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CASE REPORT

CLINICAL CASE

Competing Genetic Traits and Their Influence on LDL Cholesterol Concentration in Familial Hypercholesterolemia

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ABSTRACT

Familial hypercholesterolemia is a monogenic disorder that leads to premature atherosclerosis as a result of lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C). Both genetic traits and lifestyle factors can influence LDL-C levels. Adults with LDL-C of 170 mg/dL and higher may benefit from genetic evaluation to accurately assess their risk of atherosclerosis. (J Am Coll Cardiol Case Rep 2024;29:102171) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 36-year-old man presented with newly detected hypercholesterolemia. The results of physical examination were notable for normal body mass index (23 kg/m^2), blood pressure of 126/80 mm Hg, bilateral Achilles tendon thickening, and a crescendo-decrescendo murmur grade 1/6 suggestive of aortic sclerosis. His family history was notable for hypercholesterolemia in his father and hypercholesterolemia and Alzheimer dementia in his paternal grandfather. Neither had had a known atherosclerotic cardiovascular disease (ASCVD) event. His mother had hypertension, and his maternal grandmother had an ischemic stroke at age 80 years. The patient's fasting lipid panels are shown in Table 1. The untreated fasting lipid panel showed a total cholesterol of 229 mg/dL, low-density lipoprotein cholesterol (LDL-C) of 152 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 59 mg/dL, and triglycerides of 100 mg/dL. His primary care physician advised a low-saturated-fat diet and repeated a lipid panel, showing an LDL-C of 173 mg/dL. Given his family history of hypercholesterolemia and increasing LDL-C despite a stringent diet and exercise regimen, he was referred for further evaluation of his dyslipidemia. The Dutch Lipid Programme Clinic Score was 7 (6 points for tendinous xanthomata, 1 point for LDL-C between 155 and 189 mg/dL).

LEARNING OBJECTIVES

- To recognize LDL-C variability in FH based on incremental and competing genetic traits.
- To understand the role of genetic evaluation in tailoring treatment for hypercholesterolemia.

MEDICAL HISTORY

He had no significant medical history other than hypercholesterolemia.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

FH = familial hypercholesterolemia

HeFH = heterozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

DIFFERENTIAL DIAGNOSIS

On the basis of his LDL-C level, the differential diagnosis included secondary causes such as a high saturated fat diet, hypothyroidism, nephrotic syndrome, and obstructive hepatobiliary disease; primary monogenic such as heterozygous familial hypercholesterolemia (HeFH), APOE (pLeu167del) related familial hypercholesterolemia (FH), LDL-receptor-Adaptor-Protein-1, polygenic causes of hypercholesterolemia, familial combined hyperlipidemia, lysosomal acid lipase deficiency, high lipoprotein(a), and β-sitosterolemia.

INVESTIGATIONS

A buccal swab specimen was sent to GBinsight for evaluation of genetic dyslipidemia traits (Table 2). This analysis revealed a mutation in the LDL-receptor (*LDLR*) diagnostic of HeFH (Table 2). There were 6 additional variants: heterozygous trait for *ABCA6*, *APOA5*, and *ABCG8*, and homozygosity for *CDKn2B-AS1* (Table 2). Finally, there was a heterozygous loss-of-function variant in the *PCSK9* gene. His polygenic disease risk score placed him at the 99th percentile for hypercholesterolemia.

Other pertinent laboratory studies showed a lipoprotein(a) concentration of 25.7 nmol/L, C-reactive protein of 0.4 mg/L, and hemoglobin A1c of 5.1%. The comprehensive metabolic profile and thyroid panel were unremarkable. The urinalysis was negative for protein. Given his lack of symptoms, no further diagnostic studies were obtained.

MANAGEMENT

In as much as HeFH is considered a coronary heart disease risk equivalent, given the lifelong exposure to increased concentration of LDL particles, management centers on intensive LDL-C lowering. The goal of therapy is >50% reduction in LDL-C from baseline and <100 mg/dL. Given the cumulative burden of hypercholesterolemia and high likelihood of subclinical atherosclerosis, a goal LDL-C of <70 mg/dL is suggested.[1] These targets are to be achieved with diet and pharmacotherapy with high-intensity statins in combination with nonstatin therapies including ezetimibe, *PCSK9* inhibitor, or bempedoic acid.[2]

