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Localization of a Gene for Migraine without Aura to Chromosome 4q21

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Migraine is a common form of headache and has a significant genetic component. Here, we report linkage results from a study in Iceland of migraine without aura (MO). The study group comprised patients with migraine recruited by neurologists and from the registry of the Icelandic Migraine Society, as well as through the use of a questionnaire sent to a random sample of 20,000 Icelanders. Migraine diagnoses were made and confirmed using diagnostic criteria established by the International Headache Society. A genomewide scan with multipoint allele-sharing methods was performed on 289 patients suffering from MO. Linkage was observed to a locus on chromosome 4q21 (LOD = 2.05; $P = .001$). The locus reported here overlaps a locus (MGR1) reported elsewhere for patients with migraine with aura (MA) in the Finnish population. This replication of the MGR1 locus in families with MO indicates that the gene we have mapped may contribute to both MA and MO. Further analysis indicates that the linkage evidence improves for affected females and, especially, with a slightly relaxed definition of MO (LOD = 4.08; $P = 7.2 \times 10^{-6}$).

Introduction

Migraine (MIM 157300) is a common headache disorder that usually begins in early adulthood and affects ~18% of females and ~6% of males every year (Stewart et al. 1992). It is characterized by recurrent, unilateral, pulsating headaches of moderate-to-severe intensity, aggravated by physical activity; the headaches are of 4- to 72-h duration. Other manifestations of the disease include nausea, vomiting, photophobia, and phonophobia. The diagnostic criteria most commonly used are the standardized guidelines of the International Headache Society (IHS) (Headache Classification Committee of the International Headache Society [HCCIHS] 1988).

Migraine without aura (MO) or "common migraine," affects ~58% of migraineurs (Russell et al. 1995*b*). Migraine with aura (MA) or "classic migraine" is the form of migraine with headache attacks preceded by neurologic manifestations, called "aura," and affects ~28% of migraineurs (Russell et al. 1995*b*). Both subtypes of migraine can occur within the same family (Nyholt et al. 1998*a*, 1998*b*; Carlsson et al. 2002; Lea et al. 2002) or in the same individual (Rasmussen and Olesen 1992; Launer et al. 1999; Kallela et al. 2001*b*). A recent questionnaire-based clinical study in Finland indicates that the migraine subtype breakdown for families with four or more migraineurs is as follows: 23% have only MO, 41% experience both MA and MO episodes, 11% have only MA, 20% have unclassified aura, and 3% have migraine aura without headache (Kallela et al. 2001*b*). In a population-based twin registry, the number of discordant twins with MA or MO did not indicate that these phenotypes co-occur more frequently than by chance, which suggests that they are distinct entities, inherited independently (Russell et al. 2002). Some epidemiology studies have further emphasized differences between MA and MO, with the former commonly having unilateral headaches and photophobia and the latter having headaches of greater duration and more nausea (Kallela et al. 1999).

Twin studies of migraine with and without aura indicate a genetic component of ~40%–65% (Honkasalo et al. 1995; Larsson et al. 1995; Gervil et al. 1999*a*, 1999*b*; Ulrich et al. 1999*a*, 1999*b*). This is further supported by studies of familial clustering of migraine (Mochi et al. 1993; Russell et al. 1995*a*; Stewart et al. 1997).

The genetic component of the two major subtypes of migraine, MO and MA, was evaluated in a Danish twin study (Ulrich and Gervil 2000). The probandwise concordance rates were significantly higher for MZ twins than for DZ twins for both MO and MA, indicating a genetic component for susceptibility to migraine. Their data were also consistent with several studies indicating greater relative risks for MA than for MO (Russell and Olesen 1995; Stewart et al. 1997). The results of a Swed-

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ish twin study have suggested that the genetic component in migraine is more prominent for females than for males (Larsson et al. 1995).

