Missense CACNA1A Mutation Causing Episodic Ataxia Type 2

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Objectives: To characterize the nature of CACNA1A mutation in a previously unreported family with episodic ataxia type 2 (EA2) and to better delineate EA2 clinical features.

Background: Episodic ataxia type 2 is an autosomal dominant disorder characterized by the recurrence of acetazolamide-responsive spells of cerebellar ataxia, usually starting during childhood or adolescence. The mutated gene, CACNA1A, is located on chromosome 19 and encodes the a1A subunit voltage-dependent calcium channel. So far, most CACNA1A mutations detected in patients with EA2 have led to a truncated CACNA1A protein, whereas missense mutations cause familial hemiplegic migraine.

Methods: All 47 exons of CACNA1A were screened by a combination of single-strand conformer polymorphism and sequencing analysis.

Results: A CACNA1A missense mutation, Glu 1757 Lys, was identified. It was absent in 200 control chromosomes. It is predicted to result in an amino acid substitution at a highly phylogenetically conserved position, within a domain that plays a major role in the function of the channel.

Conclusions: The Glu 1757 Lys missense mutation is likely to be pathogenic, causing episodic ataxia within a family whose phenotype is indistinguishable from EA2 except for a slightly later age of onset. These data strongly suggest that additional work is needed to fully establish genotype/phenotype correlations for CACNA1A mutations.

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Autosomal dominant episodic ataxias are a clinically and genetically heterogeneous group of conditions characterized by recurrent paroxysmal attacks of cerebellar ataxia starting during childhood or adolescence. Episodic ataxia type 1, a condition characterized by the association of brief ataxic spells and interictal myokymias, is caused by mutations within a voltage-gated potassium channel gene, KCNA1. Episodic ataxia type 2 (EA2) is an autosomal dominant paroxysmal cerebellar ataxia, characterized by acetazolamide-responsive recurrent attacks of unsteadiness, lack of limb coordination, and dysarthria, often provoked by emotional or physical stress. Other symptoms during attacks include vertigo or dizziness, visual disturbances (diplopia or oscillopsia), and headache. Attacks last from several minutes to a few hours or days. Clinical onset occurs usually during childhood or adolescence. Findings of interictal neurological examination usually disclose a gaze-evoked nystagmus and sometimes a mild permanent gait ataxia. In a minority of patients, permanent symptoms are severe, and some patients may be wheelchair confined. Cerebral imaging often reveals a vermian cerebellar atrophy.

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Episodic ataxia type 2 is caused by mutations within the a1A subunit of a P/Q-type voltage-dependent calcium channel gene, CACNA1A. P/Q-type channels, which are expressed throughout the brain and at the neuromuscular junction, are implicated in the control of membrane excitability and neurotransmitter release. So far, 11 EA2 mutations have been reported, most of them leading to a truncated CACNA1A protein. Interestingly, distinct types of CACNA1A mutations have been reported in other autosomal dominant neurological conditions. Chromosome 19–linked familial hemiplegic migraine is caused by missense mutations. Small expansions of the CAG repeat located within the 3’ coding end of CACNA1A cause spinocerebel-
lar ataxia type 6, a late-onset, moderate to severe progressive cerebellar ataxia, without paroxysmal event. However, these strong genotype/phenotype correlations may not be absolute. Two families with a permanent progressive cerebellar ataxia, associated with paroxysmal ataxic episodes, and 1 family with pure episodic ataxia were shown to harbor CAG repeat expansions. More recently, a CACNA1A missense mutation was shown to cause a severe progressive cerebellar ataxia with early onset in several members of a family.

We report herein a missense CACNA1A mutation causing episodic ataxia within a family whose phenotype is indistinguishable from EA2 except for a slightly later onset.

REPORT OF CASES

PEDIGREE

This family included 4 symptomatic members (Figure 1, individuals I-2, II-1, II-5, and III-2). Detailed clinical information was obtained from patient III-2 and 2 of his 3 sons who were clinically examined. Clinical information regarding patients I-2, II-1, II-5 was obtained from patient III-2 (Figure 1).

