

T-CHANNEL DEFECTS IN PATIENTS WITH CHILDHOOD ABSENCE EPILEPSY

Association Between Genetic Variation of *CACNA1H* and Childhood Absence Epilepsy

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Direct sequencing of exons 3 to 35 and the exon–intron boundaries of the *CACNA1H* gene was conducted in 118 childhood absence epilepsy patients of Han ethnicity recruited from North China. Sixty-eight variations have been detected in the *CACNA1H* gene, and among the variations identified, 12 were missense mutations and found only in 14 of the 118 patients in a heterozygous state, but not in any of 230 unrelated controls. The identified missense mutations occurred in the highly conserved residues of the T-type calcium channel gene. Our results suggest that *CACNA1H* might be an important susceptibility gene involved in the pathogenesis of childhood absence epilepsy.

COMMENTARY

The discovery of thalamic T-channel blockade by succinimide and related anticonvulsants (e.g., ethosuximide, methsuximide, trimethadione) by Coulter and co-workers (1,2) more than a decade ago (1,2) led to the implicit hypothesis that altered function of these voltage-gated calcium channels might underlie the pathogenesis of 3-Hz spike-and-wave associated with generalized absence seizures (3). Since then, three members of the T class of voltage-gated calcium channels in rats have been cloned by Perez-Reyes and colleagues (4), who identified them as $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ (4), with the human analogs designated *CACNA1G*, *CACNA1H*, and *CACNA1I*. In rats, transcripts of all of these channels are expressed at medium-to-high density in specific thalamic nuclei implicated in spike–wave generation (3), with $\alpha 1G$ expressed at high levels in thalamic relay neurons, whereas in thalamic reticular neurons, $\alpha 1I$ and, to a lesser extent, $\alpha 1H$ are expressed (5). Evidence for an essential thalamic

participation in generalized spike–wave generation is extensive and includes results from clinical literature as well as a number of animal models (3). Furthermore, aside from the thalamic T-channel blockade by succinimide anticonvulsants, a number of lines of evidence indicate that T channels in thalamic cells play a central role in generalized absence seizures. First, T current–dependent burst firing in thalamic neurons is a common feature in a number of generalized absence models (3). Second, mice with a genetic knockout of $\alpha 1G$ are deficient in thalamic burst firing and are insensitive to γ -aminobutyric acid type B (GABA_B) agonist–induced spike–wave seizures (6). Third, several spontaneous mouse mutations of non-T calcium channels that are associated with a spike–wave phenotype have been shown to be associated with an upregulation of T currents in thalamic neurons (7,8), whereas crossing $\alpha 1G$ knockouts with such mice eliminated the spike–wave seizures (7). Fourth, the genetic absence epilepsy rats from Strasbourg (GAERS) inbred rat strain, which possess a characteristic spike–wave phenotype, have an upregulated T current in thalamic reticular neurons (9) and increased expression of $\alpha 1G$ and $\alpha 1H$ (10) transcripts in thalamus.

Recently Chen et al. sequenced genomic DNA for *CACNA1H*, which encodes $\alpha 1H$ calcium channels—in the most recent nomenclature, CaV3.2—from >100 childhood-onset absence epilepsy patients and compared these with adult controls without epilepsy. In the epilepsy group, 12 missense mutations were found in 14 patients, and none in >200 controls. T channels have four major domains, each made up of six transmembrane segments. Of the 12 mutations, seven were in the linker region between domains I and II, which by analogy with sodium channels, is thought to contain important regulator sites for phosphorylation and binding to accessory subunits or regulatory proteins (4). Four mutations were within domain I or II, whereas the last mutation was in domain III. Many of these mutations were in highly conserved residues of various T channels in rodents and humans, although this conservation was apparent for only three of seven mutations in the I–II linker. The report of Chen and colleagues raises the interesting possibility that dysfunction of $\alpha 1H$ may lead to absence seizure susceptibility. It will be interesting to study these mutations in expression systems to determine the resultant functional channel deficit that might include alterations in targeting, gating, modulation,

and/or permeation. It is of note that in rat models, $\alpha 1H$ is not the major T channel expressed in either thalamic reticular or relay neurons, although moderate expression is found in the former (5). This finding suggests that subtle alterations in overall cellular T-channel activity may be sufficient to trigger the hypersynchronous spike-wave seizures. Consistent with this idea is the related, yet converse finding that maximal reduction of thalamic T current by ethosuximide was modest—on the order of 30% to 40% (2), yet its effect on in vitro epileptiform events was quite powerful (4,11).

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Queries

Q1 Author: Pages?

Q2 Author: As meant?