We describe the clinical and oculographic findings in 4 families with episodic ataxia and interictal nystagmus (EA-2) linked to chromosome 19p. Episodes varied from pure ataxia to combinations of symptoms suggesting involvement of the cerebellum, brainstem, and cortex. Some affected individuals exhibited a progressive ataxia syndrome phenotypically indistinguishable from the dominantly inherited spinocerebellar ataxia (SCA) syndromes. About one-half of the affected individuals had migraine headaches and several had episodes typical of basilar migraine. Oculographic findings were localizing to the vestibulocerebellum and posterior vermis. Additional genetic and environmental factors must account for the marked clinical heterogeneity in these families with an abnormal gene on chromosome 19p.

Familial episodic ataxia is an uncommon neurologic disorder characterized by bouts of ataxia usually with minimal interictal neurologic findings [1]. At least two distinct forms have been identified, familial episodic ataxia with interictal myokymia (EA-1) characterized by brief bouts of ataxia lasting minutes and familial periodic ataxia with interictal nystagmus (EA-2) characterized by longer episodes of ataxia lasting hours [2]. Both disorders are inherited as an autosomal dominant trait and both disorders respond to treatment with acetazolamide [3, 4]. The genetic defects associated with EA-1 are point mutations in a brain potassium channel (KCNA-1) located on chromosome 12p [5, 6]. EA-2 has been linked to the same region on chromosome 19p as hemiplegic migraine, but so far the genetic defect has not been identified [1, 2, 7, 8]. Recently, in collaboration with investigators from the Oregon Health Sciences University, we briefly reported positive linkage to chromosome 19p in 3 families with EA-2 [8]. We now describe detailed clinical and oculographic findings in these 3 families and in an additional atypical family also linked to 19p. There are several phenotypic variations of EA-2 linked to chromosome 19p. Identification of the abnormal gene on 19p is the critical first step toward understanding the mechanisms accounting for these different phenotypes.

Materials and Methods

Case Material
The following 3 families have previously been reported: Family 1 [9], Family 2 [10], and Family 3 [11]. However, linkage to chromosome 19p was not known at the time of these reports. We have followed the probands in each of these 3 families for 5 to 15 years since the original reports with serial examinations. Other family members were interviewed and examined at the time of the initial reports. Follow-up information has been obtained mainly via telephone conversations. We reexamined a few key family members to document their clinical status. All members of Family 4 were interviewed and examined within the past year. Affected individuals were identified based on a report of intermittent episodes of vertigo and/or ataxia with or without associated symptoms such as nausea, vomiting, and slurred speech. Subjects were specifically asked whether the episodes were associated with headaches that met the International Headache Society (IHS) criteria for migraine [12], weakness or numbness of the extremities, visual symptoms, auditory symptoms, or decrease in the level of consciousness. Other features supportive of a diagnosis of EA-2 included interictal nystagmus, truncal instability, and beneficial response to acetazolamide.

