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Phenotypic and Genetic Analysis of a Large Family With Migraine-Associated Vertigo

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Abstract

Objectives—To describe a large multigenerational family with migraine-associated vertigo (MAV) combining a detailed phenotypic and genetic analysis.

Background—Migraine-associated vertigo is said to be highly prevalent in the general population and, like other migraine syndromes, its etiology is felt to have a strong genetic component. However, so far, there have been no reports of large families with MAV.

Methods—Detailed clinical study was conducted on a large multigenerational family with MAV. Genetic study using identical-by-descent analysis with dense single nucleotide polymorphism (SNP) arrays was performed to examine consistent inheritance pattern among the affecteds.

Results—Clinical features of MAV were variable although most had other migraine symptoms with at least some of their attacks. We did not find a region of the genome shared by all eight subjects with MAV indicating a polygenetic inheritance for MAV even in this single large family.

Conclusions—A region on 11q shared by most affected females may contain a susceptibility allele for MAV that is expressed exclusively or predominantly by women.

Keywords

migraine-associated vertigo; female predominant; identity by descent analysis

An association between migraine and vertigo was first noted in the 19th century when Liveing reported their connection in his classic book “On Megrim: Sick headaches and some allied health disorders.”¹ Since that time, there have been numerous reports documenting that vertigo is much more common in patients with migraine than in controls and, conversely, that migraine is much more common in patients presenting with vertigo than in controls.^{2–6} Overall, vertigo occurs in about a quarter of patients with migraine headaches,⁷ probably about the same frequency as that of the classic migraine visual aura. Vertigo can occur during the headache but often occurs during headache-free intervals. Follow-up studies in patients with benign paroxysmal vertigo of childhood^{8, 9} and benign recurrent vertigo in adults^{10, 11} have shown

that both of these disorders are usually associated with migraine, so-called migraine-associated vertigo (MAV).

For migraine in general, numerous studies over the years have documented familial aggregation of migraine symptoms and some have suggested that a positive family history should be part of the diagnostic criteria for migraine.¹² In nearly all studies, the frequency of a positive family history in patients with migraine headaches was significantly greater than in controls. Studies in monozygotic and dizygotic twins have also supported a strong genetic component for migraine.¹² The fact that the prevalence of migraine in African and Asian populations is lower than in European and North American populations also favors a genetic component.¹³ Despite this strong evidence for a genetic component for migraine, no predisposing genes have been identified for the common migraine syndromes, migraine with aura (MA) and migraine without aura (MO). Insight into the molecular mechanisms of migraine was provided by identification of mutations associated with a rare subtype of MA, familial hemiplegic migraine (FHM). This autosomal dominant disorder is characterized by headache attacks preceded or accompanied by episodes of hemiplegia, sometimes lasting days. Mutations in the ion channel genes CACNA1A¹⁴ and SCN1A¹⁵ and in the sodium-potassium transporter gene ATP1A2¹⁶ have been found in families with FHM. Within these reported families, some family members with FHM mutations report only MO or MA.

Classical segregation analysis in families with common migraine syndromes does not suggest an autosomal dominant or autosomal recessive inheritance but rather suggests a polygenic inheritance.^{17–19} However, segregation analysis cannot detect whether one phenotype is caused by different genotypes and does not analyze for reduced penetrance. Clearly this type of analysis does not exclude the possibility that some families such as those with MAV may have a simple Mendelian pattern of inheritance. To assess this possibility, we performed a detailed phenotype analysis of a large multigenerational family with MAV and combined this with a thorough characterization of identity-by-descent (IBD) analysis using dense single nucleotide polymorphism (SNP) arrays.

