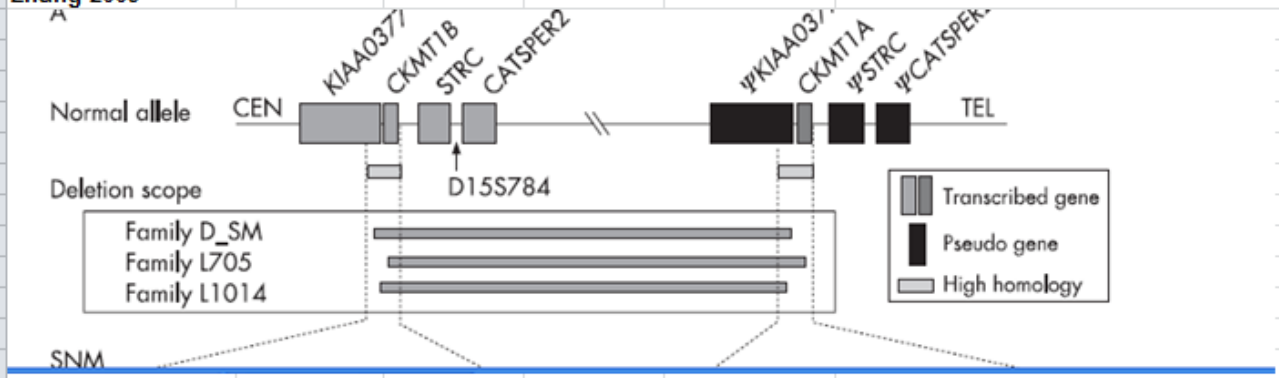
Model	Category	Affected Anatomical Systems	Similar Human Diseases	Comments
Ckmt1tm2Bew creatine kinase, mitochondrial 1, ubiquitous; targeted mutation 2, Be Wieringa	Targeted KO (exons 7-8)	behavior, hearing/vestibular/ear, nervous system, digestive/alimentary		It is unclear if the surrounding genes were affected by this targeted KO, especially given that this region is repetitive

LITERATURE SEARCH

Pubmed
GeneCards
Gene Reviews

Literature Reference	PMID	Disease Association	Mutation Type(s) Implicated	Functional Data	Comments
Zhang 2007	17098888				100Kb deletion at 15q15.3 (encompassing KIAA0377/PPIP5K1, CKMT1B, STRC, and CATSPER2) identified in three families with deafness infertility syndrome (DIS). asthenoteratozoospermia). In addition to DIS, congenital dyserythropoietic anaemia type I (CDAI) has also been described in patients with these deletions. The authors suggest that deletion of STRC is responsible for deafness, while deletion of CATSPER2 is responsible for infertility.
Cimino_2008	18561318				Upregulation of CKMT1B was associated with disease-free and overall survival in patients with breast cancer.
Zhang 2009	21686705				Basically same info as in Zhang 2007. A nearly identical copy of CKMT1B, designated CKMT1A (613415), is telomeric to CKMT1B on chromosome 15, and contains only two mismatches that predict synonymous mutations in the coding region in addition to two mismatches in the 3' UTR, suggesting CKMT1A is functional. This would suggest that CKMT1B and CKMT1A are genetically redundant and that deletion of one of these genes is unlikely to have functional consequences.

Zhang 2009



Final Variant Interpretation

Form completed by:	WJL
Accession#	
Patient Name	
Family	
Race	Black
Ethnicity	
Disease	
Gene	POU3F4
Exon	1
DNA	964G>A
Protein	Val322Met
Interpretation from Classification Rules	Unknown Significance.

Fellow Interpretation & Rationale

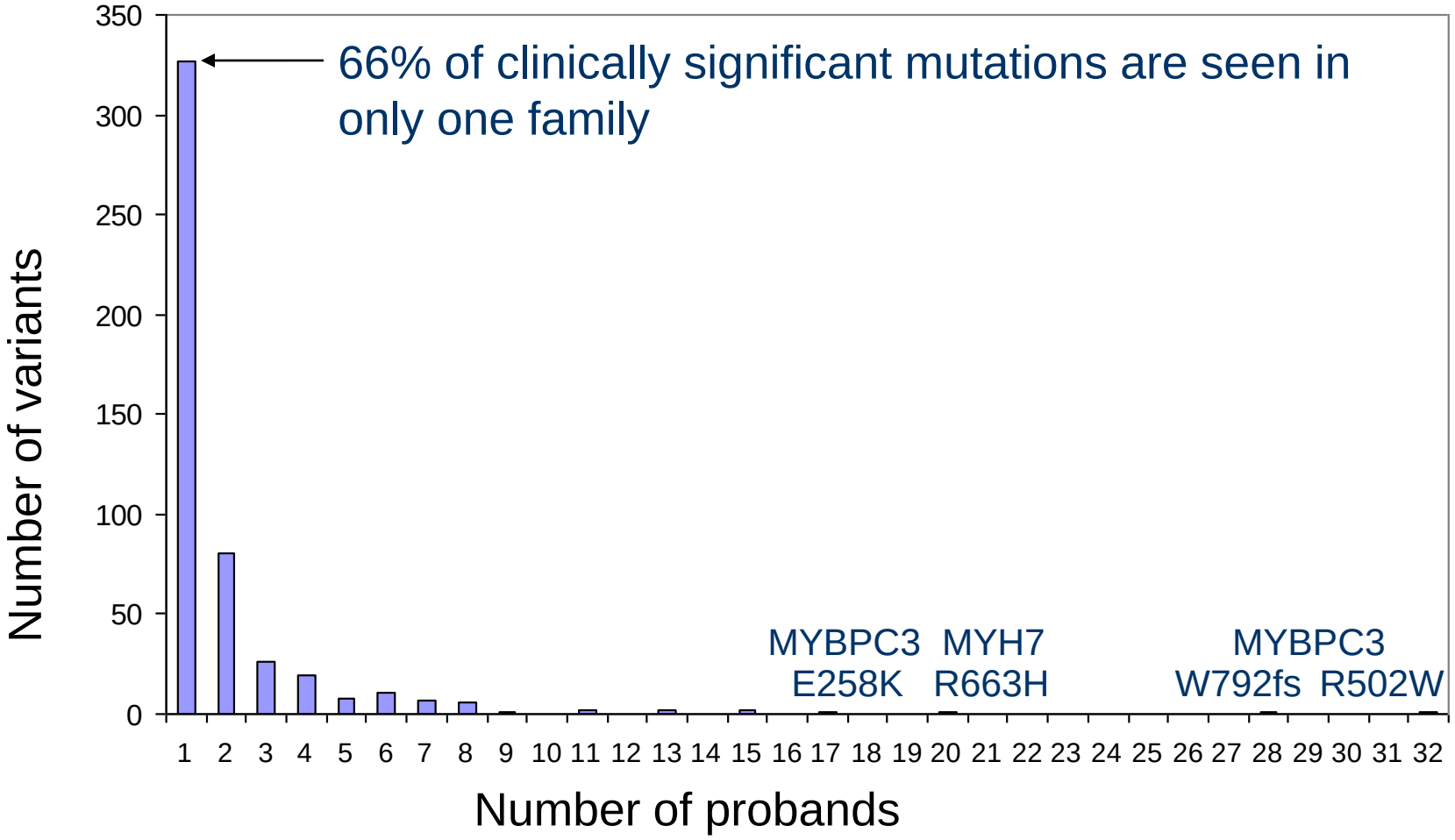
Variant Interpretation	Unknown significance-4	
Rationale Statements	The Val322Met variant in POU3F4 has not been reported in the literature, but has been previously detected in 1 of the 38 probands tested by our laboratory. However, this mutation occurs within the POU homeodomain (amino acids 279-336) where almost all pathogenic missense mutations have been identified. Valine (Val) at position 322 is conserved across mammals and other species, increasing the likelihood that the change is pathogenic. In addition, computational analyses (AlignGVGD, SIFT) suggest that the Val322Met variant may impact the protein. However, this information is not predictive enough to assume pathogenicity. In summary, the location of this variant, evolutionary conservation and computational predictions support a pathogenic role but additional studies are necessary to determine the clinical significance of the Val322Met variant with certainty.	
Entered Variant & Category in GeneInsight?	Updated	GeneInsight link
Moved case to completed in NVA log?	Y	NVA log link