Family 1
Starting at age 15, the proband (II-5, see Fig 1) experienced recurrent episodes of ataxia involving the extremities and trunk, typically triggered by stress or exercise and relieved by rest. After about one-half the attacks, he had severe headaches. He experienced his most severe attack at age 52 after a crescendo series of ataxic spells. He reported persistent bilateral weakness and paresthesias of all extremities along with frequent muscle spasms. He was hospitalized with severe vertigo, nausea and vomiting, throbbing headache, and photophobia. During a 2-week hospitalization, cerebrospinal fluid examination and cerebral angiography were normal. The severe attack resolved after about 3 days. An electroencephalogram revealed diffuse slowing and a right hemisphere focus. Although no abnormality was identified, the proband was started on clonazepam, which provided benefit. He was seen in 1989 and 1991 with an interval of 5 years between his last attacks. Two siblings (II-1, II-2) and a niece (II-3) were also affected. The proband has a total of 8 siblings, 4 of whom are alive. All the affected siblings have had ictal episodes, some of which were quite severe. None of the affected siblings has had similar attacks since the proband’s last attack in 1989. The proband has 9 nieces and nephews. Two of them (III-2, III-3) have had episodic ataxia with or without episodes of vertigo and/or nystagmus. Of particular interest is a 27-year-old male cousin (III-2), who has had episodes of vertigo and transient ataxia since age 2. He experienced a crescendo series of episodes and was hospitalized for 1 week with severe vertigo, nystagmus, nausea, vomiting, and weakness. His neurologic examination and EEG were normal. The following 3 families have been reported: Family 1 [9], Family 2 [10], and Family 3 [11]. However, linkage to chromosome 19p was not known at the time of these reports. We have followed the probands in each of these 3 families for 5 to 15 years since the original reports with serial examinations. Other family members were interviewed and examined at the time of the initial reports. Follow-up information has been obtained mainly via telephone conversations. We reexamined a few key family members to document their clinical status. All members of Family 4 were interviewed and examined within the past year. Affected individuals were identified based on a report of intermittent episodes of vertigo and/or ataxia with or without associated symptoms such as nausea, vomiting, and slurred speech. Subjects were specifically asked whether the episodes were associated with headaches that met the International Headache Society (IHS) criteria for migraine [12], weakness or numbness of the extremities, visual symptoms, auditory symptoms, or decrease in the level of consciousness. Other features supportive of a diagnosis of EA-2 included interictal nystagmus, truncal instability, and beneficial response to acetazolamide.

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gram (EEG) showed paroxysmal high-amplitude, slow and sharp activity, but a trial of phenytoin seemed to worsen his symptoms. Later, a trial of valproic acid provided no benefit.

When he initially presented to UCLA in 1981 at age 56, his neurologic examination was normal except for some mildly impaired tandem gait. There was no interictal nystagmus. Acetazolamide provided immediate benefit. He has been maintained on acetazolamide at 250 to 750 mg/day for the past 15 years with excellent results. He has occasional mild episodes of ataxia but none of the severe attacks that he experienced in the past.

AFFECTED FAMILY MEMBERS. Of the 5 other family members with episodic ataxia, 2 (II-2 and III-4) had spells with multiple associated symptoms similar to those of the proband. One of his sisters was hospitalized with a severe attack of vertigo, ataxia, numbness and paresthesias of the extremities, generalized weakness, bilateral visual blurring as if looking through a haze, and severe throbbing headache. EEG examinations in 2 (II-2 and III-4) showed bursts of 3- to 4-Hz, high-amplitude, slow and sharp activity similar to that of the proband. Two (II-2 and III-4) have been maintained on acetazolamide and report good results, although there are occasional breakthrough spells.

Family 2
The proband (II-2, see Fig 1) began having episodes of vertigo, truncal ataxia, and slurring of speech at age 3. Episodes typically lasted an hour or two and were induced by stress or exercise. With some spells, he would experience either visual blurring or blacking out of vision along with bioccipital throbbing headache. He initially presented to UCLA in 1984 at age 53, at which time his interictal examination showed gaze-evoked and rebound nystagmus along with mild truncal ataxia, most noticeable when walking in tandem. He was begun on acetazolamide 250 mg twice daily, initially with excellent results. Gradually over the subsequent years, the attacks began to recur and the acetazolamide was increased to 250 mg four times per day. In 1994, he returned for reevaluation after having been hospitalized for 2 weeks with a severe attack of vertigo, ataxia, and generalized weakness including bilateral facial weakness. This attack occurred despite being on a full dose of acetazolamide. It took approximately 2 weeks to recover from this acute attack, but his interictal examination again showed only moderate truncal ataxia and gaze-evoked nystagmus.

AFFECTED FAMILY MEMBERS. The proband’s grandson and 3 maternal cousins experienced recurrent episodes of vertigo and ataxia. The grandson and 1 of the maternal cousins (II-4) experienced bilateral throbbing headaches along with nausea and vomiting typically associated with their attacks of vertigo and ataxia. The other 2 cousins did not have headaches, but both experienced nausea and vomiting with their attacks. Of note, the proband’s daughter (III-2, mother of the affected IV-1) has never experienced an episode of dizziness or imbalance and her neurologic examination has been consistently within normal limits. The proband, his grandson, and 2 of the cousins (II-3 and II-4) who were treated with acetazolamide all reported excellent response and have continued with the medication for more than 10 years.

