

Beyond the Classic Genes: Rare Variants, Phenocopies, and Polygenic Architecture in Familial Hypercholesterolemia

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SOUHRN

Familiární hypercholesterolemie (FH) je častá dědičná porucha metabolismu lipidů, pro niž jsou charakteristické výrazně zvýšené hodnoty cholesterolu lipoproteinů o nízké hustotě (low-density lipoprotein cholesterol, LDL-C) a zvýšené riziko předčasného rozvoje aterosklerotické kardiovaskulární nemoci. Familiární hypercholesterolemie se tradičně považuje za monogenní poruchu způsobenou patogenními variantami v klasických genech *LDLR*, *APOB* nebo *PCSK9*, které naruší dráhu receptorů pro LDL a odstraňování částic LDL v játrech. U značné procenta pacientů splňujících klinická diagnostická kritéria FH však patogenní varianty uvedených genů nejsou přítomny, což ukazuje na složitější genetickou architekturu. Pokrok zaznamenaný v poslední době v oblasti sekvenování nové generace (next-generation sequencing, NGS) a stanovení polygenického rizika rozšířil poznání genetiky FH. U pacientů bez mutací mohou být zvýšené hodnoty LDL-C důsledkem polygenické hypercholesterolemie, kdy kumulativní účinek několika častých variant přispívá k výslednému fenotypu. Kromě toho může několik vzácných genů vytvořit FH-like fenotyp nebo působit jako fenokopie. Do této skupiny patří *LIPA*, *ABCG5/ABCG8*, *APOE* a *LDLRAP1*, které ovlivňují metabolismus lipidů prostřednictvím různých molekulárních mechanismů. Úloha *STAP1* je i nadále sporná, přičemž současné důkazy napovídají, že pravděpodobně nepředstavuje kauzální gen pro FH. Tento přehled shrnuje podíl vzácných variant, fenokopí a polygenické architektury na klinických projevech FH. Rozšíření panelů pro genetické testování a stanovení skóre polygenického rizika může zvýšit diagnostickou přesnost a zajistit individualizovanější léčbu pacientů s těžkou hypercholesterolemií a péči o ně.

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ABSTRACT

Familial hypercholesterolemia (FH) is a common inherited lipid disorder characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels and an increased risk of premature atherosclerotic cardiovascular disease. Traditionally, FH has been considered a monogenic disorder caused by pathogenic variants in the classical genes *LDLR*, *APOB*, or *PCSK9*, which disrupt the LDL receptor pathway and impair hepatic clearance of LDL particles. However, a substantial proportion of patients fulfilling clinical diagnostic criteria for FH do not carry pathogenic variants in these genes, indicating a more complex genetic architecture. Recent advances in next-generation sequencing (NGS) and polygenic risk assessment have broadened the understanding of FH genetics. In mutation-negative patients, elevated LDL-C levels may result from polygenic hypercholesterolemia, where the cumulative effect of multiple common variants contributes to the phenotype. In addition, several rare genes may cause FH-like phenotypes or act as phenocopies. These include *LIPA*, *ABCG5/ABCG8*, *APOE*, and *LDLRAP1*, which affect lipid metabolism through distinct molecular mechanisms. The role of *STAP1* remains controversial, with current evidence suggesting it is unlikely to represent a causal FH gene. This review summarizes the contribution of rare variants, phenocopies, and polygenic architecture to the clinical presentation of FH. Expanding genetic testing panels and integrating polygenic risk scores may improve diagnostic accuracy and facilitate more personalized management of patients with severe hypercholesterolemia.

Keywords:

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Familial hypercholesterolemia (FH) is a genetically inherited disorder characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels and a high risk of premature atherosclerotic cardiovascular disease. FH is a primary disorder of lipoprotein metabolism caused by defects in the LDL receptor pathway, leading to impaired hepatic clearance of LDL particles and progressive cholesterol accumulation within the arterial wall.

