Familial Hypercholesterolemia Panel, Sequencing

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Familial hypercholesterolemia (FH) is the most common inherited cardiovascular disease. It is characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) in the absence of an apparent secondary cause and premature atherosclerotic cardiovascular disease (ASCVD). Manifestations include coronary artery disease (CAD), cardiovascular disease (CVD), angina, myocardial infarction, xanthomas, and corneal arcus. Those with one parent with FH have a 50% chance of inheriting the condition, known as heterozygous FH (HeFH or FH).

Homozygous FH (HoFH) is a less common but more severe disorder, resulting from biallelic variants in a dominant FH-associated gene. If both parents have FH, their offspring have a 50% chance of having HeFH and a 25% chance of HoFH, which results from receiving two altered chromosomes. HoFH is characterized by severe early-onset CAD, aortic stenosis, and a high rate of coronary bypass surgery or death by teenage years. Treatment of FH commonly includes statins or lipid-lowering therapy with lifestyle modifications. FH is designated as a tier-1 genetic disorder by the CDC with proven benefit for case identification and family-based cascade screening.[1]

Featured ARUP Testing

Familial Hypercholesterolemia Panel, Sequencing 3002110

Method: Massively Parallel Sequencing

Use to confirm a diagnosis of FH.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Molecular testing may be used to confirm a diagnosis of FH in symptomatic individuals or for identification of at-risk relatives to ensure treatment prior to onset of ASCVD. Treatment guidelines for FH and HoFH have been published.[2]

Disease Overview

Associated Disorders

Heterozygous Familial Hypercholesterolemia

- LDL-C levels in untreated adults generally >190 mg/dL or total cholesterol >310 mg/dL
- LDL-C levels in untreated children or adolescents >160 mg/dL or total cholesterol >230 mg/dL
- History of premature CAD or other CVD
- Skin or tendon xanthomas
- Corneal arcus
- Family history of FH or clinical findings of FH
- Untreated men are at 50% risk for a coronary event by age 50 and untreated women are at 30% risk by age 60[3]
- FH accounts for approximately 2-3% of myocardial infarctions in those <60 years of age[3]
- Individuals with FH (LDL-C >190 mg/dL) and no FH variant are at an approximate sixfold increased risk for CAD, and those with FH and pathogenic FH mutation have an approximate 22-fold increased risk.[4]

Homozygous Familial Hypercholesterolemia

- LDL-C levels in untreated adults often >400 mg/dL
- LDL-C levels in untreated children or treated adults often lower and may not be sufficient to confirm diagnosis
- Xanthomas on tendons, around eyelids, between digits
- Severe CAD by mid-20s
- Aortic stenosis is common
- Treatment may include LDL apheresis

Typical Testing Strategy

Clinical diagnostic criteria for FH are established.[5,6]

Screening can be performed via cholesterol testing, molecular testing, or both.

- LDL-C levels may overlap in FH and non-FH individuals, especially in adults.
- An estimated 20% of affected individuals may remain undiagnosed if only LDL-C levels are obtained.[1]

Genetic testing should be offered when there is a strong clinical suspicion of FH based on clinical and/or a family history or to assess for a known pathogenic familial variant.[4]

Genetics

Genes

APOB, *LDLR*, *LDLRAP1*, *PCSK9*

Etiology

Approximately 7% of adults in the United States have severe hypercholesterolemia (untreated LDL-C >190 mg/dL) and approximately 2% of these individuals have a pathogenic identifiable FH variant.[7]

Mechanisms of pathogenesis by gene:

- *LDLR* variants cause impaired LDL receptor function or absence of LDL receptor.
- *APOB* gain-of-function variants affect binding of LDL particle to LDL receptor resulting in elevated LDL-C. This condition is also referred to as familial defective apoB and is clinically indistinguishable from FH. Loss-of-function variants in *APOB* are associated with hypobetalipoproteinemia.
- *PCSK9* gain-of-function variants may enhance affinity of PCSK9 protein binding with the LDL receptor, interfere with disassociation of LDL receptor/LDL complex, prevent recycling of receptor, or increase degradation of the LDL receptor. Loss-of-function variants are associated with hypocholesterolemia.
- *LDLRAP1* loss-of-function variants lead to absence of or nonfunctional LDL receptor adaptor protein 1, which prevents LDL receptor/LDL complex to be transported into the cell. This prevents the LDL receptor from effectively removing circulating LDL.

Penetrance

Estimated at 73-90% in individuals with molecularly confirmed FH

Influenced by gene, variant, and nongenetic factors

Prevalence

- FH: 1/250 in the general population
- HoFH: 1/200,000 in the general population
- Higher in specific founder populations

Inheritance

Autosomal dominant for *LDLR*-, *APOB*-, and *PCSK9*-associated FH; de novo variants are rare

Autosomal recessive for *LDLRAP1*-associated FH

HoFH results from biallelic variants in an autosomal dominant FH gene

Genotype-Phenotype Correlations

- LDL-C levels may be slightly lower with a pathogenic *APOB* variant compared to an *LDLR* variant.
- *LDLR* variants causing complete loss-of-function are associated with more severe disease and higher LDL-C levels than partial loss-of-function variants.
- *LDLRAP1*-associated disease typically has lipid levels between FH heterozygotes and HoFH.

Test Description

Clinical Sensitivity

Up to 85% for FH[8]

Influenced by pretest probability of FH using clinical diagnostic criteria

Contribution of genes to FH:

- *LDLR*: 60-80%
- *APOB*: <5%
- *PCSK9*: <1%
- *LDLRAP1*: very rare

Analytic Sensitivity

Majority of causative variants in the tested genes are sequence changes.

Large deletions/duplications in the tested genes account for approximately 5% of causative variants in many populations.

- In French Canadians, a large >15 kb LDLR deletion may account for 60% of FH cases and a 5 kb deletion for an additional 5%.

Variant Class	Analytic Sensitivity (PPA) Estimate[a] %)	Analytic Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of FH.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Variant in regulatory and deep intronic regions
  - Large deletions/duplications/inversions in any of the tested genes
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Genes Tested			
Gene	MIM #	Associated Disorder(s)	Inheritance
APOB	107730	Familial hypercholesterolemia 2	AD
		Familial hypobetalipoproteinemia 1	AR

Gene	MIM #	Associated Disorder(s)	Inheritance
LDLR	606945	Familial hypercholesterolemia 1	AD
LDLRAP1	605747	Familial hypercholesterolemia 4	AR
PCSK9	607786	Familial hypercholesterolemia 3	AD

AD, autosomal dominant; AR, autosomal recessive

References

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Related Information

Atherosclerotic Cardiovascular Disease Risk Assessment

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com