Gene mingling increases sudden death risk

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A multi-national research team has discovered that two genetic factors converge to increase the risk of sudden cardiac death.

The investigators - from the United States, Italy and South Africa - report in the journal *Circulation* that variations in the gene NOS1AP increase the risk of cardiac symptoms and sudden death in patients who have an inherited cardiac disease called congenital long-QT syndrome.

The findings will help in assessing the risk of sudden death - and assigning therapy - in patients with this syndrome, said senior author Alfred George Jr., M.D., director of the Division of Genetic Medicine at Vanderbilt University Medical Center.

Congenital long-QT syndrome affects the electrical activity of the heart ("QT" refers to a time measure on the electrocardiogram - it is longer than normal in patients with the syndrome). Long-QT syndrome makes patients susceptible to potentially fatal disorders of heart rhythm. It is a known cause of sudden death, especially in young adults and children, and has recently been estimated to affect about one in 2,200 individuals.

But not all people who have gene mutations that cause congenital long-QT syndrome have symptoms (fainting, cardiac arrest, sudden death). The big question mark, George said, is how to manage a patient who has a long-QT gene mutation, but doesn't have any symptoms.

"The concern of course is that the first symptom could be sudden death," he said. "And everything needs to be done to try to prevent that.

"But does every mutation carrier need an implantable defibrillator? Pharmacological therapies? Or should they just be watched?"

The variability in symptoms suggests that other factors play a role - either to promote or prevent symptoms.

George and Peter Schwartz, M.D., at the University of Pavia, Italy, have collaborated over the last seven years to search for "genetic modifiers" of long-QT syndrome - genes other than the disease-causing gene that play a role in the disease.

With collaborators in South Africa, they have focused on a family affected by long-QT syndrome. This extended South African family includes 500 characterized members, 205 of which carry the same long-QT-causing mutation. And as expected, not all of the mutation carriers have symptoms of the disease.

The gene NOS1AP (which codes for a "docking" protein for the enzyme nitric oxide synthase) was identified in a genome wide association study as being a determinant of the QT interval in healthy individuals. George, Schwartz and colleagues examined whether different versions (variants) of the NOS1AP gene impacted the symptoms and QT interval in the South African family.

They found that people who had the primary long-QT-causing mutation and one of two common variants of NOS1AP had a higher probability of cardiac arrest and sudden death than primary mutation carriers who didn't have those NOS1AP variants.

"In this case it appears that variants of NOS1AP somehow predispose those individuals to a worse form of the disease," George said.

The investigators also found that the family members who had the

NOS1AP variants had the longest QT intervals - in a group of people who all have long QT intervals.

"We're excited that these findings begin to address how to manage patients with long-QT mutations," George said.

"What we're hoping is that NOS1AP genetic testing in mutation carriers who are asymptomatic or minimally symptomatic could tip the balance toward being more aggressive in treating them or perhaps backing off and watching them for a little longer."

George and colleagues will also continue to search for other genetic modifiers, which could add to a "risk equation" to determine the best therapy.

"Individualizing therapy in this disease is really a paradigm for personalized medicine," George said. "What do we need to know to make a treatment decision? Now we're starting to see how understanding the modifiers that hover around a primary gene mutation may influence the probability of symptoms and help guide therapy."

Source: Vanderbilt University Medical Center (news : web)