Periodic paralysis study reveals gene causing disorder

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Scientists have identified a gene underlying a disease that causes temporary paralysis of skeletal muscle. The finding, they say, illustrates how investigations of rare genetic diseases can drive insights into more common ones.

The finding is reported in the January 8, 2010 issue of the journal *Cell*.

The disease, known as thyrotoxic hypokalemic periodic paralysis, causes acute attacks of weakness in muscles that control movement. Symptoms range from difficulty grasping objects or rising from a lying position to incapacitating weakness of the body that prevents movement. The condition lasts from hours to days.

Scientists have known that TPP occurs when certain people with an overactive thyroid are exposed to environmental stresses, such as resting of the muscles after exercise, stress, or low potassium levels in blood after eating a large carbohydrate meal. Treatment of the hyperthyroidism controls the disorder.

However, scientists have been puzzled by the disease. Patients often don't have the clinical symptoms of hyperthyroidism, such as bulging eyes, loss of hair and increased sweating.

Symptoms of TPP are identical to those seen in a disease known as familial hypokalemic periodic paralysis, one of several rare, inherited periodic paralysis disorders resulting from mutations in a family of

genes coding for ion channels, which regulate electrical currents between cells. In response to the environmental factors that precipitate attacks in TPP patients, those who inherit hypoKPP develop the same form of temporary paralysis. In contrast to TPP patients, however, familial hypoKPP patients do not have hyperthyroidism.

In the 1990s, the senior author of the current study, Louis Ptacek, MD, a Howard Hughes Medical Institute investigator and Coleman Distinguished Professor of Neurology at UCSF, discovered a family of ion channel genes and their role in various forms of familial periodic paralyses. The genes produce proteins that couple to form ion channels, which control the flow of sodium, calcium, chloride, or potassium ions between cell membranes, producing electrical currents that initiate actions by cells. In people with familial periodic paralyses, altering electrical signaling prevents skeletal muscle cells from contracting normally in patients in the presence of environmental factors. One of these disorders results from mutations in a potassium channel called Kir2.1.

In the current study, the team, led by Devon P. Ryan, a graduate student in the Ptacek lab, and Magnus Dias da Silva, PhD, at the time a postdoctoral fellow in the Ptacek lab, set out to determine whether TPP -- which is 10 times more common than all of the inherited periodic paralyses put together -- was also, at basis, a genetic disease, sparked by the confluence of hyperthyroidism and environmental triggers.

They did so by examining candidate genes in DNA sequences donated by study subjects. Given the similarity of TPP's clinical symptoms to those of familial hypoKPP, they focused on genes encoding proteins that form ion channels in skeletal muscle. They looked specifically at those that had "promoters" - DNA sequences that regulate genes, turning them "on" and "off" -- that appeared to be regulated by thyroid hormone.

To their surprise, while sequencing Kir 2.2, a gene related to Kir2.1, as a candidate gene, they noted variations in its DNA sequence that were at odds with what was known about the gene. By altering their screening methods, they were able to highlight a sequence of DNA that revealed that it was, in fact, a novel gene, which they dubbed Kir2.6.

"Because of the remarkable similarity of these two genes, previous studies had failed to distinguish Kir2.2 and Kir2.6," says Ptacek. The differences that had been detected in previous screening studies had been thought to be polymorphisms, or normal variations within one gene.

The team went on to determine that Kir2.6 functions as an ion channel in human kidney cells in a culture dish. They also determined that the gene was mutated in one third of unrelated TPP patients involved in the initial study, and that some of the mutations alter properties that disturb muscle membrane excitability and lead to paralysis.

While TPP is found in people of all ethnicities, it is most common in Asians, followed by Latinos, Caucasians and people of African descent, and is far more common in men than women.

While he couldn't ethically justify doing the study, says Ptacek, he predicted that if all the unaffected people in families of TPP patients were treated with high doses of synthetic thyroid hormone, the process would unmask a familial pattern of TPP. (In practice, TPP would still be considered a sporadic condition in most cases, since high thyroid hormone levels usually don't affect more than 1 or 2 people from any family in whom a mutated gene is present.)

In any case, he says, the finding exemplifies how study of familial, or inherited, forms of a disease can sometimes lay the groundwork for understanding more common non-familial, or sporadic, forms.

"Identifying the role of specific genes in complex diseases such as the sporadic form of Alzheimer's disease, Parkinson's disease and autism has proven challenging," says Ptacek. "Here's a case where we were able to identify the gene underlying a sporadic disease, by first understanding the rare familial forms."

The finding also illustrates the power of one human genetics discovery to fuel another - and possibly another yet. In his 1991 paper (*Cell*. 1991 Nov 29;67:1021-7) describing the role of ion channel mutations in familial periodic paralysis, Ptacek predicted that mutations in ion channel genes of heart muscle cells could be the cause of electrical alterations in Long-QT syndrome, a rare congenital heart arrhythmia that can be fatal, and that mutations in ion channels in the brain could be the cause of genetic forms of epilepsy and migraine. The predictions turned out to be true.

In the current paper, he suggests that the reason thyrotoxic patients frequently develop cardiac arrhythmias may be because they have genetic mutations in ion channels of heart muscle cells that are regulated by thyroid hormone. Time, and research, he says, will tell.

Provided by University of California - San Francisco