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Familial Hypercholesterolemia

Synonyms: Familial Hypercholesterolæmia, Hyperlipoproteinemia Type IIA

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Summary

Clinical characteristics

Familial hypercholesterolemia (FH) is characterized by significantly elevated low-density lipoprotein cholesterol (LDL-C) that leads to atherosclerotic plaque deposition in the coronary arteries and proximal aorta at an early age and increases the risk of premature cardiovascular events such as angina and myocardial infarction; stroke occurs more rarely. Xanthomas (cholesterol deposits in tendons) may be visible in the Achilles tendons or tendons of the hands and worsen with age as a result of extremely high cholesterol levels. Xanthelasmas (yellowish, waxy deposits) can occur around the eyelids. Individuals with FH may develop corneal arcus (white, gray, or blue opaque ring in the corneal margin as a result of cholesterol deposition) at a younger age than those without FH.

Individuals with a more severe phenotype, often as a result of biallelic variants, can present with very significant elevations in LDL-C (>500 mg/dL), early-onset coronary artery disease (CAD; presenting as early as childhood in some), and calcific aortic valve disease.

Diagnosis/testing

A clinical diagnosis of FH can be established in a proband with characteristic clinical features and significantly elevated LDL-C levels (typically >190 mg/dL in adults and >160 mg/dL in children). Three formal diagnostic criteria are used in Western countries.

The molecular diagnosis of FH can be established by identification of heterozygous or biallelic pathogenic variants in *APOB* (variants that impair binding of LDL-C to the LDL receptor), *LDLR*, or *PCSK9* (gain of function); or rarely, identification of biallelic pathogenic variants in *LDLRAP1*.

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Management

Treatment of manifestations: Adults: pharmacotherapy (statins with additional medications as needed) to reduce lipid levels; referral to a lipid specialist if necessary to reduce LDL-C levels; reduce CAD risk factors including cessation of smoking, regular physical activity, healthy diet, and weight control; treatment of hypertension; low-dose aspirin in high-risk individuals. Children: referral to a lipid specialist; diet and lifestyle modifications; statins can be used in children starting around age eight years.

Prevention of primary manifestations: Heart-healthy diet (including reduced intake of saturated fat and increased intake of soluble fiber to 10-20 g/day); increased physical activity; no smoking.

Surveillance: Monitor lipid levels from age two years; consider noninvasive imaging modalities in adults; identify modifiable risk factors (e.g., smoking, sedentary behavior, hypertension, diabetes, obesity). Individuals with severe FH (i.e., due to homozygous or compound heterozygous pathogenic variants in *APOB*, *LDLR*, or *PCSK9*) or autosomal recessive FH (due to homozygous or compound heterozygous pathogenic variants in *LDLRAP1*) should be monitored with various imaging modalities (including echocardiogram, CT angiogram, and cardiac catheterization) as recommended.

Agents/circumstances to avoid: Smoking, high intake of saturated and trans unsaturated fat, sedentary lifestyle, obesity, hypertension, and diabetes mellitus.

Evaluation of relatives at risk: Early diagnosis and treatment of first-degree and second-degree relatives at risk for FH can reduce morbidity and mortality. The genetic status of at-risk family members can be clarified by either: (1) molecular genetic testing if the pathogenic variant(s) has been identified in an affected family member; or (2) measurement of LDL-C concentration. Genetic testing is the preferred method for clarifying the diagnosis in at-risk family members, when possible.

Pregnancy management: Pregnant women should incorporate all the recommended lifestyle changes, including low saturated fat intake, no smoking, and high dietary soluble fiber. Statins are contraindicated in pregnancy because of concerns for teratogenicity and should be discontinued prior to conception. Bile acid-binding resins (e.g., colesevelam) are generally considered safe (Class B for pregnancy), and LDL apheresis is also used occasionally if there is evidence of established CAD. Use of PCSK9 inhibitors, ezetimibe, lomitapide, and bempedoic acid during pregnancy has not been well studied.

Genetic counseling

APOB-, *LDLR*-, and *PCSK9*-related FH are inherited in an autosomal dominant manner. If an individual has biallelic (homozygous or compound heterozygous) pathogenic variants in one of these three genes – a condition referred to as homozygous FH (HoFH) – the presentation becomes more severe with earlier onset of features. Some individuals with FH are heterozygous for pathogenic variants in two different FH-related genes, which may have an additive effect on the severity of FH. Each child of an individual with a heterozygous pathogenic variant in *APOB*, *LDLR*, or *PCSK9* has a 50% chance of inheriting the pathogenic variant and having FH. All children of an individual with homozygous FH will inherit a pathogenic variant and have FH. If the reproductive partner of a proband is heterozygous for an FH-related pathogenic variant in the same gene as the proband or a different FH-related gene, offspring are at risk of inheriting two pathogenic variants and having severe FH.

LDLRAP1-related FH is caused by biallelic pathogenic variants and is inherited in an autosomal recessive manner. The parents of an individual with *LDLRAP1*-related FH are presumed to be heterozygous for one pathogenic variant. If both parents are known to be heterozygous for an *LDLRAP1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Carrier testing for at-risk relatives requires prior identification of the *LDLRAP1* pathogenic variants in the family.

Once the FH-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Familial hypercholesterolemia (FH) should be suspected in individuals with the following findings.

Extreme hypercholesterolemia

- Adults (untreated):
  - Low-density lipoprotein cholesterol (LDL-C) levels >190 mg/dL (>4.9 mmol/L)
  - Total cholesterol levels >310 mg/dL (>8 mmol/L)
- Children/adolescents (untreated):
  - LDL-C levels >190 mg/dL (≥4.9 mmol/L) [Wiegman et al 2015, de Ferranti et al 2019]
  - LDL-C levels >160 mg/dL, particularly when there is a first-degree relative with hyperlipidemia and/or premature coronary artery disease (onset in males age ≤55 years and females ≤65 years) [Wiegman et al 2015, Sturm at al 2018, de Ferranti et al 2019]
  - LDL-C levels >130 mg/dL (>3.4 mmol/L) in those with a first-degree relative with FH [Wiegman et al 2015]
  - Total cholesterol levels >230 mg/dL (>6 mmol/L)

History of premature coronary artery disease (CAD) such as myocardial infarction or obstructive CAD requiring intervention or other cardiovascular disease (e.g., ischemic stroke, peripheral vascular disease). Premature CAD is typically defined as disease identified before age 55 years in males and before age 65 years in females.

Physical examination findings

- Xanthomas (cholesterol deposits in tendons) may be identified in adults but are unlikely to present in children with heterozygous familial hypercholesterolemia (HeFH).

  Note: Xanthomas can present within the first few years of life in those with a more severe phenotype due to biallelic variants [Wiegman et al 2015].

- Xanthelasmas (yellowish, waxy deposits that can occur around the eyelids)
- Corneal arcus (white, gray, or blue opaque ring in the corneal margin as a result of cholesterol deposition) is more likely to be FH-related when present in an individual younger than age 45 years.

Family history of any of the following:

- FH
- Elevated LDL-C levels
- Premature CAD
- Xanthomas/xanthelasmas

Note: (1) Age-specific LDL-C or total cholesterol levels are more specific in determining the likelihood of FH (e.g., >95th percentile for age, sex, and country) [Nordestgaard et al 2013]. (2) Electronic applications (see FH Diagnosis) can assist with the determination of the likelihood of FH based on the formal diagnostic criteria.