METHODS

Case Material

The proband presented to our Neurology Clinic reporting long-standing episodes of MA dating back to age 11, with more recent onset of spontaneous episodes of vertigo. She has a large family and reported that several cousins and their children also suffered from MAV. We asked her to contact as many family members as she could and ask them if they were willing to participate in a study on the genetics of MAV. Our study protocol was approved by the local Institutional Review Board. Phone interviews were conducted by a trained research associate using a standardized questionnaire that included questions that covered all of the International Headache Society (IHS) criteria for migraine with and without aura (available on request). The questionnaire also included detailed questions about vertigo, hearing loss, motion sickness, and general medical problems. After each interview was completed, the research associate and one of the senior authors reviewed the questionnaire data and defined the phenotype. In cases where questions arose during this review process, the patient was called back and the questionable responses were clarified. We used the IHS criteria²⁰ to define MA and MO. MAV was defined by at least 3 spontaneous attacks of vertigo (an illusion of movement) that lasted for more than a minute in a family member who met the IHS criteria for migraine. These episodes of vertigo did not have to occur with an aura but other causes of vertigo (including associated hearing loss) were ruled out. Patients with positional vertigo were excluded. All family members who agreed to participate provided a blood sample for genotyping on a 250K Affymetrix SNP array.

Genotyping

Genomic DNA from each individual was extracted from peripheral blood with the PureGene kit (Gentra System) or saliva using DNA GENOTEK kit, and diluted to 50 ng/μL with TE buffer (0.1 mM EDTA, 10 mM Tris HCL, pH 8.0). The GeneChip® Human Mapping (GHM) 250K Assay was performed according to Affymetrix GHM 250K Assay Manual (Affymetrix, Santa Clara, CA, USA, <http://www.affymetrix.com>) within the UCLA DNA Microarray Facility. In total, 19 samples were hybridized on GHM 250K NSP arrays. BRLMM analysis tool 1.0 was used for allele calling and 97.8% of the SNPs were called on average (SD = 2.0).

Ancestral IBD Analysis

For linkage analysis, ancestral IBD mapping was performed. Taking advantage of a dense SNP set, we could successfully identify IBD regions by typing only the affected individuals in the last generations of each small family branch (Fig. 1). Some of the samples that had descendants were still genotyped because of the gap in sample collections between the connecting generations and the later generations. By searching for long continuous intervals that were compatible with a common extended haplotype among all the affected individuals, we were able to identify ancestral IBD intervals.²¹ This approach is logically similar to genomic mismatch scanning.²² In regions where subjects share a DNA fragment, they must always share an allele at SNPs therein, whereas in regions where they do not share a fragment, there will be frequent occurrences of SNPs where they do not share an allele, ie, one sample is AA genotype and the other is BB genotype. An ancestral IBD mapping algorithm has been implemented in a custom script in Mathematica (Merriman et al, available on request). This algorithm reads in dense SNP genotyping data and scans for counter-evidence of a shared allele on either chromosome by tallying the frequency of AA genotype in one individual as compared to BB genotype in the other individuals in the pairwise comparison. This process is performed throughout the genome to delineate the boundaries of possible IBD fragments across multiple sample sets. A conservative error rate of 1% was used to allow the algorithm to tolerate possible genotyping errors as it scans through windows with different number of SNPs: 500, 1000, 1500, and 2000 SNPs. Intervals with no counter evidence of incompatible AA/BB comparisons over a 150 SNP interval are likely to be identical by descent. We exclude from analysis any genomic interval that is insufficiently informative with SNP density <30 SNPs/cM. Genomic regions with low SNP density like centromeric regions were excluded within the algorithm by setting the maximum gap allowed between SNPs to be 0.35 cM and we note that 85% of the genome is covered. The resulting blocks identified here, which are all larger than 5 cM, are most compatible with an underlying IBD fragment because they are substantially larger than the genomic background level of block sizes (mean = 0.5 cM (SD = 0.7 cM)). Thus, it is more likely that such a large IBD block is inherited from a recent common ancestor, and becomes a candidate region for the disease in question. Family relationships were confirmed by running pairwise comparisons between the genotyped samples, and there was no difference from the reported relationships.

