Shared loci for migraine and epilepsy on chromosomes 14q12-q23 and 12q24.2-q24.3

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ABSTRACT

Objectives: To describe clinical characteristics and to identify susceptibility loci for epilepsy and migraine in a Finnish family with a complex phenotype.

Methods: Participating family members were interviewed and medical files were reviewed. The seizure classification was made according to International League Against Epilepsy criteria. Migraine diagnosis was made using the validated Finnish Migraine Specific Questionnaire for Family Studies and criteria according to the current International Classification of Headache Disorders-II. DNA samples were obtained from 56 family members and nonparametric genome-wide linkage analyses were performed using 382 polymorphic microsatellite markers. The most promising loci were fine-mapped with additional microsatellite markers.

Results: Clinical data were obtained from 60 family members of whom 12 (20%) had idiopathic epileptic seizures. Eight of those 12 (67%) also had migraine. Altogether 33 of the 60 family members (55%) had migraine. Significant evidence of linkage was found between a locus on 14q12-q23 and migraine ($p = 0.0001$). Suggestive evidence of linkage in this region was also found for epilepsy with generalized tonic-clonic seizures ($p = 0.0034$). In addition, significant evidence of linkage was found at a locus on 12q24.2-q24.3 ($p < 0.001$) for migraine alone and for the combined phenotype of migraine and epilepsy.

Conclusions: Our data suggest the occurrence of common susceptibility loci for epilepsy and migraine on chromosomes 14q12-q23 and 12q24.2-q24.3, implicating a shared genetic etiology for these 2 diseases. *Neurology*® 2012;78:202-209

GLOSSARY

ASP = affected sib-pairs; **E** = epilepsy; **FS** = febrile seizures; **GTCS** = generalized tonic-clonic seizures; **GWS** = genome-wide scan; **M** = migraine with or without aura; **MA** = migraine with aura; **M+E** = combined migraine or epilepsy; **MO** = migraine without aura; **NCBI** = National Center for Biotechnology Information; **NPL** = nonparametric linkage; **SNP** = single nucleotide polymorphism; **SUA** = somnolence unconsciousness attacks.

Epilepsy and migraine are chronic paroxysmal neurologic disorders¹ that show high comorbidity. The prevalence of epilepsy in Europe is estimated to be 0.3–0.8%² and of migraine 11–15%.^{3–5} Of patients with migraine, 6% have epilepsy and up to 26% of patients with epilepsy have migraine.^{6–9}

Common genetic factors for epilepsy and migraine have been suggested to exist and ion channel or ion transport dysfunction has been shown to play a role in both diseases.^{10,11} In some families, mutations in *CACNA1A*,¹² *ATPIA2*,¹³ and *SCN1A*¹⁴ genes underlie the rare Mendelian subtype of migraine with aura, familial hemiplegic migraine. Mutations in these genes have also been associated with epilepsy.^{15,16} However, in the vast majority of patients with migraine or with epilepsy, causative genes or variants have remained unknown.^{11,17}

Supplemental data at
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Supplemental Data

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We hypothesized that families comorbid with both epilepsy and migraine share susceptibility variants. To address the issue, we studied a large Finnish family, segregating both conditions, and performed a genome-wide linkage analysis.

METHODS Patients. A five-generation Finnish family in which epilepsy and migraine partially cosegregate was recognized. Altogether 60 of 72 family members were interviewed.

Medical files of all patients with epilepsy were reviewed. Epilepsy and seizure types were classified according to the International League Against Epilepsy criteria.¹⁸

Migraine diagnosis, satisfying the current International Classification of Headache Disorders-II,¹⁹ was based on the validated Finnish Migraine Specific Questionnaire for Family Studies.²⁰

Standard protocol approvals, registrations, and patient consents. The Helsinki University Central Hospital Ethics Committee approved the study (approval no. 424/E7/2002 for epilepsy and approval no. 622/E0/E02 for migraine). Informed consent was obtained from all participants or their representative.

Genotyping. Blood samples of 56 family members were collected, and DNA was extracted using standard protocols. Genotyping was based on the LMS-MD10 microsatellite marker set (Applied Biosystems, Foster City, CA) of 382 markers, with an average of 9.4-cM marker distance and was performed at the Finnish Genome Center.

