New genetic risk factor for sudden cardiac death identified

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In a large and comprehensive investigation into the underlying causes of sudden cardiac death (SCD) - a surreptitious killer of hundreds of thousands annually in the United States - researchers have discovered a variation in the genome's DNA sequence that is linked to a significant increase in a person's risk of SCD.

The new finding flags a DNA sequence called the BAZ2B locus, a region along the genome containing three genes previously unknown to play any role in cardiac biology, according to a report published online June 30 in PLoS Genetics. Understanding how genetic variation in this region plays a role in the risk of SCD could eventually help those at risk take steps to prevent it, the researchers say, although they emphasize that a great deal of follow-up work is required.

"Our analysis suggests that if you have one copy of this variant, your increased risk is double that of someone who doesn't," says Dan Arking, Ph.D., lead author of the study and an associate professor in the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. "If you have two copies - having inherited one from each parent - you have almost a fourfold increased risk of SCD."

Statistically significant though it is, this variant alone doesn't give scientists the information they need to proceed with a clinically useful test or therapy, Arking says. Scientists first need to figure out which of the three genes in the region is the key player, and determine how that gene's function is compromised - likely by using model organisms to investigate their heart-related biological activity.

To identify the variant, a consortium of researchers first combined five separate genome wide association studies to survey each of the 3 billion base pairs in the DNA sequences of 1,283 individuals of European ancestry who experienced SCD, and more than 20,000 individuals without SCD. They followed up suggestive findings in an additional 3,119 SCD cases and 11,146 non-SCD control subjects from 11 European ancestry studies to confirm that the BAZ2B locus is associated with SCD.

Collecting enough DNA samples to yield statistical power has been a challenge for investigators studying SCD, Arking says. One reason is that most individuals who experience it do not have clinical signs that would suggest that they are at high-risk for SCD. In addition, only about 10 percent of people survive their initial sudden death events. (Even if the heart stops beating, a person might be saved if the heart is shocked quickly enough back into normal rhythm. The episode is still considered a sudden death event, even if the person survives, because death would have occurred without intervention.)

"SCD is a distinct disorder that involves an electrical instability in the heart," Arking says. "It's what happens when a 40-year-old guy one minute is feeling great, working out on a treadmill, and the next minute, without warning, drops dead."

Arking emphasized that based on their analyses, plenty of people are walking around with the BAZ2B variant who don't experience sudden death. SCD is a complex disease, he says, meaning this newly identified risk factor is neither necessary nor sufficient as its cause. The variant is independent of other risk factors for sudden cardiac death, which include diabetes, heart attack, and a prolonged QT interval, a measure of electrical activity in the heart obtained from a standard electrocardiogram (ECG).

"While we've done a great job of treating coronary disease and reducing the risk of heart attacks, we've made very little progress in reducing the risk of sudden cardiac death," Arking says. "The use of genetics to screen broadly is critical because we don't have other measures that will do a good job of identifying people at risk."

More information: *PLoS Genetics*, www.plosgenetics.org/search/si ... enetics&query=arking

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