A visual migraine aura locus maps to 9q21-q22

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ABSTRACT

Objective: To identify susceptibility loci for visual migraine aura in migraine families primarily affected with scintillating scotoma type of aura.

Methods: We included Finnish migraine families with at least 2 affected family members with scintillating scotoma as defined by the International Criteria for Headache Disorders-II. A total of 36 multigenerational families containing 351 individuals were included, 185 of whom have visual aura and 159 have scintillating scotoma. Parametric and nonparametric linkage analyses were performed with 378 microsatellite markers. The most promising linkage loci found were fine-mapped with additional microsatellite markers.

Results: A novel locus on chromosome 9q22-q31 for migraine aura was identified (HLOD = 4.7 at 104 cM). Fine-mapping identified a shared haplotype segment of 12 cM (9.8 Mb) on 9q21-q22 among the aura affecteds. Four other loci showed linkage to aura: a locus on 12p13 showed significant evidence of linkage, and suggestive evidence of linkage was detected to loci on chromosomes 5q13, 6q25, and 13q14.

Conclusions: A novel visual migraine aura locus has been mapped to chromosome 9q21-q22. Interestingly, this region has previously been linked to occipitotemporal lobe epilepsy with prominent visual symptoms. Our finding further supports a shared genetic background in migraine and epilepsy and suggests that susceptibility variant(s) to visual aura for both of these traits are located in the 9q21-q22 locus. **Neurology® 2010;74:1171-1177**

GLOSSARY

ASP = affected sibpairs; **CSD** = cortical spreading depression; **FHM** = familial hemiplegic migraine; **GWA** = genome-wide association; **HLOD** = lod score under locus heterogeneity; **ICHD-II** = International Classification of Headache Disorders, second edition; **MA** = migraine with aura; **MO** = migraine without aura; **NPL** = nonparametric linkage.

Migraine is a common and disabling complex brain disorder, presenting in episodic attacks that may have up to 4 phases: the prodromal phase, the aura phase, the headache phase, and the postdromal phase. According to the current definition of the International Classification of Headache Disorders, second edition (ICHD-II), by the Headache Classification Subcommittee of the International Headache Society,¹ migraine aura precedes headaches and consists of visual disturbances, hemisensoric, hemiparetic, or dysphasic symptoms, or a combination. Characteristics of migraine aura include gradual development, duration from 5 to 60 minutes, and complete reversibility. Neuronal mechanisms such as cortical spreading depression (CSD) are thought to explain part of migraine aura,² but there are still many unknown factors. Shared etiology has been suggested to exist with other common CNS disorders, including stroke, epilepsy, and depression, all well-known comorbidities of migraine.^{3,4}

The genetic background of migraine aura is not established, although several loci have been identified for common migraine, i.e., migraine with aura (MA) and migraine without aura (MO).^{5,6}

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Editorial, page 1166

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Mutations in 3 genes involved in ion transport (*CACNA1A*, *ATP1A2*, *SCN1A*) cause a rare Mendelian subtype of MA, familial hemiplegic migraine (FHM), characterized by unilateral motor weakness during the aura. As FHM is a Mendelian trait, it is reasonable to speculate that variants in these genes could be involved in the pathophysiology of migraine aura, given the high degree of correlation between the aura features of MA and FHM. However, our previous study of 155 ion transport genes on 841 unrelated Finnish MA cases and 884 unrelated non-migraine controls indicates that common variants in these genes do not have a major role in MA susceptibility.⁷ On the other hand, mutations in the FHM genes seem to be involved in some epilepsies.⁴

There are several challenges specifically related to migraine aura that complicate genetic studies. For example, the high degree of variability in aura causes MA patients to rarely describe their attacks identically. Also, the lack of available patient samples with well-defined aura subtypes places severe limits on sample size. Recent advances in genome-wide association (GWA) technology have resulted in considerable progress in identifying variants involved in common diseases.⁸ However, the combination of low sample size, high variability, and the expectation that rare variants would likely play a large role in MA made linkage analysis the preferable option for this study. Also, our sample includes large, multigenerational families, which often hold tremendous power for linkage, if similar trait features segregate within each pedigree. For our study, linkage analysis was chosen due to its robustness in identifying highly penetrant variants contributing to migraine aura.