A rare Mendelian subtype of MA is called "familial hemiplegic migraine" (FHM), which is characterized by unilateral motor weakness during the aura and by hemicranial headaches (HCCIHS 1988). Mutations at the FHM1 locus (MIM 141500), in the calcium channel gene *CACNA1A* (MIM 601011) on 19p13.1, have been shown to cause 30%–50% of the FHM cases that have been studied (Joutel et al. 1993; Ophoff et al. 1996; Ducros et al. 2001). Mutations have also been found in this gene that cause other phenotypes, such as episodic ataxia type 2 (EA2 [MIM 108500]) (Ophoff et al. 1996) and spinocerebellar ataxia type 6 (SCA6 [MIM 183086]) (Zhuchenko et al. 1997). Another FHM locus (*FHM2* [MIM 602481]) has been mapped to chromosome 1q21-q23 (Ducros et al. 1997) and mutations identified in a gene encoding a subunit of a sodium/potassium pump (*ATP1A2* [MIM 182340]) (De Fusco et al. 2003). Finally, an *FHM3* locus (MIM 607516) has been identified on chromosome 1q31 (Gardner et al. 1997), which may be the same as the typical migraine locus *MGR6* (Lea et al. 2002).

Linkage scans have been made in attempts to map migraine genes. Linkage scans with typical migraine (MO or MA) as the phenotype have reported loci on chromosome 1q31 (*MGR6* [MIM 607516]) (Lea et al. 2002), 6p21.1-p12.2 (*MGR3* [MIM 607498]) (Carlsson et al. 2002), and Xq (*MGR2* [MIM 300125]) (Nyholt et al. 1998*a*, 2000). Linkage studies show that MA maps to 4q24 (*MGR1* [MIM 157300]) (Wessman et al. 2002) and 19p13 (*MGR5* [MIM 607508]) (Jones et al. 2001), although typical migraine has also been mapped to the 19p13 locus (Nyholt et al. 1998*b*; Terwindt et al. 2001). MO has been mapped to 14q21.2-q22.3 (*MGR4* [MIM 607501]) (Soragna et al. 2003). Follow-up association analysis has been reported only for the locus on chromosome 19p13, with support for a role for the insulin receptor gene (*INSR* [MIM 147670]) (McCarthy et al. 2001).

We describe here the results of a genomewide scan for MO genes in Icelandic families and the mapping of a major gene to a locus on chromosome 4q21. The mapping of MO to the same locus, *MGR1,* as recently reported for MA, indicates that the same gene may have a role in both forms of migraine.

Materials and Methods

Patient Material

deCODE Genetics is conducting a large study of migraine in Iceland. Individuals suffering from headache have been recruited from three sources: (1) a list of patients provided by two neurologists (401 potential participants), (2) responses to an advertisement in the newsletter of the Icelandic Migraine Society (137 participants), and (3) responses to a brief screening questionnaire mailed to a random sample of 20,000 Icelanders, aged 18–50 years and living in the Reykjavik area (including 2,481 respondents who report recurrent headache attacks). From these sources, 2,611 patients with likely migraine and 1,865 of their close relatives have been recruited for a genetic study. All recruits were asked to answer a comprehensive migraine questionnaire (deCODE Genetics) before giving blood for the study. The questionnaire was patterned after the IHS criteria (HCCIHS 1988). Diagnoses of migraine through a questionnaire, as done in this study, have been shown to be highly effective (Kallela et al. 2001*a*). We have genotyped 1,943 patients with headache and 1,510 unaffected relatives, using 1,000 microsatellite markers. Of the genotyped headache-afflicted patients, 596 meet the IHS criteria for MO and did not report any aura (138 males and 458 females). There were an additional 702 patients, possibly having MO and reporting some aura symptoms, who were not included in this analysis, except as relatives with unknown affection status. Using our unique Icelandic genealogy database and clustering software (Gulcher and Stefánsson 1998; Gulcher et al. 2000), we identified 103 families with 289 MO-afflicted patients who have a relative with MO at or within 5 meioses (i.e., 5 meioses separate first cousins, once removed). This is our primary linkage cohort for the results presented in this study. This left 307 patients who were unrelated to other patients with MO within a distance of 5 meioses; thus, they were not included in the linkage analyses of the families with MO. Subsequently, in our investigation of the contribution of phenotypes to an identified locus, we attempted to increase the number of patients and families that have no reported aura by slightly relaxing the IHS criteria for MO, by dropping either pain criteria C or D but not both (appendix A). This increased the linkage cohort to 117 families with 351 affected patients. Thus, the two phenotype models are MO and a less strict version of MO, MO2. We also considered subsets of these models that consisted of only male affected members or only female affected members. The family sets, including the number of relative pairs at various meiotic distances, are described in table 1. This study was approved by the National Bioethics Committee and the Data Protection Commission of Iceland. Informed consent was obtained from all participants.

