Severe Epilepsy Linked to Gene Mutation

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University of Utah medical researchers have identified a gene with mutations that cause febrile seizures and contribute to a severe form of epilepsy known as Dravet syndrome in some of the most vulnerable patients - infants 6 months and younger.

The discovery means some infants with Dravet syndrome, a type of epilepsy that often begins with fever-induced (febrile) seizures, would benefit from genetic testing to identify whether they have a mutation in the SCN9A gene, which the researchers found causes seizures by affecting sodium channels in the brain. Infants who have the mutation might well be better off not receiving sodium channel blockers, some of the most common anticonvulsant drugs, because they could make a sodium channel-induced seizure worse, the researchers report in the Sept. 11 edition of PLoS Genetics.

The study was a collaboration of researchers from several departments in the U of U School of Medicine and College of Pharmacy, as well as national and international colleagues. First author Nanda A. Singh, Ph.D., a researcher in the University's Eccles Institute of Human Genetics, said the SCN9A mutation is the fifth gene discovered to cause febrile seizures and, before now, was not suspected in seizures or epilepsy.

"This new gene gives us a much needed novel target for developing more effective drugs to treat those children with debilitating seizures," Singh said.

Groundwork for the study was laid by two U of U School of Medicine physicians, Joel Thompson, M.D., and Francis M. Filloux, M.D., professor of pediatrics and neurology, who in the 1990s met a patient whose family had a history of the febrile seizures. After studying the DNA of 46 members of the extended family, researchers at the U of U identified an area on chromosome 2 as a likely place to find the gene mutation associated with the family's seizures. Using that data, they pinpointed the SCN9A mutation as the seizure-causing gene in the family.

To confirm SCN9A's role, the researchers used technology pioneered by the University of Utah's 2007 Nobel laureate in medicine, Mario R. Capecchi, Ph.D., to create mouse models with the gene mutation. The researchers tested the animals for seizures and found the mice with the SCN9A mutation had significantly lower thresholds for developing seizures than mice without the mutation.

"The mouse data confirmed that the SCN9A mutation is causing the febrile seizure disease in this family," Singh said. The researchers further showed the SCN9A seizure-causing role in approximately 5 percent of 92 unrelated febrile syndrome patients.

The SCN9A gene provides instructions for the body to make sodium channels, which act as conduits and gates to let sodium ions into cells and help conduct electricity for neurons to communicate. But when the gene mutates, it can cause seizures by altering sodium channel function in the brain and preventing neurons from firing properly. Mutations in four other genes had been shown in other studies to cause febrile seizures, and one sodium channel gene in particular, SCN1A, has been found in about half of patients with Dravet syndrome. In DNA collected by Belgium researchers, headed by Peter De Jonghe, Singh and her colleagues found additional SCN9A mutations in about 9 percent of Dravet syndrome patients, while 6 percent had both SCN9A and SCN1A gene mutations.

For infants and children who suffer febrile seizures or have Dravet syndrome, the study offers hope where there often is little to be found, according to Kris Hansen, president of the Epilepsy Association of Utah and mother to a child with Dravet syndrome. "Dravet is such a hard syndrome to control, and any research that gives us reasons for what is happening with our children and hope for the future is absolutely amazing," Hansen said.

"This medical breakthrough will bring prospects of relief to families dealing with the ongoing challenges of Dravet syndrome and febrile seizures."

Febrile seizures are the most common form of early childhood seizures and strike up to 1 in 20 children in North America. Most infants outgrow them, but in some cases the seizures continue into adulthood. Epilepsy is a disorder of many types of seizures that affects nearly 3 million people in the United States, with approximately 200,000 new cases reported each year. Patients with Dravet syndrome can have febrile and other seizures severe enough to stunt mental and social development.

Because half of Dravet syndrome patients have SCN1A mutations, these patients are tested for that form of the disorder for the mutation. In those who don't have the SCN1A mutation, Singh suggests a second test could determine if they have the SCN9A mutation. In patients who have one or both of the genes, treatment could be modified to exclude sodium channel-blocking drugs.

Provided by University of Utah (news : web)