Gene hunters find cause of rare movement disorder

December 16 2011

(Medical Xpress) -- After a challenging two-decade hunt, scientists have pinpointed the gene responsible for a rare disease that causes seizures in infancy and sudden, uncontrollable movements in adolescence and early adulthood.

The findings, published December 15, 2011, in *Cell Reports*, could pave the way to new therapies for more common forms of seizures and dyskinesias, or abnormal movements, the researchers say.

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"There are a lot of dyskinesias for which we don't have good treatments and they are a big problem, such as in Huntington's disease and Parkinson's disease," says Howard Hughes Medical Institute investigator Louis Ptáček, professor of neurology at the University of California San Francisco, who led the new study. "If we can understand the pathways in the brain that regulate dyskinesia, then it's my hope that we’ll be able to target better drugs."

Ptáček's interest in dyskinesia dates to 1985 when, as a third-year medical student at the University of Wisconsin, Madison, he met a 16-year-old boy who was having bizarre spasms. Every time the boy switched from one movement to another, like from sitting to standing or walking to running, his limbs would inexplicably flail or twist, as if

performing an odd dance."Nobody knew what the heck was going on," Ptáček recalls.

One night around 2 a.m., after scouring the library's medical databases, Ptáček figured out the diagnosis: paroxysmal kinesigenic dyskinesia, or PKD, which had been reported in just a handful of other cases. He knew from those papers that PKD could be treated with a low dose of a common anticonvulsant medication. When doctors gave the boy the drug, carbamazepine, he quickly improved.

"He had been having attacks hundreds of times per day. A few weeks after treatment, he was essentially having zero attacks," Ptáček says. "It felt so satisfying to have gotten it right."

Ptáček has been studying rare movement disorders ever since. In the late 1990s, PKD's name changed to PKD/IC when researchers realized that most individuals with PKD also have seizures in the first two years of life, known as infantile convulsions. Around the same time, Ptáček's team and others began identifying families in which several members had PKD/IC, pointing to genetic origins for the disorder.

Several groups, including Ptáček's, raced to find the PKD/IC gene. By comparing genetic markers among family members, the researchers independently discovered that the hotspot sat somewhere in a 180-gene segment of chromosome 16. But narrowing down the precise location of the genetic glitch turned out to be extremely difficult.

People carry two copies of each chromosome—one from the father, the other from mother—which cross over each other at random locations during cell division and swap genetic material. Genetic markers that are close together on a parental chromosome are more likely to be swapped together, or linked. By looking at the frequency of linked markers in offspring with and without disease, researchers can usually work

backwards to figure out the precise location of a disease-causing gene.

That so-called linkage analysis wasn't possible for the PKD/IC gene, however, because it was located near the centromere, or the spot where the two parental chromosomes meet when they are paired in preparation for cell division. "It's a real problem area, because there's not much recombination there. So it limits our ability to narrow the region," Ptáček says.

In the new study, the competing research teams came together to finally pin down the genetic culprit. Ptáček and collaborators from some two dozen institutions in 10 countries combined their samples and performed whole-genome sequencing—in which all 6 billion DNA letters in an individual's cells are "read" and compared to a reference genome. The teams analyzed the DNA of one member of each of the six most well-characterized families with PKD/IC. All six carried mutations in a gene called PRRT2. In a later analysis, the researchers found the same PRRT2 mutations in 24 of the 25 known PKD/IC families.

The scientists also investigated the biological function of PRRT2. Looking at neuronal cell lines from the rat brain, the researchers found that the PRRT2 protein interacts with a protein called SNAP25, which is important for healthy function of the synapse, or junction between neurons.

That result suggested to the researtchers that the protein-protein interaction is disturbed in people with PDK/IC, leading to improper signaling between brain cells. "We have not proven that yet, but we think it makes good sense," Ptáček says. He plans to test out the theory by engineering mice that lack PRRT2.

Those animals could also help researchers investigate one of the biggest mysteries about PKD/IC, which is that for some individuals, symptoms

completely disappear by middle age. This could be because of epigenetic changes, in which chemical modifications to DNA alter the way genes are expressed. Epigenetic marks—which can be controlled by a host of environmental factors, such as diet, stress, and toxins—are just beginning to be mapped in laboratory animals.

"Epigenetics is partly random, partly environmental, and that would fit with the pattern of improvement in patients with PKD/IC," Ptáček says. "We'd absolutely like to explore this in the mice."

Provided by Howard Hughes Medical Institute