Familial Hemiplegic Migraine Type 2 Is Linked to 0.9Mb Region on Chromosome 1q23

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Familial hemiplegic migraine (FHM) is a rare autosomal dominant disorder characterized by episodes of transient hemiparesis followed by headache. Two chromosomal loci are associated to FHM: FHM1 on chromosome 19 and FHM2 on chromosome 1q21-23. Mutations of the α-1A subunit of the voltage gated calcium channel (CACNA1A) are responsible for FHM1. FHM2 critical region spans 28cM, hence hampering the identification of the responsible gene. Here, we report the FHM2 locus refining by linkage analysis on two large Italian families affected by pure FHM. The new critical region covers a small area of 0.9Mb in 1q23 and renders feasible a positional candidate approach. By mutation analysis, we excluded the calsequestrin and two potassium channel genes mapping within the narrowed FHM2 locus.

Migraine is an episodic neurological disorder, with a lifetime prevalence of at least 18% in the general population.1-6 Familial hemiplegic migraine (FHM) is a rare subtype of migraine with aura and autosomal dominant, highly penetrant, inheritance.5-7 During an attack of FHM, some degree of hemiparesis can be present simultaneously with other reversible, focal, neurological signs or symptoms.5-10 The disorder is genetically heterogeneous.11-13 Approximately one half of the known FHM families show genetic linkage to chromosome 19p13.1 (FHM1 MIM 141501)14 and carry missense mutations in a neuronal P/Q calcium channel α-1A subunit gene.15

A second locus (FHM2, MIM 602481) associated with pure FHM has been mapped on chromosome 1 in three French pedigrees11,13 and a German/Native American family.16 However, the linked region on chromosome 1 is still too large to assay a positional cloning; therefore, it is crucial, to search for candidate genes, to refine the critical interval in other families.

Although FHM is an infrequent disorder, unraveling the genetics of this subtype of migraine has broader implications,17 because pathophysiological mechanisms common to migraine with typical aura can be hypothesized.18,19 Here, we present clinical and molecular data of two Italian families, which allowed the narrowing of the FHM2 locus to 0.9Mb on chromosome 1q23 and the exclusion of some candidate genes.

Subjects and Methods

Kindred 1 Ascertainment and Evaluation

The largest family comprised 65 members originating from Tuscany, Italy. The proband (Subject V-8), a 48-year-old man, was ascertained during a hospital evaluation for severe, complicated headache. He was admitted to the emergency room with blurred vision, right hemiparesis, a confusional state, and severe headache. He was treated for 3 days with nimodipine, 90mg/day PO, divided into three doses, diclofenac, 75mg/day IM, and nadroparin calcium, at 5,700 anti-Xa IU SC, once daily. During the period of observation, he was dysphasic and had right weakness resulting in gait abnormalities. An electroencephalogram (EEG), during the attack, was remarkable for δ and θ activity, mostly on the left side. A computed tomography scan was normal except for a left, subcortical frontal hypodense lesion, that a magnetic resonance imaging of the brain established an increased...
Subject with mental retardation. Decreased hearing at onset. Subject with aura without motor weakness. Subject with seizures.

A computed tomography scan and magnetic resonance imaging were normal.

Subject VI-7, a 24-year-old right-handed man, has severe obesity. His mother, also affected by FHM and obesity, has an obsessive-compulsive disorder. He reported that his first attack occurred at 14 years of age, and he suffered one to two attacks per month since that time. His attacks began with chiroaural paresthesias–associated, pronounced weakness resulting in gait abnormalities. Vision was mildly blurred and dysphasia occurred regardless of the side of the attack. Headache was throbbing, unilateral, and began 15 to 30 minutes after neurological symptoms. Nausea and vomiting, phonophobia, and photophobia were present. Headache persisted as long as 4 to 6 hours with most neurological symptoms improving within 2 to 3 hours but sometimes occurring again, during an attack, associated with similar spreading, outlasting pain. Full neurological recovery might take 24 to 72 hours. Ibuprofen, 600mg/day PO, and bed

<table>
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<th>Patient ID</th>
<th>Gender</th>
<th>Age at the study (yr)</th>
<th>Age at onset (yr)</th>
<th>Visual Disturbances*</th>
<th>Motor Disturbances*</th>
<th>Sensory/ Motor Disturbances*</th>
<th>Maximum Duration of Aura (hr)</th>
<th>Highest Attack Frequency</th>
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<td>8/yr</td>
<td>R/L alternating</td>
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</tbody>
</table>

*−, absent; +/−, rare or inconstant; +, mild; ++, moderate; +++, severe.

Subject with seizures.

Subject with aura without motor weakness.

Decreased hearing at onset.

Subject with mental retardation.

R = right; L = left; MWA = migraine without aura; TT = tension type.
rest shortened the attack. The patient also reported sleep apnea syndrome and excessive daytime somnolence.