Establishing the Diagnosis

The **clinical diagnosis** of FH can be **established** in a proband with features described in Suggestive Findings. Currently three formal diagnostic criteria for FH are widely used in Western countries: the MEDPED Criteria, the Simon Broome Criteria, and the FH Dutch Lipid Clinic Network Criteria. (See Harada-Shiba et al [2012] for criteria used in non-Western countries.) All use various FH-related features to establish the diagnosis (e.g., LDL-C levels, history of CAD, physical examination findings, family history); LDL-C levels are incorporated into all three criteria.

Note: The criteria used to establish the clinical diagnosis of FH in children varies substantially across medical centers within and outside of the United States. Some experts recommend the Simon Broome criteria in pediatric probands rather than the Dutch Lipid Clinic Network Criteria [Wiegman et al 2015].

A **molecular diagnosis** of FH can be **established** in a proband by identification of:

- A heterozygous pathogenic (or likely pathogenic) variant in *LDLR*
- A heterozygous pathogenic (or likely pathogenic) variant in *APOB* (impairing binding of LDL-C to the LDL receptor)
- A heterozygous gain-of-function pathogenic (or likely pathogenic) variant in *PCSK9*

  Note: A whole-gene duplication of *PCSK9* has also been described in individuals with severe FH [Iacocca et al 2018].
- Biallelic loss-of-function pathogenic (or likely pathogenic) variants in *APOB*, *LDLR*, *LDLRAP1*, or biallelic gain-of-function pathogenic (or likely pathogenic) variants in *PCSK9* (associated with severe FH).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a **smaller FH multigene panel** or a **broader dyslipidemia multigene panel** depending on the phenotype:

- A **smaller FH multigene panel** that includes sequence analysis and deletion/duplication analysis of *APOB*, *LDLR*, *LDLRAP1*, and *PCSK9* may be considered.
- A **broader dyslipidemia multigene panel** that includes *APOB*, *LDLR*, *LDLRAP1*, and *PCSK9* as well as *ABCG8*, *ABCG5*, *APOE*, and *LIPA* (genes associated with other lipid conditions that can cause elevated LDL-C levels and early-onset CAD; see Differential Diagnosis) may also be considered. Note: (1) The genes included and the sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Familial Hypercholesterolemia

Gene [1, 2]	Proportion of FH Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4, 5]	Gene-targeted deletion/ duplication analysis [5, 6]
APOB	~5%-10% [7]	100%	None reported
LDLR	>50% [7]	~85% [8]	~15%
LDLRAP1	<1% [9]	>80%	<20%
PCSK9	<1% [7]	~98%	2 families [10]
Unknown	~40% [11]	NA	

FH = familial hypercholesterolemia; NA = not applicable
1. Genes are listed in alphabetic order
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Sturm et al [2018]
8. Sequence analysis of *LDLR* should include the regulatory region (200 bp upstream of the initiation codon).
9. To date, only ~30 *LDLRAP1* pathogenic variants have been identified, and most have been biallelic loss-of-function variants [Fahed & Nemer 2011, Cuchel et al 2014, Hegele 2019, Petrulioniene et al 2019, D'Erasmo et al 2020, Kamar et al 2021, Nikasa et al 2021].
10. Whole-gene duplication was reported in two unrelated families with FH [Iacocca et al 2018].
11. FH disease-causing pathogenic variant(s) can be identified in ~60%-80% of adult probands with a clinical diagnosis of FH. FH disease-causing pathogenic variant(s) can be identified in ~60%-95% of pediatric probands in whom there is a strong clinical suspicion of FH [Sturm et al 2018]. Therefore, in ~40% of individuals with a clinical diagnosis of FH, a genetic cause cannot be identified.

Clinical Characteristics

Clinical Description

Heterozygous Familial Hypercholesterolemia (FH; HeFH)

Elevated low-density lipoprotein cholesterol (LDL-C) leads to atherosclerotic plaque deposition in the coronary arteries and other arterial beds starting at an early age and worsening over time. Individuals with FH have elevated LDL-C levels starting soon after birth. When left untreated, this can lead to an increased risk of angina, myocardial infarction, peripheral artery disease, and potentially stroke [Scientific Steering Committee 1991, Versmissen et al 2008, Elis et al 2011, Raal & Santos 2012]. Individuals with an LDL-C greater than 190 mg/dL (>4.9 mmol/L) and a pathogenic variant in one of the genes listed in Table 1 have a 22-fold increased risk for coronary artery disease (CAD) over the general population, while those without a pathogenic variant have a sixfold increased risk for CAD over the general population [Khera et al 2016]. Natural history studies from the pre-statin era suggest that untreated men are at 50% risk for a fatal or nonfatal coronary event by age 50 years; untreated women are at 30% risk by age 60 years [Slack 1969, Stone et al 1974, Civeira 2004, Goldberg et al 2011, Reiner et al 2011] (Figure 1). Additional studies have found that approximately one in ten individuals with a history of early-onset myocardial infarction have FH, and this risk increased in the setting of a family history of CAD [Singh et al 2019]. Of note, standard Framingham or other risk classification schemes are not applicable to persons with FH [Goldberg et al 2011, Reiner et al 2011, Nordestgaard et al 2013]. The risk of stroke in

individuals with FH is less clear, with some studies finding that this risk may not be as strongly correlated with FH as initially thought [Akioyamen et al 2019, Hovland et al 2019].

Lipid-lowering therapy with statin-based regimens (see Management, Treatment of Manifestations) significantly increases survival [Nordestgaard et al 2013, Vuorio et al 2013] and reduces morbidity [Versmissen et al 2008, Elis et al 2011, Braamskamp et al 2016]. Additional medications such as ezetimibe, bile acid-binding resins, PCSK9 inhibiters, or bempedoic acid are often necessary to achieve optimal LDL-C reduction [Gidding et al 2015]. LDL-C levels are typically unable to be lowered with lifestyle intervention alone.

Xanthomas represent cholesterol buildup in tendons of the body as a result of extremely high levels of LDL-C. Xanthomas may worsen with age in untreated persons. In persons treated with LDL-C-lowering therapy, the xanthomas can become smaller. Common locations:

- Tendonous xanthomas can occur in the elbows, hands, knees, and feet, particularly the Achilles tendon [Tsouli et al 2005, Elis et al 2011]. These are historically described in 30%-50% of persons with FH, although more recent studies show a lower prevalence, likely because of widespread statin use [Perez de Isla et al 2016].
- Interdigital xanthomas (between the fingers) occur in individuals with biallelic pathogenic variants in *APOB*, *LDLR*, or *PCSK9*.

Xanthelasmas are patches of yellowish cholesterol deposits that often occur around the eyes [Dey et al 2013].

Corneal arcus (white, gray, or blue opaque ring in the corneal margin) is caused by abnormal deposition of lipids in the cornea secondary to long-term exposure to elevated LDL-C levels. This feature develops with age and is concerning for FH when identified before age 45 years. Studies have found that this feature may present in an estimated 7%-30% of individuals with FH [Perez de Isla et al 2016, Rizos et al 2018]. It is less likely to be identified in children with heterozygous FH-related pathogenic variants and in individuals who have been on lipid-lowering medications from a young age. This feature does not resolve with treatment.

Homozygous (HoFH) and Autosomal Recessive FH

Individuals with biallelic pathogenic variants (either homozygous or compound heterozygous variants) in *APOB*, *LDLR*, *PCSK9*, or *LDLRAP1* can present with a more severe phenotype that varies by affected gene and residual enzyme function (see Table 2) [McGowan et al 2019].

