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Genetic Disorders in Familial Hypercholesterolemia

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ABSTRACT

Familial hypercholesterolemia is a genetic lipid disorder characterized by elevated levels of low-density lipoprotein cholesterol and an increased risk of premature atherosclerotic cardiovascular disease. Traditionally considered a monogenic disorder caused by mutations in genes involved in low-density lipoprotein metabolism, advances in molecular genetics have revealed more complex genetic architectures, including oligogenic and polygenic forms. Oligogenic familial hypercholesterolemia results from the interaction of multiple rare variants across genes involved in lipid metabolism, while polygenic hypercholesterolemia is caused by the cumulative effect of numerous common genetic variants that modestly increase low-density lipoprotein cholesterol levels. These genetic patterns influence disease severity, clinical diagnosis, and therapeutic approaches. This review discusses the epidemiology, genetic mechanisms, clinical manifestations, diagnostic strategies, and treatment options for oligogenic and polygenic familial hypercholesterolemia, emphasizing the importance of early detection and aggressive lipid-lowering therapy to prevent cardiovascular complications.

Keywords

Adults, Children, Cholesterol, Genetic, Treatment.

Abbreviations

APOB: Apolipoprotein B, FH: Familial Hypercholesterolemia, HeFH: Heterozygous Familial Hypercholesterolemia, HoFH: Homozygous Familial Hypercholesterolemia, LDL-c: Low Density Lipoprotein Cholesterol, LDLR: Low Density Lipoprotein Receptor, PCSK9: Proprotein Convertase Subtilisin/Kexin type 9.

Introduction

Hypercholesterolemia is one of the most important modifiable risk factors for atherosclerotic cardiovascular disease. Familial hypercholesterolemia (FH) is a hereditary disorder characterized by elevated plasma low density lipoprotein cholesterol (LDL-c) levels from birth and a significantly increased risk of premature coronary artery disease. If untreated, individuals with FH are exposed to lifelong high LDL levels, accelerating the development of atherosclerosis and cardiovascular complications [1].

Historically, FH has been described as a monogenic autosomal dominant disorder caused primarily by mutations in genes responsible for LDL clearance, including low density lipoprotein receptor (LDLR), Apolipoprotein B (APOB), and Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9). However, recent genomic studies demonstrate that many individuals with clinical features of FH do not carry mutations in these genes. Instead, they exhibit polygenic inheritance or combinations of multiple variants in lipid-regulating genes [2-5].

These findings have led to the recognition of oligogenic FH and polygenic hypercholesterolemia as distinct genetic models contributing to severe LDL elevation [3,4]. Understanding these mechanisms is essential for improving diagnosis, risk assessment,

and therapeutic strategies.

Hypercholesterolemia affects a large portion of the global population. Recent estimates indicate that heterozygous familial hypercholesterolemia (HeFH) occurs in approximately 1 in 250 individuals worldwide [1].

However, genetic testing reveals that only around 40% of individuals clinically diagnosed with FH have identifiable pathogenic mutations in classical genes. The remaining cases often result from polygenic inheritance or other complex genetic mechanisms. Polygenic hypercholesterolemia accounts for approximately 20%-30% of patients with an FH-like phenotype [2-5].

Oligogenic FH appears less common but may contribute significantly to severe phenotypes. Studies show that about 5% of individuals with elevated LDL-c may carry damaging variants in multiple lipid-related genes [6].

Because many cases remain undiagnosed, the actual prevalence of genetically determined hypercholesterolemia is likely underestimated [1].

Monogenic FH: the classical form of FH is monogenic and autosomal dominant. It results from mutations in genes involved in LDLR function and lipid metabolism. The main genes include LDLR, APOB, and PCSK9. Mutations in these genes impair hepatic clearance of LDL particles, leading to markedly elevated LDL-c levels and early development of atherosclerosis [3,5].

Although monogenic FH is well characterized, genetic testing often fails to identify mutations in many individuals with similar clinical features [4].

Oligogenic FH: occurs when multiple rare variants in different genes interact to produce a severe hypercholesterolemic phenotype. Instead of a single causative mutation, patients carry combinations of variants affecting lipid metabolism. These may include genes associated with LDL metabolism such as LDLR, APOB, PCSK9, ABCG5, ABCG8, Apolipoprotein E. The interaction between variants can amplify the effect on LDL-c levels and increase the risk of coronary artery disease [3-6].

Clinical studies show that individuals with oligogenic FH may have even higher LDL-c levels than those with monogenic mutations. The severity of the phenotype depends on the number and functional impact of the variants involved [3,6].