Geneticist Final Review

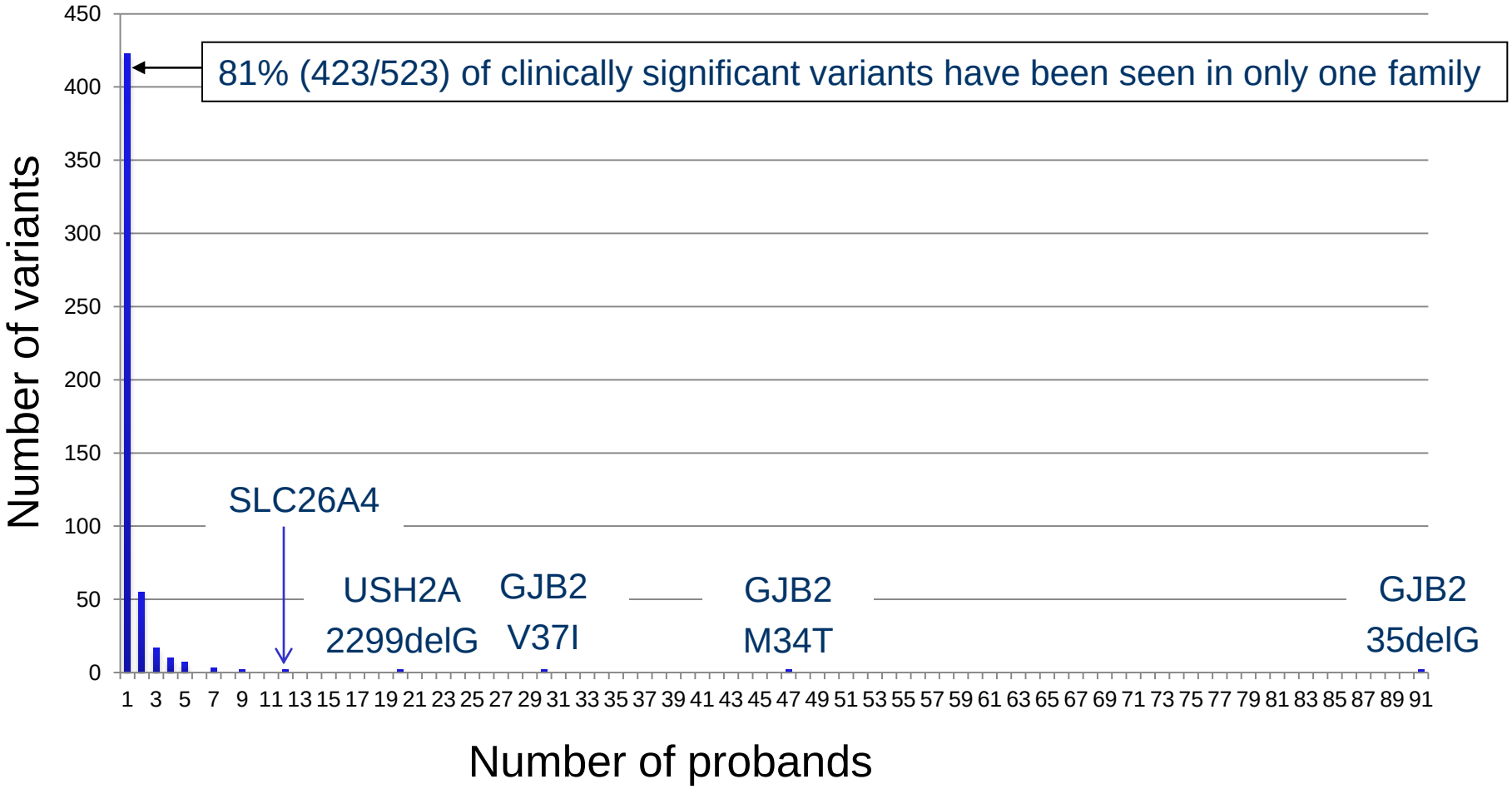
Comments on Interpretations	All your points are fine, we just reworded for consistency with our templates. I also bumped to VUS-5. I think this varaint is probably pathogenic given the very close phenotype match to POU3F4 HL subtype and location of variant.	
Final Novel Variant Assessment	Unknown significance-5	
Final Variant Interpretation (blurb)	The Val322Met variant in POU3F4 has not been reported in the literature nor previously identified by our laboratory in any other families. However, this mutation occurs within the POU homeodomain (amino acids 279-336) where almost all pathogenic missense mutations have been identified. In addition, this residue is conserved across mammals and lower species and computational analyses (PolyPhen2, SIFT, AlignGVGD, MAPP) suggest that the Val322Met variant may impact the protein. However, this information is not predictive enough to assume pathogenicity. In summary, the clinical significance of this variant cannot be determined with certainty at this time; however based upon the arguments described above, we would lean towards a more likely pathogenic role.	
Entered Interpretation in GeneInsight?		