To search for susceptibility loci for visual aura, we chose 36 migraine families from among the 1,400 Finnish families participating in the Finnish Migraine Gene Project based on the presence of scintillating scotoma in at least 2 family members. Our genome-wide linkage study revealed a locus on 9q21-q22 for visual aura. This region overlaps the locus recently pinpointed for occipitotemporal lobe epilepsy in a Belgian family that also had members with migraine with visual aura.⁹

METHODS Subjects. For this study, we identified 36 unrelated multigenerational families from a large patient collection (the Finnish Migraine Gene Project), ascertained for MA. Inclusion criteria for a family to be included in the present study were to have at least 2 affected members, preferably first-degree relatives, with scintillating scotoma type of visual aura symptoms (table e-1 on the *Neurology*[®] Web site at www.neurology.org) and MA end-diagnosis fulfilling the criteria 1.2.1 of ICHD-II for typical aura with migraine headache, i.e., requiring the presence of ICHD-II headache in addition to aura.¹ The study sample consisted of 351 genotyped subjects (224 women and 127 men) collected from clinics throughout Finland (table 1). Index patients in each family underwent an extensive neurology interview (V. Arto, M.K., S.V.). Data on the ICHD-II attack symptoms as well as aura symptoms for all participants were collected using the validated Finnish Migraine Specific Questionnaire for Family Studies.¹⁰ All participants gave informed consent, and approval to conduct the research was obtained from the Helsinki University Central Hospital Ethics Committee (approval no. 622/E0/02).

Distribution of migraine diagnoses is shown in table 2. Of the 351 genotyped individuals, 185 (52%) fulfilled the ICHD-II criteria of migraine aura. Most of the patients (n = 160) had migraine attacks fulfilling the ICHD-II criteria 1.2.1 for typical aura with migraine headache diagnosis, with both aura and migraine headache fulfilling ICHD-II criteria (MA). For the rest (n = 25), headache either did not fulfill the criteria for migraine headache (n = 21, 1.2.2 typical aura with nonmigraine headache) or was absent (n = 4, 1.2.3 typical aura without headache). The most prominent feature of aura was scintillating scotoma, present in 86% of the 185 patients with aura (table e-1). In our sample, 35 patients were diagnosed with MO.¹

Genotyping. Genotyping was based on the LMS-MD10 microsatellite marker set (Applied Biosystems, Foster City, CA) of 378 markers, with an average of 10 cM marker distance, and performed using the ABI 3730 capillary sequencing instrument.¹¹ For fine-mapping, 11 additional markers on chromosome 9q and 2 on chromosome 12p were selected using location, heterozygosity, and primer information provided by the UCSC database (<http://genome.ucsc.edu/>).¹² Mendelian inconsistencies in the genotypes were detected using PedCheck v1.1 software.¹³

Table 1 Characteristics of the 36 families selected for the study

Pedigree features	Mean	Range	Mode ^a	Total
Subjects	13.4	6-34	15	482 ^b
Generations ^c	3.4	3-5	3	—
3				21
4				14
5				1
Genotyped subjects	9.8	3-19	8	351
Visual aura	5.1	2-12	4	185
Scintillating scotoma	4.4	2-12	3	159

^aMode = the value that occurs most frequently.
^bThis number includes 131 individuals who have not provided blood sample but are important for linkage information.
^cIncludes all family members.

Table 2 Phenotypes of the genotyped individuals categorized by aura symptoms

Migraine aura	Headache type	No.	% Female
ICHD-II-aura	Migraine headache	160 ^a	79.4
	Probable migraine headache ^b	13	46.2
	Nonmigraine headache	8	25.0
	No headache	4 ^c	25.0
Total (ICHD-II-aura)		185 ^d	73.5
Unclassified aura	Migraine headache	25	72.0
	Probable migraine headache ^b	5	60.0
	Nonmigraine headache	3	100.0
	No headache	1	100.0
Total (unclassified aura)		34 ^e	73.5
No aura	Migraine headache	35 ^f	60.0
	Probable migraine headache ^b	28	42.9
	Nonmigraine headache	12	58.3
	No headache	48	37.5
Total (no aura)		123	47.2
Missing diagnosis	Missing diagnosis	9	55.6

Abbreviation: ICHD-II = the International Classification of Headache Disorders (second edition).

^aNumber of individuals with the end-diagnosis of migraine with aura.

^bProbable migraine is episodic headaches with some migrainous features that do not fulfill the ICHD-II criteria for migraine with or without aura.

^cNumber of individuals with migraine aura but without headache; i.e., equivalent migraine.

^dIndividuals with aura fulfilling the ICHD-II criteria of migraine aura but whose migraine headache does not necessarily fulfill the ICHD-II criteria.

^eIndividuals with unclassified aura have aural features that do not fulfill all the ICHD-II criteria for migraine aura. Migraine headache does not necessarily fulfill the ICHD-II criteria.

^fNumber of individuals with end-diagnosis of migraine without aura.

