Epilepsy genes may cancel each other

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Inheriting two genetic mutations that can individually cause epilepsy might actually be "seizure-protective," said Baylor College of Medicine researchers in a report that appears online today in the journal *Nature Neuroscience*.

"In the genetics of the brain, two wrongs can make a right," said Dr. Jeffrey L. Noebels, professor of neurology, neuroscience and molecular and human genetics at BCM. "We believe these findings have great significance to clinicians as we move toward relying upon genes to predict neurological disease."

In addition, the finding might point the way to new ways of treating epilepsy using gene-directed therapy.

"If you have a potassium channel defect, then a drug blocking certain calcium channels might also benefit you," said Noebels.

Noebels and his colleagues, who included first author Dr. Ed Glasscock, a post-doctoral researcher at BCM, tested this hypothesis by breeding mice with two defective genes that govern ion channels, tiny pores in cells that allow molecules such as potassium and calcium to flow in and out.

The genes were known to cause epilepsy when inherited singly within families. They have also been found in a large-scale screen of people with non-familial seizure disorders being performed in collaboration with the Baylor Human Genome Sequencing Center.

One is a mutation in the Kcna1 gene involved in the channel that allows potassium to flow in and out of the cell. It causes severe seizures affecting the brain's temporal lobe, an area of the brain involved in processing sight, sound, speech and forming memories. It can also cause sudden death in young mice.

The other mutation is in a calcium channel gene (Cacna1a) that causes a specific type of seizure associated with absence epilepsy. When people suffer these seizures, they may appear to be staring into space and do not exhibit the jerking or movements generally associated with epilepsy.

When both types of mutation occurred in the same young mouse, that animal had dramatically reduced seizures and did not suffer the sudden death associated with the potassium channel problem.

Noebels, who is also director of the Developmental Neurogenetics Laboratory funded by the National Institutes of Health and Blue Bird Circle Foundation, said, "Rather than screening for 'bad' genes one at a time, it may be essential to create a complete profile of many or even all genes in order to accurately assess the true genetic risk of any single defect in many common disorders such as epilepsy. Fortunately, this amount of background information will soon become routinely obtainable in individual patients thanks to rapid technological progress in the field of neurogenomics."

Many different genes can lead to seizure disorders. In some cases, they encode ion channels that adjust the way neurons fire. Previous work indicated that combinations of such genes could make epilepsy worse. However, certain combinations may actually prevent the abnormal patterns of epilepsy, acting as "circuit breakers," said Noebels.

Source: Baylor College of Medicine