PROBAND

Proband III-2 (Figure 1), a 53-year-old man, experienced recurrent episodes of paroxysmal cerebellar ataxia since he was 40 years old. His medical history was unremarkable except for a strabismus, which needed surgical repair at age 22 years. Ataxic spells were strongly stereotyped. Onset was sudden with brief bilateral parasthesias in upper and lower extremities, diffuse weakness, and heat sensations rapidly followed by generalized ataxic symptoms. Attacks always included severe truncal and limb ataxia with dysarthria, vertigo, and oscillopsia and diplopia sometimes associated with nausea, vomiting, and blurred vision. The patient reported headaches fulfilling International Headache Society criteria for migraine without aura, both during and between ataxic spells. Duration of ataxic episodes usually ranged from half an hour to 4 hours. They were precipitated by emotional and physical stress and spontaneously resolved with rest or sleeping.

This patient suffered from 3 to 4 attacks per month, up to 1 per day in stressful periods. He first presented to us in 1996 at age 50. Findings of interictal examination disclosed an isolated, gaze-evoked nystagmus. The remainder of his neurological examination results were normal. Brain magnetic resonance imaging revealed a mild statokinetic cerebellar ataxia. Findings of interictal electroencephalographic and electromyelographic studies were normal. The patient began treatment with 250 mg of acetazolamide twice a day, and reported a marked decrease in severity and frequency of attacks (once a month) during 1 year, but no improvement on isolated migraine episodes. In 1997, he stopped treatment during 2 months and experienced an outbreak of attacks; frequency of these attacks decreased with the reinstatement of treatment. Two years later, interictal neurologi-
Clinical manifestations observed within affected members of this family (namely, recurrent paroxysmal acetazolamide-responsive attacks of generalized cerebellar ataxia associated with interictal permanent cerebellar symptoms as well as the cerebellar atrophy evident on magnetic resonance imaging) are strongly suggestive of EA2. None of these family members suffered from hemiplegic migraine. The only subtle difference from previously reported families with EA2 was a later age of onset. Whereas in most patients with EA2 clinical onset occurs during childhood or adolescence, initial symptoms in the 4 affected members of this family occurred after age 30 years. However, clinical onset after age 30 years has been reported in a few members of families with EA2.

CACNA1A screening revealed a missense mutation, Glu 1757 Lys, while most previously described EA2 mutations led to a truncated CACNA1A protein. Multiple arguments strongly suggest that this amino acid substitution caused the disease of our patient. First, it was not detected in 200 control chromosomes, strongly suggesting that it is not a rare polymorphism. Second, this mutation affects a highly conserved amino acid located within the pore loop, which plays a major role in the function of the channel pore.

The a1A calcium channel subunit encoded by CACNA1A is formed by 4 homologous domains (Figure 2). Each domain contains 6 membrane-spanning segments (S1-S6). The central pore of the channel is delineated by the 4 pore-loop regions, which interconnect the fifth and sixth segment membrane spanning each domain. The glutamates located within each pore loop are key players for calcium selectivity. Substitution within this pore loop of a negatively charged glutamic acid for a positively charged lysine would most likely be very deleterious. In addition, glutamic acid at codon 1757 is a highly conserved amino acid from Drosophila to man. For these reasons, despite the fact that DNA from other members was not available for cosegregation analysis, we think that this missense mutation most likely caused the disease observed in this family.

To our knowledge, there is only 1 family harboring a CACNA1A missense mutation, although not affected with familial hemiplegic migraine. This family included 8 affected members who suffered from a severe progressive cerebellar ataxia, which confined some of them to wheelchairs by their 40s. Interestingly, 2 of these members had, in addition to this severe progressive ataxia, acetazolamide-resistant paroxysmal episodes of vertigo and ataxia. Mutation in this family substituted an uncharged glycine for a positively charged arginine within the pore-loop of the first domain of CACNA1A.

Although in most cases families with EA2 harbor truncating mutations in CACNA1A whereas in familial hemiplegic migraine missense mutations occur, the fami-
ily reported herein is an example of overlap between episodic neurological conditions due to CACNA1A missense mutations. These data strongly suggest that additional work is needed to fully establish genotype/phenotype correlations. The mechanisms leading from these various types of mutations to these phenotypes are not understood at present, and electrophysiological studies are strongly needed.

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