Cordis DX Dslp

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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 Dysplipidemia

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
APOB	NM_000527.5:c.10580G>A, p.(Arg3527Gln)	Pathogenic variant	Heterozygous

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Variants Details

***APOB*, Exon 26, NM_000527.5:c.10580G>A, p.(Arg3527Gln)** ClinGen HPO ClinVar

This is a single base substitution, replacing Arginine with Glutamine at codon 3527 of the APOB protein (p.Arg3527Gln). This variant is present in population databases (rs5742904, gnomAD 0.06%). This missense change has been observed in multiple individuals with hypercholesterolaemia (Bertolini et al., 2013, Garcia-Garcia et al., 2011). The mutation database ClinVar contains entries for this variant (Variation ID: 17890). Experimental studies have shown that this missense change affects APOB function (Benn et al., 2005). The classification criteria set used by the ACMG and AMP are PM2, PM5, PP2 and PP5 (Richards et al., 2018). For these reasons, this variant has been classified as Pathogenic.

The *APOB* gene encodes the main apolipoprotein of chylomicrons and low density lipoproteins (LDL), and is the ligand for the LDL receptor. It occurs in plasma in two main isoforms, a short version called apolipoprotein B-48 and a longer version known as apolipoprotein B-100, synthesized exclusively in the gut and the liver respectively. Pathogenic variants in this gene or its regulatory region cause hypobetalipoproteinemia and familial hypercholesterolemia (FH) due to ligand-defective apoB, diseases affecting plasma cholesterol and apoB levels and inherited in the recessive and dominant manner respectively (Teslovich et al., 2010). Individuals with biallelic APOB-related familial hypobetalipoproteinemia (APOB-FHBL) may present from infancy through to adulthood with a range of clinical symptoms including deficiency of fat-soluble vitamins and gastrointestinal and neurologic dysfunction. Their treatment includes low-fat diet (<30% of total calories) while ensuring adequate caloric intake and high-dose oral fat-soluble vitamin supplementation. Individuals with a heterozygous, typically truncating pathogenic variant in APOB are usually asymptomatic with mild liver dysfunction and hepatic steatosis and no treatment typically required (Burnett et al., 2021).

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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 141X with 99% of all targeted regions sequenced with >=20x depth.

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

- 34 genes described in the OMIM and HGMD databases were selected as genes associated with dyslipidemia 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)

APOB	*LDLR*	*LDLRAP1*	*LIPA*	*PCSK9*	*ANGPTL3*	*MTTP*	*SAR1B*	*ABCG5*
AGTR1	*HSD11B2*	*APOE*	*NOS2*	*APOA5*	*APOC3*	*LPL*	*CETP*	*SCARB1*
NPC1	*NPC2*	*FTO*	*MC4R*	*SMPD1*	*SCNN1A*	*SCNN1B*	*SCNN1G*	*LPA*
ABCG8	*LIPC*	*INSIG2*	*SCNN1D*	*STAP1*	*CH25H*	*PLTP*		

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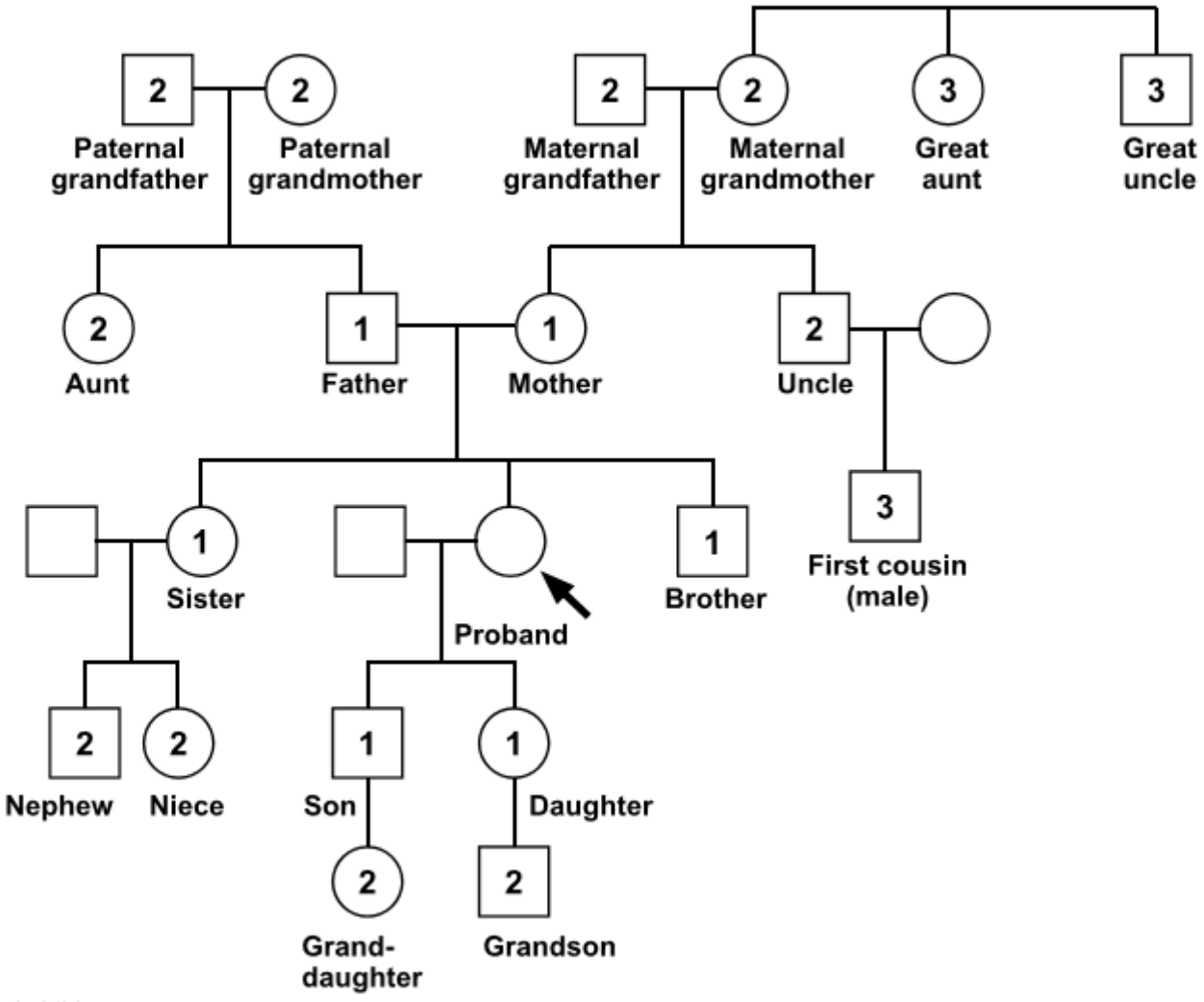
Family tree



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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