Neurogenetics (2009) 10:191–198
DOI 10.1007/s10048-008-0169-6

ORIGINAL ARTICLE

Familial hemiplegic migraine: linkage to chromosome 14q32 in a Spanish kindred

Ester Cuenca-León · Roser Corominas · Magda Montfort · Josep Artigas · Manuel Roig · Mònica Bayés · Bru Cormand · Alfons Macaya

Received: 1 November 2008 / Accepted: 11 December 2008 / Published online: 20 January 2009

Abstract We sought to map the disease-causing gene in a large Spanish kindred with familial hemiplegic migraine (FHM). Patients were classified according to the ICHD-II criteria. After ruling out linkage to known migraine genetic loci, a single nucleotide polymorphism-based, 0.62-cM density genome-wide scan was performed. Among 13 affected subjects, FHM was the prevailing migraine phenotype in six, migraine with aura in four and migraine without aura in three. Linkage analysis revealed a disease locus in a 4.15-Mb region on 14q32 with a maximum two-point logarithm of odds (LOD) score of 3.1 and a multi-point parametric LOD score of 3.8. This genomic region does not overlap with the reported migraine loci on 14q21–22. Sequence analysis of three candidate genes in the region, *SLC24A4*, *ATXN3* and *ITPK1*, failed to show disease-causing mutations in our patients. Genetic heterogeneity in FHM may be greater than previously suspected.

Keywords Migraine · Linkage · Genetics · Familial hemiplegic migraine

Electronic supplementary material The online version of this article (doi:10.1007/s10048-008-0169-6) contains supplementary material, which is available to authorized users.

E. Cuenca-León · R. Corominas · M. Roig · A. Macaya (✉)
Grup de Recerca en Neurologia Infantil i Psiquiatria Genètica,
Institut de Recerca Hospital Universitari Vall d'Hebron,
Pg. Vall d'Hebron 119–129,
08035 Barcelona, Spain
e-mail: amacaya@vhebron.net

M. Montfort · M. Bayés
Genes and Disease Program, CRG, UPF,
CIBERESP, CeGen,
Barcelona, Spain

J. Artigas
Corporació Sanitària Parc Taulí,
Sabadell, Spain

B. Cormand
Departament de Genètica, Universitat de Barcelona,
CIBERER, IBUB,
Barcelona, Spain

Introduction

Familial hemiplegic migraine (FHM) is a rare subtype of migraine with aura (MA) with autosomal dominant inheritance. In combination with sporadic hemiplegic migraine (SHM), the condition has a prevalence of 0.01% [31]. Three FHM genes have been identified, its dysfunction resulting in increased synaptic glutamate and a lower threshold for cortical spreading depression, the mechanism underlying migraine aura [14, 35]. In FHM1, mutations in the *CACNA1A* gene on chromosome 19p13.13, encoding the α subunit of the neuronal P/Q-type calcium channel (CACNA1A), were first reported in five unrelated FHM families [23]. To date, at least 21 *CACNA1A* mutations have been reported [7]. FHM2 is caused by mutations in the *ATP1A2* gene on chromosome 1q23.2; over 30 FHM2 mutations have been identified [16, 25, 32]. Only three FHM3 mutations have been described in the *SCN1A* gene, which encodes the α subunit of the neuronal voltage-gated type I sodium channel [10, 13, 33]. Mutations in these three genes account for just 50–70% of published cases of FHM. A recent population-based study from Denmark indicated greater locus heterogeneity than previously assumed [30].

In migraine families, previous genome-wide linkage scans have detected loci for MA on 4q24, 11q24 [4, 34], for migraine without aura (MO) or MA on 6p12–21 [5] and for MO on 4q21 and 14q21.2–22.3 [3, 27]. A locus on

9q21–q22 has been linked to familial occipitotemporal lobe epilepsy in a pedigree showing MA co-occurrence in five out of ten affected members [9].

Two studies using latent class analysis of migraine symptoms identified a locus on 5q21 for the cluster photophobia–phonophobia [22] and putative loci on 3q29 and 18p11 for the severe migraine phenotype [19].

We performed a genome-wide scan in a Spanish FHM multigenerational family and obtained conclusive linkage to a novel single genetic locus on chromosome 14q32.12–32.13.

Materials and methods

Patients

A multigenerational FHM family from Catalonia, North-Eastern Spain was assessed. All participants were directly interviewed by one of the authors (AM); migraine clinical diagnosis was established according to the ICHD-II criteria from the International Headache Society (IHS) [1]. For genetic analysis, any member meeting the IHS criteria for a type of migraine headache was given an affected status. This is in keeping with the current notion that the different forms of migraine may share at least part of their genetic basis [26, 35] and relies upon previous reports of pedigrees where the MO or MA phenotypes co-segregated with mutations in FHM genes [8, 11, 29, 30].

Samples

DNA was extracted from peripheral blood of 20 available family members using the QIAamp DNA Blood Maxi Kit (Hilden, Germany). Written informed consent from the participants and approval from the local ethics committee were obtained according to the guidelines of the Helsinki Declaration.

