



## Familial Hypercholesterolemia

Synonyms: Familial Hypercholesterolæmia; Hypercholesterolemia, Autosomal Dominant; Hyperlipoproteinemia Type IIA

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### Summary

#### Clinical characteristics

Familial hypercholesterolemia (FH) is characterized by severely elevated LDL cholesterol (LDL-C) levels that lead to atherosclerotic plaque deposition in the coronary arteries and proximal aorta at an early age, leading to an increased risk for cardiovascular disease. Xanthomas (patches of yellowish cholesterol buildup) may worsen with age as a result of extremely high cholesterol levels. Xanthomas can occur around the eyelids and within the tendons of the elbows, hands, knees, and feet. In FH, the more common cardiovascular disease is coronary artery disease (CAD), which may manifest as angina and myocardial infarction; stroke occurs more rarely. Untreated men are at a 50% risk for a fatal or nonfatal coronary event by age 50 years; untreated women are at a 30% risk by age 60 years.

An estimated 70%-95% of FH results from a heterozygous pathogenic variant in one of three genes (*APOB*, *LDLR*, *PCSK9*). FH is the most common inherited cardiovascular disease, with a prevalence of 1:200-250. FH likely accounts for 2%-3% of myocardial infarctions in individuals younger than age 60 years.

In contrast, homozygous FH (HoFH) results from biallelic (homozygous or compound heterozygous) pathogenic variants in one of these known genes (*APOB*, *LDLR*, *PCSK9*). Most individuals with HoFH experience severe CAD by their mid-20s and the rate of either death or coronary bypass surgery by the teenage years is high. Severe aortic stenosis is also common.

#### Diagnosis/testing

Several formal diagnostic criteria exist for FH. The diagnostic criteria most widely used in Western countries include: extreme hypercholesterolemia (untreated adults with LDL-C >190 mg/dL or total cholesterol levels >310 mg/dL; untreated children/adolescents with LDL-C levels >160 mg/dL or total cholesterol levels >230 mg/dL); history of premature CAD or other CVD; xanthomas; corneal arcus; and a family history of features suggestive

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of FH. The diagnosis of FH can also be established by identification of a heterozygous pathogenic variant in one of the three genes (*APOB*, *LDLR*, and *PCSK9*) known to be associated with FH.

The diagnosis of HoFH can be established in a proband by identification of biallelic pathogenic variants in one of the three genes (*APOB*, *LDLR*, and *PCSK9*) known to be associated with FH.

## Management

*Treatment of manifestations:* Adults with FH: 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; pharmacotherapy (statins with additional medications as needed) to reduce lipid levels; referral to a lipid specialist if necessary to reduce LDL-C levels. Children with FH: referral to a lipid specialist; diet and lifestyle modifications; statins can be used in children starting around age eight years. Children and adults with HoFH: referral to a lipid specialist or specialized center for management of multiple drug therapy; LDL apheresis is often required; liver transplantation in rare circumstances.

*Prevention of primary manifestations:* Statin-based therapy with addition of other medications as needed, in combination with a heart-healthy diet (including reduced intake of saturated fat and increased intake of soluble fiber to 10-20 g/day); increased physical activity; not smoking.

*Surveillance:* Children with an established diagnosis of FH or risk factors for FH (e.g., elevated serum cholesterol, a family history of FH, a family history of premature CAD or other CVD) should have lipid levels checked before age ten years. All individuals with FH should have lipid levels monitored as recommended. Individuals with HoFH should be monitored with various imaging modalities (including echocardiograms, CT angiograms, and cardiac catheterization) as recommended.

*Agents/circumstances to avoid:* Smoking, high intake of saturated and trans unsaturated fat, excessive intake of cholesterol, 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 has been identified in an affected family member; or (2) measurement of LDL-C concentration.

*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 due to concerns for teratogenicity and should be discontinued prior to conception. Bile acid binding resins (e.g., colestevlam) are generally considered safe (Class B for pregnancy), and LDL apheresis is also occasionally used if there is evidence of established CAD.

## Genetic counseling

Heterozygous familial hypercholesterolemia (FH) and homozygous familial hypercholesterolemia (HoFH) are inherited in an autosomal dominant manner.

Almost all individuals diagnosed with FH have an affected parent; the proportion of FH caused by a *de novo* pathogenic variant is unknown but appears to be extremely low. Each child of an individual with FH has a 50% chance of inheriting the pathogenic variant.

If both parents have FH, each child has a 50% chance of having FH, a 25% chance of having HoFH, and a 25% chance of not having FH.

If the pathogenic variant has been identified in a family member with FH (or if both pathogenic variants have been identified in a family member with HoFH), prenatal testing for pregnancies at increased risk is possible.

## GeneReview Scope

### Familial Hypercholesterolemia: Included Phenotypes

- Familial hypercholesterolemia (FH, also referred to as heterozygous FH or HeFH)
- Homozygous hypercholesterolemia (HoFH)

## Diagnosis

In this *GeneReview*:

- Familial hypercholesterolemia (FH) refers to hypercholesterolemia resulting from a heterozygous pathogenic variant in one of several genes (*APOB*, *LDLR*, and *PCSK9*); it is also referred to as heterozygous FH (HeFH). FH is a relatively common disorder (prevalence 1:200-1:250).
- Homozygous FH (HoFH) refers to familial hypercholesterolemia resulting from biallelic (including true homozygous and compound heterozygous) pathogenic variants in one of these same genes (*APOB*, *LDLR*, and *PCSK9*). HoFH is much rarer than FH (prevalence 1:160,000 to 1:250,000 [Nordestgaard et al 2013, Cuchel et al 2014]).

## 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 >130 mg/dL (>3.4 mmol/L)
    - Total cholesterol levels >230 mg/dL (>6 mmol/L)
- History of premature coronary artery disease (CAD) or other cardiovascular disease (CVD) (e.g., angina pectoris, myocardial infarction, peripheral vascular disease)
- Physical examination findings (e.g., xanthomas, corneal arcus)
- Family history of premature CAD and/or CVD

## Establishing the Diagnosis

Currently three formal diagnostic criteria for FH are widely used in Western countries. (See Harada-Shiba et al [2012] for criteria used in non-Western countries.)

