Gene variation may be why some don't respond to cholesterol-lowering drugs

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A variation in the way the body processes a single protein may explain why some people don't respond well to drugs that lower "bad" cholesterol, according to a report in *Circulation: Journal of the American Heart Association.*

The gene variation, called alternative splicing, explained 9 percent of the drugs' decreased power to reduce low-density lipoprotein (LDL) in study participants compared to people with the standard processing pathway.

The study is the first to show that a change in a biological process contributes substantially to the effectiveness of cholesterol-lowering drugs known as statins.

"Nine percent is a large number," said Ronald Krauss, M.D., senior author of the study and director of atherosclerosis research at the Children's Hospital Oakland Research Institute in California. "When we look at individual variations in genes affecting cholesterol metabolism, we can usually explain only a few percent of the variability in statin response."

The discovery could lead to improved cholesterol treatment and new therapy for other chronic ailments.

"The implications could go well beyond the efficacy of statins by helping us to understand the differences among individuals in how cholesterol is metabolized," Krauss said.

Simvastatin is one of several statin drugs that can effectively reduce the risk of heart attacks in people with high cholesterol. They work by blocking a key enzyme required for the production of cholesterol called HMGCR. However, all people don't have the same response to statins.

Krauss and his team sought a genetic explanation for this variability. They analyzed differences in how the gene responsible for producing HMGCR was processed — or spliced — among more than 900 participants enrolled in the Cholesterol and Pharmacogenetics (CAP) Study. During splicing, some portions of the gene's first product, mRNA, are removed and others are combined. The enzyme that is produced from the normally spliced HMGCR mRNA plays an early and critical role in the body's production of cholesterol, and its activity can be strongly inhibited by statins. The alternatively spliced form, on the other hand, is more resistant to statin inhibition of cholesterol production.

Researchers found that the "alternative splicing" also accounted for 15 percent of the reduced response of apolipoprotein B — a constituent of LDL — to simvastatin and 6 percent of the lower triglyceride response to the drug.

Combining factors already known to affect statin response — age, race and smoking— with alternative splicing explains 24 percent of the variation in LDL response, 29 percent for apoB and 8 percent for triglycerides, Krauss said. Despite this variability, statins are generally highly effective for prevention and treatment of heart disease, and there is not yet sufficient evidence for using genetic testing in evaluating the degree of benefit that individuals might be expected to achieve from statin treatment.

Marisa Wong Medina, Ph.D., co-author of the study, measured the two forms of spliced mRNA in cell lines grown from lymphocytes in people

in a simvastatin clinical trial. The greater the proportion of alternatively spliced copies, the lower the clinical response to the drug.

Deciphering alternative slicing promises other benefits, including a deeper understanding of cholesterol metabolism.

"We know that the pathway leading to cholesterol has many side branches, some of which are involved in inflammation," Krauss said. "Statin treatment is thought to be effective in reducing heart disease risk by blocking production of molecules in the cholesterol synthesis pathway that can lead to both cholesterol buildup and inflammatory reactions in blood vessels."

Understanding the genetic regulation of these effects, and the role of alternative splicing of HMGCR and perhaps other genes in the cholesterol pathway, could lead to the development of new drugs for reducing heart disease risk, researchers said

Source: American Heart Association