DNA analysis

Linkage between the migraine phenotype in our family and each one of six previously reported migraine genetic loci on 1q21–23 [20], 1q31–32 [12], 4q24 [34], 6p12.2–p21.1 [5], 14q21.2–22.3 [27] and 19p.13 [21] was assessed. These loci were covered with 20 microsatellite markers mainly from the MD-10 Linkage Mapping Set v2.5 (Applied Biosystems, Foster City, CA, USA) and genotypes were resolved by polyacrylamide gel electrophoresis and silver staining following standard methods. Next, samples were genotyped with the single nucleotide polymorphism (SNP)-based Linkage IVb Gold Panel (Illumina, San Diego, CA, USA) comprising 6,008 SNP markers evenly distributed across the genome. Each sample was genotyped in four highly multiplexed assays following the manufacturer's recommendations. The Illumina's BeadArray Reader was used to analyse fluorescence signals, and the Illumina's BeadStudio GenoTyping Module v.2.1.10 to normalise raw data, perform clustering and generate genotype calls.

The coding regions of the *SLC24A4*, *ATXN3* and *ITPK1* genes were polymerase chain reaction (PCR)-amplified, purified and sequenced (ABI PRISM 3700 DNA Analyzer, Applied Biosystems, Foster City, CA, USA). Primer sequences and PCR conditions are available upon request.

Statistical analysis

The simulation programme SLINK [6, 24] was used to compute the maximum expected pairwise logarithm of odds (LOD) score (Z) in our pedigree, assuming an autosomal dominant model of inheritance with a penetrance (p) of 0.95, a phenocopy rate (f) of 0.01, a disease allele frequency (q) of 0.001 and a marker heterozygosity of 0.5 over 1,000 replicates. The family was estimated to give a maximum two-point LOD score ($Z_{\max}$) of 4.04 at a recombination fraction (θ) of 0.00 from the disease gene.

The evaluation of previously reported migraine loci was performed by multipoint parametric linkage analysis between microsatellite markers and the disease phenotype using the LINKMAP software from the LINKAGE package [28] with p=0.95, f=0.01 and q=0.001 under a dominant model.

The genome-wide scan for linkage between SNP markers and migraine was performed by multipoint parametric linkage analysis, assuming $0.8 \leq p \leq 1.0$, $0.01 \leq f \leq 0.10$ and q=0.001 under dominance. Exponential multipoint non-parametric linkage (NPL) analysis was also performed to detect increased allele sharing among affected individuals, without assumption of any inheritance model. Both calculations were computed with MERLIN [2] on a split pedigree to circumvent programme constraints.

Finally, the critical disease interval was studied in more detail in the full pedigree by both two-point linkage analysis using the MLINK programme and also by multipoint parametric linkage analysis using LINKMAP and the "sliding window" method to avoid loss of information. Several values of penetrance and phenocopy rate were assumed under dominance. Both programmes are implemented in the LINKAGE package [28]. To define the

Fig. 1 Spanish migraine pedigree showing haplotypes for 20 SNP markers on chromosome 14q24.1–14q32.31. The haplotypes segregating with the disease phenotype are *boxed*. The *arrowheads* indicate the recombination points delimiting the region. The names and order of the markers are depicted in the *inset* with the genetic distances between them indicated in centimorgan. *FHM* familial hemiplegic migraine, *MA* migraine with aura, *MO* migraine without aura

