Scientists associate 6 new genetic variants with heart disease risk factor

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Using new techniques for rapidly scanning the human genome, researchers have associated levels of cholesterol and triglycerides, two fats in the blood, to 18 genetic variants, six of which represent new DNA regions never before associated with the traits. The findings, appearing in the January 13 advance online issue of *Nature Genetics*, help explain some of the variability in cholesterol and triglyceride levels that arises from genes.

With the potential to help predict a patient's genetic risk of heart disease, the six new loci may point to novel aspects of cholesterol metabolism and could also spur new cholesterol-lowering drugs.

Heart disease is a leading cause of death around the world. Researchers have known for decades that one of the strongest predictors of heart disease risk is the level of cholesterol in the blood. While differences in lifestyle, such as diet and exercise, can influence a person's cholesterol levels, differences in genes can too. Some of these culprit genes are already known, but it is clear that many others remain to be found. "By uncovering the genetic determinants of cholesterol levels and, in turn, heart disease risk, we may be able to identify high-risk patients who can benefit from early interventions, in addition to expanding our knowledge of cholesterol biology and opening doors to new treatments," said first author Sekar Kathiresan, director of preventive cardiology at Massachusetts General Hospital and a genetics researcher in the Program in Medical and Population Genetics at the Broad Institute of Harvard and MIT.

Cholesterol and triglycerides are fats known as “lipids” — normal constituents of every cell in the human body. There are two main types of cholesterol in the body, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, which are commonly known as the "bad" and "good" cholesterols, respectively." The levels of LDL and HDL cholesterol in the blood have been shown to predict future risk of heart attack and are known to be influenced by both genetic and lifestyle factors. Similarly, the amount of triglycerides in the blood is also determined by a mix of genes and lifestyle and is often considered a marker of type 2 diabetes risk, another important contributor to heart disease.

To systematically identify genetic variants associated with blood lipid levels, Kathiresan and his colleagues scanned the genomes of over 27,000 people to locate common single-letter variations called single nucleotide polymorphisms (SNPs). This work produced a list of 18 SNPs reproducibly associated with levels of LDL cholesterol, HDL cholesterol, or triglycerides. Twelve of the SNPs were already known to influence lipid levels, underscoring the power of the genome scanning technique to find key genes. Importantly, the remaining six SNPs turned out to be entirely new: two are associated with LDL cholesterol, one with HDL cholesterol, and five with triglycerides.

Kathiresan and his colleagues took the study a step further, quantifying how a single-letter change in the genetic sequence can influence the amount of lipids in the blood. For example, someone who carries a “T” at a particular spot on both copies of chromosome 19 can have an LDL cholesterol level that is 16 mg/dL lower than someone who carries the more common “G”. With an average LDL cholesterol level of roughly 130 mg/dL in adults, this may seem like a relatively minor change, but when many genetic variants —18 from this study alone — come into play, they can add up to large differences among people, explained Kathiresan.

Importantly, the study identified many of the established and emerging targets for drug therapy, such as the HMGCR gene, which is a target of so-called “statin” medications that lower LDL cholesterol, and the PCSK9 gene. This suggests that some of the newly identified gene regions may eventually become new targets for drug therapy.

Additionally, the researchers found that one of the six new SNPs altered the expression, or activity, of three nearby genes, suggesting that it somehow acts to regionally regulate them. Even more strikingly, that very same SNP was recently shown to be associated with coronary artery disease. Taken together, these findings provide a more complete picture of the path from genes to markers of heart disease like cholesterol to heart disease risk.

A primary goal of this kind of study is to learn more about human biology, which could in turn lead to new biochemical targets for therapy. But identifying SNPs is only the first step in the process. The new SNPs found by Kathiresan and his colleagues fall between the protein-coding portions of the genome, so their biological effects are not immediately clear. They may influence lipid levels by regulating the expression of nearby genes, but most of those genes have yet to be identified. That will require future laboratory work in cells or animals, in addition to continuing genetic studies in diverse human populations.

In the future, the researchers would also like to probe more deeply the DNA that surrounds the 18 genomic regions identified in the *Nature Genetics* study. “These findings give us insight into the genetic architecture of quantitative traits like blood lipid levels, but we think that our findings may underestimate the impact of these regions,” said Kathiresan. “If we look closer, we may find even more SNPs nearby that contribute to cholesterol inheritance.”

Another motive for this work is to eventually give physicians the ability

to predict whether a patient will develop high cholesterol. Today, patients are often older and have had high cholesterol for several years before they are given a cholesterol-lowering drug. With a more complete knowledge of the genetic triggers, physicians may be able to identify high-risk patients at an earlier stage and use cholesterol-lowering drugs to prevent future damage to blood vessels.

The current study builds upon the Diabetes Genetics Initiative of the Broad Institute, Lund University, and Novartis Institutes for BioMedical Research, a pioneering study of the genetics of type 2 diabetes that found three new genomic regions influencing type 2 diabetes risk, published in Science last year. That paper included an analysis of serum cholesterol and triglycerides and identified a new genetic signal for triglyceride levels in humans — a gene called GCKR. On its own, however, this study lacked power to distinguish other new potential signals from statistical noise. By combining DGI data with that of two other studies, and by extensive replication in additional samples, the current study identifies a total of 18 strong signals, six of which are new. This brings the total for the DGI and its follow-up to seven newly identified variations associated with cholesterol and triglycerides. The DGI was led by David Altshuler, director of the Broad Institute's Program in Medical and Population Genetics, and associate professor at Massachusetts General Hospital and Harvard Medical School.

Genome-wide association studies are the realization of a long-term effort to understand how human genetic variation impacts health. Built on the Human Genome Project, these studies have been made possible in the last year, driven by the recent completion of the HapMap Project and availability of large-scale research tools. Already, scientists from Broad Institute of Harvard and MIT, as well as other research organizations worldwide, have used the approach to identify genetic differences that influence a variety of disorders, including type 2 diabetes, Crohn's disease, rheumatoid arthritis, systemic lupus

erythematosus, obesity, age-related macular degeneration, and prostate cancer.

Source: MIT