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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 :	WHOLE PERIPHERAL BLOOD	**Reason of referal:**	Referral for Barth syndrome

Clinical Exome analysis by Next Generation Sequencing - Rare Diseases Panel

Results associated with the reason of referral

PATHOGENIC VARIANT IDENTIFIED

Gene	Variant	Clinical Significance	Zygosity
TAFAZZIN	NM_000116.5:c.718G>A, p.(Gly240Arg)	Pathogenic variant	Heterozygous
FLNC	NM_001458.5:c.1972A>G, p.(Ile658Val)	Variant of Uncertain Significance (VUS)	Heterozygous
SCNN1B	NM_000336.3:c.998G>A, p.(Gly333Asp)	Variant of Uncertain Significance (VUS)	Heterozygous
SMCHD1	NM_015295.3:c.263A>G, p.(Asp88Gly)	Variant of Uncertain Significance (VUS)	Heterozygous

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Name: **TUDORACHE ANDREI** Barcode : **23015982**

Variants Details

***TAFAZZIN*, Exon 10, NM_000116.5:c.718G>A, p.(Gly240Arg)** ClinGen HPO ClinVar

This sequence change replaces glycine with arginine at codon 240 of the TAZ protein (p.Gly240Arg). The glycine residue is moderately conserved and there is a moderate physicochemical difference between glycine and arginine. This variant is not present in population databases (ExAC no frequency). This missense change has been observed in individual(s) with Barth syndrome co-segregating with disease in an X-linked fashion (PMID: 4685904, 9382096, 11896212, 23345479). It has also been observed to segregate with disease in related individuals. Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may create or strengthen a splice site. The ACMG/AMP guidelines used for classification are PM3, PM2, PP3, PS1, PP2 (PMID: 31479589, 25741868).For these reasons, this variant has been classified as Pathogenic.

Cardiolipin is a complex glycerophospholipid with 4 acyl groups that localizes to the mitochondrial inner membrane and has a role in mitochondrial structure and function. TAZ is a mitochondrial transacylase that catalyzes remodeling of immature cardiolipin to its mature composition containing a predominance of tetralinoleoyl moieties (PMID: 21068380). Pathogenic/likely pathogenic mutations in TAZ (TAFAZZIN) gene cause Barth syndrome, an X-linked multi-systemic disorder with cardiac manifestations, (cyclic) neutropenia, increased urinary excretion of 3-methylglutaconic acid and skeletal myopathy (OMIM:302060). Cardiac manifestations include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), endocardial fibroelastosis, left ventricular non-compaction (LVNC), ventricular arrhythmia, sudden cardiac arrest or death, prolonged QTc and heart transplant. Not all boys with Barth syndrome have all of the above features. Due to TAZ's location on the X chromosome, males with a pathogenic variant in TAZ are at higher risk of developing Barth syndrome than females. There are a couple of case reports of females developing Barth syndrome, but that is due to extreme skewing of the expression of the X chromosome (one case) and structural/loss of function variation in another female.

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FLNC **,Exon 12, NM_001458.5:c.1972A>G, p.(Ile658Val)** 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.1972A>G, p.(Ile658Val)	
Zygosity	Heterozygous	
Type of variant	Missense	
Allele frequency (dbSNP)	0.003%	rs1180660465
Grantham score	29	
Protein position information	In a domain of the protein that is not known to be functionally important	
ClinVar	Variation ID: -	
In silico analysis	Damaging	
Clinical Significance	Variant of Uncertain Significance (VUS)	

SCNN1B **,Exon 6, NM_000336.3:c.998G>A, p.(Gly333Asp)** ClinGen HPO ClinVar

Gene	***SCNN1B***	OMIM
Disease associated with pathogenic variants in this gene	[Bronchiectasis with or without elevated sweat chloride 1;Autosomal dominant],[Liddle syndrome 1;Autosomal dominant],[Pseudohypoaldosteronism, type IB2, autosomal recessive;Autosomal recessive]	
Variant	NM_000336.3:c.998G>A, p.(Gly333Asp)	
Zygosity	Heterozygous	
Type of variant	Missense	
Allele frequency (dbSNP)	0.003%	rs766312579
Grantham score	94	

