Cardiovascular Disease Gene Panel

For Doe, John

Case ID	Family ID	Specimen type:	Collected:	Received:	Reported:
20000940	**4183**	**Other**		**Aug 27, 2020**	**May 19, 2022**

CLINICAL SUMMARY

NA

RESULT SUMMARY [SEQUENCING AND DELETION/DUPLICATION CNV ANALYSES]

SIGNIFICANCE OF THE FINDINGS	GENE	VARIANT COUNT
High Impact	--	--
Possibly High Impact	TPM1	1 (LP)

INTERPRETATION & RECOMMENDATIONS

A likely pathogenic variant, c.479G>A(p.R160H), in the TPM1 gene was detected. Defects in the TPM1 gene cause disorder(s) including Left ventricular noncompaction 9 [MIM: 611878], Autosomal dominant; Cardiomyopathy hypertrophic 3 [MIM: 115196], Autosomal dominant; Cardiomyopathy dilated 1Y [MIM: 611878], Autosomal dominant. The findings may be consistent with the clinical phenotype of this individual.

Clinical correlations and genetic counseling are recommended.

RESULT DETAILS

Possibly High Impact

TPM1

Position	Variant	Zygo-sity	Parental Results	Comments	Population Freq*	In Silico (REVEL)	Variant Sig.
15:63351866 G>A	NM_001018005.2 exon4 c.479G>A p.R160H			ACMG: PS3+PM2+PP3+PP5 PMID: 20530761, 25241052; rs199476311; ClinVarID: 31899	0/0	0.834	LP

*Total frequency/highest population frequency in gnomAD

DISEASE: Left ventricular noncompaction 9 [MIM: 611878], Autosomal dominant; Cardiomyopathy hypertrophic 3 [MIM: 115196], Autosomal dominant; Cardiomyopathy dilated 1Y [MIM: 611878], Autosomal dominant

INTERPRETATIONS:

Variant:
A likely pathogenic variant, c.479G>A(p.R160H), in the TPM1 gene was detected in this individual. The variant is currently not reported in the gnomAD database (v2.1.1). The variant was previously reported in patient(s) (PMID: 20530761, 25241052). The variant is interpreted as likely pathogenic according to ACMG/AMP guidelines.

Gene:
TPM1 encodes Tropomyosin 1, a member of the tropomyosin family of highly conserved, widely distributed actin-binding proteins involved in the contractile system of striated and smooth muscles and the cytoskeleton of non-muscle cells. Tropomyosin is composed of two alpha-helical chains arranged as a coiled-coil. It is polymerized end to end along the two grooves of actin filaments and provides stability to the filaments. The encoded protein is one type of alpha helical chain that forms the predominant tropomyosin of striated muscle, where it also functions in association with the troponin complex to regulate the calcium-dependent interaction of actin and myosin during muscle contraction. In smooth muscle and non-muscle cells, alternatively spliced transcript variants encoding a range of isoforms have been described.

Disease:
Defects in the TPM1 gene cause Cardiomyopathy, dilated 1Y [MIM:611878]: A disorder characterized by ventricular dilation and impaired systolic function, resulting in congestive heart failure and arrhythmia. Patients are at risk of premature death. The inheritance manner is autosomal dominant.
Defects in the TPM1 gene cause Left ventricular non-compaction 9 [MIM:611878]: A form of left ventricular non-compaction, a cardiomyopathy due to myocardial morphogenesis arrest and characterized by a hypertrophic left ventricle, a severely thickened 2-layered myocardium, numerous prominent trabeculations, deep intertrabecular recesses, and poor systolic function. Clinical manifestations are variable. Some affected individuals experience no symptoms at all, others develop heart failure. In some cases, left ventricular non-compaction is associated with other congenital heart anomalies. LVNC9 is an autosomal dominant condition. The inheritance manner is autosomal dominant.
Defects in the TPM1 gene cause Cardiomyopathy, familial hypertrophic 3 [MIM:115196]: A hereditary heart disorder characterized by ventricular hypertrophy, which is usually asymmetric and often involves the interventricular septum. The symptoms include dyspnea, syncope, collapse, palpitations, and chest pain. They can be readily provoked by exercise. The disorder has inter- and intrafamilial variability ranging from benign to malignant forms with high risk of cardiac failure and sudden cardiac death. The inheritance manner is autosomal dominant.
Defects in the TPM1 gene cause Cardiomyopathy, dilated 1Y [MIM:611878]: A disorder characterized by ventricular dilation and impaired systolic function, resulting in congestive heart failure and arrhythmia. Patients are at risk of premature death. The inheritance manner is autosomal dominant.
Defects in the TPM1 gene cause Left ventricular non-compaction 9 [MIM:611878]: A form of left ventricular non-compaction, a cardiomyopathy due to myocardial morphogenesis arrest and characterized by a hypertrophic left ventricle, a severely thickened

2-layered myocardium, numerous prominent trabeculations, deep intertrabecular recesses, and poor systolic function. Clinical manifestations are variable. Some affected individuals experience no symptoms at all, others develop heart failure. In some cases, left ventricular non-compaction is associated with other congenital heart anomalies. LVNC9 is an autosomal dominant condition. The inheritance manner is autosomal dominant.

