SOUTHWESTERN NEWS

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SPECIFIC GENE MUTATIONS RESPONSIBLE FOR CONGENITAL HEART DEFECTS, UT SOUTHWESTERN RESEARCHERS DISCOVER

DALLAS – July 6, 2003 – Researchers at UT Southwestern Medical Center at Dallas have discovered a gene critical to the development of the human heart and that mutations in the gene lead to congenital heart defects – the leading noninfectious cause of death in newborns.

GATA4 is only the second gene to have been identified as a cause of isolated congenital heart disease not associated with medically identified syndromes.

The findings will be published in a future edition of the journal *Nature* and appear online today.

The researchers identified mutations in the gene *GATA4* as a cause of human cardiac septal defects, which occur when the walls separating the heart's four chambers do not form properly.

"In terms of identifying genetic etiologies, there are not many discoveries that have been made," said Dr. Vidu Garg, assistant professor of pediatrics and one of the study's lead authors. "This is one of the genes responsible, and we are working to identify others."

This discovery could one day help doctors prevent congenital heart defects – the most common developmental anomaly – by fixing the problem before a baby is born, said Dr. Deepak Srivastava, associate professor of pediatrics and molecular biology and the study's senior author.

"We cannot change the fact that parents are going to pass along the mutation, but we might be able to develop a way to keep the disease from occurring," said Dr. Srivastava.

In the *Nature* study, researchers from UT Southwestern and three Japanese medical institutions examined two large families: one in Dallas that spanned five generations and included 16 members suffering from congenital heart defects, and a family from Tokyo spanning four generations and with eight members with congenital heart defects.

UT Southwestern researchers and Dr. Rumiko Matsuoka, a pediatric cardiologist from Japan, gathered data from the families' medical history. Researchers also conducted physical examinations, electrocardiograms and cardiac ultrasounds. Genomic DNA from white blood cells was used for analysis, and researchers studied medical records of family members who had died.

Researchers performed a genetic linkage analysis. The analysis helps researchers find the

(MORE)

responsible genes by comparing the genetic codes of patients suffering from heart defects with the codes of those who did not.

GATA4 mutations showed up in all family members with heart disease but not in the family members without heart disease or in 3,000 unrelated individuals.

The gene may be responsible for the defects through its interaction with TBX5, a protein that causes a subset of syndromic cardiac septal defects. Irfan Kathiriya, a student in UT Southwestern's Medical Scientist Training Program and co-lead author, found that when a single amino of *GATA4* was altered in the Dallas family, it prevented *GATA4* from associating with TBX5, suggesting that the two work together to divide the heart into four chambers.

Dr. Srivastava said the next step is to determine how common *GATA4* mutations are in the general population of children with heart defects and use that information to devise clever approaches to prevention. Eventually, broad screenings of individuals with congenital heart defects may help prepare them for the possibility of having a child with congenital heart defects, Dr. Garg said. The risk of that happening if either parent has a *GATA4* mutation is 50 percent. In general, the risk of having a child with congenital heart disease is about 1 percent and jumps to 5 percent for parents who already have a baby with congenital heart disease.

Other UT Southwestern researchers who worked on the study were Dr. Jonathan Cohen, associate professor of internal medicine; Robert Barnes, a programmer analyst in the Eugene McDermott Center for Human Growth and Development; Marie Schluterman, a research technician in pediatrics; Dr. Isabelle King, a fellow in pediatrics; Caryn Rothrock, a biochemistry student research assistant; and Dr. Reenu Eapen, assistant professor of pediatrics. Cheryl Butler, a registered nurse at Children's Medical Center of Dallas, also worked on the study.

Researchers from the Tokyo Women's Medical University, the Heart Institute of Japan and Kyusyu Kosei-Nenkin Hospital in Fukuoka also took part in the study.

The study was funded by the National Institute of Child Health and Human Development; the National Heart, Lung and Blood Institute; the March of Dimes Birth Defects Foundation; Smile Train Inc.; and the Grant for the Promotion of the Advancement of Education and Research in Graduate Schools in Japan.