

99968_Auto_Edited_055636.docx

WORD COUNT

1375

TIME SUBMITTED

15-OCT-2024 11:32AM

PAPER ID

112333271

Name of Journal: *World Journal of Experimental Medicine*

Manuscript NO: 99968

Manuscript Type: LETTER TO THE EDITOR

Familial hypercholesterolemia: Current limitations and future breakthroughs

Limitations and breakthroughs in familial hypercholesterolemia

Abstract

Familial hypercholesterolemia (FH) is characterized by elevated low-density lipoprotein cholesterol levels due to genetic mutations, presenting with xanthomas, corneal arch, and severe cardiovascular diseases. Early identification, diagnosis, and treatment are crucial to prevent severe complications like acute myocardial infarction. Statins are the primary treatment, supplemented by Ezetimibe and PCSK9 inhibitors, though their effectiveness can be limited in severe cases. Over 90% of FH cases remain undiagnosed, and current treatments are often inadequate, underscoring the need for improved diagnostic and management systems. Future strategies include advancements in gene testing, precision medicine, and novel drugs, along with gene therapy approaches like AAV-mediated gene therapy and CRISPR. Lifestyle modifications, including health education, dietary control, and regular exercise, are essential for managing FH and preventing related diseases. Research into FH-related gene mutations, especially LDLR, is critical for accurate diagnosis and effective treatment.

Key Words: Familial hypercholesterolemia; Genetic Mutations; Treatment; Limitations; Breakthroughs.

Xiang Z, Li J, Wan W, Li S, Wu J. Familial hypercholesterolemia: current limitations and future breakthroughs. *World J Exp Med* 2024; In press

Core Tip: Familial hypercholesterolemia (FH) is a genetic disorder characterized by significantly elevated levels of plasma low-density lipoprotein cholesterol, often leading to severe cardiovascular conditions such as acute myocardial infarction. Early detection, diagnosis, and treatment are crucial for improving patient outcomes. Despite growing awareness, over 90% of the estimated 30 million global FH cases remain undiagnosed, and many patients lack adequate treatment. Current management primarily involves statins, with additional therapies like Ezetimibe and PCSK9 inhibitors, though effectiveness varies, particularly in homozygous FH cases. Advancements in gene testing and precision medicine are essential for better understanding and treating FH. Future strategies include gene therapy and novel lipid-lowering drugs, alongside lifestyle modifications and genetic diagnosis for early intervention and improved prognosis.

TO THE EDITOR

Familial hypercholesterolemia (FH) refers to a ⁵ disease characterized by a significant increase in plasma low-density lipoprotein cholesterol (LDL-C) levels caused by genetic mutations[1]. FH patients have clinical manifestations such as skin and tendon xanthoma or corneal arch and may also experience cardiovascular involvement, even leading to acute myocardial infarction and other diseases in severe cases[2]. FH affects about 10 million people worldwide and is mainly a heterozygous form. This condition is usually caused by ² mutations in the LDL receptor protein gene (LDLR), but mutations in the apolipoprotein B (APOB) and proprotein convertase subtilisin /kexin type 9 (PCSK9) genes have also been implicated [3]. Of note, 17% to 33% of patients with clinically diagnosed monogenic hypercholesterolemia have no genetic cause found at known loci[4]. In recent years, the incidence of FH has been increasing year by year, and there has been growing attention towards this condition. However, despite these developments, more than 90% of the estimated 30 million people worldwide with FH remain undiagnosed. Therefore, early identification, diagnosis, and treatment of FH are particularly important.

The serum cholesterol level of FH patients is significantly increased, and the incidence of Atherosclerotic coronary artery disease (ASCVD) is markedly enhanced[5]. Severe cases can lead to acute myocardial infarction and other diseases[6]. At present, there is a lack of effective methods for the identification and long-term management of FH patients. Besides, shockingly, as many as one-third of patients do not receive any form of treatment. And the current treatment options for FH are not ideal. Once a patient is diagnosed with FH, early initiation of lipid-lowering therapy is recommended[7]. Regarding treatment approaches, both domestic and foreign guidelines recommend statins as the cornerstone therapy for FH management[8]. Additionally, the cholesterol inhibitor Ezetimibe or PCSK9 inhibitors can be added to statin therapy if necessary. Other commonly prescribed medications include lomitapide, CETP inhibitors, and other agents. Surgical interventions such as liver transplantation and partial ileal bypass are currently not widely employed in clinical practice but hold potential for future development[9]. In the future, it is necessary to strengthen the screening of FH patients and further establish a sound FH patient management system, so as to achieve **early detection, early diagnosis and early treatment to improve the prognosis of the disease.**

