

HUMAN EPILEPSY CAN BE LINKED TO A DEFECTIVE CALCIUM CHANNEL

Human Epilepsy Associated with Dysfunction of the Brain P/Q-type Calcium Channel

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BACKGROUND: The genetic basis of most common forms of human paroxysmal disorders of the central nervous system, such as epilepsy, remains unidentified. Several animal models of absence epilepsy, commonly accompanied by ataxia, are caused by mutations in the brain P/Q-type voltage-gated calcium (Ca^{2+}) channel. We aimed to determine whether the P/Q-type Ca^{2+} channel is associated with both epilepsy and episodic ataxia type 2 in human beings.

METHODS: We identified an 11-year-old boy with a complex phenotype comprising primary generalised epilepsy, episodic and progressive ataxia, and mild learning difficulties. We sequenced the entire coding region of the gene encoding the voltage-gated P/Q-type Ca^{2+} channel (CACNA1A) on chromosome 19. We then introduced the newly identified heterozygous mutation into the full-length rabbit cDNA and did detailed electrophysiologic expression studies of mutant and wild-type Ca^{2+} channels.

RESULTS: We identified a previously undescribed heterozygous point mutation (C5733T) in CACNA1A. This mutation introduces a premature stop codon (R1820stop), resulting in complete loss of the C terminal region of the pore-forming subunit of this Ca^{2+} channel. Expression studies provided direct evidence that this mutation impairs Ca^{2+} channel function. Mutant/wild-type coexpression studies indicated a dominant negative effect.

CONCLUSIONS: Human absence epilepsy can be associated with dysfunction of the brain P/Q-type voltage-gated Ca^{2+} channel. The phenotype in this patient has striking parallels with the mouse absence epilepsy models.

COMMENTARY

Jouveneau et al. reported linkage of a mutation in the *CacnA1A* gene encoding P/Q-type calcium channels with nocturnal tonic-clonic seizures ending by age 8 years and persistent daytime generalized spike-wave absence seizures. Other neurologic findings included episodic cerebellar signs, generalized interictal EEG spike-wave discharges, and an unremarkable magnetic resonance imaging (MRI). The mutation in the last transmembrane segment of the final domain (IVS6) results in loss of the C terminus of the protein, a site for modulation of the protein by interacting channel subunits, an effect similar to the *leaner* allele of the *tottering* mouse mutant. Like the mouse mutant, the mutation reduces calcium current through the P/Q type channel when coexpressed in oocytes with auxiliary channel subunits.

This is the first report in humans of an epileptic phenotype linked to a calcium channelopathy, as initially described in mutant mice. Interestingly, like the mouse mutants with epilepsy, the mutation decreases calcium entry; however, as witnessed in other channelopathies, the correlation between the site of the mutation within the gene, the measured function of the protein, and the clinical phenotype is imperfect. Some mutations within the gene lead to decreased calcium currents and the variable expression of hemiplegic migraine, episodic ataxia, coma, or nystagmus without epilepsy. Other mutations within the same gene, such as an expanded triplet repeat mutation associated with the SCA6 spinocerebellar ataxia phenotype, increase calcium currents. It seems likely that each mutation disrupts a highly specific pattern of modulation of calcium channel function within distinct neuronal pathways.

Another report (1) associated migraine and episodic ataxia with an epileptic phenotype of tonic-clonic as well as focal psychomotor seizures; however, possible mutations in the *CacnA1a* gene have not as yet been characterized.

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Reference

1. Holtmann M, Opp J, Tokarzowski M, Korn-Merker E. Human epilepsy, episodic ataxia type 2, and migraine. Lancet 2002;359:170–171.