Single gene defect can cause stroke, other artery diseases

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This is Dr. Dianna Milewicz (M.D., Ph.D.) of the University of Texas Medical School at Houston. Credit: The University of Texas Health Science Center at Houston

For the first time, scientists have discovered a single gene defect that causes thoracic aortic aneurysms and dissections as well as early onset coronary artery disease, ischemic stroke and Moyamoya disease. The research is led by scientists at The University of Texas Health Science Center at Houston.

The study, "Mutations in Smooth Muscle Alpha-Actin (ACTA2) Cause Early Onset Coronary Artery Disease, Stroke and Moyamoya Disease, Along with Thoracic Aortic Aneurysms and Dissections," was published

early online April 30 in the American Journal of Human Genetics.

"If someone is found to have an alteration or mutation in this gene, we can do screening for vascular diseases, and if diagnosed with disease, they can take medications and undergo surgical approaches to prevent premature death or disability," said senior author and principal investigator Dianna Milewicz, M.D., Ph.D., professor and director of the Division of Medical Genetics at The University of Texas Medical School at Houston.

The discovery of the causal relationship between the mutated gene ACTA2 and artery diseases has opened the door to a new way of thinking about the vascular system, Milewicz said.

"We need to look at the artery system as a continuous system or organ," said Milewicz, the President George Bush Professor in Cardiovascular Medicine. "We've been looking at it the wrong way. If you have this particular genetic mutation, it can present in several different diseases affecting different arteries."

Milewicz and her team studied 127 members of 20 families from around the world who had ACTA2 mutations.
They were phenotyped for premature vascular diseases, defined as an age of onset less than 55 years in men and less than 60 years in women.

Premature thoracic aortic aneurysms and dissections were the main vascular disease for 76 mutation carriers, while 26 had premature coronary artery disease, 15 had ischemic stroke, including Moyamoya disease, and 15 had more than one vascular disease.

In thoracic aortic disease, the wall of the aorta, the main blood vessel leading out of the heart, weakens and forms an aneurysm that can ultimately lead to an aortic dissection and death. Coronary artery disease,

the most common type of heart disease, is the leading cause of death for both men and women in the United States. Stroke is the third leading cause of death in the country.

In the study, none of the family members without the ACTA2 defect had any vascular disease, helping to rule out other genetic or environmental causes. In four families, members younger than age 20 suffered a stroke and five strokes resulted from Moyamoya disease, a rare stroke disease in which the internal carotid arteries become occluded.

The main function of smooth muscle cells is to contract in response to the stretching from pulsing blood flow. Vascular pathology from mutant aortas and analysis of smooth muscle cells removed from patients and grown in the laboratory suggest that persons with ACTA2 have increased multiplication of smooth muscle cells that contribute to blocked or enlarged arteries, according to the study.

Milewicz and her team previously discovered the role of the mutated ACTA2; mutations in ACTA2 account for 14 percent of the inherited form of thoracic aortic aneurysms and dissections, making it the major gene identified for the condition.

During the research, Milewicz identified a large family with persistent livedo reticularis, a purplish mesh-like skin discoloration caused by the occlusion of arteries in the skin. This family also had a history of premature onset coronary artery disease and premature stroke without the risk factors know to cause these diseases (smoking, high cholesterol)

"Family members asked if it all could be related and I told them at the time that they just had really bad luck with several mutated genes," Milewicz said. "It didn't occur to me until later that it might be from the same genetic defect."

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