MedicalXpress

Scientists identify genetic cause for a type of childhood epilepsy

May 29 2008

Imagine “blanking out” of consciousness up to 200 times daily while you’re learning in a classroom, playing baseball, taking ballet lessons or riding a bike. This is a common occurrence in the life of a child with childhood absence epilepsy (CAE). The condition is associated with frequent “absent” seizures where the patient’s consciousness is impaired leaving the child staring blankly ahead not aware or responsive for up to 10 seconds at a time.

UCLA/VA scientists for the first time have pinpointed the mutated gene responsible for development of CAE, which may also help explain why the disease mysteriously disappears in adulthood. Published in the May 29th online edition of the *American Journal of Human Genetics*, the finding may provide insight into developing treatments and cures for this and other forms of epilepsy.

“Childhood absence epilepsy strikes at a critical developmental age that can result in scholastic and learning disabilities as well as problems in social adaptation and family interactions,” said Dr. Antonio V. Delgado-Escueta, study author and professor-in-residence of neurology, David Geffen School of Medicine at UCLA and the Epilepsy Genetics/Genomics Laboratory, Epilepsy Center at the VA-Greater Los Angeles Healthcare System in West Los Angeles.

An inherited disorder, CAE accounts for 10 to 12 percent of epilepsy in children under age 16.

Several medications, including Valproate, Ethosuximide and Clonazepam are effective in controlling the majority of absence seizures.

UCLA/VA research scientist Dr. Miyabi Tanaka studied the DNA of 48 patients with CAE and discovered that four patients had a genetic mutation occurring in a receptor called GABAR which binds to a neurotransmitter of the brain called GABA that inhibits the excitation of nerve cells in child and adult brains. When this regulation is lost or reduced, seizures develop.

“We identified this genetic mutation in eight percent of study patients with CAE, which is significant,” said Richard W. Olsen, Ph.D., study author and professor, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA.

Scientists also found that the mutated gene affected several generations of families. Study authors noted that these variations were absent in the DNA of 630 healthy people without CAE.

Researchers located the genetic mutation in a subunit gene of GABAR called GABRB3. Genes dictate how to make over 100,000 proteins in the body that are responsible for all functions from digestion to fighting infections to movement.

Surprisingly, scientists found that the problem didn’t lie in the main body of the subunit gene, but mainly in a signal peptide that guides the genetic information, like an escort, to the factory inside the cell that manufactures the proteins ordered by the genes.

The subunit gene, GABRB3, has an alternative signal peptide called exon 1a, which is richly expressed in the fetus and developing brain, but as the child matures and becomes an adult, the expression of exon 1a is

reduced.

“This may help explain why CAE disappears during adolescence and adulthood since exon 1a is not expressed at an adult age in the critical region responsible for absence seizures,” said Tanaka, study author and research scientist, UCLA Department of Molecular and Medical Pharmacology and the Epilepsy Genetics/Genomics Laboratory, Epilepsy Center at the VA- Greater Los Angeles Healthcare System.

The team found that the signal peptide with the mutation caused the developing protein to be excessively modified by sugars, which led to a reduced number of GABARS on the surface of the nerve cell. This caused a reduction in the total GABA currents that help regulate the nerve cells, leading to the subsequent “absent” seizures found in CAE.

The scientists note that this may lead to radical new treatment approaches for epilepsy by possibly suppressing the genetic expression of the mutated signal peptide.

According to the researchers, the next step will involve studying a larger population of children with CAE that have no family history of epilepsy in order to determine how common these genetic mutations are in the patient population and general public.

Source: University of California - Los Angeles