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Abnormalities in Cellular Anchoring Protein Cause Fatal Heart Syndrome

American and French researchers have discovered that mutations that disrupt how ion channels are anchored in the cell can cause a heart condition that can lead to sudden death.

The study, published in the February 6, 2003, issue of the journal *Nature*, and led by Howard Hughes Medical Institute investigators at Duke University Medical Center, found that a rare fatal heart condition, called long QT syndrome (LQTS), can be caused by disruption of proteins that anchor ion channels in the cell.

The finding is noteworthy because most cases of LQTS, and some other known heart conditions, have involved defects in ion channels -- proteins involved in moving potassium and other ions in and out of heart cells so they can contract. In this case, however, the channels and the molecular transporters function normally, but the proteins that position and anchor the channels on the heart cells are awry.

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"It's as if the lights on your car work fine, but they are being held in the wrong positions, such as on the sides of the car, so that you can't use them to drive at night," said HHMI investigator and Duke cell biologist [Vann Bennett](#), senior member of the research team. "Here, membrane channels work properly, but they are poorly organized on the cell, and that affects a critical biological process in which multiple ion channels need to open at the right place and at the right time."

Of even more interest to researchers is the fact that the protein, ankyrin-B, is found in cells throughout the body, raising the possibility that malfunctions in this protein or in other members of the ankyrin family of molecules, may be the root of other disorders. "We have shown for the first time that a protein that most of us thought was just one of many cellular housekeepers actually has an important role in organizing ion channels," Bennett said. "And if it doesn't work right, you can have disease."

The study is both "elegant" and "exciting," said Stanley Nattel, a researcher at the Montreal Heart Institute who wrote a commentary in *Nature* on the finding. "It wasn't logical to think that a protein found throughout the body could be responsible for such a discrete disease as long QT syndrome, but this now makes sense.

"There is increasing evidence that proteins do not sit randomly in cell membranes, but require precise spatial localization, and this study shows just how important this spatial organization can be," Nattel said. "It raises the possibility that other tissues and organs are affected in this and similar genetic diseases."

Bennett said the finding could explain other heart problems "which are often caused by calcium signaling deficits," and new work in his lab already implicates the protein in a rare disease of the nervous system.

Long QT syndrome is so named because the "QT" interval on an electrocardiogram -- the length of time from electrical stimulation of the heart's pumping chambers to recharging to the next heartbeat -- is abnormally long in people with the disorder. A normal QT interval is from 0.38 to 0.44 seconds, but in people with LQTS, that period is delayed by up to 0.5 seconds. Many patients with the disorder never experience symptoms, but others are at risk of developing abnormal heartbeats and cardiac arrhythmia.

HHMI investigator Mark Keating and his colleagues have shown that several forms of LQTS are caused by genetic mutations that affect ion channel proteins. In 1995, researchers in France found a large family affected by LQTS, in which several members had died. The French investigators found that a single nucleotide change in the gene encoding the ankyrin-B protein was found in 23 of 24 family members who had either LQTS or abnormal heart rhythms, but was not present in the 400 people in their control group.

Experts in ankyrin proteins, Bennett and his research team tested loss of the ankyrin-B in a mutant mouse model. They found that two normal copies of the ankyrin-B gene were necessary for normal heart functioning, and that the loss of one normal copy led to deficits in cardiac function similar to those found in the French family, said first author Peter Mohler, an HHMI postdoctoral fellow at Duke. The researchers then stressed the mice with epinephrine -- inducing a "fight-or-flight" response -- and found that of 14 mice with the mutation, two became immediately unresponsive, and eight

died following exercise. None of the mice without the mutation showed any adverse effects. This also mirrored the two deaths that occurred in the French patients after exertion, including the sudden death of a 37-year-old after running up a hill. "Sudden death in humans with this mutation usually occurred after physical exertion or extreme emotional stress," Mohler said.

Other members of the research team are Jean-Jacques Schott, Karine Haurogne, Florence Kyndt and Denis Escander, Laboratoire de Physiopathologie et de Pharmacologie Cellulaires et Moleculaires, Hotel-Dieu, France; Herve Le Marec, Hospital G&R; Laennec, Nantes, France; Keith Dilly, Silvia Guatimosim, William H. duBell, Long-Sheng Song, Terry Rogers and W.J. Lederer, University of Maryland; and from Duke, Anthony Gramolini and Mervat Ali.