Genetic Testing as an Effective Diagnostic Tool for Familial Hypercholesterolemia

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BACKGROUND

- 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.[1]
- 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, as well as pedigrees and clinical notes submitted with orders.

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) (Figure 1).
- 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) (Figure 2).
- 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).[2]

FIGURE 1. MUTATION PERCENTAGE IN FH COHORT

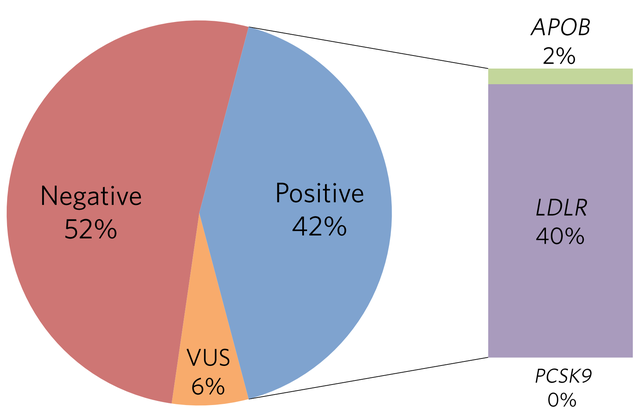

FIGURE 2. AGE, LDL, AND CHOLESTEROL DATA IN MUTATION POSITIVE AND NEGATIVE CASES

Clinical Info Provided	Mutation Positive (n=11)	Mutation Negative (n=11)
Median age at cholesterol screening (range)	22 (5-56)	37 (5-75)
Median LDL (range)	250 mg/dL (173-336)	205 mg/dL (126-400)
Median total cholesterol (range)	340 mg/dL (230-456)	273 mg/dL (209-309)

TAKE-HOME POINTS

- 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.
- As positive results from FH genetic testing have been shown to increase patient compliance with medication regimens, genetic testing could have a positive effect on cholesterol management in significant portions of the population with inherited high cholesterol.

REFERENCES

1. Nordestgaard BG et al. Eur Heart J: 2013, 34:3478-3490.
2. Goldberg AC et al. J Clin Lipidol: 2011, 5: 133–140.

DISCLOSURE

All authors are employed by Ambry Genetics Corp.