With advancements in gene testing and precision medicine technology over time, more attention has been given to studying FH-related gene mutations among individuals affected by this condition[10]. However, approximately 50% of identified mutations in FH patients are still classified as variants of unknown significance (VUS), which includes LDLR gene mutation classification. It is highly significant to study and evaluate the functional impact of LDLR gene mutations on the treatment outcomes for FH patients. LDLR gene mutations have been divided into five functional groups [11], and the common mutations with diagnostic value for FH are different in different countries or regions[12-15]. Up to now, more than 4000 kinds of LDLR mutations have been found worldwide (**University College London LDLR FH database (www.ucl.ac.uk/Ldlr)**). And identification of **LDLR** mutations plays a crucial role in the accurate diagnosis and targeted treatment of FH. For example, **the presence and type of LDLR mutations can affect the lipid profile and response to lipid-lowering therapy in Brazilian patients with**

heterozygous FH, and patients carrying null mutations have a poor prognosis[16]. Miltiadous *et al.* studied the efficacy of atorvastatin 20mg/day for 12 weeks in 49 patients with heterozygous FH, divided into two groups, class V and II, based on LDLR mutations. Patients with class V mutations had relatively lower baseline LDL-C values and better response to statin therapy[17]. Studies have demonstrated that LDLR mutations are associated with higher serum LDL-C levels and the incidence of cardiovascular disease is increased in patients with extremely high LDL-C[18]. For refractory homozygous FH patients with LDLR deletion mutations, adding cholesterol inhibitors or PCSK9 inhibitors to statin therapy has limited or even ineffective effects. Foreign guidelines suggest using class 4 Lipid-lowering drugs such as Lomitapide, Mipomersen or Evolocumab in such cases; however, their potential side effects and economic considerations need to be taken into account[19]. Therefore, there is an urgent need for a safe and cost-effective new drug along with novel therapeutic strategies to effectively reduce LDL-C levels. Gene therapy for FH is still in the exploratory phase and primarily involves adeno-associated viruses (AAVs), AAV-mediated gene therapy, and clustered regularly interspaced short palindromic repeats (CRISPR) gene therapy. The clinical applicability of these approaches requires further investigation[20]. Nonetheless, due to the demanding requirements associated with *in vitro* cell model research methods used for this purpose, it becomes challenging to widely implement them across various settings[10]. Moreover, there are variations observed when predicting functional effects and clinical.

Through health education, dietary control, lifestyle improvement, and regular exercise, the regulation of body lipid and lipoprotein metabolism can effectively achieve early prevention and treatment of FH and related cerebrovascular diseases. A randomized controlled clinical trial evaluated the effect of an individualized lifestyle intervention based on the Transtheoretical Model of Health Behavior Change on disease management in patients with FH. The results showed a significant reduction in body mass index, LDL-C and blood pressure, and an improvement in treatment adherence in the intervention group [21]. Meta-analyses have shown cholesterol-lowering effects on FH by the

additional addition of plant sterols or stanols to a low-cholesterol diet, or by the reduction of triglycerides by supplementation with omega-3 fatty acids[22].

Genetic diagnosis enables early detection and diagnosis of FH, while future advancements in personalized medicine combined with gene editing hold promising potential for curing an increasing number of rare diseases and significantly enhancing patients' quality of life. Currently, the disconnect between clinical diagnosis and interpretation of genetic results between medical staff and patients leads to underdiagnosis and treatment of FH. Phenotypic features combined with genetic diagnosis enable early detection and diagnosis of FH; however, even with early diagnosis and lipid-lowering therapy, FH patients with null LDLR mutations tend to be at increased risk. Personalized medicine combined with gene editing is expected to cure more and more rare diseases and significantly improve the quality of life of patients[23]. In the future, it is still necessary to refine LDL-C management according to LDLR mutation types, and improve the diagnosis and treatment of FH around the world through the formulation of national screening programs, new drug development, personalized lifestyle intervention, and awareness education.

8%

SIMILARITY INDEX

PRIMARY SOURCES

1 Paulo Caleb Junior Lima Santos, Aline Cruz Morgan, Cintia Elin Jannes, Luciana Turolla et al. "Presence and type of low density lipoprotein receptor (LDLR) mutation influences the lipid profile and response to lipid-lowering therapy in Brazilian patients with heterozygous familial hypercholesterolemia", *Atherosclerosis*, 2014 25 words — 2%
Crossref

2 docslib.org 20 words — 1%
Internet

3 Santos, Paulo Caleb Junior Lima, and Alexandre Costa Pereira. "Type of LDLR mutation and the pharmacogenetics of familial hypercholesterolemia treatment", *Pharmacogenomics*, 2015. 18 words — 1%
Crossref

4 Seçil Beyece İncazlı, Serap Özer, Meral Kayıkçioğlu. "Evaluation of the Effectiveness of Individually Tailored Lifestyle Intervention in Patients With Familial Hypercholesterolemia", *Journal of Cardiovascular Nursing*, 2022 13 words — 1%
Crossref

5 school.freekaoyan.com 13 words — 1%
Internet

6 www.frontiersin.org
Internet

13 words — 1%

7 Xiaohuan Cheng. "Two mutations in LDLR gene were found in two Chinese families with familial hypercholesterolemia", Molecular Biology Reports, 11/20/2008

Crossref

12 words — 1%

EXCLUDE QUOTES ON

EXCLUDE SOURCES < 12 WORDS

EXCLUDE BIBLIOGRAPHY ON

EXCLUDE MATCHES < 12 WORDS