Heart structural gene causes sudden cardiac death in animal model

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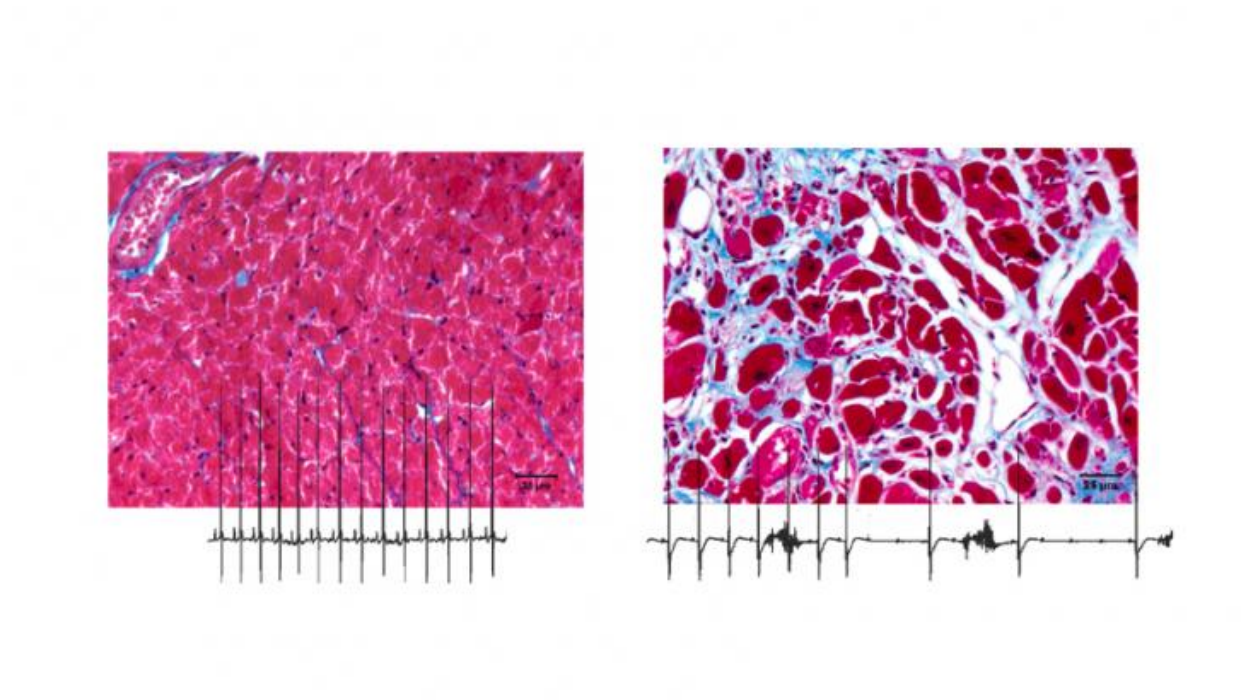

Compared to a healthy heart on the left, microscopic views of a heart from a CAP2 mutant mouse on the right identifies an area of heart disease. The electrocardiogram underneath shows that the mutant hearts skip beats during sudden cardiac death. Credit: Jeffrey Field, PhD, Perelman School of Medicine, University of Pennsylvania

The presence or absence of the CAP2 gene causes sudden cardiac death in mice, according to new research from the Perelman School of

Medicine at the University of Pennsylvania. In particular, the absence of the gene interrupts the animal's ability to send electrical signals to the heart to tell it to contract, a condition called cardiac conduction disease. The study was published in *Scientific Reports*.

"This study proves that the CAP2 gene is directly responsible for cardiac conduction disease in mice," said senior author Jeffrey Field, PhD, a professor of Systems Pharmacology and Translational Therapeutics. Heart disease is the leading cause of death among men in the United States. There are several risk factors for heart disease, many of which can be controlled with changes in behaviors and medication, but there are also hard-wired genetic factors that play a role. "Since humans have the same CAP2 gene, what we learn from the mice could advance our understanding of heart disease."

Researchers have known that the CAP2 gene could be implicated in heart disease. However, its effect on cardiac conduction in the mouse heart was a surprise, Field said. The cardiac conduction system is a molecular network that sends electrical signals to the heart, telling it to contract in the correct rhythm to keep blood flowing smoothly.

The CAP2 gene's class of protein, while known to regulate the structure or cytoskeleton of the heart, is not usually associated with cardiac conduction because this function is governed by a different family of proteins associated with cell communication. "Initially, saying that CAP2 is involved in cardiac conduction is like saying a person with a broken bone isn't able to talk," Field said. "The bone's structural function and the ability to talk are each from entirely different systems. There's no relationship. This finding merits further study to see how exactly CAP2 regulates conduction. While we don't understand how, this gene definitely has a role in controlling conduction."

CAP2 Knockouts

Using a mouse model in which the team deleted the CAP2 gene, they found that most newborn males died suddenly, soon after weaning. The males were also prone to eye infections, and their eyes developed incorrectly and could not efficiently flush away debris. The knockout mice were also smaller in overall body size.

Though rare, some of the mice also developed hearts that were overly large. "The loss of the CAP2 gene resulted in bigger hearts because the heart had trouble contracting and to compensate, it dilated in order to get more blood flowing," Field said.

The knockout mice also exhibited arrhythmia that worsened over four to five days. "We were able to monitor the mice as they died. Their hearts beat slower and slower, and they quickly died of heart block," he said. Heart block happens when the heart atriums contract, but the ventricles do not get the signal to contract. As a result, the mouse hearts missed a few beats at first, and then stopped completely. This condition is called sudden cardiac death, which is distinct from a heart attack caused by clogged arteries impeding blood supply to the heart. In this experiment, there were no observable effects of a missing CAP2 gene on the female newborns.

Parallels to Humans

Studies of some children .with a rare developmental problem, called 6p22 syndrome, hint that this gene is associated with similar cardiac issues in people. These children have deep-set eyes and cardiac problems that are not well defined. "Almost all of these children are born with a deletion of one of their copies of the CAP2 gene," Field noted.

Knowing this connection, the researchers generated mice that would exhibit only cardiac conduction disease (CCD). They reinstated the gene

but this time engineered it so they could knock it out again, but this time only in the hearts of the mice. "It took close to five years to perfect this mouse model that exhibited only the heart knockout," Field said. The researchers could then conduct experiments targeting only the heart problem, because all the other symptoms, such as the eye problems, were out of the picture.

The mice once again developed CCD, leading to sudden cardiac death from complete heart block, but there was an extra surprise this time. The female newborns also died of CCD. "That's a puzzle for us. We'd be interested in studying why the gender specificity for CAP2-related sudden cardiac death goes away when we knock the gene out just in the heart," Field said.

The team says that the study increases the understanding of how the CAP2 gene affects heart disease, but it also raises new questions that underline the need for further research heart disease and why it's a major cause of death in humans.

"It's an important problem in cardiology to understand why heart disease is more common in men versus women. This also happens with heart attacks and congenital heart disease," said Field, who surmises that male-female hormonal differences may help explain the difference.

More information: Jeffrey Field et al. CAP2 in cardiac conduction, sudden cardiac death and eye development, *Scientific Reports* (2015). DOI: 10.1038/srep17256

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