Microsatellite Markers and Genotyping

Genotypes were obtained for a marker set developed at deCODE Genetics that contains markers from the ABI Linkage marker (v.2) screening and intercalating sets and

Table 1

Summary of Linkage Families with Count of Affected Relative Pairs at Various Meiotic Distances

Phenotype	No. of Families	No. of Those Affected	No. of Those Unaffected	Meiotic Distance 2	3	⩾4
MO:						
All patients	103	289	518	67	36	150
Females only	64	167	356	36	20	79
Males only	14	31	70	6	3	8
MO2:						
All patients	117	351	553	90	48	186
Females only	77	203	406	46	25	98
Males only	18	39	85	10	4	8

NOTE.—The family counts include only genotyped persons.

500 custom-made markers. The set has 1,000 fluorescently labeled primers, with an average spacing of 3.6 cM. The set has been extensively tested for multiplex PCR results. PCR reactions were set up by Zymark SciClone (ALH-500) robots, and PCR amplifications were made on MJ Research machines (PTC-25). The reaction volume was 5 μl for each PCR reaction, and 20 ng of genomic DNA was amplified in the presence of 2 pmol of each primer, 0.25 U Ampli*Taq* Gold, 0.2 mM dNTPs, and 2.5 mM $MgCl_2$ (buffer was supplied by Applera). Cycling conditions were: 95°C for 10 min, followed by 37 cycles of 94°C for 15 s, annealing for 30 s at 55°C, and 1-min extension at 72°C. The PCR products were supplemented with the internal size standard, and the pools were separated and detected on 3700 Sequencers using Genescan (v3.0) peak calling software (Applera). The genotypes, for a total of 866 markers from the genomewide set, were used for the linkage analysis, resulting in an average intermarker distance of 4.2 cM. Alleles were automatically called using DAC, an allele-calling program developed at deCODE Genetics (Fjalldal et al. 2001), and the program DecodeGT was used to fractionate called genotypes, according to quality, and to edit, when necessary (Pálsson et al. 1999).

Statistical Methods for Linkage Analysis

To evaluate linkage, we used multipoint, affected-only allele-sharing methods. The program Allegro (Gudbjartsson et al. 2000) was used for calculating nonparametric linkage and LOD scores, as well as for producing information measures on identity-by-descent (IBD) sharing. We employed the Spairs scoring function (Whittemore and Halpern 1994; Kruglyak et al. 1996) and the exponential allele-sharing model (Kong and Cox 1997) to generate the relevant 1-df test statistic. Family scores were combined to obtain an overall score, by use of a weighting scheme that is halfway on the logarithm scale between weighting the families equally (Kruglyak et al. 1996) and by weighting the affected pairs equally; with the resulting weight equal to the geometric mean of the two weights. This scheme gives weights similar to those proposed by Weeks and Lange (1988) as an extension of the scheme Hodge designed for sibships (Hodge 1984). To increase our confidence in the evidence for linkage to a particular region, additional microsatellite markers were genotyped to increase the information on IBD sharing to ⩾85% in that region. For the families in this study, to achieve this level of information required an average spacing of markers of ~1 every 1.5 cM. The marker order and positions used in linkage analysis are from our high-resolution genetic map (Kong et al. 2002). All reported locations are in Kosambi centimorgans.

Results

A genomewide scan was made on 103 families containing 289 genotyped patients with MO and 518 of their genotyped relatives (fig. 1). Five locations had a LOD score ⩾1.5. They are on chromosomes 4p (LOD = 2.05 at D4S394), 4q (LOD = 1.96 at D4S2361), 18p (LOD = 1.57 at D18S453), 18q (LOD = 1.50 at D18S877), and 20q (LOD = 1.60 at D20S96).

