Mutations before birth might disrupt heart and nervous system development

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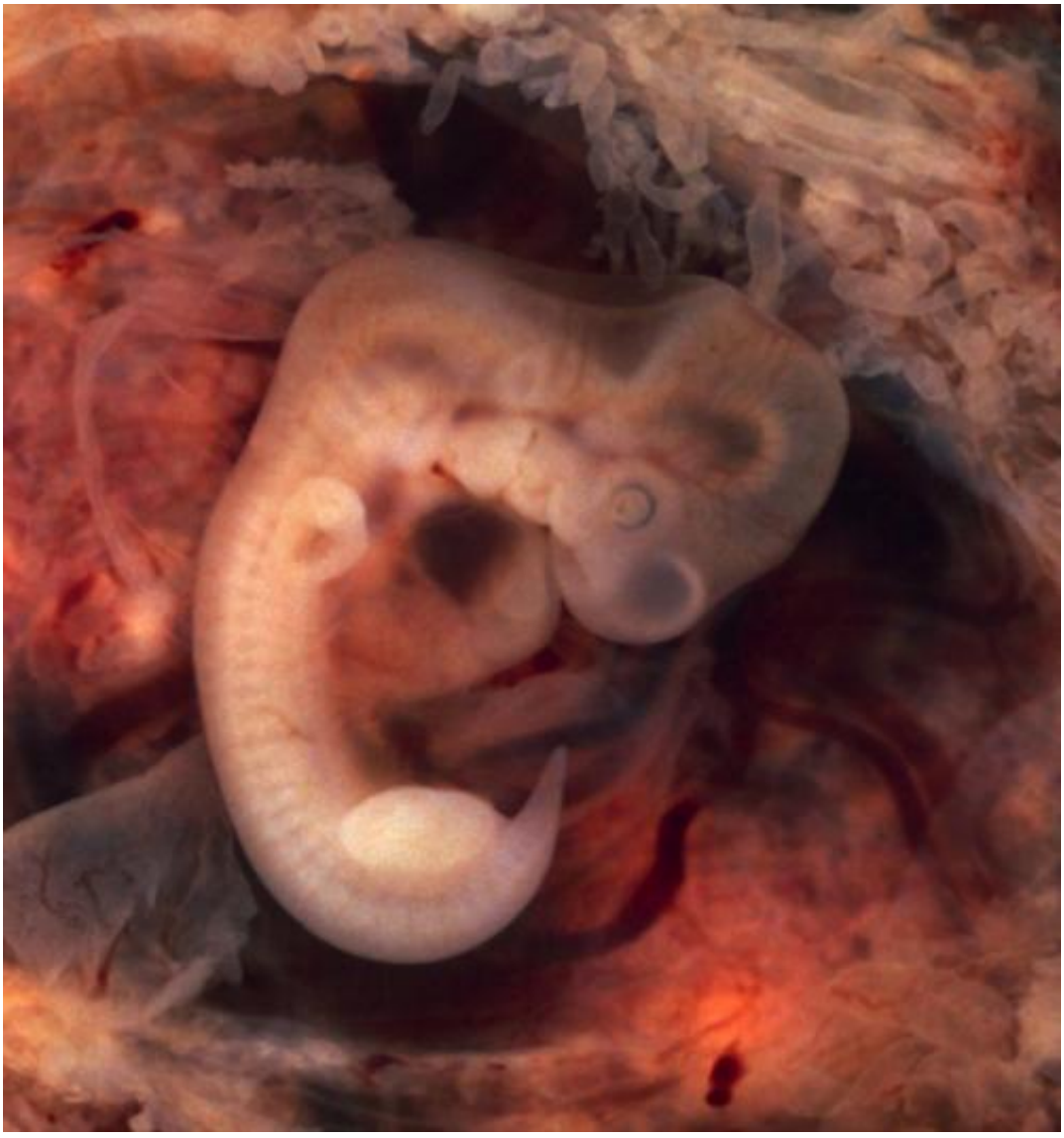

Human Embryo. Credit: Ed Uthman, MD/Wikipedia

A team of scientists has determined why some children who are born with heart defects also often have developmental disabilities such as problems with speech and muscle coordination. The research, led by Howard Hughes Medical Institute investigators Richard Lifton of Yale University and Christine Seidman of Harvard Medical School and their colleagues in the Pediatric Cardiovascular Genetics Consortium, suggests that these children accrue mutations very early in development that damage genes crucial for heart and brain formation.

About one percent of newborns suffer from congenital heart disease, in which structural flaws in the organ, such as misshapen valves or abnormal connections between major vessels, disrupt blood circulation. With surgery or less invasive procedures, doctors can now correct defects that would have killed many of these children 30 years ago. "These kids not only survive, they grow up," says Seidman. The research was published December 3, 2015 in the journal *Science*.

They aren't necessarily in the clear, however. Children with congenital heart disease are prone to other internal and external abnormalities. Moreover, they often exhibit learning disabilities, difficulties with speech, and other signs that the brain or the rest of the nervous system hasn't developed properly. "We know that there is something going on in more than the heart," says Seidman.

Researchers have offered several hypotheses to explain why congenital heart disease and other types of developmental problems often go together. Because the brain and the heart form at the same time in the embryo, a faulty heart might not be able to supply as much oxygen and nutrients as the brain needs. Alternatively, the procedures the children undergo to correct their heart abnormalities could cause stress that impairs nervous system development.

Lifton, Seidman, and their Pediatric Cardiovascular Genetics

Consortium colleagues tested a different possibility—that the defects result from new mutations that occur before birth. Most us accumulate these mutations, which are usually innocuous but sometimes harm important genes. To determine whether such novel mutations are responsible for congenital heart disease, the researchers sequenced the genes of 1,213 children who had the condition and the genes of their parents. If a child carried a specific mutation but her parents did not, the scientists concluded it was a new mutation. They then identified damaging mutations in the children that would disable the protein produced by a particular gene or alter the protein's function.

Harmful mutations were 1.4 times more common in children with congenital heart disease than in other kids. These mutations hit some crucial targets, the researchers found. They were prevalent in genes that are active during heart development, including seven genes that previous studies had linked to congenital heart disease.

Sorting the mutated genes by their functions revealed that certain categories of genes were more likely to show damage. One of these categories was chromatin-modifying genes. They produce proteins that alter how tightly DNA coils, which, in turn, helps determine whether a gene is active or inactive. Thus mutations in these molecules might lead to heart defects by preventing genes from switching on or off at the right time during development.

To figure out whether the mutations they pinpointed could influence brain development, the researchers analyzed the children with congenital heart disease who also had neurodevelopmental problems, physical abnormalities, or both. In these kids, mutations in the genes that are active during heart development were more common than the scientists expected, suggesting that the DNA changes are causing multiple harmful effects. The scientists also found that children with congenital heart disease carry large numbers of mutations in genes that are active during

brain development.

Although almost everyone acquires new mutations in at least one gene, children with congenital heart disease "have bad luck because these new mutations hit genes necessary for heart and brain development," Seidman says. But the study could be a stroke of good fortune for the children. "We've never been able to look at children with congenital heart disease and know if they will be at risk for developmental delays," Seidman says. The results open up the possibility of using DNA tests to identify these children, who might benefit from more help in school or other early measures to help them overcome their neurodevelopmental disabilities.

More information: "De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies," by J. Homsy et al. *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.aac9396

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