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Gene Variant Increases Risk of Cardiac Arrhythmia for African-Americans

A variant form of a gene found in the heart muscle of some African-Americans may increase the chances of developing a potential deadly heart condition called cardiac arrhythmia, say researchers from the Howard Hughes Medical Institute at Childrens Hospital in Boston.

The researchers estimate that 4.6 million African-Americans carry this gene variant. The finding could benefit African-Americans by making it possible to detect who is at increased risk for developing arrhythmia and allowing those affected to take preventive measures. The study is one of the first in which researchers have been able to discern how genetics influences arrhythmia risk across a range of populations of people who originated from different geographic regions.

In an article published in the August 23, 2002, issue of the journal *Science*, the research team led by HHMI investigator Mark T. Keating reported that 13.2 percent of African-Americans in the study carried an altered form of the gene *SCN5A*. This gene codes for a protein called a sodium channel, a molecular pore that initiates heartbeats by allowing sodium to flow across the membrane of the cardiac muscle cell.

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- Mark T. Keating

The variant form of the gene creates sodium channels in heart muscle cells that remain open longer than normal sodium channels, prolonging contraction of the heart and contributing to arrhythmia. Keating authored the paper with colleagues at Harvard Medical School, the University of Utah, Columbia University and St. George's Hospital Medical School in London.

Keating emphasized that although arrhythmias are serious disorders, the effect of the gene variant is subtle. "People who have this gene variant are not likely to have an arrhythmia, he said. All of us harbor gene variants that we may not know about. Fortunately, our hearts are remarkably well buffered against such problems, and arrhythmias are rare. What's often required for a dangerous arrhythmia is that several things go wrong at the same time."

Keating does not believe that routine testing is warranted. The test is fairly simple and inexpensive, so many people may elect to have it, if and when it becomes commercially available, he said. Those most likely to seek testing are people whose medical condition or medications might make them vulnerable to arrhythmias. Currently the test is available only as part of a research study.

"It is worth knowing if you have the variant because there are simple things you can do to prevent arrhythmias," he said. According to Keating, these steps include avoiding any of a broad range of drugs, including antibiotics such as erythromycin and antihistamines such as Seldane, which affect heart rhythm. People with a risk of arrhythmia should monitor their potassium levels to ensure that they remain in the normal range and take beta-blockers to stabilize the heartbeat.

In beginning their search for polymorphisms (gene variants) that might contribute to arrhythmia, Keating and his colleagues started with the gene *SCN5A* because mutations in that gene were known to play a role in rare inherited arrhythmia disorder, called long QT syndrome, that can cause sudden death.

"Almost nothing was known about the effects of polymorphisms on cardiac arrhythmias, but we were among those predicting that variants would be discovered that were reasonably common and would have a subtle effect on arrhythmia risk," said Keating. He pointed out that the effort to understand the genetic and environmental origins of arrhythmias is spurred by the seriousness of the disorder, which kills about 450,000 people in the United States each year.

In their initial studies, the scientists found the same polymorphism, which they named Y1102, in several patients with arrhythmias that did not appear to run in their families. Their studies showed that changing one nucleotide in the *SCN5A* gene resulted in a sodium channel that carried an alteration in a single amino acid.

A broader survey of several population groups revealed that the Y1102 polymorphism occurred in 19.2 percent of people of West Africans and Caribbean descent, and in 13.2 percent of African-Americans studied. However, the gene variant was not found in Caucasians or Asians, and in only one of 123 Hispanics.

Keating and his colleagues also found that the Y1102 polymorphism occurred disproportionately in African-American patients with arrhythmia and in all phenotypically affected members of one African-American family.

"It would appear that this variant originated in Africa long ago, and been in that population for some time," said Keating. "And the people who migrated out of Africa to found other populations still carry it."

The scientists also conducted cell culture studies that revealed how the Y1102 variant affected the sodium channel by subtly altering its "gating," causing it to remain open slightly longer, which prolongs action potential duration and increases the excitability of cardiac muscle cells. This effect could cause transient conduction abnormalities between heart cells, contributing to arrhythmia risk. Finally, the scientists compared a computer simulation of the effects of Y1102 with actual clinical findings of drug effects on arrhythmia, discovering that the polymorphism did produce the predicted sensitivity.

While the researchers hope their findings will benefit people who have the Y1102 variant, they also emphasize the broader implications of their discovery. "We believe this finding is especially significant because it constitutes a proof of principle that points the way to identifying more of these variants in different population groups," said Keating.

"This is among the first pieces of a big puzzle of genetic affects on arrhythmia," he said. "We need to have many more pieces before we can begin large-scale genetic testing of people for such variants. And although testing for the variant we have discovered may prove useful, it is only one of many risk factors. So, I would hope that such testing will be done in a research setting, where these findings can be confirmed and extended, and put into a larger clinical context," said Keating.

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