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RESEARCH NEWS

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Cause of Rare Genetic Disorder Points to Faulty Ion Channel

Researchers have tracked the cause of a rare disorder that produces muscle paralysis, heart arrhythmias and abnormal growth to mutations in a gene that encodes a pore-like protein that regulates the flow of potassium ions across cell membranes.

The discovery of the origin of the inherited disorder, called Andersen's syndrome, is the first known human ion channel disorder, or channelopathy, that has been linked to muscle abnormalities and developmental defects. Channelopathy is a term coined to describe diseases that are caused by defective ion channel proteins.

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> **— Louis J. Ptáček**

The finding offers a new perspective on how faulty ion channels can cause disease in humans. Ion channels are pore-like proteins that poke through cell membranes and control the flow of potassium, sodium and other ions into and out of cells. The number of diseases attributed to mutations in genes that encode ion channels is growing rapidly, according to HHMI investigator Louis J. Ptacek at the University of Utah.

In an article published in the May 18, 2001, issue of the journal *Cell,* a 22-member, international research team led by Ptacek and Utah researcher Ying-Hui Fu reported that mutations in the gene *KCNJ2* cause Andersen's syndrome. The mutations affect a potassium channel called Kir2.1—a member of a large family of potassium channels that help regulate the flow of potassium out of muscle cells. Potassium ion channels play a crucial role in generating the electrical activity required by certain types of cells. In muscle cells, for example, the concerted action of many ion channels generates the electrical action potentials that facilitate muscle contraction and recovery.

Andersen's syndrome, which was first described in 1971, is characterized by periodic muscle paralysis, cardiac arrhythmia and abnormal growth that includes short stature, and deformations of the spine, fingers, toes and face. "Even though this disorder was first described several decades ago, absolutely nothing was known about how it originated," said Ptacek. In fact, Ptacek said that the disease was not well defined clinically until co-author Rabi Tawil at the University of Rochester School of Medicine characterized the disease. "We've been collaborating for a dozen years, and it is such a rare disorder that it took us this long to collect the families that are reported in this paper," he said.

In beginning the search for the genetic cause of the syndrome, the researchers performed genetic linkage studies using a family that had a large number of members with Andersen's syndrome. The genetic analysis revealed that that affected members of the family shared a genetic abnormality in a region of human chromosome 17. A search of the human genome database at the National Center for Biotechnology Information revealed that this region contained genes for three known ion channels. Of those three ion channel genes, only the *KCNJ2* gene seemed likely to be responsible for Andersen's syndrome.

"When we focused on this particular potassium channel, we found mutations in the *KCNJ2* gene in all of the people in this family who had Andersen's syndrome," said Ptacek. "In contrast, we did not find mutations in *KCNJ2* in one hundred people we studied who did not have the syndrome."

Definitive experimental proof that mutations in the *KCNJ2* gene caused abnormal channel function came when the scientists inserted the mutated gene in frog eggs. "These studies showed that the mutations dramatically reduced the potassium current even when normal channels were present," he said.

Additional proof emerged when the researchers found eight mutations in *KCNJ2* in eight people who were unrelated to the large family that they had studied. Analyses of those mutations revealed that they altered critical segments of the Kir2.1 channel, including the pore region—through which potassium flows—and other regions that are highly conserved in mice and other organisms.

Despite pinning down Kir2.1's role in Andersen's syndrome, Ptacek cautions that the disease may have other causes. Andersen's syndrome may also arise from mutations in other Kir genes or in regulatory proteins, he says. Ptacek is leaving the door open for other possible causes of Andersen's syndrome because his group's studies showed that some of the cases of Andersen's showed only one or two of the disorder's three characteristic symptoms—muscle paralysis, cardiac arrhythmias and developmental abnormalities.

Nonetheless, the discovery that a channel disorder causes Andersen's syndrome offers important lessons for the human channelopathy field, Ptacek says. "When we cloned the first channelopathy gene ten years ago, we

predicted that ion channel disorders would be important in a number of pathologies, including cardiac dysrhythmias and epilepsy. Those predictions have been borne out, and this finding extends that relationship by linking channelopathies to a single disease that shows muscle and cardiac abnormalities.

"The second exciting implication is that this is the first example in which a human ion channel has been shown to cause both muscle and developmental abnormalities," said Ptacek. He noted, however, that a mouse mutation called *weaver* also links a potassium channel abnormality to seizures and abnormal brain development.

The finding that mutations in the *KCNJ2* gene cause Andersen's syndrome has prompted Ptacek and his colleagues to begin to use family studies and mouse models to trace how the mutation produces abnormal development. Through these studies, Ptacek and his colleagues hope to be able to probe whether the defective ion channel is responsible for other disorders.

"The Andersen's phenotype is evident in the head and middle facial structures, so one interesting possibility is that this gene has something to do with other common mid-face abnormalities, such as cleft lip and palate," said Ptacek. "Although this is speculative, it could be that *de novo* mutations in this gene might cause isolated cardiac defects that have until now remained unexplained. For example, such rare genetic defects might conceivably be one of the causes of sudden infant death syndrome," he said.