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Familial hypercholesterolemia/autosomal dominant hypercholesterolemia: Molecular defects, the LDL-C continuum, and gradients of phenotypic severity

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BACKGROUND: Familial hypercholesterolemia (FH) is a common inherited disorder in which the severity of atherosclerosis is generally proportional to the extent and duration of elevated plasma low-density lipoprotein cholesterol (LDL-C) levels. Homozygous FH (HoFH) is generally considered the most severe condition and results in very high LDL-C levels that respond only partially to statin therapy. The diagnosis of HoFH is complicated by its presentation as a phenotypic spectrum involving multiple genes.

OBJECTIVE: The objective here is to review the genetics, continuum of LDL-C concentrations, and phenotypic severity of FH.

METHODS: Multiple PubMed searches were conducted as described in the main text of this article.

RESULTS: Traditionally, FH has been considered an autosomal co-dominant disorder whereby both heterozygotes (HeFH) and homozygotes are affected. Recently, additional genes and loci for monogenic FH have been characterized that allow for the identification of double mutations in the known genes and loci and the description of novel forms of double heterozygous FH. Phenotypic expression and clinical severity of untreated HeFH, double HeFH, compound HeFH, and HoFH vary with some overlap both between and within the genotypes. In addition, there is overlap in LDL-C levels of treated HeFH and treated HoFH.

CONCLUSIONS: These discoveries raise the possibility that new combinations of molecular defects could modulate the severity of hypercholesterolemia. These defects are unlikely to represent true homozygosity. However, they are likely to result in a phenotype consistent with HoFH or severe HeFH, which will be important as new therapies become available with indications specifically for HoFH.

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that has been characterized both molecularly and clinically.[1,2] Historically, the prevalence of FH in Europe and North America has been estimated to be 1:500 for heterozygous FH (HeFH) and 1:1,000,000 for homozygous FH (HoFH), although recent

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data from the Netherlands suggest that the incidence may be higher at 1:200 for HeFH and 1:300,000 for HoFH.[3,4] The prevalence of FH in various populations is much higher: French Canadian, 1 in 270; Christian Lebanese, 1 in 85; Tunisian, 1 in 165; South African Afrikaners, 1 in 72 to 1 in 100; and South African Ashkenazi Jews, 1 in 67.[5] To estimate the prevalence of FH in the United States, a group recently analyzed data from the 36,949 adult participants in the 1999 to 2002 National Health and Education National Surveys (NHANES).[6] They estimated that the overall adult prevalence of probable or definite FH to be 1 in 250 in the United States. The CAscade SCreening for Awareness and DEtection (CASCADE) FH Registry had been launched to characterize the features, treatment, and outcomes of patients with FH in the United States.[7] Initial analysis of the CASCADE-FH registry revealed that among adult patients with FH in the United States, the prevalence of coronary heart disease is high and rates for achieving low-density lipoprotein (LDL-C) target concentrations are low.

Selecting the proper therapy for a patient with FH often requires determining whether the patient has HeFH, HoFH, or some other forms of hereditary hypercholesterolemia. Two medications, mipomersen and lomitapide, are approved by the U.S. Food and Drug Administration for treating hypercholesterolemia as adjunct to low-fat diet and other lipid-lowering therapies exclusively in individuals with HoFH (Table 1).[8–22] In 2015, evolocumab and alirocumab were approved for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH or clinical atherosclerotic cardiovascular disease, such as heart attacks or strokes, who require additional lowering of LDL-C levels.[8,11] Making a precise diagnosis of HoFH in the clinical setting may be difficult because of the phenotypic variation (including LDL-C levels) between and among heterozygotes and homozygotes and because genetic analyses are not routine.[23]

Historically, FH was characterized by mutations in the low-density lipoprotein receptor (*LDLR*) gene.[1,24,25] Patients with HoFH are classified into receptor-negative (<2% of normal LDLR activity) or receptor-defective (2% to 25% of normal LDLR activity) based on the amount of activity in skin fibroblasts. LDL-C levels are generally inversely related to the level of residual activity of LDLR. Without treatment, receptor-negative patients with HoFH rarely survive beyond the second decade of life. Receptor-defective patients have a better prognosis; however, almost all these patients will develop clinically significant atherosclerotic vascular disease by the age of 30 years and often sooner.[1] Approximately 70% to 75% of patients with HoFH have defective LDLR, about 15% have negative LDLR and the rest are unknown.[26]

According to the recommendations of the National Institute for Health and Care Excellence 2008 guidelines from the United Kingdom for the identification and management of patients with FH, all patients with a clinical diagnosis of FH should be offered a deoxyribonucleic acid (DNA) test to confirm the diagnosis. DNA testing for mutations, along with measurement of LDL-C levels, is recommended to identify affected relatives, including at least first-degree and second-degree relatives, and, when possible, third-degree relatives.[27] The European Atherosclerosis Society critically evaluated the extent to which FH is underdiagnosed and undertreated worldwide and issued a consensus statement in 2013. This statement strongly recommends molecular genetic testing in patients with definite or probable FH. When a causative mutation is found, testing for mutations should be offered to all first-degree relatives.[28] The International FH Foundation offers integrated guidance on the care of FH. DNA testing increases the accuracy of detecting FH and should be used to confirm the diagnosis when possible. Cascade screening should be a priority in first-degree relatives and should then be extended to second-degree and third-degree relatives.[29]

However, according to the National Lipid Association, genetic screening is generally not needed for diagnosis, whereas it is also noted that a negative test does not exclude FH.[30] Moreover, according to a 2013 article by Talmud et al,[31] standard molecular testing can detect a mutation that causes FH in 20% to 30% of patients (about two-thirds of patients) who possibly have FH and in 60% to 80% of patients who definitely have FH. Therefore, overall no mutation is detected in approximately 60% of patients tested. In addition, it is possible that a percentage of all clinically diagnosed cases of FH are polygenic, which would reduce the efficiency of any cascade screening program because much fewer than the expected 50% of first-degree relatives would be affected.[31]

Familial hypercholesterolemia is now recognized as a multigenetic condition. In addition to the *LDLR* gene, two other autosomal dominant genes have been associated with hereditary hypercholesterolemia, *APOB*, which encodes apolipoprotein B (apo B), and *PCSK9*, which encodes proprotein convertase subtilisin/kexin type 9 (PCSK9).[32,33] Together, mutations in *LDLR*, *APOB*, and *PCSK9* underlie most cases of autosomal dominant hypercholesterolemia (ADH).[1,32,33] A fourth locus for autosomal dominant FH, discovered in a French pedigree, has been mapped to 16q22.1 and is called *HCHOLA4*.[34] ADH can also be caused by mutations within the *APOE* gene. A large family with ADH has been described in which the ADH phenotype is associated with the *APOE p.Leu167del* mutation, making *APOE* at least the fifth locus causing ADH.[35,36] *APOE p.Leu167del* is also associated with hypertriglyceridemia with splenomegaly and sea-blue histiocytosis and familial-combined hyperlipidemia.[36] Mutations in the *STAP1* gene also have been found to be associated with ADH.[37] In patients with ADH, ~60% to 80% of the mutations are estimated to be in *LDLR*, 1% to 5% in *APOB*, and 0% to 3% in *PCSK9*. Nearly 20% of patients with the ADH phenotype are estimated to have mutations in as yet unidentified genes and gene loci.[38] The prevalence of HeFH due to *LDLR* mutations is considered to be 1:500, resulting in a HoFH prevalence