Cordis DX LDL

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece ,G.E.MI. nr: 0007856001000
email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
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 Familial Hyperholesterolaemia

Cordis Panel by Next Generation Sequencing: Οικογενής Υπερχοληστερολαιμία

Results associated with the reason of referral

PATHOGENIC VARIANT IDENTIFIED

Gene	Variant	Clinical Significance	Zygosity
LDLR	NM_000527:c.301G>A, p.Glu101Lys	Pathogenic variant	Heterozygous

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

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Variants Details

***LDLR*, Exon 4, NM_000527:c.301G>A, p.Glu101Lys** ClinGen HPO ClinVar

This is a single base substitution, replacing Glutamic acid with Lysine at codon 101 of the LDLR protein p.(Glu101Lys). This variant is present in population databases (rs144172724, gnomAD 0.003%). 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: 161266). Experimental studies have shown that this missense change affects LDLR function (Thormaehlen et al., 2015). The classification criteria set used by the ACMG and AMP are PP1, PS3, PM3, PS4, PP4, PM1, PP2, PM2 PM5, PP3 and PP5 (Richards et al., 2018). For these reasons, this variant has been classified as Pathogenic.

The *LDLR* gene encodes for the low-density lipoprotein receptor protein, a cell surface receptor that plays an important role in cholesterol homeostasis. This receptor binds to particles called low-density lipoproteins (LDLs), which are the primary carriers of cholesterol in the blood and transports them into the cell. Once inside the cell, the LDL is broken down to release cholesterol that is then used by the cell, stored, or removed from the body. Pathogenic variants in LDLR are linked to Familial hypercholesterolaemia (FH), a genetic disorder characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein cholesterol (LDL cholesterol), in the blood and early cardiovascular diseases. Familial hypercholesterolaemia (FH) can be caused by mutations in the *LDLR, APOB, PCSK9* and *LDLRAP1* genes in about 60-80% of people with FH that can be inherited from one parent (heterozygous FH), or, in rare instances, from both (homozygous FH). People with this rarer form of FH can have very high LDL cholesterol levels. FH affected individuals have an excellent prognosis if the condition is identified early and treated appropriately (Sturm et al., 2018); Defesche et al., 2017). The pharmacological options available, include statins as a first approach, ezetimibe, and the recently approved monoclonal antibodies targeting PCSK9, for the majority of heterozygous FH subjects, while for the most severe forms of homozygous FH, the addition of therapies such as lomitapide either with or without apheresis may be required (Raal et al., 2018).

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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 HyperExome Probes, 43Mb, Roche. Sequencing was carried out using MGI technology. 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. All targeted regions were sequenced with >=10x depth.

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

- The genes described in the OMIM and HPO databases were selected as genes associated with the patient phenotype.
- Variant classification was performed according to the ACMG AND AMP guidelines (PMID: 25741868)
- Analysis of the mutations described in the HGMD, 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.

*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 cancer or other diseases. 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 cancer risk. 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*	*PCSK9*

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Literature

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