The pathogenesis of FH centers on the LDL receptor-mediated endocytic pathway. Under normal conditions, LDL particles bind to the LDL receptor (LDLR) via apolipoprotein B-100, are internalized with the help of adaptor proteins, and degraded in lysosomes, releasing cholesterol for cellular use. Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates this process by promoting LDLR degradation. Pathogenic variants disrupting LDLR, APOB, or PCSK9 reduce LDL clearance and result in persistently elevated plasma LDL-C, accelerated atherosclerosis, and early coronary artery disease.¹

Traditionally, FH has been considered a monogenic disorder, in which a pathogenic variant in a single gene disrupts the LDL receptor pathway. The majority of genetically confirmed cases are caused by variants in the classical FH genes *LDLR*, *APOB*, and *PCSK9*, which together account for approximately 60–80% of molecularly diagnosed FH patients.^{2,3} However, a substantial proportion of individuals who meet the clinical criteria for FH do not carry pathogenic variants in these genes. In such cases, elevated LDL-C levels may result from a polygenic architecture, in which the cumulative effect of multiple common LDL-C – raising variants contributes to the phenotype. These variants individually exert modest effects but may collectively increase LDL-C concentrations, particularly when combined with environmental factors such as diet, obesity, or metabolic conditions.^{2,3} This model is often referred to as polygenic hypercholesterolemia and may explain a considerable proportion of mutation – negative FH cases.

Another important diagnostic category includes phenocopies, which are genetic disorders that mimic the clinical presentation of FH but arise from different molecular mechanisms. Examples include conditions caused by pathogenic variants in genes such as *LIPA*, *ABCG5/ABCG8*, or *LDLRAP1*. These disorders may present with markedly elevated LDL-C levels, tendon xanthomas, and premature atherosclerosis, making them clinically indistinguishable from FH without genetic testing.^{2,4,5} Identifying such phenocopies is clinically important because their underlying pathophysiology and optimal management strategies may differ from those of classical FH.

In patients who fulfil clinical diagnostic criteria for FH but lack pathogenic variants in the major FH genes, polygenic risk scores (PRS) have emerged as a useful tool for assessing the cumulative contribution of multiple LDL-C – associated genetic variants. PRS can help differentiate polygenic hypercholesterolemia from monogenic FH and improve diagnostic interpretation in mutation-negative individuals.³ The integration of expanded next-generation sequencing (NGS) panels and polygenic risk assessment therefore represents an important step toward more precise molecular diagnosis.

Taken together, these findings indicate that FH should be viewed as a genetically heterogeneous condition, encompassing monogenic disease, polygenic hypercholesterolemia, and phenocopies. In this manuscript, we review several less common genes that may contribute to FH – like phenotypes or modify LDL-C levels, including *STAP1*, *LIPA*, *ABCG5/ABCG8*, *APOE*, and *LDLRAP1*.

STAP1 (Signal Transducing Adaptor Family Member 1)

The association between *STAP1* and FH remains controversial, with conflicting findings across published studies. In 2014, Fouchier et al. identified *STAP1* as a potential fourth autosomal dominant hypercholesterolemia (ADH) gene in patients lacking mutations in *LDLR*, *APOB*, and *PCSK9*.⁶ Four missense variants (p. Glu97Asp, p. Leu69Ser, p. Ile71Thr, p. Asp207Asn) were identified in patients with hypercholesterolemia. Variant carriers exhibited elevated total and LDL cholesterol, although levels were generally lower than in carriers of classical FH mutations. However, subsequent studies did not confirm cosegregation between *STAP1* variants and hypercholesterolemia. Lamiqiz–Moneo et al. found no consistent association between genotype and LDL-C levels in seven families with predicted pathogenic *STAP1* variants.⁷ Some carriers had normal LDL-C, while some non-carriers displayed hypercholesterolemia. Mohebi et al. similarly reported a known *STAP1* variant (p. D207N) that did not segregate with the phenotype.⁸ Due to the lack of robust evidence, several authors have recommended excluding *STAP1* from FH diagnostic panels. Early observations suggested a possible role in mild FH, but larger studies and family-based analyses do not support *STAP1* as a causative FH gene. Current evidence suggests that *STAP1* is unlikely to represent a causal FH gene and may instead act as a genetic modifier influencing lipid levels.

LIPA (Lysosomal Acid Lipase A)

LIPA is not a primary FH gene but plays an important role as an FH phenocopy. Biallelic pathogenic mutations in *LIPA* cause cholesteryl ester storage disease (CESD), a rare autosomal recessive disorder characterised by elevated LDL-C, hepatomegaly, abnormal liver function, progressive atherosclerosis, and early cardiovascular disease. CESD may closely resemble heterozygous FH, leading to potential misdiagnosis.^{4,5} Several studies, including the Portuguese FH Study, have reported that a subset of FH-negative patients (those without *LDLR*, *APOB*, or *PCSK9* mutations) carry *LIPA* variants, underscoring its relevance as a phenocopy gene.^{2,4} As a result, *LIPA* is routinely included in expanded NGS panels for FH.^{2,5} Although *LIPA* mutations account for only a small proportion of FH – negative cases (approximately 1–2% in some cohorts), identifying CESD is clinically important because management differs from classic FH. Thus, *LIPA* contributes to enhanced diagnostic precision and avoids misclassification.

