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Scientists elucidate genetic underpinnings of congenital heart disease

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Congenital heart disease is the most common birth defect and the leading cause of all infant deaths in the United States. Mutations in the gene TBX5 have been shown to cause both rare and more prevalent forms of congenital heart disease, yet the underlying mechanisms have remained unclear.

A team led by researchers at the University of North Carolina at Chapel Hill has now found evidence pointing to a culprit. The scientists discovered that the TBX5 mutations allow other genes normally involved in cancer and the nervous system to be inappropriately "turned on" or expressed in the developing heart. This gene expression could play a major role in congenital heart disease.

The finding, published in the journal *Developmental Cell*, provides insight into how patients develop heart disease and a road map for future studies on other genetic defects that lead to a malfunctioning heart.

"Our lab and others have had a long-standing interest in the TBX5 gene because it is essential for heart development and it appears to play a critical role in human disease," said senior study author Frank L. Conlon, PhD, professor of genetics in the UNC School of Medicine and professor of biology in the UNC College of Arts and Sciences. "Yet we never would have guessed that these mutations would generate this effect on other genes. It demonstrates just how much more we have to learn about the origins of heart disease."

Heart disease is the leading cause of death and disability in the Western world. Approximately 1.4 million children and adults in the United States are currently living with a congenital heart defect. One of the most common defects is a hole in the septum - the wall that divides the right side of the heart from the left. As a result, blood flows to the wrong place or in the wrong direction, and the body's tissues stop receiving the oxygen they need to function properly.

"The health problem is compounded by the fact that most individuals are asymptomatic," said Conlon, who is a member of the UNC McAllister Heart Institute. "These kids can be living what seems like a perfectly healthy life, running around outside and stressing their heart, putting themselves into a state of oxygen deprivation, and no one knows until they fall down dead. It is absolutely devastating."

Mutations in the TBX5 gene cause the rare Holt-Oram syndrome and the more prevalent Tetralogy of Fallot, two conditions marked by septal defects. Over the last two decades, mounting evidence has indicated that this gene acts as a transcription factor, a kind of master switch that turns on other genes during development. But no one had been able to figure out which genes TBX5 controls in the developing heart, and how.

In this study, Conlon decided to apply the latest proteomic, genetic, and biochemistry tools to determine how defects in TBX5 could lead to heart disease. The project took five years and the efforts of over a dozen researchers at the Conlon lab at UNC, the Ian Davis lab at UNC Lineberger Comprehensive Cancer Center, the Ileana Cristea lab at Princeton University, and the Ivan Moskowitz lab at University of Chicago.

First, the researchers stuck a tag on the TBX5 protein so they could extract it from heart tissue along with all its other associated proteins. They pulled down approximately 100 proteins, including some members

of the "NuRD repressor complex" that is known for tightly winding up sections of DNA in a way that turns off a variety of different genes. Using molecular modeling and traditional genetic cross breeding in mice, the researchers showed that TBX5 binds to DNA and recruits this NuRD complex, which then represses genes normally activated in cancer and in the nervous system.

Finally, the group engineered tissue culture cells to carry the same mutations that cause heart disease in patients and showed that the mutations disrupted the interaction between TBX5 and NuRD, leading to the inappropriate activation of cancer and neural genes in the heart.

"We believe that these cancer genes could fuel the incorrect growth of the heart, and the neural genes could trigger cardiac conduction abnormalities, both of which are commonly found in congenital heart disease," said Conlon.

He and his colleagues believe that their proteomics-based approach coupled with molecular modeling can provide a powerful strategy for predicting which mutations are likely to be responsible for disease in patients and which are more likely to be harmless. In the future, the researchers plan to repeat their experiments with other proteins to further define the molecular mechanisms underpinning congenital heart disease.

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