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Study identifies second gene associated with specific congenital heart defects

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A gene known to be important in cardiac development has been newly associated with congenital heart malformations that result in obstruction of the left ventricular outflow tract. These are the findings from a study conducted by Nationwide Children's Hospital and appearing in the journal *Birth Defects Research Part A*.

Left ventricular outflow tract (LVOT) malformations, including aortic valve stenosis, coarctation of the aorta, hypoplastic left heart syndrome, Shone complex and interrupted aortic arch type A, are responsible for a major portion of childhood death from congenital heart malformations. Yet it is often unclear how these defects develop.

"While 10 to 15 percent of people with an LVOT defect have a chromosomal defect such as Turner syndrome, the causes for most LVOT defects remain unknown," said one of the study's authors Kim McBride, MD, MS, principal investigator in the Center for Molecular and Human Genetics at The Research Institute at Nationwide Children's Hospital.

Recent studies suggest a genetic component to these heart malformations. Aortic valve stenosis, coarctation of the aorta, hypoplastic left heart syndrome and bicuspid aortic valve have been reported to recur within single families. Nationwide Children's faculty has also identified several chromosomal regions that show evidence of being linked to LVOT malformations.

"It is estimated that there are more than 500 genes that may be important in heart development," said Dr. McBride, also a faculty member at The Ohio State University College of Medicine. "Changes in any of these genes may impact how a child's heart forms."

To identify specific genes, investigators examined the DNA of children treated for LVOT malformations and their parents, enrolled by Dr. McBride at Nationwide Children's Hospital or by Dr. John Belmont and his team in the Department of Molecular and Human Genetics, Baylor College of Medicine at Texas Children's Hospital. Research indicates that LVOT defects share a common developmental mechanism, thus they focused on genes from a signaling pathway shown to be important in cardiac development.

Findings showed an association between the gene ERBB4 and LVOT defects. ERBB4 encodes a protein that serves as an "on" or "off" switch in many cellular functions during heart development. The association with LVOT defects was noted not only for the whole group of defects, but also individually for aortic valve stenosis, coarctation of the aorta and hypoplastic left heart syndrome.

"The precise defect in this very large gene is not yet known," said Dr. McBride. "ERBB4 now joins a previously identified gene, NOTCH1, as a susceptibility gene for LVOT defects. Replication of these results in other subjects will be required to better determine its role in the development of the heart malformations."

Provided by Nationwide Children's Hospital