ABCG5 and ABCG8 (ATP-binding cassette transporters)

ABCG5 and *ABCG8* encode sterol transporters involved in the absorption and excretion of plant sterols and cholesterol. Biallelic mutations in either gene cause sitosterolemia, an autosomal recessive disorder presenting with very high LDL-C, elevated plant sterols (e. g., sitosterol, campesterol), tendon xanthomas, and premature coronary artery disease.^{9,10} Even heterozygous carriers may show modest LDL-C elevation. Several studies have reported that 1.5–2.4% of FH cohorts carry pathogenic variants in *ABCG5* or *ABCG8*.^{4,10} These variants may appear alone or alongside classical FH mutations, resulting in oligogenic FH, where combined variants worsen the lipid profile.⁹ Because clinical criteria alone may misclassify sitosterolemia as FH (especially in children), *ABCG5/ABCG8* are now standard components of expanded NGS panels. Distinguishing FH from sitosterolemia is essential because statins are often less effective in sitosterolemia, whereas dietary modification and ezetimibe have greater impact.^{2,5}

APOE (Apolipoprotein E)

APOE plays a key role in the clearance of triglyceride-rich lipoproteins (VLDL, IDL, remnants) via interactions with LDLR and related receptors. It has three common isoforms: *ApoE2* – reduced receptor binding, associated with type III hyperlipoproteinemia, *ApoE3* – neutral, *ApoE4* – associated with higher LDL-C and increased cardiovascular risk.¹¹ Rare *APOE* variants can cause autosomal dominant hypercholesterolemia. The p. Leu167del variant accounts for ~3% of LDLR/APOB/PCSK9-negative ADH cases and causes LDLR downregulation by altering VLDL structure.¹² Common *APOE* isoforms, while not causal for FH, may modify the FH phenotype. For example, *APOE4* is associated with a modest LDL-C increase, while *APOE2* is linked to lower LDL-C but predisposes homozygotes to type III hyperlipoproteinemia under certain metabolic conditions.¹¹ *APOE* variants account for ~1–3% of mutation-negative FH cases.^{5,12} Including *APOE* in NGS panels therefore improves diagnostic yield in patients with an FH phenotype but no mutations in the major FH genes.

LDLRAP1 (Low-Density Lipoprotein Receptor Adaptor Protein 1)

LDLRAP1 is essential for receptor-mediated endocytosis of LDL particles. Mutations in this gene cause autosomal recessive hypercholesterolemia (ARH), a condition that clinically resembles homozygous FH but differs in inheritance and molecular pathophysiology.^{13,14} *LDLRAP1* encodes an adaptor protein required for internalising the LDL–LDLR complex via clathrin-coated pits. Mutations disrupt this process, impairing LDL clearance and leading to markedly elevated LDL-C, early atherosclerosis, and tendon xanthomas. ARH typically presents in childhood or adolescence and should be suspected in severe FH cases

without mutations in LDLR, APOB, or PCSK9, particularly in families with parental consanguinity or multiple affected siblings.^{3,13} Although rare globally, *LDLRAP1* variants are identified in some mutation – negative FH patients through expanded NGS panels.^{2,5} For this reason, *LDLRAP1* is included among rare genes associated with FH-like phenotypes.

Conclusion

FH is increasingly recognized as a genetically heterogeneous disorder rather than a purely monogenic condition. Although pathogenic variants in *LDLR*, *APOB*, and *PCSK9* account for most molecularly confirmed cases, many patients with a clinical FH phenotype remain mutation-negative. In these individuals, elevated LDL-C levels may result from polygenic hypercholesterolemia, oligogenic interactions, or genetic phenocopies. Rare genes such as *STAP1*, *LIPA*, *ABCG5/ABCG8*, *APOE*, and *LDLRAP1* may contribute to FH-like phenotypes through different mechanisms affecting lipid metabolism. Advances in NGS and polygenic risk assessment improve diagnostic accuracy and support more personalized management of patients with severe hypercholesterolemia.

Conflict of interest

None.

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Ethical statement

The work was written in accordance with the Declaration of Helsinki.

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