Polygenic hypercholesterolemia results from the cumulative effect of numerous common genetic variants, each exerting a small influence on LDL levels. More than 50 genomic loci have been identified that influence LDL-c concentrations.

These variants are often single-nucleotide polymorphisms (SNPs) affecting genes involved in: cholesterol synthesis, lipoprotein metabolism, LDLR activity and lipid transport [2,3].

Individually, these variants cause only minor increases in LDL-c. However, when combined in a high polygenic risk score, they can lead to clinically significant hypercholesterolemia [2,4].

Environmental factors such as diet, obesity, and sedentary lifestyle may further amplify the genetic predisposition. Polygenic hypercholesterolemia typically shows less clear familial inheritance compared with monogenic FH [2,4].

LDL metabolism: LDL-c is transported in plasma lipoproteins and cleared primarily through hepatic LDLR. The normal pathway involves LDL particles binding to LDLR on hepatocytes, internalization of the LDLR complex and recycling of receptors to the cell surface. Mutations or genetic variants affecting these processes impair LDL clearance and cause elevated plasma LDL-c [3,5].

In oligogenic FH, combinations of variants disrupt multiple steps in lipid metabolism. For example: LDLR variants reduce LDLR activity, APOB variants impair LDL binding to receptors, PCSK9 variants increase degradation of LDLR. The combined effect leads to greater LDL accumulation than a single mutation alone [3,6].

Polygenic hypercholesterolemia arises from multiple genetic variants that subtly alter lipid metabolism. Mechanisms include increased hepatic cholesterol synthesis, reduced LDLR expression, altered lipoprotein transport and impaired lipid clearance. These mechanisms collectively elevate LDL-c and promote atherosclerosis [2,3].

Many individuals with hypercholesterolemia are asymptomatic until cardiovascular disease develops. Typical clinical manifestations include tendon xanthomas, xanthelasma, corneal arcus and premature coronary artery disease. These findings are more common in severe forms of FH but may also occur in oligogenic cases [1-6].

Persistent elevation of LDL-c promotes the formation of atherosclerotic plaques. Patients may develop coronary artery disease, myocardial infarction, stroke, and peripheral arterial disease. Individuals with genetically determined hypercholesterolemia have a significantly higher risk of early cardiovascular events compared with the general population [1].

Several diagnostic tools are used to identify FH, including Dutch Lipid Clinic Network criteria, Simon Broome criteria, and Make Early Diagnosis to Prevent Early Death (MEDPED). These scoring systems evaluate LDL-c levels, family history, clinical signs and genetic testing results [1].

Genetic testing is increasingly used to differentiate monogenic, oligogenic, and polygenic forms of hypercholesterolemia. Testing may include targeted gene sequencing, whole-exome sequencing, polygenic risk score analysis. Genetic identification improves risk

stratification and helps guide family screening strategies [2-4].

Lifestyle intervention is the first step in managing hypercholesterolemia. Recommended measures include reduction of saturated fat intake, increased physical activity, smoking cessation and weight management. Dietary changes alone can reduce LDL-c levels by approximately 8%-10%. However, most patients with genetic hypercholesterolemia require pharmacological therapy [1].

Statins are the cornerstone of treatment for hypercholesterolemia. Mechanism of action: inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA), increased hepatic LDLR expression, enhanced LDL clearance. Statins significantly reduce LDL-c levels and lower the risk of cardiovascular events. Long-term statin therapy has been shown to reduce coronary mortality by more than one-third in patients with FH [1].

Ezetimibe reduces cholesterol absorption in the small intestine by inhibiting the Niemann-Pick C1-like 1 (NPC1L1) transporter. When combined with statins, it can produce additional LDL reductions of approximately 15%-25%. This combination therapy is commonly used when statin monotherapy is insufficient [1].

PCSK9 inhibitors are monoclonal antibodies that prevent degradation of LDLR. By blocking PCSK9 activity, these agents increase LDLR recycling and enhance LDL clearance. PCSK9 inhibitors can reduce LDL-c levels by up to 60% in high-risk patients. They are particularly useful in severe hypercholesterolemia, statin-intolerant patients, genetically determined hypercholesterolemia [1].

Bempedoic acid inhibits ATP citrate lyase, a key enzyme in hepatic cholesterol synthesis. This medication provides additional LDL reduction and may be used in patients who cannot tolerate high-dose statins [1].

