

## A GENE POLYMORPHISM ASSOCIATED WITH TEMPORAL LOBE EPILEPSY?

**GABA(B) receptor 1 polymorphism (G1465A) is associated with temporal lobe epilepsy**

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*Neurology* 2003;60(4):560–563

**BACKGROUND:** Dysfunction of [gamma]-aminobutyric acid (GABA) (B) receptors has been implicated in the pathogenesis of temporal lobe epilepsy (TLE).

**OBJECTIVE:** To evaluate the genetic contribution of cloned human GABA(B) receptors to TLE.

**METHODS:** The authors genotyped 141 patients (78 women and 63 men; mean age =  $49.1 \pm 18.0$  years) with nonlesional TLE and 372 age- and sex-matched normal individuals for the known polymorphism G1465A in the human GABA(B) receptor 1 [GABA(B(1))] gene.

**RESULTS:** There was a highly significant overrepresentation of the G1465A heterozygote in patients with TLE compared with controls. The A/G genotype was found in 17% of the 141 patients with TLE and in only 0.5% of the 372 controls ( $P < 0.0001$ ). The authors also found that patients carrying the A allele had a significantly higher risk ( $P = 0.003$ , OR = 6.47, 95% CI = 2.02 to 20.76) of developing drug-resistant TLE. Furthermore, the age at onset of seizures tended to be lower in patients with A/G genotype, but the difference was not significant.

**CONCLUSIONS:** The results of this study indicate that the GABA(B(1)) polymorphism (G1465A) confers a highly increased susceptibility to TLE. Moreover, it seems to influence the severity of this common epileptic disorder.

into a multiple-drug-resistance gene and the discovery of a mutation in the  $\alpha_1$  subunit of the  $\gamma$ -aminobutyric acid receptor subtype A in a family with autosomal dominant juvenile myoclonic epilepsy (1). Now, in the recent paper in *Neurology* by Gambardella et al., researchers report an over-representation of a  $\gamma$ -aminobutyric acid B (GABA B) receptor polymorphism in patients with temporal lobe epilepsy—the temporal lobe being a region in which GABA B receptors are abundantly expressed.

Notably, Gambardella and colleagues established a relatively plausible link between the polymorphism that was identified and function of the GABA B receptor. Previous research demonstrated that a missense mutation in G1465A leads to an amino acid substitution in a highly conserved region of the receptor in both humans and rats (2). This region contains the ligand binding site of the GABA receptor, and therefore, an alteration may affect receptor function (3). Further research, such as creating a knockout mouse with a lower seizure threshold, certainly needs to be performed to better understand this genetic polymorphism. However, the finding by Gambardella et al., if verified, would be an important issue in understanding the development of epilepsy, in this case, related to the temporal lobe.

The present data merely show an association between presence of the GABA B polymorphism and presence of a temporal lobe epilepsy phenotype—they do not establish a causal relationship. There may be many confounders that cause the appearance of an association, in the absence of a causal link. It has been said that if an eager researcher looked for a polymorphism associated with chopstick use, one could easily be found. However, before concluding a genetic predisposition for this useful talent, upon closer analysis, it of course would be understood that Asians use chopsticks with a much higher frequency than Caucasians, and Asians may have a polymorphism that is not found in the rest of the population.

The population of temporal lobe epilepsy patients analyzed in this study is somewhat unusual. Of the 141 patients, 90% were either seizure free or experiencing not more than two disabling seizures per year, with or without appropriate antiepileptic medication. Only 14 were described as having poor control of seizures, with or without mesial temporal sclerosis. The more severe patients seemed to have a higher occurrence of the polymorphism, but the numbers were small. The benign temporal lobe epilepsy population described in this

**COMMENTARY**

Over the course of the last several years, there has been an increased interest in discovering potential genetic factors that may predispose patients to developing epilepsy, particularly medically refractory epilepsy. As has been discussed recently in the pages of *Epilepsy Currents*, the search for underlying genetic abnormalities related to epilepsy have included an investigation

study had a much milder form of the disease expressed than patients typically seen at epilepsy centers with this same disorder. How such a difference in population make up might impact the study findings is unclear. In the future, it would certainly be appropriate to further evaluate the more refractory patients.

The association between GABA B polymorphism and temporal lobe epilepsy did not account for even half of the cases seen in this study—only 17% of patients carried the A/G genotype. As noted by the authors, temporal lobe epilepsy, undoubtedly, is a multifactorial disease. However, it is critical to continue to tease out and identify the genetic associations, such as the one described in this paper, in order to better understand the disorder. Ultimately, this knowledge could lead to the development of targeted antiepileptic drug therapy. Gambardella et al., appear to have added to the growing body of information

on the genetic predisposition in patients with temporal lobe epilepsy.

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## References

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