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Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia

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ABSTRACT

BACKGROUND Approximately 7% of American adults have severe hypercholesterolemia (untreated low-density lipoprotein [LDL] cholesterol ≥190 mg/dl), which may be due to familial hypercholesterolemia (FH). Lifelong LDL cholesterol elevations in FH mutation carriers may confer coronary artery disease (CAD) risk beyond that captured by a single LDL cholesterol measurement.

OBJECTIVES This study assessed the prevalence of an FH mutation among those with severe hypercholesterolemia and determined whether CAD risk varies according to mutation status beyond the observed LDL cholesterol level.

METHODS Three genes causative for FH (*LDLR*, *APOB*, and *PCSK9*) were sequenced in 26,025 participants from 7 case-control studies (5,540 CAD case subjects, 8,577 CAD-free control subjects) 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 20,485 CAD-free control and prospective cohort participants, 1,386 (6.7%) had LDL cholesterol ≥190 mg/dl; of these, only 24 (1.7%) carried an FH mutation. Within any stratum of observed LDL cholesterol, risk of CAD was higher among FH mutation carriers than noncarriers. Compared with a reference group with LDL cholesterol <130 mg/dl and no mutation, participants with LDL cholesterol ≥190 mg/dl and no FH mutation had a 6-fold higher risk for CAD (odds ratio: 6.0; 95% confidence interval: 5.2 to 6.9), whereas those with both LDL cholesterol ≥190 mg/dl and an FH mutation demonstrated a 22-fold increased risk (odds ratio: 22.3; 95% confidence interval: 10.7 to 53.2). In an analysis of participants with serial lipid measurements over many years, FH mutation carriers had higher cumulative exposure to LDL cholesterol than noncarriers.

CONCLUSIONS Among participants with LDL cholesterol ≥190 mg/dl, gene sequencing identified an FH mutation in <2%. However, for any observed LDL cholesterol, FH mutation carriers had substantially increased risk for CAD. (J Am Coll Cardiol 2016;67:2578–89) © 2016 by the American College of Cardiology Foundation.

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Severe hypercholesterolemia, defined as having a low-density lipoprotein (LDL) cholesterol level ≥190 mg/dl, is a treatable risk factor for coronary artery disease (CAD) (1,2). Current treatment guidelines place particular emphasis on intensive life-style and pharmacological therapy in this population (3). One cause of severely elevated LDL cholesterol is familial hypercholesterolemia (FH), an autosomal dominant monogenic disorder linked to impaired hepatic clearance of LDL cholesterol particles (4). Patients with LDL cholesterol ≥190 mg/dl are often assumed to have FH, but this may not be the case. Large-scale gene sequencing provides an opportunity to clarify the diagnostic yield and clinical impact of identifying an FH mutation in severely hypercholesterolemic patients.

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Previous studies of the diagnostic yield of genetic testing in severe hypercholesterolemia have focused on subjects with clinically suspected FH and reported FH mutation prevalence has ranged from 20% to 80% (5–16). This variability is likely caused by differing ascertainment schemes utilizing family history, physical examination features, elevated LDL cholesterol at a young age, or referral to specialized clinics, each of

ABBREVIATIONS AND ACRONYMS

APOB = apolipoprotein B

CAD = coronary artery disease

CI = confidence interval

FH = familial hypercholesterolemia

LDL = low-density lipoprotein

LDLR = low-density lipoprotein receptor

OR = odds ratio

PCSK9 = proprotein convertase subtilisin/kexin type 9

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