

# Potassium channel gene modifies risk for epilepsy

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Vanderbilt University researchers have identified a new gene that can influence a person's risk for developing epilepsy. The findings, reported in the March 29 *Proceedings of the National Academy of Sciences*, could improve molecular diagnostic tools and point to novel therapeutic targets for epilepsy.

The gene, *KCNV2*, codes for a unique type of potassium channel, a [protein](#) that participates in the electrical activity of [nerve cells](#). Disturbed electrical activity in the [brain](#) – and resulting seizures – are hallmarks of epilepsy, a group of disorders that affects about 1 percent of the world's population.

A number of genetic mutations that cause inherited epilepsies have been identified. But the clinical severity of inherited epilepsies varies widely – from mild childhood seizures that resolve with age to severe lifelong seizures – even in individuals who have the same single-gene mutation, said Jennifer Kearney, Ph.D., assistant professor of Medicine in the Division of Genetic Medicine.

The range of clinical severity "tells us that there are other factors that contribute," she said. "We think that susceptibility and resistance genes that are inherited in addition to the primary mutation are probably a major factor."

Identifying susceptibility and resistance genes may suggest new targets for drugs that fine-tune neuronal excitability, rather than dampening it

completely as many current antiepileptic drugs do, Kearney said.

The investigators began to look for these types of "modifier" genes after they made a curious observation in a mouse model of epilepsy – that epilepsy severity depended on the genetic background strain of the mice.

They were studying mice with an epilepsy-causing gene mutation in a sodium channel, a protein that is important for neuronal excitability. The mice had spontaneous, progressive seizures and a reduced lifespan. But when the researchers "moved" the gene mutation into mice with a different genetic background (using breeding strategies), the epilepsy became less severe: the mice developed seizures later and had improved survival.

Using genetic strategies, the investigators zeroed in on two chromosome regions that influenced the difference in epilepsy severity in the two mouse strains. In one of these regions, the mouse *Kcnc2* gene (the mouse equivalent of the human *KCNV2* gene) appeared to be the strongest candidate gene, based on its potential for altering electrical activity in neurons.

The current report demonstrates that increased expression of the mouse *Kcnc2* gene – not changes in its coding sequence – is associated with more severe epilepsy in the susceptible mouse strain. Increasing *Kcnc2* expression in the resistant mouse strain caused these mice to develop more severe symptoms, supporting the gene's contribution as an epilepsy modifier.

The investigators then screened 209 pediatric epilepsy patients for variations in *KCNV2* and found two different variations in two unrelated patients.

Colleagues in the laboratory of Alfred George Jr., M.D., director of the

Division of Genetic Medicine, conducted electrophysiology studies in cells to examine how the two variations affected the function of the potassium channel. They found that both variations suppressed a type of potassium current that normally dampens excitability in neurons.

"The mutations make a neuron more excitable, so you could have longer periods of excitation and also repetitive excitation (that leads to seizures)," Kearney said.

The team plans to screen additional patients with epilepsy to assess the incidence of variations in KCNV2. They are also collaborating with Dave Weaver, Ph.D., director of the Vanderbilt High-Throughput Screening Facility, to find compounds that target the potassium channel and may be useful therapeutics for epilepsy.

Kearney said that understanding how genes such as KCNV2 modify the clinical severity of epilepsy is important for molecular diagnostics and genetic counseling. Patients may currently learn that they have an epilepsy-causing gene mutation, but because clinical severity varies, their prognosis may not be clear.

"We need to understand how all of these different gene interactions impact the final clinical disorder to improve risk assessment and disease management in [epilepsy](#)," Kearney said.

Provided by Vanderbilt University Medical Center

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