Researchers identify new cardiac arrest gene

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Researchers at the University of Pittsburgh School of Medicine have identified a new gene responsible for a rare, inherited form of sudden cardiac arrest, known as Brugada syndrome. With the identification of this new gene, the researchers hope this will shed light on the more common forms of sudden death in patients with heart attacks and heart failure, and will help aid in the development of new, effective therapeutic treatments that will prevent all types of fatal arrhythmias.

Lead author Barry London, M.D., Ph.D., the Harry S. Tack professor of medicine and chief, division of cardiology at the University of Pittsburgh School of Medicine and director of the University of Pittsburgh Medical Center (UPMC) Cardiovascular Institute and colleagues report their findings in the online version of Circulation: Journal of the American Heart Association. A link to the online paper, which is scheduled for the Nov. 12 print issue of *Circulation* is available at circ.ahajournals.org/ .

Brugada syndrome is a rare inherited arrhythmia, which is more commonly symptomatic in males. It can present with an abnormality on the electrocardiogram (ECG), fainting or sudden death. In about 20 percent of cases with Brugada syndrome patients, mutations in the heart's sodium channels lead to less current flow and shorter heart beats in a part of the heart. This puts patients at risk for rapid heart rhythms such as ventricular tachycardia and fibrillation. Symptoms often present with no warning, and the seemingly healthy patient passes out and/or suffers a sudden cardiac arrest from an arrhythmia.

Arrhythmias remain a major public health problem leading to more than 250,000 sudden cardiac deaths each year. Brugada syndrome was only identified approximately 15 years ago and much is still not understood about the condition. It is found all over the world and presently there is no cure. The best therapy to date is to implant a defibrillator into the chests of patients who are clinically found to be at high risk.

“In this study we found that GPD1-L, while not an ion channel itself, is a trafficking gene that allows the sodium channel to find its way to the cell membrane. The mutation interferes with the trafficking and leads to potentially fatal arrhythmias,” said Dr. London. “Equally important, we suspect that the function of the native GPD1-L gene and the mutant are influenced by oxidative stress, a process which interferes with the body’s natural ability to repair itself from antioxidant assaults, e.g., pollution, smoking or stress. Also, patients with Brugada syndrome only rarely have symptoms; they have this genetic mutation all the time. So, the question now is, why do arrhythmias or sudden death happen on any one particular day? Something else is happening concurrently with this mutation to trigger the potentially lethal rhythm problems. With the identification of this new GPD1-L gene, we hope to identify other new genes along with entirely new pathways that stabilizes the rhythm of the heart, increasing our understanding of the mechanisms that lead to sudden death in this particular condition,” added Dr. London.

Using positional cloning and gene sequencing on a family affected with Brugada syndrome, Dr. London and colleagues identified a mutation in a previously unstudied gene, GPD1-L, on chromosome 3p24. This mutation impairs the heart’s natural electrical ability to beat in a coordinated manner and maintain a stable rhythm. To date, only ion channel genes had been shown to cause Brugada syndrome.

The patient affected with Brugada syndrome in this study was first referred to Dr. London and colleagues more than 10 years ago. Since

that time, a total of 195 family members have now been enrolled and ECGs have been repeated every six months. To date, implantable cardiac defibrillators (ICDs) have been placed in four affected patients. The original family member has had two episodes of ventricular fibrillation that were corrected by ICD shocks.

“Of note, our collaborators have shown that mutations in GPD1-L also cause other heart rhythm disorders,” said Dr. London. In a related article in same issue of Circulation, Michael Ackerman, M.D., Ph.D., director of Mayo Clinic’s Long QT Syndrome Clinic and director of the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory in Rochester, Minn., and his collaborators screened GPD1-L in infants who died of sudden infant death syndrome (SIDS) and identified three mutations. Mutations in ion channels and ion channel-related genes are becoming increasingly recognized as causes of SIDS.

Source: University of Pittsburgh