We selected additional markers for fine mapping using location, heterozygosity, and primer information provided by the National Center for Biotechnology Information (NCBI) database (Build 37.2; www.ncbi.nlm.nih.gov/). We genotyped 5 additional markers on 14q11.1-q23 (extending from 28 to 64 cM with mean map distance 4.5 cM), 3 on 12q24 (from 124 to 140 cM, 4.9 cM), 9 on 9q33-q34 (from 124 to 164 cM, 3.27 cM), and 4 on 20p12-20q11.2 (from 36 to 61 cM, 5.0 cM). Genotyping was performed using Biotools DNA polymerase (B&M Labs, Madrid, Spain) reagents in standard PCR conditions, an ABI 3730 capillary sequencing instrument, and GeneMapper 4.0 genotyping software (Applied Biosystems).

Genotypes from 45 individuals were determined for the genome-wide scan (GWS) and from 56 individuals for fine-mapping.

We detected Mendelian inconsistencies in the genotypes using PedCheck v1.1 software²¹ and identified likely mistyped alleles using the mistyping analysis option of SimWalk v2.96 software.^{22,23}

Linkage analysis. We performed 2-point and multipoint nonparametric linkage (NPL) analysis. Because we assumed multilocus inheritance with variable effect and inheritance patterns, we selected model-free nonparametric analysis methods to search for loci following recessive, dominant and additive inheritance patterns. We performed analyses for each of 4 phenotypes: epilepsy (E), epilepsy with generalized tonic-clonic seizures (GTCS), migraine (M) with or without aura, and combined migraine or epilepsy (M+E). We applied an affecteds-only strategy: In each analysis, only patients who represented the selected phenotype were labeled as affected, and all other individuals were set to unknown. In all analyses, disease allele frequency was set to 0.001.

We performed 2-point NPL by analyzing the identity by descent status of affected sib-pairs (ASP) to investigate whether any of the loci act in a recessive fashion. We used AUTOGSCAN v1.0.3 software to automate the analysis of the GWS.²⁴ In the ASP analysis, suggestive evidence of linkage was indicated by a lod score greater than 2.2 and significant evidence by a lod score greater than 3.6.²⁵

We performed multipoint NPL analysis using SimWalk v2.96 under recessive (Blocks), dominant (Max-tree), and additive (NPL-pairs and NPL-all) inheritance models.²² With more than 25 or so affected, as is the case for the M and combined M+E datasets here, it is no longer feasible to calculate the NPL-all statistic. We also used Kong and Cox significance testing.²⁶ Here, $p < 0.01$ is considered suggestive evidence of linkage, and $p < 0.001$ is significant (Sobel, personal communication, 2011).

Haplotype analysis. We performed haplotype analysis on chromosomes 12 and 14 using the SimWalk v2.96 haplotyping option and the HaploPainter v.029.5 program. Haplotypes that were shared among the affected family members were assumed to be susceptibility haplotypes.

Candidate gene analysis. We selected 2 positional and functional candidate genes for sequencing analysis: *KCNH5* coding for potassium voltage-gated channel, subfamily H (eag-related), member 5 in the 14q23 region; and *CABP1* encoding calcium-binding protein 1 in the 12q24.3 region.

We performed primer design, sequencing, and sequence analysis as described previously.²⁷ Primer sequences are available upon request. Identified variants were compared with the NCBI single nucleotide polymorphism (SNP) database (Build 133; www.ncbi.nlm.nih.gov/snp/).

RESULTS Clinical data. Clinical data were available for 60 family members. Of these 40 had febrile seizures (FS), epilepsy, somnolence unconsciousness attacks (SUA), or migraine. The pedigree is shown in figure 1 and clinical information is found in table e-1 on the *Neurology*[®] Web site at www.neurology.org.

Thirteen of the 60 family members (22%) had had epileptic seizures and 7 (12%) FS (table e-1). The most common seizure type, GTCS, was present in 9 patients with epilepsy. In 10 patients, the age at onset of seizures was between 1 and 5 years, and the cessation occurred in early puberty (table e-1). In 9 of those patients, EEG indicated abnormalities (table e-1), which disappeared during teenage. In 3 patients, intermittent photic stimulation provoked abnormalities (table e-1). In 3 patients, seizures started between age 13 and 18 years (table e-1). In one of them, patient 47, the etiology of epilepsy was probably complications related to pulmonary embolism. This patient was not labeled as affected with epilepsy during the linkage analyses. Antiepileptic medication was given for all patients with epilepsy, but in most patients the seizures continued despite the treatment (table e-1). However, all patients with epilepsy, except patient 47, became seizure-free during adolescence. Seven patients had febrile seizures, without preceding vaccination. Ten family members (17%)

