

Genome Studies Point to Cholesterol-Regulating Genes

But researchers caution any possible clinical application is many years away

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WEDNESDAY, Aug. 4 (HealthDay News) -- Researchers have identified almost 100 genes in the human genome that may regulate cholesterol levels and the risk of coronary artery disease, according to a new study.

Reporting in the Aug. 5 issue of *Nature*, the authors suggest that studying these regions may illuminate the genetic basis of cholesterol levels in humans, but they caution that potential clinical applications are many years away.

"There's convincing evidence that at least some of these will be useful on a clinical level," said study co-author Dr. Sekar Kathiresan of Harvard Medical School, although exactly how most of them might regulate cholesterol metabolism remains an open question, he said.

Levels of two kinds of lipids -- cholesterol and triglycerides -- are known risk factors for heart disease, and about half of the variability in lipid levels is thought to result from genetic factors, said Kathiresan.

He and his colleagues measured lipid levels in more than 100,000 people and then scanned their genomes for genetic differences. They found 95 sites at which tiny differences in genetic sequence seemed to correlate consistently with differences in lipid levels. Together, an individual's genetic makeup at these 95 sites seems to explain about one-quarter of the genetic component of blood lipid levels, Kathiresan said.

Although the initial analysis was done in people of European descent, the researchers also performed their analyses on people of other ethnic backgrounds and found that most of the 95 regions appear to be important in individuals of African and Asian heritage as well.

About one-third of these sites were already known or suspected to be important for lipid metabolism; the other two-thirds had not been tied to lipid levels or coronary artery disease.

"We have now a long list of genes that are relevant in people, and we think it's time to start trying to understand each of those," Kathiresan said. "We think that some of these will in time turn out to be useful drug targets."

As a first step in understanding the biological mechanism through which one of these genes regulates lipid levels, the authors then conducted an in-depth analysis of one of the 95 sites. They found that the gene that had the strongest relationship to lipid levels was not actually part of the genome that codes for proteins. Instead, this "non-coding" gene is involved in regulating the expression of a different gene that directly influences lipid levels.

None of this mechanism was known before to be important in cholesterol metabolism, Kathiresan said. It's an "entirely new player in the lipid field."

Similar in-depth analysis of the other 94 sites may uncover other novel lipid regulators, Kathiresan said. "With that kind of effort, we think we'll be able to learn a lot about what is important for lipids in people," he said.

Dr. John LaRosa, of the State University of New York Downstate Medical Center in Brooklyn, cautioned that it may not be straightforward to tease apart how these genes influence lipid levels or risk of coronary artery disease. While a few of them may regulate lipid metabolism in a simple way, it's likely that many interact in extremely complex ways, which may be too much for even powerful computers to resolve, he said.

Some may be important only when triggered by an environmental factor, and others may simply be false positives that don't actually contribute to lipid metabolism, LaRosa added.

Still, the work is "great science," LaRosa said, and sets important groundwork for the future.

What does this mean for the average guy on the street?

"Probably not much," he said, "but they are important studies to do. They build up a database that we need in order to be able to dissect how the genome influences something as remote from the individual gene sites as having high cholesterol."

More information

There's much more on cholesterol at the [American Heart Association](#).

SOURCES: Sekar Kathiresan, M.D., assistant professor, medicine, Harvard Medical School, and director, preventive cardiology, Massachusetts General Hospital, Boston; John C. LaRosa, M.D., president and professor of medicine, SUNY Downstate Medical Center, Brooklyn, N.Y.; Aug. 5, 2010, Nature

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