International team discovers gene associated with epilepsy

November 18 2008

A University of Iowa-led international research team has found a new gene associated with the brain disorder epilepsy. While the PRICKLE1 gene mutation was specific to a rare form of epilepsy, the study results could help lead to new ideas for overall epilepsy treatment.

The findings, which involved nearly two dozen institutions from six different countries, appear in the Nov. 7 issue of the *American Journal of Human Genetics*.

In epilepsy, nerve cells in the brain signal abnormally and cause repeated seizures that can include strange sensations, severe muscle spasms and loss of consciousness. The seizures may not have lasting effects but can affect activities, such as limiting a person's ability to drive. Most seizures do not cause brain damage but some types of epilepsy lead to physical disabilities and cognitive problems. Medications can control symptoms, but there is no cure.

"The study results were surprising not only because the PRICKLE1 gene had never been associated with epilepsy but also because the gene was not associated with any other human disease," said the study's lead author Alex Bassuk, M.D., Ph.D., assistant professor of pediatrics at the University of Iowa Carver College of Medicine and a pediatric neurologist with University of Iowa Children's Hospital.

The nine families involved in the study all lived in the Middle East and came from one of three family lines. Of the 47 individuals in the three

family lines, 23 had a form of progressive myoclonus epilepsy accompanied by ataxia -- a condition that causes imbalance.

One family line has been extensively described by Hatem El-Shanti, M.D., a University of Iowa adjunct professor of pediatrics who now leads genetics research for the country of Qatar. The two other family lines had been researched by Sam Berkovic, M.D., at the University of Melbourne in Australia.

"By sharing and analyzing data sets, we realized there was a common mutation in the PRICKLE1 gene in the family members with this form of epilepsy," Bassuk said.

To verify that the mutation might be related to the epilepsy, the team needed to test it in an animal model. This next step to find a suitable animal model involved a surprising coincidence: Bassuk, who had only recently joined the UI, realized through online research that the PRICKLE1 gene in zebrafish had been previously identified by another University of Iowa researcher, Diane Slusarki, Ph.D., associate professor of biology in the UI College of Liberal Arts and Sciences.

"I walked across the river to Diane's side of campus, and we designed an experiment to test the human mutation in the zebrafish," Bassuk said. It was 'Iowa luck.'"

Slusarki and Bassuk's collaboration revealed that the mutated PRICKLE1 gene does not behave normally in zebrafish. Bassuk noted that collaboration, whether on-campus or international, was essential to the success of the research study.

"We never could have done, or could continue to do this type of research, with just one person thinking about it," he said. "From the clinicians who found and took histories on the study participants, to

antibody testing at Stanford University to DNA shared from colleagues in Japan, the study required a lot of collaboration and coordination. And of course, we greatly appreciated the participation of the Mideastern families."

Bassuk, and colleagues are now developing other animal models to investigate how PRICKLE1 gene is involved in epilepsy, and are investigating whether PRICKLE1 mutations are involved in the general population of patients with epilepsy. With that information, there is potential to develop new drugs for people with different forms of epilepsy in the general population, as well as for the study participants with the disease.

Source: University of Iowa