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Familial hemiplegic migraine: clinical features and probable linkage to chromosome 1 in an Italian family

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Abstract We describe an Italian family with familial hemiplegic migraine (FHM), subtle cerebellar signs and probable linkage to chromosome 1. FHM is genetically heterogeneous; in about 50% of families it is caused by mutations within the CACNA1A gene on chromosome 19. Linkage to 1q31 and 1q21-23 has also been established. Other families do not link either to chromosome 19 or 1. Chromosome 19-linked FHM may display nystagmus and cerebellar ataxia. Affected family members were neurologically examined; linkage analysis was performed with markers for chromosomes 19p13, 1q21-23 and 1q32. Five family members had hemiplegic migraine, and 3 displayed additional cerebellar signs (scanning speech and nystagmus). In 1 patient, episodes of hemiplegic migraine triggered by mild head trauma. Epilepsy and mental retardation were also found in 1 affected relative each. Lod scores for linkage to 19p13 were negative, while the maximum two-point lod score was 1.81 to 1q21-23. This family with FHM and associated subtle cerebellar signs, epilepsy and mental retardation showed probable linkage to 1q21-23.

Key words Familial hemiplegic migraine • Linkage analysis • Cerebellar disease

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Introduction

Familial hemiplegic migraine (FHM) is an autosomal dominant subtype of migraine with aura, characterized by the occurrence of hemiplegia during the aura [1]. In about 50% of the families, FHM maps to chromosome 19p13 [2]; in these families FHM is caused by mutations in the neuronal P/Q type calcium channel alpha-1 subunit gene CACNA1A. This subunit forms the pore of the calcium channel. Ophoff et al. [3] originally described four missense mutations of the CACNA1A gene in FHM. Subsequently several other missense mutations in the CACNA1A have been reported in familial and sporadic cases of hemiplegic migraine [4]. Progressive cerebellar ataxia and nystagmus are found in some FHM pedigrees linked to chromosome 19. Attacks may be precipitated by even trivial head trauma [5].

Recently, Gardner et al. [6] established linkage to chromosome 1q31 in a German-American family with FHM, while Ducros et al. [7] found linkage to chromosome 1q21-23 in three families previously shown to be unlinked to chromosome 19. Cerebellar ataxia and nystagmus have not been observed in FHM families linked to chromosome 1, and thus appear to be specific signs for mutations in the CACNA1A gene [5, 8].

We studied an Italian family with FHM probably linked to chromosome 1 and displaying subtle cerebellar signs, and triggering by mild head trauma. In particular, we compared clinical and neurological results with those of a molecular analysis of lymphocyte DNA.

Material and methods

An Italian family with FHM was examined. Available affected members were directly examined; information about other subjects was collected from relatives. The diagnosis of FHM was based on the criteria of the International Headache Society [1].

DNA was extracted from lymphocytes and linkage analysis was performed as previously described [9] using polymorphic markers for chromosome 19p13 (CA repeats in LDL receptor gene and in intron 7 of the CACNA1A gene, and CAG repeats in 3' untranslated region (UTR) of the CACNA1A gene), for chromosome 1q21-23 (D1S2707 and ApoA2), and for chromosome 1q32 (CA repeats in CACNL1A3 gene) in the same region as that described by Ducros et al. [7]. All nucleotide sequences are available from the Genome Data Base (www.gdb.org). A two-point lod score was calculated using the MLINK option of the LINKAGE package [10].

All affected individuals were also tested for the original mutations of the CACNA1A gene in exons 4 (G→A at nt 850), 17 (T→C at nt 2416), 36 (A→G at nt 5706) and 16 (C→T at nt 2272), by means of polymerase chain reaction (PCR) with primers for exons 4, 17 and 36 [3]. For exon 16 we synthesized a reverse primer (GTACATGATCTCGTTCCAGTCTTCGCACGT) with a mismatch that creates a restriction site recognised by enzyme Tai I in normal but not in mutated DNA.

Family members presenting with FHM underwent neurological examination.

Results

The pedigree of an Italian family with FHM is shown in Fig. 1. Over two generations, there were 5 subjects with FHM, 2 with migraine without aura, and 4 with no history of headache; two further individuals (II:2 and III:2) not available for interview were reported to be free from headache by relatives. Neurological examination was normal in all 4 individuals with no headache history and in the two subjects with migraine.