METHODOLOGY & LIMITATIONS

Next generation sequencing (NGS): for the paired-end pre-capture library procedure, genomic DNA was fragmented by and ligated to multiplexing PE adapters. The adapter-ligated DNA was then PCR amplified using primers with sequencing barcodes (indexes). For target enrichment procedure, the pre-capture library was enriched by hybridizing to biotin labeled in-solution probes. For massively parallel sequencing, the post-capture library DNA was subjected to sequence analysis on an NGS sequencing platform. The following quality control metrics of the sequencing data are generally achieved: >=90% target base covered at >=20X, mean coverage of target bases >=100X. Usually pathogenic or likely pathogenic Copy Number Variations (CNVs) affecting three or more exons will be included in the report. This test may not provide detections of certain genes or portions of certain genes due to local sequence characteristics or the presence of closely related pseudogenes. Some deletions or duplications, or changes from repetitive sequences may not be accurately identified by this methodology. Genes included in this test are listed in the supplementary table.

Data analysis and interpretation (NGS pipeline version 1.1): The output data were converted from BCL file to FASTQ file, and then mapped by BWA program (reference sequence: GRCh37/Hg19). The variant calls were performed using GATK and annotations were performed using in-house developed pipelines. Synonymous variants, deep intronic variants not affecting splicing site, and common benign variants were excluded from interpretation unless they were previously reported as pathogenic variants. The variants were interpreted according to ACMG guidelines (Richards, et al. Genetics in Medicine (2015) 17, 405) and patient phenotypes and were classified as pathogenic (P), likely pathogenic (LP), unknown significance (VUS), likely benign (LB) or benign (B). It should be noted that the data interpretations were based on our current understanding of genes and variants at the time of reporting. Usually only P and LP variants will be included in the report.

Supplementary Table 1. CARDIOVASUCLAR DISEASE GENE PANEL – 174 GENES

ABCC9	ABCG5	ABCG8	ACTA1	ACTA2	ACTC1	ACTN2	AKAP9	ALMS1	ANK2
ANKRD1	APOA4	APOA5	APOB	APOC2	APOE	BAG3	BRAF	CACNA1C	CACNA2D1
CACNB2	CALM1	CALR3	CASQ2	CAV3	CAVIN4	CBL	CBS	CETP	COL3A1
COL5A1	COL5A2	COX15	CREB3L3	CRELD1	CRYAB	CSRP3	CTF1	DES	DMD
DNAJC19	DOLK	DPP6	DSC2	DSG2	DSP	DTNA	EFEMP2	ELN	EMD
EYA4	FBN1	FBN2	FHL1	FHL2	FKRP	FKTN	FXN	GAA	GATAD1
GCKR	GJA5	GLA	GPD1L	GPIHBP1	HADHA	HCN4	HFE	HRAS	HSPB8
ILK	JAG1	JPH2	JUP	KCNA5	KCND3	KCNE1	KCNE2	KCNE3	KCNH2
KCNJ2	KCNJ5	KCNJ8	KCNQ1	KLF10	KRAS	LAMA2	LAMA4	LAMP2	LDB3
LDLR	LDLRAP1	LMF1	LMNA	LPL	LTBP2	MAP2K1	MAP2K2	MIB1	MYBPC3
MYH11	MYH6	MYH7	MYL2	MYL3	MYLK	MYLK2	MYO6	MYOZ2	MYPN
NEXN	NKX2-5	NODAL	NOTCH1	NPPA	NRAS	PCSK9	PDLIM3	PKP2	PLN
PRDM16	PRKAG2	PRKAR1A	PTPN11	RAF1	RANGRF	RBM20	RYR1	RYR2	SALL4
SCN1B	SCN2B	SCN3B	SCN4B	SCN5A	SCO2	SDHA	SELENON	SGCB	SGCD
SGCG	SHOC2	SLC25A4	SLC2A10	SMAD3	SMAD4	SNTA1	SOS1	SREBF2	TAFAZZIN
TBX20	TBX3	TBX5	TCAP	TGFB2	TGFB3	TGFBR1	TGFBR2	TMEM43	TMPO
TNNC1	TNNI3	TNNT2	TPM1	TRDN	TRIM63	TRPM4	TTN	TTR	TXNRD2
VCL	ZBTB17	ZHX3	ZIC3						