Researchers link PRKG1 genetic mutation to thoracic aortic disease

15 August 2013

From left, this is the Harris family in 2000: Jenny, Lisa, Amy, Cheryl, Steve and Andra. Credit: The Harris Family

A multi-institutional team led by Dianna Milewicz, M.D., Ph.D., of The University of Texas Health Science Center at Houston (UTHealth) has found a recurrent genetic mutation that has been linked to deadly thoracic aortic dissections in family members as young as 17 years of age.

The gene known as PRKG1 makes a protein called cGMP-dependent kinase, type I. The PRKG1 mutation alters the function of the protein and causes the muscle cells in the wall of the aorta to respond incorrectly to pulsatile blood flow from the heart, and the change in this one protein ultimately causes thoracic aortic aneurysm and acute aortic dissection. The mutation was identified in four families, including three in the United States. The majority of the affected family members suffered acute aortic dissections at young ages (17 to 51 years).

"What is unique about this finding is that we identified four unrelated families from around the world and of different ethnicities who have the exact same genetic mutation, which is one altered base pair out of the 3 billion base pairs that make up our DNA," said Milewicz, senior author of the study. "The protein is normally regulated but this mutation causes the protein to be always active, almost like the brakes have gone out on a car and it cannot stop." The study was published in today's online issue of the *American Journal of Human Genetics*. Milewicz is professor and director of the Division of Genetics at the UTHealth Medical School and holds the President George H.W. Bush Chair in Cardiovascular Research. She is also on the faculty of The University of Texas Graduate School of Biomedical Sciences and director of the John Ritter Research Program in Aortic and Vascular Disease.

For families in the study, knowing who carries the gene defect could help them make important medical decisions.

"The fact we will have a positive identification gives us a clearer picture of what to do next," said Stephen Harris of Montana, who lost one of his four daughters to the disease. "If my daughters are not carrying the gene defect, it gives them more freedom to have a baby. And they can make a decision about whether to have elective surgery sooner."

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. There are few symptoms until the aorta begins to dissect, or tear, requiring emergency surgery. Thoracic aortic aneurysms and dissections are familial in up to 20 percent of all cases. Researchers have now discovered nine different genes linked to familial thoracic aortic disease.

Family members who have inherited the mutated gene will need to be monitored by a cardiologist, undergo regular imaging of the aorta and take medications to control high blood pressure and reduce the stress on the aorta. When the aorta

enlarges to a certain size, elective surgery can be performed in order to avoid emergency repair to attempt to repair a catastrophic aortic dissection or rupture. Using this management protocol, acute aortic dissections and the associated premature deaths can be prevented.

Stephen Harris' brother was the first to have symptoms of an aortic dissection when he was 51 years old and was found to have a descending thoracic aortic dissection. Cheryl Harris, Stephen's wife, said their daughter Jenny was eight months pregnant in 2006 when she began to have severe pain in her back just like her uncle but since aortic disease mostly affects older men, they didn't connect it to her. She died suddenly six days later from a dissected aorta and the baby also did not survive. In June of 2012, daughter Andra Arterbury, then 27, felt the classic symptom of extreme back pain, which radiated into her neck. She insisted on a scan at the hospital emergency room and went immediately to life-saving surgery when it showed that the aorta was dissected up into her carotid artery and down nearly to her groin.

Steve Harris traveled to Houston to consult with Milewicz and the clinical team at the Multidisciplinary Aortic and Vascular Disease Clinic. He was also found to have aortic root dilation and because of his family history of early thoracic aortic dissections at diameters smaller than 5 centimeters, he elected to have surgery. In October 2012, Anthony Estrera, M.D., associate professor of cardiovascular surgery at the UTHealth Medical School and the Memorial Hermann Heart and Vascular Institute, performed the graft replacement of his aortic root.

Wendy Amaya, 40, of Albuquerque and her family members have also suffered from the disease. Her mother, 43; brother, 35; and nephew, 23, all died from thoracic aortic dissections. Her 19-year-old son required surgery to repair a dissection in 2012 and another son has an aneurysm that is being monitored. Amaya had surgical repairs for her aorta in 2004 and 2012.

"The imaging is expensive, so it's important to find out if they have the genetic mutation. I have younger children and nieces and nephews," Amaya said.

Now that the causative genetic mutation has been identified, genetic testing can identify family members who carry the familial mutation and need aortic surveillance.

Of the individuals who have the mutation, 63 percent had acute aortic dissections and 37 percent have aortic root enlargement. Of the 19 family members with dissections, five had a diagnosis of hypertension and five had evidence of damage associated with hypertension such as left ventricular hypertrophy or chronic small vessel cerebrovascular disease.

More information:
www.ncbi.nlm.nih.gov/pubmed/23910461

Provided by University of Texas Health Science Center at Houston