- [US MEDPED Program](#)
- [UK Simon Broome Familial Hypercholesterolaemia Registry](#)
- [Dutch Lipid Clinic Network](#)

All three criteria rely on a combination of the following:

- Extreme hypercholesterolemia
- History of premature CAD or other CVD
- Findings on physical examination
- Family history of premature CAD or other CVD
- Identification of a pathogenic variant in a gene known to be associated with FH (see Table 1)

### Extreme hypercholesterolemia

- Adults (untreated):
  - LDL-C levels >190 mg/dL (>4.9 mmol/L)
  - Total cholesterol levels >310 mg/dL (>8 mmol/L)
- Children or adolescents (untreated):
  - LDL-C levels >160 mg/dL (>4 mmol/L)
  - Total cholesterol levels >230 mg/dL (>6 mmol/L)

Note: (1) A non-fasting lipid panel can be obtained first in the initial evaluation of children, and, if abnormal or borderline, a fasting LDL-C level should be obtained [Martin et al 2013]. Elevation of two consecutive LDL-C levels is often recommended to confirm the diagnosis. (2) Age-specific LDL-C or total cholesterol levels are more specific in determining the likelihood of FH; for instance, LDL-C or total cholesterol levels >95th percentile for age, gender, and country [Starr et al 2008, Nordestgaard et al 2013]. (3) Computer (including mobile or smart phone-based) applications (see [FH Diagnosis](#)) can assist with the determination of the likelihood of FH based on the formal diagnostic criteria.

### History of premature CAD or other CVD

- Angina pectoris
- Myocardial infarction
- Peripheral vascular diseases

Note: Although stroke is possible, it is less common in FH than premature CAD [Huxley et al 2003].

### Physical examination findings

- Xanthomas (patches of yellowish cholesterol buildup). Common locations include around the eyelids, tendons of the elbows, hands, knees, and feet, particularly the Achilles tendon. Interdigital xanthomas occur in individuals with homozygous FH.
- Corneal arcus (white, gray, or blue opaque ring in the corneal margin). Because this becomes increasingly common in the general population with age, it is only diagnostic in younger individuals, particularly before age 45 years.

Note: As statin treatment has become more common, it is possible that individuals have fewer visible signs of FH, complicating the application of the diagnostic criteria.

### Family history of any of the following

- Familial hypercholesterolemia
- High levels of LDL-C
- Early-onset (i.e., age <50 years) CAD (especially myocardial infarction)
- Xanthomas

**Identification of a pathogenic variant in a gene known to be associated with FH** (see Table 1) is the gold standard for diagnosis accepted in many countries [Nordestgaard et al 2013].

- The likelihood of identifying a pathogenic variant by molecular testing increases with higher LDL-C levels.
- In the United States, genetic testing is recommended when other laboratory tests have not definitively established the diagnosis of FH.

Molecular genetic testing approaches can include **serial single-gene testing** and use of a **multigene panel**:

- **Serial single-gene testing** can be considered. Sequence analysis of *LDLR* is performed first and followed by *LDLR* deletion/duplication analysis if no pathogenic variant is found. Sequence analysis of *APOB* and *PCSK9* can be performed next if no pathogenic variant is found.
- **A multigene panel** that includes *APOB*, *LDLR*, *PCSK9*, and other genes of interest (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 at the most reasonable cost 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 (FH)

Gene <sup>1</sup>	Proportion of FH Attributed to Pathogenic Variants in This Gene <sup>2</sup>	Proportion of Pathogenic Variants <sup>3</sup> Detectable by Method	
		Sequence analysis <sup>4</sup>	Gene-targeted deletion/duplication analysis <sup>5</sup>
<i>APOB</i>	1%-5%	>99%	1 individual <sup>6</sup>
<i>LDLR</i>	60%-80%	>90% <sup>7</sup>	~2.5%-10% <sup>8</sup>
<i>PCSK9</i>	0%-3%	~100%	None reported <sup>9</sup>
Unknown <sup>10, 11</sup>	20%-40%	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.

2. The yield for genetic testing varies by the pre-test probability of the disease as determined by the clinical diagnostic criteria. In "definite" FH the yield of genetic testing for identification of a pathogenic variant approaches 95%; in "probable" or "possible" FH the yield is lower (~70%) [Motazacker et al 2012, Awan et al 2013].

3. See Molecular Genetics for information on allelic variants detected in this gene.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Huang et al [1989]

7. The majority of pathogenic variants in *LDLR* are detectable by sequence analysis, including those in the regulatory region (the majority occurring within 200 bp upstream of the initiation codon) if that region is targeted for sequencing [Dedoussis et al 2004].

8. Horsthemke et al [1987], Dedoussis et al [2004], Bertolini et al [2013]

9. No deletions or duplications involving *PCSK9* have been reported to cause familial hypercholesterolemia [De Castro-Orós et al 2010].

10. De Castro-Orós et al [2010]

11. It has been suggested that a polygenic etiology is most likely in the majority of individuals with a clinical diagnosis of FH in whom no pathogenic variant in one of the three known genes can be identified. This suggestion is based on the presence in these individuals of a greater than average number of common LDL-C-raising variants (i.e., a high "LDL-SNP score") [Talmud et al 2013].

## Clinical Characteristics

### Clinical Description

#### Familial Hypercholesterolemia (FH)

**Coronary artery disease (CAD) and cardiovascular disease (CVD).** Elevated LDL cholesterol (LDL-C) leads to atherosclerotic plaque deposition in the coronary arteries and proximal aorta at an early age, leading over time to an increased risk for cardiovascular disease (CVD), which by definition includes coronary artery disease (CAD) (manifest as angina and myocardial infarction) and stroke [Scientific Steering Committee 1991, Versmissen et al 2008, Elis et al 2011, Raal & Santos 2012]. In FH, CAD is the more common cardiovascular disease; stroke occurs more rarely and some evidence suggests that the risk for stroke may not be greater than in the general population [Huxley et al 2003].

All individuals with FH should be considered "high risk" (i.e., increased ~20-fold) for CAD. Recent data suggest that individuals with an LDL-C >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 CAD 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]. See Figure 1. 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].