HCM Gene Mutations – 3000 cases tested

>500 clinically significant mutations identified



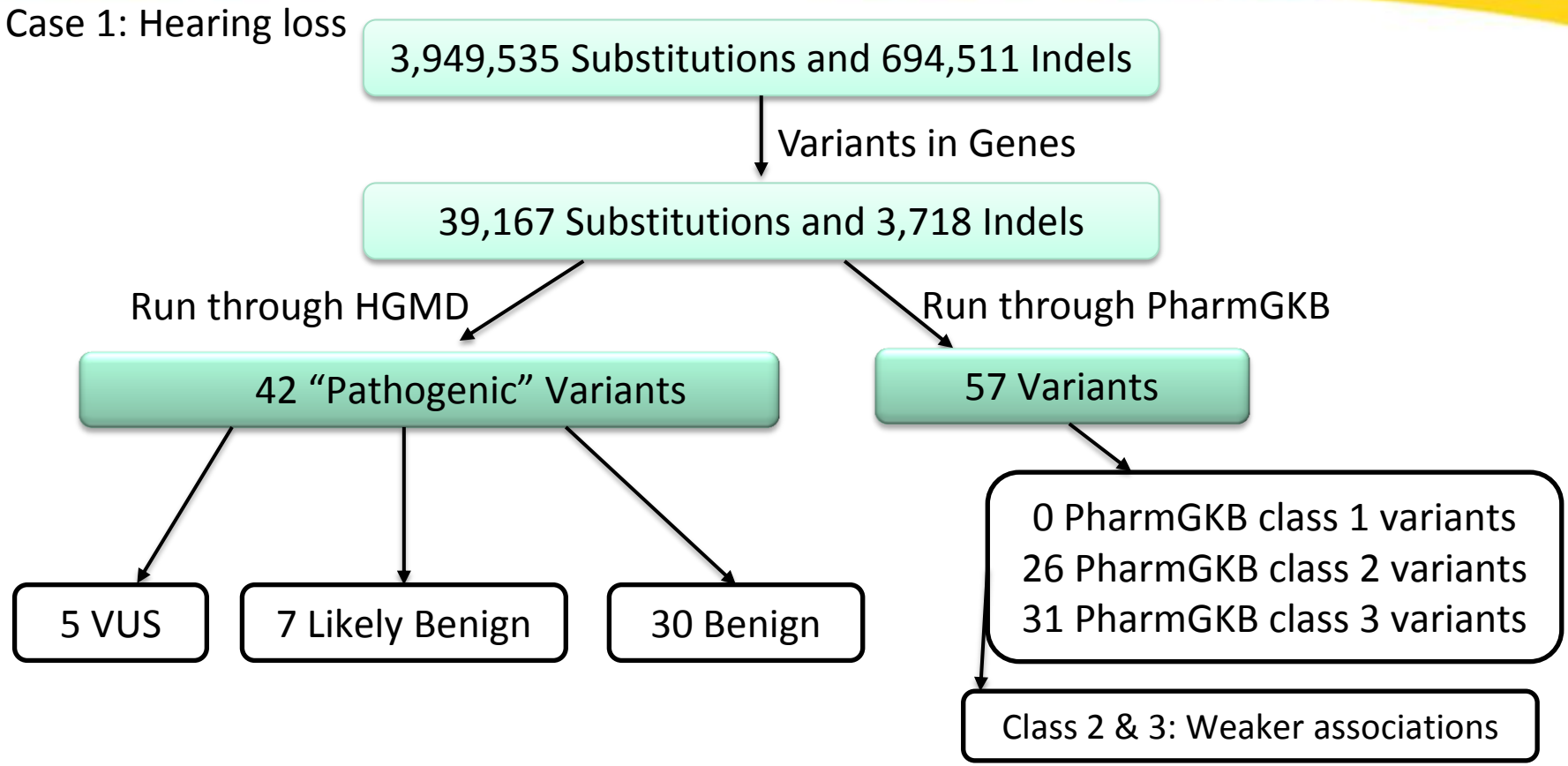
Hearing Loss Gene Mutations – 2000 Cases Tested



