Sick Kids-led study uncovers novel gene that causes rare congenital heart defect

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Congenital heart defects (CHD) are the most common birth defect affecting one in 100 children worldwide. The cause of heart defects is understood in only about 20 per cent of cases, but the other 80 per cent remain unknown. In a novel study led by The Hospital for Sick Children (SickKids), researchers offer insight into the cause of a subtype of congenital heart defects called atrioventricular septal defects (AVSDs). The team sequenced the DNA of patients and families with this type of heart defect and found several mutations in a gene, NR2F2, that is very important for heart development.

The study, published in the April 3 online edition of *The American Journal of Human Genetics*, is the first in Canada to use large-scale whole-exome sequencing in children born with heart disease and is also the first to demonstrate this gene's role in human heart disease.

Atrioventricular septal defect (AVSD) is a heart condition characterized by malformed and leaking valves and holes in the heart. To treat this condition, babies often require one or more open heart surgeries within their first year. AVSDs are relatively rare in the general population, making up five per cent of babies born with congenital heart defects. However, among children with multisystem genetic disorders like Down syndrome the prevalence can be as high as 40 per cent. For this study, the research team focused on the role genes play in AVSDs among patients who do not have other genetic disorders.

"Unless we know what's causing the disease, we cannot know how to best treat our patients," says Dr. Seema Mital, Principal Investigator of the study, Staff Cardiologist and Senior Scientist in Genetics & Genome Biology at SickKids. "Our findings will help us counsel families about the cause of the birth defect but more importantly it will help us to develop new medicines that may allow the heart to grow better after birth, which could eventually reduce the need for frequent operations in these young babies and help them live more normal lives."

Researchers analyzed the DNA of 13 patient families, and 112 unrelated individuals with AVSDs, and found four families who each carried unique mutations in the *NR2F2* gene. “Each family had their own type of mutation that was not seen in the other families, but in every case it affected the function of the same gene,” says Mital. “It was incredible to find these hidden needles in a haystack.”

She adds that by searching the entire exome, the team was able to find that some mutations occurred for the first time in the baby, while others had inherited the genetic defect. The team then sequenced the DNA of 300 other patients with congenital heart defects, but not this specific subtype, and found four other patients with mutations in *NR2F2*. To confirm these results, the findings were compared with a control group of more than 5,000 people, none of whom had similar mutations in *NR2F2*.

In addition to causing AVSDs, other researchers have found that *NR2F2* may be affected by environmental factors such as high glucose and retinoic acid (a derivative of vitamin A) during pregnancy. Further investigation in needed to determine how glucose and retinoic acid levels may affect the gene’s expression in the developing heart, explains Mital.

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