Electronically Signed by -
- George Nasioulas, PhD Molecular Biologist, Scientific Director, AMKA:26025301255

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Protein position information	In a domain of the protein that is not known to be functionally important
ClinVar	Variation ID: -
In silico analysis	Damaging
Clinical Significance	Variant of Uncertain Significance (VUS)

***SMCHD1* ,Exon 3, NM_015295.3:c.263A>G, p.(Asp88Gly)** ClinGen HPO ClinVar

Gene	***SMCHD1***	OMIM
Disease associated with pathogenic variants in this gene	[Bosma arhinia microphthalmia syndrome;Autosomal dominant],[Fascioscapulohumeral muscular dystrophy 2, digenic;Digenic dominant]	
Variant	NM_015295.3:c.263A>G, p.(Asp88Gly)	
Zygosity	Heterozygous	
Type of variant	Missense	
Allele frequency (dbSNP)	0,03%	rs766312579
Grantham score	94	
Protein position information	In a domain of the protein that is not known to be functionally important	
ClinVar	Variation ID: 252695	
In silico analysis	Tolerated	
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 (Kapa Hyper Cap,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 151X with 99% of all targeted regions sequenced with >=20x depth.

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

- 180 genes described in the OMIM and HGMD databases were selected as genes associated with cardiomyopathy 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	*ABCC6*	*ABCC9*	*ACAD9*	*ACADVL*	*ACTA1*	*ACTC1*	*ACTN2*	*AGK*
AGL	*ALMS1*	*ALPK3*	*ANO5*	*APOA1*	*BAG3*	*BRAF*	*CACNA1C*	*CALM3*
CAPN3	*CASQ2*	*CAV3*	*CBL*	*CDH2*	*COX15*	*CPT2*	*CRPPA*	*CRYAB*
CSRP3	*CTC1*	*DBH*	*DES*	*DMD*	*DNAJC19*	*DOLK*	*DPM3*	*DSC2*
DSG2	*DSP*	*DYSF*	*EEF1A2*	*ELAC2*	*EMD*	*EPG5*	*ETFA*	*ETFB*
ETFDH	*EYA4*	*FBXL4*	*FHL1*	*FHOD3*	*FKRP*	*FKTN*	*FLNC*	*FXN*
GAA	*GATA4*	*GATA6*	*GBE1*	*GLA*	*GLB1*	*GMPPB*	*GTPBP3*	*GUSB*
HADHA	*HCN4*	*HFE*	*HRAS*	*IDUA*	*JPH2*	*JUP*	*KCNQ1*	*KLHL24*
KRAS	*LAMA2*	*LAMP2*	*LDB3*	*LMNA*	*LZTR1*	*MAP2K1*	*MAP2K2*	*MED12*
MIB1	*MIPEP*	*MLYCD*	*MTO1*	*MYBPC3*	*MYH6*	*MYH7*	*MYL2*	*MYL3*
MYOT	*MYPN*	*NDUFAF2*	*NEXN*	*NF1*	*NKX2-5*	*NONO*	*NRAS*	*PCCA*
PCCB	*PDLIM3*	*PKP2*	*PLEC*	*PLN*	*PNPLA2*	*PPA2*	*PPP1CB*	*PRKAG2*
PTPN11	*QRSL1*	*RAF1*	*RASA1*	*RBCK1*	*RBM20*	*RIT1*	*RMND1*	*RYR2*
SCN5A	*SCNN1B*	*SCNN1G*	*SCO1*	*SCO2*	*SDHA*	*SGCA*	*SGCB*	*SGCD*
SGCG	*SHOC2*	*SLC22A5*	*SLC25A20*	*SLC25A4*	*SMCHD1*	*SOS1*	*SOS2*	*SPEG*
SPRED1	*TAB2*	*TAFAZZIN*	*TBX20*	*TBX5*	*TCAP*	*TGFB3*	*TMEM43*	*TMEM70*
TNNC1	*TNNI3*	*TNNI3K*	*TNNT2*	*TPM1*	*TRIM32*	*TSFM*	*TTN*	*TTR*
VCL	*VCP*	*VPS13A*						