Given that the prevalence of MO in women is three times that in men, we decided to investigate families restricted to either male patients or female patients. For males with MO, the LOD scores on chromosomes 4 and 18 dropped to <0.3, whereas the peak on chromosome 20 dropped to <1.0. No LOD score >1.5 was observed. For females with MO, however, whereas the 4p, 18p, 18q, and 20q peaks dropped to <1.5, the LOD score at chromosome 4q rose to 2.68 at D4S2361. Figure 2 shows a comparison of linkage scans on chromosome 4 in males and females with MO. A region on chromosome 21q also achieved a LOD score >1.5 for females with MO (LOD = 1.74 between D21S1896 and D21S1442).

The 4q peak is interesting, since it overlaps with the *MGR1* locus that was reported by a Finnish group as being linked to MA (Wessman et al. 2002). We decided to genotype 15 additional markers at this locus to increase the information on IBD sharing of alleles by affected relatives and to determine if that would support genetic sharing in the region. After this higher-resolution mapping, the MO phenotype gave a LOD score of 2.05 (P = .001) at D4S1534 (93.19 cM), thus confirming the *MGR1* locus. The run for males with MO continued to show no evidence for linkage to this region, and the run for females with MO produced a slightly lower LOD score than for the framework mapping (LOD = 2.33 at D4S1534). A summary of the fine-mapping results is displayed in table 2.

We then expanded our study cohort by including patients who scored positive for all MO diagnostic criteria except either criteria C or D but not both (appendix A).

