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## Genes discovered for sudden death syndrome, a silent killer of young adults

Researchers at the Howard Hughes Medical Institute at the University of Utah have discovered two genes that cause long QT syndrome, an inherited disorder that causes sudden death in young, otherwise healthy people.

In two papers published in the March 10 issue of *Cell*, HHMI researchers report that mutations in genes encoding proteins that comprise part of the heart's electrical system cause increased risk of sudden death from an abnormal, chaotic heart rhythm. The findings are the first to uncover the molecular basis for cardiac arrhythmias, abnormal heart beats which can disrupt blood flow to the brain and other vital organs.

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Long QT syndrome causes episodes of arrhythmia, and although this specific inherited syndrome is not a common disorder, cardiac arrhythmias kill about 300,000 Americans each year, said principal investigator Mark T. Keating of HHMI at the University of Utah.

Keating's group identified mutations in two of the heart's ion channels, which are proteins embedded in the surface of heart cells. Under normal circumstances, the channels open and close rhythmically. This process ensures an orderly flow of the chemicals necessary to sustain the heartbeat. "Both mutant genes cause an increase in the excitability of heart tissue, a dangerous situation that can prime the pump for the development of life-threatening arrhythmias," Keating said.

Long QT is primarily an inherited disorder, but Keating said that some individuals may develop a drug-inducible form of the syndrome while they are on certain medications. Many drugs are known to induce long QT, including erythromycin, antihistamines, and some anti-arrhythmic

medications.

The reason these drugs can have a potentially lethal impact on some people and not others is unknown. "We believe that drug-inducible long QT may result from subtle mutations in cardiac ion channels," Keating said. Up to six percent of people in the United States may have these more subtle mutations, he said.

For patients with hereditary long QT syndrome, these discoveries will provide a fast, accurate diagnostic test for the presence of the disorder in their newborn children. The work also opens the door for development of routine diagnostic tests that would alert otherwise healthy individuals who may be at increased risk for arrhythmia.

"This is great news," said Doris Goldman, an Irvine, Calif., woman whose family has been devastated by long QT syndrome. Sixteen years ago, her son Jack Toran died in his sleep after several weeks of hiking in the Grand Teton mountain range. Twelve years after Jack's death, his younger sister Sharon Turner, a new mother, went to bed as usual and never awoke.

Goldman, outraged by the loss of two children, pursued a medical explanation for the cause of the deaths. There were no clues that Goldman's two children had an irregular heartbeat other than a one-time fainting episode with each child. "Unfortunately, long QT can only be diagnosed with an electrocardiogram test, a test not often given to young adults," Keating said.

Goldman's perseverance paid off when researchers agreed to test her family for genetic markers that would indicate long QT syndrome. The researchers at Utah found a suspicious defect in a gene linked to chromosome 7. Further testing would confirm that 21 members of Doris Goldman's family share this genetic defect, including her only surviving daughter Nancy Duitch and Sharon Turner's young son. But for Goldman that knowledge is priceless. "I didn't expect to see this in my lifetime," Goldman said. "This came too late for Jack and Sharon but if these findings can help put a stop to the deaths it will be a fabulous legacy for them."