Rare Heart Disease Linked to Oncogene

The discovery should lead to improved diagnosis and treatment of the disorder, a serious cardiac arrythmia

BECAUSE IT HAS BEEN IMPLICATED IN THE development of several cancers, the *ras* gene has long been familiar to cancer biologists. Now cardiologists may have to get to know *ras*, too. On p. 704, a research team from the University of Utah Health Sciences Center reports that the gene may be the site of the defect that causes a rare hereditary—and often fatal—heart rhythm disturbance known as the "long QT syndrome."

Until now, says geneticist Kenneth Kidd of Yale University Medical School, no one could be absolutely sure that the syndrome was caused by a single gene defect. But, he asserts, "all these residual uncertainties have been wiped off the board by the finding of this linkage."

The discovery is of more than theoretical interest. Effective therapies already exist for long QT syndrome, but the patients may not get them in time because the condition, which can kill quickly, is very hard to diagnose. The genetic linkage should soon lead to an accurate diagnostic test.

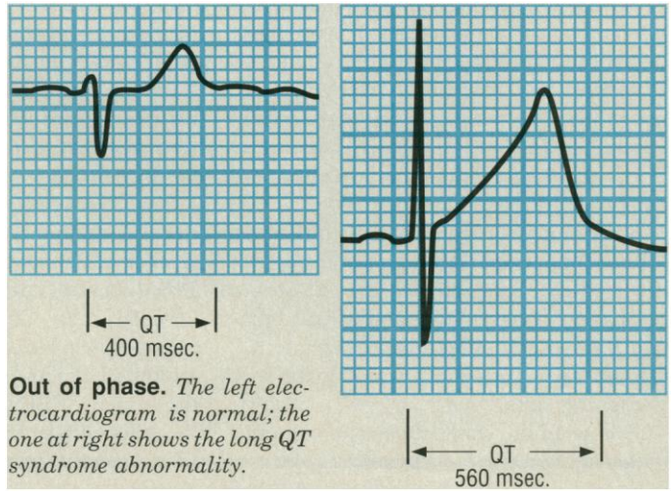
Long QT syndrome is so called because the patients' electrocardiograms often show an abnormality in which the interval between the Q and T waves is longer than normal. That change is caused by an underlying defect in the electrical responsiveness of the heart muscle—a defect that is extremely dangerous because it predisposes the patients to a serious arrhythmia called ventricular fibrillation in which the heart contracts in a rapid, uncoordinated manner and is unable to pump blood to the brain and other tissues. Treatment needs to be initiated within 4 minutes, to prevent the patient from succumbing to what the cardiologists call "sudden death."

Unfortunately, however, the size of the QT interval shows a great deal of natural variation and is therefore not a reliable indicator of whether an individual has long QT syndrome. Indeed, says Mark Keating, the leader of the group that linked the condition to the *ras* gene, "it's not uncommon for the first symptom to be sudden death."

That's where the discovery of the *ras* gene linkage comes in. It should be possible to design a molecular probe that can unequivocally detect those people who carry the long QT syndrome gene so that they can receive treatment to prevent cardiac fibrillation. Moreover, says Jay Mason, chief of cardiology at the Utah Health Sciences Center, such a test could have a much wider clinical application than just in long QT syndrome families. Although the syndrome appears rare—the worldwide registry of families has only about 350 listings—Keating suggests that this is just the tip of the iceberg.

And as Mason points out, ventricular fibrillation is very common, usually—but not always—being associated with the heart muscle damage caused by classical heart attacks. "So many times," Mason says, "the question arises, does this patient have long QT syndrome. And it's usually not satisfactorily resolved." The answer makes a difference, he explains, because treatment for the syndrome is drastically different from that for other conditions that predispose to ventricular fibrillation.

Keating and his colleagues found the linkage between long QT syndrome and the *ras* gene in a classic genetic analysis of a large family affected by the disease. It was not easy, but one thing that helped, says molecular geneticist Keating, was his close collaboration with Utah cardiologist Mike Vincent, who has been studying the syndrome for several years.



Out of phase. *The left electrocardiogram is normal; the one at right shows the long QT syndrome abnormality.*

First, the researchers had to confront the diagnosis problem. If they misclassified any of the family members, it would confound their efforts to identify a linkage. They decided to play it safe by excluding from the study family members whose QT intervals were too long to be obviously normal but too short to put them clearly in the affected group, says Keating.

Then the researchers began surveying the remaining 75 family members for linkages to specific gene markers. That proved to be a tedious task. The first 245 markers came up empty. But finally, one Saturday last fall at about 5 p.m., Keating hit pay dirt. When he was analyzing the data on the latest marker, for the Harvey *ras* gene, he realized that he had finally found a linkage—and a very tight one at that. The LOD score came out to be 16, which means that the odds in favor of the linkage are 10^{16} to 1. A LOD score of 3 is the minimal acceptable for showing linkage, Kidd says.

That does not prove that the Harvey *ras* gene is the actual site of the defect that causes long QT syndrome, but the defective gene has to be very close to the *ras* gene, which is located on chromosome 11. Still, Keating says, the Harvey *ras* gene is a very good candidate for the long QT gene. He has since found the linkage in an additional six families. And in no case does the marker fail to be inherited with the disease.

And there are physiological reasons, as well as the genetic ones, for thinking that the long QT defect might be in the *ras* gene. The protein encoded by the gene is one of the G proteins (so called because they bind guanosine nucleotides) that are very important for transmitting signals from the cell membrane to the interior. These include growth stimulatory signals that might play a key role in producing the uncontrolled growth of cancer cells. In addition, last year researchers from the Cetus Corporation and Baylor College of Medicine showed that *ras* proteins help control the passage of potassium ions through membrane channels. Defective control of ion movements might well lead to abnormal electrical properties in heart muscle and contribute to the dangerous arrhythmias that strike people with long QT syndrome.

Even if the Harvey *ras* gene does not prove to be *the* long QT syndrome gene, the marker is so tightly linked to the disease that it could still be useful in a diagnostic test. And if it is the gene, understanding the biochemical defect might lead to better drugs for controlling the arrhythmias. So either way, cancer biology and cardiology have joined in an unexpected linkage. ■ JEAN MARX