Genetic Testing as an Effective Diagnostic Tool for Familial Hypercholesterolemia

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Introduction: Hypercholesterolemia is characterized by high levels of plasma low density lipoprotein (LDL) in the blood and an increased risk for coronary artery disease (CAD). Familial hypercholesterolemia (FH) can be caused by mutations in the *LDLR*, *APOB*, and *PCSK9* genes and has an estimated prevalence of 1 in 250. Since FH patients carrying identified mutations are at significantly higher risk for CAD than non-carriers, genetic testing can inform management and prognosis for both an affected proband and at-risk family members.

Methods: Next-generation sequencing of *LDLR*, *APOB*, and *PCSK9*, plus deletion/duplication analysis of *LDLR* was performed using a multigene panel on 217 cases tested from April 2014-August 2016. Clinical information was obtained from test requisition forms.

Results: In total, 90 (41.5%) cases were positive for a mutation and 14 (6.5%) were found to have a variant of unknown significance (VUS). Among individuals who provided cholesterol screening data prior to any pharmacologic intervention, those with a gene mutation (n=11) had a median age at cholesterol screening of 22 (range: 5-56) with a median LDL of 250 mg/dL (range: 173-336 mg/dL; n=8) and median total cholesterol of 340 mg/dL (range: 230-456 mg/dL; n=9); those without a mutation (n=11) had a median age at cholesterol screening of 37 (range: 5-75) with a median LDL of 205 mg/dL (range: 126-400 mg/dL; n=9) and median total cholesterol of 273 mg/dL (range: 209-309 mg/dL; n=8). While cholesterol levels were higher overall for positive cases, the range is quite large, and one individual screened at age 36 had an LDL of 173 mg/dL, which is below the professional guideline-recommended threshold for suspected FH (>190 mg/dL for individuals over 20).

Conclusions: Multigene panel testing for FH has a relatively high diagnostic yield, with 42% of total cases having a positive result that can impact care for patients and their relatives. Genetic testing as a tool for assessing familial risk has been largely underutilized in individuals with FH. Our data demonstrate the value of genetic testing on individuals with a wide range of elevated cholesterol levels. Genetic testing can help confirm the diagnosis of FH and guide pharmacologic management, such as treatment with PCSK9 inhibitors.