Phenotype Correlations by Gene

Table 2. Familial Hypercholesterolemia: Phenotype Correlations by Gene

Gene	MOI	Phenotype [1]
APOB	AD	Can be assoc w/↓ LDL-C levels & less severe presentation than *LDLR*-related HeFH
	AR	Rare, w/few persons reported. Presentation is reported to be more similar to *LDLR*-related HeFH, & less severe than *LDLR*-related HoFH (e.g., ↓ LDL-C levels, later onset of CAD).
LDLR	AD	↑ LDL-C often >190 mg/dL, ↑ risk of premature CAD; physical exam findings (e.g., xanthomas) may develop over time.
	AR	• Untreated adults often have LDL-C levels >500 mg/dL (>13 mmol/L). In addition to xanthelasmas & tendonous xanthomas, interdigital xanthomas (between fingers) can also occur & develop in childhood. Most persons develop severe CAD by their mid-20s. The rate of either death or coronary bypass surgery by teen years is high [Raal & Santos 2012]. Severe aortic stenosis is also common [Raal & Santos 2012, Raal et al 2016a, Raal et al 2016b]. • Statins are often relatively ineffective because their efficacy largely depends on upregulation of functional LDL receptors in liver [Raal & Santos 2012]; thus, therapy often requires LDL apheresis in addition to use of multiple other medications, some of which are specifically approved for HoFH, incl PCSK9 inhibitors, lomitapide, & evinacumab (see Management, Treatment of Manifestations).

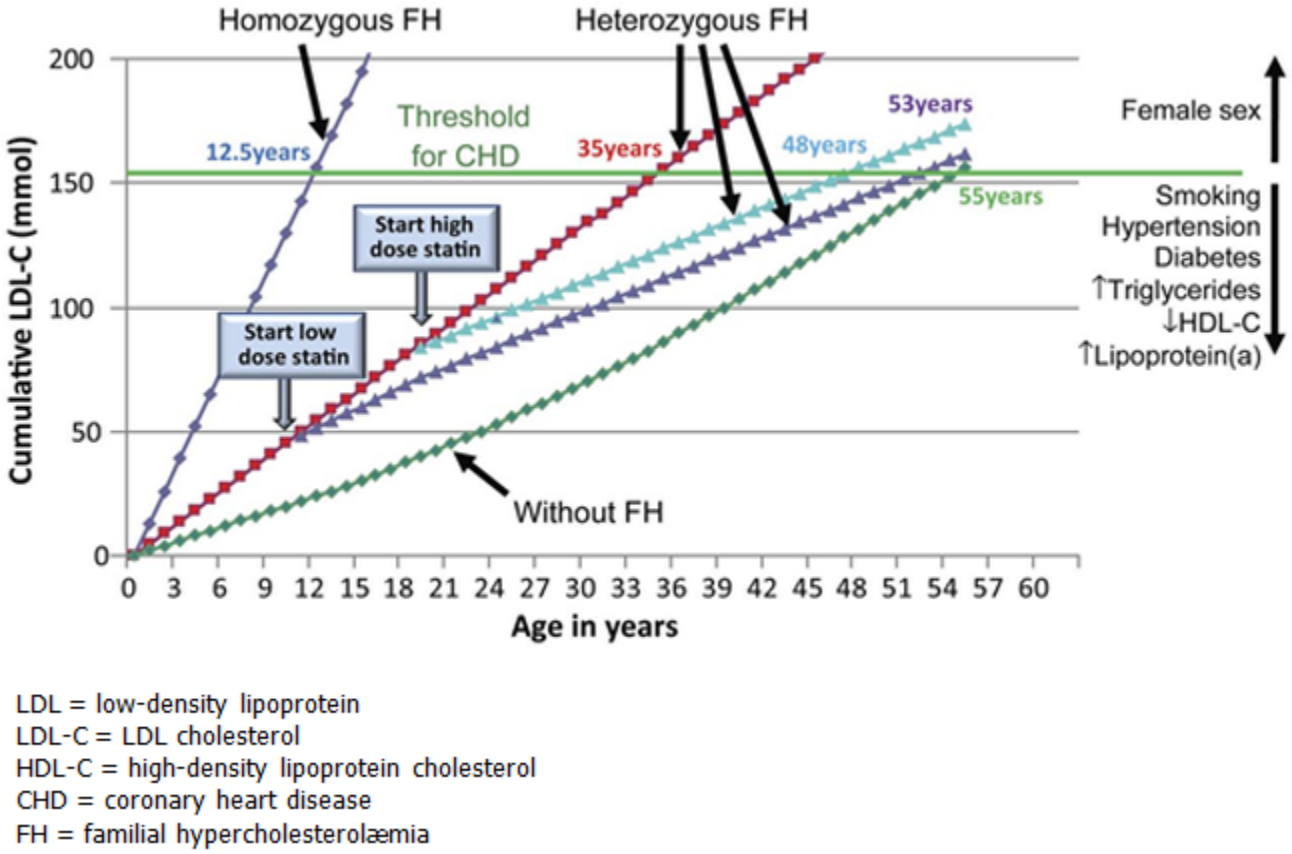

Figure 1. LDL cholesterol burden in individuals with or without familial hypercholesterolemia as a function of the age of initiation of statin therapy

Data derived from Starr et al [2008] and Huijgen et al [2012]. Figure from Nordestgaard et al [2013]; used by permission of Oxford University Press.

Table 2. continued from previous page.

Gene	MOI	Phenotype [1]
LDLRAP1	AR	Presentation similar to *LDLR*-related HoFH incl LDL-C >500 mg/dL, early-onset CAD, & aortic valve stenosis. Planar, tuberous, or tendon xanthomas have also been reported to develop in childhood. Persons have had variable response to lipid-lowering therapies, often requiring >1 &/or requiring LDL apheresis. [2]
PCSK9	AD	• Can be assoc w/↓ LDL-C levels & less severe presentation than *LDLR*-related HeFH • Severe, early-onset FH has been reported in a few persons w/whole-gene duplication [Iacocca et al 2018].
	AR	Rare, w/few persons reported. Presentation reported to be more similar to that of *LDLR*-related HeFH & less severe than *LDLR*-related HoFH (e.g., ↓ LDL-C levels, later onset of CAD).

AD = autosomal dominant; AR = autosomal recessive; CAD = coronary artery disease; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = familial hypercholesterolemia due to biallelic (homozygous or compound heterozygous) pathogenic variants in *APOB, LDLR*, or *PCSK9*; LDL-C = low-density lipoprotein cholesterol; MOI = mode of inheritance

1. Moyer & Baudhuin [2015]

2. Data on *LDLRAP1* variants is still relatively limited and may evolve over time.

Penetrance

APOB. Penetrance for FH may be reduced in persons with a heterozygous *APOB* variant [Doi et al 2021, Kamar et al 2021].

LDLR. Studies report that only 73% of individuals with a heterozygous *LDLR* variant (especially partial loss-of-function variants) have an LDL-C level >130 mg/dL, suggesting lower penetrance than previously proposed [Khera et al 2016].

PCSK9

- Penetrance is approximately 90% in persons heterozygous for the c.381T>A (p.Ser127Arg) pathogenic variant [Dullaart 2017].
- Penetrance in persons heterozygous for the p.Asp374Tyr pathogenic variant is high, with FH manifesting at a young age [Naoumova et al 2005].
- Penetrance for other heterozygous *PCSK9* variants remains largely unknown [Cariou et al 2011].