Family 3
The proband (III-3, see Fig 1) began having attacks of vertigo, ataxia, and slurred speech at age 15. The attacks were typically precipitated by stress, exercise, and fatigue, and invariably began with a pressure-like headache in the occipital region bilaterally. These attacks initially occurred once or twice a month and he was able to carry on most activities including graduating from college. He initially presented to UCLA at age 36 in 1990, complaining of increased frequency and severity of his attacks of vertigo and ataxia. He was tried on acetazolamide without any benefit (up to a maximum dose of 1,500 mg/day). His neurologic examination showed rebound nystagmus and downbeat nystagmus on lateral gaze and truncal ataxia with inability to take even a single step in tandem without a side step. He reported severe left-sided throbbing headaches that occurred with the attacks or separately from the attacks. In early 1995, he presented in the middle of a severe prolonged attack that had already lasted for 3 days. On examination there was prominent downbeat nystagmus in the primary position that increased in amplitude with gaze to either side and generalized ataxia involving the upper extremities and trunk. He was unable to stand or walk without assistance. The remainder of the neurologic examination was unremarkable. In addition to the vertigo and ataxia, he complained of a generalized throbbing headache along with severe nausea and recurrent vomiting. He was treated with promethazine (Phenergan) 25 to 50 mg for symptomatic relief, but it was approximately 2 weeks before this severe attack resolved. His baseline truncal ataxia was more pronounced after this severe prolonged attack.

AFFECTED FAMILY MEMBERS. Of the 12 affected family members, 10 exhibited interictal nystagmus and truncal ataxia. Of these, 2 (I-1 and II-2) reported no episodic features. Three (II-4, III-5, and III-10) were tried on acetazolamide and each reported an excellent response. Four (II-4, III-1, III-10, and III-14) described headaches with their episodes.

Family 4
At age 42, the proband (IV-1) developed dizzy spells that lasted for hours to as long as a day. During these spells, she preferred to sit perfectly still in a chair, because any head movement would trigger vertigo. Even when sitting still she felt light-headed and “foggy.” She was insecure if she attempted to walk. Between these episodes she experienced positional vertigo when lying flat so she slept with several pillows. Beginning at age 43, she noticed mild imbalance between her spells of dizziness. She first presented to UCLA in 1994 at age 47, reporting a gradually increasing frequency of her dizzy spells and worsening of her positional vertigo. On examination she exhibited a prominent downbeat nystagmus after moving from the sitting to supine position. This downbeat nystagmus persisted for as long as the head was held in that position. However, she could not maintain the position for more than...
There was no spontaneous or gaze-evoked nystagmus in the affected family members. Four of the 5 living affected members reported episodes of dizziness and imbalance. All but the least affected (III-7) had interictal gaze-evoked rebound nystagmus. One (III-4) developed slowly progressive ataxia, beginning in his late 50s, without episodes. Another (III-6) reported episodes of severe occipital headache, dizziness, and generalized weakness beginning at age 16. These acute episodes occurred over 13 years and then spontaneously disappeared, only to be followed by a gradual progressive ataxia beginning with truncal instability and then by extremitat axia and slurring of speech. By age 46, the ataxia was so severe that she could no longer work, and now at age 59, she can ambulate only with the use of a walker. Her mother (II-3) also developed episodes of dizziness, imbalance, and occipital headache, beginning at age 17 followed by progressive ataxia beginning in her late 30s. She was confined to a wheelchair for the last 27 years of her life. The proband’s father, uncle, and paternal grandmother all have developed severe progressive ataxia and require either a wheelchair or a walker. In addition, the father (III-2, age 71) and paternal grandmother (II-2, age 86) exhibited spasticity and hyperreflexia of the lower extremities with bilateral extensor plantar responses.

