UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers find gene mutation that leads to 'broken hearts'

DALLAS – July 20, 2006 –Researchers at UT Southwestern Medical Center have identified a group of fruit fly gene mutations responsible for "broken hearts" in the embryonic stages of development, a discovery that could help identify genes that cause human heart defects.

"We engineered a fruit fly so that the heart would glow in the dark and found a new type of malformation, completely unexpectedly," said Dr. Eric Olson, chairman of molecular biology at UT Southwestern and senior author of the study appearing in today's issue of *Science*. "We coined the term 'brokenhearted' for this defect because two kinds of cardiac cells separated, thus causing the heart to fall apart, with a loss of heart function and embryonic death."

The heart is the first organ to form and function in the embryo. Abnormalities in the complex process of heart formation result in congenital heart defects, the most common birth defects in humans afflicting about 1 percent of newborns. Because the events of heart formation are very similar throughout the animal world, the fruit fly is a useful model to study the causes of heart defects in mammals, Dr. Olson said.

The researchers found that mutations in genes encoding enzymes in a pathway for synthesis of a small lipid caused this broken heart defect in fruit flies. One of these enzymes, HMG CoA reductase, also plays a key role in the synthesis of cholesterol in humans. In fruit flies, these enzymes are required to generate a small lipid to modify a signaling protein, which is required for heart formation. The study suggests the involvement of the same biochemical pathway in human heart formation and congenital heart disease.

"We were surprised to discover that a group of enzymes involved in lipid synthesis plays a previously unrecognized role in assembling the heart. The same mechanism is likely to be involved in human-heart development," said Dr. Olson, director of the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and the Nearburg Family Center for Basic Research in Pediatric Oncology.

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The findings further our understanding of the identity of genes that can cause heart defects and also serve as a step in developing genetic screening for such defects, Dr. Olson said.

"It was very interesting because so little is known about how the heart forms and we did not anticipate that the same enzymes involved in cholesterol and lipid synthesis might play an important role in the development of an organ," he said.

One of the goals of this research is to define the genetic blueprint for how the heart forms. In order to do that, the UT Southwestern scientists engineered fruit flies whose hearts glow by expressing a gene coding for green fluorescent protein specifically in the heart. "This fly with a glowing heart enables us to visualize the details of heart development with high resolution in living animals and to detect cardiac defects that have never been described before", said Dr. Zhe Han, research instructor and co-first / co-senior author of this study.

Other molecular biology researchers from UT Southwestern involved in the study were Peng Yi, graduate student and Xiumin Li, research associate.

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