MedicalXpress

International study points to inflammation as a cause of plaque buildup in heart vessels

December 2 2012

Fifteen new genetic regions associated with coronary artery disease have been identified by a large, international consortium of scientists—including researchers at the Stanford University School of Medicine—taking a significant step forward in understanding the root causes of this deadly disease. The new research brings the total number of validated genetic links with heart disease discovered through genome-wide association studies to 46.

Coronary artery disease is the process by which plaque builds up in the wall of heart vessels, eventually leading to chest pain and potentially lethal heart attacks. It is the leading cause of death worldwide.

The study, which will be published online Dec. 2 in *Nature Genetics*, provides insights into the molecular pathways causing coronary artery disease, which is also known as coronary atherosclerosis.

"Perhaps the most interesting results of this study show that some people may be born with a predisposition to the development of coronary atherosclerosis because they have inherited mutations in some key genes related to inflammation," said Themistocles (Tim) Assimes, MD, PhD, a Stanford assistant professor of medicine and one of the study's lead authors. "There has been much debate as to whether inflammation seen in plaque buildup in heart vessels is a cause or a consequence of the plaques themselves. Our network analysis of the top approximately 240 genetic signals in this study seems to provide evidence that genetic defects in some pathways related to inflammation are a cause."

More than 170 researchers were involved in this massive meta-analysis combining genetic data from more than 190,000 research participants. Interestingly, about a quarter of the genetic regions associated with coronary disease or heart attack were also found to be strongly associated with cholesterol, especially high levels of the so-called bad cholesterol known as LDL. Another 10 percent were associated with high blood pressure. Both of these conditions are known risk factors for coronary artery disease.

"The signals that do not point to known risk factors may be pointing to novel mechanisms of disease," Assimes said. "It is imperative that we quickly gain a better understanding of how these regions are linked to heart disease, as such understanding will greatly facilitate the development of new drugs to prevent heart disease."

Genome-wide association studies, or GWAS, were first introduced in 2005 as a way of quickly scanning the entire genome to identify differences in the DNA code, or "polymporphisms," that predispose people to various common but genetically complex diseases. Results of these studies have shown that conditions such as heart disease involve the combined, subtle effects of far more polymorphisms than initially expected, requiring multiple massive meta-analyses such as this one to reliably uncover all of these genetic signals. The hope of scientists is that by working together in ongoing worldwide collaborations, the entire genetic contribution to the cause of heart disease will eventually be identified.

"Studies like this one help provide new pathways for scientists to investigate in more detail," said co-author Thomas Quertermous, MD, a Stanford professor of medicine. "The promise is in providing better insights into the pathophysiology of this disease."

This meta-analysis study built upon previous research published last year

in Nature Genetics. In that study, investigators examined 2.5 million SNPs (genetic variants at specific locations on individual chromosomes) from 14 GWA studies, which led to the discovery of 13 new gene regions associated with heart disease. Investigators looked at data from the complete genetic profiles of more than 22,000 people of European descent with heart disease and more than 64,000 healthy people.

In the new study, scientists used all information from last year's study then added to it, reaching 41,513 patients with heart disease and 65,919 control patients. To genetically fingerprint a large number of subjects in a very cost-effective manner, the researchers used a specialized genetic chip that incorporated only the top signals from the original meta-analysis of the initial 14 GWA studies.

Provided by Stanford University Medical Center