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]. Additional medications such as ezetimibe, bile acid binding resins, or PCSK9 inhibitors are often necessary to achieve optimal LDL-C reduction [Gidding et al 2015].

Data from the CASCADE-FH registry reveals that upwards of 61% of adults with FH have at least one modifiable cardiovascular risk factor. Coronary heart disease was reported in 47% of men with FH, with a median age of onset of 47 years. Coronary heart disease was reported in 29% of women with FH, with a median age of onset of 55 years. A high-dose statin was being taken by 42% of individuals with FH, 33% of individuals were on a low-dose statin, and 25% of individuals were not taking a statin. The most common reasons for lack of statin use included intolerance or allergy (60%), patient preference (11%), physician preference (11%), pregnancy (3%), cost (1%), and clinical trial participation (1%). Twenty-five percent of treated individuals had an LDL-C below 100 mg/dL and 41% of individuals achieved a 50% or greater reduction in LDL-C from untreated values [deGoma et al 2016].

**Xanthomas** are patches of yellowish cholesterol buildup in particular areas of the body as a result of extremely high levels of LDL-C. Xanthomas may worsen with age in persons who are not treated. In persons treated with LDL-C-lowering therapy, the xanthomas can become smaller. Common locations:

- Xanthomas often occur around the eyelids (xanthelasma palpebrarum or more commonly just xanthelasma) [Dey et al 2013].
- 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 due to widespread statin use [Perez de Isla et al 2016].
- Interdigital xanthomas (between the fingers) occur in individuals with homozygous FH.

**Corneal arcus** (white, gray, or blue opaque ring in the corneal margin). Because corneal arcus becomes increasingly common in the general population with age, it is only diagnostic in younger individuals, particularly before age 45 years.

## Homozygous Familial Hypercholesterolemia (HoFH)

Homozygous familial hypercholesterolemia refers to familial hypercholesterolemia resulting from biallelic (homozygous or compound heterozygous) pathogenic variants in one of the genes listed in Table 1 (*APOB*, *LDLR*, and *PCSK9*). The prevalence of HoFH, estimated at 1:160,000 to 1:250,000, is much lower than FH [Nordestgaard et al 2013, Cuchel et al 2014].

In adults with HoFH, untreated LDL-C levels are generally, but not always, >500 mg/dL (>13 mmol/L). Levels can be lower in children or in treated individuals. Thus, LDL-C levels are not sufficient to confirm a diagnosis [Cuchel et al 2014].

In addition to xanthomas around the eyelids and tendonous xanthomas, individuals with HoFH can have interdigital xanthomas (between the fingers).

The natural history of HoFH differs from that of FH. Most individuals with HoFH experience severe CAD by their mid-20s. The rate of either death or coronary bypass surgery by the teenage 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 in the treatment of HoFH because their efficacy largely depends on the upregulation of functional LDL receptors in the liver. In individuals with HoFH, activity of both copies of the LDL receptor are absent or greatly reduced [Raal & Santos 2012]; therefore, therapy for HoFH often requires LDL apheresis in addition to the use of multiple other medications (see **Management**, Treatment of Manifestations) [Raal et al 2010, Raal 2013, Cuchel et al 2014].

## Phenotype Correlations by Gene

***APOB***. FH caused by a heterozygous *APOB* pathogenic variant is reported to be less severe than FH caused by a heterozygous pathogenic variant in *LDLR* or *PCSK9* [Hopkins et al 2011].

## Genotype-Phenotype Correlations

***LDLR***. Complete loss-of-function variants in *LDLR* generally lead to more severe disease due to higher LDL-C levels [Khera et al 2016]. Partial loss-of-function variants in *LDLR* result in less severe disease due to lower LDL-C levels.

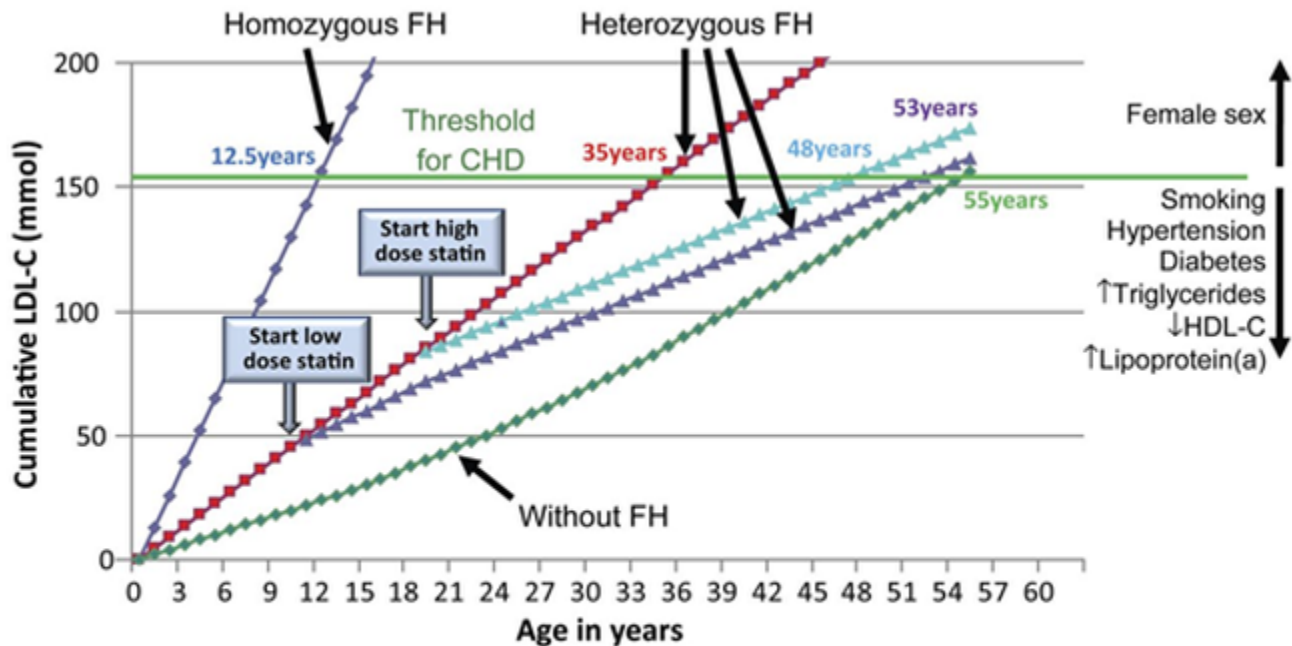
## Penetrance

***APOB***. Penetrance for FH can be incomplete in persons with a heterozygous *APOB* pathogenic variant [Fahed & Nemer 2011].