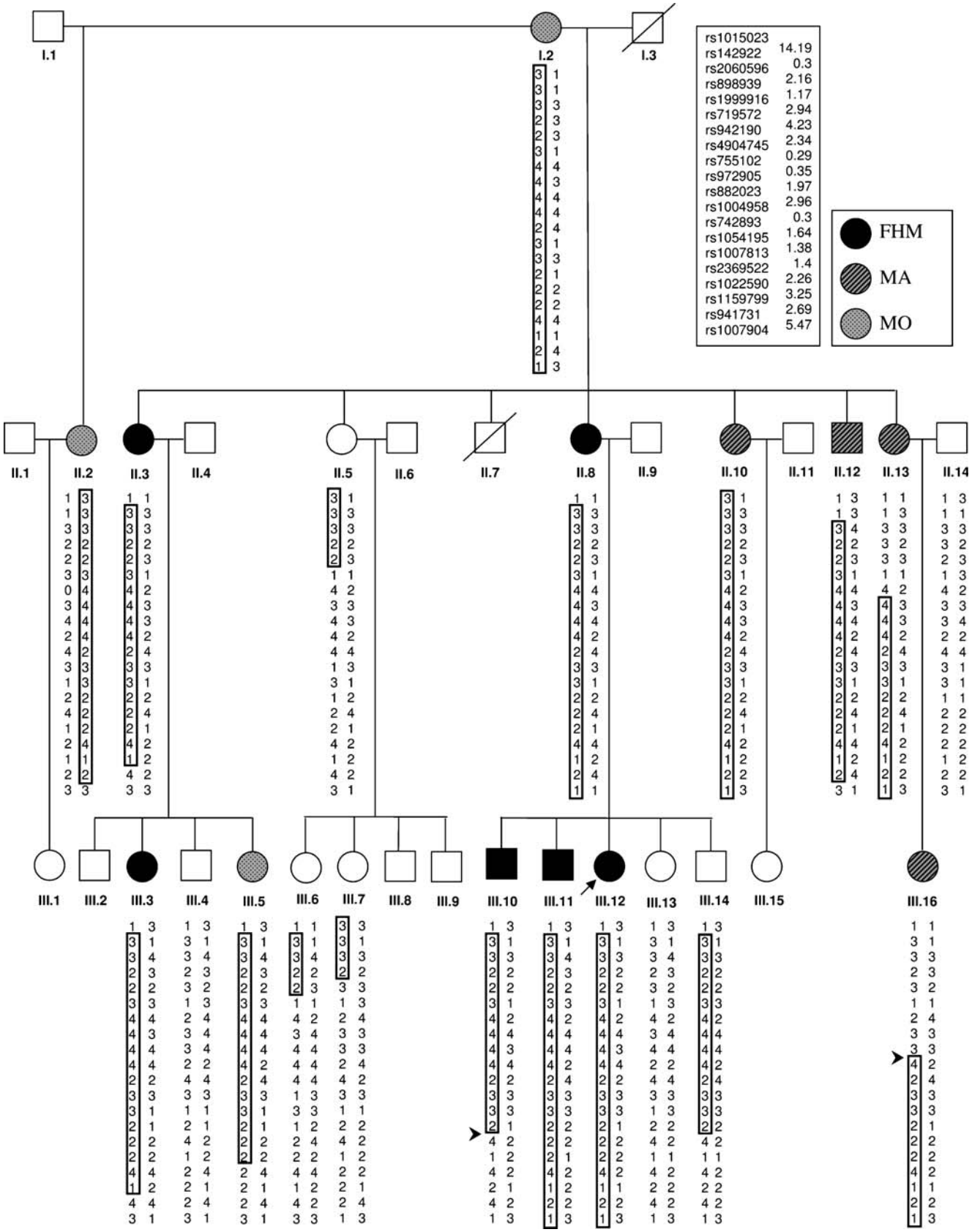
I.1
I.2
I.3
rs1015023
rs142922 14.19
rs2060596 0.3
rs898939 2.16
rs1999916 1.17
rs719572 2.94
rs942190 4.23
rs4904745 2.34
rs755102 0.29
rs972905 0.35
rs882023 1.97
rs1004958 2.96
rs742893 0.3
rs1054195 1.64
rs1007813 1.38
rs2369522 1.4
rs1022590 2.26
rs1159799 3.25
rs941731 2.69
rs1007904 5.47
FHM
MA
MO
II.1
II.2
II.3
II.4
II.5
II.6
II.7
II.8
II.9
II.10
II.11
II.12
II.13
II.14
III.1
III.2
III.3
III.4
III.5
III.6
III.7
III.8
III.9
III.10
III.11
III.12
III.13
III.14
III.15
III.16

Table 1 Patients' clinical features

Individual	I.2	II.2	II.3	II.8	II.10	II.12	II.13	III.3	III.5	III.10	III.11	III.12	III.16
Gender	F	F	F	F	F	M	F	F	F	M	M	F	F
Age at onset (years)	14	28	13	12	10	16	12	5	5	12	10	12	7
Unilateral pain	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No
Pulsating pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Aggravation by physical activity	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	No
Pain intensity	+++	++	+++	NA	+++	+++	+++	++	+++	+++	NA	NA	++
Nausea	No	No	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes	No
Vomiting	No	No	No	No	Yes	No	No	Yes	No	No	Yes	Yes	No
Photophobia	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Phonophobia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Highest attack frequency	2/mo	2/wk	5 FHM/y, 2 MO/mo	2/y	1/mo	2/y	2/mo	3 FHM, 1 MO/wk	1/mo	3/y	6/y	2/mo	2/mo
Visual disturbances	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Language disturbances	No	No	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
Sensory/motor deficit	No	No	Yes/yes	Yes/yes	No	No	Yes/no	Yes/yes	No	Yes/yes	Yes/yes	Yes/yes	No
Cerebellar signs	No	No	No	No	No	No	No	No	No	No	No	No	No
Vertigo	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Clinical diagnoses	MO	MO	FHM, MO	FHM, MA, MO	MA, MO	MA	MA, MO	FHM, MO	MO	FHM	FHM	FHM	MA

NA not available, *FHM* familial hemiplegic migraine, *MA* migraine with aura, *MO* migraine without aura

boundaries of the critical interval, haplotypes were constructed with MERLIN [2] by minimising the number of recombination events.

For the genome-wide screen, the SNP allele frequencies were considered to be equal, whilst for the analysis of the critical interval on chromosome 14, Caucasoid allele frequencies from the Central European HapMap database were used (http://www.hapmap.org).