RESULTS

Clinical Data

The proband was a 49-year-old woman who presented with recurrent episodes of vertigo dating back about 5 years. She had a prior history of MA since age 11 years. Her aura was typically composed of a scintillating scotoma along with left-sided numbness which was usually followed by a right unilateral throbbing headache. Photophobia, phonophobia, nausea, and vomiting accompanied the headaches. The vertigo attacks occurred spontaneously separate from her other migraine symptoms, usually lasting for several hours at a time. She also had a long-standing history of motion sensitivity both for self and surround motion.

Her neurological examination was normal. A magnetic resonance imaging scan of the brain, audio-metric testing, and vestibular function testing were within normal limits. The diagnosis of MAV was made and she was started on amitriptyline 25 mg at night but she discontinued this medication after several weeks because of excessive drowsiness. She then started paroxetine 20 mg at night and reported good results with a marked decrease in the frequency of her headaches and vertigo attacks. She has remained on paroxetine for several years and she uses meclizine on an as-needed basis for breakthrough vertigo spells. She uses sumatriptan for relief of her migraine headaches.

The extended pedigree of this large family with MAV is shown in Figure 1. Overall, we interviewed 45 family members, 8 of whom met the criteria for MAV (Table 1). In all cases, the vertigo attacks began either around the time of migraine headaches (2 of 8) or years after the onset of headaches (6 of 8). The age of onset of MAV ranged from 7 to 47 years. The duration of vertigo attacks ranged from minutes to days, and the frequency of attacks varied from a few per week to a total of 4 over a lifetime. All but one patient with MAV reported nausea at the time of the vertigo attacks, and all reported imbalance. Photophobia, tinnitus, and headache were reported less frequently with the vertigo attacks. Five of 7 women with MAV also reported severe motion sensitivity throughout their lifetime, whereas the only man with MAV reported only mild motion sensitivity.

Of the 39 family members interviewed (spouses excluded), 20 met the IHS criteria for MA or MO (Table 2). Ten of 20 had aura with at least some of their headaches, and one had aura without headache. All 11 patients with aura had classical visual symptoms at some time, but 7 also reported hemisensory loss with some of the aura. Four reported aphasia with some of the aura and 2 reported unilateral weakness with some of the aura. These 2 meet the criteria for FHM according to the new IHS criteria. In 11 of 20, migraine (MO or MA) started at or before the age of 16, and 19 of 20 with headaches graded their headaches as severe.

We had little information on the first and second generations since most of these subjects had died, and the single remaining subject did not remember ever having any migraine symptoms (II-9). It is possible that affected family members were overrepresented in the interview sample (since they had more motivation to participate). Interestingly, 2 of 6 in-laws who participated met the IHS criteria for MO, consistent with the high prevalence of MO in the general population. Within this large pedigree, there was no consistence pattern for inheritance of combinations of migraine symptoms. Parents with or without aura could have children with or without aura. Parents and siblings with complicated migraine symptoms had children and other siblings with MO.

Genetic Studies

On examining the pedigree (Fig. 1), there are multiple members in the third and fourth generations with migraine symptoms including MAV. It is possible that a simple autosomal dominant trait with decreased penetrance in men could explain the inheritance of all migraine symptoms although the number of affecteds is greater than would be anticipated. Furthermore, there are affecteds in every branch of this large pedigree, suggesting the likelihood of a polygenic inheritance.

Eight first and second cousins affected with MAV were available for analysis. The initial analysis was to determine if all affecteds with MAV shared a common interval of their genome that was inherited IBD from a shared ancestor within the pedigree. Analysis was done in a pairwise fashion (total 28 pairwise scans) and then the area of maximal overlap was identified. We set the minimum interval size of each pairwise comparison at 20 cM such that chance sharing of such large intervals is small (empiric probability of finding intervals >20 cM is 3.7×10^{-4} based on 16,325 random pairwise comparisons between unrelated individuals.)

