MedicalXpress

Researchers identify genes tied to sudden thoracic aortic dissections

September 19 2016

On Super Bowl Sunday, Tina Wilkins was relaxing in her recliner while she chatted on the phone with her mother and waited for the game to begin. She had recently lost 63 pounds and was in better shape than she had been in years.

So the pain, swift and so sharp that it robbed her of breath, came out of the blue. It brutally hit her neck, chest, abdomen and back at the same time. With every beat of her heart, she felt like she was being squeezed in a vice.

She told her mother she had to go and gasped out to her husband, "Call 9-1-1. I'm having a heart attack."

But Wilkins wasn't having a heart attack. Instead, her thoracic aorta, the critical artery that carries blood from a pumping heart to other parts of the body, was dissecting – shredding, tearing – as blood seeped out of it.

Wilkins didn't know it, but like a time bomb, an altered gene linked to thoracic aortic dissections resided in her body.

For more than two decades, Dianna Milewicz, M.D., Ph.D., President George H.W. Bush Chair of Cardiovascular Medicine at McGovern Medical School at The University of Texas Health Science Center at Houston, has been researching the biochemistry and genetics underlying thoracic aortic dissections. Milewicz, the director of the Division of Medical Genetics and vice-chair of the Department of Internal

Medicine, announced her first discovery of a gene linked to aneurysms and dissections in 2001.

The disease is responsible for the deaths of up to 20,000 Americans every year.

An aneurysm is a ballooning or enlargement of the aorta that typically causes no symptoms. But an aneurysm progressively enlarges until it becomes unstable and can lead to an aortic dissection, a tear in the aortic wall. Half the people who have a dissection die before they get to a hospital. Wilkins was one of the lucky ones and made it to the hospital for emergency surgical repair of her aorta.

Genetic alternations causing a predisposition for aneurysms leading to dissection can run in families in about 25 percent of cases. If detected early enough, the aneurysm can be repaired. If an identified, altered gene runs in a family, other family members can be tested and monitored so aortic aneurysm surgical repair can be done before the aorta dissects.

But sometimes a family's history is not known and – in up to 50 percent of cases – the dissection occurs with little to no enlargement of the aorta.

Milewicz and her team began to search for genetic variants linked to sporadic dissections in the 75 percent of people who do not appear to have a familial genetic variation. They genotyped 753 people with non-familial aortic dissections and compared them with a control group from the Atherosclerosis Risk in Communities study with help from the lab of Eric Boerwinkle, Ph.D., dean of UTHealth School of Public Health.

The work led them to the discovery of changes in two genes, LRP1 and ULK4, which alter the risk for dissection. These findings were published recently in the *American Journal of Human Genetics*.

"We decided to look at patients with dissections because this is the deadly complication associated with thoracic aortic disease," Milewicz said. "What we found were two genes that had variants linked to dissections. Interestingly, variants in these same genes have previously been linked to other diseases, including hypertension and dissections of the arteries in the brain. This tells us that there are overlapping pathways for cerebral or aortic dissections."

Milewicz is also on the faculty of The University of Texas Graduate School of Biomedical Sciences at Houston and Director of the John Ritter Research Program in Aortic and Vascular Diseases at UTHealth.

At the time of her sudden dissection, thoracic aortic disease wasn't on Wilkins' radar. The 46-year-old remained convinced she was having a heart attack. Along with the intense pain, both arms became numb. Initial tests at the hospital didn't pick up the dissection, in part because her aorta didn't appear to be enlarged.

But as he studied the ultrasound of her heart, something nagged at attending physician Michael Chanler, M.D., a family practitioner who works shifts in the emergency department at the small hospital in Minden, La.

The tipping point for him was when medications such as blood thinners that would have alleviated a heart attack made her symptoms worse.

"He stopped everything and said, 'I want to see a CT scan now!' He was very forceful," Wilkins said.

Even before the results of the scan revealed the unraveling dissection, Chanler was instructing nurses to give Wilkins drugs to counter the blood thinners. The only option for treatment of a dissection is surgery. After Chanler hurriedly called major centers and secured transportation,

Wilkins was headed to Memorial Hermann-Texas Medical Center, where physicians from McGovern Medical School at UTHealth are internationally known for thoracic surgery.

"Dr. Chanler told me he was going to put me on a plane to Houston and I looked up at him and said, 'I'm not going to make it to Houston.' There were 30 people in my ER room, which is usually never allowed so I think he thought I was going to die, too," Wilkins said. "I started praying, 'God, there is nothing I can do to change this except stay calm. Please help me stay calm.' "

Seven hours passed from the time of her first symptoms to her arrival at Memorial Hermann-TMC via a medical transport plane. Because she initially had been given blood thinners, physicians waited until 2 p.m. the next afternoon to do the surgery. The surgical team included Steven Eisenberg, M.D., assistant professor of cardiothoracic and vascular surgery at McGovern Medical School, and Hazim Safi, M.D., professor and chair of the Department of Cardiothoracic and Vascular Surgery and chief of Cardiovascular & Vascular Surgery at Memorial Hermann Heart & Vascular Institute-Texas Medical Center.

Wilkins, who spent 10 days in the hospital, said she thought she was delivered a death sentence when she heard the words "aortic dissection" on the night of Feb. 7, 2016.

"I told my family and friends that I was going to die," she said. "But Dr. Chanler, Dr. Eisenberg and Dr. Safi were 'rock stars.' They saved my life."

Provided by University of Texas Health Science Center at Houston