Results

A three-generation pedigree with 13 affected and seven healthy individuals, shown in Fig. 1, was analysed. The 16-year-old proband (III.12) was the youngest FHM patient with episodes starting at age 12. She had five relatives diagnosed with FHM, including her mother and two siblings, four with the main diagnosis of MA and three

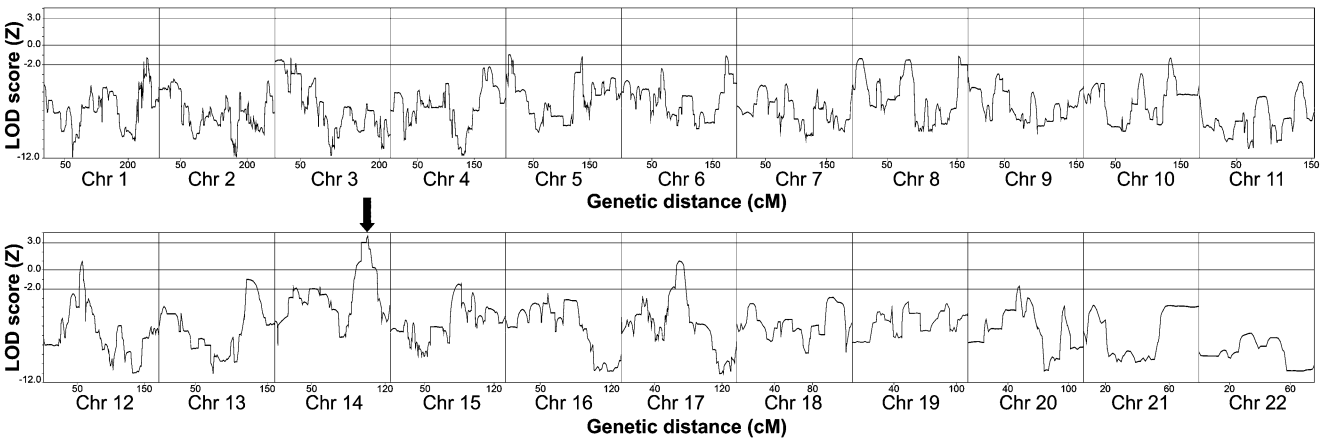

Fig. 2 Whole-genome parametric multipoint linkage analysis between the disease phenotype and 5,627 autosomal SNPs from the Linkage IVb Gold Panel (Illumina, San Diego, CA, USA). The −2 and +3 LOD score thresholds are indicated with *horizontal lines* within the graph. The *arrow* shows the linked area on chromosome 14q32

Table 2 Two-point LOD scores between migraine (FHM, MA, MO) and chromosome 14q31–q32 markers

Marker	Position		LOD score at θ=							Z_{max}	θ_{max}
	cM	Mb	0.00	0.01	0.05	0.10	0.20	0.30	0.40		
rs1999916	84.31	85.53	−2.12	−0.75	0.15	0.53	0.69	0.54	0.26	0.69	0.19
rs719572	87.25	88.45	−2.40	−0.76	−0.01	0.29	0.46	0.38	0.17	0.46	0.21
rs972905	94.46	91.27	1.74	1.71	1.61	1.47	1.18	0.84	0.45	1.74	0.00
rs882023	96.43	92.60	3.11	3.06	2.84	2.56	1.94	1.26	0.53	3.11	0.00
rs1004958	99.39	94.11	1.78	1.75	1.63	1.46	1.11	0.71	0.27	1.78	0.00
rs742893	99.69	94.22	1.01	1.05	1.14	1.15	1.01	0.76	0.42	1.15	0.08
rs1054195	101.33	94.72	1.78	1.75	1.62	1.46	1.11	0.71	0.27	1.78	0.00
rs1007813	102.71	95.08	1.22	1.25	1.32	1.31	1.15	0.86	0.48	1.33	0.07
rs2369522	104.11	95.81	1.94	1.92	1.80	1.64	1.31	0.93	0.50	1.94	0.00
rs1159799	109.62	98.32	0.94	0.93	0.91	0.86	0.72	0.54	0.30	0.94	0.00
rs941731	112.31	98.96	−1.77	−1.28	−0.64	−0.36	−0.22	−0.23	−0.14	0.00	0.50
rs1007904	117.78	101.03	−2.99	−1.40	−0.72	−0.45	−0.20	−0.08	−0.02	0.00	0.50

with MO. The pedigree's detailed clinical data are shown in Table 1; all subjects fulfilled the ICHD-II criteria regarding the number and duration (4–72 h) of episodes. The hemiplegic aura lasted between 30 and 60 min in all six affected cases, which consisted of severe brachiocrural weakness with associated dysarthria and tended to recur on the same side of the body, although two patients recalled an occasional contralateral episode. Clinical diagnosis in family members with MA ranged from typical visual aura with migraine headache in individual II.10 to visual aura with non-migraine headache in II.12 and typical aura without ensuing headache in III.16. Patient II.13 had simultaneous bilateral paresthesia, the occasional feature of FHM and of basilar-type migraine, occurring as the single aura manifestation. Most patients presented in childhood or early puberty and, over time, five patients displayed more than one subtype of migraine. Interictal neurological examination was normal in all cases; specifically, no cerebellar signs were recorded. Brain magnetic resonance imaging in the proband and in patients II.3 and II.13 were normal. No patient or non-migraineur in the pedigree displayed ataxia, seizures or any other paroxysmal neurological sign.

