MedicalXpress

First common gene found for congenital heart disease

May 26 2010

Although congenital heart disease represents the most common major birth defect, scientists have not previously identified the common variation in the genes that give rise to it. Now genetics and cardiology researchers, two of them brothers, have discovered a genetic variant on chromosome 5 that strongly raises the risk of congenital heart disease.

"This gene, ISL1, plays a key role in regulating early cardiac development, so there is a compelling biological reason for investigating it as a genetic risk factor for CHD," said study leader Peter J. Gruber, M.D., Ph.D., a pediatric cardiothoracic surgeon and developmental biologist at The Children's Hospital of Philadelphia. Gruber collaborated with his brother, Stephen B. Gruber, M.D., Ph.D., a geneticist and epidemiologist at the University of Michigan Medical School.

The study appeared online today in the journal *Public Library of Science One*.

Congenital heart disease (CHD), said Peter Gruber, is the "Wild West" of genetics, largely unexplored when compared to diseases such as cancer. Researchers have identified genes involved in chromosomal abnormalities and rare genetic syndromes that include heart defects, but no common gene variant had previously been found for non-syndromic complex CHD.

CHD affects at least one in 100 live births. It ranges widely in severity, from tiny holes between heart chambers that close naturally, to life-

threatening abnormal structures such as hypoplastic left-heart syndrome that require a series of complicated surgeries.

CHD can affect a variety of different structures in the heart, but the researchers decided to focus on the earliest period of the organ's development. "Instead of assuming separate genes would govern each specific defect, we formed the hypothesis that a common gene variant operates early in the biological pathway of heart formation, thus affecting multiple subtypes of congenital heart disease," said Peter Gruber.

In Peter Gruber's previous research in human cardiac stem cells, he found that a gene called ISL1 was crucial in regulating the development of early cardiac progenitor cells.

Suspecting that ISL1 was a likely candidate gene involved in human CHD, he designed a study in collaboration with two genetics teams, one in Philadelphia, the other in Michigan.

At the Children's Hospital of Philadelphia, he worked with Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics, one of the world's largest centers for pediatric genotyping. Gruber collected DNA samples from 300 children with CHD at the hospital's comprehensive Cardiac Center, and from 2,200 healthy children at the Center for Applied Genomics. Hakonarson's team did the initial genotyping—looking for gene variants (mutations) in the DNA of genes in or near the ISL1 gene. When combined with results from the genetics team at the University of Michigan, the researchers found eight of these alternative spellings in DNA bases (single-nucleotide polymorphisms, or SNPs) raised the risk of CHD.

Stephen Gruber and colleagues at the University of Michigan performed second-stage studies on the initial data, analyzing specific DNA

sequences and performing "fine mapping" research—focusing in sharper detail on the gene regions of interest. "It was challenging to analyze how genetic variation contributes to complex congenital heart disease," Stephen Gruber said. "We combined expertise in cardiology, epidemiology, genetics and developmental biology that led to an interesting discovery."

Adding DNA from medical programs in Canada and the Netherlands to the U.S. samples, the researchers studied genes from a total of 1,344 children with CHD and 6,135 healthy controls, and confirmed in replication studies that variants in the ISL1 gene had strong associations with CHD. Within that gene, they found that one SNP raised the risk for white children, and a different SNP increased the risk for African American children.

While the gene findings do not directly affect treatment for children with CHD, Peter Gruber said that better knowledge of the molecular basis of heart disease may provide eventual benefits for the children he sees as a surgeon. "As future studies better define exactly how a mutation leads to a specific type of heart defect, we may be better able to predict how a gene variant affects other organ systems," he added. "We may be better able to understand how a child will respond to surgery, and when or even perhaps how to best perform perioperative, intraoperative or postoperative care. A greater understanding of molecular events in early development brings us that much closer to personalized medicine."

The Leducq Foundation provided funding support for this study. Co-authors with the Grubers and Hakonarson were Kristen N. Stevens, from the University of Michigan; Cecilia E. Kim, Jennifer Raue, Joseph T. Glessner and Anne Granger, of The Children's Hospital of Philadelphia; and collaborators from the Netherlands, Canada and Spain. In addition to his post at Children's Hospital, Peter Gruber is a member of the Penn

Cardiovascular Institute and the Institute for Regenerative Medicine, both at the University of Pennsylvania School of Medicine.

More information: "Common variation in ISL1 confers genetic susceptibility for human congenital heart disease," PLoS One, published May 26, 2010. To reporters: please link to the freely available research in your reports: dx.plos.org/10.1371/journal.pone.0010855

Provided by University of Michigan Health System