Nineteen members satisfied the International Headache Society diagnosis of FHM; 3 of 32 other subjects reported migraine aura without motor weakness.

**Kindred 2 Ascertainment and Evaluation**

A second unrelated family, with similar phenotype, originating from Sicily, has been identified. Among seven subjects, six had a diagnosis of FHM and another (Fig. B, III-2) suffered migraine with visual aura. Clinical features of the affected members are shown in Table 1.

**Linkage Studies**

Fluorescence-labeled polymorphic dinucleotide markers were visualized on automated sequencer (MegaBace 1000; Amersham Biosciences, Piscataway, NJ). For linkage calculations, FHM was modeled as an autosomal dominant trait with a variable penetrance, identifying two liability classes: 0.95 penetrance for subjects with FHM symptoms; 0.60 penetrance for patients showing aura without motor weakness (V-6, V-13, VI-2 from Family 1; III-2 from Family 2). No age-dependent penetrance was assumed; Subjects VI-4 (19 years old) and VI-6 (15 years old) were close to the average age-at-onset of Family 1 and therefore were introduced as

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**Fig. Pedigrees 1 (A) and 2 (B) showing FHM2 locus haplotypes for markers D1S498, D1S2635, CRP-CA, D1S2707, FHM2-CA, CASQI-SNP, D1S2705, and D1S196, top to bottom, respectively. Disease haplotype is boxed in Family 1. Gray symbols indicate subjects with aura without motor weakness. Arrowheads show recombination events.**
“affecton unknown” in the linkage calculation. Recombina-
tion frequencies for males and female subjects were assumed
to be equal. Published allele frequencies were used. Two-
point logarithm of odds (LOD) scores were calculated by
MLINK (LINKAGE software package)

Marker FHM2-CA identifies a dinucleotide repeat (nine
alleles; allelic size and frequency calculated on family
founders are as follows: 1: 202bp, 0.09; 2: 204bp, 0.09; 3:
206bp, 0.09; 4: 208bp, 0.09; 5: 210bp, 0.05; 6: 212bp,
0.14; 7: 214bp, 0.09; 8: 216bp, 0.27; 9: 218bp, 0.09; forward
primer GATCCACAGGCGCAAGT, reverse primer CT-
CAGGTCCCTCCAGTCATT) included in the genomic
clone RP11-536c5, which maps 11kb telomeric to D1S2707
and 720kb centromeric to D1S2705.

CASQ1-SNP is a single nucleotide polymorphism (for-
ward primer, CCCAGCTACCTCTTCTGGAC; reverse
primer, TGGGTGTAGGATAGGGGATTC; 401bp) within
the first exon of calsequestrin gene contained in the genomic
clone RP11-536c5, which maps 11kb telomeric to D1S2707
and 720kb centromeric to D1S2705.

Mutation analysis of CASQ1, KCNJ9, and KCNJ10, as
well as the detection of CASQ-SNP polymorphism, was con-
ducted by D-HPLC (Wave; Transgenomic, Crewe, UK) and
by direct sequencing (DYEnamic ET Dye Terminator Kit;
Amersham Biosciences, Piscataway, NJ) of the exonic frag-
ments, including intron–exon junctions.

Results

Clinical Features of Family 1

Among the 19 FHM patients, neurological deficits
during attacks included significant hemiparesthesias,
mild to moderate hemiaparesis, and less severe homon-
ymous hemianopia or other visual disturbances. Dysar-
thria, dysphasia, and confusion were common (see
Table 1). All subjects from generations IV and V reported the
highest frequency of attacks in the second and third
decades. All of the 22 affected family members re-
ported onset before age 20 years, and 6 of 22 reported
onset by age 10 years (range, 2–15 years). Most pa-
tients reported that the number of attacks declined
dramatically after middle age. Five members reported
premonitory symptoms such as insomnia, yawning, fa-
tigue, or irritability. Triggering factors for migraine
were usually unknown. In three subjects (V-4, VI-1, VI-2), a history of seizures was reported at ages 3, 6,
and 2 years, respectively, but the course was benign
with remission. Cerebrovascular risk factors included
cigarette smoking and concurrent hypertension in three
members (IV-15, V-12, V-15), bypass for coronary ar-
tery disease in one (IV-14), and aortofemoral bypass
plus right carotid endarterectomy in another (V-1). No
one had ataxia, dementia, psoriasis, or signs of vas-
cular retinopathy, cereboretival vasculopathy, or ne-
phropathy.

Two members showed obesity (V-15, VI-7); mild or
moderate mental retardation was evident in two sub-
jects (V-13, VI-2) and was reported in another de-
ceased member (IV-8). In five affected members older
than 40 years, a magnetic resonance imaging examination
showed white matter abnormalities. The signals
were hyperintense in T2 WI and PD WI and hypoint-
tense on T1 WI and could represent small foci of ischemic
changes. In the remaining subjects, the neurora-
diological examinations were normal. Ergotamines,
triptans, and acetazolamide were never used. Prophy-
lactic headache medications (amitriptyline and chlordi-
zepoxide, flunarizine, and propranolol) were reported to
reduce attacks in five cases.

