Team identifies first gene that causes mitral valve prolapse

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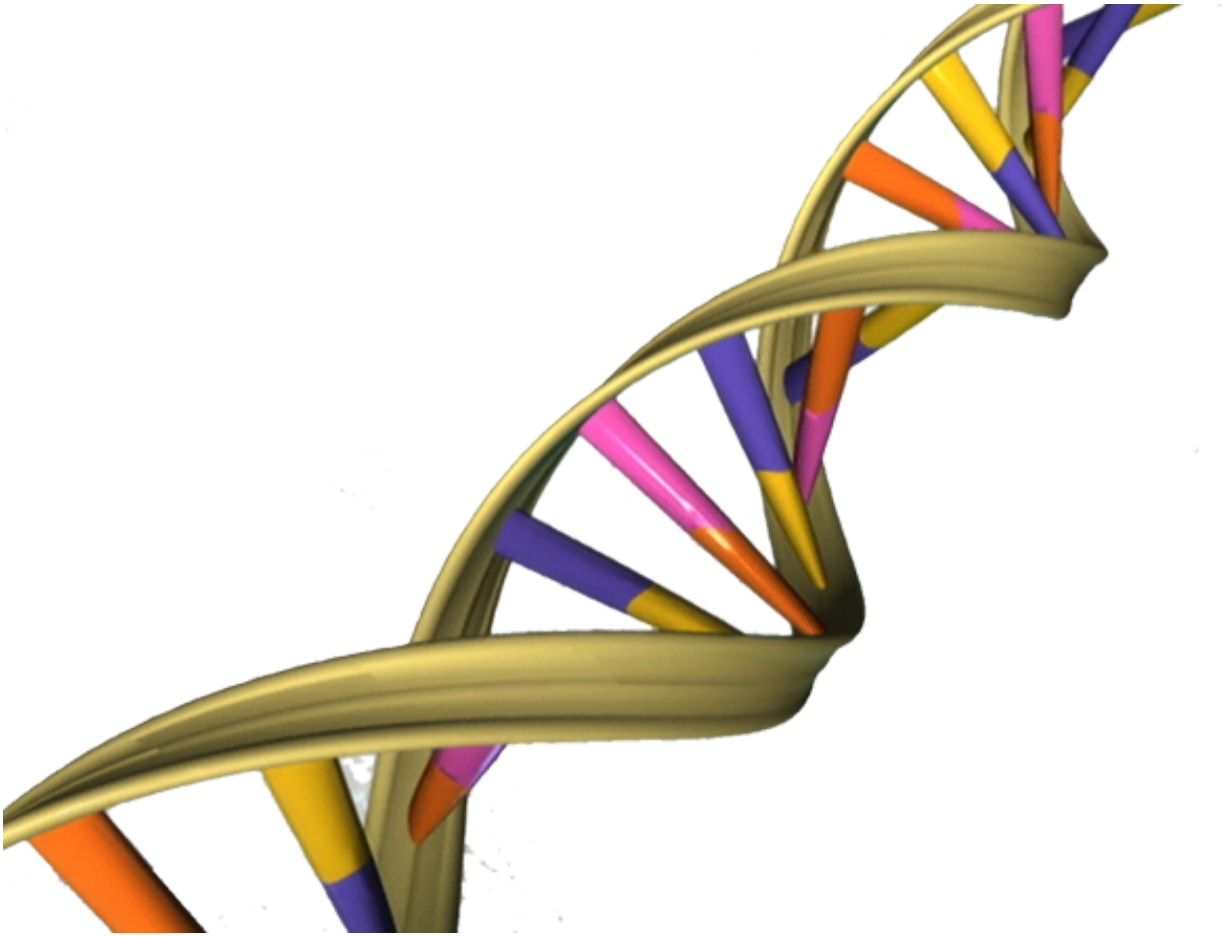

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

An international research collaboration led by Massachusetts General Hospital (MGH) investigators has identified the first gene in which mutations cause the common form of mitral valve prolapse (MVP), a heart valve disorder that affects almost 2.5 percent of the population. In a paper receiving advance online publication in *Nature*, the research team reports finding mutations in a gene called DCHS1 in affected members of three families in which MVP is inherited.

