# Genetic testing for *APOB*, *LDLR*, *PCSK9*, and *LDLRAP1* suggest that FH testing may be underutilized

Christin Collins[1]; Abhinav Mathur[1]; Sharoni Jacobs[2]; Elissa Levin[2]; Madhuri Hegde[1]

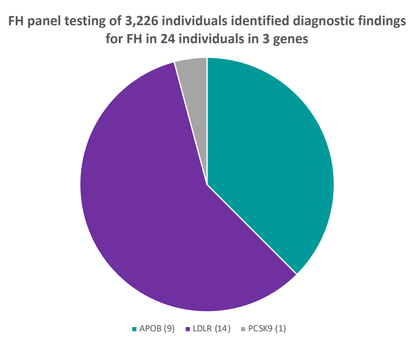
[1]PerkinElmer Genomics; [2]Helix

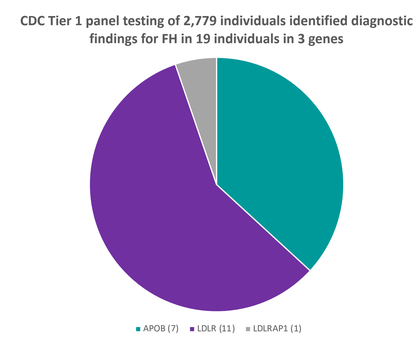
## BACKGROUND

- Familial hypercholesterolemia (FH) is characterized by elevation of LDL-cholesterol (LDL-C) that leads to atherosclerotic-based cardiovascular disease.
- Familial hypercholesterolemia is thought to be the most common cause of cardiovascular disease, with data estimating the prevalence as high as 1 in 220 to 1 in 313 individuals (PMID 30071997, 32439005, 27246162).
- Familial hypercholesterolemia is subclassified as autosomal dominant heterozygous FH (HeFH) and autosomal recessive homozygous FH (HoFH).
- While the diagnosis of FH can be made clinically, many diagnostic criteria include genetic testing as a component in the diagnostic algorithm (PMID: 15199434, 1933004, 26510694).
- Genetic testing can provide prognostic information and better risk stratification by informing of increased risk of coronary heart disease (CAD) and varying levels of low-density lipoprotein cholesterol (LDL-C) (PMID 24404629, 30071997).
- Estimates available suggest that more than 30 million individuals with FH worldwide are undiagnosed (PMID: 28419271, 30071997).
- In our laboratory, we have performed next-generation panel sequencing on reportedly healthy adults in two independent testing cohorts: one being screened for four genes associated with FH (*APOB*, *LDLR*, *PCSK9*, and *LDLRAP1*) and another screened for the CDC Tier 1 genes (*APOB*, *LDLR*, *PCSK9*, *LDLRAP1*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*).

## RESULTS

- Of the 3,226 individuals tested using the FH panel, 24 individuals were found to have diagnostic findings for FH (~1 in 135 individuals).
- Of the 2,779 individuals tested using the CDC Tier 1 panel, 19 individuals were found to have diagnostic findings for FH (~1 in 146 individuals).
- Overall, diagnostic findings were returned for 43 individuals, with pathogenic variants found in the *LDLR* gene (n = 25), *APOB* gene (n = 16), *PCSK9* gene (n = 1), and *LDLRAP1* gene (n = 1 homozygote).




## Genetic Results in FH

*Genetic Results help stratify risk*

- Genetic testing can provide prognostic information and better risk stratification by informing of increased risk of coronary heart disease (CAD) and varying levels of low-density lipoprotein cholesterol (LDL-C) (PMID 24404629, 30071997).
- Studies have shown an association of higher levels of LDL-C in HeFH in individuals with a null variant in the *LDLR* gene when compared to those individuals with missense changes in the gene (PMID 27050191, 28353356, 31883481).
- Individuals with pathogenic variants detected were found to have higher odds ratios for coronary artery disease compared individuals without identified FH variants; null alleles in *LDLR* were reported to have an odds ratio (OR) for coronary artery disease (CAD) of 9.5 and individuals with missense variants in *LDLR* were reported to have an OR for CAD of 3.5 (PMID 27050191, 31883481).
- Of the 43 samples for which a diagnostic finding was returned for FH in the testing cohorts presented here, 25 were returned a result of a pathogenic/likely pathogenic variant in the *LDLR* gene (18 missense variants, 7 null variants).
    - In our *LDLR* positive cohort, the 7 individuals with null variants are at higher risk for CAD than the 18 individuals with missense variants.

*Genetic Results help determine treatment response*

- Identification of individuals with FH is especially important given the availability of effective lipid-lowering drugs.
- The response of LDL-C levels to statin treatment may vary depending on the genotype status of the patient.
- Evidence suggests patients with no pathogenic variant detected (presumed polygenic) respond best to statin treatment. Patients with missense pathogenic variants in the *LDLR* gene had an intermediate response. Patients with a null variant in the *LDLR* gene had the worst response (PMID: 24529145).
- Individuals with HeFH (both null *LDLR* variants and missense *LDLR* variants) respond well to PCSK9 inhibitors (PMID: 25282519).
- Patients with two *LDLR* null alleles had no response to treatment with PCSK9 inhibitors but showed some response if one of the variants present had residual activity (PMID: 25282520).
- Genotype information can help predict response to treatment with PCSK9 inhibitors for patients with HoFH.

## CONCLUSION

- The prevalence of FH in our testing cohorts suggests this disorder may be more common than expected.
- Genetic results help to inform of disease risk and response to treatment, leading to positive health outcomes for patients and their families.
- The benefits associated with a genetic diagnosis illustrates the need for increased genetic screening for this disorder.

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