CARDIOVASCULAR ENDOCRINOLOGY

Lipids and cardiovascular disease risk: genetic insights

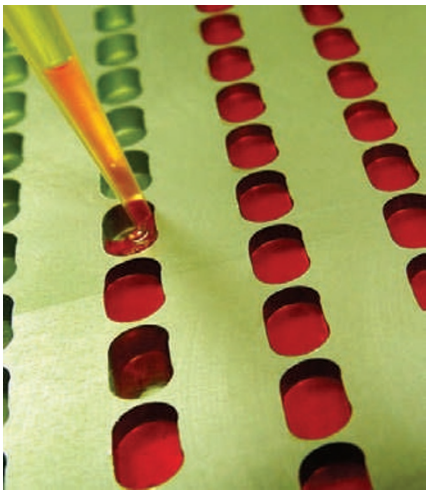
Two multicenter teams have used data from genome-wide association studies (GWAS) to unravel the link between cardiovascular disease risk and variation in blood lipid levels.

Cardiovascular disease risk is heavily influenced by the levels of lipids—LDL cholesterol, HDL cholesterol and triglycerides—in the blood. Identification of genetic variants associated with disruptions in levels of blood lipids is hoped to provide biologic and, ultimately, therapeutic insights, but Teslovich *et al.* wanted to find out if GWAS can really deliver. Namely, can the strategy help identify genes of biological relevance, provide information of clinical relevance that can be harnessed to help identify novel drug targets and determine loci important in different global populations.

The researchers pooled results from 46 GWAS for lipid traits in a meta-analysis that included >100,000 individuals of European descent. They identified 95 loci with significant genome-wide association with lipid traits, of which 59 were novel loci.

The loci included variants near or in genes that encode known lipid regulators and drug targets for hyperlipidemia, but also revealed novel lipid genes—*GALNT2*, *PPPIR3B* and *TTC39B*. Upon functional validation of *GALNT2* in mouse models, the team discovered a role of the encoded protein—an enzyme of the *N*-acetylgalactosamine-transferase family—in the regulation of HDL cholesterol levels in the blood. Clinical relevance was also established, as some loci are associated with coronary artery disease risk and others contribute to extreme lipid phenotypes if a combination of common variants is present. Lastly, the researchers confirmed that the loci also contribute to lipid traits in non-Europeans—including East Asian, South Asian and African American populations.

A different article by Musunuru *et al.* used a GWAS-identified locus as a starting point to uncover a novel pathway of lipoprotein regulation. The studied locus was known to be strongly associated with elevated blood LDL cholesterol levels and the risk of myocardial infarction. Through studies in humans and human-derived liver cells, these researchers found that a noncoding polymorphism (rs12740374) creates a transcription factor binding site that effects expression of the *SORT1* gene in the liver. Manipulation of *SORT1* expression in the liver of mice showed that the gene—which encodes the protein sortilin—effects secretion of VLDL by liver cells and, in so doing, affects levels of LDL cholesterol and VLDL particles in the blood.



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Future investigations of the new loci should provide further insights, which supports the view that large, pooled GWAS combined with functional studies can drive biologic and therapeutic advances for cardiovascular and other complex diseases.

Carol Wilson

Original articles Teslovich, T. M. *et al.* Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707–713 (2010) | Musunuru, K. *et al.* From noncoding variant to phenotype via *SORT1* at the 1p13 cholesterol locus. *Nature* **466**, 714–719 (2010)