However, no single large region was found that all 8 shared. Since females are predominantly affected with MAV in this family and as sex-split analysis is common for migraine genetic studies because of the high female to male ratio, we analyzed just the 7 females with MAV in a similar manner to ascertain if a large IBD interval was shared among all 7. Again, no single interval was detected. However, we observed a 6.7 Mb interval on chromosome 11q (67957871-74605123 NCBI Build 34), which included 312 SNPs and was shared by 6 of the 7 affected females (Fig. 2, Table 2). This same interval on chromosome 11q was shared by 11 of 15 affected females with migraine (MO or MA). No other region of the genome was shared by as many affected family members. While this interval is highlighted relative to the remainder of the genome, the overall linkage signal of the inferred haplotype was not significant. We assigned a rare allele frequency to the haplotype of 0.1%. The significance of the putative susceptibility haplotype was calculated for this interval using Simwalk2.²³ The logarithm of odds (LOD) score ranged between 1.34–1.57 with the penetrance of 20–40% and phenocopy of 1%²⁴ for the 6 MAV females and 1.86–1.9 with the penetrance of 60–80% and phenocopy of 15%²⁵ for the 11 migraine females. A range of possible penetrances of the disease allele were used because we have little relevant data on penetrance of the disease allele. We assumed a higher prevalence and penetrance for the migraine phenotype relative to the rarer MAV. The shared segment analysis demonstrated here may highlight an interval of interest within this family that would not be readily detected by standard linkage analysis.

DISCUSSION

In this large multigenerational family, we analyzed 8 cousins and second cousins with MAV by careful phenotypic assessment and complete genomic SNP typing. Twenty of the individuals within the family met the IHS criteria for migraine, which included all 8 individuals with vertigo. Remarkably, just about every migraine related phenotype was observed in this family. In addition to vertigo attacks and classical migraine visual aura, 7 subjects reported hemisensory loss, 4 aphasia, and 2 hemiparesis with some of their aura.

With regard to the MAV, nausea and imbalance were consistently associated symptoms whereas photophobia and headache were less consistently associated symptoms. Three of 8 family members with MAV had isolated vertigo attacks without any other associated migraine symptoms. In most, the vertigo attacks began many years after the onset of migraine, although in 2 the vertigo attacks began at about the same time as other migraine symptoms. The duration of vertigo attacks ranged from minutes to days and the frequency of attacks varied from a few per week to a total of 4 over a lifetime. This variability in clinical features of MAV has been found in prior studies^{4,26,27} and suggests that even within a single family, the phenotype of MAV can be quite variable.

Using a 250K SNP array which provides excellent coverage to thoroughly assess IBD sharing between close relatives even in the absence of some family members being available, we could not find any region of the genome that was shared IBD by all affected family members with migraine or MAV. This would be consistent with a polygenetic inheritance of migraine and MAV even in this single multigenerational family. Thus, some individuals have different risk alleles or nongenetic causes of their migraine. The most compelling genetic finding extended from the thorough search for IBD intervals across subsets of the sample defined by sex and migraine related symptoms. This analysis revealed a 6.7 Mb interval on 11q which was shared by 6 of 7 females with MAV. We proposed that this region may contain a susceptibility allele for MAV that is penetrant exclusively or predominantly in women. A feature of migraine and MAV that must be explained with any genetic model is the marked female predominance seen with both of these conditions. The likelihood that genetic polymorphisms could affect females differently than males is not far-fetched. Many genes have different expression profiles in the brains of females and males and hormonal differences could affect the gene products

differentially in females and males. For example, polymorphisms in the estrogen and progesterone receptors have been identified as possible susceptibility alleles for migraine.²⁸

Some of the candidate genes in the region are KCNE3, SHANK2, PDE2A, and DHCR7 based on their high brain expression, roles in cation transport and synapse association. No copy number variations (CNVs) were identified within the region based on the analysis of intensity values from the 250K SNP arrays. There have been numerous genome wide scans performed on families with MO and MA and multiple different genetic loci have been linked to MO and MA.^{29,30} However, the chromosome 11q locus found here has not been previously identified. Also, numerous potential susceptibility alleles for migraine have been reported but none of them reside in the 11q locus.³¹ The finding of multiple different loci for migraine syndromes is not unexpected since there has been similar experience with other complex traits with polygenetic inheritance including hypertension, diabetes, and schizophrenia.