For severe or refractory cases, lipoprotein apheresis may be required [1]. This extracorporeal procedure removes LDL particles from the blood and can reduce LDL levels by 50%-70% per session. It is typically used in patients with severe FH who do not respond adequately to pharmacologic therapy.

Recent advances in biotechnology have introduced new therapeutic strategies. Emerging treatments include small interfering RNA therapies targeting PCSK9, gene editing approaches and antisense oligonucleotide therapies. These novel approaches may significantly improve treatment outcomes for patients with severe genetic hypercholesterolemia [1-5].

Early detection is essential to prevent cardiovascular complications. Recommended strategies include lipid screening in children and adults, cascade screening of family members, genetic testing in suspected cases. Early treatment significantly reduces the lifetime risk of cardiovascular disease [1].

Genetic hypercholesterolemias are defined by very high LDL-c levels, above 194 mg/dL, in the absence of secondary causes (Tables 1 and 2). Clinical suspicion of monogenic hypercholesterolemias includes presentation of the phenotype at younger ages, presence of specific clinical features, and a known family history of dyslipidemia and/or premature atherosclerosis (Figure 1).

Table 1: Causal mutations of monogenic hypercholesterolemia.

Disorder	Gene inheritance/chromosomal	
Group 1: Monogenic hypercholesterolemia		
Heterozygous familial hypercholesterolemia and	Low density lipoprotein receptor/19q13 Apoprotein B/2p24	Autosomal semidominant
Homozygous familial hypercholesterolemia	Proprotein Convertase Subtilisin/Kexin type 9/1p32	Autosomal semidominant
Autosomal recessive hypercholesterolemia	Low Density Lipoprotein Receptor Adaptor Protein 1/1p35	Autosomal recessive
Sitosterolemia	ABCG5/2p21 ABCG8/2p21	Autosomal recessive
Lysosomal acid lipase deficiency	LIPA/10923	Autosomal recessive

Table 2: Secondary causes of dyslipidemia.

Secondary lifestyle factors and medical conditions associated with dyslipidemia			
	↑ Low Density Lipoprotein Cholesterol	**↑ Triglycerides**	**↓ High Density Lipoprotein Cholesterol**
Lifestyle			
Obesity	✓	✓	✓
Physical inactivity	✓	✓	✓
Excess alcohol		✓	
Smoking			✓
Diet			
High trans-fat content	✓		
High saturated fat content	✓		
High carbohydrate content		✓	✓
Medical conditions			
Obstructive liver disease	✓		
Hypothyroidism	✓		
Nephrotic syndrome	✓		
Anorexia	✓		

HeFH is the most frequent cause of high cholesterol among monogenic causes. It is defined as semi-dominant autosomal inheritance: individuals with one copy of a pathogenic variant (i.e., monoallelic or "heterozygous") have an abnormal phenotype, intermediate between individuals without genetic alteration and those with two copies of a pathogenic variant (biallelics, often encompassed by the nonspecific term "homozygous"). The monoallelic form of HeFH has a population prevalence of approximately 1 in 300 individuals.

Three major genes are associated with HeFH, including mutations with loss of function of LDLR (85% to 90% of cases), defective variants in the gene encoding APOB (5% to 10% of cases), as well

as mutations with gains in function of the PCSK9 protein (<1% of cases.) (Table 1).

