No Mutations in CACNA1A and ATP1A2 in Probands With Common Types of Migraine

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Background: Mutations in CACNA1A, encoding a neuronal calcium channel subunit, and ATP1A2, encoding a catalytic subunit of a sodium-potassium-ATPase, have been found in some families with dominantly inherited hemiplegic migraine.

Objective: To determine the prevalence of mutations in these genes in individuals with different migraine syndromes.

Design: Prospective screening study.

Setting: University outpatient neurology clinic.

Subjects: Probands of 19 families with hemiplegic migraine, 7 with basilar migraine, 25 with migraine without aura, and 18 with migraine with aura, as well as 40 unaffected relatives of probands.

Interventions: All known exons and flanking introns of CACNA1A and ATP1A2 were subjected to denaturing high-performance liquid chromatography analysis of polymerase chain reaction–amplified genomic DNA. Exons with atypical elution patterns were sequenced by standard techniques.

Main Outcome Measures: Presence of mutations in CACNA1A and ATP1A2.

Results: A single mutation (T666M) was found in CACNA1A in a patient with hemiplegic migraine and ataxia. No other mutation was identified in either gene. The frequency of a previously reported intronic insertion in ATP1A2 was not significantly different between patients with migraine and control subjects.

Conclusion: These 2 genes are not associated with more common migraine syndromes and are not the most common hemiplegic migraine genes.

Arch Neurol. 2004;61:926-928

Hemiplegic migraine is a unique migraine syndrome characterized by episodes of hemiplegia and hemianesthesia followed by headache.\(^1\) It can occur in families as an autosomal dominant trait but can also occur sporadically.\(^2\) Within well-documented families with hemiplegic migraine, some members have only migraine without aura (MO) or migraine with aura (MA). In addition, patients with hemiplegic migraine (familial and sporadic) will often have other brainstem and cerebellar symptoms; there appears to be an overlap between the clinical features of hemiplegic migraine and basilar migraine.\(^3\) Linkage studies in large families with hemiplegic migraine have clearly documented genetic heterogeneity.\(^7\)

To date, mutations in 2 genes have been identified in families with hemiplegic migraine: CACNA1A, encoding a neuronal calcium channel subunit, and ATP1A2, encoding a catalytic subunit of a sodium-potassium-ATPase.\(^5,6\) Both of these genes code for transmembrane ion channels and transporters heavily expressed in the brain. Mutations in CACNA1A also cause episodic and progressive ataxia.\(^5,7,8\) and most families with hemiplegic migraine caused by mutations in CACNA1A have either episodic or progressive ataxia and interictal nystagmus.\(^9\) So far only 2 families have been described with hemiplegic migraine caused by mutations in ATP1A2, and members of both of these families had seizures in addition to hemiplegic migraine episodes.\(^8\)

In this report, we address 2 questions regarding CACNA1A and ATP1A2 and migraine: (1) How often are mutations in either of these 2 genes seen in patients with hemiplegic and basilar migraine? (2) Are mutation in these 2 genes associated with the more common MO and MA syndromes? Previous genetic and clinical studies suggest that CACNA1A and ATP1A2 could be important for MO and MA.\(^10,11\)
The majority of probands with hemiplegic migraine did not have other family members with episodes of hemiplegia (Table). Only 8 of 19 had 1 other family member with hemiplegic episodes. However, all except the 3 who were adopted had other family members with MO or MA, and most had 3 or more first-degree family members with MO or MA. The age at onset of hemiplegic episodes varied from 4 to 52 years, and the typical duration of episodes varied from minutes to days. Also, most of the probeands with hemiplegic migraine also had episodes of MO or MA separate from the episodes of hemiplegia. Vertigo and ataxia were the most common associated symptoms. All of the probeands experienced numbness and paresthesias with at least some of the episodes of hemiparesis. Only 2 of the 19 probands had interictal neurologic findings (both had mild truncal ataxia and gaze-evoked nystagmus).

The 7 probands with basilar migraine had vertigo plus at least 1 other posterior circulation symptom (blacking or blurring of vision were common). Three had other family members with basilar migraine, and all 7 had at least 1 first-degree family member with MO or MA. All of the probands with MA had at least 1 first-degree family member with MO or MA, and all but 3 of the probeands with MO had at least 1 first-degree family member with MO or MA. Results of neurologic examination were normal in all probeands with basilar migraine, MA, and MO.

**METHODS**

**SUBJECTS**

Informed consent was obtained from all individuals in accordance with our institutional review board procedures. Blood samples were obtained from all probands, and DNA was extracted by standard techniques. We studied 19 probands with hemiplegic migraine, 7 with basilar migraine (all female), 25 with MO (16 female and 9 male), 18 with MA (16 female and 2 male), and 40 unaffected relatives of probands (18 female and 22 male), who reported no history of migraine symptoms. International Headache Society criteria were used to define each migraine syndrome.1 A detailed history was obtained in each case by an experienced neurologist, and each proband was examined by a neurologist. Family history was documented by interviewing all family members who agreed to participate. These interviews were done over the telephone, with the use of a standardized migraine questionnaire (available on request).