Human Gene Mutation Database

CM023927	CGC-CTC	Arg32Leu	c.95G>T	p.R32L	Deafness	Wu (2002) Genet Med **4,** 279	DM G
CM108184	tCGC-AGC	Arg32Ser	c.94C>A	p.R32S	Sensorineural hearing loss	Hayashi (2010) Int J Pediatr Otorhinolaryngol **75,** 211	DM G
CM106662	ATT-AAT	Ile33Asn	c.98T>A	p.I33N	Hearing loss	Tsukada (2010) Clin Genet **78,** 464	DM? G
CM091631	ATT-ACT	Ile33Thr	c.98T>C	p.I33T	Deafness	Mani (2009) Eur J Hum Genet **17,** 502	DM G
CM077555	ATG-AGG	Met34Arg	c.101T>G	p.M34R	Sensorineural hearing loss	Putcha (2007) Genet Med **9,** 413	DM G
CM057547	ATGa-ATA	Met34Ile	c.102G>A	p.M34I	Deafness	Snoeckx (2005) Am J Hum Genet **77,** 945	C DM G
CM014357	tATG-TTG	Met34Leu	c.100A>T	p.M34L	Deafness	Kudo (2001) Otol Neurotol **22,** 858	DM G
CM970679	ATG-ACG	Met34Thr	c.101T>C	p.M34T	Deafness, autosomal dominant 3	Kelsell (1997) Nature **387,** 80 Martin (1999) *Hum Mol Genet* **8:** 2369 [Functional characterisation] Houseman (2001) *J Med Genet* **38:** 20 [Additional phenotype] 5 more reference(s)...	DM? dbSNP FREQ
CM098251	tATG-GTG	Met34Val	c.100A>G	p.M34V	Hearing impairment, nonsyndromic	Yilmaz (2009) Biochem Genet **48,** 248	DM G
CM014708	ATC-AGC	Ile35Ser	c.104T>G	p.I35S	Deafness	Dahl (2001) Med J Aust **175,** 191 Mani (2009) *Eur J Hum Genet* **17:** 502 [Functional characterisation]	DM G
CM065234	CTC-CCC	Leu36Pro	c.107T>C	p.L36P	Deafness	Propst (2006) Laryngoscope **116,** 317	DM G
CM042707	GTT-GCT	Val37Ala	c.110T>C	p.V37A	Deafness	Azaiez (2004) Hum Mutat **24,** 305	DM dbSNP G
CM000016	cGTT-ATT	Val37Ile	c.109G>A	p.V37I	Deafness, autosomal recessive 1	Abe (2000) J Med Genet **37,** 41 Wilcox (2000) *Hum Genet* **106:** 399 [Additional report] Bruzzone (2003) *FEBS Lett* **533:** 79 [Functional characterisation]	DM? dbSNP FREQ G

Variant Analysis for General Genome Report

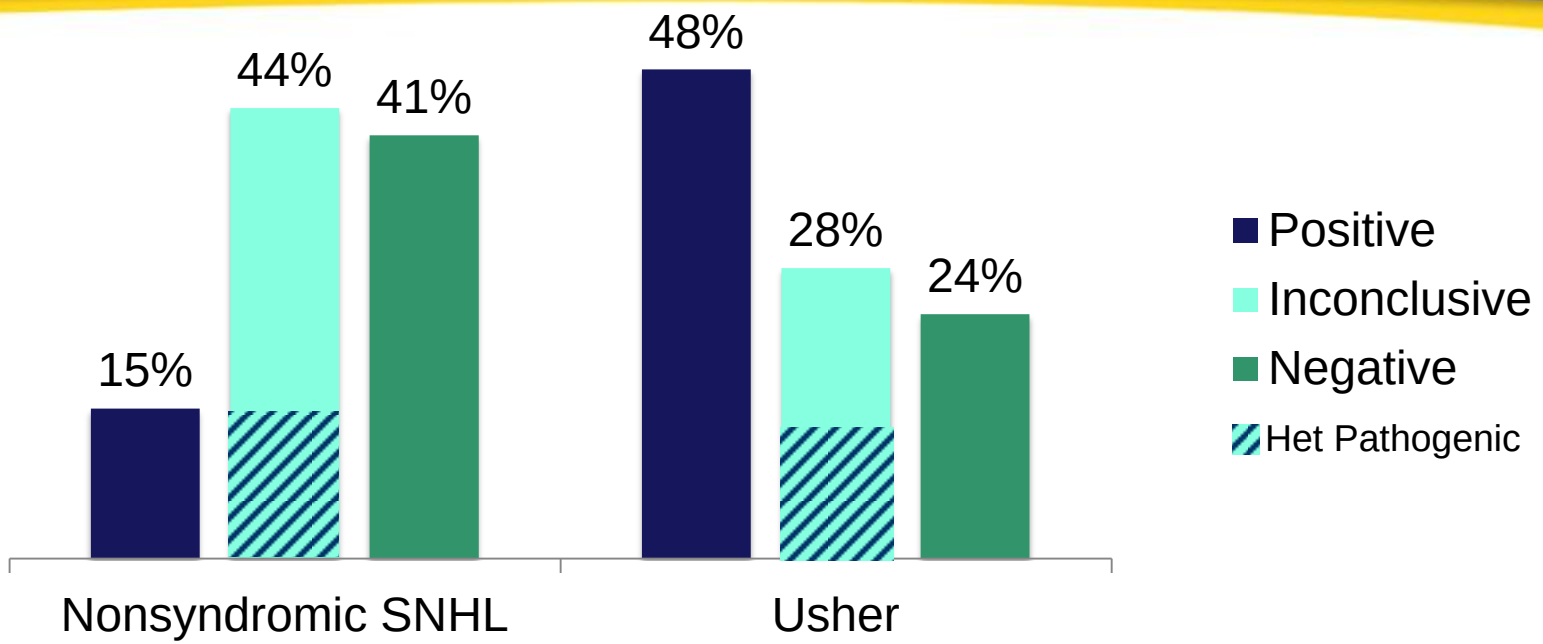


Take home:

No variants met criteria for return as secondary findings in this patient

HGMD (representing published literature, has many incorrect classifications)

OtoChip Results – 293 Cases Analyzed



15/186 (8%) of early childhood (≤10yr) HL cases tested positive for an Usher gene mutation

Fumbled DNA Tests Mean Peril for Breast-Cancer Patients

By Robert Langreth - Sep 10, 2012 12:00 AM ET

Debbie McCarron was prepared to get both of her breasts taken off if a blood test in December 2006 revealed she carried a gene that vastly increases the risk of breast cancer. Having survived the disease five years earlier, she didn't want to risk getting it again.

To her relief, her oncologist told her the test, done by Myriad Genetics Inc. (MYGN), had come back negative, "just like I knew it would," McCarron recalls her doctor saying.