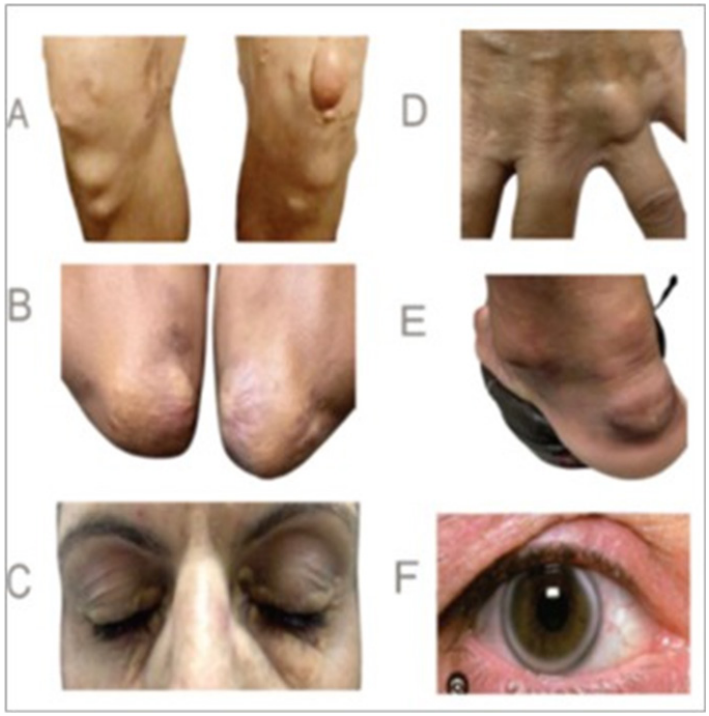

Figure 1: A: Tuberous xanthomas: homozygous familial hypercholesterolemia, **B**: Flat xanthomas in elbows: sitosterolemia, **C**: Eyelid xanthelasma: sitosterolemia, **D**: Xanthoma in the flexor tendon of the hand: sitosterolemia, **E**: Xanthomas in the Achilles tendon: homozygous familial hypercholesterolemia, **F**: Corneal arch: heterozygous familial hypercholesterolemia.

Physical manifestations of HeFH include tendon xanthomas that are most commonly seen in the Achilles tendon and extensor tendons of the fingers, and patellar tendons. They are practically pathognomonic of FH and occur in less than 50% of cases. The corneal arch in individuals younger than 45 years, in addition to LDL-c levels above the 95th percentile or >194 mg/dL in adults and > 160 mg/dL in children (Figure 1).

The diagnosis of HeFH can be established by several criteria that incorporate clinical variables such as family and personal history of premature atherosclerotic cardiovascular disease, patient and family cholesterol levels, presence of corneal arch or xanthomas, and genetic test results. The Update of the Brazilian Guideline on Familial Hypercholesterolemia adopts the modified criterion of the Dutch Lipid Clinic Network [7]. (Table 3).

HeFH is a common genetic cause of premature coronary heart disease, especially myocardial infarction resulting from lifetime exposure to high LDL-c concentrations. If left untreated, HeFH is associated with the premature development of atherosclerotic cardiovascular disease, predisposing to cardiovascular events, stroke, and peripheral limb ischemia. If left untreated, men and women with HeFH and total cholesterol of 310 to 580 mg/dl will develop coronary artery disease before the ages of 55 and 60, respectively.

Universal screening is performed by measuring the lipid profile in all children, with the justification that early identification and treatment of pediatric dyslipidemias, especially FH, will reduce the risk of atherosclerotic cardiovascular disease. It is performed between 9 and 11 years old and again between 17 and 21 years

Table 3: Diagnostic criteria for heterozygous familial hypercholesterolemia based on the criteria of Dutch Lipid Clinic Network (Dutch Make Early Diagnosis to Prevent Early Death). Modified from Dutch Lipid Clinic Network, adopting a criterion from the Simon Broome Register Group.

Family history	**Points**
First-degree relative with premature vascular/coronary artery disease (men under 55 years of age, women under 60 years of age) OR Adult relative with total cholesterol > 290 mg/dl	1
First-degree relative with tendon and/or corneal arch xanthoma OR First-degree relative < 16 years with cholesterol > 260 mg/dl	2
Clinical history	
Patient with premature coronary heart disease (men under 55 years of age, women under 60 years of age)	2
Patient with premature brain or peripheral disease (men under 55 years of age, women under 60 years of age)	1
Physical examination	
Xanthoma tendinosus	6
45<yearold corneal arch	4
Low-density lipoprotein (LDL-c) cholesterol levels (mg/dl)	
≥ 330	8
250 to 329	5
190 to 249	3
155 to 189	1
Deoxyribonucleic acid analysis (DNA)	
Presence of functional mutation of the LDL receptor gene, Apolipoprotein B-100 OR Proprotein Convertase Subtilisin/Kexin Type 9	8
Diagnosis of familial hypercholesterolemia	
Sure if	> 8
Likely to be	6 to 8
Possible if	3 to 5

old. As lipid profile values can change during puberty, screening between 12 and 16 years of age may be altered due to hormonal causes.

In special populations, screening is done in children over the age of 2 years, in the presence of a family history of premature atherosclerotic cardiovascular disease, or suspected HeFH, or the presence of risk factors for atherosclerotic cardiovascular disease.

Cascade screening involves determining the lipid profile in all first-degree relatives (father, mother, and siblings) of patients diagnosed with HeFH. This measure is considered to be the most cost-effective for the identification of HeFH carriers.

Genetic screening is cost-effective and can be performed on all patients and first-degree relatives of individuals diagnosed with HeFH. The most cost-effective cascade screening is one that uses genetic information from affected individuals in whom a disease-causing mutation has been identified [8-11].