***LDLR***. Recent findings suggest that only 73% of individuals with a heterozygous *LDLR* pathogenic variant have an LDL 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.
- Penetrance in persons heterozygous for the p.Asp374Tyr pathogenic variant is high, with FH manifesting at a young age [Naoumova et al 2005].



LDL = low-density lipoprotein  
 LDL-C = LDL cholesterol  
 HDL-C = high-density lipoprotein cholesterol  
 CHD = coronary heart disease  
 FH = familial hypercholesterolaemia

**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.

- Penetrance for other heterozygous *PCSK9* pathogenic variants remains largely unknown [Cariou et al 2011].

## Prevalence

The prevalence of FH in the general population has traditionally been cited as 1:500. However, emerging data suggest that the prevalence of FH is higher in white/European populations, perhaps as common as 1:200 [Benn et al 2012, Nordestgaard et al 2013].

FH is more common (due to founder effects) in several populations (Table 2). Of note, data are limited on prevalence of FH in most African and South Asian/Indian populations.

**Table 2.** Prevalence of FH in Select Populations

Population	Prevalence
General population	1:250
French Canadian <sup>1</sup>	1:270
Old Order Amish <sup>2</sup>	1:10
Christian Lebanese	1:85



Table 2. continued from previous page.

Population	Prevalence
Tunisia	1:165
South African Afrikaners	1:72 to 1:100
South African Ashkenazi Jews	1:67

Austin et al [2004]

1. A common >15-kb (60% of alleles) and an ~5-kb (5% of alleles) *LDLR* deletion results in a significant increase in LDL-C [Simard et al 2004].

2. Amish individuals heterozygous for *APOB* p.Arg3500Gln (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 occurred in heterozygous Amish individuals with lower average LDL-C levels [Andersen et al 2016].

## Genetically Related (Allelic) Disorders

***APOB***. Homozygous or heterozygous loss-of-function pathogenic variants in *APOB* cause familial hypobetalipoproteinemia (OMIM 615558) characterized by extremely low levels of LDL-C [Burnett et al 2012].

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

***PCSK9***. Heterozygous or homozygous loss-of-function pathogenic variants in *PCSK9* cause hypocholesterolemia (reduced blood cholesterol levels). Loss-of-function pathogenic variants lead to an increase in the number of low-density lipoprotein receptors on the surface of liver cells, resulting in quicker than usual removal of LDL-C from the blood and, hence, a reduced risk for coronary heart disease [Cohen et al 2006, Pandit et al 2008].

## Differential Diagnosis

Conditions with **clinical findings** similar to those of familial hypercholesterolemia (FH) include the following:

- **27-hydroxylase deficiency (cerebrotendinous xanthomatosis)**, which is characterized by xanthomas. Distinguishing features are normal LDL cholesterol (LDL-C) levels and the presence of dementia, ataxia, and cataracts. Biallelic pathogenic variants in *CYP27A1* are causative; inheritance is autosomal recessive.
- **Hyperlipoproteinemia type III (familial dysbetalipoproteinemia)** (OMIM 107741). Clinical features may include xanthomas. Hyperlipoproteinemia type III is caused by biallelic pathogenic variants in *APOE*. Inheritance is autosomal recessive [Fung et al 2011].
- **Sitosterolemia** (phytosterolemia), which is distinguished by normal or only mildly elevated LDL-C levels. Biallelic pathogenic variants in either *ABCG5* or *ABCG8* are causative; inheritance is autosomal recessive.
- **Polygenic hypercholesterolemia**. Talmud et al [2013] found that individuals with features suggestive of FH in whom an *LDLR*, *PCSK9*, or *APOB* pathogenic variant was not identified are in fact likely to have polygenic hypercholesterolemia. In this case, individuals have a high genetic risk score for more common LDL-C raising alleles.
- **Extremely elevated lipoprotein a (Lpa)** (OMIM 152200). Individuals with very high Lpa often have a personal and family history of early-onset CAD and very elevated LDL-C levels [Langsted et al 2016]. High Lpa levels are also widely appreciated to synergistically increase risk in individuals with FH. The disorder is inherited in an autosomal dominant manner and caused by variants in the number of kringle IV type 2 repeats in *LPL*.

Conditions with **laboratory findings** similar to those of FH include the following [Goldberg et al 2011]:

- **Hypercholesterolemia** secondary to obesity, diabetes mellitus, hypothyroidism, drugs (e.g., steroids), or kidney disease. Inheritance follows a non-Mendelian pattern.
- **Autosomal recessive hypercholesterolemia** (OMIM 603813) caused by biallelic pathogenic variants in *LDLRAP1*. Persons with biallelic pathogenic variants have LDL-C >400 mg/dL (>10 mmol/L), whereas heterozygotes have normal LDL-C levels.
- **Familial combined hyperlipidemia (FCHL)** (OMIM 144250), associated with elevated LDL-C and triglycerides. FCHL is genetically heterogeneous. Only 10%-20% of individuals show elevated levels in childhood (usually in the form of hypertriglyceridemia). FCHL is inherited in an autosomal dominant manner and caused by pathogenic variants in *LPL* [Brahm & Hegele 2016]. Additional loci have been mapped to *APOB* and *USF1* in a minority of families [Naukkarinen et al 2006, Hegele et al 2009].