Enlarge image

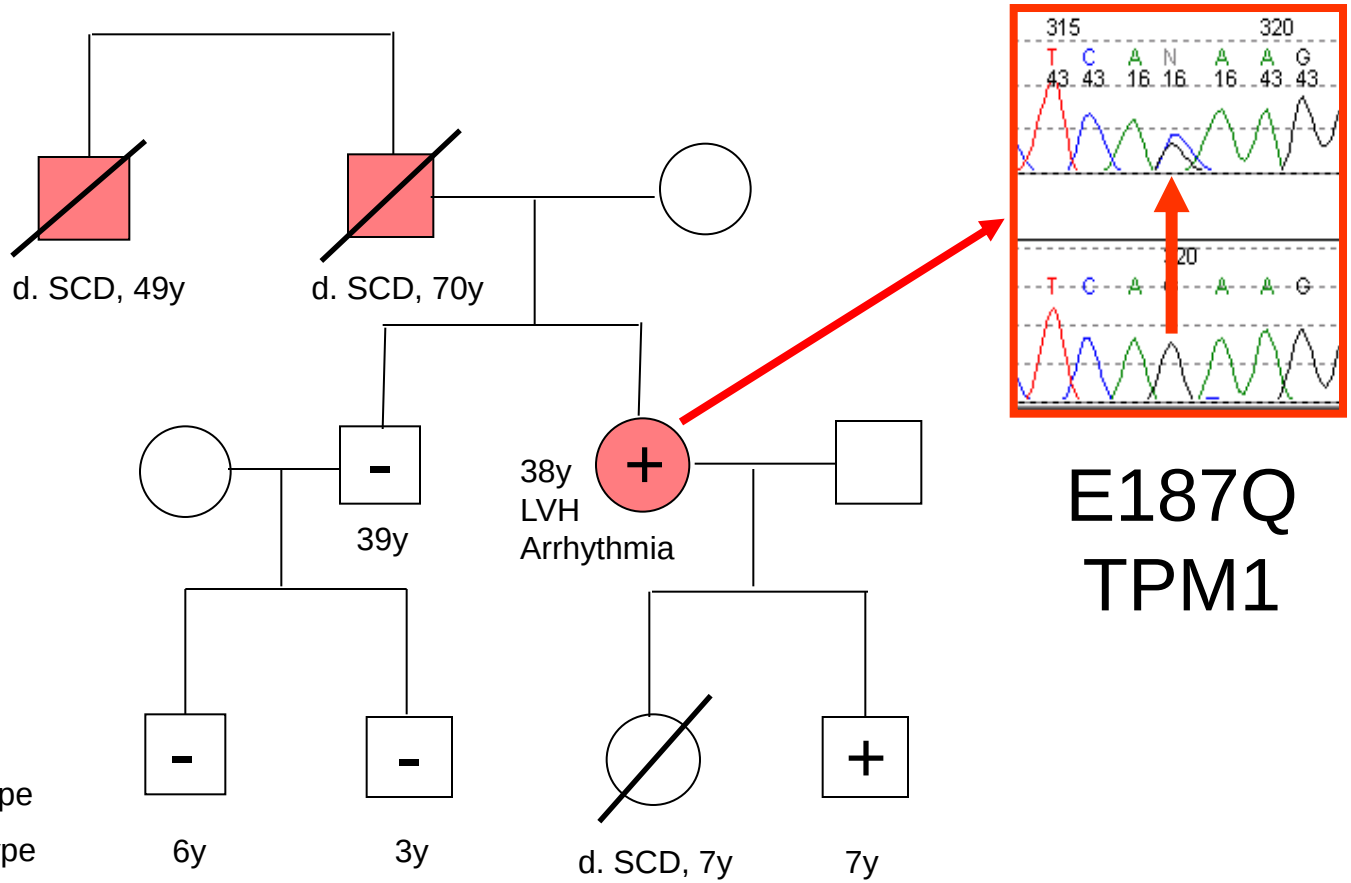
Debbie McCarron, right, with her genetic counselor, Mariana Niell. Source: Bloomberg

He was wrong. The results, in fact, were positive. McCarron didn't learn this, though, until July 2009, more than two years later, when a genetic counselor reviewed the test following McCarron's surgery to remove a new malignant breast tumor. Since then, her oncologist, Haresh Jhangiani, told Bloomberg he isn't clear about what happened.

"I don't think she was positive. Was she positive?" the doctor said. "I would not tell her it was negative if the test was positive, there must be something more to it."

McCarron, now 50, was devastated when she found out. "The

HCM Family 90



Legend:

= Affected Individuals

\+ = E187Q positive genotype

\- = E187Q negative genotype

SCD = Sudden Cardiac Death

LVH = Left Ventricular Hypertrophy

Disease-causing mutations in the human beta-cardiac Myosin Heavy Chain gene

- 194 hypertrophic cardiomyopathy mutations
- 13 dilated cardiomyopathy mutations
- 7 other mutations
- 7 variants of uncertain effect
- 15 polymorphisms

