Medical Xpress

Scientists discover genetic variant tied to increased stroke risk

April 15 2009

Millions of people have a genetic variant linked to increased risk of ischemic stroke, reports an international research team including scientists at The University of Texas Health Science Center at Houston in a study published online by *The New England Journal of Medicine* on April 15.

Ischemic stroke accounts for nearly 90 percent of all strokes and is caused by blockage of blood to the brain. More than 150,000 Americans succumb to stroke every year, making it the third leading cause of death. Survivors often experience permanent stoke-related disabilities.

Data gleaned from four large genome-wide association studies in the United States and Europe revealed that about 20 percent of whites and 10 percent of blacks have at least one copy of this genetic variant and that each copy increases the risk of ischemic stroke by approximately 30 percent.

The contributors from the UT Health Science Center at Houston are on the faculty of the university's Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM), which includes the Senator Lloyd and B.A. Bentsen Center for Stroke Research, and The University of Texas School of Public Health.

The team's discovery could lead to the development of new strategies to detect those at increased risk of stroke prior to the onset of symptoms and to the creation of treatments intended to target the molecular

mechanisms underlying stroke risk. "This is the first study to identify a common genetic variant influencing the risk of stroke in the United States," said Eric Boerwinkle, Ph.D., one of the study's authors and Kozmetsky Family Chair in Human Genetics at the UT Health Science Center.

The variant was found during an analysis of the genomes, or DNA, of almost 20,000 individuals from the United States and Europe, and, importantly, the study included both whites and blacks. The variant was not associated with increased risk for non-ischemic stroke.

While there have been previous genetic studies on stroke, the researchers wrote in their paper that the "genes underlying the risk of stroke in the general population remain undetermined."

"This research gives us a pointer or a beacon on the genome where we can look further," said Myriam Fornage, Ph.D., one of the study's lead authors and holder of the Laurence & Johanna Favrot Distinguished Professorship in Cardiology at the UT Health Science Center.

The variant was found on chromosome 12 near one gene associated with brain injury repair called NINJ2 and another connected to blood pressure control called WNK1. "Additional research is required because we don't know if NINJ2 is really the culprit," Fornage said.

In the study, researchers combined the results of genome-wide association data gathered from population-based studies comprising the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium.

"These studies, carried out at our Institute of Molecular Medicine and the School of Public Health, illustrate important advances in the detection and prevention of human diseases that can come from the

application of the most sophisticated new genetic technologies to the study of devastating diseases such as stroke," said Peter Davies, M.D., Ph.D., executive vice president for research at the UT Health Science Center.

"The discoveries made by the IMM team, and many similar discoveries that are emerging from studies being conducted by other research groups around the world, are providing the foundation for our ability to deliver on the promise of the next era of medicine: the promise to deliver truly personalized health care to our communities and our patients," Davies said.

The human genome is comprised of about 3 billion DNA base pairs. Among individuals, at some of the positions, there are differences in the DNA sequence, which are called single nucleotide polymorphisms (SNPs). The researchers use these SNPs as guideposts to map the locations of disease genes in the genome.

In the study, scientists linked two markers to increased ischemic stroke risk by comparing the genomes of 1,544 individuals who developed stroke with the genomes of 18,058 individuals who did not develop stroke. The novel discoveries were subsequently replicated in separate studies of blacks and whites.

"Identification of genes that predispose to stroke may aid in the identification of persons at increased risk of stroke in whom particularly vigorous attention to preventive measures can be applied," said Philip A. Wolf, M.D., one of the study's lead authors and principal investigator for the Framingham Heart Study in Framingham, Mass., which is in the CHARGE Consortium "It may also lead to the development of medications to reduce this increased stroke risk."

Environmental factors such as cigarette smoking and high blood pressure

also influence predisposition to stroke. "Your risk of disease is the combination of your genetic makeup and environmental factors," Boerwinkle said.

"Even though this variant is common, it has a modest effect on stroke risk," Boerwinkle said. "Therefore, everyone, whether they carry this variant or not, should be aware of the risk factors for stroke, such as high blood pressure and smoking, and do everything they can to avoid those risk factors."

Boerwinkle, who is the principal investigator for the largest study in the CHARGE Consortium, The Atherosclerosis Risk in Communities (ARIC) study, said, "We formed a consortium of the largest studies to permit rapid replication. If you only have one study, there is a chance of a false positive. Here we're doing millions of statistical tests and replication is necessary to rule out false positives." ARIC is a prospective epidemiologic study conducted in four U.S. communities and sponsored by the National Heart, Lung and Blood Institute (NHLBI).

Source: University of Texas Health Science Center at Houston (news : web)