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In the genome, an answer to a mysterious movement disorder

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Children with a rather mysterious movement disorder can have hundreds of attacks every day in which they inexplicably make sudden movements or sudden changes in the speed of their movements. New evidence reported in an early online publication from the January 2012 inaugural issue of *Cell Reports*, the first open-access journal of Cell Press, provides an answer for them. Contrary to expectations, the trouble stems from a defective version of a little-known gene that is important for communication from one neuron to the next.

The findings might lead to new strategies for treating a variety of movement disorders, the researchers say.

"People with this disorder look and feel normal," said Louis Ptáček of the University of California, San Francisco. "They might be sitting there, get up to go to the kitchen, and start writhing for five or ten seconds."

Any time they transition from one thing to another—sitting to standing, walking to running—they might suffer an attack. "Sometimes they will experience an attack even if they think about moving," he added. "It's always been completely fascinating to me."

Ptáček has a personal connection to the condition, known as paroxysmal kinesigenic dyskinesia (PKD): he made his first diagnosis as a medical student. He recalls that people suspected that first patient's symptoms were all in his head. "They thought he was crazy," Ptáček said.

PKD can also be associated with brain tumors or other structural problems in the brain, he explained, but those with the inherited form of the disease suffer the same abnormalities in movement even as their brains appear perfectly normal. When Ptáček read about the condition in the library late at night those many years ago, he knew he had found a diagnosis. He got that first patient the medication he needed, essentially curing him. It was part of what made Ptáček decide to continue on in neurology, and he never forgot it.

In the new study, Ptáček's team sequenced the genomes of six people from families with well-defined PKD, finding that nearly all of those individuals carried one mutation or another in the gene PRRT2 (proline-rich transmembrane protein 2). Similar mutations in that gene also turned up in many individuals from a second group of families with the disorder.

The disease apparently results when people make half as much PRRT2 protein in their axons, the "cables" that send signals from one neuron on to the next. Indeed, PRRT2 is known to interact with another protein that is also important for neural communication. With too little PRRT2, neurons become hyperexcitable, leading to the abnormal movements recognized as PKD.

PKD responds to treatment with drugs that target ion channels with links to epilepsy. As a result, scientists had suspected that PKD was a "channelopathy." The new findings refute that notion, but "it's all connected," Ptáček says. The defects that his team has uncovered in PRRT2 likely do influence the function of those channels that are so critical for the delivery of nerve messages.

New treatments aren't needed for PKD, Ptáček says, noting that the condition can be well controlled with existing drugs and often goes away with age for reasons that are as mysterious as its origins once were.

Nevertheless, he adds, these new biological insights might lead to drugs for other neurological disorders, such as Huntington's or Parkinson's disease, that aren't so easily treated.

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