Nomenclature

While the term "homozygous" is generally used in genetics to denote the presence of the same pathogenic variant in both alleles of a given gene, the term "homozygous FH" or "HoFH" is used in the medical literature to denote the presence of any two pathogenic variants (compound heterozygous or homozygous) on both alleles of *APOB*, *LDLR*, or *PCSK9*.

The term "autosomal recessive FH" refers to FH caused by biallelic pathogenic variants in *LDLRAP1*.

Prevalence

The prevalence of HeFH in the general population was traditionally cited as 1:500; however, data suggest that it may be as high as ~1:250 [Benn et al 2012, Nordestgaard et al 2013]. This prevalence has been primarily based on studies from Europe, North America, East Asia, and Australia. The prevalence of HeFH remains unknown in 90% of countries in the world, including countries in Africa, Asia, and South America [Beheshti et al 2020, Hu et al 2020].

The prevalence of HoFH due to biallelic pathogenic variants in *APOB*, *LDLR*, or *PCSK9* is estimated at 1:160,000 to 1:400,000 [Nordestgaard et al 2013, Cuchel et al 2014, Beheshti et al 2020].

The prevalence of autosomal recessive FH due to biallelic pathogenic variants in *LDLRAP1* is lower than 1:1,000,000 [D'Erasmo et al 2020]. An increased carrier frequency of 1:143 in Sardinia, Italy, for autosomal recessive *LDLRAP1*-related FH is the result of founder variants (see Table 11).

FH is more common in several populations (Table 3) because of founder variants (see Table 11).

Table 3. Prevalence of Familial Hypercholesterolemia in Select Populations

Population	Prevalence [1]
General population	~1:250
French Canadian	1:80 [2, 3]
Old Order Amish	1:10 [4]
Christian Lebanese	1:85
Tunisia	1:165
South African Afrikaner	1:72 to 1:100
South African Ashkenazi Jew	1:67

Table 3. continued from previous page.

Population	Prevalence [1]
Icelandic	1:836 [3]

1. Austin et al [2004]
2. A common >10-kb *LDLR* deletion that includes exon 1 (60% of alleles) and a ~5-kb *LDLR* deletion (5% of alleles) result in a significant increase in LDL-C [Simard et al 2004].
3. Brunham & Hegele [2021]
4. Amish individuals heterozygous for *APOB* variant p.Arg3527Gln (the most common pathogenic variant in the Amish community) have average LDL-C levels below the suggested minimum for a diagnosis of FH. However, coronary artery calcification and atherosclerosis still occur in heterozygous Amish individuals with lower average LDL-C levels [Andersen et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *LDLR* or *LDLRAP1*.

Other phenotypes associated with germline pathogenic variants in *APOB* and *PCSK9* are summarized in Table 4.

Table 4. Allelic Phenotypes

Gene	Phenotype	Pathogenic Variants	Clinical Characteristics
APOB	*APOB*-related familial hypobetalipoproteinemia	Typically truncating biallelic or heterozygous variants	• Homozygous: hepatomegaly, steatorrhea, growth deficiency, deficiency of fat-soluble vitamins, GI, & neurologic dysfunction; plasma total cholesterol, LDL-C, & apo B levels typically <5% for age & sex • Heterozygous: possible risk of liver dysfunction & hepatic steatosis; rarely (~5%-10% of persons), severe nonalcoholic steatosis → cirrhosis
PCSK9	Hypocholesterolemia w/↓ LDL cholesterol (OMIM 603776)	Loss-of-function variants	↑ LDL receptors on surface of liver cells, ↑ removal of LDL-C from blood (& therefore ↓ LDL-C levels) & ↓ risk for CAD.

CAD = coronary artery disease; GI = gastrointestinal

Differential Diagnosis

Genetic conditions with clinical and/or laboratory findings similar to those of familial hypercholesterolemia (FH) are summarized in Table 5.

Table 5. Genetic Disorders with Feature(s) Similar to Those of Familial Hypercholesterolemia

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Similar to FH	Distinguishing from FH
ABCG5 ABCG8	Sitosterolemia	AR	Xanthomas; susceptibility to early-onset CAD. Some persons may present w/↑ plasma cholesterol/LDL-C (often presents in childhood).	Hematologic abnormalities (hemolytic anemia, thrombocytopenia, stomatocytes); xanthomas in childhood (particularly in absence of hyperlipidemia in parents); poor response to statins

Table 5. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Similar to FH	Distinguishing from FH
APOE	p.Leu167del-related AD hypercholesterolemia [1]	AD	Persons may present w/↑ LDL & ↑ risk of CAD.	Splenomegaly, sea-blue histiocytosis, thrombocytopenia, & ↑ triglycerides reported in some p.Leu167del heterozygotes
	Hyperlipoproteinemia type III (familial dysbetalipoproteinemia [FD]) (OMIM 617347)	AR AD [2]	Persons w/predisposing *APOE* variants are at risk of developing xanthomas (more commonly cutaneous & tuberous) & premature CAD. Most common *APOE* genotype assoc w/FD: homozygosity for E2 allele (p.Arg176Cys); however, >30 *APOE* variants have been assoc w/FD. [2]	Persons w/FD are at risk of developing ↑ triglycerides.
CYP27A1	Cerebrotendinous xanthomatosis (CTX)	AR	Xanthomas	Dementia, ataxia, & cataracts; normal LDL-C
LIPA	Lysosomal acid lipase deficiency	AR	↑ LDL-C; risk of CAD	• In infantile onset (Wolman disease): ↑ triglycerides, malnutrition, hepatosplenomegaly, liver disease, adrenal cortical insufficiency • In adult onset (cholesterol-ester storage disease): hepatosplenomegaly &/or ↑ liver enzymes, ↑ triglycerides

AD = autosomal dominant; AR = autosomal recessive; CAD = coronary artery disease; DiffDx = differential diagnosis; FH = familial hypercholesterolemia; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MOI = mode of inheritance

1. Cenarro et al [2016]

2. Khalil et al [2021]

Hypercholesterolemia secondary to acquired conditions including obesity, diabetes mellitus, obstructive liver disease, hypothyroidism, drugs (e.g., steroids), or kidney disease can also be associated with laboratory findings similar to those of FH [Goldberg et al 2011].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with familial hypercholesterolemia (FH), the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Familial Hypercholesterolemia

System/Concern	Evaluation	Comment
Cardiovascular	Measurement of pre-treatment lipid values when possible: TC, LDL-C, HDL-C, triglycerides, lipoprotein(a)	
	Consultation w/lipid specialist or clinician w/expertise in FH	
	Consider noninvasive imaging modalities (e.g., measurement of carotid intima-media thickness) to help inform treatment decisions, esp in those w/HoFH or AR FH.	Recommended in some guidelines [1]
	Eval for concurrent illnesses (kidney disease, obstructive liver disease, acute myocardial infarction, hypothyroidism) that can affect lipid values	
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of FH to facilitate medical & personal decision making

AR = autosomal recessive; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HoFH = FH resulting from biallelic (homozygous or compound heterozygous) pathogenic variants in *APOB, LDLR*, or *PCSK9*; LDL-C = low-density lipoprotein cholesterol; MOI = mode of inheritance; TC = total cholesterol

1. Martin et al [2013]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Adults with FH

All individuals with FH should be considered at high risk for coronary artery disease (CAD) and should be treated actively to lower cholesterol levels. Note that standard Framingham or other risk classification schemes are not applicable [Goldberg et al 2011, Hopkins et al 2011, Stone et al 2014]. The most current recommendations (summarized here) for the management of FH used in the United States are from the American Heart Association [Gidding et al 2015] (full text) and largely reflect earlier recommendations from the National Lipid Association.

