# One gene mutation, two diseases, many insights into human heart function

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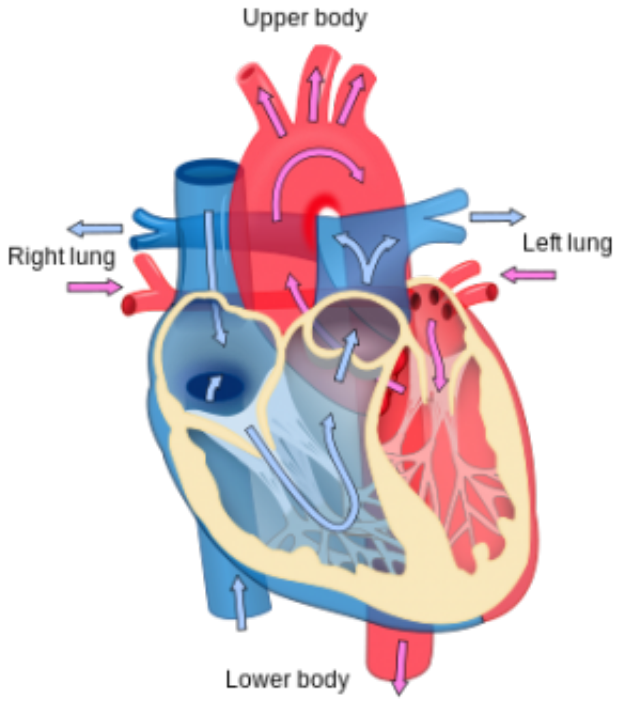


Heart diagram. Credit: Wikipedia

Scientists at the Gladstone Institutes linked a single gene mutation to two types of heart disease: one causes a hole in the heart of infants, and the other causes heart failure. Using cells donated by a family with the mutation, the researchers gained insight into congenital heart disease, human heart development, and healthy heart function.

"Studying what goes wrong in disease can provide us with important insights into basic biology and how it's supposed to go right," said Deepak Srivastava, MD, director of the Gladstone Institute of Cardiovascular Disease and senior author on the new study. "The lessons we learned about cardiac gene networks from this family and their mutation will inform the development of treatments not only for their form of heart disease, but for many others."

## A Family Affair: Gene Mutations and Congenital Heart Disease

Congenital heart disease afflicts almost one percent of all newborn babies. In a particularly common type, a hole forms in the wall (called the septum) between two chambers of the heart. One cause of these septal defects is a mutation in the GATA4 gene, which is essential for normal heart development and healthy heart function. The GATA4 gene encodes a "master regulator" protein of the same name that activates or silences other genes involved in heart development.

The current study, published in the journal *Cell*, involved a family of patients who suffer from congenital heart disease and carry a mutation in GATA4. The family first approached Srivastava in 2003 after half of the babies in the family were born with a septal defect. Using gene sequencing, the researchers learned that every member of the family with congenital heart disease had the same mutation in GATA4—a change in a single letter in the gene.

Seven years later, several of the family members, now adolescents, developed a separate disease of the heart muscle that caused it to pump abnormally. The scientists concluded that the same GATA4 mutation was to blame for the heart muscle dysfunction, but they did not know why.

# GATA4 Cause and Effect

To answer this question, the Srivastava team took skin cells from the family and reprogrammed them using stem cell technology into beating heart cells. This technique enabled the scientists to study heart cells with an identical genetic make-up as the patients to determine how the GATA4 mutation was causing the two forms of disease.

The scientists noticed several abnormalities in the heart cells created from the patients: the cells beat weaker than normal, and numerous genes in the cells were abnormally activated or silenced. For example, genes involved in heart formation were not properly turned on, including genes that control septum formation. In contrast, genes involved in the development of other organs were turned on when they should have been off.

"By studying the patients' heart cells in a dish, we were able to figure out why their hearts were not pumping properly," explained Srivastava. "Investigating their genetic mutation revealed a whole network of genes that went awry, first causing septal defects and then the heart muscle dysfunction."

The researchers discovered that the GATA4 mutation prevented another master regulator protein, TBX5, from being recruited to genes needed for heart development and muscle contraction. GATA4 and TBX5 work together to activate genes responsible for heart formation and function, and silence genes involved in other organs. However, if one protein is mutated, then the other does not work well. Because of the single mutation in GATA4, virtually the entire network of genes regulated by GATA4 and TBX5 were disrupted, resulting in disease. Interestingly, human mutations in TBX5 also result in holes in the heart.

"It was surprising how widespread the effect was. We changed one letter

in one gene, and the entire cardiac development process was upended," said first author Yen-Sin Ang, PhD, a research scientist at Gladstone. "This work reveals how a single mutation in a key cardiac gene can lead to at least two forms of disease."

## Deep Probe Opens Door to Treatment

It is difficult to target master regulator proteins, such as GATA4, with drugs because their influence is so widespread. However, the researchers did find a potential therapeutic target downstream of GATA4 that might be used to treat heart disease.

Using computational modeling to extend their research in the cells, the scientists identified a hub of genes controlled by GATA4 that is important for heart function. They think this gene hub could be targeted with drugs to correct some of the damage caused by GATA4 mutations. Notably, a drug that affects this pathway already exists, and the researchers are pursuing it as a potential treatment for heart disease.

"It's amazing that by studying genes in a two-dimensional cluster of heart cells, we were able to discover insights into a disease that affects a complicated three-dimensional organ," said Ang. "We think this conceptual framework could be used to study other diseases caused by mutations in proteins that serve as master regulators of whole gene networks."

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