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In early heart development, genes work in tandem

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Studying genes that regulate early heart development in animals, scientists have solved a puzzle about one gene's role, finding that it acts in concert with a related gene. Their finding contributes to understanding how the earliest stages of heart development may go awry, resulting in congenital heart defects in humans.

Peter J. Gruber, M.D., Ph.D., a cardiothoracic surgeon at The Children's Hospital of Philadelphia, led a study published this week in the Jan. 15 issue of the Journal of Biological Chemistry. Occurring in approximately 1 in 200 children, congenital heart defects represent the most common human birth defect.

"We uncovered a role for the Gata5 gene, a role that has been unappreciated in vertebrate cardiac development," said Gruber. "Gata5 is a gene that is essential to heart development in other animals, such as frogs and zebrafish, but contrary to expectations, deleting this gene seemed to have no effect on the hearts of mammals. We found, however, that in mice, this gene cooperates closely with other genes to affect heart development. It may work similarly in humans."

The Gata5 gene expresses the protein GATA5, which is a member of a family of zinc-finger transcription factors—proteins that act as switches to turn gene activity on or off. Transcription factors regulate how DNA carries its instructions into messenger RNA, and RNA in turn helps produce a specific protein with particular functions in biological processes. The GATA transcription factors carry out important tasks

during an organism's development.

Working in mice, Gruber's study team genetically engineered mice in which Gata5 genes were inactive, and found the animals were healthy, with normally functioning hearts. They did find, however, that those mice showed increased expression of another gene in the same family, Gata4, which suggested that Gata4 might compensate for the loss of Gata5.

When they bred a new group of mice in which Gata5 was inactive and had only one functioning Gata4 allele (each gene has two alleles) those mice all had profound cardiac defects and died before birth. (Mice with a normal Gata 5 gene and only one functioning Gata4 allele were normal.)

"Our research suggests that Gata5 has a previously unsuspected role during cardiac development, acting cooperatively with Gata4 to direct the heart to form normal structures," said Gruber. "If the same process occurs in humans, that tells us something new about prenatal heart development. The research also shows that studying a single gene in isolation may not be sufficient. Here one gene buffers the effects of losing another gene."

In people, genes in the GATA family regulate the development of heart muscle in particular structures that divide the left and right sides of the heart. Gruber's team is carrying follow-up studies, investigating how the genes seen in mice may be analogous to genes involved in embryonic heart development in humans. "Although a long way off, greater understanding of biological mechanisms during early heart development may eventually provide useful targets for more accurate diagnosis or personalized treatment of children with congenital heart disease," added Gruber.

More information: Singh MK, Li Y, Li S, Cobb RM, Zhou D, Lu MM, Epstein JA, Morrisey EE, Gruber PJ. Gata4 and Gata5 cooperatively regulate cardiac myocyte proliferation in mice. Journal of Biological Chemistry. 2010;285(3):1765-1772. doi:10.1074/jbc.M109.038539