Table 7a. Treatment of Manifestations in Adults with Familial Hypercholesterolemia

Manifestation/Concern	Treatment	Considerations/Other
Hyperlipidemia	• Regular physical activity • Healthy diet (↓ saturated fat intake, ↑ intake of soluble fiber to 10-20 g/day) • Weight control &/or weight loss as needed	
	Statin therapy to ↓ LDL-C level by ≥50% or to <100 mg/dL (<2.6 mmol/L). [1] Dose should be titrated every few mos to highest tolerated dose.	Many guidelines suggest a target LDL-C of <100 mg/dL even in those w/o CAD due to lifelong high LDL-C. [2] If there is a history of CAD or stroke, target LDL-C levels should be lower (LDL-C <70 mg/dL).
	Consider referral to lipid specialist w/expertise in FH if LDL-C levels cannot be reduced by ≥50% or to <100 mg/dL w/maximal medical therapy over 6 mos.	

Table 7a. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
	Addl treatments if targeted LDL-C level is not achieved: • Ezetimibe • Bile acid sequestrants • PCSK9 inhibitors • Bempedoic acid	The potential benefit of multidrug regimens should be weighed against ↑ cost & potential for adverse effects & ↓ adherence. Note: Niacin was used historically but is generally not favored before other options (Table 7b) have been exhausted.
	More aggressive treatment may be needed in those w/the following CAD risk factors: • Clinically evident CAD or other atherosclerotic CVD; goal is LDL-C level of <70 mg/dL (<1.8 mmol/L) • Diabetes mellitus or metabolic syndrome • Family history of very early CAD (CAD diagnosed in men age <45 yrs; women age <55 yrs) • Current smoking • High lipoprotein(a) (≥50 mg/dL [≥1.3 mmol/L] using an isoform-insensitive assay)	
CVD / Compounding risk factors	• Consider low-dose aspirin (75-81 mg/day) in those w/ CAD, prior stroke, or at high risk for CAD or stroke. • Smoking cessation • Measure serum lipoprotein(a).	
	• Treatment for diabetes mellitus • Treatment of hypertension	Treat blood pressure to 140/90 mm Hg (or 130/80 mm Hg in those w/diabetes mellitus).

CAD = coronary artery disease; CVD = cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol

1. Hopkins et al [2011], Nordestgaard et al [2013]

2. Gidding et al [2015]

Table 7b. Current Recommended Drug Therapies for Adults with Familial Hypercholesterolemia

Class	Primary (1^O) and Secondary (2^O) Mechanism of Action	LDL-Lowering Response
Statins	↑ LDLR activity (1^O) Inhibition of cholesterol biosynthesis through HMG-CoA reductase	50% [1, 2]
Cholesterol absorption inhibitors (ezetimibe)	↓ cholesterol absorption (1^O) ↑ LDLR activity (2^O)	15% [1, 3]
MTP inhibitor (lomitapide) [4]	↓ microsomal triglyceride transfer protein activity (1^O) Inhibition of LDL production (2^O)	50% [5]
PCSK9 inhibitors (alirocumab, evolocumab, inclisiran)	↓ LDLR degradation	50% [6]
Bile acid sequestrants (cholestyramine, colesevelam)	↓ bile acid reabsorption (1^O) ↑ LDLR activity (2^O)	15% [1, 3]
Stanol esters	↓ cholesterol absorption (1^O) ↑ LDLR activity (2^O)	10% [1, 3]
Bempedoic acid	↑ LDLR activity (1^O) Inhibition of cholesterol biosynthesis by inhibiting ATP-citrate lyase	15%

Table 7b. continued from previous page.

Class	Primary (1^{O}) and Secondary (2^{O}) Mechanism of Action	LDL-Lowering Response
Evinacumab [4]	Inhibition of ANGPTL3, which results in ↑ lipoprotein lipase activity ↓ VLDL	50%

Some guidelines call for the addition of n-3 polyunsaturated fatty acids or fibrates if triglycerides remain elevated after the LDL-C level is controlled.

LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor

1. Often ineffective in HoFH due to biallelic pathogenic variants in *APOB, LDLR*, or *PCSK9*.

2. Kastelein et al [2008]

3. Rader et al [2003]

4. Approved only for HoFH

5. Cuchel et al [2014]

6. Raal & Santos [2012]

7. Approved only for adults with HoFH [Rosenson et al 2020]

Children with FH

Guidelines for the management of children have been published by multiple national and international organizations [DeMott et al 2008, Descamps et al 2011, Martin et al 2013, de Ferranti et al 2019] (see Published Guidelines / Consensus Statements).

Table 7c. Treatment of Manifestations in Children with Familial Hypercholesterolemia

Manifestation/Concern	Treatment	Considerations/Other
Hyperlipidemia	• Regular physical activity & limited screen time • Healthy diet: high in fiber, low in saturated fat (≤7% of calories), avoidance of trans fats, <200 mg/day of dietary cholesterol • Maintenance of healthy weight	
	Statin therapy as first-line agent for most children [1] • Children w/LDL-C ≥190 mg/dL [2] • In children w/LDL-C 130-189 mg/dL, the initiation of statins depends on assessment of family history, risk factors, & comorbidities.	• Pharmacotherapy is typically considered as early as age 10 yrs, but statins may be used as early as age 8 yrs. • Some experts recommend target LDL-C of ≤130 mg/dL or a 50% reduction. [3] Others rely on adult LDL-C targets for severe FH of <100 mg/dL. [4]
	Consider additional lipid-lowering therapy (ezetimibe, evolocumab, & bile acid sequestrants) if target LDL-C is not achieved w/lifestyle modification & statins.	
	Referral to lipid specialist w/expertise in FH if LDL-C remains ≥130 mg/dL after treatment [2]	

Table 7c. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Compounding risk factors	Cessation of smoking & exposure to secondhand smoke	
	Consider measurement of serum lipoprotein(a).	Some experts recommend this, but the practice is not universal. [3, 5]
	• Treatment for diabetes mellitus • Treatment of hypertension	See AHA scientific statement on cardiovascular risk reduction in high-risk children. [3]

FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol
1. The safety and efficacy of statins in children is supported by clinical trial data and by long-term observational data [Kusters et al 2014, Luirink et al 2019, Vuorio et al 2019].
2. NHLBI [2011]
3. de Ferranti et al [2019]
4. Grundy et al [2019]
5. Wiegman et al [2015]

Children and Adults with HoFH

National Lipid Association guidelines for severe FH (also referred to as HoFH; see Nomenclature) due to biallelic pathogenic variants in *APOB, LDLR*, or *PCSK9* have been published (full text).

