Calcium-binding protein mutations found in heart rhythm disorders

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A team led by Vanderbilt University investigators has discovered two new genes – both coding for the signaling protein calmodulin – associated with severe early-onset disorders of heart rhythm. The findings, reported online Feb. 6 in the journal *Circulation*, expand the list of culprits that can cause sudden cardiac death and may point to new therapeutic approaches.

Nearly two decades of research have identified more than 25 genes in which mutations can increase risk for life-threatening cardiac arrhythmias, said Alfred George, Jr., M.D., chief of the Division of Genetic Medicine at Vanderbilt.

"Despite all this information, there are still cases that have no genetic diagnosis – they don't have mutations in any of the known genes," he said.

Two such cases recently came to George's attention. They were both infants – one in Italy, one in Chicago – who suffered from early and repeated cardiac arrests requiring resuscitation, medications, and eventually, implantable defibrillators. Both infants had healthy parents with no symptoms and no family history of heart rhythm disorders, suggesting that the children had a de novo (spontaneous, non-inherited) mutation in a previously unknown arrhythmia susceptibility gene.

George and his colleagues recognized that these parent-child "trios" offered a unique opportunity to discover novel arrhythmia susceptibility

genes.

At the time, Vanderbilt was building its resources in next-generation DNA sequencing, in part with funding from a National Institutes of Health instrumentation grant that George wrote. The researchers decided to use the new technology to scan the protein-coding regions across the genome (exome sequencing) in the parent-child trios. Using the trios allowed the investigators to zero in on the mutation causing the life-threatening disease.

"One of the biggest challenges in exome sequencing is sorting through the hundreds of thousands of gene variants to determine which one likely causes the disease," George explained. "In these cases, in which we suspected de novo mutations, we eliminated more than 90 percent of all the variants we found because they were transmitted from a parent."

Exome sequencing is a powerful approach and "is now a widely accepted strategy for discovering new gene mutations," George said.

In the infants, George and his colleagues discovered de novo mutations in two of the three genes coding for calmodulin, a calcium-binding protein essential for intracellular signaling in multiple tissues including heart.

The researchers also screened a group of patients with long QT syndrome (a condition that increases risk for fatal arrhythmias) who did not have any of the known long QT-associated genetic mutations. They discovered calmodulin mutations in two of these patients.

Walter Chazin, Ph.D., and Christopher Johnson, Ph.D., in the Vanderbilt Center for Structural Biology, investigated the impact of the mutations on calmodulin function. They found that all of the mutations impaired the ability of calmodulin to bind calcium.

"Calmodulin is known to interact with a whole host of proteins that we know are critically important for maintaining heart rhythm," George said. "So a dysfunctional calmodulin that can't bind calcium will almost certainly create an abnormal electrical effect in the heart."

The researchers are currently exploring how dysfunctional calmodulin affects electrical activity and causes arrhythmias. They also are working with pediatric cardiologists to identify additional parent-child trios (child with unexplained early-onset arrhythmia) for exome sequencing studies.

The hope, George said, is to fully understand the "pathways and networks of genes that cause early-onset severe arrhythmias" and to use that information to inspire new therapeutic approaches.

The genetic testing companies that screen for mutations in children with arrhythmias probably need to add the calmodulin genes to their list, George said.

George and his colleagues also plan to look for calmodulin gene mutations in cases of sudden infant death syndrome (SIDS) and late pregnancy stillbirth that have no clear cause of death.

"We know from previous studies that 10 percent of SIDS occurs because of a genetic arrhythmia predisposition," George said. "That percentage will likely increase when we screen new arrhythmia susceptibility genes, such as the calmodulin genes, for mutations."

The current study is the first published exome study using next-generation sequencing instrumentation in the VANTAGE (VANderbilt Technologies for Advanced Genomics) shared resource. It will not be the last, George said.

VANTAGE has now processed "several hundred exome sequencing

samples," said Travis Clark, Ph.D., who was recruited from the biotechnology industry to lead VANTAGE's sequencing efforts.

"We have built up impressive genomics facilities at Vanderbilt," Clark added.

Provided by Vanderbilt University Medical Center