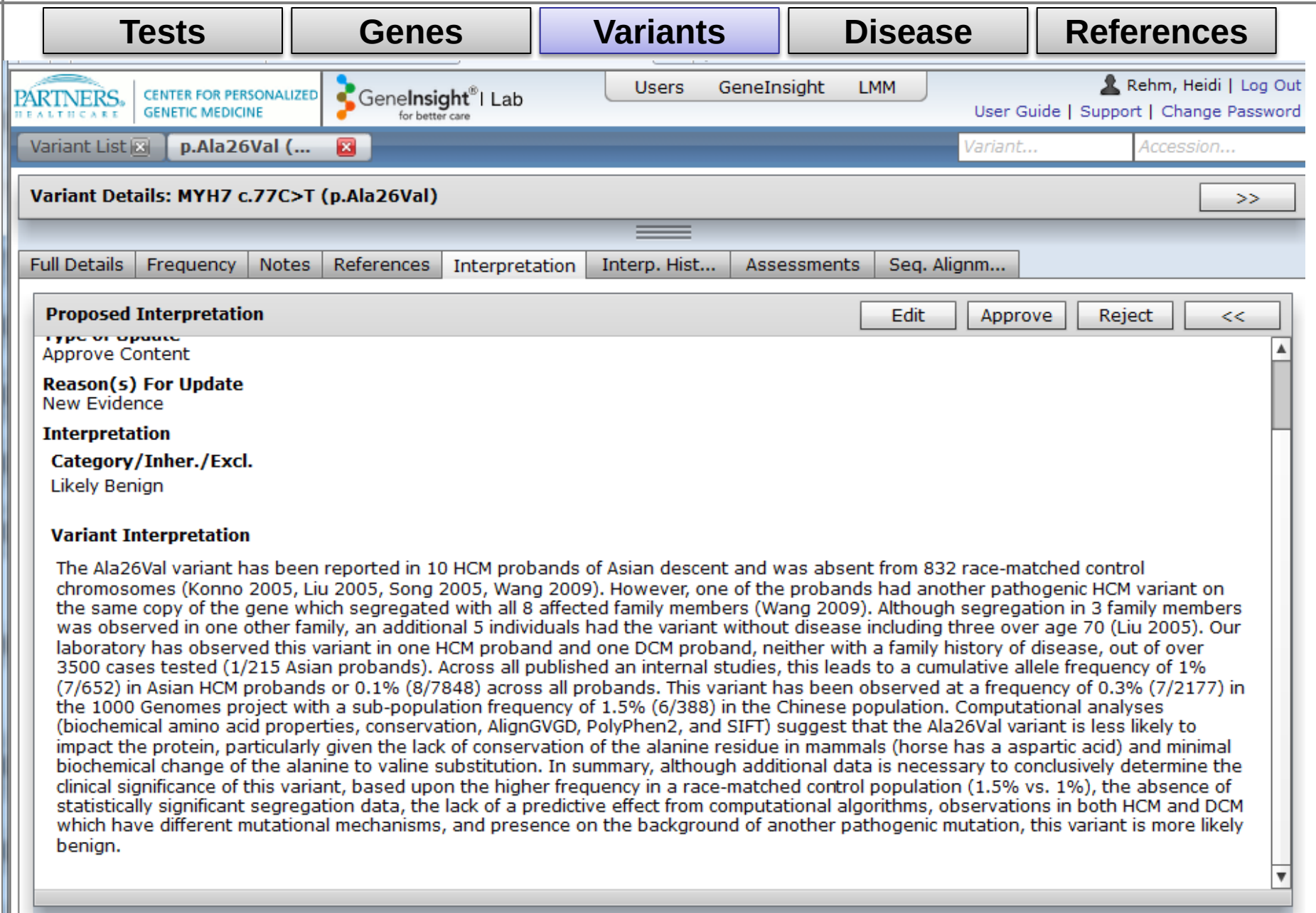
hypertrophic cardiomyopathy mutations

Mutation	Disease	position in M57965.1	UCSC hg17 position	exon/intron
Gly10del	HCM	5748..5750	22972754..22972752	3
Ala26Val	HCM	5797	22972705	3
Val39Met	HCM	5835	22972667	3
Val59Ile	HCM	5895	22972607	3
Tyr115His	HCM	6366	22972135	4
Thr124Ile	HCM	6682	22971819	5
Arg143Gly	HCM	6738		5
Arg143Trp	HCM	6738	22971763	5
Arg143Gln	HCM	6739	22971762	5

