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Diagnostic Yield of Sequencing Familial Hypercholesterolemia Genes in Patients with Severe Hypercholesterolemia

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Abstract

Background

About 7% of US adults have severe hypercholesterolemia (untreated LDL cholesterol ≥190 mg/dl). Such high LDL levels may be due to familial hypercholesterolemia (FH), a condition caused by a single mutation in any of three genes. Lifelong elevations in LDL cholesterol in FH mutation carriers may confer CAD risk beyond that captured by a single LDL cholesterol measurement.

Objectives

Assess the prevalence of a FH mutation among those with severe hypercholesterolemia and determine whether CAD risk varies according to mutation status beyond the observed LDL cholesterol.

Methods

Three genes causative for FH (*LDLR*, *APOB*, *PCSK9*) were sequenced in 26,025 participants from 7 case-control studies (5,540 CAD cases, 8,577 CAD-free controls) and 5 prospective cohort studies (11,908 participants). FH mutations included loss-of-function variants in *LDLR*, missense mutations in *LDLR* predicted to be damaging, and variants linked to FH in ClinVar, a clinical genetics database.

Results

Among 8,577 CAD-free control participants, 430 had LDL cholesterol ≥190 mg/dl; of

these, only eight (1.9%) carried a FH mutation. Similarly, among 11,908 participants from 5 prospective cohorts, 956 had LDL cholesterol ≥190 mg/dl and of these, only 16 (1.7%) carried a FH mutation. Within any stratum of observed LDL cholesterol, risk of CAD was higher among FH mutation carriers when compared with non-carriers. When compared to a reference group with LDL cholesterol <130 mg/dl and no mutation, participants with LDL cholesterol ≥190 mg/dl and no FH mutation had six-fold higher risk for CAD (OR 6.0; 95%CI 5.2–6.9) whereas those with LDL cholesterol ≥190 mg/dl as well as a FH mutation demonstrated twenty-two fold increased risk (OR 22.3; 95%CI 10.7–53.2).

Conclusions

Among individuals with LDL cholesterol ≥190 mg/dl, gene sequencing identified a FH mutation in <2%. However, for any given observed LDL cholesterol, FH mutation carriers are at substantially increased risk for CAD.

Keywords

familial hypercholesterolemia; low-density lipoprotein cholesterol; gene sequencing; coronary artery disease; genetics

Abbreviations

APOB, apolipoprotein B; CAD, coronary artery disease; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9

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