Researchers identify genetic mutation linked to congenital heart disease

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A mutation in a gene crucial to normal heart development could play a role in some types of congenital heart disease—the most common birth defect in the U.S. The finding, from a team in The Research Institute at Nationwide Children's Hospital, could help narrow the search for genes that contribute to this defect, which affects as many as 40,000 newborns a year. The findings were published in a recent issue of in *Human Mutation*.

Several hundred genes have been implicated in the formation of the heart, and a mutation in any of them could contribute to a cardiac defect. Identifying which of these genes is involved in human congenital heart disease has been a challenge for scientists in the field, says Vidu Garg, MD, senior author of the new study, principal investigator in the Center for Cardiovascular and Pulmonary Research and director of Translational Research in The Heart Center at Nationwide Children's.

"We have to ask ourselves, what subset of the more than 20,000 genes that make up the human genome are contributing to congenital heart disease?" he says. "Right now, we don't know enough about a lot of those genes, so this study provides another piece of the puzzle."

That piece is FOXP1, a member of a large gene family that helps regulate tissues throughout the body, including in the heart, lungs and brain. A few studies on FOXP1 had described its function and role in cardiac development in animal models, but it wasn't until a former colleague called with an interesting case that Dr. Garg decided the gene was worth a closer look.

While analyzing a DNA sample from an 8-month-old infant who died from complications of complex congenital heart disease, Linda Baker, MD, at the University of Texas Southwestern Medical Center, had found a rare genetic abnormality—a small chromosomal deletion—in the patient's FOXP1 gene.

A search of DNA samples from patients with congenital heart disease in a repository at Nationwide Children's—one of the largest in the nation—revealed two additional patients with a similar complex heart defect who had a rare mutation in the same gene. On further analysis, Dr. Garg's team found that this mutation affected the gene's ability to express a transcription factor called Nkx2.5, which has been implicated in congenital heart disease.

"If you have three unrelated people with an abnormality in the same gene with the same phenotype, and they also have the same extremely rare type of congenital heart disease, there's a high likelihood that the gene is involved in contributing to the condition," says Dr. Garg, who also is an associate professor of pediatrics at The Ohio State University College of Medicine. "Understanding how either deletion or loss of FOXP1 affects normal heart development could help contribute to our understanding of congenital heart disease."

The next step in the research is to see if they can find the FOXP1 mutation in patients with different types of congenital heart disease. From there, they will begin to look at how the gene interacts with others involved in the formation of a normal heart. Given that congenital heart disease is probably the result of mutations in many genes, Dr. Garg says, it's quite possible that by studying this gene, we can uncover other potential candidate genes for heart malformations.

Provided by Nationwide Children's Hospital