ISSN 2220-315x (online)

World Journal of *Experimental Medicine*

Quarterly Volume 14 Number 4 December 20, 2024

Published by Baishideng Publishing Group Inc

World Journal of Experimental Medicine

Contents

Quarterly Volume 14 Number 4 December 20, 2024

EDITORIAL

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

World Journal of Experimental Medicine

Quarterly Volume 14 Number 4 December 20, 2024

Contents

World Journal of Experimental Medicine

Quarterly Volume 14 Number 4 December 20, 2024

Contents

NAME OF JOURNAL
World Journal of Experimental Medicine

ISSN
ISSN 2220-315x (online)

LAUNCH DATE
December 20, 2011

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Jian Wu

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
Fang Gong

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-315x/editorialboard.htm

PUBLICATION DATE
December 20, 2024

PUBLISHING PARTNER
Department of Clinical Laboratory, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
http://www.smh.cc/home2020/page/index/index.html

World Journal of Experimental Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Exp Med 2024 December 20; 14(4): 99968

DOI: 10.5493/wjem.v14.i4.99968

ISSN 2220-315x (online)

LETTER TO THE EDITOR

Familial hypercholesterolemia: Current limitations and future breakthroughs

Ze Xiang, Jia-Rui Li, Wei-Min Wan, Shu-Hui Li, Jian Wu

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Nguyen PD

Received: August 4, 2024
Revised: October 2, 2024
Accepted: October 16, 2024
Published online: December 20, 2024
Processing time: 88 Days and 1.6 Hours

Ze Xiang, Jia-Rui Li, Shu-Hui Li, School of Medicine, Zhejiang University, Hangzhou 310058, Zhejiang Province, China

Wei-Min Wan, Jian Wu, Department of Clinical Laboratory, Suzhou Municipal Hospital, Suzhou 215008, Jiangsu Province, China

Co-first authors: Ze Xiang and Jia-Rui Li.

Corresponding author: Jian Wu, MD, PhD, Professor, Department of Clinical Laboratory, Suzhou Municipal Hospital, No. 242 Guangji Road, Suzhou 215008, Jiangsu Province, China. wujianglinxing@163.com

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 proprotein convertase subtilisin/kexin type 9 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 clustered regularly interspaced short palindromic repeats. 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

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 proprotein convertase subtilisin/kexin type 9 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.

Citation: Xiang Z, Li JR, Wan WM, Li SH, Wu J. Familial hypercholesterolemia: Current limitations and future breakthroughs. *World J Exp Med* 2024; 14(4): 99968
URL: https://www.wjgnet.com/2220-315x/full/v14/i4/99968.htm
DOI: https://dx.doi.org/10.5493/wjem.v14.i4.99968

TO THE EDITOR

Familial hypercholesterolemia (FH) refers to a 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 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 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, 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*[17] studied the efficacy of atorvastatin 20 mg/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. 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.

FOOTNOTES

Author contributions: Wu J designed study and revised the manuscript; Xiang Z and Li JR wrote the paper; Wan WM and Li SH searched the literature; All authors reviewed and approved the final version; Xiang Z and Li JR contributed equally to this work.

Supported by National Key Research and Development Program of China, No. 2022YFE0209900.

Conflict-of-interest statement: The authors declare that there are no competing interests associated with this manuscript.

Country of origin: China

ORCID number: Jian Wu 0000-0003-0087-3744.

S-Editor: Gao CC
L-Editor: A
P-Editor: Zhang L

REFERENCES

1 **Hao HM**, Guo YN, Fu DX, Cao BY, Wei HY. [Clinical analysis of 4 children with hereditary hypercholesterolemia]. *Zhonghua Er Ke Za Zhi* 2022; **60**: 1327-1331 [PMID: 36444439 DOI: 10.3760/cma.j.cn112140-20220508-00427]

2 **Chen PP**, Feng SQ, Tian Z, Zhang SY. [Impact of orthotopic liver transplantation on serum lipid level and growing development in patients with homozygous or compound heterozygous familial hypercholesterolemia]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2023; **51**: 270-277 [PMID: 36925137 DOI: 10.3760/cma.j.cn112148-20221231-01027]

3 **Watts GF**, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, Bruckert E, Defesche J, Lin KK, Livingston M, Mata P, Parhofer KG, Raal FJ, Santos RD, Sijbrands EJ, Simpson WG, Sullivan DR, Susekov AV, Tomlinson B, Wiegman A, Yamashita S, Kastelein JJ. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol* 2014; **171**: 309-325 [PMID: 24418289 DOI: 10.1016/j.ijcard.2013.11.025]

4 **Graham CA**, McIlhatton BP, Kirk CW, Beattie ED, Lyttle K, Hart P, Neely RD, Young IS, Nicholls DP. Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. *Atherosclerosis* 2005; **182**: 331-340 [PMID: 16159606 DOI: 10.1016/j.atherosclerosis.2005.02.016]

5 **Leren TP**, Manshaus TE, Ose L, Berge KE. [Lipid profile in children and adolescents with familial hypercholesterolemia]. *Tidsskr Nor Laegeforen* 2007; **127**: 2363-2366 [PMID: 17895939]

6 **Fearon WF**, Cooke JP. Acute myocardial infarction in a young woman with systemic lupus erythematosus. *Vasc Med* 1996; **1**: 19-23 [PMID: 9546909 DOI: 10.1177/1358863X9600100104]