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with familial hypercholesterolemia (FH) the following evaluations are recommended in adults and children:

- Measurement of pre-treatment lipid values and lipoprotein(a) levels when possible
- Exclusion of concurrent illnesses (kidney disease, acute myocardial infarction, infection) that can affect lipid values
- Lipid panel including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides
- Consultation with a lipid specialist or clinician with expertise in FH
- Recommended in some guidelines: noninvasive imaging modalities in children (e.g., measurement of carotid intima-media thickness) to help inform treatment decisions [Martin et al 2013]
- Consultation with a clinical geneticist and/or genetic counselor

### Treatment of Manifestations

#### Adults with FH

All individuals with FH should be considered "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 (NLA).

For adults, treatment should begin as soon as possible after diagnosis. All adults with FH require diet/lifestyle management, and almost without exception will also require cholesterol-lowering drug therapy.

- Risk factors (e.g., smoking, diabetes mellitus, hypertension) are the same in FH as in the general population; aggressive management is required to reduce CAD risk, with special attention to smoking cessation.
- Regular physical activity, a healthy diet (reduce saturated fat intake, increase intake of soluble fiber to 10-20 g/day), and weight control should be emphasized.
- Blood pressure should be treated to 140/90mm Hg (or 130/80 mm Hg in those with diabetes mellitus).
- Low-dose aspirin (75-81 mg/day) should be considered in those at high risk for CAD or stroke.
- Consider referral to a lipid specialist with expertise in FH if LDL-C concentrations are not reduced with maximal medical therapy. (Note: Although it has not been specified, this recommendation generally

pertains to LDL-C levels that cannot be reduced by  $\geq 50\%$  with maximal medical therapy over a 6-month period.)

- Testing of first-degree and second-degree relatives should be recommended to all individuals with FH (see Evaluation of Relatives at Risk).
- For adults with FH age 20 years or older, treatment with statins should be initiated to reduce the LDL-C level  $\geq 50\%$  or to  $< 100$  mg/dL ( $< 2.6$  mmol/L) [Hopkins et al 2011, Nordestgaard et al 2013]. Many guidelines suggest a target LDL-C of  $< 100$  mg/dL even in those without known CAD as individuals with FH have had a lifelong burden of high LDL-C [Gidding et al 2015].

**For persons with FH with any of the following CAD risk factors**, drug treatment may need to be intensified (see \*Note) to achieve more aggressive treatment goals (LDL-C  $< 100$  mg/dL [ $< 2.6$  mmol/L] and non-HDL-C  $< 130$  mg/dL [ $< 3.4$  mmol/L]). Risk factors:

- Clinically evident CAD or other atherosclerotic cardiovascular disease; the goal is LDL-C level of  $< 70$  mg/dL ( $< 1.8$  mmol/L)
- Diabetes mellitus or metabolic syndrome
- Family history of very early CAD (men age  $< 45$  years; women age  $< 55$  years)
- Current smoking
- High lipoprotein(a) ( $\geq 50$  mg/dL [ $\geq 1.3$  mmol/L] using an isoform insensitive assay)

The second-line agent for individuals with FH who do not achieve acceptable LDL-C levels is generally ezetimibe. Treatment options for intensification of therapy after ezetimibe or for those intolerant of statins include bile acid sequestrants and/or PCSK9 inhibitors. Although niacin has been used as an adjunctive therapy in individuals with FH, given recent data, niacin is generally not favored before the other options have been exhausted [Guyton et al 2013, FDA 2016] (see Table 3).

**In persons with FH without any of the CAD risk factors** listed above, intensification of drug therapy (see \*Note) should be strongly considered if 50% reduction in LDL-C is not achieved after six months on maximum statin therapy. For adults, some guidelines call for intensification of treatment if the goal LDL-C of  $< 100$  mg/dL ( $< 2.6$  mmol/L) is not achieved [Nordestgaard et al 2013].

\*Note: (1) The lipid-lowering therapy should initially be statin-based with titration of doses every few months in order to use the highest tolerated dose of a potent statin, followed by addition of other drugs if the targeted LDL-C level is not achieved. (2) The potential benefit of multidrug regimens should be weighed against the increased cost and potential for adverse effects and decreased adherence.

**Table 3.** Current Recommended Drug Therapies for Adults with FH

Class	Primary (1 <sup>o</sup> ) and Secondary (2 <sup>o</sup> ) Mechanism of Action	LDL-Lowering Response
Statins	↑ LDLR activity (1 <sup>o</sup> )	$> 35\%$ <sup>1, 2</sup>
Cholesterol absorption inhibitors (ezetimibe)	↓ Cholesterol absorption (1 <sup>o</sup> ) ↑ LDLR activity (2 <sup>o</sup> )	15% <sup>1, 3</sup>
Mipomersen (APOB antisense) <sup>4</sup>	Blocks APOB production in the liver	50% <sup>5</sup>
MTP inhibitor (lomitapide) <sup>4</sup>	↓ microsomal triglyceride transfer protein activity (1 <sup>o</sup> ) Inhibition of LDL production (2 <sup>o</sup> )	50% <sup>5</sup>
PCSK9 inhibitors (alirocumab, evolocumab)	↓ LDL-receptor degradation	50% <sup>6</sup>
Bile acid sequestrants (cholestyramine, colesevelam)	↓ Bile acid reabsorption (1 <sup>o</sup> ) ↑ LDLR activity (2 <sup>o</sup> )	15% <sup>1, 3</sup>

Table 3. continued from previous page.

Class	Primary (1 <sup>O</sup> ) and Secondary (2 <sup>O</sup> ) Mechanism of Action	LDL-Lowering Response
Stanol esters	↓ Cholesterol absorption (1 <sup>O</sup> ) ↑ LDLR activity (2 <sup>O</sup> )	10% <sup>1, 3</sup>

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

1. Often ineffective in HoFH

2. Kastelein et al [2008]

3. Rader et al [2003]

4. Approved only for adults with HoFH

5. Cuchel et al [2014]

6. Raal & Santos [2012]

## Children with FH

Guidelines for the management of children and individuals up to age 21 years have been published by the National Heart, Lung, and Blood Institute ([full text](#)). Children should be considered for drug treatment with statin-based regimens when:

- LDL-C levels are  $\geq 190$  mg/dL ( $\geq 4.9$  mmol/L).
- LDL-C levels are  $\geq 160$  mg/dL ( $\geq 4.1$  mmol/L) and at least two other risk factors are present.