**Eye Movement Recordings**

Eye movements were recorded with direct current electro-oculography. Detailed descriptions of the recording system and data analysis have been reported [13, 14]. With the subject seated and head fixed by a brace, saccades were generated by a laser target moving in a square-wave pattern of pseudo-random frequency, direction, and amplitude. Smooth pursuit was generated with the same laser target moving in a sinusoidal pattern (0.2 and 0.4 Hz; peak velocities, 23 degrees and 45 degrees/sec, respectively). Optokinetic nystagmus was induced with the subject sitting inside a cloth drum of 1-m diameter. The drum was made of black cloth with 3-degree wide vertical stripes spaced at 15.6-degree intervals. The drum was rotated at a constant velocity of 30 degrees/sec clockwise and counterclockwise as well as sinusoidally (0.05 Hz; peak velocity, 60 degrees/sec). The vestibuloocular reflex (VOR) was tested by sinusoidal (0.05 Hz; peak velocity, 60 degrees/sec) rotations with the subject’s eyes open in darkness. Fixation–suppression of the VOR was tested by sinusoidally (0.05 Hz; peak velocity, 60 degrees/sec) rotating the subject in the dark with a small fixation light attached to the chair directly in front of the subject.

**Genetic Studies**

After obtaining informed consent of family members, we isolated DNA from peripheral blood [15] and typed a series of microsatellite markers on 19p [16] with the following loci: D19S413–5cM—D19S221–6cM—D19S226/D19S415 [17]. We used the MINK option in FASTLINK [18] for two-point linkage analysis, assuming autosomal dominant inheritance of a rare gene (frequency, 0.0001).

**Results**

**Genetic Data**

Haplotype data for the 4 families are given in Figure 1. The strongest evidence for linkage occurred at D19S221 (total lod score of 5.91 at Θ = 0.01), which was the only locus with no obligate crossovers in any of the 4 kindreds. There was also significant linkage to both D19S413 and D19S226/D19S415, with total lod scores of 4.13 and 4.24, respectively, at Θ = 0.10. Critical crossovers occurred on the disease-bearing chromosomes of 2 affected individuals; II-3 of Family 2 had a crossover between D19S413 and D19S221 and III-10 of Family 3 had a crossover between D19S221 and D19S226. Affected status was confirmed in both cases. We concluded that the gene for EA-2 is located within an 11-cM region flanked by D19S413 and D19S226/D19S415.

**Clinical Data**

Most affected members reported that their episodes were triggered by emotional upset and physical exertion. Some could reliably produce attacks with activities such as running up a flight of stairs or running around the block. Several noted that alcohol induced attacks. The age of onset of episodic ataxia varied from age 3 to 44 years (Table 1) and remained about the same over 3 generations; i.e., there was no evidence of anticipation. All but 1 affected member of Families 1, 2, and 3 had onset before age 20. Family 4 had a later onset of episodes and earlier, more severe, interictal ataxia. Eleven of 12 affected individuals treated with acetazolamide had a good response (see Table 1). The single exception was the proband in Family 3 who had no response to a maximum dose of 1,500 mg of acetazolamide per day. The proband of Family 2 initially had a good response to acetazolamide, but the benefits decreased over time. Twenty-three of 28 affected individuals who were examined had interictal nystagmus, 4 of which had nystagmus but no episodes of ataxia (see Table 1). About one-half the affected members in the 4 families reported sick headaches that met the criteria for migraine, and 7 affected members had episodes that met the IHS criteria for basilar migraine (see Table 1). None reported classic migraine visual aura.