**CLINICAL FEATURES**

A single mutation (T666M) was found in CACNA1A in a proband with hemiplegic migraine. The patient had interictal ataxia and gaze-evoked nystagmus similar to other families previously described with this mutation. Unfortunately, no other family members were available, since he was adopted and had no children. No mutations were found in CACNA1A or ATP1A2 in the other probands with hemiplegic migraine or in probands with basilar migraine, MA, or MO. (Benign polymorphisms from our screen that have not previously been reported are available on request from the authors.)
Previously, a polymorphism consisting of a 4-base pair (bp) insertion 12 bp upstream from the start of exon 2 of ATP1A2 was identified in 37% of persons of European descent.\textsuperscript{13} We performed an association study between this polymorphism and the different migraine syndromes, and the frequencies of ATP1A2 are given in the following tabulation.

<table>
<thead>
<tr>
<th>Category</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>8/40 (20)</td>
</tr>
<tr>
<td>Hemiplegic migraine</td>
<td>4/19 (21)</td>
</tr>
<tr>
<td>Basilar migraine</td>
<td>1/7 (14)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>6/18 (33)</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>8/25 (32)</td>
</tr>
<tr>
<td>All Subjects</td>
<td>27/109 (25)</td>
</tr>
</tbody>
</table>

We did not find a significant difference in the frequency of this polymorphism between any of the probands with migraine and controls, indicating that this variation is not a major susceptibility factor for migraine.

We found no mutations in the hemiplegic migraine genes CACNA1A and ATP1A2 in 50 probands with basilar migraine, MA, or MO and found only 1 mutation in 19 probands with hemiplegic migraine. This suggests that these 2 genes are not associated with the more common migraine syndromes and, indeed, they are not the most common hemiplegic migraine genes. First, it is useful to consider how our families with hemiplegic migraine compare with previously studied families found to have mutations in CACNA1A or ATP1A2. Most families with hemiplegic migraine found to have mutations in CACNA1A also had episodic and progressive ataxia and interictal nystagmus, sometimes overlapping with the clinical syndrome of episodic ataxia type 2.\textsuperscript{9,14} Of our 19 probands with hemiplegic migraine, only 2 had interictal ataxia and nystagmus, and 1 of these was found to have a mutation in CACNA1A. The only 2 described families with hemiplegic migraine caused by mutations in ATP1A2 did not have interictal ataxia, but had members with seizures.\textsuperscript{6} None of our 19 probands with hemiplegic migraine had seizures.

In our clinical experience, the typical patient with hemiplegic migraine has a sporadic case or has only 1 other family member with hemiplegic episodes (see Table). However, when a family history was obtainable, all had other family members with MO or MA. Within these families, vertigo and other features of complicated migraine were common, suggesting that hemiplegic episodes were only one of multiple features of complicated migraine. By contrast, in the families reported with mutations in CACNA1A or ATP1A2, most of the affected members had episodes of hemiplegic migraine, i.e., autosomal dominant inheritance with relatively high penetrance.\textsuperscript{5,6,9}

Even though no mutations were found in CACNA1A and ATP1A2 in our probands with these common migraine syndromes, it is possible that polymorphisms in these genes could be susceptibility factors for developing migraine. We did identify multiple polymorphisms in the coding region of these 2 genes, but none was more common in the patients with migraine than in the controls. We also studied the frequency of a previously reported intronic polymorphism consisting of a 4-bp insertion, 12 bp upstream from the start of exon 2 of ATP1A2, but again there was no significant difference in the frequency of this polymorphism in the migraine probands and the controls.\textsuperscript{15} However, because the number of patients studied was small, it is possible that polymorphisms in these genes may yet be found to play a minor role in increased risk of migraine. Also, other intronic polymorphisms that could alter expression of these genes, which we did not study, might also play a role in increased risk of migraine susceptibility.

Accepted for publication November 11, 2003.

Author contributions: Study concept and design (Drs Jen and Baloh); acquisition of data (Drs Jen and Baloh, Mr Kim, and Ms Dudding); analysis and interpretation of data (Drs Jen and Baloh); drafting of the manuscript (Drs Jen and Baloh, Mr Kim, and Ms Dudding); critical revision of the manuscript for important intellectual content (Drs Jen and Baloh); obtained funding (Drs Jen and Baloh); administrative, technical, and material support (Drs Jen and Baloh, Mr Kim, and Ms Dudding); study supervision (Drs Jen and Baloh).

This study was supported by grants DC05524 and DC000162 from the National Institute of Deafness and Other Communication Disorders, Bethesda, Md, and Department of Neurology, University of California, Los Angeles.

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