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Researchers Pinpoint Cause of a Severe Cardiac Arrhythmia

Howard Hughes Medical Institute researchers have pinpointed the genetic cause of a devastating but rare childhood disorder, called Timothy syndrome, which underlies a form of severe cardiac arrhythmia.

The research shows that the syndrome results from spontaneous genetic mutations that interfere with calcium channels that regulate the excitation and contraction of the heart. In defining the precise nature of the molecular abnormality, however, the researchers have also identified a class of drugs that they hope will alleviate the arrhythmia.

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— **Mark T. Keating**

Timothy syndrome may also cause a form of autism in those affected, and there is the possibility that understanding more about the nature of these calcium channel defects could improve understanding of autism, which affects 200,000 to 400,000 children in the United States. 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.

Howard Hughes Medical Institute investigator Mark T. Keating and his colleagues reported in the October 1, 2004, issue of the journal *Cell*, that a pinpoint mutation in the Ca_v1.2 calcium channel was the sole cause of Timothy syndrome. Keating collaborated on the studies with researchers from Children's Hospital, Boston, Harvard Medical School, the University of Utah, the University of Pavia in Italy and the Boston University School of Medicine.

The scientific path that led to the identification of the cause of Timothy syndrome began in 1989 with the identification of a single child with the then nameless disorder by Katherine W. Timothy of the University of Utah. That child presented with cardiac arrhythmia and a webbing, or syndactyly, of the

hands and feet - characteristics of what has now come to be called Timothy syndrome in honor of Katherine Timothy's long and distinguished career as a scientist investigating the causes of cardiac arrhythmias, said Keating.

Timothy knew that Keating, who was at the University of Utah at the time, had a longstanding interest in arrhythmias, so she began collaborating with him to understand the disorder. Tragically, the first child died quickly, so the scientists were unable to explore the effects of the disease in that patient.

“At that point, we only knew we were dealing with a severe arrhythmia of a type we had not seen before,” said Keating. “But as we were able to treat these children more successfully, it became clear that they had other problems, including congenital heart disease, intermittent hypoglycemia, cognitive abnormalities and autism.”

The researchers then began the laborious process of attempting to trace the genetic cause of the disease. Familial studies revealed that it was not inherited, but caused by a mutation that occurred spontaneously. Eventually their analyses of a multitude of genes revealed that in all the patients, the disorder was caused by a change in a single DNA unit, or nucleotide, in the Ca_v1.2 calcium channel.

“This channel was known to be important for the excitation and contraction of the heart, but its role in other parts of the body were less clear,” said Keating.

Studies of the pattern of activity of the gene for the channel in humans and mice revealed that it was 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. In particular, said Keating, mouse studies showed the gene to be active in brain regions that were known to show abnormalities in autism.

Cell culture studies of the mutated version of the channel revealed that it did not react properly to block calcium flow at the appropriate time. This abnormality could explain the lethal cardiac arrhythmias in Timothy syndrome patients, said Keating.

Further genetic analyses of the particular mutation also showed why it occurred in the same place in all instances of the disease. That analysis revealed that the particular site of the mutation was a hotspot in the genome that was more prone to spontaneous mutation, said Keating.

“With these findings, we had a good handle on why this particular mutation would cause an arrhythmia and also how we could reduce the risk of arrhythmia in these children by blocking that channel,” said Keating. The investigators hope that calcium-channel-blocking medications may reduce arrhythmia and improve cognitive function in this disorder.

“While there are developmental abnormalities that we can't treat, it is very gratifying for us and for the families of these children that we may be able to

deal with some of their physiological abnormalities,” said Keating.

According to Keating, discovery of the genetic basis of Timothy syndrome has implications for understanding the function and importance of calcium channels in general. “Our findings showed that the mutated region is required for inactivation of the channel, which was not previously appreciated,” he said. “More broadly, this finding really highlights in a way that I haven't seen before the fundamental importance of calcium metabolism in development and physiology in humans.”

While Keating emphasized that autism remains a deeply mysterious and complex disorder, “it certainly is a reasonable hypothesis that abnormal calcium signaling could contribute to the disorder in some cases,” he said.