Familial Migraine With Vertigo: No Mutations Found in CACNA1A

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We searched for mutations in the voltage-gated calcium channel gene, CACNA1A, in nine propositi of families with migraine headaches and episodic vertigo inherited in an autosomal dominant pattern. All 47 exons and flanking introns in CACNA1A were subjected to single-strand conformation polymorphism analysis of polymerase chain reaction-amplified genomic DNA. Exons with aberrantly migrating fragments were sequenced using standard techniques. We also determined the CAG repeat length at the 3' end of CACNA1A. Several polymorphisms were found but no mutations identified in any of the 47 exons of the 9 patients. No index-case had a CAG repeat length greater than 13 (normal <17). Mutations in CACNA1A are not common in families with migraine headaches and episodic vertigo. Other ion channel genes expressed in the brain and inner ear remain candidate genes. Am. J. Med. Genet. 79:148–151, 1998. © 1998 Wiley-Liss, Inc.

KEY WORDS: migraine; vertigo; genetics

INTRODUCTION

Hereditary factors are thought to play an important role in the susceptibility to migraine [Russell et al., 1993]. Recently missense mutations were found in the voltage-gated calcium channel gene, CACNA1A, in four families with hemiplegic migraine (FHM) [Ophoff et al., 1996]. This gene located on chromosome region 19p codes for the a1 subunit of the P/Q-type calcium channel, which is expressed throughout the brain but most prominently in the cerebellum [Mori et al., 1991; Volersen et al., 1995]. Vertigo and other posterior fossa symptoms are common in patients with FHM, and Haan et al. [1995] questioned whether FHM is a form of basilar migraine. Therefore we searched for mutations in CACNA1A in families with migraine headache and episodic vertigo.

MATERIAL AND METHODS

Patient and Family Data

We studied the index-cases of nine families with migraine and spontaneous attacks of vertigo followed in our neurotologic clinic. Other causes of vertigo were ruled out, and a diagnosis of migraine associated vertigo was made in each case. All had multiple relatives with migraine headaches and episodic vertigo inherited in an autosomal dominant pattern (Fig. 1). Migraine headaches were defined by the criteria of the International Headache Society (IHS) [Headache Classification Committee of the International Headache Society, 1988]. Vertigo was defined as an illusion of rotation of the environment. The diagnosis of migraine headache and vertigo in relatives was made by a mailed questionnaire. In equivocal cases, we interviewed the relatives by telephone.

Families 1 to 4 have been reported previously [Baloh et al., 1994, 1996]. Several members of Families 1 to 3 developed a progressive bilateral vestibulopathy after repeated episodes of vertigo. Families 4, 6, and 9 had multiple members with migraine headaches, recurrent episodes of vertigo, and essential tremor. In each family, the pattern of inheritance was consistent with an autosomal dominant trait (Fig. 1). The clinical profiles of the propositi are summarized in Table I. In addition to the propositi, there was a total of 67 relatives with migraine or episodic vertigo in the 9 families. Fifty-two of them had migraine headaches. Episodic vertigo was reported in 42. In 27, headaches were associated with vertigo.

SSCP Analysis

After obtaining informed consent from propositi, we isolated genomic DNA from peripheral blood with a DNA-extraction kit (Gentra system, Minneapolis, MN). Polymerase chain reaction (PCR) products of exons in CACNA1A were screened for molecular variants, by
SSCP analysis [Orita et al., 1989; Ravnik-Glavak et al., 1994]. The published primers [Ophoff et al., 1996] were used to amplify all 47 exons from the introns flanking each exon, except for exons 37 and 43, for which the primers had to be redesigned [Yue et al., 1997]. PCR was performed under conditions optimized for each individual primer pair. All 47 exons were amplified in 9 propositi. Products were labeled by inclusion of $[\alpha-^{32}P]$-d-CTP in the PCR. PCR products then were denatured and loaded onto 0.5 × mutation-detection enhancement gels (AT Biochem, Malvern, PA) and were electrophoresed at 4°C, with or without 10% glycerol. After autoradiography of the gels, conformers were identified by visual inspection.

**CAG)n-Repeat Analysis**

Determination of the number of CAG repeats at the 3' end of CACNA1A was described elsewhere [Zhuchenko et al., 1997]. In brief, PCR products were electrophoresed in denaturing polyacrylamide gels and were compared with a sequencing ladder. Homozygous alleles were sequenced to confirm the number of CAG repeats.

**RESULTS**

In SSCP analysis, we found 4 new (not previously published) polymorphisms in 4 propositi (Table II) but identified no mutation in any of the 47 exons of the 9 propositi. No propositus had a CAG repeat length greater than 13 (normal <17).

**DISCUSSION**

**Vertigo and Migraine**

Spontaneous episodes of vertigo occur in about 25% of patients with migraine [Kayan and Hood, 1984]. Whether vertiginous migraine represents a distinct genetic variant such as FHM or whether vertigo occurs with many different varieties of migraine is unknown. The additional finding of bilateral vestibulopathy in three families (1–3) and essential tremor in three other families (4–9) suggests a genetic basis for these symptoms.