Multipoint analysis encompassing six loci previously linked to migraine allowed formal exclusion of linkage ($Z<-2.0$) to five of them in our pedigree and displayed negative scores ($Z<-0.6$) at the 4q24 locus, as depicted in Fig. S1 of the Electronic Supplementary Material. Haplotype analysis for markers within each of these loci revealed no co-segregation with either migraine or pure FHM phenotypes. The results of linkage to 5,627 autosomal SNPs are shown in Fig. 2; sex-linked inheritance was ruled out in this pedigree. The average genotype call rate was 99.58±1.52% after excluding 36 SNPs (0.64%) with genotype calls <80%. Evidence of linkage to chromosome 14q32.12–32.13 was found. Table 2 shows the highest two-point LOD score value, obtained with marker rs882023 ($Z_{max}=3.11$ at $\theta=0.00$) with several close markers preserving positive LOD scores under the assumption of 95% penetrance and 1% phenocopy rate. In line was the multipoint parametric linkage analysis which provided strong evidence of linkage to disease between markers rs972905 and rs1054195 ($Z>3$) with a maximum LOD score of 3.83 at marker rs1054195, as shown in Fig. 3. No other region in the whole genome surpassed a LOD score value of 1 and, indeed, 95.7% of the genome was ruled out to hold the causative gene ($Z<-2$). Exponential NPL analysis reached its highest value in the same region of chromosome 14 ($Z=2.71$, $p=0.0002$).

The limits of the disease-causing haplotype, spanning 4.15 Mb, were set by a proximal recombination between rs755102 and rs972905 in III.16, a MA patient, and a distal recombination between rs1054195 and rs1007813 in III.10, a FHM patient. It was shared by all the affected members whilst the unaffected members carried a different haplotype, as illustrated in Fig. 1. The only exception was individual III.14, a 12-year-old boy that either was presymptomatic at the time of the study or displayed incomplete penetrance of the disease phenotype.

Several candidate genes are located within the defined critical interval. These include the *SLC24A4* gene, encoding a potassium-dependent sodium/calcium exchanger, the *ATXN3* gene encoding ataxin 3 and the *ITPK1* gene encoding inositol 1,3,4-triphosphate kinase. Sequence analysis of all exons and intronic flanking regions of these genes was carried out in affected individuals, but no potential disease-causing mutations were found.

Discussion

Whole-genome linkage analysis on a single multigenerational dominant pedigree revealed a novel FHM locus on

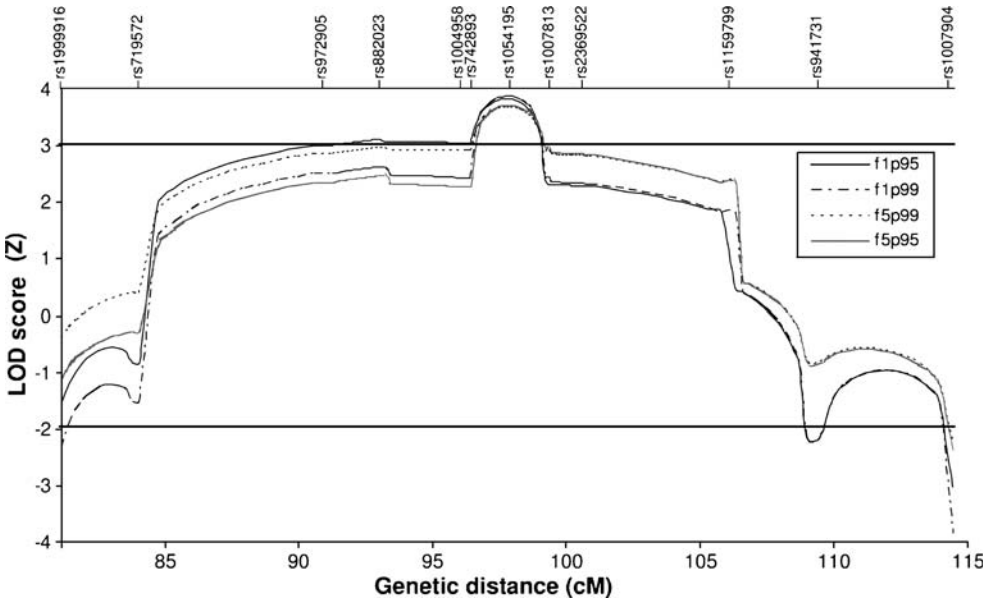

Fig. 3 Parametric multipoint linkage analysis between the disease phenotype and 12 SNP markers on chromosome 14q31–q32. The marker names are indicated on the *top* of the graph. The LOD scores, on the *y*-axis, were calculated with the LINKMAP software assuming different penetrance (*p*) and phenocopy (*f*) values, which are indicated in percent in the *inset*. The −2 and +3 LOD score thresholds are indicated with *horizontal lines* within the graph. On the *x*-axis, genetic distances in centimorgan from the 14p telomere, as defined in the Linkage IVb Gold Panel (Illumina, San Diego, CA, USA) and in the deCODE Genetics recombination map (http://www.decode.com)

