

## 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, MTP, 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.<sup>1</sup> 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.<sup>2</sup> 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)
<i>ABCA1</i>	ATP-BINDING CASSETTE, SUBFAMILY A, MEMBER 1	AR; AD	Tangier disease; Familial hypoalphalipoproteinemia /

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

			disease and Wolman disease)
<i>IPC</i>	HEPATIC LIPASE	AR	Hepatic lipase deficiency
<i>MF1</i>	LIPASE MATURATION FACTOR 1	AR	Combined lipase deficiency
<i>LPL</i>	LIPOPROTEIN LIPASE	AR; AD	Lipoprotein lipase deficiency; familial combined hyperlipidemia
<i>TTP</i>	MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN	AR	Abetalipoproteinemia
<i>PCSK9</i>	PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9	AD/SD	Familial hypercholesterolemia (includes HeFH, and HoFH);Hypocholesterolemia
<i>SAR1B</i>	SAR1, S. CEREVISIAE, HOMOLOG B	AR	CMRD (Anderson Disease)
<i>SCARB1</i>	SCAVENGER RECEPTOR CLASS B, MEMBER 1	AD/AR	SCARB1 deficiency (with elevated HDL levels)
<i>STAP1</i>	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.