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 :**	XXXXXXXXEN
Material :	-	**Reason for Referral:**	-

Cordis Panel by Next Generation Sequencing

Result

PATHOGENIC VARIANT IDENTIFIED

Gene	Variant	clinical Significance	Zygosity
LAMP2	NM_002294:c.877C>T, p.(Arg293*)	Pathogenic variant	Heterozygous

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Variant Details

***LAMP2*, Exon 7, NM_002294:c.877C>T, p.(Arg293*)** ClinGen HPO ClinVar

This is a replacement of a nucleotide base at position 877 of the *LAMP2* gene leading to the replacement of Arginine by a termination codon at position 293 of the *LAMP2* protein. The resulting protein is expected to be truncated and inactive. This mutation has been described in the international literature in individuals with Danon syndrome and hypertrophic cardiomyopathy (PMID: 20960602, 21896538, 23168931). In the mutation database ClinVar it is described as a pathogen (Variation ID: 163812). The ACMG / AMP guidelines codes used for the classification are as follows: PVS1, PM2, PP1, PP5 and PS2 (PMID: 31479589, 25741868). For the above reasons, this mutation is characterized as pathogenic. Based on the international literature, it is recommended to check the relatives of the examinee for this mutation.

The *LAMP2* gene encodes lysosomal membrane protein-2, a major component of lysosomal membrane glycoproteins with a key role in the targeted introduction of cytoplasmic proteins into lysosomes for degradation (PMID: 8146882). The LAMP2 gene is associated with Danon disease a (MedGen UID: 209235, PMID: 31424795). Danon disease is a rare genetic disorder characterized by an X-linked dominant inheritance pattern, as a result of which males are more severely affected than females (PMID: 30857840). It is characterized by weakening of the heart muscle (cardiomyopathy), weakening of the skeletal muscles (myopathy) and mental retardation. Individuals with mutations in the *LAMP2* gene who develop hypertrophic cardiomyopathy without the other characteristic features of Danon disease have been described (PMID: 20960602, 21896538, 23168931).

Genetic counseling is recommended to better explain the result. First-degree relatives have a 50% possibility of having inherited the same mutation and it is recommended that they undergo genetic testing.

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Methodology

Genomic DNA was extracted from the sample under investigation and was analysed by a solution based capture approach using SureSelect Custom Constitutional Panel 17 Mb (Agilent Technologies). These regions include exons and adjacent intronic regions of the genes analyzed. Sequencing was carried out using is carried out using the DNBSEQ-G50 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. All targeted regions were sequenced with ≥20x depth. 158 Genes described in OMIM and HGMD databases as genes associated with disease were selected (Table 1). The presence of large genomic rearrangements (LGRs), is investigated using the commercial computational algorithm SeqPilot Version 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; AJHG 67:841-50, 2000).*Notes:

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.

The method used achieves 99% sensitivity and specificity for single nucleotide variants and insertions and deletions <15bp. Sensitivity to detect genomic rearrangements smaller than two full exons may be reduced. Balanced genomic rearrangements cannot be detected.

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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 disease. When identified, variants of uncertain significance (VUS) are reported. Benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased disease risk. Present evidence does not suggest that non-clinically significant variant findings can 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)