14q32, although the underlying gene remains to be identified. The prevailing phenotype of the affected members in this family was FHM, without associated episodic or progressive ataxia; the seven cases of MA or MO were considered as affected in the linkage calculations, since occurrence of non-hemiplegic migraine within FHM pedigrees is well-acknowledged. Indeed, co-occurrence of MO and MA is observed in some FHM patients during their lifetime, both in our family and in other reports [30]. Thus, although FHM1 does not appear to be a major susceptibility locus for non-hemiplegic migraine [4, 15, 18], mutations in the *CACNA1A* gene are often expressed as MA or MO [11, 29, 30]. It is noteworthy that, among carriers of the prototypic FHM1 mutation, p.T666M, there are individuals with MO or even tension-type headaches [30]. Furthermore, individuals with MO or MA who carried mutations in *CACNA1A* and had offspring with FHM have been reported [11]. This is analogous to the situation of individual I.2 in our kindred, a MO patient who had two offspring with HM, one with MO and three with MA, all sharing the risk haplotype. Whatever the genetic trait shared by the six FHM individuals in our pedigree, individual I.2 is an obligate carrier. That dissimilar migraine phenotypes may share the same molecular defect is also illustrated by some FHM2 pedigrees where mutations in the *ATP1A2* gene have been reported in MA individuals [8].

All the affected members of the pedigree shared a common haplotype spanning 4.15 Mb, regardless of their specific migraine phenotype (FHM, MA, MO). Only one asymptomatic individual (III.14) was a carrier of the disease haplotype, and the question remains whether he will develop migraine symptoms in the future. Using the stringent phenotype FHM-only, the haplotypes segregating with the disease defined a wider disease-harbouring interval of about 28 Mb (between rs1015023 and rs1007813) that included the 4.15-Mb region defined when patients with FHM or MA or patients with any of the three migraine phenotypes were considered. A recombination in individual III.10, an FHM individual, defined the distal limit of the smaller critical region, whereas III.16, a MA patient, defined the proximal border.

Our study used a SNP-based linkage analysis to identify a new locus in FHM. A LOD score of 3 as a cutoff for significance has been used historically in linkage studies, but the issue has been raised as to whether this threshold should remain applicable after the advent of high-throughput SNP genotyping technologies where the number of polymorphic markers that can be inspected in genome-wide screenings has increased substantially. Of note, under the parametric approach, the increment in the number of SNPs analysed has no effect in the number of potential false-positive results because the linkage information is the same for all SNPs that are not recombining, as long as the SNPs are studied in clusters, as in multipoint analysis. In fact, a comparison of the performance of several marker sets in a linkage study on extended pedigrees revealed that, under genetic homogeneity, the densest SNP map produced no significant improvement in linkage signals [36]. Regarding our results, the maximum expected parametric LOD score given by our pedigree was calculated as 4.04, whilst the

actual screen showed maximum Z values of 3.1 in the single-point analysis and of 3.8 in the multipoint analysis, thus approaching the maximum expected value. No other linkage signal surpassed a LOD score of 2, and only two signals over 1 were observed, reinforcing the value of our best hit.

The newly identified locus shows no overlap with a previous one described on chromosome 14q21 in a large Italian MO family [27]. Considering the disease-associated haplotypes in each family, the two loci are more than 30 Mb apart. A latent class analysis in families from Australia [19] found suggestive linkage of migraine symptoms to a locus on 14q22 (Z=2.06, p=0.002), in close proximity (<5 cM) to the critical region in the above-mentioned Italian family. Again, the locus does not overlap with the one described in this study, although it is conceivable that a cluster of genes conferring increased susceptibility to migraine may reside in this region on chromosome 14q.

The UCSC Human Genome Browser database (http://genome.ucsc.edu/, NCBI Build 36.1) lists 47 genes within the critical disease interval. On the basis of their genomic position, expression profile and function, three of these genes were screened as potential candidates to cause the disease: (1) *SLC24A4* OMIM 609840, encoding a multi-pass membrane protein for ion exchange; (2) the *ATXN3* gene OMIM 607047, encoding ataxin 3, whose expansion at a (CAG)*n* repeat is responsible for Machado–Joseph disease (SCA3) [17] and (3) *ITPK1* OMIM 601838, encoding inositol 1,3,4-triphosphate kinase, which indirectly regulates plasma membrane Ca^{2+}-activated chloride channels. Even though we failed to detect putative disease-causing mutations, the possibility remains of changes outside the coding region or that may have gone undetected by PCR and direct sequencing.

Linkage to a single locus in our family adds to the existing evidence that FHM is usually inherited as a monogenic defect and that genetic heterogeneity in FHM appears to be greater than previously suspected. Further studies are warranted to ascertain the relevance of this locus in other large migraine families. Identification of the disease gene in the locus described in this study may lead to a better understanding of the complex molecular mechanisms involved in this condition.