Table 7d. Treatment of Manifestations in Children and Adults with Severe Familial Hypercholesterolemia (HoFH)

Manifestation/Concern	Treatment	Considerations/Other
Hyperlipidemia	• Referral to lipid specialist w/expertise in FH • Multi-drug therapy usually required (See Table 7b.)	
	Evolocumab, alicrocumab (PCSK9 inhibitors)	• 40% mean reduction in LDL-C compared w/placebo; however, persons w/biallelic loss-of-function variants saw no response. [1] • To date, only evolocumab has been approved for children w/FH & HoFH. [2]
	In those w/some residual LDLR activity: • High-dose statins • Ezetimibe • Bile acid-binding resins	Medications that target the LDLR may be ineffective in persons w/biallelic loss-of function *LDLR* pathogenic variants.
	Lomitapide	Effective even w/complete loss of LDLR function; though not formally FDA approved for children, should strongly be considered.
	Evinacumab (ANGPTL3 inhibitor) [3]	• Recombinant human monoclonal antibody that binds to & inhibits ANGPTL3 • Available for adults & children ≥12 yrs w/HoFH • Used in conjunction w/other lipid-lowering therapies
	LDL apheresis (≤2x/wk) is often required from a young age.	Apheresis can ↓ LDL-C levels by 80% acutely & 30% chronically (weekly or biweekly). Apheresis is offered at a limited number (~40-50) of centers in the US.
	Liver transplantation	Used in rare cases in some centers [4]

Table 7d. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Atherosclerotic CVD	Severe FH can lead to clinical manifestations of atherosclerosis (incl myocardial infarction) in childhood. Children & adults w/clinical atherosclerotic CVD should be evaluated & treated by cardiovascular specialists.	

CVD = cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor
1. Raal et al [2015]
2. REPATHA (evolocumab) prescribing information (pdf)
3. Rosenson et al [2020]
4. Martinez et al [2016]

Prevention of Primary Manifestations

To prevent primary manifestations, the following are recommended:

- Reduce saturated fat intake.
- Increase intake of soluble fiber to 10-20 g/day.
- Increase physical activity.
- Do not smoke.

Surveillance

During treatment, individuals of any age with:

- FH should have lipid levels monitored as recommended;
- Severe FH (HoFH due to homozygous or compound heterozygous pathogenic variants in *APOB*, *LDLR*, or *PCSK9*, or autosomal recessive FH due to homozygous or compound heterozygous pathogenic variants in *LDLRAP1*) should be monitored with various imaging modalities (including echocardiogram, CT angiogram, and cardiac catheterization) as recommended [Raal & Santos 2012].

Additional recommended evaluations include those in Table 8.

Table 8. Recommended Surveillance in Individuals with Familial Hypercholesterolemia

System/Concern	Evaluation	Comment
Cardiovascular	Measurement of lipid levels: TC, LDL-C, HDL-C, triglycerides, lipoprotein(a)	• In children: Begin at age 2 yrs & monitor closely. At a minimum reassess cholesterol levels between age 9-11 yrs. [1] Some experts advocate for screening children for ↑ lipoprotein(a), but this practice is not universal. [1, 2] • In adults: The interval of follow-up testing TBD by care team & based on presence of other risk factors
	Consider noninvasive imaging modalities (e.g., measurement of carotid intima-media thickness) to help inform treatment decisions.	In children: Currently, the routine use of imaging (e.g., measurement of carotid intima-media thickness) is not recommended.
	Identify modifiable risk factors: smoking, sedentary behavior, hypertension, diabetes, & obesity.	

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TBD = to be determined; TC = total cholesterol

1. de Ferranti et al [2019]

2. Wiegman et al [2015]

Agents/Circumstances to Avoid

The following should be avoided:

- Smoking
- High intake of saturated and trans unsaturated fat
- Sedentary lifestyle
- Obesity
- Hypertension
- Type II diabetes mellitus

Evaluation of Relatives at Risk

The CDC has classified FH as a Tier 1 condition, indicating a significant benefit from performing family-based cascade screening. Cholesterol testing, with or without molecular testing in relatives of affected persons with FH, can be used to identify individuals with FH and provide them with lifesaving treatment. Early diagnosis and treatment of relatives at risk for FH can reduce morbidity and mortality [Knowles et al 2017, Sturm et al 2018].

The genetic status of at-risk family members can be clarified by EITHER of the following:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Measurement of low-density lipoprotein cholesterol (LDL-C) level if the pathogenic variant(s) in the family are not known.

In children with a family history of FH, non-fasting lipid level should be measured by age two years. If lipid level is borderline, measure LDL-C level. An LDL-C level of >130 mg/dL in a child is suspicious for FH in the setting of a known family history of FH, and an LDL-C level of >160 mg/dL is relatively specific for FH.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnant women should incorporate all the other recommended lifestyle changes, including low saturated and trans unsaturated fat intake, no smoking, and high dietary soluble fiber intake.

Pharmacologic treatment during pregnancy:

- Statins are contraindicated in pregnancy because of concerns for teratogenicity; women with FH who are considering a pregnancy should be counseled of this risk and statins should be discontinued prior to conception. The use of statins during human pregnancy has not been definitively associated with adverse fetal outcome; however, the role of cholesterol in embryologic development has led to theoretic concerns about the effect of these medications on a developing fetus and a recommendation that alternative medications be considered during pregnancy and lactation. Nursing mothers should not take statins.
- Bile acid-binding resins (colesevelam, cholestyramine) are generally considered safe (Class B for pregnancy). Based primarily on animal studies, cholestyramine use during pregnancy has not been associated with an increased risk of fetal anomalies. However, use of cholestyramine could theoretically cause depletion of maternal fat-soluble vitamins, including vitamin K.
- LDL apheresis is also occasionally used.
- Use of PCSK9 inhibitors, ezetimibe, lomitapide, and bempedoic acid during pregnancy has not been well studied.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

APOB-, *LDLR*-, and *PCSK9*-related familial hypercholesterolemia (FH) are inherited in an autosomal dominant manner. If an individual has biallelic (homozygous or compound heterozygous) pathogenic variants in one of these three genes – a condition referred to as homozygous FH or HoFH – the presentation becomes more severe with earlier onset of features. The spectrum of severity in HoFH depends on the genes affected and impact of the pathogenic variant on protein function [Trinder et al 2020a, Trinder et al 2020b]. Some individuals with FH are heterozygous for pathogenic variants in two different FH-related genes, which may have an additive effect on the severity of FH [Kamar et al 2021].

LDLRAP1-related FH (reported to have a presentation similar to *LDLR*-related HoFH) is caused by biallelic pathogenic variants and is inherited in an autosomal recessive manner.

APOB-, *LDLR*-, and *PCSK9*-Related FH – Risk to Family Members

Parents of a proband

- Almost all individuals with FH resulting from a heterozygous pathogenic variant in *APOB*, *LDLR*, or *PCSK9* have an affected parent.

- The proportion of probands with FH who have a *de novo* pathogenic variant is unknown but appears to be very low.
- Recommendations for the parents of the proband include the following:
  - Measurement of cholesterol (recommended for both the parents of a proband with a known *APOB*, *LDLR*, or *PCSK9* pathogenic variant or with a clinical diagnosis of FH in the absence of a known FH-causing pathogenic variant) [Knowles et al 2017] (See Management, Evaluation of Relatives at Risk.)
  - Targeted molecular genetic testing if an *APOB*, *LDLR*, or *PCSK9* pathogenic variant has been identified in the proband
- If the proband has a known pathogenic variant that is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- Although most individuals diagnosed with FH have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, lack of knowledge regarding family member's cholesterol levels and heart disease history, or late onset of the disorder in the affected parent. If heterozygous family members have been on statins for many years, there may not be a prominent family history of premature CAD. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.
- The parents of an individual with biallelic pathogenic variants in *APOB*, *LDLR*, or *PCSK9* are obligate heterozygotes and are thus presumed to have FH [Mabuchi et al 2014].

