SOUTHWESTERN NEWS

Media contact: Heather Stieglitz
(214) 648-3404
or e-mail: heather.stieglitz@email.swmed.edu

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RESEARCHERS ISOLATE GENE FOR DiGEORGE SYNDROME

DALLAS — February 19, 1999 — Researchers at UT Southwestern Medical Center at Dallas have isolated the gene they believe is responsible for the most common genetic cause of heart and facial birth defects.

Scientists have suspected for many years that a gene on chromosome 22 is responsible for these birth defects, but the identification of a single gene that could be involved in cardiac and facial defects has been elusive. In the February 19 issue of *Science*, Dr. Deepak Srivastava, assistant professor of pediatrics and molecular biology and oncology, and colleagues demonstrate that deletion of part of one gene can cause the variety of anomalies found in children known to be missing a piece of chromosome 22 (22q11).

Children with chromosome 22 deletion syndrome, also known as DiGeorge syndrome, can suffer cardiac defects, abnormal facial features, immune deficiencies, cleft palate and low blood calcium. Although the defects seem unrelated to one another, all the affected tissues share a common embryologic origin, suggesting that a single gene may be important for both heart and facial formation.

The researchers discovered a candidate gene in mice. They then established that only one instead of the two usual copies of the gene are present in children known to have the chromosome 22 deletion. They confirmed their hypothesis that the presence of only one gene copy was sufficient to cause the associated physical anomalies by finding a child who exhibited the cardiac and facial defects characteristic of chromosome 22 deletion syndrome, and who had only a single copy of this gene while the rest of chromosome 22 was normal.

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CHROMOSOME 22 -- 2

One in 4,000 children is born with chromosome 22 deletion syndrome, making it one of the most common genetic abnormalities in children. Many children with just facial or just cardiac defects also have the same deletion, which is the second-most common genetic cause of congenital heart defects (CHD). CHD affects one in 100 births.

Over the last 10 years, many researchers have examined the deleted region of chromosome 22 trying to identify the gene responsible for the anomalies. Last year Srivastava and his colleagues, who have been studying cardiac development, noticed that mutant mice with improper heart development had characteristics similar to those found with the chromosome 22 deletion. These mice lacked a small protein and also had a less-than-normal amount of an important cardiac- gene regulator, dHAND, whose job is to turn heart-specific genes on and off. But the human genes for these proteins did not lie on chromosome 22.

"We suspected that the heart-regulatory protein, dHAND, was probably somehow involved with the critical gene on chromosome 22," said Srivastava, an attending cardiologist at Children's Medical Center of Dallas. "So we looked for genes that were regulated by dHAND."

They identified several genes found in mice with normal hearts but missing in those with mutant dHAND genes. The human corresponding copy of one of those genes, *UFD1*, is located on chromosome 22 in the region that is missing in the 22q11 deletion.

Using molecular techniques, the researchers looked in mice to see where the gene is active. They found that *UFD1* normally was turned on in mice in the tissues that are affected in children with the 22q11 deletion. Next they turned to humans and examined the deoxyribonucleic acid (DNA) from 182 chromosome 22 deletion patients to see if the *UDF1* gene was missing. All 182 lacked one copy of the gene. Srivastava believes that having only half the normal amount of this gene leads to a dysregulation of the quantity of critical proteins involved in the formation of cardiac and craniofacial structures.

Because the syndrome includes a broad variety of defects and not all patients are the same, it is possible that other genes in this region are also involved in some features. The patient with a single *UFD1* gene also has a neighboring gene, *CDC45*, missing. However, the scientists feel that it is unlikely that *CDC45* is involved in this syndrome because it is active in all cells.

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"This paper represents a unique combination of studies," said Srivastava. "Dissection of a molecular pathway regulating embryogenesis in mice led to the identification of a human disease gene. This study will help us to further understand the mechanisms that control cardiac and craniofacial development."

Other UT Southwestern researchers participating in this study were pediatric research fellows Dr. Hiroyuki Yamagishi and Dr. Vidu Garg, and Tiffani Thomas, a research assistant in pediatrics. Dr. Rumiko Matsuoka of the Heart Institute of Japan at Tokyo Women's Medical University also was a co-author.

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