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FAMILIAL HYPERCHOLESTEROLEMIA: ADVANCES IN MOLECULAR PATHOGENESIS, CLINICAL DIAGNOSIS, AND EMERGING LIPID-LOWERING THERAPIES

Naveen Prabakaran C
Associate Professor of Biochemistry
Asia International University, Bhukara, Uzbekistan
drcnpkaran.oxu@gmail.com

Abstract

Familial hypercholesterolemia (FH) is an autosomal dominant disorder of lipoprotein metabolism, primarily driven by pathogenic mutations in the LDLR, APOB, or PCSK9 genes, leading to severely elevated low-density lipoprotein cholesterol (LDL-C) from birth. The hallmark of FH is, accelerated atherosclerosis, culminating in premature coronary artery disease if untreated. While heterozygous FH (HeFH) affects approximately 1 in 200-250 individuals, the rarer homozygous form (HoFH) presents with more extreme lipid elevations and cardiovascular events in early childhood. This review examines the shift from traditional lipid-lowering therapies such as statins and ezetimibe, toward a new generation of biologics. These include monoclonal antibodies targeting PCSK9 (alirocumab, evolocumab), the small interfering RNA agent inclisiran, and the ANGPTL3 inhibitor evinacumab, the latter offering an LDL receptor-independent pathway. With the advent of these agents, a substantial proportion of FH patients can now achieve recommended LDL-C targets, ushering in an era of precision management for this once-formidable genetic condition.

Keywords: Familial hypercholesterolemia; LDL receptor; PCSK9; atherosclerosis; inclisiran; precision medicine

1. Introduction

Familial hypercholesterolemia serves as a paradigm for the translation of genetic discovery into clinical practice. The seminal work of Goldstein and Brown in the 1970s, which elucidated the LDL receptor pathway and earned them the Nobel Prize, laid the groundwork for understanding this condition [1]. FH results from inherited defects in the clearance of LDL particles, leading to a lifelong elevation of plasma LDL-C and a dramatically increased risk of premature atherosclerotic cardiovascular disease (ASCVD) [2]. Beyond the classic LDLR mutations, the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a critical regulator of LDL receptor turnover has transformed both the molecular understanding and therapeutic landscape of FH [3]. Despite being one of the most common monogenic disorders worldwide, fewer than 10% of affected individuals are diagnosed in most countries, representing a substantial gap in cardiovascular prevention [4]. This review examines recent advances in the molecular pathogenesis of FH, compares contemporary diagnostic strategies, and highlights emerging lipid-lowering biologics that are shifting the paradigm from lifelong symptomatic management toward precision-based, and potentially curative, interventions.

2. Literature Review

2.1. Epidemiology

FH is among the most common monogenic disorders globally. Heterozygous FH is estimated to affect 1 in 200-250 individuals, with a prevalence of approximately 1 in 288 in the United Kingdom [3, 4]. HoFH is far rarer, with a prevalence of approximately 1 in 315,000 individuals, though this can be higher in founder populations [5]. Despite its prevalence, FH stays grossly under-diagnosed, with most cases worldwide unidentified [2].

2.2. Genetic & Molecular Basis

The molecular pathology of FH centres on impaired LDL receptor (LDLR)-mediated clearance of LDL from the circulation. Pathogenic variants in LDLR account for 85-90% of FH cases, with over 1,700 mutations described that disrupt receptor synthesis, transport, or function [3]. Approximately 5% of cases involve mutations in APOB, encoding the ligand for the LDLR, while gain-of-function mutations in PCSK9 account for a small fraction, increasing degradation of the LDLR [6]. In normolipidemic plasma, 30-40% of PCSK9 is bound to LDL particles; gain-of-function mutations in PCSK9 enhance LDLR degradation, exacerbating hypercholesterolemia [7]. A polygenic component contributes to the phenotype in about 10% of patients with clinical FH who lack a monogenic mutation [6].

2.3. Clinical Manifestations

The clinical stigmata of FH include tendon xanthomas (affecting the Achilles tendon or digital extensors), corneal arcus, and xanthelasma [8]. In HeFH, coronary artery disease typically manifests between the ages of 40 and 50 years; in HoFH, myocardial infarction can occur before the age of 20 [3]. Physical signs are less common in children with HeFH, who are often asymptomatic, underscoring the need for lipid-based screening rather than reliance on physical findings for diagnosis [9].

3. Discussion

3.1. Diagnostic Approaches

The diagnosis of FH integrates clinical assessment with lipid profiling and genetic testing. The Dutch Lipid Clinic Network (DLCN) criteria, which assign points based on LDL-C levels, family history of premature ASCVD, physical signs, and genetic findings, are widely used [10]. A DLCN score >8 indicates “definite” FH. However, studies show that clinical criteria alone, particularly in young adults and children, have suboptimal sensitivity compared to genetic testing [11, 12]. Novel pediatric diagnostic scores (e.g., FH-PeDS) have been developed to improve early detection, but genetic confirmation remains the gold standard [11].

3.2. Management & Emerging Therapies

The management of FH has traditionally relied on statins and ezetimibe. However, the last decade has witnessed a revolution in lipid-lowering pharmacotherapy. Monoclonal antibodies against PCSK9 (alirocumab, evolocumab) bind circulating PCSK9, preventing LDLR degradation and reducing LDL-C by approximately 60%. Inclisiran, a small interfering RNA, offers a novel approach by inhibiting hepatic translation of PCSK9, with a twice-yearly dosing schedule. A 2025 meta-analysis of 23 randomized controlled trials confirmed that both PCSK9 inhibitors and inclisiran produce substantial, sustained reductions in LDL-C and apolipoprotein B, with a favourable safety profile [13]. For the most severely affected patients with HoFH, evinacumab, a monoclonal antibody targeting ANGPTL3, has proven transformative. By inhibiting ANGPTL3, evinacumab lowers LDL-C through an LDLR-independent pathway, making it effective even in receptor-negative HoFH [14, 15].

3.4 Future Research

The frontier of FH therapy lies in gene editing. First-in-human trials of CRISPR-Cas9 therapies targeting ANGPTL3 (CTX310) have shown promising reductions in LDL-C and triglycerides following a single infusion [16]. While safety concerns persist, the prospect of a one-time “cure” for FH is on the horizon. Concurrently, the persistent challenge of underdiagnosis, particularly in pediatric populations where early intervention could prevent decades of exposure to elevated LDL-C demands urgent health system attention [2, 12].

4. Summary

Once considered an untreatable genetic risk for premature death, FH has become a model for precision cardiovascular medicine. The translation of molecular insights into targeted

biologics now allows most patients to achieve guideline-recommended LDL-C goals. The remaining challenge is no longer therapeutic efficacy but rather systematic implementation: ensuring that every child with severe hypercholesterolemia receives a timely diagnosis and access to these life-saving therapies.

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