

Mutations in the *EFHC1* gene as causes of epilepsy

Stogmann et al. studied 61 patients with idiopathic generalized epilepsy syndromes for mutations in the *EFHC1* gene and detected three novel heterozygous missense mutations (I174V, C259Y, A394S) and one possibly pathogenic variant in the 3'UTR (2014t>c). Mutations in this gene may underlie different epilepsy syndromes.

see page 2029

Epilepsy genetics: Complexity unmasked, conundrums revealed

Commentary by Samuel F. Berkovic, MD

Molecular genetics has transformed the diagnosis and understanding of numerous single gene disorders. This success has rarely been duplicated in common neurologic disorders with complex inheritance.

Idiopathic generalized epilepsies, including the common syndrome of juvenile myoclonic epilepsy (JME), are a good example. In 1988 a locus for JME on chromosome 6p was reported.¹ The finding was replicated by some but not others, it was said to be specific to JME by some but not all, there was debate as to the precise location and number of loci for JME on chromosome 6, and no causative gene was definitively identified. Frustratingly, such inconsistency across laboratories is usual in complex disorders.

Finally, in 2004, a consortium led by Japanese and US investigators found mutations

in the gene *EFHC1* on chromosome 6 in a few JME families.² This was an important advance, but the frequency of families with mutations could not account for the positive linkage signals. Stogmann et al.³ now report mutations in an independent Austrian sample, in sporadic (as opposed to familial) cases and in a wider spectrum of phenotypes, including other forms of idiopathic generalized epilepsy and one case of temporal lobe epilepsy. The case for these mutations being causative is not completely conclusive since functional studies of mutant channels have not yet been carried out. Nonetheless, their findings strengthen the case for *EFHC1* contributing to the complex inheritance of idiopathic epilepsies.

Conundrums remain in terms of reconciling the early linkage studies and determining the at-

tributable risk of *EFHC1* mutations in particular epilepsies. The function of *EFHC1* is unclear; roles in apoptosis² and ciliary function⁴ have been proposed. Importantly, *EFHC1* is not known to have a direct or indirect role in ion channel function, as opposed to other confirmed idiopathic epilepsy genes.

References

1. Greenberg DA, Delgado-Escueta AV, Widelitz H, et al. Juvenile myoclonic epilepsy may be linked to the Bf and HLA loci on human chromosome 6. *Am J Med Genet* 1988;31:185-192.
2. Suzuki T, Delgado-Escueta AV, Aguan K, et al. Mutations in *EFHC1* cause juvenile myoclonic epilepsy. *Nat Genet* 2004;36:842-849.
3. Stogmann E, Lichtner P, Baumgartner C, et al. Idiopathic generalized epilepsy phenotypes associated with different *EFHC1* mutations. *Neurology* 2006;67:2029-2031.
4. King SM. Axonemal protofilament ribbons, DM10 domains and the link to juvenile myoclonic epilepsy. *Cell Motil Cytoskeleton* 2006;63:245-253.

see page 2029

Neurology[®]

December 12 Highlight and Commentary: Epilepsy genetics: Complexity unmasked, conundrums revealed

Neurology 2006;67;1907

DOI 10.1212/01.wnl.0000251315.84454.07

This information is current as of December 11, 2006

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/67/11/1907.full>

References

This article cites 4 articles, 1 of which you can access for free at:
<http://n.neurology.org/content/67/11/1907.full#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

