Study links genetic variation to possible protection against sudden cardiac arrest

March 25 2010

Physician-scientists at the Cedars-Sinai Heart Institute have found that a genetic variation is associated with lower risk of sudden cardiac arrest, a disorder that gives little warning and is fatal in about 95 percent of cases. Findings will be published tomorrow by the Public Library of Science (*PloS One*).

The discovery came from a genome-wide association study, which examines the entire set of human genes to detect possible links between genetic variations and specific conditions or diseases. In this study, the Cedars-Sinai Heart Institute researchers compared the genetic makeup of 424 subjects who had experienced sudden cardiac arrest to the DNA of 226 control subjects who had no history of the disorder. All patients had a history of coronary artery disease, which commonly underlies sudden cardiac arrest.

Based on a comparison of the two groups, a genetic variation at the location of the GPC5 gene - a genetic sequence called rs3864180 - was found to be associated with a reduced risk of sudden cardiac arrest.

"If you have this genetic variation in your DNA, it appears that you may have a 15 percent lower likelihood of sudden cardiac arrest," said Sumeet S. Chugh, M.D., associate director of the Cedars-Sinai Heart Institute, holder of The Pauline and Harold Price Chair in Cardiac Electrophysiology Research, and one of the senior authors of the study.

"This kind of genetic analysis is not aimed at identifying a single big

gene defect or mutation," he said. "The goal is to identify a series of smaller novel gene defects that, when grouped together, collectively result in either a protective effect or an increased susceptibility to sudden cardiac arrest."

Chugh leads the Oregon Sudden Unexpected Death Study, a comprehensive, 16-hospital, multi-year assessment of cardiac deaths in the 1 million population Portland, Ore. metropolitan area. Funded in part by the National Heart Lung and Blood Institute, the study's goal is to shed light on the risk factors, triggers and genetic defects associated with sudden cardiac death.

All patients in the genome-wide study were part of the Oregon Sudden Unexpected Death Study. Subjects included both survivors and deceased victims of sudden cardiac arrest, but excluded individuals who had a chronic terminal illness or were known to have died suddenly from non-cardiac-related causes related to trauma, overdose, drowning or suicide.

The authors note that while the protective variant rs3864180 occurs within the GPC5 gene, their results do not definitively prove that the gene itself is involved in sudden cardiac death risk. It is possible, for example, that rs386410 modifies the actions of a different gene or is in proximity to another gene of interest.

Genome-wide association studies are intended to identify regions of the human genome that are associated with development of specific diseases. The GPC5 gene encodes glypican 5, one of the six members of the heparan sulfate proteoglycan (HSPG) family. In the cardiovascular system, cell surfaces and surrounding supportive material express large amounts of these proteins, which are involved in a wide variety of critical cell functions. Additional study of rs3864180 and other variations of the GPC5 gene may lead to a better understanding of the mechanisms leading to sudden cardiac arrest.

Unlike heart attacks (myocardial infarction), which are typically caused by clogged coronary arteries reducing blood flow to the heart muscle, sudden cardiac arrest is the result of defective electrical impulses. Patients may have little or no warning, and the disorder usually causes nearly instantaneous death. Every year, 250,000 to 300,000 people in the U.S. and up to 5 million worldwide die from sudden cardiac arrest.

Despite years of significant advances in emergency medicine and resuscitation, just five percent of those who suffer sudden cardiac arrest survive. For patients at known risk for this or other heart rhythm abnormalities, an implantable cardioverter-defibrillator (ICD) may be placed in the chest or abdomen to detect faulty electrical impulses and provide a shock to return normal rhythm. Better genetic predictors of risk may someday enable the accurate prediction of which patients are most likely to benefit from costly ICD therapy.

Provided by Cedars-Sinai Medical Center