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Single gene mutation responsible for 'catastrophic epilepsy'

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Catastrophic epilepsy - characterized by severe muscle spasms, persistent seizures, mental retardation and sometimes autism - results from a mutation in a single gene, said Baylor College of Medicine researchers in a report that appears in the current issue of the *Journal of Neuroscience*.

The BCM department of neurology team replicated the defect in mice, developing a mouse model of the disease that could help researchers figure out effective treatments for and new approaches to curing the disease, said Dr. Jeffrey Noebels, professor of neurology, neuroscience and molecular and human genetics at BCM and director of the Blue Bird Circle Developmental Neurogenetics Laboratory at BCM, where the research was performed.

"While many genes underlying various forms of childhood epilepsy have been identified in the past decade, most cause a disorder of 'pure' seizures," said Noebels. Why some children have a more complicated set of disorders beginning with major motor spasms in infancy followed by cognitive dysfunction and developmental disorders such as autism remained a mystery until the discovery by the BCM team that a mutation in only a single gene explains all four features of catastrophic epilepsy.

A gene known as Aristaless-related homeobox or ARX has a specific mutation called a triplet repeat, which means that a particular genetic (in this case, GCG) is repeated many times in the gene. When the researchers duplicated this particular mutation in specially bred mice,

the animals had motor spasm similar to those seen in human infants. Recordings of their brain waves showed that they had several kinds of seizes, included absence epilepsy and general convulsion. They also had learning disabilities and were four times more likely to avoid contact with other mice than their normal counterparts. This behavior is similar to that seen in children with autism or similar disorders in the same spectrum.

"The new model is an essential tool to find a cure for the disorder," said Noebels.

"Mutation of the ARX gene was previously known to affect interneurons, a class of cells that inhibit electrical activity in the brain," said Dr. Maureen Price, the report's lead author and an instructor in neurology at BCM.

When researchers evaluated the brains of the adult mice with the mutated gene, they found that a special class of interneurons had never developed in specific brain regions.

"Further study will allow use to pinpoint which brain region is liked to the autistic-like behavior," said Price.

Two members of the research team - Dr. James Frost, professor of neurology at BCM, who developed the concept of the special mouse, and Dr. Richard Hrachovy, also a professor of neurology at BCM - are pioneers in the study of human infantile spasms.

"At present there is no proven cure to offer children with this specific epilepsy", said Noebels. "We now have new clues into the mechanism and have already initiated studies with a new class of drugs not previously explored for this disorder." The new drug testing is supported by the private foundation People Against Childhood Epilepsy.

More information: www.jneurosci.org/

Source: Baylor College of Medicine (news : web)