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Abbreviations

IBD	identity-by-descent
MAV	migraine-associated-vertigo

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Fig 1.

Pedigree of the family. Individuals affected with vertigo, migraine headaches, and visual aura are shown. Dots indicate no information (no interview). Open symbols indicate unaffected family members. Proband is denoted with a filled arrowhead. The 3 patients with isolated vertigo are denoted with cross and the 2 patients with unilateral weakness are denoted with double cross right to each sample. Samples that were genotyped are denoted with asterisk.

Fig 2.

Genome wide ancestral IBD mapping scan for 6 of 7 females with MAV. After all 7 affected females were scanned for IBD and shown to have no longer block shared by all than the noise level, each of the 7 samples were removed from the remaining 6 and reanalyzed. When sample IV-6 was removed, a long IBD interval shared by the remaining 6 affected on chromosome 11 was detected. IBD block size is plotted along the y-axis in cM and SNPs along the x-axis. Chromosomes are listed in numerical order across the top. IBD = identity-by-descent; MAV = migraine-associated vertigo; SNP = single nucleotide polymorphism.

Table 1

Clinical Features in Family Members With Recurrent Vertigo

ID	Age (years)/sex	Age of onset		Vertigo attack			Motion sensitivity
		Migraine	Vertigo	Duration	Frequency	Associated symptoms	
III—25	49/F	11	44	Hours	1–2/week	Imbalance bilateral tinnitus	Severe
III—16	66/F	7	7	Minutes	Weekly stopped age 45	Photophobia nausea imbalance headache	Mild
III—14	60/F	5	40	Minutes	4–5/year	Nausea imbalance photophobia	Severe
III—2	64/F	19	30	Days	4 Total	Nausea headaches imbalance	Severe
IV—20	37/F	15	33	Hours	2/week	Nausea imbalance	Severe
IV—6	34/F	16	23	Minutes	20 Total	Nausea photophobia headache imbalance	Mild
IV—5	23/F	20	20	Minutes	2/year	Nausea photophobia headache	Severe
IV—16	48/M	22	47	Days	1/month	Imbalance	Mild

F = female; M = male.

Table 2

Migraine and Vertigo Status in Affected Members

ID	Age (years)/sex	IHS migraine headache	IHS aura	Onset ≤ 16	Vertigo	Haplotype [‡] sharing
1	III—25	49/F	+	+	+	+
2	III—23	65/F	+	—	—	—
3 [‡]	III—21	63/F	—	—	—	+
4	III—20	46/F	+	—	—	—
5	III—18	59/M	—	+	—	—
6	III—16	66/F	—	+	+	+
7	III—14	60/F	—	+	+	+
8	III—10	71/M	+	+	—	—
9	III—9	60/F	+	+	—	+
10	III—2	64/F	+	—	+	+
11	IV—22	40/F	+	+	—	+
12	IV—20	37/F	+	+	+	+
13	IV—18	37/F	—	+	—	+
14	IV—16	48/M	—	—	+	—
15	IV—15	42/F	+	—	—	—
16	IV—12	34/M	—	—	—	+
17	IV—10	34/M	—	—	—	—
18	IV—9	39/F	+	+	—	+
19	IV—6	34/F	+	+	+	—
20	IV—5	23/F	+	—	+	+
	15F/5M	19/20	11/20	11/20	8/20	12/20

[‡] Status of ch11q haplotype sharing.

[‡] Excluded from genotyping because the sample was a connecting generation. Haplotypes were inferred from the descendants.

F = female; IHS = International Headache Society; M = male.