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GENETICS

Mutations in potassium channel KCNT1—a novel driver of epilepsy pathogenesis

Two studies have identified mutations in a sodium-gated potassium channel gene, *KCNT1*, as a cause of two forms of early-onset epileptic disorders.

> “...the spectrum of epilepsies caused by mutations in *KCNT1* may be wider than we thought...”

Sam Berkovic and colleagues focused on autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). The group had previously found mutations in the nicotinic acetylcholine receptor in patients with this disorder, but only in about 10% of cases. “Using the new technology of whole-exome capture and sequencing, we identified involvement of a new gene, *KCNT1*, in a family with severe ADNFLE involving more-refractory seizures and psychiatric features,” says Berkovic. Mutations in this gene occurred in a region encoding the highly conserved C-terminal domain of KCNT1, and showed complete cosegregation with disease. These findings were then confirmed in two further families with ADNFLE and in a sporadic case.

The other study involved patients with malignant migrating partial seizures of infancy—a rare epileptic encephalopathy characterized by drug-resistant seizures and developmental delay. Using exome sequencing, Rima Nabbout and colleagues identified *de novo* mutations in the C-terminal domain of *KCNT1* in six of 12 patients tested. “This is the first study using trios and exome sequencing in homogeneous sporadic cases of epilepsy,” says Nabbout.

Next, the researchers performed functional studies in *Xenopus laevis* oocytes transfected with rat mutant *Kcnt1* constructs. They found that the mutation enhanced potassium currents through the channel, in a manner that mimicked the physiological response to phosphorylation of the channel by protein kinase C.

In addition to ion conductance, KCNT1 has nonconducting function in developmental signalling pathways. “Mutations in *KCNT1* might, therefore, be linked not only to epileptic activity in these severe epilepsies, but also to the brain development protein cascade,” explains Nabbout.

“Together, the two studies suggest that the spectrum of epilepsies caused by mutations in *KCNT1* may be wider than we thought,” says Berkovic.

Katie Kingwell

Original articles Heron, S. E. *et al.* Missense mutations in the sodium-gated potassium channel gene *KCNT1* cause severe autosomal dominant nocturnal frontal lobe epilepsy. *Nat. Genet.* **44**, 1188–1190 (2012) | Barcia, G. *et al.* *De novo* gain-of-function *KCNT1* channel mutations cause malignant migrating partial seizures of infancy. *Nat. Genet.* **44,** 1255–1259 (2012)