A2ML1	*ABCC6*	*ABCC8*	*ABCC9*	*ABL1*	*ACAD9*	*ACTA1*	*ACTA2*	*ACTC1*
ACTN2	*ACVRL1*	*ADAMTS10*	*ADAMTS17*	*ADAMTSL4*	*AGK*	*AGL*	*AKAP9*	*ALDH18A1*
ALMS1	*ALPK3*	*ANK2*	*ANKRD1*	*APOA1*	*AQP1*	*ATP7A*	*B3GAT3*	*BAG3*
BGN	*BMPR1B*	*BMPR2*	*BRAF*	*CACNA1C*	*CACNA2D1*	*CACNB2*	*CALM1*	*CALM2*
CALM3	*CALR3*	*CASQ2*	*CASZ1*	*CAV1*	*CAV3*	*CBL*	*CBS*	*CDH2*
CHRM2	*CHST14*	*COL1A1*	*COL1A2*	*COL2A1*	*COL3A1*	*COL4A5*	*COL5A1*	*COL5A2*
COL5A2	*COX15*	*CRYAB*	*CSRP3*	*CTC1*	*CTNNA3*	*DBH*	*DEPDC5*	*DES*
DMD	*DOLK*	*DPM3*	*DSC2*	*DSG2*	*DSP*	*DTNA*	*DYSF*	*EEF1A2*
EFEMP2	*EIF2AK4*	*ELAC2*	*ELN*	*EMD*	*ENG*	*ENPP1*	*EPG5*	*ETFA*
ETFB	*ETFDH*	*EYA4*	*FBLN5*	*FBN1*	*FBN2*	*FBXL4*	*FHL1*	*FHL2*
FHOD3	*FKBP14*	*FKRP*	*FKTN*	*FLNA*	*FLNC*	*FOXE3*	*FXN*	*GAA*
GATA4	*GATA5*	*GATAD1*	*GBE1*	*GDF2*	*GJA5*	*GLA*	*GLB1*	*GPD1L*
GSK3B	*GYS1*	*HADHA*	*HAND1*	*HCN4*	*HFE*	*HRAS*	*ILK*	*JPH2*
JUP	*KCNA1*	*KCNA5*	*KCND3*	*KCNE1*	*KCNE2*	*KCNE3*	*KCNE5*	*KCNH2*
KCNJ2	*KCNJ5*	*KCNJ8*	*KCNK3*	*KCNQ1*	*KCNQ2*	*KCNQ3*	*KCNT1*	*KLHL24*
KRAS	*LAMA4*	*LAMP2*	*LDB3*	*LMNA*	*LOX*	*LZTR1*	*MAP2K1*	*MAP2K2*
MAT2A	*MED12*	*MEF2A*	*MFAP5*	*MIB1*	*MLYCD*	*MRAS*	*MYBPC3*	*MYH11*
MYH6	*MYH7*	*MYL2*	*MYL3*	*MYL4*	*MYLK*	*MYLK2*	*MYOT*	*MYOZ2*
MYPN	*NDUFAF2*	*NEBL*	*NEXN*	*NF1*	*NFU1*	*NKX2-5*	*NOS1AP*	*NOTCH1*
NOTCH3	*NPPA*	*NRAS*	*NUP155*	*PCCA*	*PCCB*	*PCDH19*	*PDLIM3*	*PKP2*
PLEC	*PLN*	*PLOD1*	*PRDM16*	*PRKAG2*	*PRKG1*	*PTPN11*	*RAF1*	*RANGRF*
RASA1	*RASA2*	*RBCK1*	*RBM20*	*RIT1*	*RMND1*	*RYR1*	*RYR2*	*SALL4*
SARS2	*SCN10A*	*SCN1A*	*SCN1B*	*SCN2B*	*SCN3B*	*SCN4B*	*SCN5A*	*SCN8A*
SCN9A	*SDHA*	*SGCD*	*SHOC2*	*SKI*	*SLC25A4*	*SLC2A1*	*SLC2A10*	*SLC39A13*
SLMAP	*SMAD2*	*SMAD3*	*SMAD4*	*SMAD6*	*SMAD9*	*SNTA1*	*SOS1*	*SOS2*
SOX17	*SPRED1*	*STRA6*	*SYNE1*	*SYNE2*	*TAB2*	*TAZ*	*TBX20*	*TBX4*
TBX5	*TCAP*	*TECRL*	*TGFB2*	*TGFB3*	*TGFBR1*	*TGFBR2*	*TMEM43*	*TMPO*
TNNC1	*TNNI3*	*TNNI3K*	*TNNT2*	*TPM1*	*TRDN*	*TRPM4*	*TTN*	*TTR*
TXNRD2	*VCL*	*VPS13A*	*XK*	*ZDHHC9*	*ZNF469*			

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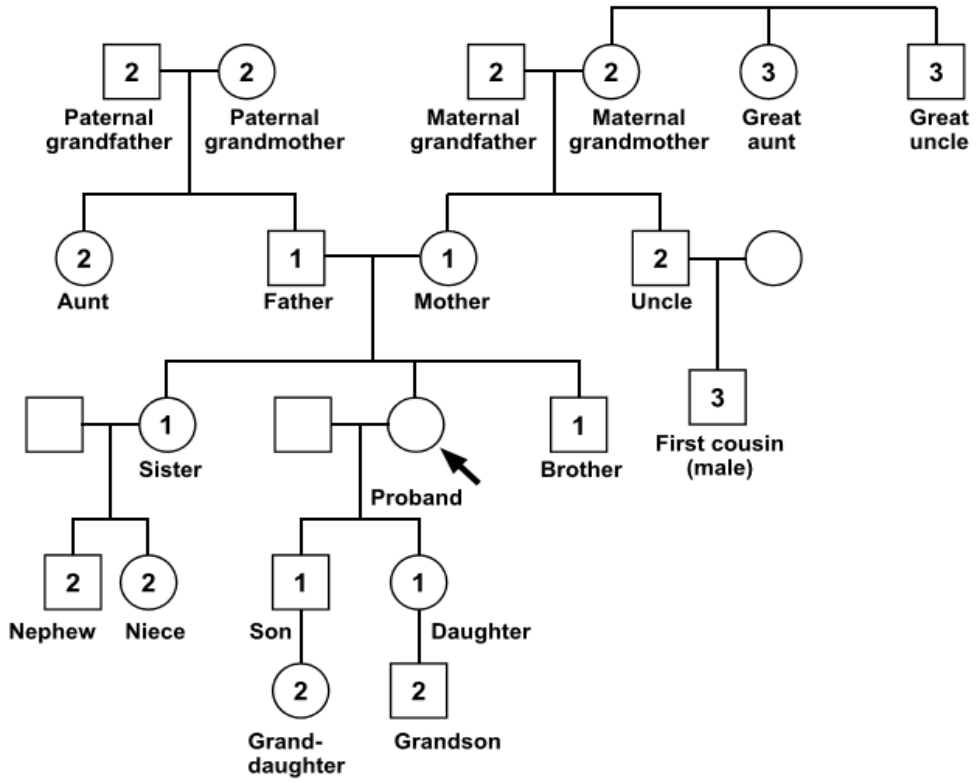
Family tree



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

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