

New cause of heart arrhythmia found

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A new study shows that atrial fibrillation--the most common form of sustained heart arrhythmia--can be caused in an unexpected way. Researchers report in the December 12th issue of the journal *Cell*, a Cell Press publication, the first evidence that a rare and particularly severe form of the disease stems from a gene involved in shuttling other molecules in and out of the cell nucleus, where the DNA that serves as the blueprint for life is housed.

"The common thinking is that atrial fibrillation is an electrical problem of the heart," said Qing Kenneth Wang of the Cleveland Clinic. That has led to the notion that ion channels are primarily responsible since they control the electrical impulses that keep the heart beating.

Wang's team now shows that defects in a gene known as NUP155, a key component of the so-called nuclear pore complex, also leads to arrhythmia in patients with two abnormal copies of the gene. "It's unexpected," he said. "We never thought a gene like this could lead to atrial fibrillation."

Atrial fibrillation is characterized by uncoordinated beating of the hearts upper chambers. The heartbeat in patients with atrial fibrillation is not only uncoordinated, Wang said, but also very chaotic and rapid. Whereas a normal heart beats 70 or 80 times a minute, in atrial fibrillation that rate can jump to 300 beats per minute. As the population ages, the incidence of the disease is rising in step and atrial fibrillation is now responsible for an estimated 15 percent of all strokes.

In most people, the disease stems from a complex interplay of genetic and environmental causes. In some 30 percent, however, the disease is tied directly to single genes that are passed down over generations, spurring disease in some cases with a single abnormal copy and in others only in those with two defective variants. In a handful of families, those rare genes have been linked to ion channels, but in many cases the function of the genes responsible remains a mystery.

Wang's team had earlier traced the gene responsible for atrial fibrillation in one family to a region on chromosome 5. Family members with two copies of the offending variant develop symptoms of the disease and can suffer sudden death in early childhood. They now find that the root cause is NUP155.

To further work out what the NUP155 gene does in the new study, the researchers studied mice with the mutation. Mice with two defective copies of NUP155 die very early, but those with only one copy live and show signs of atrial fibrillation. The nuclear pore complex that includes NUP155 is responsible for the transport of many proteins and messenger RNAs (mRNAs) transcribed from DNA in and out of the cell nucleus. Once transported out of the nucleus, mRNA is translated into proteins that do the work of the cell, and Wang's team finds that loss of fully functional NUP155 causes a particular problem in moving the mRNA that encodes a gene known as heat shock protein 70 (Hsp70) out of the cell nucleus and in moving the Hsp70 protein back in.

"Hsp70 has an important role in protecting the heart from stress damage," Wang said. "We think when NUP155 is mutated it leads to a decline in expression of Hsp70 and the heart is unprotected from damages. That may be why people develop atrial fibrillation."

NUP155 likely controls the movement of many other molecules as well, he added. If those responsible for atrial fibrillation can be found,

NUP155 itself along with any of those important downstream genes its effects may make potentially good targets for drugs designed to combat atrial fibrillation. The molecular identification of NUP155 as an atrial fibrillation gene may also facilitate the development of new diagnostic tools for catching the disease early and perhaps even preventing it, the researchers said.

While the specific mutation in NUP155 Wang's team studied is rare, he nevertheless suspects the newly identified mechanism could play a role in other cases of the disease as well. For one thing, mice develop atrial fibrillation with just one copy of the gene, suggesting that people carrying a single mutant copy or variants of the gene with more subtle effects might also be more susceptible to the disease. "It may be a more common cause of the disease than we realize," he said.

Source: Cell Press

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