Gene for cholesterol and cardiovascular disease identified through genome scan

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Researchers at the University of Pennsylvania School of Medicine, the Broad Institute, Massachusetts General Hospital, and Alnylam Pharmaceuticals Inc., are some of the first to prove that a gene linked to a disease trait by genome wide association studies (GWAS) can be clinically relevant and an important determinant of disease risk.

"One of the criticisms of genome-wide association studies has been that they fail to identify specific genes that cause disease," says co-lead author Daniel J Rader, MD, professor of Medicine and Pharmacology at Penn. "This is one of the first examples in which a spot on a chromosome identified by GWAS has been extended to pinpoint the causal gene and relevant physiology."

In a study published this week in *Nature*, the team of investigators describes how a region on chromosome 1 previously found by GWAS to be associated with both low-density lipoprotein cholesterol (LDL-C, the "bad" cholesterol) and myocardial infarction (MI) regulates LDL-C levels.

The study shows that a common gene variant on chromosome 1 creates a transcription factor binding site, which allows for increased transcription of several genes in the liver. Using a combination of over-expression and RNA silencing techniques, Sort1, a gene encoding a protein known as sortilin, was identified as the gene responsible for the associated cardiovascular effects on chromosome 1. Specifically, animals treated with a silencing RNA capable of reducing liver sortilin by 90 percent

had a 30 percent increase in plasma cholesterol at two weeks post-injection, while mice injected with an adeno-associated virus (AAV) to increase liver sortilin protein had an 80 percent reduction in plasma cholesterol at two weeks.

This reduction in plasma cholesterol was found to be due to reduced secretion of the LDL precursor VLDL into the blood. From other studies, there is a known association between reducing LDL and a reduced risk of heart attacks.

Taken together, these findings provide evidence for a new regulatory system for lipoprotein metabolism and suggest that activating the Sort1 pathway may alter risk for heart attacks in humans. This would be an important breakthrough in cardiovascular disease treatment, notes Rader, as although cholesterol-lowering medications such as statins are used widely, many people do not respond favorably to this class of drugs.

"These results identify Sort1 as the causal gene responsible for the association of a part of chromosome 1 with LDL-C levels in the blood and therefore heart disease, as well as point to a potential new target for the development of new therapies," says Rader.

In a second Nature paper describing a consortium of GWAS for blood lipids involving more than 100,000 individuals of European ancestry, the researchers report 95 spots in the human genome significantly associated with lipid-related traits for coronary artery disease, 59 of which are novel. Among those, Sort1 showed the strongest statistical relationship to LDL-C levels in the human genome.

"This remarkable international consortium highlights scores of genes not previously implicated in lipoprotein metabolism," notes Rader, also a co-author on the second Nature paper. "The 95 loci contribute not only to normal variation in lipid traits but also to extreme lipid phenotypes and

impact lipid traits in multiple non-European populations, such as East Asians, South Asians, and African Americans. These results identify several novel loci associated with serum lipids that are also associated with coronary artery disease, highlighting potential targets for new therapies."

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