Study finds specific genetic cue for sudden cardiac death syndrome

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UC Irvine researchers have found a specific genetic flaw that is connected to sudden death due to heart arrhythmia – a leading cause of mortality for adults around the world.

While a number of genes have been linked with arrhythmias, UC Irvine's Geoffrey Abbott and his colleagues discovered that the functional impairment of a gene called KCNE2 underlies a multisystem syndrome that affects both heart rhythm and blood flow and can activate chemical triggers that can cause sudden cardiac death.

"With these findings, we can now explore improved early detection and prevention strategies for people who are at higher risk of sudden cardiac death, such as those with diabetes," said Abbott, a professor of pharmacology and physiology & biophysics in the UC Irvine School of Medicine.

Study results appear in the February issue of *Circulation: Cardiovascular Genetics*, a publication of the American Heart Association.

Distinct from a heart attack, in which the heart continues to beat but blood flow is blocked, sudden cardiac death occurs when the heart ceases to beat because of the uncontrolled twitching of muscle fibers in its ventricles. Without defibrillation within minutes, this type of event is fatal.

In studies on a mouse model with the KCNE2 gene removed, Abbott and

his colleagues had found catalysts for sudden cardiac death – including high blood cholesterol, anemia, high blood potassium, an age-related delay in the return to a resting position of the ventricle after contraction and, most surprisingly, diabetes.

Abbott said this link to diabetes and other systemic disturbances is significant because genes such as KCNE2 are better known for directly controlling the electrical signaling that ensures a steady heartbeat. The KCNE2 gene provides instructions for making a protein that regulates the activity of potassium channels, which play a key role in a cell's ability to generate and transmit electrical signals. Channels regulated by the KCNE2 protein are present in heart muscles and help recharge them after each heartbeat to maintain a regular rhythm.

In the current study, the researchers expanded on their previous work by showing that KCNE2 disruptions affect these rhythms in cardiac cells, which increases the risk of arrhythmia. Abbott said the major breakthrough in this study is that KCNE2 deletion could adversely affect so many other tissues outside the heart and that this dramatically worsened the outcome of cardiac electrical disturbances.

"Our discovery that a single gene disruption can give rise to a multitissue syndrome that predisposes one to sudden cardiac death challenges the established thinking that this type of genetic disruption can only give rise to a single component, such as abnormal electrical signaling in cardiac cells," Abbott said.

He pointed out that the use of full-gene knockout mice presents an exaggerated form of what occurs in human genetic syndromes.

"It's important to note that the mouse heart is very resistant to developing ventricular fibrillation," he said. "So the fact that we kept seeing this arrhythmia in the KCNE2-deleted mice gives us confidence that these

findings are significant. We're currently using the same mouse model to investigate the mechanisms of myocardial infarction, another major cause of mortality recently associated with the KCNE2 gene."

The gene's relationship to diabetes is another area Abbott's group is exploring. He said that one of the potassium channels regulated by KCNE2 is strongly linked to human diabetes and is present in the islet cells of the pancreas, so one goal is to screen people with diabetes for DNA sequence variances in KCNE2.

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