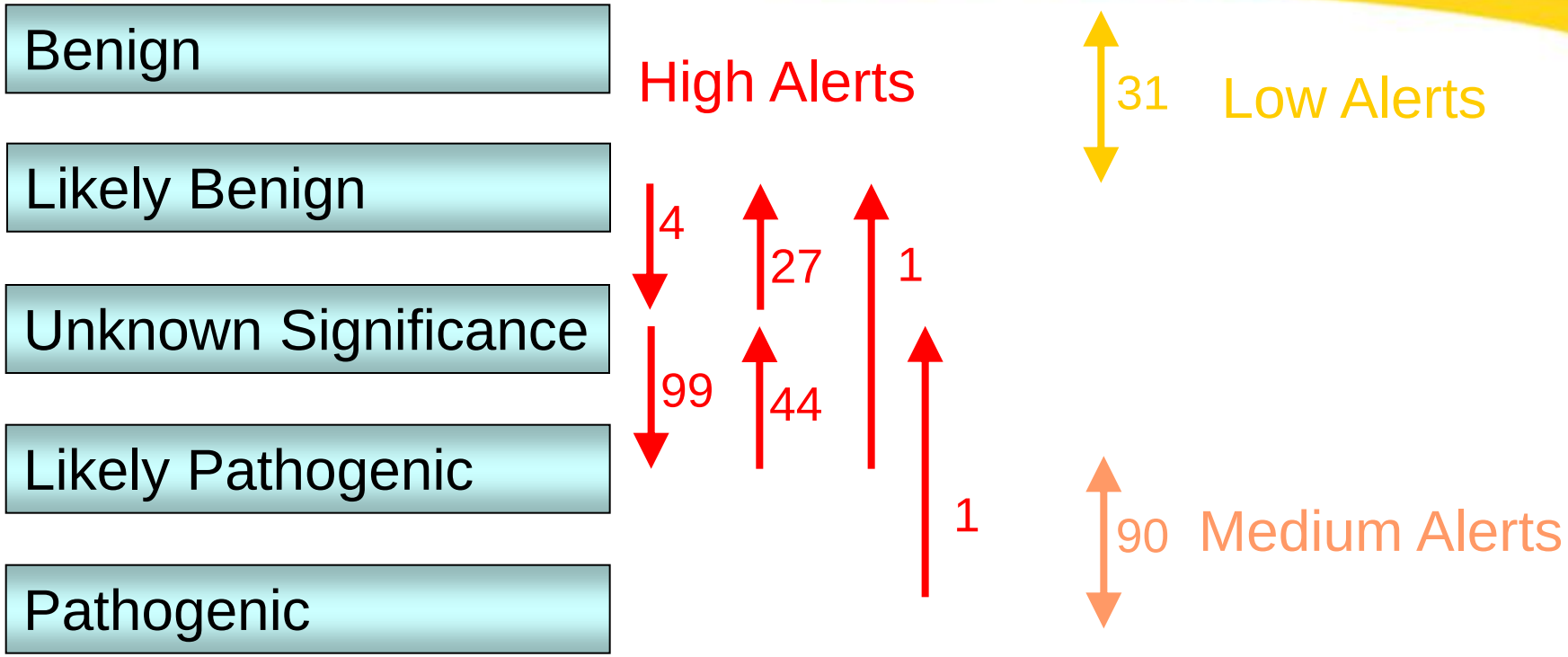
Documenting Logic

The Ala26Val variant has been reported in 10 HCM probands of Asian descent and was absent from 832 race-matched control chromosomes (Konno 2005, Liu 2005, Song 2005, Wang 2009). However, one of the probands had another pathogenic HCM variant on the same copy of the gene which segregated with all 8 affected family members (Wang 2009). Although segregation in 3 family members was observed in one other family, an additional 5 individuals had the variant without disease including three over age 70 (Liu 2005). Our laboratory has observed this variant in one HCM proband and one DCM proband, neither with a family history of disease, out of over 3500 cases tested (1/215 Asian probands). Across all published and internal studies, this leads to a cumulative allele frequency of 1% (7/652) in Asian HCM probands or 0.1% (8/7848) across all probands. This variant has been observed at a frequency of 0.3% (7/2177) in the 1000 Genomes project with a sub-population frequency of 1.5% (6/388) in the Chinese population. Computational analyses (biochemical amino acid properties, conservation, AlignGVGD, PolyPhen2, and SIFT) suggest that the Ala26Val variant is less likely to impact the protein, particularly given the lack of conservation of the alanine residue in mammals (horse has an aspartic acid) and minimal biochemical change of the alanine to valine substitution. In summary, although additional data is necessary to conclusively determine the clinical significance of this variant, based upon the higher frequency in a race-matched control population (1.5% vs. 1%), the absence of statistically significant segregation data, the lack of a predictive effect from computational algorithms, observations in both HCM and DCM which have different mutational mechanisms, and presence on the background of another pathogenic mutation, this variant is more likely benign.

Variant Interpretations Maintained in GeneInsight



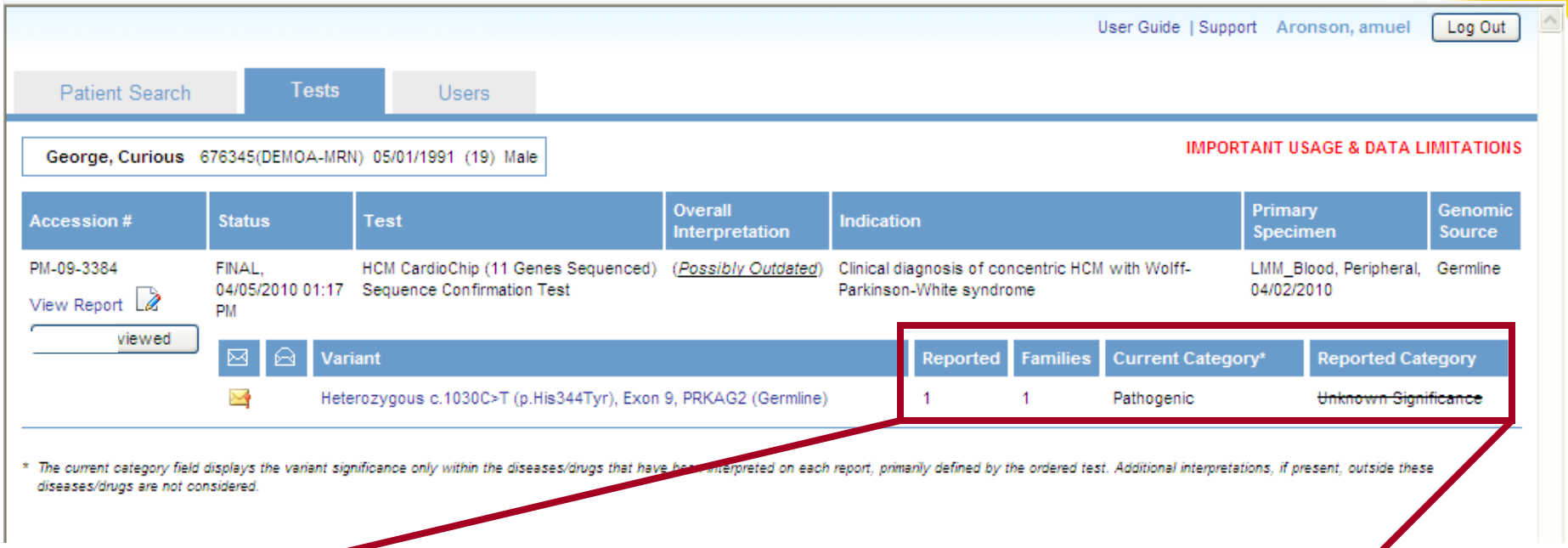
Variant Classification Changes – HCM Data

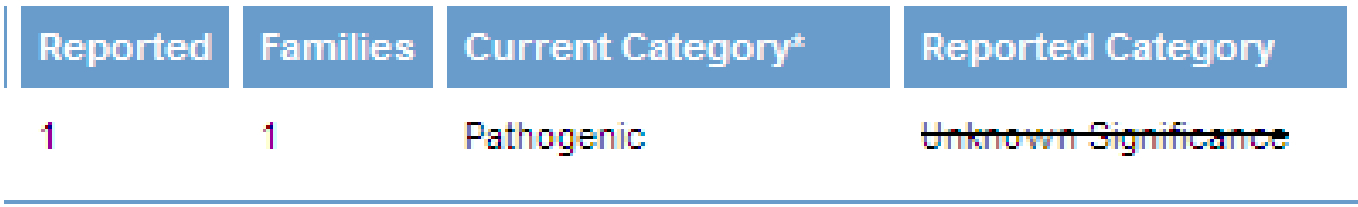


~300 category changes over 5 year (~4% of reports/yr)

Aronson SJ, Clark EH, Varugheese M, Baxter S, Babb LJ, Rehm HL. Communicating new knowledge on previously reported genetic variants**.** *Genet Med 2012:14(8):713-719*.

