Single-gene mutations account for only 2 percent of cases of severely elevated cholesterol

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A study from an international research team finds that familial hypercholesterolemia (FH) - a genetic condition that causes greatly elevated levels of LDL cholesterol throughout life - accounts for less than 2 percent of severely elevated LDL in the general population. But the team also found that the risk of coronary artery disease is significantly higher in individuals with FH than in people with similarly elevated LDL levels who do not have these mutations. The report is receiving advance online publication in the *Journal of the American College of Cardiology* to coincide with a presentation at the American College of Cardiology's 65th Annual Scientific Session.

"We performed gene sequencing of blood samples from more than 26,000 individuals to determine how often these FH mutations were found in individuals with very high LDL levels and whether those mutations confer a greater risk of coronary artery disease than does LDL alone," says Amit V. Khera, MD, of the Massachusetts General Hospital (MGH) Center for Human Genetic Research and the MGH Cardiology Division , the co-lead author of the *JACC* paper who is making the ACC meeting presentation. "These findings suggest that, beyond simply measuring LDL, gene sequencing may identify individuals at very high risk who need additional preventive therapies."

It is well known that severe hypercholesterolemia - defined as LDL levels of 190 mg/dl or higher - is a major risk factor for coronary artery disease, and it has often been assumed that many of those with such high LDL levels have FH. But previous studies of the prevalence of the condition - which is caused by mutations in one of three different genes - have primarily included participants already suspected of having FH based on family history, the presence of high LDL at a young age or other factors. Only in recent years has the cost of gene sequencing dropped to a level at which testing people selected only on the basis of elevated LDL cholesterol becomes feasible.

To get a clearer sense of the prevalence of FH mutations, the researchers sequenced blood samples from 26,025 participants in 12 studies - seven comparing individuals with coronary artery disease to healthy controls and five long-term epidemiologic studies - conducted in Europe, North America and South Asia. While 7 percent of participants overall met criteria for severe hypercholesterolemia, fewer than 2 percent of those with an LDL over 190 mg/dl had a mutation in one of the FH-associated genes. Other factors leading to severely elevated LDL can include inheriting many genetic variants that each confer a small increase in LDL - FH involves a single mutation - hormonal or kidney diseases, or diet and other lifestyle factors.

While the presence of severe hypercholesterolemia without a FH mutation conferred a six-fold greater risk of coronary artery disease than did LDL levels below 130 mg/dl, adding an FH mutation to elevated cholesterol resulted in a 22-fold increased risk. Even at considerably lower LDL levels, individuals with FH mutations had a significantly greater risk of heart disease risk than did those without.

Sekar Kathiresan, MD, director of the MGH Center for Human Genetic Research and senior author of the current study says, "We are in the early days of incorporating genetic testing into routine clinical practice, but this work suggests that, beyond measuring patients' LDL cholesterol levels, checking whether they might have an FH mutation could help more accurately predict their risk of heart disease and guide treatment planning. And among those who do have a mutation, around half

their first-degree relatives will also have it, indicating a need to advise testing among their family members." An associate professor of Medicine at Harvard Medical School, Kathiresan is also an Institute Member of the Broad Institute.

Khera adds that follow-up studies being conducted at the MGH and other institutions are investigating the potential impact of patients' learning they carry an FH-associated mutation. "Would they be motivated to improve their lifestyle to reduce risk or would they believe that a heart attack is inevitable because they carry a 'bad gene'? Would they be more likely to take cholesterol-lowering medications, and most importantly can gene sequencing help prevent patients from suffering and dying from heart attacks?" he says.

More information: Amit V. Khera et al. Diagnostic Yield of Sequencing Familial Hypercholesterolemia Genes in Patients with Severe Hypercholesterolemia, *Journal of the American College of Cardiology* (2016). DOI: 10.1016/j.jacc.2016.03.520

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