**Quantitative Eye Movement Testing**

There was a range of oculomotor findings in the probands and affected members (Table 2). Interictal nystagmus usually had features of rebound nystagmus.
Fig 1. Pedigrees of families studied and haplotypes of chromosome 19p loci. Blackened symbols denote affected individuals, all of whom were examined except for deceased individuals, in which case information was obtained from other family members. Question marks indicate no information available. Genotypes are listed in the order given by the maps to the left of each pedigree. The haplotype of the disease-bearing chromosome is boxed.
Table 1. Summary of Clinical Features in Affected Members of 4 Families with EA-2 Linked to Chromosome 19p

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at Onset of Attacks (yr)</th>
<th>Affected Individuals Examined</th>
<th>Response to Acetazolamide</th>
<th>Interictal Nystagmus</th>
<th>No Attacks but Nystagmus and Ataxia</th>
<th>Headaches with IHS Criteria for Migraine</th>
<th>Episodes with IHS Criteria for Basilar Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>10-20</td>
<td>5</td>
<td>3/3</td>
<td>2/5</td>
<td>0/5</td>
<td>3/5</td>
<td>3/5</td>
</tr>
<tr>
<td>Family 2</td>
<td>3-29</td>
<td>5</td>
<td>4/4</td>
<td>5/5</td>
<td>1/5</td>
<td>3/5</td>
<td>2/5</td>
</tr>
<tr>
<td>Family 3</td>
<td>10-20</td>
<td>12</td>
<td>3/4</td>
<td>10/12</td>
<td>2/12</td>
<td>4/10</td>
<td>1/10</td>
</tr>
<tr>
<td>Family 4</td>
<td>16-44</td>
<td>6</td>
<td>1/1</td>
<td>5/6</td>
<td>1/6</td>
<td>2/6</td>
<td>1/6</td>
</tr>
</tbody>
</table>

1In some subjects, frequency and severity of attacks did not warrant treatment. Some members of Family 4 only recently started treatment. Benefit decreased with time in the proband of Family 2.
2Presence of ataxia was excluded from the criteria.
3Information not available in 2 subjects.

Table 2. Results of Quantitative Oculomotor Testing in Affected Members of 4 Families with EA-2

<table>
<thead>
<tr>
<th>Group</th>
<th>Age when Rebound Nystagmus Tested (yr)</th>
<th>Saccade Accuracy</th>
<th>Pursuit</th>
<th>OKN</th>
<th>VOR-Fix</th>
<th>VOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100%</td>
<td>&gt;0.89</td>
<td>&gt;0.57</td>
<td>&lt;0.05</td>
<td>&gt;0.30</td>
<td></td>
</tr>
<tr>
<td>Family 1</td>
<td>11-5</td>
<td>+</td>
<td>88%</td>
<td>0.52</td>
<td>0.27</td>
<td>0.20</td>
</tr>
<tr>
<td>Family 4</td>
<td>16-44</td>
<td>5</td>
<td>107%</td>
<td>0.26</td>
<td>0.10</td>
<td>0.30</td>
</tr>
<tr>
<td>Family 3</td>
<td>11-2</td>
<td>32</td>
<td>-</td>
<td>95%</td>
<td>0.98</td>
<td>0.67</td>
</tr>
<tr>
<td>Family 4</td>
<td>16-44</td>
<td>5</td>
<td>107%</td>
<td>0.26</td>
<td>0.10</td>
<td>0.30</td>
</tr>
<tr>
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<tr>
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<td>0.10</td>
<td>0.30</td>
</tr>
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</table>

1Saccade amplitude/target displacement amplitude x 100, average of 40 target displacements.
2Peak eye velocity/peak stimulus velocity, 0.2 Hz.
3Peak eye velocity/peak stimulus velocity; Families 1–3: 0.05 Hz, 60 degrees/sec; Family 4: 30 degrees/sec, constant velocity.
4Peak eye velocity/peak stimulus velocity, 0.05 Hz, 60 degrees/sec.
5Abnormal result.