Likely mistyped alleles were identified using SimWalk v2.91 software.^{14,15}

Statistical analyses. Two-point parametric and nonparametric linkage (NPL) analysis and multipoint NPL were performed. We applied an affecteds-only strategy; only individuals fulfilling ICHD-II diagnostic criteria of aura were treated as affecteds and all other individuals were set to unknown. In the parametric analyses, we used a dominant model of inheritance: disease allele frequency was set to 0.001 with a reduced penetrance rate of 0.9 and a phenocopy rate of 0.024.^{16,17} Allele frequencies were calculated from the genotypes of all individuals.

Two-point parametric linkage analysis was performed both under locus homogeneity and under locus heterogeneity by the computer programs LINKAGE and HOMOG.^{18,19} The AUTOGSCAN v1.0.3 software was used to automate the genome-wide linkage analyses.²⁰ A lod score under locus heterogeneity (HLOD) greater than 3.3 is considered significant evidence of linkage,²¹ and HLOD threshold of 1.9 indicates suggestive evidence of linkage. The significance of the highest observed lod score was tested by simulating 1,000 replicates using the program SIMULATE,²² using allele frequencies from the microsatellite marker at the peak lod score.

In addition, 2-point NPL was performed by analyzing the identity by descent status of affected sibpairs (ASP) to investigate whether any of the putative migraine loci act in a recessive fashion. In the ASP analysis, suggestive evidence of linkage was indicated by a lod score greater than 1.74.¹¹

Finally, multipoint NPL was performed using SimWalk v2.93, modeling both dominant and additive inheritance patterns without subdividing large families.¹⁴ For modeling dominance we used the Max-Tree NPL statistic; for additive we used NPL-all. We also used the Kong and Cox significance testing procedure, which is more robust to missing data and less conservative than previous procedures (Day-Williams et al., unpublished data).²³ Here, a *p* value ≤ 0.001 was considered as significant evidence of linkage and a *p* value ≤ 0.01 as suggestive evidence of linkage.

Haplotype analysis on 9q21-q31 was performed on families showing evidence of linkage to this region, using both GENEHUNTER v2.1_r6 software²⁴ and the SimWalk v2.91 haplotyping option. Linked families were identified by their family-specific, multipoint NPL *p* values in this region.

RESULTS Genome-wide 2-point linkage analysis.

The parametric 2-point linkage analysis showed significant evidence of linkage, HLOD 4.7 ($\theta = 0.12$), between migraine aura ($n = 185$) and a locus on 9q31, D9S1690 at 104 cM. No other marker reached genome-wide significance levels. The ASP 2-point linkage analysis also found evidence of linkage at D9S1690, ASP lod 2.6. Evidence of linkage to 3 other markers surrounding D9S1690 in 9q21-q31 was also detected in the ASP analysis (ASP lod > 1.74). The maximum ASP lod was 2.7 for D9S283 at 93 cM. The plots of both 2-point parametric HLOD and ASP lod scores for chromosomes 1–22 and X are shown in figure 1. An additional test of significance, by simulating 1,000 replicates of 36 families assuming no linkage at the marker D9S1690, showed that suggestive evidence of linkage was reached one time by chance but no significant evidence of linkage was gained. The maximum simulated lod score was 2.3 in these families.

In addition to chromosome 9, the ASP analysis found suggestive evidence of linkage between migraine aura and 5q13, ASP lod 1.8, at 91 cM. Parametric analysis found nearly suggestive evidence of linkage to 12p13, HLOD 1.8 ($\theta = 0.0$), at 15 cM.

Genome-wide multipoint NPL analysis. Multipoint NPL analysis using an additive model indicated a *p* value ≤ 0.0001 between migraine aura and a marker D9S1690 at 104 cM in 9q31. Using the Max-Tree NPL statistic, which is designed to detect dominant inheritance patterns, significant evidence of linkage was detected in 9q22-q31. Note that both statistical analysis methods, 2-point parametric linkage and multipoint NPL, found significant evidence of linkage at D9S1690. In addition to chromosome 9, multipoint NPL also found evidence of linkage at 15 cM in 12p13 using an additive model (*p* = 0.0003), and suggestive evidence of linkage both in 6q25 and 13q14

Figure 1 Results of the genome-wide linkage analyses for visual migraine aura

(A) Plots of parametric (black bars) and nonparametric (gray bars) 2-point linkage analysis for chromosomes 1-22 and X. (B) Plots of multipoint nonparametric linkage (NPL) analysis using statistics that model dominant (black squares) and additive (white circles) inheritance patterns for chromosomes 1-22. Horizontal line shows a significance threshold for the significant HLOD (A) and NPL (B) results. ASP = affected sibpairs; HLOD = lod score under locus heterogeneity.

using both a dominant and an additive model. The summary plots of the multipoint NPL analyses are shown in figure 1.