Clinical Features of Family 2

A typical phenotype of hemiplegic migraine has been
observed in patients from a three-generation family.
However, one of them (see Fig, B, III-2) suffered only
migraine with visual aura. This subject and his sister
(III-1) were treated successfully with barbiturates and
phenytoin for partial seizures secondarily generalized,
starting with visual disturbances. The neurological ex-
aminations and neuroradiological investigations were
otherwise unremarkable.

Genetic Linkage Analysis

FHM1 locus on chromosome 19q13 was excluded from
linkage to both families, as shown in Table 2. Chromosome 1q31 locus, previously reported as asso-
ciated to FHM22 and recently retracted,23 was ex-
cluded as well. On the contrary, markers spanning the
FHM2 locus, which identifies a large region on chro-
mosome 1q, gave positive results. A maximum two-
point LOD score value of 7.87 was obtained with
marker FHM2-CA (considering equifrequent alleles)
for the large Family 1 (Table 3). By introducing the allelic frequencies calculated on families’ founders (see Subjects and Methods), we obtained a two-point LOD score value of 8.43 at no recombination for Family 1. The common haplotype 3_4_9 for markers CRP-
CA,24 D1S2707, and FHM2-CA was shared by all af-
fected members of Family 1 (see Fig, A). Recombinant
subject IV-18 and IV-15 allowed the definition of the
new centromeric and telomeric boundaries of the
FHM2-linked area. Therefore, the narrowed critical re-

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region of FHM2 is now comprised between markers
D1S2635 and CASQ1-SNP (see Subjects and Meth-
ods) and spans 1.8cM in 1q2325 corresponding to
0.9Mb on the physical map (http://genome.ucsc.edu/).
Family 2, because of a smaller informative content
than Family 1, showed a larger chromosomal region
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Family 2, because of a smaller informative content
than Family 1, showed a larger chromosomal region
compatible with linkage to FHM2 (see Fig, B) and
reaching a suggestive, although not significant, LOD
score value of 1.51 with several markers in the region
(see Table 3).

The new FHM2 critical region includes several genes.
Among the known genes, we recognized the following:
transgelin 2 (TAGLN2), serum amyloid P-component

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Table 3. Two-Point LOD Score Values for FHM2 Markers

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The relative genetic distances between contiguous markers are as follows (in cM, from top to bottom): 9.3, 0.22, 1.6, 1.4 (from D1S2707 to D1S2705), 11.9.

LOD = logarithm of odds; n.i. = not informative.

Discussion

We have ascertained two unrelated Italian families segregating for FHM and report clinical and genetic studies. Affected subjects reported characteristic episodic headaches with pronounced hemisensory disturbances and mild to moderately severe hemiparesis. Dysarthria, aphasia, confusion, hemianopia, and other visual disturbances also are commonly described with the attacks. The phenotype of hemiplegic migraine in these
families can be considered pure; indeed, there were no interictal cerebellar signs in any of the affected family members. However, the disease haplotype was also inherited by four subjects, three of whom described migraine with visual aura (Subjects V-13 and VI-2 from Family 1 and Subject III-2 from Family 2) and a 52-year-old man (Subject V-6 from Family 1), who denied any history of headache but described hemisensory attacks and language symptoms similar to other affected members. The presence of migraine aura without headache and the other additional features in these subjects help to define the spectrum of clinical presentation in FHM and strongly suggest that they were in fact affected subjects. Three subjects (V-4, VI-1, VI-2 from Family 1) and two (III-1 and III-2 from Family 2) reported a history of seizures, similar to migraine-triggered seizures observed in FHM1 patients and to the reported FHM2 families.

Genetic linkage to FHM2 and exclusion of FHM1 was highly significant for Family 1. A few recombinants of this large family allowed us to narrow the large chromosomal region associated to FHM2 to 0.9Mb, therefore making feasible the identification of the FHM2-responsible gene. Although the FHM2 locus is now significantly reduced, several genes reside in this area. We failed to find mutations in three genes, CASQ1, KCNJ9, and KCNJ10 in both families. Recently, Keryanov and Gardner reported the absence of mutations responsible for FHM2 in both sodium pump subunits (ATP1A2 and ATP1A4), though the exclusion of ATP1A2 was not conclusive. Therefore, the data reported here will definitely foster the identification of the FHM2 gene and the specific pathogenetic mechanism, thereby, we hope, opening new pharmacological strategies for FHM and the more common forms of migraine.

This work was partially supported by the Italian Telethon Foundation (F.1, G. C. and M.D.).

We thank the families members for their kind collaboration and G. Abbuzzese, P. Balestri, G. Del Curatolo, and C. Paradiso for referring their patients.

References

Marconi et al: FHM2 Map to 1q23