DISCUSSION

FH is a genetic condition, usually caused by a pathogenic variant in 1 of 3 major genes (*LDLR*, genes encoding *APOB*, and *PCSK9*). Less commonly it may involve LDL-receptor-adaptor-protein-1 (autosomal recessive) and homozygosity for apoprotein E genes (pLeu167del). It is the most common genetic cause of cardiovascular disease, estimated to affect between 1 in 200 and 1 in 333 persons.[2] This condition leads to premature atherosclerosis related to lifelong exposure to elevated LDL-C. The variability in LDL-C levels and onset of atherosclerosis depends on the severity of the underlying mutation, with higher risk seen for mutations in *LDLR* than in *APOB* or *PCSK9*, polygenic cholesterol traits, and risk modifiers such as lipoprotein(a).[3,4] These patients are at increased risk compared with matched cohorts with similar LDL-C levels, and early treatment can help mitigate the risk of ASCVD events to levels comparable with those in individuals without FH.[5]

Despite the global prevalence of FH, this condition is severely underdiagnosed or is diagnosed after a cardiovascular event.[5] Hypercholesterolemia in a patient using a low-fat diet prompts an evaluation for primary and secondary causes of hypercholesterolemia. Our patient was initially presumed to have nongenetic-related hypercholesterolemia because of his initial LDL-C of 152 mg/dL as well as the absence of ASCVD in his first-degree relatives. FH can have a broad range of LDL-C levels because there can be many genetic variants within the cholesterol synthesis, excretion, and absorption pathways as well as differences in lifestyle patterns.[3] Interestingly, 55% of patients with genetically confirmed FH had LDL-C levels <190 mg/dL, and 27% had an LDL-C <130 mg/dL in registry studies.[6] Diagnosis of FH improves ASCVD risk assessment, guides earlier implementation of lipid-lowering therapy, and guides increased use of nonstatin medications.[2] A genetic diagnosis of FH also prompts cascade genetic screening of family members.

Our patient had a heterozygous pathogenic *LDLR* mutation, and major secondary causes of hypercholesterolemia were excluded. The patient adhered to a low-saturated-fat diet and exercise regimen. He did

TABLE 1 Lipid Panels

Factor	2021	3/2023	6/2023
Medications	None	None	Rosuvastatin 10 mg daily
Total cholesterol, mg/dL	229	244	132
LDL-C, mg/dL	152	173	72
HDL-C, mg/dL	59	60	49
Triglycerides, mg/dL	100	67	55
Lipoprotein(a), nmol/L		25.7	

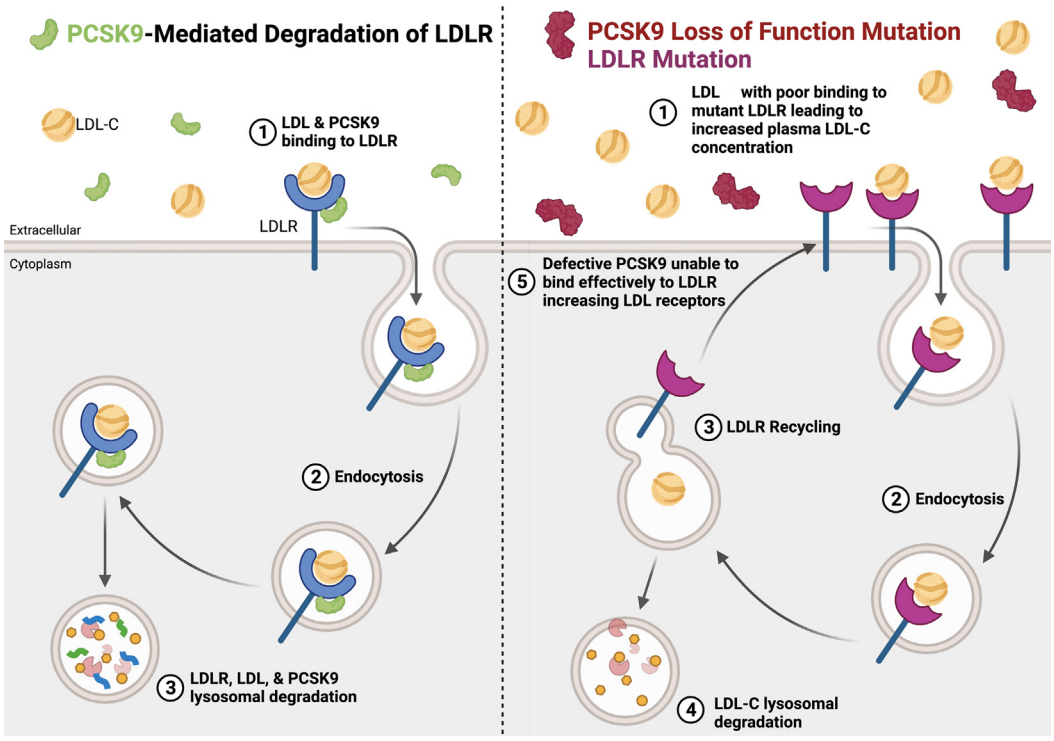
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