Fine-mapping of 9q21-q31. Due to the consensus, significant evidence of linkage to 9q21-q31, we fine-mapped the region. Eleven additional microsatellite markers were genotyped in the region extending from 86 cM to 124 cM on 9q to increase linkage information and further localize the signal. The mean map distance became 2.7 cM in this region. Multipoint NPL analysis found significant evidence of linkage in this region with both the dominant and additive model statistics. Significant linkage was found between the 9q21-q31 locus and the presence of visual aura. The p value of 0.0002 was found with 2 adjacent markers D9S1690 and D9S271 in 9q31 when modeling additive inheritance. Four other markers, at 86-95 cM in 9q21-q22, also passed the signifi-

cance threshold. Table e-2 includes linkage results from fine-mapping of 9q21-q31.

Sex-specific analysis. We also performed a sex-specific parametric linkage analysis of chromosome 9 since previous studies had indicated gender-specific differences at linked loci for migraine.^{11,17,25} No improvement in the linkage signal was seen. At the peak marker D9S1690, when only females with aura were considered affected ($n = 136$), suggestive evidence of linkage was detected, HLOD 2.9. When only males with aura were considered affected ($n = 49$), nominal evidence of linkage was observed, HLOD 1.3.

Haplotype analysis on 9q21-q31. Individual families, for which visual migraine aura was linked to 9q21-q31, were identified by their family-specific, multipoint NPL p values in this region. The 22 families identified contain 208 genotyped individuals of which 106 are considered affected with visual aura.

In 17 out of the 22 families, all or almost all affected individuals shared a family-specific haplotype at the markers D9S253, D9S283, and D9S1796 from approximately 86 cM to 98 cM. Eight families exhibit recombinations in their haplotypes that define one or both ends of this 12-cM (9.8 Mb) region. A summary of the haplotyping results for 9q21-q31 is shown in figure e-1.

Linkage analyses for migraine with aura end-diagnosis and for migraine headache. To investigate linkage between patients with MA end-diagnosis ($n = 160$) and the 9q21-9q31 region, 2-point parametric linkage analysis was performed. With this alternative phenotype, significant but reduced evidence of linkage to the marker D9S1690 was observed, HLOD 4.3 ($\theta = 0.14$). To ascertain that the identified region predisposes to migraine aura and not to migraine headache, we performed an analysis with all 220 individuals fulfilling ICHD-II criteria for migraine headache as affecteds, including the 160 individuals with MA end-diagnosis. The 2-point parametric linkage analysis showed only suggestive evidence of linkage to D9S1690, HLOD 2.9.

Fine-mapping of the 12p13 region. Due to the significant evidence of linkage in 12p13, we reanalyzed the region with 2 additional markers, D12S1725 and D12S1625. The mean interval in this region became 3.1 cM. The parametric linkage results did not improve. However, the multipoint NPL results enhanced significantly when 2 additional markers were included in the analysis; significant evidence of linkage was detected among 4 markers in 12p13 and visual aura trait using the additive model. Table e-2 includes linkage results from fine-mapping of 12p13.

DISCUSSION We found significant evidence of linkage between visual migraine aura and the chromosomal region 9q21-q31 using 36 multigenerational Finnish migraine families. Haplotype analysis restricted the linked region to 9.8 Mb (12 cM) on 9q21-q22, which contains more than 30 coding genes. This region stands out among other identified migraine loci because it had previously been linked to occipitotemporal lobe epilepsy, which also has prominent visual symptoms.⁹ The underlying pathophysiology for typical visual symptoms in MA and epilepsy is presently unknown. We believe the variants in this locus are likely to significantly contribute to the visual aura symptoms in migraine.

The Finnish families selected for this study were primarily affected with the scintillating scotoma type of aura. The largest parametric linkage signal on 9q31, HLOD 4.7, was detected when all subjects with aura ($n = 185$) were considered affected, in-

cluding those having aura but not migraine headache ($n = 25$). The evidence of linkage at this locus decreased ($n = 160$, HLOD 4.3) using MA end-diagnosis and decreased further when considering only ICHD-II migraine headache ($n = 220$, HLOD 2.9). The difference in lod scores suggests a direct link between this locus and the aura pathophysiology. No gender-specific linkage was detected at this locus.

