Familial Hypercholesterolemia

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KEYWORDS

• Familial hypercholesterolemia • Statins • Ezetimibe • Bile acid sequestrants
• LDL apheresis • Lomitapide • Mipomersen

KEY POINTS

- Familial hypercholesterolemia (FH) is a common genetic disorder leading to high cholesterol levels from birth and increased risk of atherosclerotic cardiovascular disease.
- Heterozygous FH occurs in approximately 1 in 250 people in many populations.
- Homozygous FH can lead to coronary artery disease in childhood and adolescence.
- Early treatment can decrease the risk of premature atherosclerotic cardiovascular disease in FH patients.

INTRODUCTION

Familial hypercholesterolemia (FH) is an inherited condition resulting in high levels of low-density lipoprotein cholesterol (LDL-C) and increased risk of premature cardiovascular disease in men and women. FH causes lifetime exposure to high LDL-C levels. It is not rare, but it is underdiagnosed. Although therapies for FH are available, it is commonly undertreated. Early diagnosis and treatment mitigate the excess risk of premature atherosclerotic cardiovascular disease that occurs with FH.[1–3]

Pathophysiology

The pathophysiology of FH is due to decreased function of LDL receptors (LDLRs) (**Box 1**).

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Box 1
Pathophysiology of familial hypercholesterolemia

- Decreased LDLR function due to a genetic defect, typically one of the following classes[1]:
  - LDLR is not synthesized
  - LDLR is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface
  - LDLR does not properly bind LDL on the cell surface
  - LDLR does not properly cluster in clathrin-coated pits for receptor endocytosis
  - LDLR is not recycled back to the cell surface
- Therefore, LDLR-mediated endocytosis is decreased
- Leading to markedly elevated LDL levels
- Premature development of atherosclerotic plaque

Genetics of Familial Hypercholesterolemia

FH is an autosomal-dominant disorder with a gene dosage effect. Patients who are homozygotes (or compound heterozygotes) have much higher LDL-C levels and earlier coronary artery disease (CAD) onset than heterozygous patients.[1–4] The underlying defect in FH was initially thought to be due to increased synthesis of cholesterol, but it is now known that the fractional catabolic rate of LDL is decreased in heterozygous FH individuals compared with normal subjects.[5] The LDLR pathway was characterized by Brown and Goldstein and revealed receptor-mediated endocytosis.[6]

The most common form of FH is a monogenic, autosomal-dominant disorder, which causes defects in the gene that encodes the LDLR.[1–3]

More than 900 mutations of this gene have been identified,[1] most pathogenic, leading to the LDLR having decreased capacity to clear LDL from the circulation.

There are also defects in the LDLR binding region of apolipoprotein B (apoB)[1] and rare gain-of-function proprotein convertase subtilisin/kexin type 9 (PCSK9) gene mutations.[7] A rare autosomal-recessive form of FH caused by loss-of-function mutations in the LDL receptor adaptor protein 1 (LDLRAP1), which encodes a protein required for clathrin-mediated internalization of the LDLR, has also been described (**Table 1**).[3]

Table 1
Types of mutations causing familial hypercholesterolemia

Mutation	Gene	Mechanism	Numbers of Mutations (% of FH Cases)
LDLR	*LDLR*	LDLR is absent or has decreased capacity to clear LDL from circulation	>900 (85%–90%)
ApoB (also known as familial defective apoB)	*ApoB*	Impaired LDLR binding—mutation at binding site on LDL particle	Mutations around the 3500 residues–most common is Arg3500Gln (5%–10%)
PCSK9 gain of function	*PCSK9*	Increased PCSK9 level leads to increased degradation of LDLRs	Rare
LDLR adaptor protein	*LDLRAP1*	Protein needed for clathrin-mediated internalization of LDLR	Rare; autosomal-recessive hypercholesterolemia