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DISCOVERING GENETICS OF HEART DEFECTS POINTS TO NEW DIRECTIONS IN CARDIAC CARE

DALLAS — May 3, 1996 — Researchers at UT Southwestern Medical Center at Dallas say understanding the genetics of heart defects may spur the design of new treatment approaches to heart disease.

Dr. Eric N. Olson and Dr. Deepak Srivastava reviewed the latest research on the molecular biology of heart development in a report published in the May 3 issue of *Science*. Olson directs the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and holds the Nancy B. and Jake L. Hamon Distinguished Chair in Basic Cancer Research. Srivastava is an assistant professor of pediatrics.

"Cardiac anomalies represent the largest number of human birth defects," Olson said. "This reflects the complexity of the events associated with the formation of the cardiovascular system."

In their review, the researchers examined the genetic mechanisms that control the stages of heart development, revealing the molecular basis for several heart defects. As understanding of these genetic mechanisms advances, it "may ultimately provide opportunities for genetic testing and intervention," Olson added.

The researchers found defects related to the looping of the cardiac tube on the right (normal development) or left (abnormal development) side of the heart particularly interesting. After a cardiac tube forms — completing one of the earliest stages in heart development — it begins to loop to the right before the heart chambers are formed. This is the first sign of left-right asymmetry in the embryo and establishes the orientation of the heart's left and right ventricles.

Olson and Srivastava believe two genes recently identified in their lab, dHAND and

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eHAND, may be important in regulating the functions of the left and right sides of the heart. In a report published by the researchers in a December 1995 issue of *Science*, they demonstrated that the HAND genes, which belong to a class of master regulator genes, are important in the cardiac looping pathway.

Their more recent findings indicate that each of the HAND genes is expressed at varying levels in the ventricles. Specifically, eHAND is dominant in the left ventricle, and dHAND is dominant in the right. They are the earliest regulatory genes known to show this left-right asymmetry. One of the next challenges of their research is to understand why the levels are different and whether they cause the ventricles to perform unique functions.

Improper looping is responsible for a number of heart problems that are generally treated surgically but with limited long-term success. For example, some procedures result in the right ventricle becoming a high pressure pump to the body instead of being the low pressure pump to the lungs.

"The patients who have this procedure do fine for several years," Srivastava explained, "but for some reason, when they reach their 20s and 30s, they have heart failure because the right ventricle gives out. The right ventricle must be intrinsically different from the left and probably was just not meant to pump at high pressures over a lifetime."

The discovery of genes such as the HAND genes and other morphogenetic substances important in heart development have begun to give researchers insight into the cause of some heart defects. A group of children with looping defects were recently identified who shared mutations in the connexin 43 gene.

Understanding the genes that make the ventricles unique could perhaps lead to therapy allowing them to perform the opposite function if they become transposed during development.

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