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Genetic Testing for Familial Hypercholesterolemia

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BACKGROUND

- Familial hypercholesterolemia (FH) can be caused by mutations in the *LDLR, APOB, PCSK9,* and *LDLRAP1* genes, and has an estimated prevalence of 1 in 250[1].
- Despite this high prevalence, it is estimated that only up to 10% of those with FH have a formal diagnosis[1].
- Genetic testing can confirm a clinical diagnosis and inform prognosis for both an affected proband and at-risk family members.

OBJECTIVE & METHODS

- **Objective:** To further characterize the relationship between FH mutation status and LDL-level.
- 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, family pedigrees, and reported clinical notes.
- 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 pathogenic/likely pathogenic mutation and 51 (10.5%) were found to have a variant of unknown significance (VUS) (Figure 1).
- Among positive cases, 150 (83.8%) had one mutation in *LDLR,* 16 (8.9%) had one mutation in *APOB,* 12 (6.7%) had two or more mutations in *LDLR* (5 confirmed homozygous), and one case (0.6%) had one mutation each in *LDLR* and *APOB* (Figure 1).
- 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) (Figure 2).
- 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) (Figure 2).

FIGURE 1: Mutation Detection Results

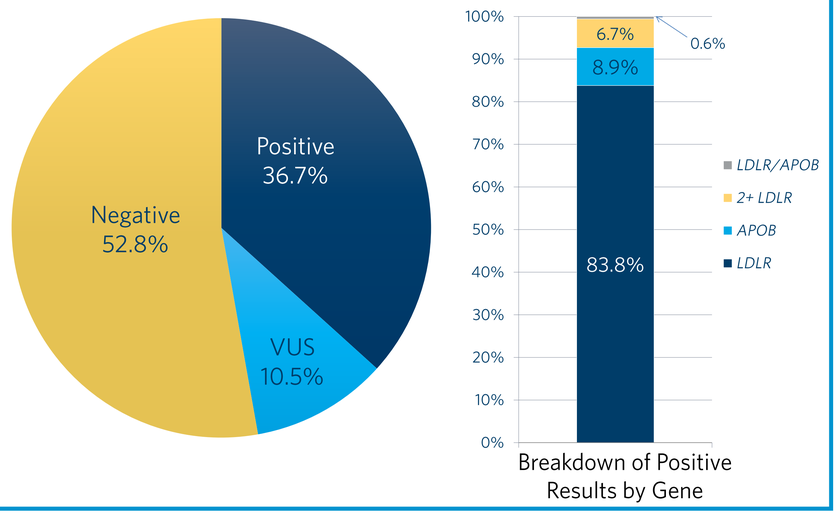

FIGURE 2: Clinical LDL Data by Genotype

Clinical Info Provided	Mutation Positive (n=23)	Mutation Negative (n=26)
Median age at cholesterol screening (range)	25 (2-62)	49 (5-75)
Median LDL (range)	270 mg/dL (173-668)	199 mg/dL (108-332)

Clinical Info Provided	Homozygous *LDLR* (n=2)	Heterozygous *LDLR* (n=17)	Heterozygous *APOB* (n=4)
Mean pre-treatment LDL levels	580 mg/dL	278 mg/dL	220 mg/dL

TAKE-HOME POINTS

- 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/dL, which is below the professionally recommended threshold for suspected FH (>190 mg/dL for individuals over 20[2]).
- 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[3].

REFERENCES

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