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Rare genetic variants linked to bicuspid aortic valve disease in young adults identified

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Genetic variants linked to a rare form of bicuspid aortic valve disease that affects young adults and can lead to dangerous and potentially life-threatening aortic complications have been identified by researchers at UTHealth Houston.

The study was published in the *American Journal of Human Genetics*.

"We previously found that young individuals who present due to early onset thoracic aortic dissections are more likely to have bicuspid aortic valves and more likely to have rare variants in bicuspid aortic valve -associated genes," said Siddharth Prakash, MD, Ph.D., co-principal investigator of the study and associate professor of medical genetics and cardiovascular medicine in the Department of Internal Medicine at McGovern Medical School at UTHealth Houston.

"When we observed that bicuspid aortic valve is kind of a risk marker for this group with bad outcomes, we specifically wanted to see whether young individuals who present clinically due to problems related to bicuspid aortic valve disease may also have rare genetic variants that predict complications such as needing valve surgery."

About 1 in 100 people are born with a bicuspid aortic valve, making it the most common cause of congenital heart disease.

The comparison between the rare subgroup of early onset bicuspid aortic valve to the common population of the disease allowed researchers to determine which group of patients will benefit from genetic testing, enabling earlier, more aggressive treatment.

According to researchers, patients with bicuspid aortic valve disease often wait too long to be seen, leading to more severe cardiovascular symptoms, such as heart failure and even sudden death.

A bicuspid aortic valve is a congenital heart defect where the value has two flaps, or cusps, instead of three, so the valve does not open and close properly with each heartbeat. This can lead to complications such as blocked, reduced, or backward blood flow through the heart chambers, causing shortness of breath, chest pain, fainting, and difficulty exercising. In more severe cases, the disease can lead to an aortic dissection, or tear in the aorta, a life-threatening condition.

Researchers studied individuals who presented with specific complications of the disease before age 30 or who were immediate relatives to someone with early onset bicuspid aortic valve disease. Early onset symptoms of the disease were defined as moderate or severe aortic stenosis or aortic regurgitation, a large thoracic aortic aneurysm, needing to have aortic surgery, or aortic dissection.

Researchers aimed to identify genetic variants that may lead to an increased risk of the disease in young adults. "The average person in this study was affected in their 20s and had relatives with the disease, so we traced the onset of the disease in the families and we reported rare genetic variants that segregated with the disease in these participants and their relatives," Prakash said.

Prakash and his team analyzed whole-exome sequencing data, sourced from 215 families from over 20 institutions to identify the rare genetic variants known to cause congenital heart disease in early onset bicuspid aortic valve disease in this rare subgroup. They compared those findings to the more common population of patients with later-onset bicuspid aortic valve disease.

The identified genes included genes that cause isolated nonsyndromic bicuspid aortic valve, as well as other types of congenital heart disease that are associated with bicuspid aortic valve or related congenital malformations. Researchers found damaging variants of genes with moderate or strong evidence to cause developmental cardiac phenotypes in 107, or 50%, of affected families in the study.

"We showed that the older patients with bicuspid aortic valves are unlikely to benefit from genetic testing because they are unlikely to have these kinds of genetic variants," Prakash said.

"It's important for people to realize, as we saw in this study, that a lot of

people with bicuspid aortic valves have affected relatives. In the future, family members may be tested for genetic variants that cause bicuspid aortic valve complications, and people who have these genetic variants could be treated early to prevent future complications from developing."

More information: Whole-exome sequencing uncovers the genetic complexity of bicuspid aortic valve in families with early-onset complications, *American Journal of Human Genetics* (2024). On *medRxiv*: www.medrxiv.org/content/10.110 … 024.02.07.24302406v1

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