Familial Dyslipidemia Panel

Disorder also known as: Hyperlipidemia, Hypercholesterolemia, Hyperlipoproteinemia, Combined hyperlipidemia

Panel Gene List: *ABCA1, ABCG5, ABCG8, ANGPTL3, APOA1, APOA5, APOB, APOC2, APOC3, APOE, CETP, CYP7A1, CYP27A1, GCKR, GPD1, GPIHBP1, LCAT, LDLR, LDLRAP1, LIPA, LIPC, LMF1, LPL, MTTP, PCSK9, SAR1B, SCARB1, STAP1*

Clinical Features:

Primary or familial dyslipidemias are a group of clinically and genetically heterogeneous disorders characterized by abnormal plasma levels of total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or triglycerides.[1] Lipoproteins are a group of proteins responsible for the transport and processing of lipids in the blood plasma. These abnormal plasma levels of lipids and lipoproteins are responsible for approximately 50% of the attributable risk for the development of atherosclerotic cardiovascular diseases.[2] Dyslipidemias can have a monogenic cause, or may be associated with other conditions such as diabetes and thyroid disease, or other lifestyle factors.

Inheritance Pattern/Genetics: Autosomal Dominant, Semi-Dominant, and Autosomal Recessive

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: APOA1, LCAT, and LMF1 genes only whole gene deletions or duplications may be detected. For the GCKR gene, sequencing, but not deletion/duplication analysis, was performed.

Gene	Protein	Inheritance	Disease Association(s)
ABCA1	ATP-BINDING CASSETTE, SUBFAMILY A, MEMBER 1	AR; AD	Tangier disease; Familial hypoalphalipoproteinemia / High density lipoprotein deficiency
ABCG5	ATP-BINDING CASSETTE, SUBFAMILY G, MEMBER 5	AR	Sitosterolemia
ABCG8	ATP-BINDING CASSETTE, SUBFAMILY G, MEMBER 8	AR	Sitosterolemia
ANGPTL3	ANGIOPOIETIN-LIKE 3	AR	Familial hypobetalipoproteinemia; Familial combined hypolipidemia
APOA1	APOLIPOPROTEIN A-I	AD	Hypoalphalipoproteinemia; Hereditary apoAI amyloidosis
APOA5	APOLIPOPROTEIN A-V	AD	Late-onset Hyperchylomicronemia; Hypertriglyceridemia
APOB	APOLIPOPROTEIN B	AD/SD; AR	Familial hypercholesterolemia (includes HeFH andHoFH); hypobetalipoproteinemia
APOC2	APOLIPOPROTEIN C-II	AR	Hyperlipoproteinemia type Ib, or Apolipoprotein C-II deficiency
APOC3	APOLIPOPROTEIN C-III	AD	Apolipoprotein C-III deficiency
APOE	APOLIPOPROTEIN E	AD	Hyperlipoproteinemia type III
CETP	PLASMA CHOLESTERYL ESTER TRANSFER PROTEIN	AD	Hyperalphalipoproteinemia
CYP7A1	CYTOCHROME P450, SUBFAMILY VIIA, POLYPEPTIDE 1	AR	Hyperlipidemia
CYP27A1	CYTOCHROME P450, SUBFAMILY XXVIIA, POLYPEPTIDE 1	AR	CTX
GCKR	GLUCOKINASE REGULATORY PROTEIN	AD	FGQTL5
GPD1	GLYCEROL-3-PHOSPHATE DEHYDROGENASE 1	AR	Transient infantile hypertriglyceridemia
GPIHBP1	GLYCOSYLPHOSPHATIDYLINOSITOL-ANCHORED HIGH DENSITY LIPOPROTEIN-BINDING PROTEIN 1	AR	Hyperlipoproteinemia 1D
LCAT	LECITHIN:CHOLESTEROL ACYLTRANSFERASE	AR	Familial LCAT deficiency (includes Fish-eye disease and Norum disease)
LDLR	LOW-DENSITY LIPOPROTEIN RECEPTOR	AD/SD	Familial hypercholesterolemia (includes HeFH andHoFH)
LDLRAP1	LOW-DENSITY LIPOPROTEIN RECEPTOR ADAPTOR PROTEIN 1	AR	Familial hypercholesterolemia
LIPA	LYSOSOMAL ACID LIPASE A	AR	LAL deficiency (includes cholesteryl ester storage disease and Wolman disease)

Gene (cont.)	Protein	Inheritance	Disease Association(s)
LIPC	HEPATIC LIPASE	AR	Hepatic lipase deficiency
LMF1	LIPASE MATURATION FACTOR 1	AR	Combined lipase deficiency
LPL	LIPOPROTEIN LIPASE	AR; AD	Lipoprotein lipase deficiency; familial combined hyperlipidemia
MTTP	MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN	AR	Abetalipoproteinemia
PCSK9	PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9	AD/SD	Familial hypercholesterolemia (includes HeFH, and HoFH);Hypocholesterolemia
SAR1B	SAR1, S. CEREVISIAE, HOMOLOG B	AR	CMRD (Anderson Disease)
SCARB1	SCAVENGER RECEPTOR CLASS B, MEMBER 1	AD/AR	SCARB1 deficiency (with elevated HDL levels)
STAP1	SIGNAL TRANSDUCING ADAPTOR FAMILY MEMBER 1	AD	Familial hypercholesteremia

Abbreviations: AD – Autosomal dominant; SD – Semi-dominant; AR – Autosomal recessive; HeFH - Heterozygous Familial Hypercholesterolemia; HoFH – Homozygous Familial Hypercholesterolemia; CTX – Cerebrotendinous Xanthomatosis; FGQTL5 - Hypertriglyceridemia and lower fasting glucose and insulin levels; LCAT – Lecithin:cholesterol acyltransferase; LAL – Lysosomal acid lipase; CMRD – Chylomicron retention disease

References:

1. Dron JS and Hegele RA. Genetics of Lipid and Lipoprotein Disorders and Traits. Curr Genet Med Rep. 2016. 4(3): 130-141.
2. Di Angelantonio E et al. Emerging risk factors collaboration: major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009. 302(18): 1993-2000.