

First gene detected for most common form of mitral valve prolapse

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Research on the DNA of a large multi-generational family has provided a genetic clue that enabled scientists to pinpoint a gene that plays a role in mitral valve prolapse (MVP), a common cardiac disease that is a leading cause of heart failure, according to a study presented today (Thursday, Oct. 24) at the American Society of Human Genetics 2013 meeting in Boston.

The scientists who located the gene, named DCSH1, also determined how mutations in this gene disrupt the normal embryonic development of the [mitral valve](#), one of the valves that controls blood flow in the heart.

"This work provides insights into the pathways regulating valve growth and development," said Susan Slaughaupt, Ph.D., Associate Professor of Neurology in the Center for Human Genetic Research at Massachusetts General Hospital and Harvard Medical School and one of the lead scientists in the collaborative group that conducted the research.

"The results implicate a previously unrecognized paradigm in the development of long-term structural integrity in the mitral valve," said Ronen Y. Durst, M.D., former member of Dr. Slaughaupt's lab and now a senior cardiologist at Hebrew University and Hadassah Medical Center in Jerusalem. Dr. Durst presented the study this afternoon at ASHG 2013.

The researchers' first step was to link MVP to a region on human chromosome 11 in the DNA of the group of relatives with the heart disorder. By sequencing that DNA region in family members, the scientists were able to link mutations in DCSH1 to MVP.

To understand the normal biological functions altered by the mutated copy of DCSH1, the researchers turned to two animal models, zebrafish and mice. Experimentally reducing the expression

level of the zebrafish version of DCSH1 resulted in abnormal heart development.

"Treating the zebrafish embryos with the normal copy of the DCSH1 gene rescued the lesion, while the mutated human DCSH1 gene did not," said Dr. Slaughaupt. "This finding constitutes strong evidence that the mutation disrupts the normal function of DCSH1."

To begin to understand the normal function of DCSH1 in the valve, the researchers obliterated, or knocked out, the gene in mice. The mice were born with excessive connective tissue in the mitral valve that was elongated, thickened, and the valve prolapsed into the left atrium, as in the human disease.

The scientists then traced the excessive connective tissue to developmental errors in the alignment of interstitial cells responsible for proper [heart](#) valve development and growth. "These developmental errors cause mitral valve prolapse and regurgitation in adult mice," said Dr. Slaughaupt.

DCSH1 is the first gene implicated in the most common form of MVP, which is not associated with other syndromes. MVP is the most common indication for surgical intervention to repair the mitral valve.

Dr. Slaughaupt said that the research was an interdisciplinary collaboration among scientists specializing in [human genetics](#), cardiac imaging, zebrafish modeling and developmental biology with mouse modeling, with funding provided by the Leducq Foundation Transatlantic Network of Excellence for Mitral Valve Disease.

More information: The scientists' ASHG abstract is titled, "Mutations in the DCSH1 Gene Cause Mitral Valve Prolapse In Humans." Link to online abstract: www.ashg.org/2013meeting/abstr.../text/f130122729.htm

Provided by American Society of Human Genetics

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