SOUTHWESTERN NEWS

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RESEARCHERS IDENTIFY GENE THAT CONTROLS FORMATION OF HEART CHAMBERS

DALLAS – April 1, 2002 – Scientists at UT Southwestern Medical Center at Dallas and their colleagues at UT Austin have identified a gene that controls formation of the heart's ventricles – a finding that may eventually lead to preventing some of the most lethal heart defects in American children.

"We found that the gene named *Bop* is the primary controller in a cascade of genetic events that include activating another gene, *Hand2*, that we previously found to be fundamental to the formation of the right ventricle and proper development of the left ventricle," said Dr. Deepak Srivastava, associate professor of pediatrics and molecular biology at UT Southwestern.

Dr. Paul D. Gottlieb, professor of molecular genetics and microbiology at UT Austin and a principal investigator on the study, said, "We had previously discovered that *Bop* was in the mouse immune system's T cells, or bone marrow white cells, and in adult heart and skeletal muscle cells. But it wasn't clear what its function was. Now we know that *Bop* encodes a protein instrumental in controlling the early steps of embryonic cells differentiating into mature cardiac muscle cells."

Srivastava, senior author of the study and holder of the Joel B. Steinberg, M.D., Chair in Pediatrics at UT Southwestern, said, "We have taken a critical step along the ongoing path to developing preventives for heart defects affecting nearly one out of 100 American children."

The study, to be posted April 1 on the *Nature Genetics* Web site and published in the journal's May 1 issue, reports that deleting *Bop* in mouse embryos consistently disrupted maturation of heart-muscle cells and stymied formation of the right ventricle.

The findings should be applicable to humans, Srivastava said, because genetic parallels can be found in heart development among all animal species, including the fruit fly.

"That's the beauty of the heart: It's at the core of survival and the pressures for survival. Hence the genetic regulation of the heart is tightly controlled and conserved among all animal species," he said. Further studies are necessary to confirm the correlation between *Bop*, or other genes affected by *Bop*, and ventricular heart defects in children.

(MORE)

"Ventricle defects, including the absence of the right or left ventricle, are the most lethal of pediatric heart problems, accounting for nearly 25 percent of all pediatric deaths from heart defects and making congenital heart disease the leading noninfectious cause of death in the first year of life," said Srivastava.

"Now with several genes – including *Bop* and *Hand2* – identified as controllers of heart development, preventives are finally conceivable," Srivastava said. "The next major research steps to achieve this goal are already under way: to catalog and understand the mechanisms of all genes with critical roles in heart development and to correlate specific gene mutations with each specific heart defect in children."

A current pilot study of 50 children will soon be expanded to all UT Southwestern pediatric cardiology surgery patients, he said. DNA samples will be collected to establish the correlations between specific gene mutations and heart defects. Once the links are made, the research team will try to determine how to prevent or modify exposure of the fetus to the contributing factors resulting in heart defects.

"We're seeking the folic-acid equivalent for heart defects," he said, referring to the discovery that supplementing folic acid in expectant mothers' diets leads to a lower incidence of spinal-cord defects.

Stephanie Pierce, a fourth-year Southwestern Graduate School of Biomedical Sciences student and a research assistant in pediatrics and molecular biology, and Robert Sims III, a fifth-year cellular and molecular biology graduate student at UT Austin, were primary contributors to the study. Other UT Southwestern contributors included Drs. Hiroyuki Yamagishi and Osama Nakagawa, both instructors of molecular biology, and Dr. Eric Olson, chairman of molecular biology.

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