The potential benefits of genetic testing include establishing a clear diagnosis of dyslipidemia, which eliminates uncertainty for both the patient and the healthcare provider and allows for more personalized management. This includes a better understanding of the overall prognosis and a better selection of targeted pharmacologic agents. Another benefit is the ability to screen for genetic risk in family members who may be presymptomatic and could benefit from early intervention or more frequent monitoring.

Risk stratification in HeFH is critical since atherosclerotic cardiovascular disease is the final event to be prevented and treated. But not all patients with HeFH will develop myocardial infarction or stroke. Currently, three models for predicting the risk of atherosclerotic cardiovascular disease have been specifically developed for adults with HeFH: the Montreal-FH score (MFHS), the SAFEHEART risk equation, and the FH-SCORE. All these scores are derived from historical cohorts of patients with HeFH generally consider the presence of classic risk factors and factors such as body mass index, LDL-c, Lipoprotein(a) among others, in the risk predictor equations. The application of these prediction models should be adapted to the specific population profile, recognizing the limitations of each model.

In line with the heterogeneity of cardiovascular risk among individuals with HeFH, there is also a corresponding variability in the burden of subclinical atherosclerosis.

The coronary calcium score is an important tool to assess cardiovascular risk in these individuals, improving the discrimination of events. It has not yet been determined whether computed tomography angiography provides greater discriminatory power than coronary calcium score alone for cardiovascular events in this population.

Based on the presence of significant overt or subclinical atherosclerotic disease, classic and additional risk factors (initiation of lipid-lowering treatment after 40 years of age, HDL-c < 40 mg/dl, Lipoprotein(a) > 50 mg/dL or > 125 nmol/L, xanthomas in the Achilles tendon, coronary calcium greater than 100 AU or > the 75th percentile, atherosclerotic plaque with obstruction greater than 50% in any arterial territory); very high LDL-c, individuals with HeFH can be classified into three risk categories:

Very high risk: when faced with clinically manifest atherosclerotic disease, defined as previous myocardial infarction, angina pectoris, previous myocardial revascularization, ischemic or transient stroke, or intermittent claudication. In the presence of advanced atherosclerotic subclinical disease diagnosed with a calcium score greater than 100 AU or 75% of the percentile for age and sex, or coronary computed tomography angiography presenting coronary obstructions in more than 50% or the presence of non-obstructive plaques in more than one vessel.

High risk: in the primary prevention of HeFH, with LDL-c > 400 mg/dl, even without risk factors. In the primary prevention of HeFH, but with additional risk factors. Note: if LDL-c is > 310 mg/dl with one of the high-risk situations; LDL-c > 190 mg/dl with two of the high-risk conditions.

Intermediate risk: in the primary prevention of HeFH, without additional risk factors.

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disease, with autosomal semidominant, biallelic transmission (two copies of a pathogenic variant), one copy coming from the father and one from the mother. Prevalence is approximately 1 in 300,000 to 400,000 population. Mutations occur in both alleles of the LDLR genes or, less frequently, in the APOB, the PCSK9 protein, or the LDLR adaptor protein (recessive form).

Extremely high plasma concentrations of LDL-c, detectable at birth, are characteristic of these patients. If left untreated, elevated plasma LDL-c levels are deposited in tendons, skin tissues, vessels including the aortic root, aortic valve, supra-aortic valve, and coronary ostium. Severe, disseminated atherosclerosis occurs in all major arterial beds and often manifests clinically at very early ages. The severity of atherosclerosis tends to be proportional to the extent and duration of elevated LDL-c levels. Although severe coronary atherosclerosis is the leading cause of death, aortic stenosis is also a major and potentially life-threatening complication in many young individuals with HoFH, and one that often requires aortic valve replacement.

Diagnostic criteria for HoFH: untreated LDL-c > 400 mg/dL suggests HoFH, requiring further investigation for diagnostic confirmation.

Additional clinical criteria: cutaneous or tendon xanthomas before 10 years of age and/or untreated elevated LDL-c levels compatible with HeFH in both parents. In the digenic form (two different causative genes), one parent may have normal LDL-c levels and the other may have LDL-c levels compatible with HoFH.

Genetic criteria: genetic confirmation of biallelic pathogenic/probably pathogenic variants on different chromosomes in the LDLR, APOB, PCSK9, LDLR adaptor protein genes, or ≥ 2 variants of this type at different loci. There is complex genetic variability of HoFH and should be considered in the interpretation of genetic testing.

