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PHARMACOGENETICS

Gene Mutation May Boost Risk of Heart Arrhythmias

The rare event often sheds light on the commonplace. And human disease is no exception. Over the past few years, researchers have identified several mutant genes that cause rare and potentially fatal heart arrhythmias. That has helped researchers understand both normal heart cell function and how it might be disrupted, with life-threatening consequence. Now, Mark Keating of Children's Hospital and Harvard Medical School in Boston and his colleagues, including Igor Splawski, also at Children's, have taken a new step. On page 1333, they offer tantalizing evidence that a different variation in one of those genes, dubbed *SCN5A*, might increase the risk of heart rhythm disturbances in members of the population at large, not just in those few people with the hereditary arrhythmias.

The variant gene, found primarily in persons of African descent, isn't likely to cause problems on its own. "I'm not saying that people who carry this variant should lose sleep over it," Keating says. But numerous medications, including some antihistamines and drugs used to treat high blood pressure, have also been linked to an increased risk of cardiac arrhythmias, and persons carrying the variant might be more likely to fall victim to that untoward drug side effect.

Indeed, people vary widely in their responses to both the benefits and harmful side effects of therapeutic drugs, and researchers think that genetic variations such as the one in *SCN5A* might be at the root of those differences. The vast majority of those variations have yet to be identified, however. That's why the Keating group's discovery is "important and significant," says arrhythmia researcher Arthur Moss of the University of Rochester Medical Center in New York state. It contributes to the fledgling science of pharmacogenetics, which seeks to understand how genes affect drug responses. Eventually, researchers hope that, by screening patients for such genetic variations, they will be able to select or even design more effective and less dangerous drug therapies for them.

Keating's interest in *SCN5A* dates back to 1995, when his group and that of Paul Bennett and Alfred George at Vanderbilt University Medical Center showed that mutations in the *SCN5A* gene cause "long QT syndrome," a rare hereditary heart rhythm disturbance that was so named because of a characteristic change in patients' electrocardiograms. Keating then set out to find whether variations in *SCN5A* might also influence the risk of arrhythmias in the general population.

He and his colleagues examined the gene in people hospitalized with heart arrhythmias. Eventually they found a particular change—a single-base substitution that changes just one amino acid in the SCN5A protein—in an African-American woman. Her heart problems could not be linked to any of the mutations already known to cause cardiac arrhythmias, raising the possibility that this *SCN5A* variation might somehow contribute to the irregularity.

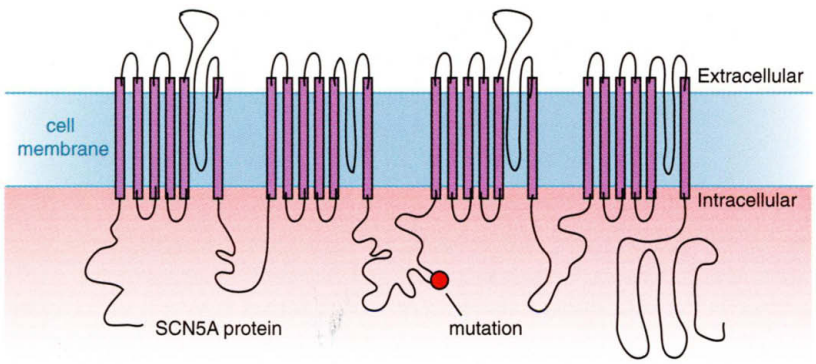
Subsequent screening of the general population showed that the variant is widespread among blacks. The researchers found it in about 19% of 468 West Africans and Caribbeans and in 13% of 205 African Americans. In contrast, the researchers did not find it in 511 Caucasians or 578 Asians, and it turned up in only one of the 123 Hispanics they studied. Moreover, Keating and his colleagues found that the variant is far more common in African Americans being treated for arrhythmias than in healthy controls, suggesting that it does increase risk.

To explore how the *SCN5A* variant might increase susceptibility to arrhythmias, the Keating team, with that of Robert Kass of Columbia University's College of Physicians and Surgeons, introduced the gene into human cells. Research had already established that the SCN5A protein forms a sodium channel that opens, when appropriately stimulated, to let sodium ions flow into heart muscle cells, thus providing the trigger for the cells to contract. The team found that a small percentage of the variant channels reopen at a time when they are supposed to be closed, a change that could make the heart more prone to developing arrhythmias.

Keating notes, however, that the differences weren't large and that the variant alone isn't likely to cause problems for the individuals carrying it. But, he suggests, the variant might increase an individual's susceptibility to the arrhythmias triggered directly or indirectly by certain medications, including the diuretics used to lower high blood pressure, a condition that tends to be more common in blacks than in whites. If that theory is confirmed, Keating says, then it would be relatively easy to devise a test to identify the carriers, who could then avoid taking risky medications.

Keating cautions, however, that "this paper shouldn't be interpreted as showing that African Americans are at increased risk of arrhythmias." He just happened to find the variant in that population. Other groups might carry different variations, in either *SCN5A* or one of the other genes that can cause arrhythmias, that could affect their risk.

—JEAN MARX



A subtle difference. The SCN5A protein winds through the membrane of heart muscle cells, forming a channel that opens to let sodium ions flow into the cells. A single amino acid change (red dot) in this large protein may make people more susceptible to heart arrhythmias.

SOURCE: ADAPTED FROM M.T. KEATING