characterized by a gaze-evoked nystagmus with decreasing slow-phase velocity on maintained lateral gaze and a transient nystagmus in the primary position with the fast component in the direction of the return saccade (Fig 2A). Two had a downbeating component on lateral gaze to either side. One member of Family 4 had positional downbeat nystagmus only. Saccade overshoot dysmetria occurred in more than one-half the affected individuals tested (see Table 2). Overshoot dysmetria was present with both centripetal and centrifugal saccades. Saccade velocity measurements were normal in all subjects. Most affected members exhibited impaired smooth pursuit, impaired optokinetic responses, and impaired fixation-suppression of vestibular nystagmus (see Table 2; Fig 2B and C). Vestibular responses, on the other hand, were normal in all but 1 individual (II-2, Family 4). One individual who is an obligate carrier of the abnormal gene on chromosome 19p (III-2, Family 2) was asymptomatic and had normal quantitative oculomotor function testing (see Table 2). This woman was reevaluated at age 39 and was still asymptomatic with normal oculomotor function testing.

Discussion

Clinical Features

These 4 families with EA-2 linked to chromosome 19p showed variability in clinical symptoms and signs.
Fig 2. Typical examples of abnormal ocular motor findings in the 4 families with EA-2 linked to chromosome 19p. (A) Rebound nystagmus in II-4, Family 2; nystagmus decays as lateral position is held and occurs in the opposite direction on returning to the center position. (B) Impaired smooth pursuit in II-2, Family 2; frequent catch-up saccades are required. Upper trace, stimulus; lower trace, horizontal eye position (0.2 Hz, 22.6°/sec). (C) Impaired fixation—suppression of vestibular nystagmus in III-3, Family 3; normal subjects have minimal or no nystagmus with fixation in response to this stimulus. Upper trace, chair velocity; lower trace, horizontal eye position (0.05 Hz, 60°/sec).

There was variability in the type of attacks within individual patients and within families. Three of the families had at least one asymptomatic member with positive linkage. Episodes varied from pure ataxia to combinations of symptoms suggesting involvement of the cerebellum, brainstem, and cortex. About one-half the patients in each family reported headaches that met the IHS criteria for migraine and some had episodes that met the IHS criteria for basilar migraine (see Table 1).

With our 4 families, there have now been a total of 9 families reported with EA-2 linked to chromosome 19p. There are features in common among these 9 families [1, 2, 7]. The age of onset is usually before 20 years, although several members of Family 4 had a later onset. Although Teh and colleagues [2] suggested the possibility of anticipation in 1 of their 2 families with EA-2 linked to chromosome 19p, there was no evidence of anticipation in any of the other families. Episodes are typically triggered by exercise and emotional stress and relieved by acetazolamide (the only exceptions were the probands of our Families 2 and 3). Other than our study, only von Brederlow and associates [7] mentioned the occurrence of migraine headaches with EA-2. The lack of reported headaches in the other families, however, may reflect the lack of ascertainment. Vertigo, nausea, and vomiting were the most common associated symptoms, being present in some members of all 9 reported families.

Episodes of truncal ataxia and dysarthria and interictal findings of rebound and downbeat nystagmus are localizing to the cerebellum. Bilateral weakness and numbness of the extremities and face suggest brainstem involvement. Two members of Family 4 had interictal corticospinal tract signs indicating either spinal cord or brainstem involvement. Bilateral visual loss during attacks suggested occipital lobe involvement in a few patients. EEGs showed nonspecific high-amplitude bursts of slow and sharp activity in 3 patients from Family 1. Van Bogaert and co-workers [19] performed a positron emission tomographic study in a patient with EA-2, between episodes, and demonstrated a decrease in glucose metabolism in the cerebellum, the inferior part of the temporal lobes, and both thalami.
Thus, there is clear evidence for diffuse involvement of the brain in some patients with EA-2.

Quantitative Oculographic Findings
The characteristic combination of interictal oculographic findings in these 4 families was gaze-evoked rebound nystagmus, impaired smooth pursuit and optokinetic responses, and impaired fixation-suppression of vestibular nystagmus. These findings are localized to the vestibulocerebellum [20]. About one-half the patients showed saccade overshoot dysmetria, a finding localizing to the oculomotor region of the posterior vermis (lobules VIc and VII) and the fastigial nuclei [21]. This pattern has been reported in several previous families with EA-2 [10, 19] and is now shown to be characteristic of the variety linked to chromosome 19p. This pattern has also been reported in patients with dominantly inherited olivocerebellar atrophy [14]. Oculographic recordings are useful for quantification, but all of the eye movement abnormalities associated with EA-2 can be observed at the bedside.