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If one parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of having FH is 50%.
- If both parents of the proband are affected with FH and are known to have an FH-related pathogenic variant, there is a 50% risk that sibs will inherit one pathogenic variant and have FH, a 25% risk that sibs will inherit two pathogenic variants and have severe FH, and a 25% chance that sibs will inherit neither of the familial pathogenic variants.

  The severity of HoFH varies. HoFH caused by homozygous loss-of-function *LDLR* pathogenic variants is typically associated with the most severe presentation, followed by HoFH caused by compound heterozygous *LDLR* pathogenic variants [Cuchel et al 2014, Bertolini et al 2020].
- If the proband has a known FH-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. All sibs should undergo predictive genetic testing and cholesterol screening.
- If the parents are clinically unaffected but their genetic status is unknown, sibs should still be considered at risk for FH because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism. All sibs should undergo predictive genetic testing and cholesterol screening.

Offspring of a proband

- Each child of an individual with FH caused by a heterozygous pathogenic variant in *APOB*, *LDLR*, or *PCSK9* has a 50% chance of inheriting the pathogenic variant and having FH.

- All children of an individual with HoFH (i.e., biallelic FH-related pathogenic variants) will inherit a pathogenic variant and have FH.
- If the reproductive partner of a proband is heterozygous for an FH-related pathogenic variant in the same gene as the proband or a different FH-related gene, offspring are at risk of inheriting two pathogenic variants and having severe FH. Cholesterol screening – followed by genetic counseling and genetic testing if cholesterol levels and family history are concerning for FH – should be offered to the reproductive partner to assess this risk. (FH is more common in several populations [see Prevalence] as a result of founder variants.)

Other family members. The risk to other family members depends on the status of the proband's parents: if one or both parents have an FH-related pathogenic variant, sibs and parents of the proband's parents are at 50% risk of having a pathogenic variant and, thus, FH.

LDLRAP1-Related Autosomal Recessive FH – Risk to Family Members

Parents of a proband

- The parents of an individual with *LDLRAP1*-related FH are presumed to be heterozygous for one pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *LDLRAP1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous (i.e., the same two) pathogenic variants, additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Individuals who are heterozygous for an *LDLRAP1* pathogenic variant (i.e., carriers) are typically asymptomatic.

Sibs of a proband

- If both parents are known to be heterozygous for an *LDLRAP1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Individuals who are heterozygous for an *LDLRAP1* pathogenic variant (i.e., carriers) are typically asymptomatic.

Offspring of a proband

- The offspring of an individual with *LDLRAP1*-related FH are obligate heterozygotes (carriers) for a pathogenic variant in *LDLRAP1* (individuals who are heterozygous for an *LDLRAP1* pathogenic variant are typically asymptomatic).
- If the reproductive partner of a proband is heterozygous for an *LDLRAP1* pathogenic variant, offspring are at risk of inheriting biallelic pathogenic variants and having *LDLRAP1*-related FH. Genetic counseling and genetic testing can be offered to the reproductive partner to assess this risk.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *LDLRAP1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *LDLRAP1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family-based cascade screening. The CDC has classified FH as a Tier 1 condition, indicating a significant benefit from performing family-based cascade screening. Cholesterol testing, with or without molecular testing in relatives of affected persons with FH, can be used to identify individuals with FH and provide them with lifesaving treatment. Early diagnosis and treatment of relatives at risk for FH can reduce morbidity and mortality [Knowles et al 2017, Sturm et al 2018].

Predictive genetic testing for asymptomatic family members at risk for FH requires prior identification of the pathogenic variant(s) in the family. If the FH-related pathogenic variant(s) in the family are known, it is recommended that all first-degree family members be offered predictive genetic testing.

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- Young women with FH should receive counseling regarding contraindications of lipid-lowering therapies during pregnancy (see Management, Pregnancy Management).
- The proband's reproductive partner should be offered cholesterol screening, followed by genetic counseling and genetic testing if cholesterol levels and family history are concerning for FH. Ideally, this should be offered prior to conception to assess the risk of having a child with HoFH.
- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the FH-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **British Heart Foundation**
  Familial Hypercholesterolaemia

- **FH Australasia Network**
  AAS Secretariat
  Phone: 61 3 5967 4479
  Fax: 61 3 9015 6409
  Email: aas@meetingsfirst.com.au
  www.athero.org.au/FH

- **FH Foundation**
  959 East Walnut Street
  Suite 220
  Pasadena CA 91106
  Phone: 626-583-4674
  Email: info@thefhfoundation.org
  www.thefhfoundation.org

- **FH Norway, Norwegian FH Patient Organization**
  www.f-h.no

- **FH Portugal, Portuguese FH Patient Organization**
  www.fhportugal.pt

- **FHChol Austria**
  Austria
  Phone: 43 (0) 677 6307 46 6
  Email: info@fhchol.at
  www.fhchol.at

- **Fundación Hipercolesterolemia Familiar**
  Spain
  Phone: 91 504 22 06; 91 557 00 71
  Fax: 91 504 22 06
  Email: info@colesterolfamiliar.org
  www.colesterolfamiliar.org

- **German FH Patient Organization**
  Germany
  www.cholco.org

- **International FH Foundation**
  Wien
  Austria
  Phone: 0664 653 59 32
  Email: info@fhchol.at
  www.fhchol.at

- **MedlinePlus**
  Familial hypercholesterolemia

- **Preventive Cardiovascular Nurses Association**
  PCNA National Office
  613 Williamson Street
  Suite 200

Madison WI 53703
Phone: 608-250-2440
www.pcna.net

- **HEART UK**
  United Kingdom
  Phone: 0845 450 5988
  Email: ask@heartuk.org.uk
  www.heartuk.org.uk
- **Japan Atherosclerosis Society**
  Japan
  www.j-athero.org
- **Learn Your Lipids**
  www.learnyourlipids.com
- **National Lipid Association (NLA)**
  6816 Southpoint Parkway
  Suite 1000
  Jacksonville FL 32216
  Phone: 904-998-0854
  Fax: 904-998-0855
  www.lipid.org
- **CASCADE FH Registry**
  CASCADE FH Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Familial Hypercholesterolemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
APOB	2p24.1	Apolipoprotein B-100	APOB database	APOB	APOB
LDLR	19p13.2	Low-density lipoprotein receptor	LDLR @ LOVD	LDLR	LDLR
LDLRAP1	1p36.11	Low density lipoprotein receptor adapter protein 1	The low density lipoprotein receptor adaptor (LDLRAP1) gene LDLRAP1 @ LOVD	LDLRAP1	LDLRAP1
PCSK9	1p32.3	Proprotein convertase subtilisin/kexin type 9	PCSK9 @ LOVD	PCSK9	PCSK9

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Familial Hypercholesterolemia (View All in OMIM)

107730	APOLIPOPROTEIN B; APOB
143890	HYPERCHOLESTEROLEMIA, FAMILIAL, 1; FHCL1
144010	HYPERCHOLESTEROLEMIA, FAMILIAL, 2; FHCL2
603776	HYPERCHOLESTEROLEMIA, FAMILIAL, 3; FHCL3
603813	HYPERCHOLESTEROLEMIA, FAMILIAL, 4; FHCL4
605747	LOW DENSITY LIPOPROTEIN RECEPTOR ADAPTOR PROTEIN 1; LDLRAP1
606945	LOW DENSITY LIPOPROTEIN RECEPTOR; LDLR
607786	PROPROTEIN CONVERTASE, SUBTILISIN/KEXIN-TYPE, 9; PCSK9

Molecular Pathogenesis

LDLR encodes low-density lipoprotein receptor (LDLR), a cell surface protein involved in endocytosis of low-density lipoprotein cholesterol (LDL-C). After LDL-C is bound at the cell membrane, it is taken into the cell and to lysosomes where the protein moiety is degraded and the cholesterol molecule suppresses cholesterol synthesis via negative feedback. Pathogenic variants in *LDLR* usually either reduce the number of receptors produced within the cells or disrupt the ability of the receptor to bind LDL-C, resulting in high levels of plasma LDL-C.