"This work provides insights into the pathways regulating valve growth and development and implicates a previously unrecognized basis for the long-term structural integrity of the mitral valve," says senior author Susan A. Slaugenhaupt, PhD, scientific director of the MGH Research Institute, an investigator at the MGH Center for Human Genetic Research, a professor of Genetics (Neurology) at Harvard Medical School (HMS), and one of the lead scientists in the collaborative group that conducted the research.

Robert Levine, MD, of the MGH Corrigan Minehan Heart Center, co-senior author of the *Nature* paper, says, "This finding can teach us how to prevent this inborn disease from manifesting as an illness in people who inherit mutated forms of this gene. Understanding how defects in this gene cause errors in early valve formation can point to ways we can prevent the progression of this condition to keep the valve and the heart healthy and help the patient avoid complications." The other MGH co-senior author -David Milan, MD, of the MGH Cardiovascular Research Center- led studies of gene impact on the heart in zebrafish models.

One of four valves controlling the flow of blood through the heart, the mitral valve lies between the left atrium and the left ventricle, which handle oxygenated blood returning from the lungs. The valve consists of two leaflets that open to let blood pass through and close to keep it from moving backwards. In MVP, the leaflets become thickened, elongated and floppy, preventing the valve from closing completely and allowing

blood to leak backwards in a process called regurgitation. Patients with serious MVP can develop shortness of breath, cardiac arrhythmia, heart failure or an infection of the heart valves; and MVP is the most common reason for mitral valve surgery.

While MVP can accompany connective tissue disorders such as Marfan Syndrome, most commonly it runs in families without such syndromes. A specific genetic cause of familial MVP had not previously been identified, and the MGH research team's first step was to link the occurrence of MVP in one large family to a genetic risk factor located on chromosome 11. That work depended on advanced diagnostics developed by Levine and colleagues in the MGH Cardiac Ultrasound Laboratory that relied on their discovery of the three-dimensional shape of the mitral valve.

In the current study, detailed DNA analysis of the affected members of that family identified two rare mutations in DCHS1, a chromosome 11 gene previously studied in fruitflies. Experiments in zebrafish by Milan and his team revealed that inactivation of an analogous gene led to significant defects in development of the heart at the site corresponding to the mitral valve, defects that could be prevented by the introduction of the normal copy of the human DCHS1 gene but not the mutated version.

Based on those findings, the MGH team sought to collaborate with other groups studying MVP in order to determine whether the same mutations had a role in other families with the condition. A major grant from the Leducq Foundation in Paris enabled the formation of a network consisting of 11 centers in the U.S. and four European countries, and analysis of DNA from those centers identified two French families in which MVP was caused by another DCHS1 mutation.

Further experiments in cells indicated that the MVP-associated mutations significantly reduced the expression of the DCHS1 protein,

which helps organize how cells are patterned into tissues. Co-senior author Russell Norris, PhD, and his team at the Medical University of South Carolina analyzed the development of mice in which one copy of the DCHS1 gene was mutated, as it is in affected family members. Their findings revealed that the gene plays a critical role in the proper formation of the mitral valve, the first evidence for the gene's role in cardiac development, and that the mutation led to mitral valve changes resembling the human disease.

"This discovery required the cooperation of multiple disciplines and teams - ranging from clinical cardiology and ultrasound diagnostics to classical genetics, screening of potential mutations in zebrafish and functional studies in our mouse models," says Levine, who is a professor of Medicine at HMS.

Milan, an assistant professor of Medicine at HMS, adds, "As a follow up, this same international network has been seeking other genes that cause MVP across the population, which should point us to common pathways that could be targets of therapies designed to prevent progression into symptomatic disease."

More information: Mutations in DCHS1 cause mitral valve prolapse, *Nature*, DOI: 10.1038/nature14670

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