FEATURED ARTICLES

Complements will get you everywhere*Neuroscience Gateway* (December 2007) | doi:10.1038/aba1798**Epilepsy-associated mutations with opposing cellular effects cancel each other out.**

Two wrongs can sometimes make a right. Generally, one disease-associated mutation is bad, and two are worse, increasing disease risk or severity. However, what if the mutations have opposing effects on cellular function? Glasscock *et al.* report reductions in seizure number and severity in mice with two loss-of-function mutations associated with epilepsy in a recent article in *Nature Neuroscience*.

There are multiple types of epileptic seizure, including tonic-clonic, which induces loss of consciousness as well as muscle rigidity and contraction, and absence, which induces brief periods of behavioral arrest. Tonic-clonic seizures last for several minutes and can occur multiple times a day, whereas absence seizures last for several seconds and can occur many times per hour.

Multiple ion channel mutations are associated with epilepsy. For example, a missense mutation in [KCNJ1](#), which encodes a subunit of a voltage-gated potassium channel, is associated with tonic-clonic seizures and temporal lobe epilepsy, and a partial loss-of-function mutation of [CACNA1A](#), which encodes a subunit of the P/Q-type Ca^{2+} channel, is associated with childhood spike-wave absence epilepsy. Potassium channels containing the *Kcna1*-encoded Kv1.1 subunit are delayed rectifiers that help neurons repolarize after action potentials, so loss of *Kcna1* function should increase neural excitability. In contrast, P/Q-type Ca^{2+} channels are important in neurotransmitter release, so deficits in *Cacna1a* should impair synaptic transmission. The authors generated mice with mutations in both *Kcna1* and *Cacna1a* to see if their effects would cancel each other out.

Kcna1 knockout mice showed tonic-clonic seizures, and many died within a few weeks of birth. Only 26% of *Kcna1* knockout mice survived to 10 weeks of age. However, 74% of *Kcna1* knockout mice carrying one (*Kcna1*^{-/-}; *Cacna1a*^{tg/+}) and 87% of *Kcna1* knockout mice carrying two (*Kcna1*^{-/-}; *Cacna1a*^{tg/tg}) alleles of a naturally occurring partial loss-of-function mutation in *Cacna1a* survived to ten weeks of age, suggesting that the *Cacna1a* mutation reduced the severity of the *Kcna1* mutation phenotype.

Relative to single mutants, double-mutant (*Kcna1*^{-/-}; *Cacna1a*^{tg/tg}) mice showed reduced seizure activity. Double-mutant mice showed no spike-wave seizures and a 60% reduction in tonic-clonic seizures relative to *Kcna1* knockout mice. The severity of tonic-clonic seizures was milder in *Kcna1*^{-/-}; *Cacna1a*^{tg/tg} than in *Kcna1*^{-/-} knockout mice.

The non-specific potassium channel blocker 4-aminopyridine

suppressed seizures in *Cacna1a^{tg/tg}* mice, phenocopying the effect of *Kcna1* deficiency. These data suggest that drugs that compensate for deficits in neuronal excitability may benefit people with specific types of epilepsy. These data may also affect disease diagnosis. If multiple mutations can cancel each other out in people, then genetic tests for single alleles may inaccurately predict disease risk.

Debra Speert

1. Glasscock, E., Qian, J., Yoo, J. W. & Noebels, J. L. Masking epilepsy by combining two epilepsy genes. *Nature Neuroscience* **10**, 1554–1558 (2007). | [Article](#) | [PubMed](#) |