Acknowledgements This study was supported by grants from Ministerio de Educación y Ciencia SAF 2003/04704, SAF2006-13893-C02-01, Fundació La Marató de TV3 061330 and AGAUR 2005SGR00848, Spain. E.C.-L. is funded by Ministerio de Educación y Ciencia and R.C. by Institut de Recerca Vall d'Hebron, Spain. M.B. and M.M. are recipients of a Ramon y Cajal and a Juan de la Cierva contracts from Ministerio de Ciencia e Innovación, Spain, respectively. The authors declare that the experiments described in this work comply with the current laws of Spain.

References

1. International Headache Society (2004) The International Classification of Headache Disorders: 2nd edition. Cephalalgia 24(Suppl 1):9–160. doi:10.1111/j.1468-2982.2003.00824.x
2. Abecasis GR, Cherny SS, Cookson WO, Cardon LR (2002) Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. Nat Genet 30:97–101. doi:10.1038/ng786
3. Bjornsson A, Gudmundsson G, Gudfinnsson E, Hrafnsdottir M, Benedikz J, Skuladottir S, Kristjansson K, Frigge ML, Kong A, Stefansson K, Gulcher JR (2003) Localization of a gene for migraine without aura to chromosome 4q21. Am J Hum Genet 73:986–993. doi:10.1086/378417
4. Cader ZM, Noble-Topham S, Dyment DA, Cherny SS, Brown JD, Rice GP, Ebers GC (2003) Significant linkage to migraine with aura on chromosome 11q24. Hum Mol Genet 12:2511–2517. doi:10.1093/hmg/ddg252
5. Carlsson A, Forsgren L, Nylander PO, Hellman U, Forsman-Semb K, Holmgren G, Holmberg D, Holmberg M (2002) Identification of a susceptibility locus for migraine with and without aura on 6p12.2–p21.1. Neurology 59:1804–1807
6. Cottingham RW Jr, Idury RM, Schaffer AA (1993) Faster sequential genetic linkage computations. Am J Hum Genet 53:252–263
7. Cuenca-Leon E, Corominas R, Fernandez-Castillo N, Volpini V, Del Toro M, Roig M, Macaya A, Cormand B (2008) Genetic analysis of 27 Spanish patients with hemiplegic migraine, basilar-type migraine and childhood periodic syndromes. Cephalalgia 28:1039–1047. doi:10.1111/j.1468-2982.2008.01645.x
8. De Fusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, Morgante L, Ballabio A, Aridon P, Casari G (2003) Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 33:192–196. doi:10.1038/ng1081
9. Deprez L, Peeters K, Van Paesschen W, Claeys KG, Claes LR, Suls A, Audenaert D, Van Dyck T, Goossens D, Del-Favero J, De Jonghe P (2007) Familial occipitotemporal lobe epilepsy and migraine with visual aura: linkage to chromosome 9q. Neurology 68:1995–2002. doi:10.1212/01.wnl.0000262764.78511.17
10. Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, Ferrari MD, Herzog J, van den Maagdenberg AM, Pusch M, Strom TM (2005) Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 366:371–377. doi:10.1016/S0140-6736(05)66786-4
11. Ducros A, Denier C, Joutel A, Cecillon M, Lescoat C, Vahedi K, Darcel F, Vicaut E, Bousser MG, Tournier-Lasserve E (2001) The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. N Engl J Med 345:17–24. doi:10.1056/NEJM200107053450103
12. Gardner K, Barmada MM, Ptacek LJ, Hoffman EP (1997) A new locus for hemiplegic migraine maps to chromosome 1q31. Neurology 49:1231–1238
13. Gargus JJ, Tournay A (2007) Novel mutation confirms seizure locus SCN1A is also familial hemiplegic migraine locus FHM3. Pediatr Neurol 37:407–410. doi:10.1016/j.pediatrneurol.2007.06.016
14. Goadsby PJ (2007) Recent advances in understanding migraine mechanisms, molecules and therapeutics. Trends Mol Med 13:39–44. doi:10.1016/j.molmed.2006.11.005
15. Jen JC, Kim GW, Dudding KA, Baloh RW (2004) No mutations in CACNA1A and ATP1A2 in probands with common types of migraine. Arch Neurol 61:926–928. doi:10.1001/archneur.61.6.926
16. Jen JC, Klein A, Boltshauser E, Cartwright MS, Roach ES, Mamsa H, Baloh RW (2007) Prolonged hemiplegic episodes in