**TABLE I. Clinical Profiles of Index Cases**

<table>
<thead>
<tr>
<th>Index Case</th>
<th>Sex/Age</th>
<th>Subtype of migraine*</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>M/34</td>
<td>MWOA</td>
<td>Bilateral vestibulopathy</td>
</tr>
<tr>
<td>Family 2</td>
<td>M/53</td>
<td>MWOA</td>
<td>Bilateral vestibulopathy</td>
</tr>
<tr>
<td>Family 3</td>
<td>F/47</td>
<td>MWA</td>
<td></td>
</tr>
<tr>
<td>Family 4</td>
<td>F/44</td>
<td>MWA</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>Family 5</td>
<td>F/49</td>
<td>MWA</td>
<td></td>
</tr>
<tr>
<td>Family 6</td>
<td>M/33</td>
<td>MWA</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>Family 7</td>
<td>F/64</td>
<td>Visual aura</td>
<td></td>
</tr>
<tr>
<td>Family 8</td>
<td>F/31</td>
<td>MWA</td>
<td></td>
</tr>
<tr>
<td>Family 9</td>
<td>F/7</td>
<td>MWA</td>
<td>Essential tremor</td>
</tr>
</tbody>
</table>

*MWOA: migraine without aura, MWA: migraine with aura.
families 4, 6, 8) suggests that vertigo might be part of several migraine syndromes. Migraine is most likely a polygenic disorder. Different mutations within the same gene may cause distinct clinical disorders, while mutations in different genes may result in very similar phenotypes [Bulman, 1997]. Recent studies showed that FHM, episodic ataxia type-2 (EA-2), spinocerebellar ataxia type 6 (SCA-6), and progressive ataxia are allelic disorders due to mutations in the α subunit of the P/Q-type calcium channel gene (CACNA1A) [Ophoff et al., 1996; Yue et al., 1997; Zhuchenko et al., 1997]. Patients with FHM and EA-2 commonly have migraine headaches and episodic vertigo [Baloh et al., 1996]. The phenotypic variations and clinical overlap in these disorders suggests that other types of vertiginous migraine may also show mutations in CACNA1A.

All the propositi in our study had recurrent episodes of vertigo without a known cause, a past history of migraine, and multiple relatives with migraine headaches and episodic vertigo. One propositus (Family 7) had episodic vertigo and visual aura without headache (acephalgic migraine). The precise mechanism of vertigo in migraine is unknown. The sudden episodes of vertigo associated with migraine could be explained on the basis of vasospasm of the vestibular branches of the internal auditory artery. Also, a defective ion channel shared by the brain and inner ear could lead to reversible hair cell depolarization and vertigo [Baloh et al., 1996]. The identification of abnormal genes in families with migraine headaches and vertigo should lead to a more complete explanation.

Other Candidate Genes for Migraine

Serotonin (5-HT) has long been implicated in the pathophysiology of migraine, but preliminary studies using linkage analysis have excluded mutations in the 5-HT_{2A} and 5-HT_{2C} receptor genes [Buchwalder et al., 1996; Nyholt et al., 1996]. The dopamine receptor gene, DRD2, is a candidate gene for migraine since DRD2 antagonists are effective in the acute treatment of migraine, and alterations in dopaminergic neurotransmission are common in migraineurs [Hakkarainen and Allonen, 1982; Sicuteri, 1977]. Peroutka et al. [1997] found an increased frequency of the DRD2 NcoI C allele in individuals with migraine with aura compared with a control group. Paterna et al. [1997] studied the ACE gene deletion polymorphism in patients with migraine based on the finding that the ACE inhibitor, captopril, was effective in reducing the frequency, duration, and severity of migraine. They found an increased frequency of the DD genotype in subjects with migraine without aura compared with controls. The mechanism underlying the positive associations between migraine and the DRD2 NcoI C and ACE-D alleles remains to be elucidated. Linkage studies of the CACNA1A locus on chromosome 19p in patients with uncomplicated migraine have produced mixed results [May et al., 1995; Hovatta et al., 1994]. We previously ruled out linkage to markers on chromosome 19p in Family 4 [Baloh et al., 1996]. In this study, we directly screened for mutations in CACNA1A in nine propositi with migraine using SSCP analysis. SSCP is a reasonably sensitive (75–98%) method for screening suspected genes of point mutations as long as the fragments are not longer than 200 bases [Ravnik-Glavac et al., 1994].

**Ion Channel and Migraine**

Heterogeneity of inherited migraine syndromes can be explained by genetic defects that code for a family of proteins with similar properties and functions [Baloh et al., 1996]. Ion channel genes have received the most attention as candidate genes in migraine because many of the migraine syndromes share the manifestations of the known inherited ion channel disorders (channelopathy) [Ptáček, 1997]. The finding of a defective CACNA1A gene in FHM firmly establishes it as a channelopathy. Recently another FHM locus was identified on the long arm of chromosome 1 documenting the heterogeneity of this disorder. There are two known ion channel genes in the linked region, the calcium channel gene CACNA1E and the potassium channel gene GIRK3. Though we did not find mutations in CACNA1A in our families with migraine headaches and episodic vertigo, other ion channel genes expressed in the brain and inner ear remain as candidate genes.

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**REFERENCES**


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**TABLE II. Polymorphisms**

<table>
<thead>
<tr>
<th>Index case</th>
<th>Location</th>
<th>Nucleotide change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>Intron 10 nt 1723 + 7</td>
<td>C → T</td>
</tr>
<tr>
<td>Family 3</td>
<td>Intron 8 nt 1474 – 31</td>
<td>A → G</td>
</tr>
<tr>
<td>Family 4</td>
<td>Exon 29 nt 4898</td>
<td>Ala_{154} → Thr</td>
</tr>
<tr>
<td>Family 9</td>
<td>Exon 3 nt 737</td>
<td>Ser_{1541} → Cys</td>
</tr>
</tbody>
</table>

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**REFERENCES**


