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Genetic Testing for Familial Hypercholesterolemia

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Background/Synopsis: Familial hypercholesterolemia (FH) can be caused by mutations in the *LDLR, APOB, PCSK9,* and *LDLRAP1* genes and has an estimated prevalence of 1 in 200. Despite this high prevalence, it is estimated that only up to 10% of those affected have a formal diagnosis.

Objective/Purpose: To further characterize the relationship between FH mutation status and LDL level.

Methods: Next-generation sequencing of *LDLR, APOB,* and *PCSK9*, plus deletion/duplication analysis of *LDLR* (at a minimum), was performed on 488 cases from September 2010 - June 2017. Clinical and demographic information was obtained from test requisition forms, pedigrees, and reported clinical notes. Chi-square tests were used to assess significance of demographic factors on test results, and an independent t-test was used to compare LDL levels between heterozygous *LDLR* and *APOB* mutation carriers.

Results: In total, 179 (36.7%) cases were positive for a mutation and 51 (10.5%) were found to have a variant of unknown significance (VUS). Among individuals who provided cholesterol screening data prior to pharmacologic intervention, those with a gene mutation (n=23) had a median age at cholesterol screening of 25 (range: 2-62) and a median LDL of 270 mg/dL (range: 173-668 mg/dL), while those without a mutation (n=26) had a median age at cholesterol screening of 49 (range 5-75) and a median LDL of 199 mg/dL (range: 108-332 mg/dL). 163 (91%) positive cases had at least one mutation in *LDLR,* 15 (8%) positive cases had one mutation in *APOB,* and one case (0.5%) had one mutation each in *LDLR* and *APOB*. Mean pre-treatment LDL levels were 580 mg/dL (n=2) for homozygous *LDLR* mutation carriers, 278 mg/dL (n=17) for heterozygous *LDLR* mutation carriers, and 220 mg/dL for heterozygous *APOB* mutation carriers (n=4). Ethnicity was not found to significantly impact the overall test result (p=0.068), nor the causative gene amongst mutation carriers (p=0.210).

Conclusion: Comprehensive genetic analysis of patients at risk for FH identified causative mutations in 37% of cases, confirming a diagnosis and allowing for potential cascade screening of first-degree relatives at risk. While cholesterol levels were higher overall for positive cases, the range was relatively large, and one individual screened at age 36 had an LDL of 173 mg/uL, below the professionally recommended threshold for suspected FH (>190 mg/dL for individuals over 20). Although not technically significant (p=0.052), patients heterozygous for *APOB* mutations had lower mean LDL levels than *LDLR* heterozygotes, supporting similar reports of milder presentations with *APOB* mutations.

1. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. European heart journal 2013.