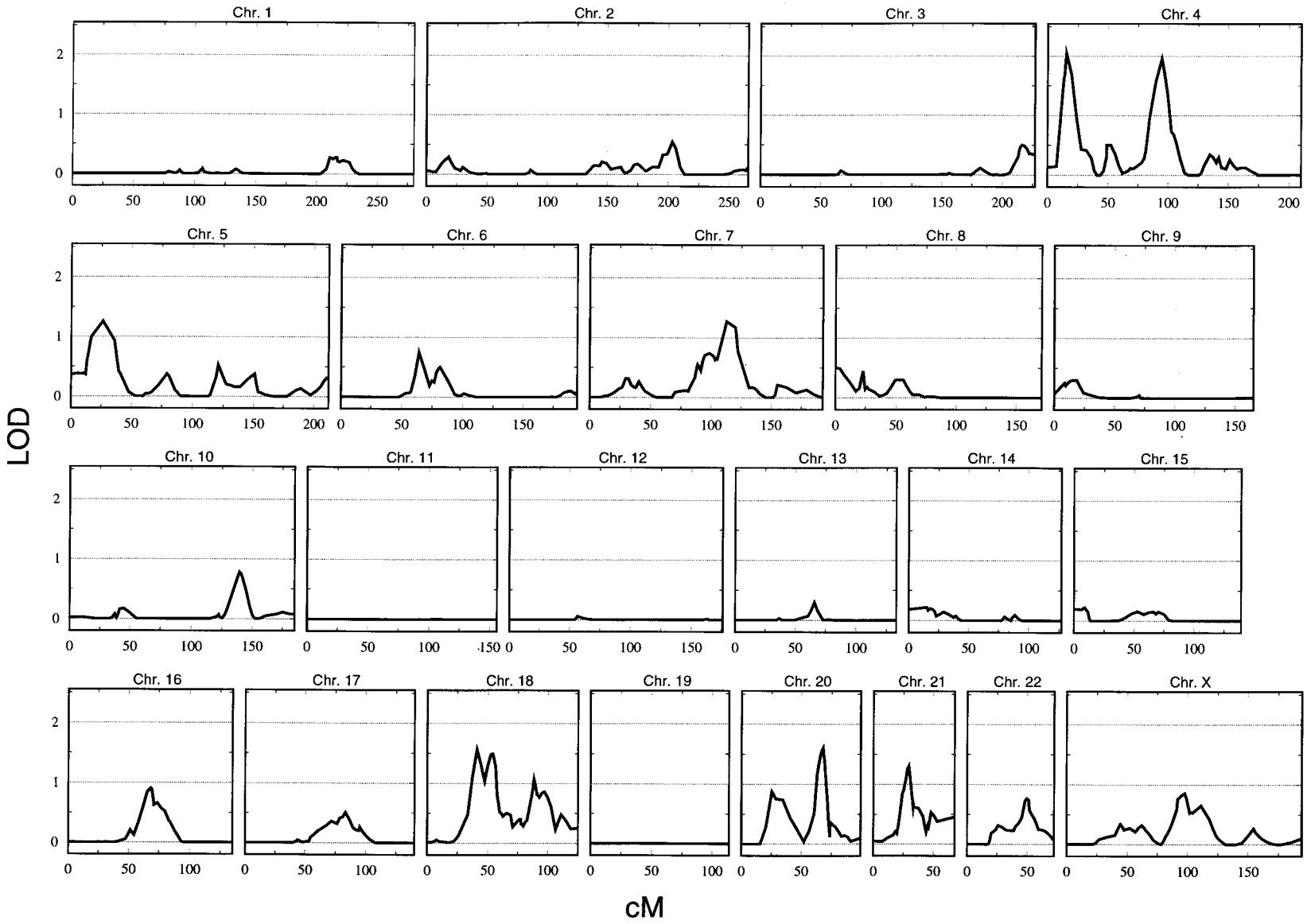

Figure 1 Genomewide linkage analysis of patients with MO. This analysis includes 103 families, with 289 affected and 518 relatives. The multipoint allele-sharing LOD score is shown on the vertical axis, and the distance (in Kosambi cM) from the chromosomal p terminus is on the horizontal axis.

For the 117 families containing 351 genotyped patients who were diagnosed according to this MO2 criterion, we observed a LOD score of 2.87, again at D4S1534. The males with MO2 showed some linkage, with a LOD score of 0.66, but the females with MO2 gave a very striking result (LOD = 4.08; $P = 7.2 \times 10^{-6}$; D4S2409; 94.23 cM). The region corresponding to a drop of 1 in LOD is flanked by markers D4S2627 (91.86 cM) and D4S423 (100.16 cM). Figure 3 shows the high-resolution mapping of chromosome 4 for males and females with MO2.

Table 2

Summary of Fine-Mapping Results at the Chromosome 4q21 Locus

Phenotype	Peak Marker	Position (cM)	LOD
MO:			
All patients	D4S1534	93.19	2.05
Females only	D4S1534	93.19	2.33
Males only[a]	…	…	…
MO2:			
All patients	D4S1534	93.19	2.87
Females only	D4S2409	94.23	4.08
Males only	D4S2361	92.30	.79

[a] In the results for only males with MO, the LOD score is <.10 throughout the region.

Discussion

Our linkage analysis places a gene for MO in Icelandic families on chromosome 4q21. Our data indicate that this MO locus overlaps with a known MA locus, *MGR1,* that is reported by a Finnish study (Wessman et al. 2002). This locus for MA, with peak marker D4S1647 (103.77 cM), was identified using a parametric two-point linkage model, assuming a dominant mode of inheritance. The Finnish group also reported its best multipoint parametric and nonparametric linkage for MA between markers D4S2409 and D4S2380, slightly centromeric to marker D4S1647. We map our peak marker for MO, D4S1534, to within 1.1 cM of D4S2409, which is near the peak of the reported *MGR1* multipoint locus. This locus is most prominent for female patients with MO, especially when including headache patients who were diagnosed with slightly relaxed criteria for MO (dropping IHS criteria class C or D) (appendix A). We note that D4S2409 is also in the center of our most prominent peak for females with MO2. Since D4S2409 maps to the same physical location as cytogenetic band 4q21, we suggest that 4q21 may be a better localization for the *MGR1* locus than 4q24.

