

JUNE 05, 1998

Gene Discovery Provides Insights Into Epilepsy

A faulty conduit into nerve cells that causes them to fire uncontrollably appears to trigger the brief seizures present in some forms of absence, or petit mal, epilepsy, say investigators from the Howard Hughes Medical Institute at the University of Iowa College of Medicine and their colleagues at The Jackson Laboratory.

In research performed on the mutant "stargazer" strain of mice that serves as a model for absence epilepsy, HHMI investigator Kevin P. Campbell and collaborators Verity A. Letts and Wayne N. Frankel of The Jackson Laboratory have traced the seizures to a mutation in a gene called *Cacng2*, which codes for part of the "gate" that controls the flow of calcium into brain cells. Calcium is critical to regulating the release of neurotransmitters, the chemicals that brain cells use to communicate.

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— **Kevin P. Campbell**

The functional gates, called calcium channels, are composed of four protein subunits, and the newly discovered stargazer mouse gene encodes the fourth or gamma subunit of the channel. The stargazer mutation results in the nearly complete absence of the gamma subunit protein, named stargazin, thereby altering the ability of the assembled calcium channel to properly control the flow of calcium into a nerve cell, explains Campbell.

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open," Campbell said. "But in the mutant mice lacking stargazin, all of the gates would be able to open. We believe that the increased flow of calcium that results causes an abnormal firing of brain cells." Stargazer mice get their name from the way in which the animals toss their heads during the 100 or more seizures, each lasting about 6 seconds, they experience each hour.

Epilepsy is a neurological disorder that occurs in about 20 forms and affects approximately one percent of the U.S. population. Absence, or petit mal, epilepsy occurs primarily in children and its seizures are characterized by brief lapses in consciousness during which a person appears to be staring into space. Half of all forms of epilepsy are thought to have a genetic basis, which is at present poorly understood.

The discovery of the novel gene, reported in the August 1998 edition of the journal *Nature Genetics*, shows that calcium channels are important in initiating epilepsy. This research will make it possible to discern more about role of calcium channels in the brain, Campbell said. It also suggests new therapeutic possibilities, but first it will be necessary to find a comparable gene in humans. It then may become possible to develop drugs that block calcium channels at low doses and thereby retard the electrical disruption characteristic of absence epilepsy. Campbell also said that it is "not farfetched to foresee gene therapy" in which surgeons replace the defective brain-specific gene and restore the normal function of its protein product.

Campbell first purified the calcium channel's four main subunits in muscle cells in 1988. Two years later, his lab reported the structure of the gamma subunit. "The gene we found initially was for the gamma subunit present in skeletal muscle calcium channels and it was not expressed in brain tissue," he said. When Frankel and Letts identified the stargazer mouse gene and saw that it resembled the gamma subunit gene Campbell had described, they contacted the Hughes investigator. Together, the two laboratories characterized the mutation and its effects on calcium channel function.