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Findings in epilepsy gene in animals may guide treatment directions for infants

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Researchers studying a difficult-to-treat form of childhood epilepsy called infantile spasms have developed a line of mice that experiences seizures with features closely resembling those occurring in patients with infantile seizures. These genetically engineered mice provide a new opportunity for scientists to test treatments that may benefit children.

Approximately one out of every 100 infants has a seizure. Many of them go on to have epilepsy—characterized by recurrent seizures. One obstacle to developing better therapies for children has been the lack of a good animal model," said study leader Jeffrey A. Golden, M.D., pathologist-in-chief at The Children's Hospital of Philadelphia.

Golden's team described a new mouse model for infantile spasms on May 12 in an online study in the journal *Brain*.

Infantile spasms are a type of seizure that occurs in an estimated 1 in 2000 to 1 in 6000 babies, with onset between ages three months and one year. During the seizures, infants have jerking movements and abnormal brain waves (seen on EEGs). "Children with infantile spasms often have a poor developmental outcome," said Golden. "Despite current treatment, many children with infantile spasms go on to develop lifelong epilepsy and varying degrees of mental retardation."

Finding a treatment for infantile spasms is crucial. "If we could better treat the infantile spasms, it is very possible some of these later problems could be prevented," added Golden.

Neurologists previously knew that mutations in Arx, the X-linked aristaless-related homeobox gene, were associated with abnormal brain development, neurocognitive problems, and with childhood neurological conditions involving seizures and spasms.

Golden's team developed genetically engineered mice in which the Arx gene was removed from interneurons, a type of brain cell that inhibits electrical firing in brain circuits. Removing the gene's role appears to have resulted in overexcited brain cells and seizures in the mice. The seizures resembled human infantile spasms. Equally exciting to the researchers, these mice had another brain wave abnormality similar to that found in children with infantile spasms--an abnormal background EEG.

"This is the first genetic model of a developmental epilepsy, and even more importantly, it was generated by mutating the same gene that can be found mutated in humans with infantile spasms," said Golden. In an unexpected development, the researchers found that half of the female mice carrying the mutation also developed seizures. Because the mutation occurs on the X chromosome, it was expected that male mice would have seizures, which was true, and that all the females would be unaffected carriers, which was not the case.

This discovery prompted the researchers to take a closer look at human families with an infantile spasms patient. They found that the patients' mothers (14 women) had experienced normal development. But of the patients' nine other relatives—sisters, aunts and a cousin—six had neurological problems, including four with epilepsy. The neurological problems included varying degrees of mental retardation or other learning disabilities. These findings, said Golden, will immediately change the evaluation and testing of women with mental retardation and epilepsy, particularly in families with other affected individuals.

This new finding will also assist genetic counselors in advising parents who already have a child with an Arx mutation and are contemplating having another child.

Going forward, Golden said, this new animal model provides an important tool: an opportunity to begin testing drugs in the mice to identify potential treatments for children. "We can screen existing drugs to see if they are effective against this type of epilepsy," said Golden, adding that understanding the biological mechanism by which infantile spasms develop may also lead to more specific treatments.

More information: Marsh et al, "Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females," *Brain*, published online May 12, 2009.

Source: Children's Hospital of Philadelphia (news : web)