Cordis DX

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Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name :	-	**Date Received :**	-
Medical ID :	-	**Date of Report :**	-
Date of Birth :	-	**Req. Physician :**	-
Location :	-	**Barcode :**	-
Material :	-	**Reason of referal:**	-

Cordis Panel by Next Generation Sequencing

Results associated with the reason of referral

PATHOGENIC VARIANT IDENTIFIED

Gene	Variant	Clinical Significance	Zygosity
MYBPC3	NM_000256.3:c.1505G>A, p.(Arg502Gln)	Pathogenic variant	Heterozygous
FLNC	NM_001458.5:c.5668+6G>A	Variant of Uncertain Significance (VUS)	Heterozygous

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Variants Details

MYBPC3, Exon 16, NM_000256.3:c.1505G>A, p.(Arg502Gln)

ClinGen | HPO | ClinVar

This sequence change replaces arginine, which is basic and polar, with glutamine, which is neutral and polar, at codon 502 of the MYBPC3 protein (p.Arg502Gln). This variant is not present in population databases (gnomAD no frequency). This missense change has been observed in individuals with hypertrophic cardiomyopathy (PMID: 9562578, 16566405, 18403758, 18533079, 20433692, 22386539). ClinVar contains an entry for this variant (Variation ID: 42541). Algorithms developed to predict the effect of missense changes on protein structure and function (SIFT, PolyPhen-2, Align-GVGD) all suggest that this variant is likely to be disruptive. This variant disrupts the p.Arg502 amino acid residue in MYBPC3. Other variant(s) that disrupt this residue have been determined to be pathogenic (PMID: 12707239, 20378854, 22267749, 23396983). This suggests that this residue is clinically significant, and that variants that disrupt this residue are likely to be disease-causing. For these reasons, this variant has been classified as Pathogenic.

MYBPC3 encodes the cardiac isoform of myosin-binding protein C. Myosin-binding protein C is a myosin-associated protein found in the cross-bridge-bearing zone (C region) of A bands in striated muscle. MYBPC3 is expressed exclusively in heart muscle and is a key regulator of cardiac contraction. Pathogenic/likely pathogenic variants in MYBPC3 gene are the cause of familial hypertrophic cardiomyopathy in 15-40% of the cases (PMID: 30674652, 20031618).

FLNC ,Intron 34, NM_001458.5:c.5668+6G>A

ClinGen | HPO | ClinVar

Gene	***FLNC***	OMIM
Disease associated with pathogenic variants in this gene	[Arrhythmogenic right ventricular dysplasia, familial;Autosomal dominant],[Cardiomyopathy, familial hypertrophic, 26;Autosomal dominant],[Cardiomyopathy, familial restrictive 5;Autosomal dominant],[Myopathy, distal, 4;Autosomal dominant],[Myopathy, myofibrillar, 5;Autosomal dominant]	
Variant	NM_001458.5:c.5668+6G>A	
Zygosity	Heterozygous	
Type of variant	Splicing/Intronic	
Allele frequency (dbSNP)	0.0004%	rs773119692
Grantham score	-	

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Protein position information	-
ClinVar	Variation ID: 539341
In silico analysis	Probably not affecting splicing
Clinical Significance	Variant of Uncertain Significance (VUS)

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Methodology

Genomic DNA was extracted from the sample under investigation and was analysed by a solution based capture approach using the target enrichment panel (KapaHyperCap Heredity Panel,ROCHE). Sequencing was carried out using the DNBSEQ-G400 sequencing platform (MGI). Reads were aligned to the reference sequence (GRCh37), and sequence changes were identified and interpreted in the context of a single clinically relevant transcript. Unless otherwise stated, this assay targets all coding regions of the indicated transcripts and 10 base pairs of flanking intronic sequences. The mean coverage was 198X with 99% of all targeted regions sequenced with >=10x depth.

Based on the available patient information, the following diagnostic algorithm was used.

- All genes associated with cardiomyopathy and described in the OMIM and HGMD databases were selected.
- Variant classification was performed according to the ACMG AND AMP guidelines (PMID: 25741868)
- Analysis of the mutations with damaging effect (frameshift, nonsense, missense, splicing mutations etc.) as well as de novo mutations was obtained.
- All clinically significant observations were confirmed by Sanger Sequencing analysis on SeqStudio Genetic Analyzer (Thermo Fisher Scientific). The presence of large genomic rearrangements (LGRs), was investigated using the commercial computational algorithm SeqPilotVersion 4.4 Build 505 (JSI Medical System). The presence of LGRs is verified by use the MLPA method (Multiplex Ligation-dependent Probe Amplification, MRC Holland; PMID: 10978226).

*Note:

Every molecular test has an internal 0,5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples. Unless otherwise stated, this assay targets all coding regions of the indicated transcripts and 10 base pairs of flanking intronic sequences. Therefore, this method cannot detect variants in deep intronic or enhancer/promoter regions.

