Robotic technology speeds arrhythmia gene classification

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Vanderbilt University Medical Center investigators have used high-throughput robotic technology to rapidly study and classify variations in a gene linked to heart rhythm disorders and cardiac conditions.

The findings, reported in the *American Journal of Human Genetics*, support continued use of the technology to understand genetic mutations and improve the accuracy and scope of genetic medicine.

"We would like to be able to use genome sequencing to find mutations that put people at risk of disease, in order to prevent disease. But this idea of genetic or precision medicine doesn't work well when we don't know the impact of the mutations we find," said Andrew Glazer, Ph.D., a postdoctoral fellow in the Vanderbilt Center for Arrhythmia Research and Therapeutics and lead author of the current study.

Glazer works with Dan Roden, MD, Senior Vice President for Personalized Medicine at VUMC, studying inherited arrhythmia syndromes that increase an individual's risk for sudden cardiac death.

In the current study, their team focused on the cardiac sodium channel gene, SCN5A. Mutations that cause partial or complete loss of sodium channel function are the most common genetic cause of Brugada Syndrome. The risk of sudden cardiac death associated with Brugada Syndrome in individuals with disease-causing mutations can be reduced with extra cardiac monitoring, medications and implantable defibrillators.

The challenge is that the majority of the 1,712 mutations that have been identified in SCN5A are "variants of uncertain significance," Glazer said. "That basically means that we're not sure whether or not they cause disease. They might cause disease; they might not. We don't know."

The "gold standard" for studying ion channel function is a technique called patch clamp electrophysiology. Until recently, however, this tool was slow, labor-intensive and technically challenging. Now, automated robotic patch clamp electrophysiology systems exist that allow for high-throughput assessments of ion channel function.

Vanderbilt was awarded a National Institutes of Health High-End Instrumentation (HEI) grant in 2018 to purchase an automated electrophysiology system. Dave Weaver, Ph.D., associate professor of Pharmacology and scientific director of the High-Throughput Screening Facility, was the principal investigator of the HEI grant.

Vanderbilt is one of few academic centers with a high-throughput electrophysiology system, and the

current studies are the first to be reported that used it.

"That system really enabled the science because we could study lots of mutants in lots of replicate cells relatively quickly," Glazer said.

The researchers evaluated 83 variants in SCN5A, 10 of which had been previously characterized as controls. They identified 44 new partial or total loss of function variants and reclassified 49 of 61 variants of uncertain significance. They also used structural modeling to identify likely mechanisms for loss of function including altered thermostability and disruptions to critical protein features.

The Vanderbilt team will continue to study variants in the SCN5A gene. Researchers at other institutions are studying different ion channel gene variants linked to arrhythmias.

"I'm hopeful over the next few years that as a field, we will really be able to refine our understanding of which mutations cause disease and put that knowledge to use in precision medicine applications," Glazer said.

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