

## 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*

*Additional genes from our cardiology test menu may be added to this panel by selecting test code J556C.*

### 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.<sup>1</sup> 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).<sup>1</sup> 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).<sup>1</sup> 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.<sup>2-5</sup> Individuals can also have visible lipid deposits in the skin (tendon xanthoma) or eyes (cornea arcus).<sup>2-5</sup> Diagnostic criteria and management guidelines for FH are available from numerous national and international organizations.<sup>1</sup>

**Inheritance Pattern/Genetics:** Autosomal Dominant or Autosomal Recessive

### Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the 4 genes are enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel using exon-level oligo array CGH (ExonArrayDx). Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CGH analysis. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

## Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 4 genes included in the FH Panel depends in part on the patient's clinical phenotype, family history, and ethnic background. In general, the sensitivity is highest for individuals with clearly defined hypercholesterolemia and a family history of disease. The technical sensitivity of the sequencing test is estimated to be 98%. The sequencing panel will not reliably detect deletions, insertions, or rearrangements greater than or equal to five base pairs (bp). Deletions or duplications of less than 500 bp are not reliably detected by array CGH.

Gene	Protein	Inheritance	Disease Association(s)
<i>LDLR</i>	LOW-DENSITY LIPOPROTEIN RECEPTOR	AD	HeFH/HoFH
<i>APOB</i>	APOLIPOPROTEIN B	AD	HeFH/HoFH
<i>PCSK9</i>	PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9	AD	HeFH/HoFH
<i>LDLRAP1</i>	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:

1. Youngblom E, Knowles JW. Familial Hypercholesterolemia. 2014 Jan 2. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK174884/>
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)