GeneInsight Clinic℠ Interface





Registered with FDA as a Class I Exempt Medical Device
Integrated into EMR at MGH and BWH

Updated Variant Information

Individual Reported Variant Interpretation History (Variant 1 of 1)

IMPORTANT USAGE & DATA LIMITATIONS

Warning: This page only lists information on a single variant. This is outside of the patient report context and may be insufficient for re-interpretation of the patient report.

Heterozygous c.1030C>T (p.His344Tyr), Exon 9, PRKAG2 (Germline)

Report	PM-09-3384 (FINAL, 04/05/2010 01:17 PM), HCM CardioChip (11 Genes Sequenced), Sequence Confirmation Test
Patient	George, Curious 676345(DEMOA-MRN) 05/01/1991 (19) Male
Current Category*	(Reported: ~~Unknown Significance~~)
Counts	Reports (1), Families (1)

Alerts

Status	!	Date	Type	Message
Unreviewed	!	04/06/2010 10:27 AM	Non-incidental Level Change	The category for the PRKAG2 c.1030C>T (p.His344Tyr) association to HCM changed from Unknown Significance to Pathogenic.

Mark Reviewed

Current Knowledge** Approved 04/05/2010 01:22 PM by Matthew Varugheese

Diseases/Drugs	Category	Variant Interpretation
HCM	Pathogenic	The His344Tyr variant has not been reported in the literature nor previously identified in our laboratory. The His344 residue is well conserved from fruitfly to mammals, and the His344Tyr variant occurs within the CBS domain region where all pathogenic PRKAG2 variants have been identified to date. In addition, the presence of concentric HCM and Wolff-Parkinson-White syndrome in the first proband identified with this mutation, which are clinical features consistent with PRKAG2 mutations, as well as follow-up testing showing that the variant arose de novo, provide strong support for this variant being pathogenic.

- Physicians receive alerts via email to be notified of variant changes on their patients

Data in this slide should not be used for any clinical purpose.

Documenting Logic

The Ala26Val variant has been reported in 10 HCM probands of Asian descent and was absent from 832 race-matched control chromosomes (Konno 2005, Liu 2005, Song 2005, Wang 2009). However, one of the probands had another pathogenic HCM variant on the same copy of the gene which segregated with all 8 affected family members (Wang 2009). Although segregation in 3 family members was observed in one other family, an additional 5 individuals had the variant without disease including three over age 70 (Liu 2005). Our laboratory has observed this variant in one HCM proband and one DCM proband, neither with a family history of disease, out of over 3500 cases tested (1/215 Asian probands). Across all published and internal studies, this leads to a cumulative allele frequency of 1% (7/652) in Asian HCM probands or 0.1% (8/7848) across all probands. This variant has been observed at a frequency of 0.3% (7/2177) in the 1000 Genomes project with a sub-population frequency of 1.5% (6/388) in the Chinese population. Computational analyses (biochemical amino acid properties, conservation, AlignGVGD, PolyPhen2, and SIFT) suggest that the Ala26Val variant is less likely to impact the protein, particularly given the lack of conservation of the alanine residue in mammals (horse has an aspartic acid) and minimal biochemical change of the alanine to valine substitution. In summary, although additional data is necessary to conclusively determine the clinical significance of this variant, based upon the higher frequency in a race-matched control population (1.5% vs. 1%), the absence of statistically significant segregation data, the lack of a predictive effect from computational algorithms, observations in both HCM and DCM which have different mutational mechanisms, and presence on the background of another pathogenic mutation, this variant is more likely benign.

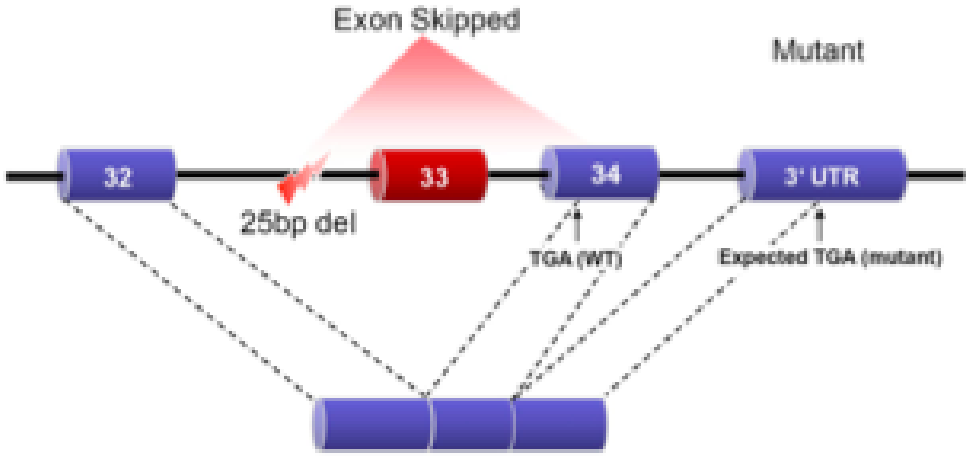
Caution!

Control samples, can, and do, have pathogenic variants, particularly for recessive, late-onset, or low-penetrant diseases.

A common *MYBPC3* (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia

Variant found in 4-8% of South Asians

Dhandapany et al. Nat Genet. 2009. 41(2):187-91



Case-Control Study

Group 1

	(D,D)(D,W)	(W,W)	Total
Cases	49 (3DD)	305	354
Controls	7	231	238

OR=5.30

Group 2

	(D,D)(D,W)	(W,W)	Total
Cases	38 (3DD)	408	446
Controls	5	461	466

OR=8.59

Combined odds ratio from both studied = 6.99

- two homozygotes died as children younger than 3 years
- controls matched for ancestry, age, sex and geography.

MYBPC3 Intron 32 variant in congenital HCM Case