Figure 1 Pedigree of the family

Pedigree shows the segregation of the chromosome 14 and 12 susceptibility haplotypes. Haplotypes are shown below symbols of each individual. Marker names are indicated below individual 1. Susceptibility haplotype for migraine (M) and generalized tonic-clonic seizures (GTCS) on chromosome 14q12-q23 is highlighted in yellow. The upper black frame on 14q12-q23 delimits the shortest susceptibility haplotype for M and the lowest black frame for GTCS. Susceptibility haplotype for M on chromosome 12q24.2-q24.3 is highlighted in green. Black frame delimits the shortest susceptibility haplotype for M.

had sudden somnolence leading to transient unconsciousness and inability to be awoken (hereafter called SUA) (table e-1). These attacks lasted from a few minutes to 2 hours, and in some patients were associated with nystagmus. The symptoms of SUA were similar from one episode to the next in each patient and also between individuals. In 9 patients with SUA, early-onset epilepsy was also present. The age at onset of SUA was similar to that for epilepsy, varying from 1 to 5 years, the cessation occurred in early puberty, and EEG normalization occurred during teenage. All patients with centrottemporal EEG abnormalities had SUA.

Thirty-three of the 60 family members (55%) had migraine: 20 (33%) patients had migraine without aura (MO) and 13 (22%) had migraine with aura (MA) (figure 1, table e-1). Four of the 13 patients with MA had migraine aura without headache. Some common factors, such as light and minor head trauma, precipitated migraine attacks in patients (table e-1). The most effective medicines used for migraine treatment in these patients were paracetamol, nonsteroid anti-inflammatory drugs, and triptans (table e-1). There were no significant differences between MA and MO in medication.

Thirty-seven of the 60 family members (62%) had either M or E (figure 1, table e-1). Nine family members had them both: 27% of the patients with migraine had epilepsy and 69% of the patients with epilepsy had migraine. Six of the 10 patients (60%) with SUA had migraine. In all but 3 cases, migraine started later than epilepsy; in patients with SUA, it started 3–20 years later.

Linkage results. Genome-wide linkage results are shown in figure e-1 and a summary of the suggestive findings is shown in table 1. We selected loci that reached the suggestive threshold for linkage on chromosomes 9, 12, 14, and 20 for fine-mapping analysis.

In fine-mapping analysis, we observed significant evidence of linkage for several phenotypes on chromosomes 14q11.2 and 12q24.2. Detailed results and haplotype findings for these loci are presented below and in figure 2, A and B. For the loci in 9q34.1 and 20q11.2-q12, linkage values obtained in fine-mapping analysis were not significant (figure 2, C and D).

Chromosome 14q11-q23 locus. After fine-mapping, we observed in multipoint NPL analysis significant evidence of linkage between the D14S70 marker and M ($p = 0.0001$) and suggestive evidence of linkage between D14S70 and the M+E phenotype ($p = 0.0005$) (figure 2A). In addition, we found suggestive

Table 1 Summary of the genome-wide nonparametric linkage results for epilepsy and migraine^a

Phenotype	Marker	Nonparametric		Statistics
		Two-point: ASP lod scores	Multipoint: empirical p values	
E	D9S290	2.245	0.0311	NPL-pair
	D9S164	2.539	0.0155	NPL-pair
GTCS	D20S195	0.886	0.0094	NPL-all
M	D12S86	2.289	0.0037	Max-Tree ^b
	D14S70	1.593	0.0018	Max-Tree ^b
M + E	D12S86	1.403	0.0031	Max-Tree ^b
	D14S276	0.809	0.0057	Max-Tree ^b
	D20S195	0.853	0.0051	Max-Tree ^b

Abbreviations: ASP = affected sib pair; E = epilepsy; GTCS = generalized tonic-clonic seizures; M = migraine; M+E = migraine or epilepsy; NPL = nonparametric linkage. ^a All results that reach the threshold for suggestive evidence of linkage for at least one of the analyses are included; i.e., ASP lod score values >2.2 or multipoint NPL $p < 0.01$. Significant evidence of linkage was not observed in any analysis. ^b NPL-all was not calculated because of a large number of affecteds.

evidence of linkage between GTCS and D14S276 ($p = 0.0034$) (figure 2A).

The minimum susceptibility haplotype for migraine on 14q12-q21 covers a 13 Mb/16 cM region between markers D14S1071 and D14S288 with 4 recombination events both proximally (individuals 8, 41, 44, and 55) and distally (individuals 4, 45, 47, and 49) defining the region (figure 1). Twenty-six descendants of individuals 84 and 85 are known to have had migraine and 24 (92%) of them share this major susceptibility haplotype (figure 1). The remaining 7 known patients with migraine in this pedigree, of which almost all were married into the family, do not seem to share this haplotype (figure 1).

