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# 'SORTing' out the genetic and biological links between cholesterol and coronary heart disease

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The true power of genomic research lies in its ability to help scientists understand biological processes, particularly those that - when altered - can lead to disease. This power is demonstrated dramatically in a pair of papers published today in the journal *Nature*.

In the first, a global team of researchers describes 95 different variations across the genome that contribute in different degrees to alterations in blood cholesterol and triglyceride levels in multiple human populations. In the second report, close examination of just one of these common variants not only reveals the involvement of an unexpected genetic pathway in lipid metabolism but also provides a blueprint for using genomic findings to unravel biological connections between lipid levels and coronary heart disease.

"Although blood concentrations of cholesterol and triglycerides have long been known as risk factors for cardiovascular disease, the extent to which genetics contributes to those concentrations and just how alterations in the underlying genes leads to the development of disease has been incredibly difficult to piece together," said Dr. Sekar Kathiresan, director of Preventive Cardiology at Massachusetts General Hospital (MGH), an associate member of the Broad Institute of Harvard and MIT, and co-senior author on both papers. "In these two papers, we provide 95 signposts indicating genes that contribute to plasma lipid concentrations. In addition, we delve deeper into one specific signpost

and move from genomic localization to biologic understanding by discovering how genetic variation leads to clinical symptoms in living organisms. We believe our approach is a model for many other such studies across multiple diseases."

Rebuffing recent concerns that genome-wide association studies (GWAS) are not powerful enough to truly get at the biological and clinical underpinnings of human disease, the team of investigators from 17 countries worked together to examine genetic scans of over 100,000 individuals. They found 95 genetic loci - 59 previously unknown - significantly associated with blood lipid levels. These associations were validated across multiple human populations (Eastern and Southern Asian, European, and African-American), and several were also validated in mouse models.

Of the 95 loci examined, a site on chromosome 1 was associated strongly with variations in the serum levels of low-density lipoprotein cholesterol (LDL-C), the so-called "bad cholesterol." The approximately 1 in 5 people that carried a particular variant at this site had lower LDL-C levels. However, this variation appears in a non-coding region of the chromosome - one that does not carry instructions for protein synthesis. How could a non-coding change lead to lower LDL-C and, as a result, a decreased risk of heart attack?

In the second report, scientists from 13 institutions brought to bear powerful new laboratory tools - including small inhibitory RNA, mouse models, and viral-mediated gene transfer - and demonstrated that a common change in one genetic "letter" created a novel sequence to which a specialized protein known as a transcription factor could bind and ramp up the "reading" of another gene known as SORT1 in liver cells. The investigators then found that the protein encoded by SORT1 directly altered the levels of both LDL and the related very-low-density lipoprotein (VLDL) by modulating their secretion from the liver,

ultimately controlling lipid levels in the blood and the relative risk of coronary disease.

"These studies demonstrate that GWAS - done at the proper scale and with the proper tools - remain a powerful approach to understanding biology and disease, and that even non-coding variants can have a clinical effect," said Dr. Kiran Musunuru, clinical and research fellow at Massachusetts General Hospital and research affiliate at the Broad Institute, who is a co-lead author of both papers. "The SORT1 pathway is an unexpected but promising new target for therapeutic intervention to reduce LDL cholesterol and, in turn, heart attacks."

**More information:** Musunuru et al. From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. Nature DOI:10.1038/nature09266

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