7 **Zhang H**, Ye PC, Wang XM, Wu X, Peng J, Wang SL, Lin J. [The relationship between genotype of familial hypercholesterolemia and the efficacy of PCSK9 inhibitors]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2021; **49**: 572-579 [PMID: 34126724 DOI: 10.3760/cma.j.cn112148-20210322-00257]

8 **Freiberger T**, Vaclová M, Tichý L, Soška V, Bláha V, Fajkusová L, Češka R, Vrablík M. [Familial hypercholesterolemia in the Czech Republic in 2016]. *Vnitr Lek* 2016; **62**: 924-928 [PMID: 28128581]

9 **Alenizi MM**, Almushir S, Suliman I. Surgical Management and Outcomes of Homozygous Familial Hypercholesterolemia in Two Cousins: A Rare Case Report. *Cureus* 2020; **12**: e11692 [PMID: 33391926 DOI: 10.7759/cureus.11692]

10 **Wang DY**, Zhang YM, Che FY, Chu JP, Zhang LY, Li H, Liu BL, Yao ZY, Zhao YW. [Genotype-phenotype analysis of a homozygous familial hypercholesterolemia pedigree]. *Zhonghua Er Ke Za Zhi* 2020; **58**: 101-106 [PMID: 32102145 DOI: 10.3760/cma.j.issn.0578-1310.2020.02.007]

11 **Hobbs HH**, Russell DW, Brown MS, Goldstein JL. The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. *Annu Rev Genet* 1990; **24**: 133-170 [PMID: 2088165 DOI: 10.1146/annurev.ge.24.120190.001025]

12 **Cheng X**, Ding J, Zheng F, Zhou X, Xiong C. Two mutations in LDLR gene were found in two Chinese families with familial hypercholesterolemia. *Mol Biol Rep* 2009; **36**: 2053-2057 [PMID: 19020990 DOI: 10.1007/s11033-008-9416-z]

13 **Salazar LA**, Hirata MH, Cavalli SA, Nakandakare ER, Forti N, Diament J, Giannini SD, Bertolami MC, Hirata RD. Molecular basis of familial hypercholesterolemia in Brazil: Identification of seven novel LDLR gene mutations. *Hum Mutat* 2002; **19**: 462-463 [PMID: 11933210 DOI: 10.1002/humu.9032]

14 **Diakou M**, Miltiadous G, Xenophontos SL, Manoli P, Cariolou MA, Elisaf M. Spectrum of LDLR gene mutations, including a novel mutation causing familial hypercholesterolaemia, in North-western Greece. *Eur J Intern Med* 2011; **22**: e55-e59 [PMID: 21925044 DOI: 10.1016/j.ejim.2011.01.003]

15 **Lombardi MP**, Redeker EJ, Defesche JC, Kamerling SW, Trip MD, Mannens MM, Havekes LM, Kastelein JJ. Molecular genetic testing for familial hypercholesterolemia: spectrum of LDL receptor gene mutations in The Netherlands. *Clin Genet* 2000; **57**: 116-124 [PMID: 10735632 DOI: 10.1034/j.1399-0004.2000.570205.x]

16 **Santos PC**, Morgan AC, Jannes CE, Turolla L, Krieger JE, Santos RD, Pereira AC. 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; **233**: 206-210 [PMID: 24529145 DOI: 10.1016/j.atherosclerosis.2013.12.028]

17 **Miltiadous G**, Xenophontos S, Bairaktari E, Ganotakis M, Cariolou M, Elisaf M. Genetic and environmental factors affecting the response to statin therapy in patients with molecularly defined familial hypercholesterolaemia. *Pharmacogenet Genomics* 2005; **15**: 219-225 [PMID: 15864114 DOI: 10.1097/01213011-200504000-00005]

18 **Tada H**, Kawashiri MA, Nomura A, Teramoto R, Hosomichi K, Nohara A, Inazu A, Mabuchi H, Tajima A, Yamagishi M. Oligogenic familial hypercholesterolemia, LDL cholesterol, and coronary artery disease. *J Clin Lipidol* 2018; **12**: 1436-1444 [PMID: 30241732 DOI: 10.1016/j.jacl.2018.08.006]

19 **Češka R**, Táborský M, Vrablík M. [Consensus statement of professional associations on prescribing of PCSK9-inhibitors]. *Vnitr Lek* 2019; **64**: 1131-1136 [PMID: 30704246]

20 **Rissanen TT**, Ylä-Herttuala S. Current status of cardiovascular gene therapy. *Mol Ther* 2007; **15**: 1233-1247 [PMID: 17505481 DOI: 10.1038/sj.mt.6300175]

21 **Beyece İncazli S**, Özer S, Kayikçioğlu M. Evaluation of the Effectiveness of Individually Tailored Lifestyle Intervention in Patients With Familial Hypercholesterolemia. *J Cardiovasc Nurs* 2022; **37**: 465-474 [PMID: 35952313 DOI: 10.1097/JCN.0000000000000896]

22 **Barkas F**, Nomikos T, Liberopoulos E, Panagiotakos D. Diet and Cardiovascular Disease Risk Among Individuals with Familial Hypercholesterolemia: Systematic Review and Meta-Analysis. *Nutrients* 2020; **12**: 2436 [PMID: 32823643 DOI: 10.3390/nu12082436]

23 **Vohnout B**, Gabcova D, Huckova M, Klimes I, Gasperikova D, Raslova K. Genetic testing of familial hypercholesterolemia in a real clinical setting. *Wien Klin Wochenschr* 2016; **128**: 916-921 [PMID: 27542166 DOI: 10.1007/s00508-016-1053-2]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com