TABLE 2 Genetic Analysis

Variant	Type	Genotype	dbSNP/ClinVar	Phenotype	Classification
Pathogenic variant					
LDLR c.1897C>T (p.Arg633Cys) missense	SNV	Heterozygous	rs746118995 ClinVar: 226379	Familial hypercholesterolemia autosomal dominant	Pathogenic
Variants of uncertain significance and high-risk variants					
PCSK9 c. 137G>T (p.Arg46Leu) missense	SNV	Heterozygous	rs11591147 ClinVar: 2878	Hypocholesterolemia	Association
ABCA6 c.4075T>C (p.Cys1359Arg) missense	SNV	Heterozygous	rs77542162	Hypercholesterolemia	Strong risk factor
APOA5 c. 56C>G (p.Ser19Trp) missense	SNV	Heterozygous	rs3135506 ClinVar: 4403	Hypertriglyceridemia	Risk factor
ABCG8 c. 55G>C (p.Asp19His) missense	SNV	Heterozygous	rs11887534 ClinVar: 4975	Increased sterol excretion and risk of gallbladder disease	Association
COQ2 c.64A>T (p.Arg22Ter) Stop_gain	SNV	Heterozygous	rs112033303	Statin-induced myopathy	VUS-likely strong risk factor

not exhibit the typical finding of hypertriglyceridemia seen in familial combined hyperlipidemia, a metabolic disorder with increased production of VLDL and concomitant cholesterol and triglyceride elevations. Despite having an *APOA5* variant, which is associated with hypertriglyceridemia, serum triglycerides were normal. β-sitosterolemia, a rare autosomal recessive condition leading to hyperabsorption and reduced excretion of dietary sterols, was also a consideration, given his tendinous xanthomata and LDL-C levels.[7] Serum plant sterols, especially sitosterol, campesterol, and stigmasterol can be obtained to make this diagnosis.[7] However, sitosterolemia was unlikely because his genetic testing revealed a specific mutation in the *ABCG8* gene (encodes for proteins that transport sterols across cells) that leads to increased

FIGURE 1 *LDLR* and *PCSK9* Pathways



sterol excretion and is associated with reduced plasma LDL-C levels. He also had a mutant *CDKN2B-AS1* gene, which is associated with an increased risk of coronary atherosclerosis and myocardial infarction. Although the exact mechanism by which this increases risk is unclear, it is coinherited with other known risk variants in the same chromosome, such as *rs10757272*. Furthermore, this patient had a mutation in the *ABCA6* gene (ATP binding cassette-subfamily-A-member-6: protein that helps transports cholesterol out of cells). This gene has been associated with hypercholesterolemia in genome-wide association studies (**Table 2**). Finally, his polygenic risk score for hypercholesterolemia was at the 99th percentile, signifying a heightened risk for further elevation in LDL-C.

These LDL-C raising traits were mainly offset by a loss-of-function heterozygous *PCSK9* mutation and to a lesser extent from an *ABCG8* mutation. In normal physiology, *PCSK9*-bound *LDLR* leads to lysosomal destruction of the *LDLR*. With reduced *PCSK9* activity or inhibition, there are more available *LDLR*s to bind and eliminate plasma LDL (**Figure 1**). The response to *PCSK9* inhibition in patients with FH depends on residual *LDLR* activity. However, studies have shown *PCSK9* inhibitors to have similar efficacy in patients with HeFH compared with those without FH[2] By contrast, the LDL-C lowering efficacy in HeFH patients is much less.[2] This case underscores the intricate and complex interplay of genetic factors in influencing plasma LDL-C levels in FH.

FOLLOW-UP

The patient was recommended to begin rosuvastatin 40 mg daily but requested a lower dose of 10 mg daily, which lowered the LDL-C to 72 mg/dL. To further reduce his LDL-C and ASCVD risk and concerns of statin-associated muscle events that would impair his exercise capacity, he was prescribed combination therapy with ezetimibe 10 mg daily.

CONCLUSIONS

Patients with LDL-C <190 mg/dL may still be at risk for having FH because competing genetic traits and lifestyle factors can influence LDL-C levels. Patients with a family history of hypercholesterolemia and significantly elevated LDL-C without other major comorbidities can be evaluated with genetics to further elucidate their overall cardiovascular risk profile and alter management.

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