MedicalXpress

Researchers discover gene defect for new syndrome

July 9 2012

Research teams from The University of Texas Health Science Center at Houston (UTHealth) and Paris, France have discovered a gene defect linked to a cluster of systemic complications, including life-threatening thoracic aortic disease and intracranial aneurysms. The new syndrome is similar, but distinct from known syndromes such as Marfan and Loeys-Dietz syndrome.

Genome-wide analysis of two unrelated families, one in the United States and one in France, identified mutations in transforming growth factor beta-2 (TGFB2), which plays a key role in the formation of cells in the walls of arteries. These changes can affect the ability of these cells that line the aorta and other blood vessels to function properly, leading to aortic aneurysms and dissections and intracranial aneurysms. Other systemic signs of the new syndrome include groin hernias, pectus deformities, joint hyperflexibility, mitral valve prolapse and skin stretch marks.

The findings were published in the July 8 online of the journal *Nature Genetics*. The French team included researchers from the Assistance Publique – Hopitaux de Paris and the Institut National de la Sante et de la Recherche Medicále (INSERM).

"Identifying this gene as a cause of aortic and intracranial aneurysms can tell us who is at risk in a family before these aneurysms cause an acute aortic dissection or stroke," said Dianna Milewicz, M.D., Ph.D., professor, the President George H.W. Bush Chair in Cardiovascular

Research and director of the Division of Medical Genetics at the UTHealth Medical School. "If we know who is at risk, we can prevent these life-threatening complications of these aneurysms before they occur and prevent premature death or disability."

Milewicz is the senior author of the paper, a multi-institutional collaboration. The lead author is Catherine Boileau of INSERM.

Incorrect function of the cells can cause a weakness in the wall of the thoracic aorta, which carries blood from the heart to the rest of the body. The result can be an aneurysm which can lead to a dissection and cause sudden death. An estimated 8,000 people die annually from thoracic aortic aneurysms and dissections (TAAD). Intracranial aneurysms occur in up to 6 percent of adults and are more common in women. Both types of aneurysms are typically asymptomatic and often undetected until a dissection or rupture occurs. Intracranial aneurysms that rupture and bleed into the brain, known as hemorrhagic stroke, have a mortality rate of up to 50 percent, according to the American Heart Association.

For the UTHealth research team, this is the fifth gene defect discovery for thoracic aortic aneurysms and the second with a link to both thoracic aortic aneurysms and intracranial aneurysms.

The researchers found that although the defect caused half of the normal amount of TGFB2 protein, called TGF-beta2, at the cellular level, the actual diseased arteries showed a large increase in TGF-beta2. "So we believe the body responds to less TGF-beta2 by overcompensating and producing more, causing the disease," said Milewicz, who is also director of the John Ritter Research Program Aortic and Vascular Diseases at UTHealth. "The primary defect is less TGF-beta2 with a secondary response to make more."

Milewicz said the availability of exome sequencing through the National

Heart, Lung and Blood Institute's (NHLBI) Go Exome Sequencing Project and INSERM in Paris, was a key component in the ability to locate the defective gene in two distantly related cousins in each of the two families. The NHLBI is part of the National Institutes of Health and the sequencing was done at the Northwest Genome Institute at the University of Washington in Seattle.

For family members in the United States, the discovery that they might carry a gene defect helped shed light on their tragic history of losing loved ones in the peak of their lives. It also allowed them to save a younger generation.

"My dad died suddenly at the age of 57 and they told us it was a heart attack," said one of the female members of the American family, which wishes to remain anonymous. "We assume now he died of an aortic dissection. After one of my cousins discovered this might be genetic, we all got tested."

Imaging of the thoracic aorta led to the discovery that one of her brothers, then 35 with young children, had an aortic root enlargement of 5.4 centimeters, large enough to require immediate surgery.

"He was a walking time bomb," she said. "He had surgery in 2005 and seven years later, he's doing great. I'm the most scanned and monitored person in the world, which is fine. As pieces of the puzzle come together, we hope we'll prevent any more premature deaths from this in our family." She undergoes regular echocardiographic and brain magnetic resonance imaging.

Provided by University of Texas Health Science Center at Houston