

## GABA<sub>A</sub> RECEPTOR DEFECTS CAN CAUSE EPILEPSY

### Mutant GABA<sub>A</sub> Receptor $\gamma$ 2-subunit in Childhood Absence Epilepsy and Febrile Seizures

Wallace RH, Marini C, Petrou S, Harkin LA, Bowser DN, Panchal RG, Williams DA, Sutherland GR, Mulley JC, Scheffer IE, Berkovic SF

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Epilepsies affect at least 2% of the population at some time in life, and many forms have genetic determinants. We have found a mutation in a gene encoding a GABA<sub>A</sub> receptor subunit in a large family with epilepsy. The two main phenotypes were childhood absence epilepsy (CAE) and febrile seizures (FS). There is a recognized genetic relationship between FS and CAE, yet the two syndromes have different ages of onset, and the physiology of absences and convulsions is distinct. This suggests the mutation has age-dependent effects on different neuronal networks that influence the expression of these clinically distinct, but genetically related, epilepsy phenotypes. We found that the mutation in GABRG<sub>2</sub> (encoding the  $\gamma$ 2-subunit) abolished in vitro sensitivity to diazepam, raising the possibility that endozepines do in fact exist and have a physiological role in preventing seizures.

### First Genetic Evidence of GABA<sub>A</sub> Receptor Dysfunction in Epilepsy: A Mutation in the $\gamma$ 2-subunit Gene

Baulac S, Huberfeld G, Gourfinkel-An I, Mitropoulou G, Beranger A, Prud'homme JF, Baulac M, Brice A, Bruzzone R, LeGuern E

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Major advances in the identification of genes implicated in idiopathic epilepsy have been made. Generalized epilepsy with febrile seizures plus (GEFS+), benign familial neonatal convulsions and nocturnal frontal lobe epi-

lepsy, three autosomal dominant idiopathic epilepsies, result from mutations affecting voltage-gated sodium and potassium channels, and nicotinic acetylcholine receptors, respectively. Disruption of GABAergic neurotransmission mediated by  $\gamma$ -aminobutyric acid (GABA) has been implicated in epilepsy for many decades. We now report a K289M mutation in the GABA<sub>A</sub> receptor  $\gamma$ 2-subunit gene (GABRG<sub>2</sub>) that segregates in a family with a phenotype closely related to GEFS+, an autosomal dominant disorder associating febrile seizures and generalized epilepsy previously linked to mutations in sodium channel genes. The K289M mutation affects a highly conserved residue located in the extracellular loop between transmembrane segments M2 and M3. Analysis of the mutated and wild-type alleles in *Xenopus laevis* oocytes confirmed the predicted effect of the mutation, a decrease in the amplitude of GABA-activated currents. We thus provide the first genetic evidence that a GABA<sub>A</sub> receptor is directly involved in human idiopathic epilepsy.

### Commentary

GABA is the primary inhibitory neurotransmitter in the CNS. The GABA<sub>A</sub> receptor channel is the major postsynaptic receptor for GABA and is responsible for the majority of fast inhibition in the CNS. Disruption of GABAergic inhibition by drugs has been known for decades to produce seizures, and it was commonly assumed, therefore, that the pathophysiology of many seizure disorders would result from an alteration in GABA<sub>A</sub> receptor channels. It was somewhat surprising, therefore, that the early identification of channelopathies resulting in familial epilepsies did not include mutation of one of the 19 GABA<sub>A</sub> receptor genes. GABA<sub>A</sub> receptors are pentameric combinations of different subunit subtypes but are generally thought to be composed primarily of two  $\alpha$  subunits, two  $\beta$  subunits and a  $\gamma$ ,  $\delta$  or other subunit.

The wait to prove the common assumption that mutation of GABA<sub>A</sub> receptors is associated with familial epilepsy is over. In independent studies, Baulac et al. and Wallace et al. have now confirmed that disruption GABA<sub>A</sub> receptors are associated with familial epilepsies. Interestingly, both groups identi-

fied a mutation of the  $\gamma 2$  subunit, but the mutations are in remarkably different regions of the subunit. All GABA<sub>A</sub> receptor subunits, including the  $\gamma 2$  subunit, are thought to be composed of a large extracellular domain where GABA and allosteric modulators bind four transmembrane domains (TM1–TM4), a short extracellular linker between TM2 and TM3, a short intracellular linker between the TM1 and TM2, and a large, quite variable intracellular linker between the TM3 and TM4.

Baulac et al. studied a family with an autosomal dominant disorder associating febrile seizures with generalized epilepsy (GEFS+). They identified a methionine to lysine mutation (K289M) located in the small extracellular loop between TM2 and TM3. They expressed  $\alpha 1\beta 2\gamma 2$  receptors with wild type and mutant  $\gamma 2$  subunits in *Xenopus oocytes* and demonstrated a reduction in the amplitude of GABA<sub>A</sub> receptor current when equal amounts of wild type or mutant GABA mRNA were included in the injection.

In contrast, Wallace et al. studied a family with childhood absence epilepsy and febrile seizures and demonstrated a mu-

tation in the distal extracellular N terminal domain of the  $\gamma 2$  subunit where a glutamine was substituted for an arginine (R43Q). When  $\alpha 1\beta 2\gamma 2$  receptors with wild type and mutant  $\gamma 2$  subunits receptor subunits were expressed in *Xenopus oocytes*, the only abnormality noted was that the receptors with the mutant subunit became insensitive to the enhancement produced by diazepam. This led these investigators to propose that endogenous benzodiazepines (endozepines), which have not been conclusively identified, may have a physiological role in preventing both febrile seizures and absence seizures.

These two studies demonstrate for the first time that mutations in GABA<sub>A</sub> receptors can lead to familial epilepsy. Of interest, the seizure phenotypes produced by these mutations were similar to those produced by alterations in sodium channel genes, suggesting that altering different genes that regulate neuronal excitability may produce similar seizure types by activating similar final common generalized epilepsy pathways.

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