US-based guidelines from the NLA ([full text](#)):

- Consultation or referral to a lipid specialist is recommended.
- Management of diet and physical activity is recommended at an early age.
- Statins are the preferred initial pharmacologic treatment in children. Consideration should be given to starting statin treatment at age eight years or older. In special cases, such as children with homozygous FH, drug treatment needs to be initiated prior to age eight years.
- The goal of lipid-lowering therapy in children with FH is a  $\geq 50\%$  reduction in LDL-C or LDL-C  $< 130$  mg/dL ( $< 3.4$  mmol/L). Note: More aggressive lowering of LDL-C levels should be considered for children with additional CAD risk factors (e.g., family history of CAD, high blood pressure, unhealthy diet or exercise behaviors, obesity).

## Children and Adults with Homozygous FH (HoFH)

NLA guidelines for homozygous FH ([full text](#)):

- Referral to a lipid specialist is indicated.
- Early initiation of therapy and monitoring are recommended.
- Multiple drug therapy is usually needed. Several different classes of medications are currently being used to treat HoFH (see Table 3).
- Since many cholesterol-lowering medications target the LDL receptor, effectiveness in persons with FH with biallelic loss-of function *LDLR* pathogenic variants can be limited [Cuchel et al 2014]. Statins are often relatively ineffective in the treatment of HoFH because their efficacy largely depends on the upregulation of functional LDL receptors in the liver. In HoFH, both copies of the LDL receptor have absent or greatly reduced activity [Raal & Santos 2012].
- High-dose statins, ezetimibe, and bile-acid binding resins may be effective in some persons with HoFH, especially those with some residual LDLR activity.

- For HoFH, evolocumab is a PCSK9 inhibitor that showed a 40% mean reduction in LDL-C compared with placebo; however, individuals with two loss-of-function variants saw no response [Raal et al 2015]. PCSK9 inhibitors have not been formally approved in children with FH.
- HoFH-specific medications (lomitapide and mipomersen) are effective even with complete loss of LDL receptor function and – though not formally FDA approved for children – should strongly be considered.
- Despite these options, many individuals with HoFH (especially those with complete loss of LDL receptor function) will require ongoing LDL apheresis. LDL apheresis ( $\leq 2$ x/week) is often required starting from a young age. Apheresis can lower LDL-C levels by 80% acutely and 30% chronically (weekly or biweekly). Apheresis is offered at a limited number (~40-50) of centers in the United States; many states do not have an apheresis center.
- Liver transplantation is also being used in rare circumstances in some centers [Martinez et al 2016]

## Prevention of Primary Manifestations

Preventive measures include the following:

- Statin-based therapy with addition of other medications as needed
- Reduced intake of saturated fat
- Increased intake of soluble fiber to 10-20 g/day
- Increased physical activity
- Not smoking

## Surveillance

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

A child who has a family history of FH or of premature CAD, who is heterozygous for the FH pathogenic variant in his or her family, or who has an elevated serum cholesterol concentration should have lipid levels checked starting as early as age two years [Goldberg et al 2011]. It is reasonable to check a non-fasting lipid level first and, if borderline, to follow with measurement of LDL-C. Some guidelines state that elevation of two consecutive measures of LDL-C are needed to confirm a diagnosis of FH [Martin et al 2013].

An LDL-C level of  $>130$  mg/dL ( $>3.4$  mmol/L) in a child is suspicious for FH and an LDL of  $>160$  mg/dL ( $>4.1$  mmol/L) is relatively specific for FH.

**During treatment, individuals of any age with:**

- **FH** should have lipid levels monitored as recommended;
- **HoFH** should be monitored with various imaging modalities (including echocardiogram, CT angiogram, and cardiac catheterization) as recommended [Raal & Santos 2012].

## Agents/Circumstances to Avoid

The following should be avoided:

- Smoking
- High intake of saturated and trans unsaturated fat
- Excessive intake of cholesterol
- Sedentary lifestyle
- Obesity
- Hypertension

- 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 using cholesterol testing with or without DNA analysis on relatives of affected persons with FH in order to identify previously unknown cases of FH and provide those people with lifesaving treatment. Early diagnosis and treatment of relatives at risk for FH can reduce morbidity and mortality [Goldberg et al 2011, Ned & Sijbrands 2011, Reiner et al 2011].

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

- Molecular genetic testing if the pathogenic variant has been identified in an affected family member
- Measurement of LDL-C level. Table 4 provides age-specific total cholesterol and LDL-C levels [Williams et al 1993]. Note: Age-specific LDL cut-offs are also available based on more contemporary data from the United Kingdom [Starr et al 2008].

**Table 4.** Total and LDL Cholesterol Levels in Heterozygotes for FH Based on Degree of Relatedness to an Individual with FH

Degree of Relatedness to an Affected Individual		First Degree <sup>1</sup>	Second Degree <sup>2</sup>	Third Degree <sup>3</sup>
Cholesterol Levels		Total Cholesterol (LDL Cholesterol) in mg/dL		
Age	<20	220 (155)	230 (165)	240 (170)
	20-29	240 (170)	250 (180)	260 (185)
	30-39	270 (190)	280 (200)	290 (210)
	40+	290 (205)	300 (215)	310 (225)

1. A parent, sib, or child. First-degree relatives share about half of their genes.

2. An uncle, aunt, nephew, niece, grandparent, grandchild, or half-sib. Second-degree relatives share about one quarter of their genes.

3. A first cousin, great-grandparent, or great-grandchild. Third-degree relatives share about one eighth of their genes.

Of note, all national and international guidelines for FH call for "cascade testing" of relatives at risk (i.e., systematic testing of first- and second-degree relatives of the index case [proband]). Evidence supports the use of genetic testing in cascade testing algorithms to improve the detection of FH [DeMott et al 2008, Wierzbicki et al 2008, Wald et al 2016].

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

## Pregnancy Management

Statins are contraindicated during pregnancy; women with FH who are considering a pregnancy should be counseled of this risk and statins should be discontinued prior to conception.

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 (see Agents/Circumstances to Avoid).

