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Discovery sheds more light on deadly thoracic aortic disease

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Discovery of a fifth gene defect and the identification of 47 DNA regions linked to thoracic aortic disease are the subject of studies released this month involving researchers at The University of Texas Health Science Center at Houston (UTHealth).

In both studies, the investigators have identified alterations in the genetic material or DNA that affect the ability of smooth muscle cells, which line the aorta and other blood vessels, to contract. This can lead to a weakening of the wall of the aorta, the main blood vessel leading out of the heart. One of the studies was published in the November issue and the other was published online today in the American Journal of Human Genetics.

"Both discoveries are more confirmation of the role that proper contraction of smooth muscle cells has on the aorta and they increase our knowledge of the pathway of the disease," said Dianna M. Milewicz, M.D., Ph.D., a senior author of both studies, professor and the President George H.W. Bush Chair in Cardiovascular Research and director of the Division of Medical Genetics at The University of Texas Medical School at Houston, part of UTHealth. "That allows us to figure out how to potentially block or reverse the disease, which is our ultimate goal."

In thoracic aortic disease, the deterioration of the wall of the aorta can cause an aneurysm, or ballooning of the vessel, that can lead to dissection or rupture and sudden death. If caught early enough, people with the familiar genetic defect can take medications and/or undergo

surgery to repair the damage. An estimated 8,000 people die annually from thoracic aortic disease.

Using the UTHealth database of more than 600 families affected by thoracic aortic disease, Milewicz and her research team members have previously identified four gene defects associated with the familial form of the disease, which runs in families. Of people who have the disease, 20 percent have the familial form. The aortas of family members who test positive for the gene defect can be routinely scanned, monitored and repaired, saving lives. Research continues through the John Ritter Research Program at UTHealth, founded by his widow Amy Yasbeck. The beloved actor died from a thoracic aortic dissection.

The discovery of the fifth gene defect is reported in the article "Mutations in Myosin Light Chain Kinase (MYLK) Cause Familial Aortic Dissections." Kinases act on proteins, transmitting signals and controlling complex processes in cells. MYKL is a kinase that controls the contraction of smooth muscle cells. In families with genetic alterations or mutations in this gene, the kinase does not work properly, leading eventually to the weakening in the wall of the aorta.

The second article deals with entire regions of the DNA with variants linked to the disease, but in people who do not have the familial form of thoracic aortic aneurysms.

"These are regions of the DNA where genes are missing or there might be three copies of a region of DNA instead of two," Milewicz said. "We don't understand these types of variations in the DNA yet because we all having missing or duplicated regions of DNA and these variants seems to be all over the genome. In patients with thoracic aortic disease, these regions of DNA that are missing or an extra copy is present appear to disrupt the smooth muscle cells and their ability to contract or gain a 'footing' to contract properly. These gene variants, combined with

environmental factors, could result in a predisposition to thoracic aortic disease."

Co-senior author of the article with Milewicz is John W. Belmont, M.D., Ph.D., professor of molecular medicine and human genetics at Baylor College of Medicine (BCM). Colleagues from UTHealth and BCM did a genome-wide analysis of thoracic aortic aneurysms and dissections in 418 patients. They identified 47 variant regions that were unique to these patients.

"For a long time, we concentrated on single mutations that would, by themselves, cause disease. "Now we have come up with a new paradigm where we see different types of mutations – rare mutations. Instead of one gene, dozens of genes may be involved in the disease and each gene variant may account for a few cases. Together, they affect a common biological mechanism that causes the disease," said Siddharth Prakash, assistant professor of molecular and human genetics at BCM and first author of "Rare Copy Variants Disrupt Genes Regulating Vascular Smooth Muscle Cell Adhesion and Contractibility in Sporadic Thoracic Aortic Aneurysms and Dissections."

Provided by University of Texas Health Science Center at Houston