The peak that we observe on chromosome 18q, at marker D18S877 in our strict MO linkage run (fig. 1), is also in the Finnish linkage data (Wessman et al. 2002). Their peak has the same top marker. However,

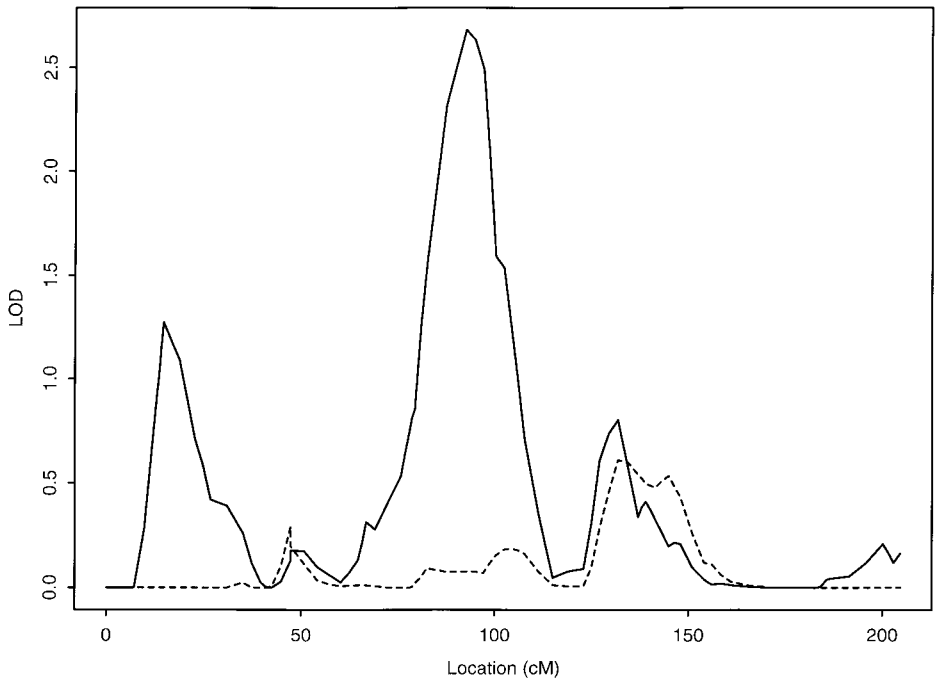

Figure 2 Multipoint allele-sharing LOD scores for chromosome 4 of females with MO (*solid line*) and males with MO (*dashed line*). The multipoint allele-sharing LOD score is shown on the vertical axis, and the distance (in Kosambi cM) from the chromosomal p terminus is on the horizontal axis.