The method used achieves 99% sensitivity and specificity for single nucleotide variants and insertions and deletions

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Details about non-pathogenic variants

All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of the disease. When identified, variants of uncertain significance (VUS) are reported. Findings of variants of uncertain significance (VUS) in autosomal recessive diseases are not reported unless they co-exist with another finding (pathogenic, likely pathogenic or VUS in the same gene). Benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased risk of the disease. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Genes Analyzed (Table 1)

AARS2	*ABCA1*	*ABCC6*	*ABCC8*	*ABCC9*	*ABCG5*	*ABCG8*	*ABL1*	*ACAD9*
ACADVL	*ACTA1*	*ACTA2*	*ACTB*	*ACTC1*	*ACTG1*	*ACTN2*	*ACVRL1*	*ADAMTS10*
ADAMTS17	*ADAMTS2*	*ADAMTSL4*	*AGK*	*AGL*	*ALDH18A1*	*ALMS1*	*ALPK3*	*ANK2*
ANO5	*APOA1*	*APOA5*	*APOB*	*APOC2*	*APOE*	*ATP6V0A2*	*ATP7A*	*B3GAT3*
B4GALT7	*BAG3*	*BGN*	*BMPR1B*	*BRAF*	*CACNA1C*	*CALM1*	*CALM2*	*CALM3*
CAPN3	*CASQ2*	*CAV1*	*CAV3*	*CBL*	*CBS*	*CDC42*	*CHD7*	*CHST14*
COL11A1	*COL11A2*	*COL1A1*	*COL1A2*	*COL2A1*	*COL3A1*	*COL4A5*	*COL5A1*	*COL5A2*
COX15	*CPT2*	*CREB3L3*	*CRYAB*	*CSRP3*	*CTC1*	*CYP27A1*	*DBH*	*DEPDC5*
DES	*DHCR7*	*DLG4*	*DMD*	*DNAJC19*	*DOLK*	*DPM3*	*DSC2*	*DSG2*
DSP	*DYSF*	*EEF1A2*	*EFEMP2*	*EIF2AK4*	*ELAC2*	*ELN*	*EMD*	*ENG*
ENPP1	*EPG5*	*EPHB4*	*ETFA*	*ETFB*	*ETFDH*	*EYA4*	*F2*	*F5*
FBLN5	*FBN1*	*FBN2*	*FBXL4*	*FGD1*	*FHL1*	*FKBP14*	*FKRP*	*FKTN*
FLNA	*FLNC*	*FOXE3*	*FOXF1*	*FXN*	*GAA*	*GATA4*	*GATA6*	*GBE1*
GDF2	*GJA1*	*GLA*	*GLB1*	*GMPPB*	*GPD1*	*GPIHBP1*	*GTPBP3*	*GUSB*
GYS1	*HADHA*	*HCN4*	*HFE*	*HRAS*	*IDUA*	*CRPPA*	*JAG1*	*JPH2*
JUP	*KAT6B*	*KCNA1*	*KCND3*	*KCNE1*	*KCNE2*	*KCNH2*	*KCNJ2*	*KCNJ5*
KCNK3	*KCNQ1*	*KCNQ2*	*KCNQ3*	*KCNT1*	*KLHL24*	*KRAS*	*LAMA2*	*LAMP2*
LCAT	*LDB3*	*LDLR*	*LDLRAP1*	*LIPA*	*LMF1*	*LMNA*	*LPL*	*LZTR1*
MAP2K1	*MAP2K2*	*MED12*	*MFAP5*	*MIB1*	*MIPEP*	*MLYCD*	*MTO1*	*MYBPC3*
MYH11	*MYH6*	*MYH7*	*MYL2*	*MYL3*	*MYLK*	*MYOT*	*MYPN*	*NDUFAF2*
NEXN	*NF1*	*NF2*	*NFU1*	*NKX2-5*	*NONO*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NRAS	*NSUN2*	*PCCA*	*PCCB*	*PCDH19*	*PCSK9*	*PDLIM3*	*PKP2*	*PLEC*
PLN	*PLOD1*	*PNPLA2*	*PPA2*	*PPP1CB*	*PRKAG2*	*PRKG1*	*PTPN11*	*PYCR1*
QRSL1	*RAF1*	*RASA1*	*RBCK1*	*RBM20*	*RIT1*	*RMND1*	*RYR1*	*RYR2*
SALL4	*SARS2*	*SASH1*	*SCN10A*	*SCN1A*	*SCN1B*	*SCN5A*	*SCN8A*	*SCN9A*
SCNN1B	*SCNN1G*	*SCO1*	*SCO2*	*SDHA*	*SGCA*	*SGCB*	*SGCD*	*SGCG*

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SHOC2	*SKI*	*SLC22A5*	*SLC25A20*	*SLC25A4*	*SLC2A1*	*SLC2A10*	*SLC39A13*	*SMAD2*
SMAD3	*SMAD4*	*SMAD6*	*SMARCB1*	*SMCHD1*	*SOS1*	*SOS2*	*SOX17*	*SPEG*
SPRED1	*STAMBP*	*STRA6*	*SYNE1*	*SYNE2*	*SYNGAP1*	*TAB2*	*TAFAZZIN*	*TBX1*
TBX20	*TBX4*	*TBX5*	*TCAP*	*TFAP2B*	*TGFB2*	*TGFB3*	*TGFBR1*	*TGFBR2*
TMEM43	*TMEM70*	*TNNC1*	*TNNI3*	*TNNI3K*	*TNNT2*	*TNXB*	*TPM1*	*TRDN*
TRIM32	*TRPM4*	*TSFM*	*TTN*	*TTR*	*UPF3B*	*VCAN*	*VCL*	*VCP*
VPS13A	*XK*	*ZDHHC9*	*ZNF469*					

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Family tree

Note: **The information shown on the family tree has been provided by the patient and not by medical records.**

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Literature

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