Genetic testing in HoFH is important as it allows for a definitive diagnosis as well as objective visualization of the underlying genetic complexity, as well as promoting access to appropriate current and emerging therapies and participation in clinical trials. Similar conditions that require further treatment (e.g., sitosterolemia) can be ruled out. Triggers cascade screening to find new patients with phenotypic HeFH or HoFH. It can facilitate prenatal genetic counseling.

HoFH remains a difficult condition to treat, but lipid-lowering therapy, with or without LDL-c apheresis, should be instituted at the time of diagnosis and as early as possible. Despite modestly reducing LDL-c, statin therapy reduced cardiovascular mortality in HoFH patients, with remaining LDL-c levels always very high. Patients with HoFH require multiple lipid-lowering drugs in addition to statins, including ezetimibe, PCSK9 inhibitors, and the LDL receptor-independent therapies lomitapide and angiopoietin-like receptor 3 (ANGPTL3)-targeted therapies for further reductions in LDL-c values. Lipoprotein apheresis can be used as adjunctive therapy for patients with HoFH, who have an inadequate response to medical therapy alone.

Extremely rare autosomal recessive hypercholesterolemia is phenotypically similar to HoFH, with parents having normal cholesterol levels. Children with autosomal recessive hypercholesterolemia have a phenotype that is indistinguishable from children with HoFH, and the definitive diagnosis is made by genetic testing (Table 1).

Sitosterolemia is an extremely rare autosomal recessive disorder of lipid metabolism characterized by increased absorption and decreased bile excretion of plant sterols and cholesterol, resulting in markedly elevated serum concentrations of sitosterol, campesterol, and stigmasterol.

It is caused by biallelic mutations (homozygous/heterozygous compounds) of loss of function of the ABCG5 and ABCG8 genes responsible for sterol efflux through the liver and intestine. In patients with sitosterolemia, intestinal cholesterol absorption increases by about 30%, while intestinal sitosterol absorption increases dramatically by about 800%. Patients with sitosterolemia present mainly tendon and tuberous xanthomas and premature coronary atherosclerosis, characteristics similar to those observed in FH, and are considered a phenocopy of FH. Clinical presentation may include hemolysis, splenomegaly, platelet abnormalities, and arthralgia/arthritis.

Diagnostic criteria for sitosterolemia: cutaneous clinical xanthomas, premature coronary artery disease, serum sitosterol ≥ 1 mg/dL (10 μg/mL).

Genetic criterion: pathogenic mutations in the ABCG5 or ABCG8 genes.

Differential diagnosis: with FH and cerebrotendinous xanthomatosis.

Diagnosis in clinical practice: in patients with premature coronary artery disease in the absence of a family history of hypercholesterolemia and atherosclerotic cardiovascular disease, the diagnosis of sitosterolemia should be considered.

The tendon xanthomas of sitosterolemia tend to be more severe than those of HeFH, even with lower LDL-c levels. Thus, sitosterolemia should be considered in the differential diagnosis of HeFH. In addition, LDL cholesterol levels in patients with sitosterolemia tend to vary dramatically depending on the most recent dietary intake of plant sterols. The exacerbated cholesterol-lowering response to ezetimibe compared with statin reduction may also indicate sitosterolemia.

Treatment: there is no definitive evidence of an association between sitosterol reduction and the prevention of atherosclerotic cardiovascular disease. Consequently, LDL-c, not sitosterol, should be the primary therapeutic target in the treatment of sitosterolemia. Dietary restriction of plant sterols, ezetimibe, bile acid sequestering resins have been shown to reduce LDL-c and sitosterol levels, and therefore these strategies should be considered as standard treatment for patients with sitosterolemia.

Conclusion

Monogenic, oligogenic and polygenic FH represent important genetic causes of elevated LDL-c levels and increased cardiovascular risk. Advances in molecular genetics have revealed that hypercholesterolemia often involves complex genetic interactions rather than single-gene mutations. Oligogenic FH arises from combinations of rare variants in lipid-related genes, while polygenic hypercholesterolemia results from the cumulative effect of multiple common genetic polymorphisms. Both forms contribute to the phenotypic spectrum of severe hypercholesterolemia.

Early diagnosis, genetic testing, and aggressive lipid-lowering therapy are essential for preventing atherosclerotic cardiovascular disease. Future research focusing on genomic medicine and novel therapeutics may further improve management and outcomes for patients with these conditions.

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