### Pharmacologic treatment during pregnancy

- Statins are contraindicated in pregnancy due to concerns for teratogenicity. The use of statins during human pregnancy has not definitively been 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.
- Regarding other agents:
  - PCSK9 inhibitors. Use during pregnancy has not been well studied.
  - Ezetimibe. Use during human pregnancy has not been well studied.
  - Niacin. The use of pharmacologic doses of niacin, an essential vitamin, has not been studied in human pregnancy. The recommended upper limit of niacin intake during pregnancy is 30-35 mg/day; higher doses have been associated with toxicity.

## Therapies Under Investigation

CAD outcome trials of PCSK9 inhibitors are currently underway.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Heterozygous familial hypercholesterolemia (FH, HeFH) and homozygous familial hypercholesterolemia (HoFH) are inherited in an autosomal dominant manner.

## Risk to Family Members

### Heterozygous Familial Hypercholesterolemia (FH)

#### Parents of a proband

- Almost all individuals diagnosed with FH have an affected parent.
- A proband with FH may have the disorder as the result of a *de novo* pathogenic variant. Because simplex cases (i.e., a single occurrence in a family) have not yet been evaluated sufficiently to determine if the pathogenic variant occurred *de novo*, the proportion of FH caused by *de novo* pathogenic variants is unknown but appears to be very low.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing if the pathogenic variant has been identified in the proband, or cholesterol testing if the pathogenic variant has not been identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

- Note: 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, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

### Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected or has a pathogenic variant, the risk to the sibs is 50%.
- If both parents of the proband are affected with FH or have a pathogenic variant, the risk to sibs of having FH is 50%, the risk to sibs having HoFH is 25%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be very low.
- The sibs of a proband with clinically unaffected parents are still at increased risk for familial hypercholesterolemia because of the possibility of reduced penetrance in a parent. However, this is a very unlikely scenario.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the theoretic possibility of parental germline mosaicism.

### Offspring of a proband

- Each child of an individual with FH has a 50% chance of inheriting the pathogenic variant.
- If both parents of a child are affected with FH, the child has a 50% chance of having FH and a 25% chance of having HoFH.

**Other family members.** The risk to other family members depends on the status of the proband's parents. If a parent is affected or has a pathogenic variant, his or her family members may be at risk.

**Considerations in families with an apparent *de novo* pathogenic variant.** When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband, the pathogenic variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

## Homozygous Familial Hypercholesterolemia (HoFH)

### Parents of a proband

- The parents of an affected individual are obligate heterozygotes and thus have one familial hypercholesterolemia-related pathogenic variant.
- Individuals with one pathogenic variant have FH.

**Sibs of a proband.** The risk to sibs of having FH is 50%; the risk to sibs of having HoFH is 25%.

**Offspring of a proband.** The offspring of an individual with HoFH are obligate heterozygotes for a pathogenic variant; thus, all will have FH.

**Other family members.** Sibs of the proband's parents are at 50% risk of having a pathogenic variant and, thus, FH.

## Related Genetic Counseling Issues

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

**Specific risk issues.** Individuals inheriting pathogenic variants from both parents will develop a severe form of familial hypercholesterolemia (HoFH).



**Predictive genetic testing** for asymptomatic adult family members at risk for FH requires prior identification of the pathogenic variant in the family.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

## Prenatal Testing and Preimplantation Genetic Diagnosis

Once the pathogenic variant has been identified in a family member with FH (or both pathogenic variants have been identified in a family member with HoFH), prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

## 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](mailto:aas@meetingsfirst.com.au)  
[www.athero.org.au/FH](http://www.athero.org.au/FH)
- **FH Foundation**  
959 East Walnut Street  
Suite 220  
Pasadena CA 91106  
**Phone:** 626-583-4674  
**Email:** [info@thefhfoundation.org](mailto:info@thefhfoundation.org)  
[www.thefhfoundation.org](http://www.thefhfoundation.org)
- **FH Norway, Norwegian FH Patient Organization**  
[www.f-h.no](http://www.f-h.no)
- **FH Portugal, Portuguese FH Patient Organization**  
[www.fhportugal.pt](http://www.fhportugal.pt)

- **FHChol Austria, Austrian FH Patient Organization**  
Austria  
[www.fhchol.at](http://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](mailto:info@colesterolfamiliar.org)  
[www.colesterolfamiliar.org](http://www.colesterolfamiliar.org)
- **German FH Patient Organization**  
Germany  
[www.cholco.org](http://www.cholco.org)
- **International FH Foundation**  
FHchol Austria  
Fürst Liechtensteinstraße 2/9  
Wien 1230  
Austria  
**Phone:** 0664 653 59 32  
**Email:** [info@fhchol.at](mailto:info@fhchol.at)  
[www.fhchol.at](http://www.fhchol.at)
- **Make Early Diagnosis Prevent Early Death (MEDPED)**  
[www.medped.org](http://www.medped.org)
- **Medline Plus**  
[Familial hypercholesterolemia](#)
- **My46 Trait Profile**  
[Familial Hypercholesterolemia](#)
- **National Library of Medicine Genetics Home Reference**  
[Hypercholesterolemia](#)
- **Preventive Cardiovascular Nurses Association**  
PCNA National Office  
613 Williamson Street  
Suite 200  
Madison WI 53703  
**Phone:** 608-250-2440  
[www.pcna.net](http://www.pcna.net)
- **HEART UK**  
United Kingdom  
**Phone:** 0845 450 5988  
**Email:** [ask@heartuk.org.uk](mailto:ask@heartuk.org.uk)  
[www.heartuk.org.uk](http://www.heartuk.org.uk)
- **Japan Atherosclerosis Society**  
Japan  
[www.j-athero.org](http://www.j-athero.org)

- **Learn Your Lipids**  
[www.learnyourlipids.com](http://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](http://www.lipid.org)
- **CASCADE FH Registry**  
[www.thefhfoundation.org/registry](http://www.thefhfoundation.org/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
<i>APOB</i>	2p24.1	Apolipoprotein B-100	<a href="#">APOB database</a>	<a href="#">APOB</a>	<a href="#">APOB</a>
<i>LDLR</i>	19p13.2	Low-density lipoprotein receptor	<a href="#">LDLR @ LOVD</a>	<a href="#">LDLR</a>	<a href="#">LDLR</a>
<i>PCSK9</i>	1p32.3	Proprotein convertase subtilisin/kexin type 9	<a href="#">PCSK9 @ LOVD</a>	<a href="#">PCSK9</a>	<a href="#">PCSK9</a>

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; FCHL2
603776	HYPERCHOLESTEROLEMIA, FAMILIAL, 3; FHCL3
606945	LOW DENSITY LIPOPROTEIN RECEPTOR; LDLR
607786	PROPROTEIN CONVERTASE, SUBTILISIN/KEXIN-TYPE, 9; PCSK9

### *APOB*

**Gene structure.** *APOB* is 42,216 base pairs in length, comprising 28 introns and 29 exons. It has an open reading frame of 13,692 bases.

