Clues to genetics of congenital heart defects emerge from Down syndrome study

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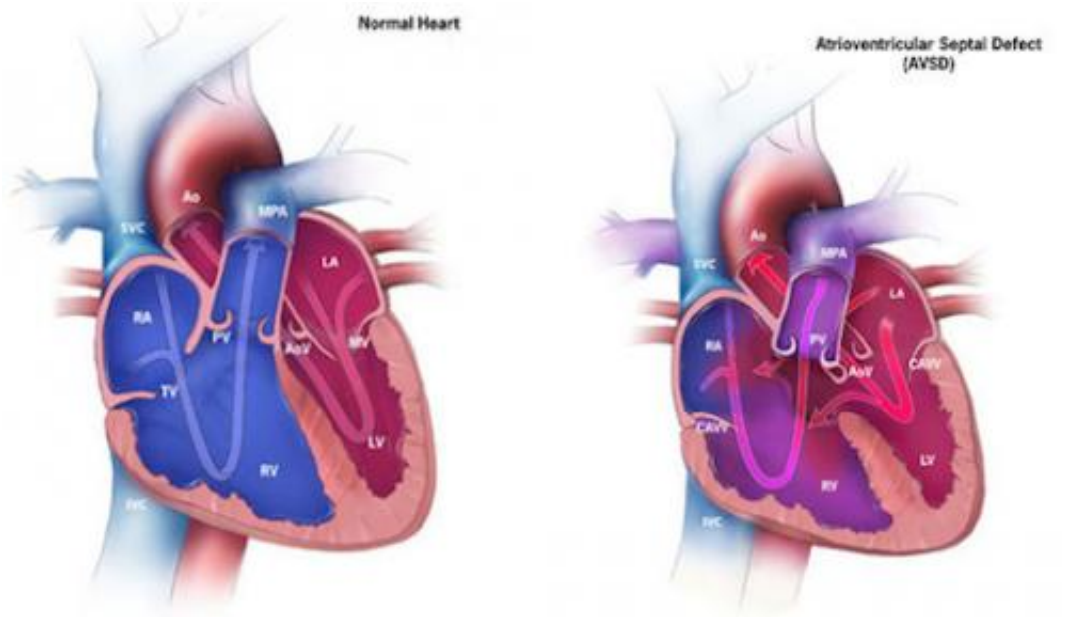

Down syndrome is the most common chromosomal abnormality in humans, involving a third copy of all or part of chromosome 21. In addition to intellectual disability, individuals with Down syndrome have a high risk of congenital heart defects. However, not all people with Down syndrome have them – about half have structurally normal hearts.

Geneticists have been learning about the causes of congenital heart defects by studying people with Down syndrome. The high risk for

congenital heart defects in this group provides a tool to identify changes in genes, both on and off chromosome 21, which are involved in abnormal heart development.

Researchers at Emory University School of Medicine, with colleagues at Johns Hopkins University, Oregon Health Science University, and University of Pittsburgh, report results from the largest genetic study of congenital heart defects in individuals with Down syndrome in the journal *Genetics in Medicine*.

The team found that infants with congenital heart defects, in the context of Down syndrome, were more likely to have rare, large genetic deletions. Those deletions tended to involve genes that affect cilia, cellular structures that are important for signaling and patterning in embryonic development.

These new findings, along with other recent studies, suggest that the risk for congenital heart defects in Down syndrome can come from several genes and environmental factors, in addition to the substantial risk from the extra chromosome 21.

"In Down syndrome, there's a 50-fold increase in risk for heart defects, which is enormous," says senior author Michael Zwick, PhD, associate professor of human genetics and pediatrics at Emory. "Studying congenital heart defects in the 'at risk' Down syndrome population can make it possible to reveal genes that impact the risk of heart defects in all children, including those with typical number of chromosomes."

"Understanding the origin of heart disorders in individuals with Down syndrome may reveal aspects of biology that would allow better personalization of their health care, since genetic alterations that affect the heart may also affect other organs, such as the lungs or gut," Zwick says.

"Our partnership with families who have a child with Down syndrome and our investment in a comprehensive clinical data and biorepository will continue to provide resources to study not only heart defects, but also other Down-syndrome associated medical conditions such as cognitive function, leukemia, and dementia," says co-author Stephanie Sherman, PhD, professor of human genetics at Emory University School of Medicine.

Sherman says the study was a collaborative effort involving participants with Down syndrome, their families and assessment sites across the United States, including those mentioned above along with Kennedy Krieger Institute, Children's National Medical Center and Ohio Nationwide Children's Hospital.

The first author was Emory postdoctoral fellow Dhanya Ramachandran, PhD, working with Zwick. Emory co-authors included assistant professors Lori Bean, PhD, Tracie Rosser, PhD and David Cutler, PhD, in the Department of Human Genetics, and Jennifer Mulle, PhD, assistant professor of epidemiology in the Rollins School of Public Health. Ken Dooley, MD, associate professor of pediatrics at Emory and pediatric cardiologist at Children's Healthcare of Atlanta, reviewed medical records and made definitive diagnoses for all study participants.

The study included 452 individuals with Down syndrome. 210 had complete atrioventricular septal defects (AVSDs), a serious heart defect that is relatively common among those with Down syndrome (about 20 percent). The remaining 242 had structurally normal hearts. The Emory team used high density microarrays to probe more than 900,000 sites across the human genome to detect structural variation, including deletions or duplications of DNA.

An atrioventricular septal defect means that the central region of the heart separating the atria from the ventricles has failed to form properly.

Such defects increase the workload on the heart, and a complete AVSD leads to heart failure: fluid buildup in the lungs and difficulty breathing, requiring surgery in the first year of life.

The team's results add to evidence for a connection between AVSDs and cilia. Ciliopathies are a class of genetic disorders that include kidney, eye, and neurodevelopmental disorders. Cells in the airways have mobile cilia which sweep mucus and dirt out of the lungs, but almost every cell in the body has a primary (sensory) cilium.

"The finding that ciliome genes may be disrupted in children with Down syndrome and AVSD may indicate differences in life-time care for these individuals," Zwick says. "This is a suggestive result that needs replication in a larger group."

To confirm and strengthen the findings, Zwick and his team are currently performing an independent study of individuals with Down syndrome, using whole genome sequencing to further delineate alterations in genes that perturb heart development in children.

Provided by Emory University