children due to mutations in ATP1A2. J Neurol Neurosurg Psychiatry 78:523–526. doi:10.1136/jnnp.2006.103267
17. Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H, Nakamura S, Nishimura M, Akiguchi I et al (1994) CAG expansions in a novel gene for Machado–Joseph disease at chromosome 14q32.1. Nat Genet 8:221–228. doi:10.1038/ng1194-221
18. Lea RA, Curtain RP, Hutchins C, Brimage PJ, Griffiths LR (2001) Investigation of the CACNA1A gene as a candidate for typical migraine susceptibility. Am J Med Genet 105:707–712. doi:10.1002/ajmg.1609
19. Lea RA, Nyholt DR, Curtain RP, Ovcaric M, Sciascia R, Bellis C, Macmillan J, Quinlan S, Gibson RA, McCarthy LC, Riley JH, Smithies YJ, Kinrade S, Griffiths LR (2005) A genome-wide scan provides evidence for loci influencing a severe heritable form of common migraine. Neurogenetics 6:67–72. doi:10.1007/s10048-005-0215-6
20. Marconi R, De Fusco M, Aridon P, Plewnia K, Rossi M, Carapelli S, Ballabio A, Morgante L, Musolino R, Epifanio A, Micieli G, De Michele G, Casari G (2003) Familial hemiplegic migraine type 2 is linked to 0.9 Mb region on chromosome 1q23. Ann Neurol 53:376–381. doi:10.1002/ana.10464
21. Nyholt DR, Lea RA, Goadsby PJ, Brimage PJ, Griffiths LR (1998) Familial typical migraine: linkage to chromosome 19p13 and evidence for genetic heterogeneity. Neurology 50:1428–1432
22. Nyholt DR, Morley KI, Ferreira MA, Medland SE, Boomsma DI, Heath AC, Merikangas KR, Montgomery GW, Martin NG (2005) Genomewide significant linkage to migrainous headache on chromosome 5q21. Am J Hum Genet 77:500–512. doi:10.1086/444510
23. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, Lamerdin JE, Mohrenweiser HW, Bulman DE, Ferrari M, Haan J, Lindhout D, van Ommen GJ, Hofker MH, Ferrari MD, Frants RR (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 87:543–552. doi:10.1016/S0092-8674(00)81373-2
24. Ott J (1989) Computer-simulation methods in human linkage analysis. Proc Natl Acad Sci U S A 86:4175–4178. doi:10.1073/pnas.86.11.4175
25. Pietrobon D (2007) Familial hemiplegic migraine. Neurotherapeutics 4:274–284. doi:10.1016/j.nurt.2007.01.008
26. Russell MB (2008) Is migraine a genetic illness? The various forms of migraine share a common genetic cause. Neurol Sci 29 (Suppl 1):S52–S54. doi:10.1007/s10072-008-0887-4
27. Soragna D, Vettori A, Carraro G, Marchioni E, Vazza G, Bellini S, Tupler R, Savoldi F, Mostacciuolo ML (2003) A locus for migraine without aura maps on chromosome 14q21.2–q22.3. Am J Hum Genet 72:161–167. doi:10.1086/345298
28. Terwilliger JOJ (1994) Handbook of human genetic linkage. The John Hopkins University Press, Baltimore
29. Terwindt GM, Ophoff RA, Haan J, Vergouwe MN, van Eijk R, Frants RR, Ferrari MD (1998) Variable clinical expression of mutations in the P/Q-type calcium channel gene in familial hemiplegic migraine. Dutch Migraine Genetics Research Group. Neurology 50:1105–1110
30. Thomsen LL, Kirchmann M, Bjornsson A, Stefansson H, Jensen RM, Fasquel AC, Petursson H, Stefansson M, Frigge ML, Kong A, Gulcher J, Stefansson K, Olesen J (2007) The genetic spectrum of a population-based sample of familial hemiplegic migraine. Brain 130:346–356. doi:10.1093/brain/awl334
31. Thomsen LL, Olesen J (2004) Sporadic hemiplegic migraine. Cephalalgia 24:1016–1023. doi:10.1111/j.1468-2982.2004.00788.x
32. Tonelli A, Gallanti A, Bersano A, Cardin V, Ballabio E, Airoldi G, Redaelli F, Candelise L, Bresolin N, Bassi MT (2007) Amino acid changes in the amino terminus of the Na,K-adenosine triphosphatase alpha-2 subunit associated to familial and sporadic hemiplegic migraine. Clin Genet 72:517–523
33. Vanmolkot KR, Babini E, de Vries B, Stam AH, Freilinger T, Terwindt GM, Norris L, Haan J, Frants RR, Ramadan NM, Ferrari MD, Pusch M, van den Maagdenberg AM, Dichgans M (2007) The novel p.L1649Q mutation in the SCN1A epilepsy gene is associated with familial hemiplegic migraine: genetic and functional studies. Mutation in brief #957. Online. Hum Mutat 28:522. doi:10.1002/humu.9486
34. Wessman M, Kallela M, Kaunisto MA, Marttila P, Sobel E, Hartiala J, Oswell G, Leal SM, Papp JC, Hamalainen E, Broas P, Joslyn G, Hovatta I, Hiekkalinna T, Kaprio J, Ott J, Cantor RM, Zwart JA, Ilmavirta M, Havanka H, Farkkila M, Peltonen L, Palotie A (2002) A susceptibility locus for migraine with aura, on chromosome 4q24. Am J Hum Genet 70:652–662. doi:10.1086/339078
35. Wessman M, Terwindt GM, Kaunisto MA, Palotie A, Ophoff RA (2007) Migraine: a complex genetic disorder. Lancet Neurol 6:521–532. doi:10.1016/S1474-4422(07)70126-6
36. Yang XR, Jacobs K, Kerstann KF, Bergen AW, Goldstein AM, Goldin LR (2005) Linkage analysis of the GAW14 simulated dataset with microsatellite and single-nucleotide polymorphism markers in large pedigrees. BMC Genet 6(Suppl 1):S14. doi:10.1186/1471-2156-6-S1-S14