As mentioned, our linked region overlaps with the linked locus detected in a Belgian family with occipitotemporal lobe epilepsy.⁹ Some members of this family also have migraine with visual aura. One of the genes in this region, *SCH3*, is highly expressed in occipital and temporal lobes, and regulates the adaptive response of neurons against environmental stress.²⁶ In our data set, 7 of the 351 genotyped individuals from 5 different families reported having epilepsy. Of these 7 individuals, 5 had idiopathic epilepsy. Of those 5, 3 also had migraine aura. One family in our data set had 3 epilepsy patients. Due to the low number of epilepsy patients in our data set, no statistical analysis regarding epilepsy was conducted.

Clinical similarities of migraine and epilepsy are self-evident. Both are episodic disorders associated with cortical hyperexcitability with neurologic manifestations. They also tend to cluster together in some families.⁴ Some observant clinicians have even characterized migraine as “epileptic attacks in slow motion,” based on similarities in their clinical manifestations. Epidemiologic studies have shown that patients with epilepsy have over 2 times higher prevalence of migraine than controls,²⁷ and adolescents with MA have 8 times higher risk for epilepsy than controls.²⁸ Also, in the Finnish migraine cohort comorbidity between migraine and epilepsy has been detected, especially in men with MA.²⁹

Similarities in ionic imbalance make the colocalization of migraine aura and occipital epilepsy an intriguing possibility. In migraine, neural excitability may lower the threshold for CSD, which is considered the correlate of visual migraine aura.³⁰ CSD induces secretion of Ca^{2+} , Na^{+} , and K^{+} ions in migraine aura. A similar increase of extracellular K^{+} has been observed in human epileptic brain tissue.³¹ Mutations in the 3 FHM genes induce ionic imbalance, and these genes are involved in rare polygenic epilepsies, for example generalized epilepsy with febrile seizures.³² However, the role of ion channel genes in common migraine has not yet been established.⁷ Several antiepileptic drugs that suppress ion signaling are efficacious as prophylactic medication for migraine. Among these drugs, lamotrigine is of

particular interest since there is some evidence that it especially inhibits aura.³³

In addition to the 9q21-q31 locus, another interesting finding in our study is significant evidence for linkage of visual migraine aura to a locus on 12p13. This region contains 3 cerebral expressed genes encoding members of potassium voltage-gated channel subunits. These genes showed no evidence of association with MA in our previous case-control study on 155 ion channel genes.⁷ However, that study would likely not have found rare variants (minor allele frequency <10%) contributing to MA or visual aura. Thus, additional family-based analyses would be useful to determine the possible role of these 3 genes in migraine.

Suggestive evidence of linkage to 3 other loci was also detected. Both 5q13 and 13q14 reside in the proximity of previously reported migraine loci.^{6,34} The locus on 6q25 has not been previously reported in genome-wide linkage studies.

Several previously detected migraine loci, 4q21-q24,^{16,17,25} 6p12-p21,³⁵ 10q22-q23,¹¹ 11q24,³⁶ 14q21-q22,³⁷ and 17p13,¹⁷ failed to show even suggestive evidence of linkage in this study. This was expected considering the specialized family selection criteria used here. The target phenotype was a homogenous visual migraine aura throughout each family, regardless of the associated headache characteristics. The 9q21-q22 locus may be highly specific to visual migraine aura. In our previous studies, the loci 4q24,^{16,17} 10q22-q23,¹¹ and 17p13¹⁷ are likely to be linked to typical migraine headache. Loci for aura and headache therefore seem to differ, although they may overlap at some loci as well. Careful phenotyping of migraine is clearly crucial when choosing families for linkage studies. At one end of the spectrum are families with prominent visual aura, at the other end families with migraine headache, while most families lie in between. Large family collections are crucial to finding families with sufficiently homogenous phenotypes.

We believe it is an important finding that 2 “visual forms” of neurologic disorders, MA and occipitotemporal lobe epilepsy, are linked to the same 9q21-q22 locus. The phenotype heterogeneity caused by mutations in the FHM genes³⁸ allows one to speculate that a gene at this 9q locus also has various manifestations. However, despite the natural urge to conclude that there is a specific, shared genetic etiology, this is far from proven. One of the limitations of family-based linkage methods is that the linked region is typically large, harboring dozens of genes. We must remember that there are as many differences between migraine and epilepsy as there are similarities.³⁹ A case-control association study re-

stricted to this region might provide better resolution, but would require a large sample size with strict phenotype requirements, which is not currently available. In spite of these limitations, based on evidence presented here, it is reasonable to hypothesize that genetic variants at 9q21-q22 contribute to overall neuronal excitability, which in some families lead to visual migraine aura, and in others to epilepsy, depending on other genetic and environmental influences.

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by Dr. Päivi Tikka-Kleemola.

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