Researchers identify gene variant linked to effectiveness of plavix

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Researchers at the University of Maryland School of Medicine have identified a common gene variant carried by as many as a third of the general population that is believed to play a major role in determining why people do not respond to a popular anti-clotting medication, Plavix. If the medication doesn't work, patients are at increased risk for subsequent heart attacks, strokes and other serious cardiovascular problems.

The results of the study, published in the Aug. 26, 2009, issue of the Journal of the American Medical Association (*JAMA*), confirm a previously reported link between people's decreased response to Plavix, also known as clopidogrel, and common variations of the CYP2C19 gene. The study is the first to identify a common variant of this gene by using a sophisticated technique called a genome-wide association study to rapidly scan hundreds of thousands of genetic markers in the DNA of participants. More than 400 members of the Old Order Amish community in Pennsylvania took part in the study.

"By scanning the entire genome, we found compelling evidence that the CYP2C19 gene is a key determinant of how people respond to this medication," says the lead author, Alan R. Shuldiner, M.D., professor of medicine and director of the Program in Genetics and Genomic Medicine at the University of Maryland School of Medicine in Baltimore. "We didn't detect any other common gene variants that appear to be as significant as CYP2C19, but our research suggests that people's response to clopidrogel is largely inherited and additional

common and rare gene variants most likely are involved."

Dr. Shuldiner says he will continue his research to search for these gene variants. "The more we know about how genes affect people's response to medicines, the better able we are to develop effective new therapies and tailor treatment to an individual patient's genetic make-up," he says.

About 30 percent of the general population in the United States has the CYP2C19 variant identified in the study. Dr. Shuldiner says that it can be detected by a simple genetic test using DNA from blood or saliva. "If people have the gene variant, they might need to take a higher dose of clopidrogel or a different medication altogether," he says, adding that more research is needed before such testing becomes routine.

Plavix is one of the world's best-selling medications. It is used to prevent platelets from sticking together and causing blood clots in patients with cardiovascular disease who are at risk of having future heart attacks and strokes. (Platelets are fragments of bone marrow cells that help the blood to clot.) Despite its widespread use, up to 32 percent of people don't respond to the therapy and as a result, experience serious cardiovascular events. Researchers don't know the exact reason, but they believe that one important factor is the difference among individuals in their ability to metabolize the drug due to variation in the CYP2C19 gene.

"People who have this gene variant are less able to convert clopidrogel into its active form. They also have poorer platelet response to the medication and are at a 2.4-fold-higher risk of dying or having a serious cardiac event resulting from a blocked artery than those who don't have the variant," Dr. Shuldiner says.

E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs at the University of Maryland and dean of the University of Maryland School of Medicine, says, "Dr. Shuldiner is a nationally recognized

leader in pharmacogenetics research, and the results of this study are very impressive and important, given the huge number of people with cardiovascular disease who depend on Plavix to prevent future heart attacks and strokes. This research significantly advances the science in this area and moves us forward in our quest to offer individualized treatments to our patients."

Dr. Shuldiner and his colleagues analyzed the DNA of 429 healthy members of the Amish community in Lancaster County, Pa. They gave the study participants Plavix for seven days and then looked at how their blood platelets responded. They also studied the participants' DNA, searching for common gene variations. The researchers collaborated with investigators at the Sinai Center for Thrombosis Research in Baltimore, confirming their findings by studying a group of 227 people who received Plavix after having stents implanted to open blocked coronary arteries at Sinai Hospital.

Paul A. Gurbel, M.D., senior author of the study and director of the Sinai Center for Thrombosis Research, says that "patients with the CYP2C19 variant had a diminished platelet response to clopidrogrel treatment and poorer cardiovascular outcomes." Patients with the gene variant were more likely (20.9 percent vs. 10 percent) to have a heart attack or other serious cardiovascular event in the year following initiation of treatment.

In 2003, Dr. Gurbel and his colleagues at Sinai were the first to report that some people don't respond to clopidogrel therapy. Two years later, they went on to demonstrate the important connection between this non-responsiveness and patients having adverse cardiovascular events.

"When we initially reported non-responsiveness to clopidogrel, the cause was unclear," adds Dr. Gurbel. "Since then, this field has rapidly evolved as demonstrated in this important study. The results of the study lend

support to genotyping and platelet function testing as potential future strategies for optimal antiplatelet drug selection in treating patients with cardiovascular disease." This study is among the first to demonstrate in a single group of patients a link between a gene variant and responsiveness to clopidogrel that in turn is associated with outcomes after coronary stenting, he says.

Dr. Shuldiner says that about 30 percent of the Amish population has the CYP2C19 variant, which is similar to the general population. He notes that by studying the Amish - a genetically homogenous people, most of whom are related - researchers were able to estimate that 70 percent of the variation in clopidrogel response is due to genes and other shared factors among family members, such as their environment. In genetic research, 70 percent is considered extremely high "heritability," he says.

The researchers estimate that the CYP2C19 variant accounts for 12 percent of the platelet response to the drug, and other factors, such as age, body mass index and cholesterol levels in the blood, account for another 10 percent. But, Dr. Shuldiner says most of the difference in response to the medicine remains unexplained. "Additional studies in larger populations will be necessary to find additional genes that influence response to clopidogrel," Dr. Shuldiner says.

Source: University of Maryland Medical Center