The susceptibility haplotype for GTCS that can be derived from this dataset covers 33 Mb between D14S1071 and D14S63 and overlaps with the migraine susceptibility haplotype between markers D14S1071 and D14S288 (figure 1). Eight GTCS patients with idiopathic origin share this haplotype (figure 1). In patient 27, one proximal recombination event defines a shorter 12-Mb region between D14S1018 and D14S63 on 14q22-q23 (figure 1).

Chromosome 12q24 locus. Fine-mapping increased evidence of linkage to 12q24 (figure 2B). We detected significant evidence of linkage between M and D12S86 ($p = 0.0004$) and between the M+E phenotype and D12S86 ($p = 0.0003$) (figure 2B).

Figure 2 Results of the fine-mapping nonparametric linkage (NPL) analyses for migraine and epilepsy on chromosomes 14, 12, 9, and 20

Plots of multipoint NPL scores, $-\log_{10}(p)$ value, for fine-mapping on chromosomes 14 (A), 12 (B), 9 (C), and 20 (D). Results are shown for 4 phenotypes: migraine (M; blue line), migraine or epilepsy (M+E; red line), generalized tonic-clonic seizures (GTCS; green line), and epilepsy (E; orange line). Because of the large number of patients with migraine, the NPL-all statistic could not be used for the M and M+E phenotypes. The Max-Tree statistic scores NPL using a dominant inheritance model, and the NPL-all and NPL-pair statistic scores using an additive model.

The shortest shared susceptibility haplotype on 12q24.2-q24.3 for the M or E phenotype covered an 18 cM/13 Mb region between markers D12S79 and D12S1659 (figure 1). Of the 30 descendants of parents 84 and 85 who are known to have had either migraine or epilepsy, at least 25 (83%) share this susceptibility haplotype (figure 1).

Considering only the descendants of parents 84 and 85, out of the 26 subjects known to have had migraine, 19 (73%) have both the 14q12-q21 and 12q24.2-q24.3 susceptibility haplotypes, and all 26 have 1 or the other (figure 1). Similarly, of the 7 descendants with GTCS, 5 (71%) have both the 14q12-q23 and the 12q24.2-q24.3 susceptibility haplotypes, and all 7 have 1 or the other (figure 1).

Candidate gene analysis. Sequencing of the *KCNH5* gene on 14q23 revealed 8 SNPs. Three of them were heterozygous in patients and segregated with the GTCS susceptibility haplotype. All were common in

European populations, with frequencies of the corresponding genotypes ranging from 0.450 to 0.533 (SNP database: www.ncbi.nlm.nih.gov/snp/). In the *CABP1* gene on 12q24.3, we detected only one SNP, which did not segregate with the disease haplotype.

DISCUSSION Our approach to study a family comorbid with epilepsy and migraine proved to be fruitful because we detected linkage between both phenotypes and chromosomes 14 and 12. The chromosome 14 result, showing significant evidence of linkage to migraine is important, because it both replicates findings of 2 previous reports^{28,29} and indicates linkage to GTCS. Conversely the locus we identified on chromosome 12 represents a novel migraine locus that has previously been linked to FS.³⁰

The clinical data analysis revealed great variation in the epilepsy and migraine symptoms and phenotypes. Patients had febrile, tonic-clonic, tonic and clonic generalized seizures, and focal seizures such as

absences, visual elementary, and motor and autonomic seizures. Variability of phenotype within a family is a common phenomenon in epilepsy.¹⁰ The patients also represented the whole spectrum of migraine: MO and MA and hemiplegic migraine. The majority of the patients with migraine had MO, i.e., migrainous headache. This is somewhat unexpected, because MA is the type of migraine usually associated with epilepsy.³¹ It is possible that some patients with MO will have their first attacks with aura later in their life, and the family phenotype thus will still become more aural. In addition to epilepsy and migraine, some family members had an interesting phenotype: SUA. Because epilepsy and SUA occurred at similar ages in the patients having both, contrary to migraine, which in most patients started later, it is possible that SUA is an epilepsy-related rather than a migraine-related symptom. Unfortunately, no ictal EEG recordings of SUA episodes were obtained. There are some similarities between SUA and narcolepsy, but these 2 syndromes can be clearly separated: the patients with SUA lacked excessive daytime sleepiness, other sleep-related problems and cataplexy that are typical narcolepsy-related symptoms.³² In addition, SUA disappeared with age, contrary to narcolepsy, which has a lifelong duration.

