

A GENE FOR JME AT LAST: THE $\alpha 1$ GABA RECEPTOR SUBUNIT

Mutation of GABRA1 in an Autosomal Dominant Form of Juvenile Myoclonic Epilepsy

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Although many genes that predispose for epilepsy in humans have been determined, those that underlie the classical syndromes of idiopathic generalized epilepsy (IGE) have yet to be identified. We report that an Ala322Asp mutation in GABRA1, encoding the alpha1 subunit of the gamma-aminobutyric acid receptor subtype A (GABA(A)), is found in affected individuals of a large French Canadian family with juvenile myoclonic epilepsy. Compared with wildtype receptors, GABA(A) receptors that contain the mutant subunit show a lesser amplitude of GABA-activated currents *in vitro*, indicating that seizures may result from loss of function of this inhibitory ligand-gated channel. Our results confirm that mutation of GABRA1 predisposes towards a common idiopathic generalized epilepsy syndrome in humans.

COMMENTARY

In 1985, Janz (1) described a syndrome of primary generalized epilepsy he termed “epilepsy with impulsive petit mal,” now known as juvenile myoclonic epilepsy (JME). JME has an onset between 12 and 18 years, and is characterized clinically by irregular jerks of the upper arms, typically upon awakening, often followed by generalized tonic-clonic seizures. Bilateral 4–6/s spike-wave complexes, often in the form of multispikes, are associated with absence seizures. This article is the first to report on a specific mutation in a gene linked to this phenotype, answering a long debated question, and in so doing answers a second.

First, consider the mutation itself, which turns out to be a substitution of an aspartate for an alanine residue in the $\alpha 1$ subunit of the heteropentameric GABA_A receptor complex. All eight affected individuals within a large family each inherited a single copy of the mutant gene (localized to chr. 5q34), which

was not present in six unaffected family members nor in 200 controls. This particular residue lies deep in the third transmembrane domain, and is conserved in all 5 remaining α subunits ($\alpha 2$ – $\alpha 6$) of the GABA receptor. Application of GABA to HEK cells expressing receptor complexes that included the mutant subunit showed a reduced chloride flux compared to receptors formed with wild type subunits. Potentiation of GABA currents by diazepam was unaffected. These properties distinguish this subunit mutation from recent reports of GABA receptor γ subunit mutations in a separate epilepsy syndrome, GEFS+ (2,3). The data in this paper were obtained from an “idealized” GABA receptor created by coexpressing α , β , and γ subunits.

This article raises many new questions, as all gene discoveries do. How can we reconcile the diffuse expression pattern of the $\alpha 1$ subunit gene in the brain with the very specific clinical seizure pattern? Why are many networks in the brain where the mutant gene is also expressed clinically silent? What determines the adolescent age window in JME patients? Perhaps these questions can be answered by variable rearrangements in the stoichiometries of GABA receptor complexes made up of the remaining 16 GABA receptor subunit types; alternatively, other long term plasticities may arise in specific brain networks. These are questions that mouse models of this disorder will one day hopefully address.

In identifying this gene, the study answers a second question. Does the gene mutation from a rare pedigree showing autosomal dominant transmission account for most other cases of JME, a syndrome known for its multiple published linkages to other chromosomal loci? Apparently not. Since 31 unrelated patients with JME in the study were shown to possess normal copies of this gene, $\alpha 1$ mutations appear to be an uncommon cause of JME, as had been noted earlier in linkage studies by Sander (4). What other kinds of genes beyond those encoding GABA receptors may be involved is not yet known, however we now understand conclusively that JME is genetically heterogeneous, and novel gene discoveries from other mapped loci are anticipated. Nevertheless, we learn even from rare causes of disease, and in this case, considering that the culprit was the first alpha subunit of the principle receptor subtype for inhibitory neurotransmission in the brain, perhaps the most obvious lesson is that looking under the lamppost may indeed be the best place to start.

References

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