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Researchers use genetic signals affecting lipid levels to probe heart disease risk

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New genetic evidence strengthens the case that one well-known type of cholesterol is a likely suspect in causing heart disease, but also casts further doubt on the causal role played by another type. The findings may guide the search for improved treatments for heart disease.

Most of us have heard of "good cholesterol" and "bad cholesterol" coursing through our bloodstream. In the conventional health wisdom of the past 30 years, having more of the "good" variety (high-density lipoprotein, or HDL) lowers your risk of heart disease, while more of the bad one (low-density lipoprotein, LDL) increases your risk. Indeed, over the years, clinical trials and other studies have found that drugs that lower LDL also lower your probability of heart disease.

On the other hand, drug trials have not shown heart-health benefits to increasing HDL or to lowering triglycerides, a third type of blood lipid. Now a new study co-led by scientists at The Children's Hospital of Philadelphia and Penn Medicine sheds light on the role of genes and blood lipid levels in cardiovascular health. Newer tools for gene analysis show how variations in DNA are underlying actors affecting heart disease—a major worldwide cause of death and disability.

"Now we are able to pinpoint gene signals that actually cause some of these conditions," says geneticist Brendan J. Keating, D. Phil., of The Center for Applied Genomics at The Children's Hospital of Philadelphia. "Unraveling how genetic variants that influence lipid traits are related to heart disease risk is a step toward designing treatments."

Keating and his colleagues, working in large international collaborative groups, are wielding advanced gene-analysis tools to uncover important clues to heart disease.

Keating collaborated with clinical epidemiologist Michael V. Holmes, M.D., Ph.D., of the Perelman School of Medicine at the University of Pennsylvania, in a blood lipid study published online Jan. 27 in the *European Heart Journal*. Research co-authors were from six countries and various centers, including the University College London in the U.K.

The study team used a recently developed epidemiology tool called Mendelian randomization (MR). MR analyzes genetic variations using a method that identifies genes responsible for particular diseases, independent of confounding factors such as differences in behavior or environmental influences that often limit the conclusions of epidemiology research. This was one of the largest studies to date using MR, as well as the largest to use an allele-score method, described below.

The researchers analyzed DNA data from 17 studies including over 60,000 individuals, of whom more than 12,000 had experienced coronary heart disease, including heart attacks. Because previous studies had found signals from nearly 200 genes to be associated with blood lipid levels, the study team aggregated data into composite groups, called allele scores, for each of three blood lipids: LDL, HDL and triglycerides, then calculated their relationship to coronary heart disease.

As expected, the current study confirmed that higher levels of LDL, the "bad cholesterol," were more likely to cause heart disease. But there were new results: high levels of triglyceride also caused higher risk of heart disease. At the same time, there was little evidence that higher levels of HDL, the "good cholesterol," had a protective effect.

The novelty of their approach, say the authors, lies in their use of a gene score MR analysis using individual participant data. These results build on previous findings and help clarify in further detail the separate roles of triglycerides and HDL in risk for coronary heart disease.

Previous genetic studies, including by Keating and others, found associations among gene variations (single nucleotide polymorphisms, or SNPs) and heart disease, but did not indicate causality, as found in the current study. Holmes said, "These findings are important in understanding which blood lipids cause heart disease, and will enable clinicians to better target those lipids with drugs to reduce the risk of heart disease."

More information: "Mendelian randomization of blood lipids for coronary heart disease," *European Heart Journal*, published online Jan. 27, 2014. doi.org/10.1093/eurheartj/eht571

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