Careful clinical characterization of patients has proven to be important in genome-wide linkage and association studies. Selection of patients with one strict clinically characterized phenotype is usual. Often families with complex and protean phenotypes are disfavored. In our study, we selected differently by choosing a family with very complex phenotypes. In addition, we did not split the phenotypes into more than 4 classes. Our success in finding susceptibility loci with this approach may suggest that large families with complex and protean phenotypes might be particularly informative for finding shared genetic factors for comorbid disorders. A limitation of this approach may be that it might pinpoint rare family specific mutations rather than common genetic factors affecting the disease.

Our linkage finding on 14q12-q21 is not specific to this one family because it confirms 2 previous findings: a migraine with aura locus reported in a large Italian family²⁸ and a migraine locus in an Australian sample of 125 independent nuclear families.²⁹ Replication of a locus in 3 different populations as genetically diverse as Finns, Italians, and Australians provides strong evidence for a shared migraine pathway or mechanism. The comparison between the migraine susceptibility haplotype of the Finnish family and the Italian family,²⁸ however, reveals no overlap but instead shows an 0.8-Mb gap between the limit-

ing markers (figure e-2). No haplotype data are available for the Australian families, but the marker (D14S288) showing linkage to Australian families is located between the Finnish and the Italian susceptibility haplotypes. It remains possible that there are 2 nonoverlapping susceptibility loci for migraine on this region.

Suggestive evidence of linkage and the determined susceptibility haplotype for GTCS on chromosome 14q are new findings. However, evidence of linkage has also been found between idiopathic generalized epilepsy and D14S63,³³ the marker that determines the lower limit of our GTCS susceptibility haplotype (figure e-2). GTCS is a common seizure type in idiopathic generalized epilepsy,¹⁰ and the possibility of overlapping haplotypes may not be excluded. Conversely, the observation that the proximal part of the GTCS susceptibility haplotype in this study overlaps the migraine susceptibility haplotype (figure 1) raises a possibility that common susceptibility factors for these diseases are located in this region. These findings could also indicate that the chromosome 14q migraine susceptibility locus would be necessary but not sufficient to cause GTCS, for which a second GTCS allele in the 14q21-q23 region would be needed (figure 1).

Because it is possible that the 14q12-q23 susceptibility region contains more than one genetic factor affecting both migraine and epilepsy, caution will be needed to determine the risk alleles. The major migraine locus on 14q contains about 50 genes, and the extended haplotype contains 140 more. Several relevant candidate genes are located in these regions, but sequencing of the known ion channel gene, *KCNH5/EAG2*,³⁴ showed no plausible disease-associated variants in exons.

We also identified a new migraine locus on 12q24.2-q24.3. Although migraine alone showed significant evidence of linkage to 12q24 region, broadening of the phenotype to contain both migraine and epilepsy led to an even more significant finding. This result suggests that the locus on 12q24.2-q24.3 may be a susceptibility locus for both conditions. Interestingly, the migraine-epilepsy susceptibility haplotype that we identified shares a 22-kb region with a febrile and an afebrile seizure susceptibility haplotype of a North American Caucasian family.³⁰ Altogether 115 protein coding genes are located in the 12q24.2-q24.3 region. Our selection of *CABP1*, a Ca^{2+} channel regulating protein gene,³⁵ for sequencing did not reveal any causative mutations in the coding region.

Our findings indicate a presence of shared loci for epilepsy and migraine on 14q12-q23 and 12q24.2-q24.3 and strengthen the theory of common genetic

factors being involved in these 2 diseases. However, it remains to be seen whether the same or distinct variants in these regions carry susceptibility to both epilepsy and migraine and whether the variants affect the same or distinct molecular pathways in disease pathogenesis.

AUTHOR CONTRIBUTIONS

Dr. Polvi contributed in designing the study, performed statistical analysis and coordinated the study, analyzed and interpreted the data, and drafted the manuscript for content. Dr. Siren contributed in designing the study, acquisition of clinical data and DNA, analysis and interpretation of clinical data, and drafting and revising the manuscript for content. Dr. Kallela contributed in acquisition, analysis, and interpretation of clinical data and drafting and revising the manuscript for content. Dr. Rantala contributed in acquisition, analysis, and interpretation of clinical data and revising the manuscript for content. Dr. Arto contributed in interpretation of clinical data and revising the manuscript for content. Dr. Sobel contributed in supervising statistical analysis and interpretation of statistical results, and revised the manuscript for content. Dr. Palotie contributed in designing the study and revising the manuscript for content. Dr. Lehesjoki was the principal author in the epilepsy-related part of the study, contributed in designing the study, interpretation of the genetic data, revising the manuscript for content, and study supervision. Dr. Wessman was the principal author in the migraine related part of the study, contributed in designing the study, interpretation of the genetic data, revising the manuscript for content, and study supervision.

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