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Genetic defects hold clues to risk for sudden cardiac death

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Sudden cardiac death is always a shocking, tragic event, especially when it occurs at a young age. But, for the first time, scientists are unraveling how genetic defects can help predict the risk of dying suddenly in individuals with one of the leading causes of this unfortunate phenomenon.

This knowledge could guide treatment and potentially lessen the occurrence of sudden cardiac death in patients with Long QT syndrome, a rare, inherited heart rhythm disorder. It could also provide insight into the assessment and treatment of the millions of people who experience cardiac arrhythmias – irregular heart rhythms that cause the heart to beat too fast or too slow and can lead to sudden death if not corrected.

The new study, published recently in the journal *Science Translational Medicine*, shows that the function of specific genetic mutations – namely, the defects these mutations cause – are strong predictors of risk of sudden death and other cardiac events in patients with Long QT.

The finding is especially relevant for individuals who have the condition but don't have particularly pronounced clinical risk factors, such as a very prolonged QT interval – the time it takes for the heart's electrical system to recharge after each heartbeat and get ready for the next (hence, the name "Long QT" syndrome). When the QT interval is prolonged, the heart is more susceptible to arrhythmias.

These tricky, in-between patients, who make up about 70 percent of the

Long QT syndrome population, often fall into a treatment gray area. In the future, lead study author Coeli Lopes, Ph.D., hopes that physicians may be able to use mutation-specific information to better identify high-risk individuals in this group who should be followed more carefully and treated more aggressively.

"To our knowledge, this is the first time anyone's linked the activity of specific mutations to actual risk in patients," said Lopes, assistant professor at the Aab Cardiovascular Research Institute at the University of Rochester Medical Center. "We're literally going from studying mutant proteins in cells in the lab to risk assessment in the clinic, which is an exciting and very promising concept."

Long QT occurs most visibly in teens with otherwise healthy hearts and may go unnoticed until a stressful event, like swimming, jumping into cold water or hearing a particularly loud noise jolts the heart out of rhythm, leading to fainting, cardiac arrest or sudden death.

"Before we had such robust genetic information, we based risk solely on clinical measurements, such as the length of the QT interval and if patients had passed out in the past," said Arthur J. Moss, M.D., professor of Cardiology at the Medical Center and the world's foremost authority on the diagnosis and treatment of Long QT syndrome. "These results mean we can be much more specific in prescribing preventive therapy, which is terrific news for patients and their families."

Current treatment options for patients with Long QT include beta blockers, which relieve stress on the heart by slowing the heart rate, and implantable cardioverter defibrillators or ICDs, which detect irregular and potentially fatal heartbeats and shock the heart back into a normal rhythm. Better knowledge of risk will help physicians decide if patients need treatment with a beta blocker, an ICD or both.

In the study, researchers looked at the most frequent mutations found in patients with Long QT syndrome type 1, one of the most common forms of the disease, and analyzed their influence on ion channels – small pores or holes on the surface of each heart muscle cell. These channels open and close to let electrically charged particles flow into and out of the cell, generating the signal the heart needs to stop contracting and relax after pumping blood throughout the body.

When they compared the results with patient outcomes, they discovered that mutations that cause ion channels to open more slowly than they should were strongly associated with increased risk for cardiac events. Patients with these slow activating channels were twice as likely as patients with other mutations to die before the age of 30 or experience serious symptoms.

Even for patients who lacked telltale clinical symptoms, the presence of mutations linked with slow-to-open ion channels was still associated with an increased risk of cardiac events.

"This study creates a paradigm that we not only have to take into account the presence of mutations, but the potential consequences of mutations as well," noted Wojciech Zareba, M.D., Ph.D., director of the Heart Research Follow-up Program and an expert on Long QT. "Some mutations may be more benign and others less so and more research is needed to understand why this is the case."

The team looked at the function of 17 common mutations found in approximately 390 patients drawn from the International Long QT Registry. In the lab, they recreated the mutant proteins and put them in cells to study their effect on ion channels. They used clinical follow-up data from the registry to relate mutant function to cardiac risk.

While this process of testing mutant function is a starting point, Lopes

says that in the future new, emerging stem cell technologies may allow physicians to take cells (such as skin cells) directly from patients and turn them into heart cells to more precisely determine mutant function.

"Similar to genetic testing, a simple, standardized way to test mutation function on a large scale is needed in order for this method to be widely adopted in clinical practice," noted Lopes.

Provided by University of Rochester Medical Center

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