The distribution of the introns within the gene is unusual in that 24 of the 29 introns occur in the 5' terminus. More than half of the protein is coded by the 7,572-bp exon 26, one of the largest exons reported in the human genome. One of the two main isoforms, apoB-100, synthesized exclusively in the liver, is responsible for complications related to FH [Whitfield et al 2004]. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** More than five pathogenic variants have been reported to be associated with FH, two of which are repeatedly found to be significant:

- p.Arg3527Gln, found mainly in people with European ancestry
- p.Arg3527Trp, which tends to be found mostly within Asian populations [Calandra et al 2011]

Pathogenic variants in this locus account for approximately 1%-5% of all persons with FH.

See also Table A, **ClinVar**.

**Table 5.** *APOB* Selected Pathogenic Variants

DNA Nucleotide Change (Alias <sup>1</sup> )	Predicted Protein Change (Alias <sup>1</sup> )	Reference Sequences
c.10580G>A <sup>2</sup> (9775G>A)	p.Arg3527Gln (Arg3500Gln)	NM_000384.2 NP_000375.2
c.10579C>T (9774C>T)	p.Arg3527Trp (Arg3500Trp)	
c.10672C>T	p.Arg3558Cys	

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

Amino acids are numbered from the beginning of the protein precursor, including signal sequence, and nucleotides from first base of the ATG initiation codon.

1. 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.

2. [rs5742904](https://rsb.nlm.nih.gov/variant/2/rs5742904)

**Normal gene product.** The gene product is the main apolipoprotein of chylomicrons and low-density lipoproteins. Human *APOB* mRNA is 14.5 kb in length and codes for a mature protein of 4,560 amino acids [[UCSC Genome Browser, \*APOB\*](#); accessed July 10, 2013].

*APOB* has four functional domains [Innerarity et al 1990]:

- Synthesis, assembly, and secretion of hepatic triglyceride-rich lipoproteins
- Binding of lipids and serving as a structural component of very low-density lipoproteins (VLDL) and LDL
- Binding of heparin and various proteoglycans found in the arterial wall
- Interaction with the LDL receptor, important for clearance of LDL from plasma

**Abnormal gene product.** *APOB* is generally involved in aiding the binding of LDL-C to its receptor on the cell surface. *APOB* pathogenic variants alter the ability of protein to effectively bind LDL-C to *LDLR*, causing fewer LDL-C particles to be removed from the blood.

## ***LDLR***

**Gene structure.** *LDLR* spans 45 kb, comprising 18 exons and 17 introns. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** Pathogenic variants have been reported in the promoter, introns, and exons of *LDLR*. The majority of pathogenic variants fall within the ligand-binding (40%) or epidermal growth factor precursor-like (47%) domains, with the highest frequency of pathogenic variants reported in exon 4 (20%) [Leigh et al 2008, Usifo et al 2012]. More than 1,500 *LDLR* pathogenic variants have been reported in the University College

London (UCL) database, highlighting the molecular heterogeneity of the disorder. See Table A, **Locus-Specific Databases** and **ClinVar**, for a list of reported variants.

**Table 6.** *LDLR* Selected Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
>15-kb del <sup>1</sup> (5' of gene through exon 1)	--	NM_000527.4 NP_000518.1
5-kb del <sup>1</sup> (deletion of exons 2 and 3)	--	

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** *LDLR* encodes a mature protein product of 839 amino acids [NP\_000518.1]. *LDLR* has four distinct functional domains that can function independently of each other [NCBI Conserved *LDLR* Domains; accessed July 10, 2013]:

- LDL receptor domain class A (LDLa)
- Epidermal growth factor-like domain (EGF)
- Calcium-binding EGF-like domain (EGF-CA)
- LDL receptor repeat class B (LDLb)

*LDLR* consists of cell surface proteins involved in endocytosis of LDL 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.

**Abnormal gene product.** Pathogenic variants in *LDLR* usually either reduce the number of LDL receptors produced within the cells or disrupt the ability of the receptor to bind LDL-C. Either way, heterozygous pathogenic variants in *LDLR* cause high levels of plasma LDL-C [UCSC Genome Browser, *LDLR*; accessed July 10, 2013].

## ***PCSK9***

**Gene structure.** *PCSK9* has a transcript size of 25,378 bp and 12 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** Approximately 100 variants in *PCSK9* have been submitted to the University College London database [Abifadel et al 2003]. Although many are hypothesized to be pathogenic, few have been consistently and significantly associated with FH [Naoumova et al 2005]. For a complete list of reported variants, see Table A, **Locus-Specific Databases** and **ClinVar**.

**Table 7.** PCSK9 Selected Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.381T>A	p.Ser127Arg	NM_174936.3 NP_777596.2
c.644G>A	p.Arg215His	
c.646T>C	p.Phe216Leu	
c.1120G>T	p.Asp374Tyr	
c.1486C>T	p.Arg496Trp	

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

**Normal gene product.** *PCSK9* encodes a protein consisting of 692 amino acids and three main domains:

- Prodomain
- Catalytic domain
- C-terminal domain

**Abnormal gene product.** The *PCSK9* protein product binds to LDL lipid receptors and promotes their degradation in intracellular acidic compartments.

Pathogenic variants in this gene 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].

## References

### Published Guidelines / Consensus Statements

- American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons, Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Available [online](#). 2011. Accessed 10-21-19.
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