



Disease Information

Familial hypercholesterolemia (FH) is typically an autosomal dominant disease characterized by the presence of high levels of plasma LDL (low density lipoproteins) cholesterol in the body, increasing the risk for premature coronary heart disease (CHD) and myocardial infarction.¹ The majority of autosomal dominant FH cases are associated with loss-of-function mutations in the gene for the low-density lipoprotein receptor (*LDLR*).² Affected individuals present high levels of plasma LDL cholesterol, which increases the risk of premature coronary artery disease, myocardial infarction, and atherosclerotic plaque formation. Defective LDL-receptors cause deposition of cholesterol in different parts of the body causing diseases such as xanthelasma (skin), xanthomas (tendons), and coronary arteries (atherosclerosis).^{3,4}

There are approximately 1 in 500 individuals with heterozygous *LDLR* mutations and 1 in a million individuals with homozygous mutations in the general population.^{1,2} Heterozygotes present a 2- to 3- fold elevation in plasma LDL-cholesterol and develop symptoms such as tendinous xanthomas, corneal arcus, and premature coronary artery disease.^{2,4} Homozygotes also present planar xanthomas, with plasma LDL-cholesterol increases 6- to 8-fold, and death from myocardial infarctions during the first two decades of life is common.⁵ As a result of founder effect, FH is much more common in some population groups such as French Canadians, Afrikaners, Lebanese, Finns, and Ashkenazi Jews.⁶

In addition to mutations in the *LDLR* gene, mutations in the *APOB* and *PCSK9* genes contribute to two other types of familial hypercholesterolemia known as familial defective apolipoprotein B-100 (FDB)^{3,7}, and autosomal dominant hypercholesterolemia 3 (HCHOLA3) respectively. Apolipoprotein B-100 (*APOB*) is the major component of low density lipoproteins (LDL) and plays a crucial role in the binding of LDL with LDL receptors.⁷ These *APOB* mutations fall within the receptor binding domain of the gene and decrease the binding efficiency of lipoproteins with LDL receptors, leading to the accumulation of plasma LDL in FDB.

Proprotein convertase subtilisin kexin type 9 (*PCSK9*) is serine protease mainly expressed in the liver and the intestine, that acts as a chaperone that binds the LDLR, targeting it for internalization and degradation.⁹ *PCSK9* can also act on the LDLR after biosynthesis before it reaches the basolateral surface of the cell.¹⁰ Gain-of-function mutations in *PCSK9* lead to a reduction in LDLR levels, therefore causing hypercholesterolemia¹¹; while loss-of-function mutations are associated with a reduction of plasma LDL cholesterol level.¹² *PCSK9* SNPs are unequally distributed in different ethnic groups. Besides the rare mutations implicated in ADH, some variants are functionally relevant in cholesterol regulation and their distribution and impact vary in different populations.¹³

Proper diet, exercise, and certain medications can aid in the treatment of FH. Heterozygous patients usually respond well with a combination of diet change and drugs (e.g. statins), while in some cases, surgery such as a liver transplant might be needed for homozygous patients.⁸ Proactive diagnosis, in combination with selective treatments, will help to decrease incidence and progression of FH and FDB effects.

Testing Benefits & Indications

Early diagnostic testing for individuals known or suspected to have Familial Hypercholesterolemia will help decrease the risks associated with FH. Carrier screening for relatives of FH patients, at risk pregnancies, and carrier testing for known familial mutations will also decrease the risk of known hypercholesterolemia effects.

Test Description

LDLR exons 1-18 plus at least 20 bases into the 5' and 3' ends of all the introns are analyzed. For *APOB* sequence analysis, a 708 base pair fragment of *APOB* exon 26 containing the most frequently occurring mutations associated with FH is analyzed. *PCSK9* exons 1-12 plus at least 50 bases into the 5' and 3' ends of all the introns are analyzed. The following sites are used to search for previously described *LDLR*, *APOB* and *PCSK9* mutations and polymorphisms: <http://www.ucl.ac.uk/ldlr/LOVDv.1.1.0> (*LDLR* only), Human Gene Mutation Database (HGMD), and online search engines (e.g., PubMed).

Mutation Detection Rate

The Ambry Test: Familial Hypercholesterolemia (*LDLR*, *APOB* and *PCSK9*) is designed and validated to be capable of detecting > 99% of described mutations in *LDLR* and *PCSK9* (considering less than 1% to be the other types of mutations) and > 80% of described mutations in *APOB* relevant for FH.

Turn-Around-Time

Familial Hypercholesterolemia Panel	
- <i>LDLR</i> GSA + <i>APOB</i> PGA	14 – 28 days
Familial Hypercholesterolemia AMPLIFIED	
- <i>LDLR</i> + <i>APOB</i> GSA reflex to <i>LDLR</i> Del/Dup	14 – 28 days
Familial Hypercholesterolemia Comprehensive	14 – 28 days
- <i>LDLR</i> GSA + <i>del/dup</i> + <i>APOB</i> PGA+ <i>PCSK9</i> GSA	
<i>LDLR</i> Gene Sequence Analysis	14 – 21 days
<i>LDLR</i> Del/Dup	7 – 14 days
<i>APOB</i> Partial Gene Analysis	14 – 21 days
<i>PCSK9</i> Related Hypercholesterolemia	14 - 21 days

Specimen Requirements

Blood: Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

Blood Spot: Call for availability.

Saliva: Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

DNA: Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

Prenatal: Prenatal testing is available. Please call an Ambry Genetic Counselor to discuss your case.

CPT Codes

Gene sequence or specific mutation analysis83891, 83894, 83898, 83904, 83909, 83912

References

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- ¹² Cohen JA et al. *Nat Genet* 2005; 37: 161-5.
- ¹³ Abifadel et al. *Hum Mutat* 2009; 30:520-9.