Familial Hypercholesterolemia Panel

Disorder also known as:

Familial Hyperlipoproteinemia, Type IIA; Hyper-Low-Density-Lipoproteinemia; Hypercholesterolemic Xanthomatosis; Familial LDL Receptor Disorder

Panel Gene List: *APOB, LDLR, LDLRAP1, PCSK9*

Clinical Features:

Familial hypercholesterolemia (FH) is an inherited disorder of cholesterol metabolism, characterized by high levels of low-density lipoprotein cholesterol (LDL-C) in the blood.[1] In untreated adults, LDL-C levels can be >190 mg/dL (>4.9 mmol/L) or total cholesterol levels can be >310 mg/dL (>8 mmol/L) .[1] In untreated children or adolescents, LDL-C levels can be >160 mg/dL (>4 mmol/L) or total cholesterol levels can be >230 mg/dL (>6 mmol/L).[1] High levels of LDL-C causes premature atherosclerosis, which results in an increased risk for premature coronary heart disease (CHD), which most commonly manifests as a myocardial infarction or angina pectoris.[2-5] Individuals can also have visible lipid deposits in the skin (tendon xanthoma) or eyes (cornea arcus).[2-5] Diagnostic criteria and management guidelines for FH are available from numerous national and international organizations.[1]

Inheritance Pattern/Genetics: Autosomal Dominant or Autosomal Recessive.

Test Methods:

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request

Test Sensitivity:

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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Gene	Protein	Inheritance	Disease Association(s)
LDLR	LOW-DENSITY LIPOPROTEIN RECEPTOR	AD	HeFH/HoFH
APOB	APOLIPOPROTEIN B	AD	HeFH/HoFH
PCSK9	PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9	AD	HeFH/HoFH
LDLRAP1	LOW-DENSITY LIPOPROTEIN RECEPTOR ADAPTOR PROTEIN 1	AR	ARFH

Abbreviations: AD – Autosomal dominant; AR – Autosomal recessive; ARFH – Autosomal recessive familial hypercholesterolemia; HeFH - Heterozygous FH; HoFH – Homozygous FH

REFERENCES:

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2.Nordestgaard et al. (2013) European Heart Journal 34 (45):3478-90a (PMID: 23956253)
3.Hovingh et al. (2013) European Heart Journal 34 (13):962-71 (PMID: 23416791)
4.Robinson, et al. (2013) Journal of Managed Care Pharmacy: JMCP 19 (2):139-49 (PMID: 23461430)
5.Sniderman et al. (2014) Journal of the American College of Cardiology 63 (19):1935-47 (PMID: 24632267)

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