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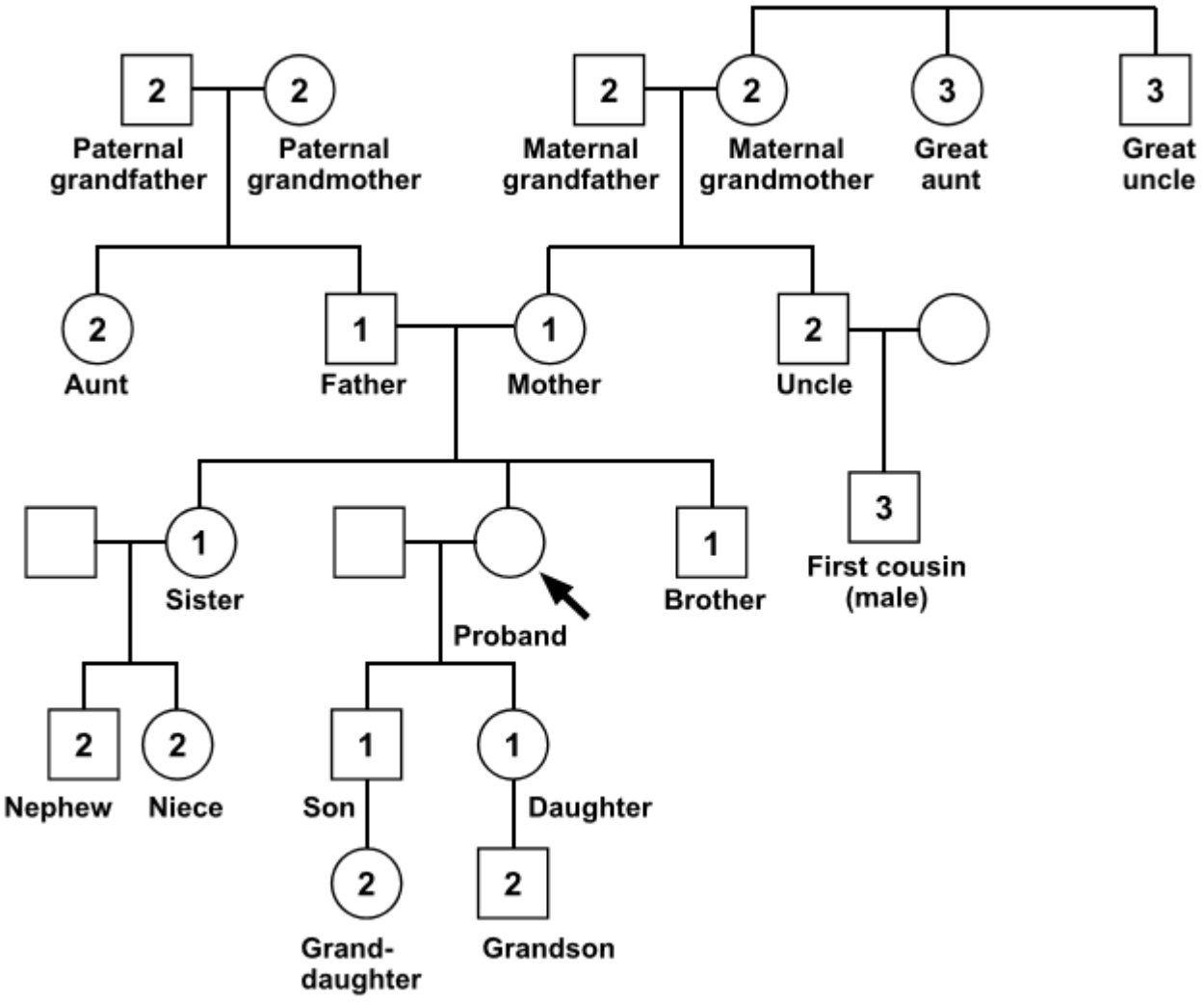
Family tree



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

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