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International collaborative identifies 13 new heart-disease-associated gene sites

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Thirteen new gene regions have been convincingly linked to coronary atherosclerosis in a massive, new, international genetics study involving investigators from the Stanford University School of Medicine.

The results of the study, to be published online March 6 in *Nature Genetics,* provide 13 vital new clues on the etiology of this disease, the most common cause of death worldwide. The study doubles the number of gene regions previously known to predispose people to this condition. Coronary atherosclerosis is the process by which plaque builds up in the wall of heart vessels, eventually leading to chest pain and potentially lethal heart attacks.

The study was conducted by an international consortium, which pooled resources to analyze data from 14 genome-wide association studies. Consortium investigators examined the complete genetic profiles of more than 22,000 people of European descent with coronary heart disease or a heart attack history and 60,000 healthy people — close to 10 times more than the next-largest whole-genome study to date.

"These new discoveries will allow scientists worldwide to eventually better understand the root causes of coronary atherosclerosis, possibly leading to important new drug therapies that may profoundly reduce the risk of having a heart attack," said Thomas Quertermous, MD, the William G. Irwin Professor in Cardiovascular Medicine at Stanford. Quertermous is the principal investigator of the Stanford/Kaiser ADVANCE study of heart disease, which joined this consortium early in

its formation.

Investigators were able to examine an average of 2.5 million common single nucleotide polymorphisms, or SNPs, in each of the 14 genome-wide association studies. SNPs are genetic variants at specific locations on individual chromosomes. New genomic technology allows hundreds of thousands of SNPs to be reliably scanned in a person. Variants in 23 regions that appeared most likely to predispose people to coronary atherosclerosis were then studied in about 25,000 subjects with disease and about 25,000 healthy subjects from multiple additional studies. Thirteen of those 23 regions passed the threshold of statistical evidence for validation.

"Out of the roughly 3 billion bases in our DNA code, we're talking about finding a few bases that are different in some people, and that difference leads to a change in the function of a gene or a set of genes that in turn changes your lifetime risk of having heart disease. That is like looking for a change in one letter in one word in the Encyclopedia Britannica," Quertermous said. "That is amazing."

Combining genetic data from multiple studies is absolutely critical to identifying these needles in the haystack, as the genetic architecture of coronary atherosclerosis has proven to be far more complex than anticipated. "The signals from these gene regions are all rather subtle, making large-scale collaborations a prerequisite for any meaningful progress," said Themistocles (Tim) Assimes, MD, PhD, assistant professor of medicine at Stanford and one of the study's 10 lead authors.

The results also suggest that it may be worthwhile to determine an individual's profile of genetic variants for heart attacks as part of routine clinical care in the near future. "With such information we should be able to better identify people at high risk early on in life and quickly take the steps to neutralize that excess risk by strongly recommending

lifestyle and pharmacological therapies that we already know substantially reduce risk," Assimes said. "Although we are inching closer to that day, we will probably need to reliably identify many more variants predisposing to heart attacks over the next few years before it becomes useful to perform this genetic profiling in a doctor's office."

Interestingly, only three of the 13 new gene regions appear to be linked to coronary atherosclerosis through traditional risk factors such as high cholesterol and blood pressure, diabetes, smoking and obesity. "This leaves open the possibility that many of the other gene regions are pointing to biological processes in the vessel wall that are reacting to the plaque-promoting effects of traditional risk factors," said Assimes.

"Cancer geneticists and cancer biologists have had access to the genes that are associated with cancer and have made a lot of progress," Quertermous said. "We've been slow in understanding the molecular pathways associated with the disease process in the walls of blood vessels. Studying the function of the genes in these gene regions should teach us how we can block the process of plaque development in the vessel wall. Currently there are no drugs that directly target the vessel wall," he said. "Heart disease drugs, such as statins and beta blockers, or blood pressure medications target bad cholesterol or hypertension and other risk factors but not necessarily the molecular mechanisms that are directly responsible for forming plaque.

"I've been waiting my entire life to see the names of these genes," said Quertermous, who has worked in the field for 20 years. "We are making huge progress but there is much work left to do."

The researchers indicated that the next steps would be to push forward with more meta-analyses of existing genome data to uncover yet more novel gene regions and to sequence the established gene regions in a large number of individuals. The latter will likely identify less common

genetic mistakes in these same gene regions that also predispose to coronary disease. These efforts are ongoing and are expected to further improve the ability to reliably predict who will have a heart attack and to develop new life-saving drugs.

Provided by Stanford University Medical Center