Genetic underpinning found for shared risk of congenital heart and neurodevelopmental disease

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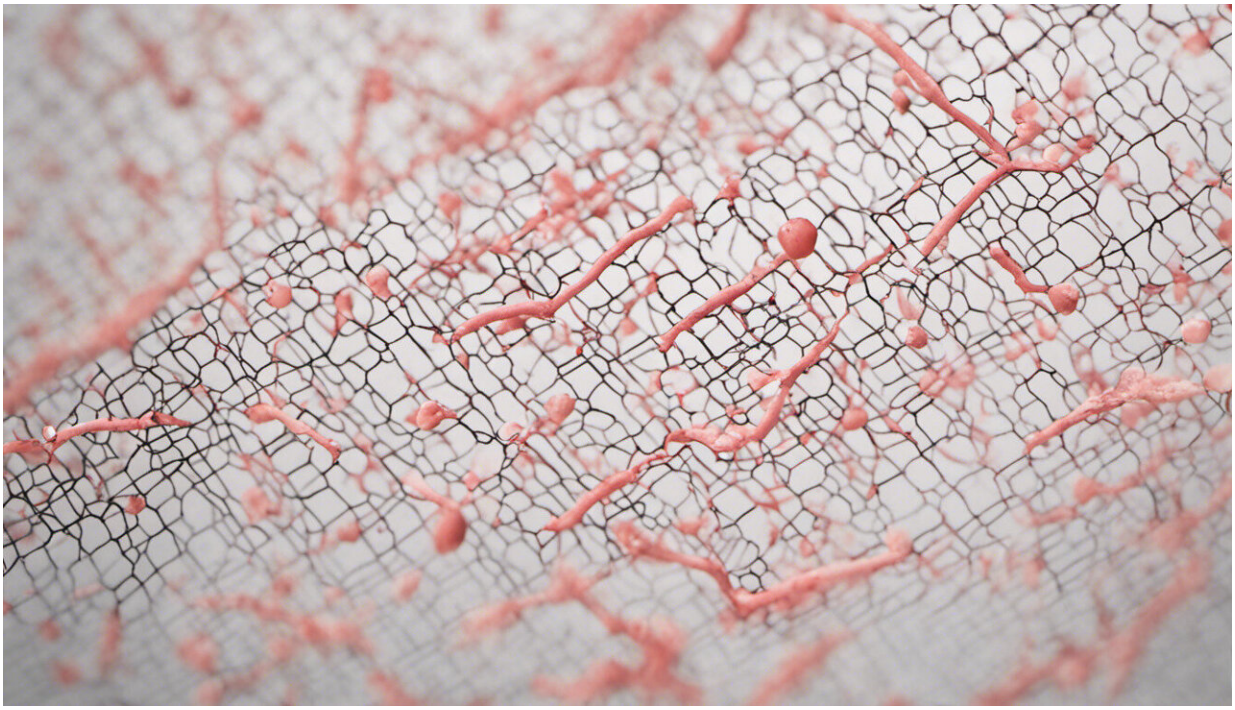

Credit: AI-generated image

Children with significant congenital heart disease have a far better chance of surviving today than in decades past, thanks to major advances in surgery. But some infants who recover from repairs to their hearts later show the effects of delays in brain development, including

impairments to cognitive, language and social functioning. Such impairments can affect how well these children do in school and in the workplace; they can even diminish their overall quality of life.

Epidemiological studies have given numbers to what doctors and families have long observed: The risk of neurodevelopmental delays is tenfold higher for children with moderate to severe congenital heart disease than for other children.

But why?

Over the years, those who study these phenomena have considered several possible reasons. Do the rigors of open-heart surgery so soon after birth play a role? Could heart defects limit nutrients and oxygen needed by the fetus? Or could spontaneous genetic mutations cause congenital problems that affect both the heart and the brain of a child?

Now, the "why" may have been answered by the efforts of the Pediatric Cardiovascular Genetics Consortium, led by a team of Harvard Medical School scientists. In a recent issue of Science the consortium reported exome sequence analyses of more than 1,200 children and their parents and showed that children with both congenital heart disease and neurodevelopmental delays share certain genetic mutations that thwart the normal development of both the heart and the brain.

Using a mathematical model created by co-authors Kaitlin Samocha and Mark Daly of the Analytical and Translational Genetics Unit at Massachusetts General Hospital, the team analyzed mutations in the protein-coding portion of the genomes of children with congenital heart disease that were not present in their parents' genomes. They found that these children have more of these de novo mutations in genes that are highly expressed in the developing heart, compared to a control cohort of children without congenital heart disease.

The de novo mutations were also found to be more frequent in children with congenital heart disease plus another birth defect, either neurodevelopmental delay or more-subtle abnormalities of finger or ear shape. These findings bolster the case for shared genetic causes of the cardiac and extra-cardiac abnormalities rather than surgeries or environmental factors.

"We're homing in on a set of genes that have multiple different roles in multiple different tissues during development: heart tissue, brain tissue, other developing organs, limb tissue," said Jason Homsy, an HMS LaDue Fellow who trained at Mass General and co-lead author of the *Science* paper. "Our study shows a common genetic link for the development of these diseases."

Potential for early testing

According to Homsy and co-senior author Christine Seidman, the HMS Thomas W. Smith Professor of Genetics and Medicine at Brigham and Women's Hospital and a Howard Hughes Medical Institute investigator, these findings could lead to early testing that would help identify newborns with congenital heart disease who are at high risk of neurodevelopmental difficulties.

"We can pretty clearly tell the parents of children with congenital heart disease what's going to happen after the heart surgery, but there's always a big question: Will my kid learn well in school?" Seidman said. "If we could identify children at high risk for neurodevelopmental delays, they could receive increased surveillance and earlier interventions than occur now."

The mutations primarily affected genes involved in three areas: morphogenesis, chromatin modification and transcriptional regulation. If any one of these processes is perturbed even slightly at a critical time in

development, the heart is malformed; sometimes another developmental defect occurs, such as a missed connection in the brain.

'Master regulators'

"These genes are not just involved in shaping the heart," Seidman said. "They are master regulators of organ development."

One of the mutated genes is RBFOX2, which encodes a molecule that regulates RNA splicing. Although RBFOX2 has not been previously implicated in congenital heart disease, de novo mutations were identified in multiple affected children.

"There are still many unanswered questions, including why the same mutation can cause very different clinical manifestations," Seidman said. Perhaps additional genetic variants in the multiple layers of transcriptional regulation allow compensation for some mutations but worsen the consequences of others. For now, Seidman said, knowing that a genetic mutation is present is different from knowing the outcome.

"It's a long, long, long way down the road," Seidman said, "but we'd like to believe that if you knew the steps by which these mutations perturbed the regulation of gene expression, there might even be ways to actually treat it."

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