EA-2 and Hemiplegic Migraine
EA-2 and hemiplegic migraine have been linked to the same region on chromosome 19p, and there is an overlap of clinical symptoms and signs in families with EA-2 and hemiplegic migraine [22, 23]. Several families with hemiplegic migraine have been reported with interictal nystagmus and ataxia [22, 24, 25]. Haan and collaborators [26] questioned whether familial hemiplegic migraine was a hereditary form of basilar migraine. They studied aura symptoms in 83 patients from 6 unrelated families with hemiplegic migraine and found that 55 of the patients reported symptoms that met the IHS criteria for basilar migraine. As noted above, several of our patients with EA-2 also met the IHS criteria for basilar migraine. Elliott and colleagues [27] recently reported quantitative oculographic findings in a family with familial hemiplegic migraine, nystagmus, and cerebellar atrophy, and the pattern of these abnormalities was identical to the pattern found in our 4 families with EA-2. It may be that EA-2 and familial hemiplegic migraine will be shown to be allelic genetic disorders.

EA-2 and CADASIL
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a progressive neurologic disorder characterized by subcortical infarcts, usually leading to dementia and early death [28]. It was initially linked to a region on chromosome 19p overlapping the regions linked to EA-2 and hemiplegic migraine [23, 29]. Several families with CADASIL have been reported to have migraine headaches and basilar migraine-like attacks, and in some families, migraine is an early and prominent feature. Verin and co-workers [30] suggested a new acronym for such families, i.e., CADASIL-M, emphasizing CADASIL with migraine. A characteristic finding with CADASIL is subcortical T1 intense lesions on magnetic resonance imaging, a finding sometimes seen in patients with migraine [31]. However, the most recent linkage analysis in 15 families with CADASIL mapped the genetic defect to a 2-cM interval centromeric to D19S226 (between D19S226 and D19S199 on 19p13.1) [32]. Since the genetic defect with EA-2 and hemiplegic migraine is localized distal to D19S226, it appears that CADASIL is not allelic with EA-2 and familial hemiplegic migraine. However, additional families must be studied before such a conclusion can be drawn.

EA-2 and Other Types of Migraine
Episodes of vertigo and imbalance commonly occur in patients with migraine, with about the same frequency as the classic visual aura (in about one-fourth of patients) [33, 34]. Whether vertiginous migraine represents a specific genetic subcategory such as hemiplegic migraine or whether vertigo spells occur with many different types of migraine is unclear. Vertigo is a prominent symptom with basilar migraine and, as mentioned above, there is overlap in the clinical syndromes of basilar migraine, EA-2, and hemiplegic migraine. We recently reported a family with migraine headaches, episodic vertigo, and essential tremor, all of which responded dramatically to acetazolamide [35]. Linkage analysis ruled out linkage to the region on 19p known to be linked with EA-2 and hemiplegic migraine. That this family with migraine and episodic vertigo and other families with migraine with and without aura are not linked to chromosome 19p [36] indicates that there is genetic heterogeneity with migraine and that the genetic defect on chromosome 19p is probably not associated with more common varieties of migraine. Yet patients in families with hemiplegic migraine with documented linkage to a genetic defect on 19p have typical migraine headaches and classic visual aura identical to those reported by patients whose genetic defect is not localized to 19p [22, 23]. One way to explain this heterogeneity of migraine syndromes is mutations in genes that code for a family of proteins with similar properties and functions. A family of ion channels is appealing, since these syndromes share the clinical features of the known inherited ion channel disorders [35]. Each of the inherited acetazolamide-responsive periodic neurologic diseases in which the causative gene has been identified is associated with an ion channel defect [37]. As noted earlier, the genetic defect with EA-1 is a point mutation in a brain potassium channel (KCNA1) [6]. Acetazolamide presumably works by stabilizing the abnormal ion channels.
through changes in extracellular pH [38]. The genetic defect on chromosome 19p associated with EA-2 and hemiplegic migraine must yet be determined, but an abnormal ion channel is suspected although so far there are no known ion channels on 19p [39].

