

APRIL 26, 2005

## Researchers Make Progress in Understanding Devastating Childhood Arrhythmia

Researchers who previously pinpointed the genetic cause of a rare but severe form of cardiac arrhythmia that affects children have now identified a second, closely related mutation that also causes the disease.

Their research shows that, like the better known form of Timothy syndrome (TS), the newly discovered atypical TS2 form is also caused by spontaneous genetic mutations that interfere with calcium channels. These channels are responsible for regulating the excitation and contraction of the heart. However, TS2 arises from mutations in a slightly different form of the gene, which is more heavily expressed in the heart and brain. As a result, children with TS2 show more severe arrhythmias and cognitive impairment, the researchers found.

---

"This is only one of what we believe is a spectrum of mutations in this gene that cause a variety of cardiac arrhythmias."

— **Mark T. Keating**

---

Mark T. Keating, a Howard Hughes Medical Institute investigator, and his colleagues at Children's Hospital Boston and Harvard Medical School published their findings April 26, 2005, in the early online edition of the *Proceedings of the National Academy of Sciences*. They collaborated with Katherine Timothy—for whom the syndrome is named—and her colleagues at the University of Utah.

Children with Timothy syndrome have a range of problems, including congenital heart disease, immune deficiency, intermittent low blood sugar, cognitive abnormalities, and autism. They also show a characteristic webbing, or syndactyly, of the hands and feet.

In earlier research reported in the October 1, 2004, issue of the journal *Cell*, Keating, Igor Splawski, Timothy, and their colleagues reported that a mutation in the gene for a particular calcium channel known as  $Ca_v1.2$  was the cause of Timothy syndrome. Calcium channels are pore-like proteins that

nestle in cell membranes and control the flow of calcium into and out of the cell. Calcium is one of the most important signaling molecules in the body, and perturbing calcium transport can cause a wide range of disorders.

The gene for the  $\text{Ca}_v1.2$  channel is expressed not only in heart muscle cells, but also in adult and fetal tissues of the brain, gastrointestinal system, lungs, immune system, smooth muscle, and testis.

During normal heart function, calcium channels must inactivate between heartbeats to enable cardiac cells to recover their electrical polarity. The researchers found in their earlier studies in patients with TS, however, that the mutated channel did not inactivate itself properly to block calcium flow at the appropriate time. This results in cardiac arrhythmias which can be life-threatening, said Keating.

“One thing that surprised us in the earlier study was that all the subjects had exactly the same mutation,” he said. “That is very unusual in any disorder, even one as unusual as TS. We found it difficult to believe that there would not be other mutations in this gene that would cause significant characteristic abnormalities.”

Thus, the researchers sought other patients who had similar characteristics as TS patients, but also showed distinct differences. The researchers found two such patients, a boy and a girl with the same kinds of cardiac arrhythmias. “These patients had very severe arrhythmias, even more severe than in TS,” said Keating. “In fact, this is probably the most severe arrhythmia syndrome that I'm aware of.”

Keating noted that the children with atypical TS2 showed more severe mental retardation, and neither had the characteristic syndactyly of TS.

The researchers' genetic analysis of the two children revealed a mutation closely related to that which causes TS. Children with TS have a mutation in a region of the calcium channel gene called exon 8A. However, the children with TS2 showed mutations in a region of the gene called exon 8, which produces a slightly different version of the channel protein than exon 8A.

The exon 8 region of the gene is expressed in many tissues when the calcium channel gene is copied to messenger RNA to produce the protein channel, but it is snipped apart and rearranged in a slightly different way than exon 8A.

“It was surprising that the TS2 mutations ended up being in the alternatively spliced form of exon 8, and in the same general location as the TS mutation,” said Keating. The researchers' analysis also revealed that the exon 8 form of the gene is the predominant form expressed in the heart and brain, which likely explains why TS2 was associated with such severe cardiac arrhythmias and mental retardation, said Keating.

“This study tells us that whether it's exon 8A or 8, mutations in either can cause a form of Timothy syndrome,” said Keating. “They're basically interchangeable, like replacing a car bumper with another one with only a

slight variation. However, the study did point to a couple of amino acids in the channel protein that we previously did not appreciate to be important for activating this channel, but they are clearly very important.

“And while this discovery of the new form of Timothy syndrome does help flesh out our understanding of this disorder, it is certainly not the end of the story,” he said. “This is only one of what we believe is a spectrum of mutations in this gene that cause a variety of cardiac arrhythmias. There are many more out there to identify, but we just haven't found the right patients yet.”

The new form of Timothy syndrome, like the first one, might be treatable by existing drugs that block calcium channels, said Keating. “The ideal drug would be a calcium channel blocker that prefers mutant channels, and so is selective for this particular altered channel,” he said. “There are some drugs that have such a potential, but given the rarity of this disorder, drug trials would be very difficult and expensive,” he said. Clinicians with such patients could choose to conduct their own trial of such drugs, he added.