MedicalXpress

Study finds protein that plays key role in early embryonic development

May 12 2010

Researchers studying the common genetic disorder chromosome 22q.11 deletion syndrome have identified key proteins that act together to regulate early embryonic development. One protein is essential to life; in animal studies, embryos without the protein do not survive past the first few days of gestation.

Although the findings do not currently affect treatments for chromosome 22q.11 deletion syndrome, they shed light on the biological events that give rise to the syndrome, which often includes congenital heart defects. They also reveal the previously unsuspected importance of one protein in the earliest stages of development.

"The heart is among the first organs to develop in humans and other mammals," said neonatologist Jason Z. Stoller, M.D., of The Children's Hospital of Philadelphia, corresponding author of the study, appearing online today in the May issue of the journal Experimental Biology and Medicine. Stoller collaborated with Jonathan A. Epstein, M.D., scientific director of the Penn Cardiovascular Institute at the University of Pennsylvania, and senior author of the study.

Chromosome 22q.11 deletion syndrome, also known as DiGeorge syndrome, is the most common human disorder caused by a missing chromosome region, occurring at least once in 4,000 live births. It can vary in severity, but may affect many parts of the body, with symptoms including heart defects, immune and endocrine problems, cleft palate, gastrointestinal conditions, growth delay and neuropsychiatric

abnormalities. The 22q and You Center at Children's Hospital is an international leader in clinical care and research in this syndrome, providing multidisciplinary evaluation and treatment for hundreds of patients from over 40 states and 15 countries.

Because of structural instability in a portion of chromosome 22, one region may be deleted, typically containing 30 genes. One of those genes, TBX1, holds the genetic code for a type of protein called a transcription factor—which regulates other genes. In 2005, Stoller and Epstein found that within this protein, also called TBX1, a particular domain was crucial and played a key role in chromosome 22q.11 deletion syndrome.

The current study, said Stoller, aimed to discover proteins that interact with the Tbx1 protein and to identify some of the biological events that give rise to chromosome 22q.11 deletion syndrome. The study team identified the protein Ash2l as an important partner of Tbx1. "The two proteins act together to influence other genes that may impair biological systems affected in the deletion syndrome," said Stoller. "Ash2l is important in epigenetics—changes in gene activity that do not involve alterations to the genetic code spelled out in DNA." In epigenetic processes, chemical groups attached either to DNA, or to DNA-associated proteins called histones, switch gene activity on or off.

Many other steps resulting from this protein interaction have yet to be discovered, to determine how these molecular events cause specific effects, such as cleft palate or abnormalities in the thymus gland that occur in chromosome 22q.11 deletion syndrome. Said Stoller, "As with much research in basic science, discovering gene pathways and biological mechanisms may lay the foundation for future development of drugs or other therapies to act on these pathways, but such clinical applications are still in the future."

Another finding in the current study does not directly affect patients with the deletion syndrome, but shows that the Ash2l protein is absolutely essential to normal development. Mice that were bred to lack the gene for Ash2l produced embryos that, without exception, died very early in gestation. "The fact that this protein is necessary to early embryonic survival suggests that Ash2l regulates many genes during the early stages of development," said Stoller.

More information: "Ash21 interacts with Tbx1 and is required during early embryogenesis," Experimental Biology and Medicine, May 2010, published online May 12, 2010. doi:10.1258/ebm.2010.009318

Provided by Children's Hospital of Philadelphia