**EA-2 and the Other Autosomal Dominant Cerebellar Ataxias**

Classification of the autosomal dominant cerebellar ataxia syndromes is rapidly evolving as genetic loci and specific genetic defects are discovered. Traditionally, familial episodic ataxia has been classified separately from the progressive cerebellar ataxia syndromes [40]. However, patients with EA-2 can develop severe progressive ataxia (eg, members of Family 4) clinically indistinguishable from the dominantly inherited spinocerebellar ataxia (SCA) syndromes. So far, six chromosomal loci have been associated with the progressive dominantly inherited ataxias [41, 42]; none of these overlaps the region on 19p associated with EA-2. Two of these disorders, SCA-1 and SCA-3, are due to expanded trinucleotide repeats (CAG repeats) [42]. Trinucleotide repeat expansions are also candidates for mutation with SCA-2, SCA-5, and SCA-7, since anticipation has been demonstrated in families with these disorders [41]. As noted earlier, there is little evidence of anticipation in the families with EA-2. Furthermore, Teh and coworkers [2] did not find trinucleotide repeat expansions in their 2 families with EA-2 linked to 19p.

In addition to EA-2, clinical heterogeneity has been documented with other dominantly inherited SCA syndromes. Probably the most remarkable phenotypic variability has been seen with SCA-3 [41]. Families with SCA-3 may present with clinical features typical of Machado-Joseph disease (multisystem involvement), while others show a relatively pure cerebellar syndrome. Even within the same family with SCA-3, members can have a range of phenotypic expressions. The age of onset of the various SCA syndromes is usually after 20 years of age [40], whereas most of our patients with EA-2 began having episodes prior to 20 years of age. However, the onset of progressive interictal ataxia was much later in patients with EA-2, overlapping the age of onset seen with the SCA syndromes. Indeed, members of our Family 4 were diagnosed as having spinocerebellar atrophy prior to our identification of younger members with episodic features.

There are at least four different clinical profiles associated with the abnormal gene on chromosome 19p, as follows: I, basilar migraine-like attacks with minimal or no interictal signs; II, episodes of ataxia with interictal nystagmus and mild progressive truncal ataxia; III, ill-defined episodes of dizziness with progressive SCA; and IV, hemiplegic migraine. EA-2 should be considered in any patient presenting with these clinical features. Phenotypic profiles tend to run true within a family (eg, type I, Family 1; type II, Families 2 and 3; and type III, Family 4), although most families have members with different clinical presentations and some members move from one clinical profile to another over time. As noted earlier, families have been reported with familial hemiplegic migraine, interictal nystagmus, and progressive truncal ataxia, and basilar migraine-like attacks are common in families with hemiplegic migraine [26]. Given the clinical heterogeneity in families reported to date, we may not yet know the full scope of the clinical disorders associated with the abnormal gene on chromosome 19p.

The mechanism for this phenotypic variability in families with EA-2 linked to chromosome 19p is unclear. With SCA-1 and SCA-3, the age of onset and some clinical variability are related to the number of CAG repeats in each affected member [41]. However, other clinical features do not seem to be related to the number of CAG repeats. Factors such as features of the normal allele and features of other similar genes and modifying genes could determine the phenotypic expression. Environmental factors may also be important. If the abnormal gene on chromosome 19p is an ion channel as speculated earlier, then the location of the mutation in the ion channel would be critical in determining phenotypic expression. A defect in a key position of the pore region of the ion channel would produce a more severe clinical syndrome than a mutation in a less critical region of the ion channel.

**Note Added in Proof**

Since this article was accepted for publication, the gene on 19p for episodic ataxia type 2 and hemiplegic migraine was identified [43]. In addition, another gene was found responsible for CADASIL [44].

**References**