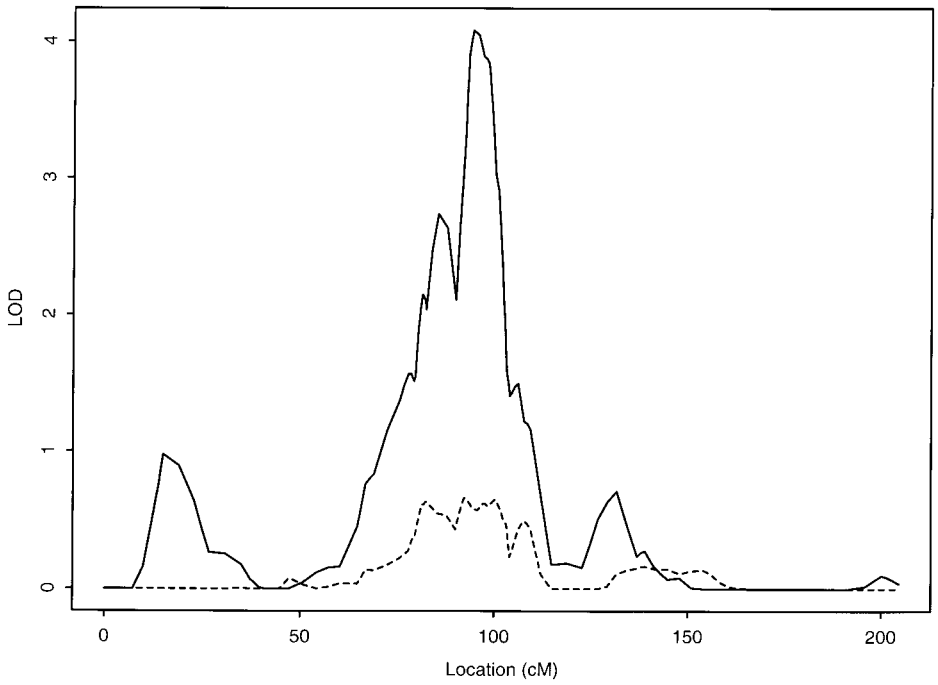

Figure 3 Multipoint allele-sharing LOD scores for chromosome 4 of females with MO2 (*solid line*) and males with MO2 (*dashed line*), with a higher-resolution map. With an average intermarker distance of 1.5 cM in the linked region, a multipoint LOD score of 4.08 was detected at marker D4S2409 (94.23 cM). The multipoint allele-sharing LOD score is shown on the vertical axis, and the distance (in Kosambi cM) from the chromosomal p terminus is on the horizontal axis.

this linkage decreases when the MO2 phenotype model is analyzed.

An MO locus has been mapped to chromosome 14q21.2-q22.3 in a large Italian pedigree that has a dominant inheritance pattern (Soragna et al. 2003). We have no evidence for linkage in this region. Also, no linkage >1 in LOD score is observed for typical migraine loci on chromosome 1q31 (*MGR6*) (Lea et al. 2002), 6p21.1-p12.2 (*MGR3*) (Carlsson et al. 2002), 19p13 (*MGR5*) (Nyholt et al. 1998*b*), or Xq (*MGR2*) (Nyholt et al. 1998*a*, 2000).

The *MGR1* locus reported elsewhere is based on 50 Finnish families that have three or more first-degree relatives with MA, with a seemingly dominant mode of inheritance (Wessman et al. 2002). In contrast, the Icelandic cohort with MO is defined as "MO patients who do not report any symptoms that can be interpreted as aura." Headache patients who report only one aura episode but otherwise five or more MO attacks are not included in our cohort with MO. We are currently evaluating the Icelandic MA material and intend to report our findings on it and other phenotype breakdowns as soon as they become available.

Our data show that the chromosome 4q21 locus is more significant when only females are analyzed. This may relate to the stronger genetic effect that has been reported for females (Larsson et al. 1995). Epidemiologic studies (Rasmussen and Olesen 1992; Russell et al. 1996; Launer et al. 1999) and population-based twin studies (Kallela et al. 1999; Ulrich et al. 1999*a*; Svensson et al. 2002) show that MO is more frequent in females than males. Our cohort with MO has, similarly, more affected females than males (458 females and 138 males). The preponderance of females with MO could relate to a stronger genetic component. We note, however, that the smaller number of male patients in our study decreases the power of detecting linkage for males, and the affect of a gene at this locus on susceptibility in males may bear further investigation.

On the basis of our data and the Finnish work, the *MGR1* locus may be best characterized as "containing a gene predisposing to typical migraine that contributes to both MA and MO," and the type may be decided by other gene(s) or environmental factors. However, further work is necessary to support this conclusion, since no linkage study has been published on MO in the Finnish population or on MA in the Icelandic populations.

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Appendix A

Migraine without Aura: International Headache Society Criteria

Previously used terms: common migraine, hemicrania simplex.

Diagnostic criteria:

1. At least five attacks fulfilling items B–D.
2. Headache lasting 4–72 hours (untreated or unsuccessfully treated).
3. Headache with at least two of the following characteristics:
   A. Unilateral location.
   B. Pulsating quality.
   C. Moderate or severe intensity (inhibits or prohibits daily activities).
   D. Aggravation by walking stairs or similar routine physical activity.
4. During headache, at least one of the following:
   A. Nausea and/or vomiting.
   B. Photophobia and phonophobia.
5. At least one of the following:
   A. History and physical and neurologic examinations do not suggest one of the disorders listed in groups 5–11 (organic disorders).
   B. History and/or physical and/or neurologic examinations suggest such disorder, but it is ruled out by appropriate investigations.
   C. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Electronic-Database Information

URLs for data presented herein are as follows:

deCODE Genetics, http://www.decode.com/migraine/questionnaire (for the English translation of the Icelandic, deCODE migraine questionnaire used in this study)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *MGR1, MGR2, MGR3, MGR4, MGR5, MGR6, FHM1, FHM2, FHM3, EA2, SCA6, CACNA1A, ATP1A2,* and *INSR*)

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