Genetic Screening of a Reportedly Healthy Population for Familial Hypercholesterolemia

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BACKGROUND

- Familial hypercholesterolemia (FH) is the most common cause of genetic cardiovascular disease with an estimated prevalence of approximately 1 in 220 individuals (PMID 30071997).
- It is estimated that 70 – 95% of FH is a result of a heterozygous pathogenic variant in one of three genes (*APOB, LDLR, PCSK9*) (PMID 24404629). A more severe clinical presentation can be seen with homozygous familial hypercholesterolemia (HoFH) which is caused by biallelic (homozygous or compound heterozygous) pathogenic variants in the *APOB, LDLR, PCSK9, or LDLRAP1* genes (PMID 24404629).
- 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).
- Evidence demonstrating the benefits of using statins in children with a diagnosis of FH as young as 8 – 10 years of age (PMID 26009596) shows that treated children have significantly lower event rates than their affected parents (PMID 26821635) and the LDL-C burden appears closer to nonaffected individuals for patients with earlier treatment initiation (PMID 23141908).
- Estimates available suggest that more than 30 million individuals with FH worldwide are undiagnosed (PMID: 28419271, 30071997).

RESULTS

- A cohort of 1,996 reportedly healthy individuals was sequenced at PerkinElmer Genomics for variants causative of Familial hypercholesterolemia (FH).
- Genetic screening for pathogenic sequence variants and copy number variants was performed using a next generation sequencing panel that consists of four genes associated with FH (*APOB, LDLR, LDLRAP1, PCSK9*).
- Diagnostic findings were returned for 15 individuals tested (~1 in 133 individuals tested)
  - The incidence of FH in our cohort is higher than the current estimated prevalence. Additional samples are need to confirm.
- Pathogenic variants were detected in the *LDLR* gene (9/15 positives) and the *APOB* gene (6/15 positives).

Pathogenic Variants Identified

Sample	Gender	Age	Gene	OMIM	Disease	Inheritance	DNA change	Protein Change	Zygosity	Classification
1	female	32	*APOB*	107730	Familial Hypercholesterolemia 2	Autosomal Dominant	c.10580G>A	p.Arg3527Gln	Het	Pathogenic
2	female	51	*APOB*	107730	Familial Hypercholesterolemia 2	Autosomal Dominant	c.10580G>A	p.Arg3527Gln	Het	Pathogenic
3	female	34	*APOB*	107730	Familial Hypercholesterolemia 2	Autosomal Dominant	c.10580G>A	p.Arg3527Gln	Het	Pathogenic
4	female	36	*APOB*	107730	Familial Hypercholesterolemia 2	Autosomal Dominant	c.10580G>A	p.Arg3527Gln	Het	Pathogenic
5	female	25	*APOB*	107730	Familial Hypercholesterolemia 2	Autosomal Dominant	c.10580G>A	p.Arg3527Gln	Het	Pathogenic
6	female	40	*APOB*	107730	Familial Hypercholesterolemia 2	Autosomal Dominant	c.10580G>A	p.Arg3527Gln	Het	Pathogenic
7	male	38	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.1646G>A	p.Gly549Asp	Het	Pathogenic
8	female	25	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.1747C>T	p.His583Tyr	Het	Pathogenic
9	male	44	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.2054C>T	p.Pro685Leu	Het	Pathogenic
10	female	67	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.2311+1G>T	-	Het	Pathogenic
11	male	44	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.2311+1G>T	-	Het	Pathogenic
12	female	64	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.530C>T	p.Ser177Leu	Het	Pathogenic
13	male	27	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.682G>T	p.Glu228Ter	Het	Pathogenic
14*	male	48	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.798T>A	p.Asp266Glu	Het	Pathogenic
15*	female	72	*LDLR*	606945	Familial Hypercholesterolemia 1	Autosomal Dominant	c.798T>A	p.Asp266Glu	Het	Pathogenic

*samples 14 and 15 are related

- All six individuals with a pathogenic variant in the *APOB* gene were found to have the c.10580G>A (p.Arg3527Gln) change, which has been reported to be found mainly in people of European ancestry (PMID 24404629).
- Careful understanding of variant classification and the relationship of variants to mechanism of disease is essential in being able to return accurate and appropriate findings.
  - For the *APOB* gene, only pathogenic autosomal dominant gain-of-function (GOF) variants associated with FH are reported.
  - For the *APOB* gene, pathogenic autosomal recessive loss-of-function (LOF) variants associated with hypobetalipoproteinemia are not reported for this assay.
  - Pathogenic autosomal recessive LOF variants in the *APOB* gene were identified (and not reported) in 7 individuals tested in this cohort.

CONCLUSION

- In our cohort, the prevalence of individuals with diagnostic findings consistent with FH were identified in ~1 in 133 individuals.
- Pathogenic variants associated with FH were detected in the *LDLR* and *APOB* genes.
- These results illustrate the benefits of genetic screening in identifying individuals with FH who can now be can be clinically managed to minimize risk of adverse medical events.