APOB encodes apolipoprotein B-100. *APOB* pathogenic variants alter the ability of apolipoprotein B-100 to effectively bind LDL-C to LDLR on the cell surface, causing fewer LDL-C particles to be removed from the blood.

The PCSK9 protein product binds to LDLRs and promotes their degradation in intracellular acidic compartments. Pathogenic variants in *PCSK9* have been associated both with hypercholesterolemia and hypocholesterolemia. Gain-of-function pathogenic variants cause hypercholesterolemia by excessive degradation of LDLRs, reducing the amount of LDL-C removed from the blood. Loss-of-function pathogenic variants cause hypocholesterolemia (reduced blood cholesterol levels) by increasing the number of LDLRs on the surface of liver cells, resulting in a quicker-than-usual removal of LDL-C from the blood and reduced incidence of coronary artery disease [Cohen et al 2006, Pandit et al 2008].

The LDLRAP1 protein plays an important role in moving LDLRs and their attached LDL particles into the liver cells for recycling. Biallelic loss-of-function *LDLRAP1* variants have been the primary disease mechanism reported and inhibit the removal of LDL-C from the blood [D'Erasmo et al 2020].

Table 9. Familial Hypercholesterolemia: Mechanism of Disease Causation

Gene [1]	Mechanism of Disease Causation
APOB	Loss-of-function variants that typically impair LDL-C binding to the LDLR
LDLR	Loss of function
LDLRAP1	Loss of function; however, may change over time, as data on variants in this gene are currently limited.
PCSK9	Gain of function

1. Genes from Table 1 in alphabetic order

Table 10. Familial Hypercholesterolemia: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
APOB	Intron distribution w/in *APOB* is unusual: 24 of the 29 introns occur in the 5' terminus. >50% of the protein is encoded by 7,572-bp exon 26, 1 of the largest exons reported in the human genome. 1 of the 2 main isoforms, apolipoprotein B-100, synthesized exclusively in the liver, is responsible for complications related to FH [Whitfield et al 2004].
LDLR	Exon 4 encodes LDLR type A repeats 3, 4, & 5, located in the ligand-binding domain. This region is considered a hot spot & has been reported to have the most disease-causing variants per nucleotide. Exons 2-8 & exon 14 contain a total of 60 highly conserved cysteine residues that are vital for proper protein folding & function [Chora et al 2022].
PCSK9	*PCSK9* pathogenic variants are assoc w/both hypercholesterolemia & hypocholesterolemia. Gain-of-function pathogenic variants cause hypercholesterolemia by excessive degradation of LDLRs, ↓ing the amount of LDL-C removed from blood. Loss-of-function pathogenic variants cause hypocholesterolemia by ↑ing the number of LDLRs on the surface of liver cells, resulting in ↑ed removal of LDL-C from blood & ↓ed incidence of coronary artery disease [Cohen et al 2006, Pandit et al 2008].

1. Genes from Table 1 in alphabetic order

Table 11. Familial Hypercholesterolemia: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change (Alias [2])	Predicted Protein Change (Alias [2])	Comment [Reference]
APOB	NM_000384.3 NP_000375.3	c.10580G>A [3] (9775G>A)	p.Arg3527Gln (Arg3500Gln)	Founder variant in Amish; common variant in persons of European ancestry [Shen et al 2010]
		c.10579C>T (9774C>T)	p.Arg3527Trp (Arg3500Trp)	Common variant in Asian populations [Calandra et al 2011]
LDLR	NM_000527.5 NP_000518.1	c.655_657delGGC	p.Gly219del	Founder variant in Ashkenazi Jews; 1:67 Ashkenazi Jewish from Lithuania are heterozygous [Durst et al 2001].
		c.564C>G	p.Tyr188Ter	Common variant in Druze of Golan Heights [Landsberger et al 1992]
		c.925_931delCCCATCA	p.Pro309LysfsTer59	Founder variants in Finnish population [Lahtinen et al 2015]
		c.1784G>A	p.Arg595Gln	
	NG_009060.1	g.39215_47749del8535	--	
		>10-kb del [2] [incl exon 1]	--	Founder variant in French Canadians [Hobbs et al 1987]
LDLRAP1	NM_015627.3 NP_056442.2	c.431dupA (c.432_433insA)	p.His144GlnfsTer27	Founder variant in Sardinians [Fellin et al 2015]
		c.65G>A	p.Trp22Ter	
PCSK9	NM_174936.4 NP_777596.2	c.381T>A	p.Ser127Arg	Penetrance is ~90% in heterozygotes [Dullaart 2017].
		c.1120G>T	p.Asp374Tyr	Penetrance is high, w/onset at young age in heterozygotes [Naoumova et al 2005].

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Genes from Table 1 in alphabetic order

2. Variant designation that does not conform to current naming conventions. In this case, numbering is based on mature peptide before cleavage of signal peptide and corresponding nucleotides.

3. rs5742904

Chapter Notes

Author Notes

Dr Knowles is a physician-scientist, and the overall theme of his research is the genetic basis of cardiovascular disease, with contributions across the continuum from discovery to the development of model systems to the translation of these findings to the clinic and most recently to the public health aspect of genetics. Currently his discovery and basic translational efforts center on understanding the genetic basis of insulin resistance using GWAS studies coupled with exploration in model systems including standard cell lines, induced pluripotent stem cells and murine models. These efforts are funded through the NIH. His clinical translational focus is on the intersection of lipids and insulin resistance, particularly defining how statins increase the risk of diabetes (Doris Duke Foundation grant). His clinical role at Stanford is as a lipidologist and director of the Familial Hypercholesterolemia (FH) clinic, where they provide world-class care to individuals with FH and related lipid disorders. His interest in FH has led him to explore innovative ways of addressing the major public health impact of this genetic condition. As the volunteer Chief Medical Advisor of the FH Foundation (a patient-led research and advocacy organization), he led the FH Foundation's efforts to establish a national patient registry for FH (CASCADE FH) and apply for an ICD10 code for FH. He has used cutting-edge "big-data" approaches to identify previously undiagnosed FH patients in electronic medical records (the FIND FH project, partly funded by the AHA).

Hannah Ison is a licensed Cardiovascular Genetic Counselor at the Stanford Center for Inherited Cardiovascular Disease. In her role she primarily specializes in caring for patients and families with inherited dyslipidemias and has been actively involved in efforts to identify and care for individuals at risk for familial hypercholesterolemia (FH) for close to five years. She works with both adult and pediatric patients and has assisted with and managed the development of the Pediatric Lipid Clinic at Stanford Children's Hospital. Additionally, she is a member of the National Society of Genetic Counselors and is co-chair of the Dyslipidemia Working Group through this organization.

Shoa Clarke is a preventive cardiologist and a geneticist. He is boarded in internal medicine, pediatrics, and cardiovascular medicine. He cares for adults, children, and families with genetic risk factors for cardiovascular disease, including familial hypercholesterolemia.

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