Study raises questions over effectiveness of recommended genetic testing strategy for inherited high cholesterol

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Research published Online First in *The Lancet* provides new evidence that a substantial proportion of individuals with a clinical diagnosis of Familial Hypercholesterolaemia (FH) inherit a combination of small-effect changes in several genes (polygenic) rather than a large-effect mutation in a single gene (monogenic). These findings have implications for the majority of national guidelines on family screening for FH, that advocate testing relatives of all individuals with a clinical diagnosis of FH, including those of the UK National Institute for Health and Clinical Excellence (NICE).

"Cascade [family] testing of the roughly 40% of patients with a clinical diagnosis of FH and an identifiable causative mutation would eliminate staff and screening costs associated with screening relatives of the remaining 60% of patients without an identifiable mutation. This is very likely to be more cost-effective, but proving this will require a more detailed analysis", says British Heart Foundation Professor Steve Humphries from University College London, who led the research.

FH is one of the most common inherited disorders affecting over 12 million people worldwide (1 in 500 of the general population). It causes very high levels of low-density lipoprotein cholesterol (LDL-C) or "bad cholesterol" in the blood, and if untreated, results in a five to eight times greater risk of early coronary heart disease (CHD). Identification of patients with FH needs to be improved because at least 75% of cases

remain undetected, untreated, or improperly treated, despite good evidence that early detection and treatment with statins can significantly improve life expectancy.

DNA-based cascade screening to identify other family members with FH, who would benefit from treatment, has been recommended by NICE on the presumption of a monogenic inheritance of the disorder, where first-degree relatives would have a 50:50 chance of having the condition. However, 60% of people with clinically suspected FH have no identifiable mutation in any of the three genes (LDLR, APOB, or PCSK9) known to cause FH.

"The current study was designed to investigate whether individuals who inherit many, small-effect, LDL-cholesterol raising sequence differences in a wide range of genes might have received a clinical diagnosis of FH, which would influence the efficacy of any cascade screening programme since the odds of finding relatives with grossly elevated LDL-C in such cases would be less than the expected 50%", explains Humphries.

Recent genetic studies have identified many common genetic variants associated with a small increment in LDL-C levels. Genotyping for 12 of these single nucleotide polymorphisms (SNPs) was done on blood samples from 321 mutation-negative UK patients with FH, as well as 319 UK patients with FH with a known mutation, and 3020 healthy individuals (controls) from the UK Whitehall II study.

Each participant was assigned a weighted LDL-C-raising gene score based on the number of risk-associated gene copies inherited. The results were validated by repeating the analysis in a sample of over 700 patients with FH from Belgium.

The findings showed that clinically suspected, but mutation negative FH, was associated with inheritance of a greater than average number of

small-effect LDL-C-raising sequence differences.

According to Humphries, "We propose that the clinical diagnosis of FH should be restricted to those in whom a mutation can be identified, whereas those with no detected mutation should be given the clinical diagnosis of polygenic hypercholesterolaemia. Both groups of patients will need statin therapy, but the cost effectiveness of FH cascade testing will differ depending on whether or not there is a polygenic or a single mutation cause."

Writing in a linked Comment, Evan Stein from the Metabolic and Atherosclerosis Research Center in Cincinnati, USA and Frederick Raal from the University of Witwatersrand, Johannesburg, South Africa say, "All people, irrespective of age, with raised LDL-C concentrations in whom no secondary cause can be identified, especially if they have a family history of premature coronary artery disease, should be treated as presumptive FH according to clinical criteria. To add the complexity of SNP analysis for minor genes and eliminate cascade LDL-C and clinical testing of relatives of patients with polygenic FH does not appear warranted and could even be diversionary."

More information: www.thelancet.com/journals/lan … (12)62127-8/abstract

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