Medical Xpress

Large international study finds 21 genes tied to cholesterol levels

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In the largest-ever genetic study of cholesterol and other blood lipids, an international consortium has identified 21 new gene variants associated with risks of heart disease and metabolic disorders. The findings expand the list of potential targets for drugs and other treatments for lipid-related cardiovascular disease, a leading global cause of death and disability.

The International IBC Lipid Genetics Consortium used the Cardiochip, a gene analysis tool invented by Brendan J. Keating, Ph.D., a scientist at the Center for Applied Genomics at The Children's Hospital of Philadelphia. Since its creation in 2006, researchers have used the Cardiochip to pinpoint gene variants in dozens of studies. The device contains approximately 50,000 DNA markers across 2000 genes implicated in cardiovascular disease.

Keating and Fotios Drenos, Ph.D., of University College London, are senior authors of the current study, published today in the American Journal of Human Genetics.

Comprising over 180 researchers worldwide, the consortium analyzed genetic data from over 90,000 individuals of European ancestry. First the researchers used the Cardiochip in a discovery dataset of over 65,000 individuals from 32 previous studies. They then sought independent replication in other studies covering over 25,000 individuals, as well as in a previously reported study of 100,000 individuals.

From this meta-analysis, the consortium identified 21 novel genes associated with levels of low-density lipoproteins (LDL, or "bad cholesterol"), high-density lipoproteins (HDL, "good cholesterol"), total cholesterol (TC), and triglycerides (TG), as well as verifying 49 known signals. The researchers also found that some of the strongest signals appeared to be gender-specific—some variants were more likely to appear in men, others in women.

Keating said, "To date, this is the largest number of DNA samples ever used in a study for lipid traits, it clearly shows the value of using broad-ranging global scientific collaborations to yield new gene signals."

Drenos added, "While each of the genetic variants has a small effect on the specific lipid trait, their cumulative effect can significantly add up to put people at risk for disease." He continued, "This study underscores how international sharing of resources and datasets paves the way for robust, continuing discoveries of new and unexpected information from human genetic studies."

Keating and Drenos coordinated efforts among four main data coordinating sites: the Center for Applied Genomics at The Children's Hospital of Philadelphia; the Institute of Cardiovascular Sciences at University College London; AMC, Amsterdam; and the Department of Cardiology at the University Medical Center, Utrecht.

The consortium is following this published work with a project to identify which of the loci reported directly cause disease, and how this knowledge can help in the development of novel drugs. The consortium will also devote its significant pooled resources to identifying interactions among genetic polymorphisms (single-base variations in DNA) and biological markers of downstream cardiovascular disease.

Lead author Folkert Asselbergs, M.D., Ph.D., of University Medical

Center, Utrecht, added, "Next to already established drug targets such as the LDL receptor and PCSK9, the current study identified 21 potential new targets for drug development that may be beneficial for the treatment of dyslipidaemia in the future. Our team of researchers are now initiating additional studies to investigate the impact of the found genes on cardiovascular disease."

More information: "Large-Scale Gene-Centric Meta-analysis across 32 Studies Identifies Multiple Lipid Loci," *American Journal of Human Genetics*, published Oct. 11, 2012.

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