Medical history and neurological examination

The clinical findings in the 5 family members with FHM are as follows:

- Patient II:1 is a 54-year-old alcoholic; he was not available for interview. According to his sister (patient II:6) who witnessed him, he had recurrent attacks of FHM since youth.
- Patient II:6 is a 46-year-old woman who has suffered from migraine with aura since age 11 years. Attacks usually started with blurring of vision on the left, followed by left hemiparesthesia, lasting 15–20 min. Since the age of 23 years, the sensitive aura was followed by left hemiparesis that could persist for two days, and occasional dysphasia. A migrainous throbbing headache, with nausea and vomiting, developed soon after the end of the aura. Attacks could be triggered by mild head trauma. Attacks decreased in frequency and intensity through the years: currently the patient has 1 attack of migraine with visual aura and 1 of migraine without aura each month, and 1 of hemiplegic migraine each year. Neurologic examination was notable for gaze-evoked nystagmus, more evident on

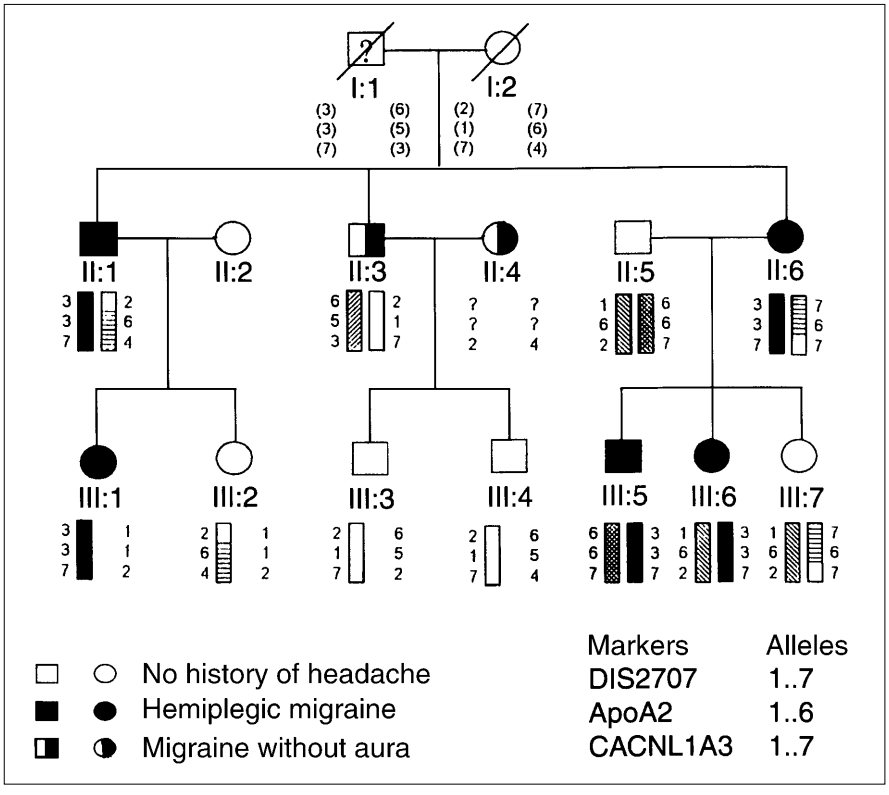

Fig. 1 Pedigree of family with familial hemiplegic migraine (FHM) and haplotypes for chromosome 1 markers

the right, and scanning speech. Brain magnetic resonance imaging (MRI) was normal. Electroencephalography (EEG) during a left-sided hemiplegic attack showed right hemisphere and left posterior slowing (not shown).

– Patient III:1, a 19-year-old woman, had been adopted into another family during adolescence and has only dim memories about her infancy. Notes of physicians who had visited her during her infancy were however available, and reported tonic-clonic epileptic seizures in apyrexia from 8 months to 2 years of age, and occipital throbbing headache since age 11 years. According to her paternal aunt (patient II:6), she also had attacks of hemipìlegic migraine. Neurologic examination showed mild cerebellar dysarthria.
– Patient III:5 is a 29-year-old man who has experienced, since childhood, attacks of hemiparesthesia, alternatively involving the right or left side of the body but not the face, that each lasted 10 minutes and were followed by hemiplegia or upper limb weakness. Hemiplegia was followed by migrainous headache after a free interval of 10 minutes. The patient experienced 2 attacks per year until the age of 23 years. Interictal neurological examination was normal.
– Patient III:6 is a 26-year-old woman who, since the age of 3 years, has experienced attacks of phosphenes starting centrally and migrating peripherally. The attacks were followed by right hemiparesthesia, including the hemiface and the hemitongue, right hemiplegia and motor aphasia, lasting about 30 minutes, and right-sided migrainous headache persisting for 48 hours. The frequency of the attacks is 3–4 per year. She also has had 3–4 attacks of migraine without aura per month since the age of 15 years. The patient was determined to be mentally retarded at the age of 4 years. Neurological examination showed right gaze-evoked nystagmus and mild cerebellar dysarthria. Brain MRI was normal. EEG during a right hemiplegic attack showed left hemisphere slowing.

Molecular findings

The mutations previously described by Ophoff et al. [3] on chromosome 19 were absent in all examined individuals, and negative lod scores were found with markers in chromosome 19p13. Lod scores using markers for chromosome 1q21-23 (D1S2707 and ApoA2) and 1q32 (CA repeats in CACNL1A3 gene) are reported in Tables 1 and 2. Maximum two-point lod scores were obtained with markers D1S2707 and ApoA2 (Zmax=1.81) at a recombination fraction θ=0 when adopting full penetrance. When adopting a penetrance of 0.90, Zmax was 1.71 (Table 2).

Discussion

In this FHM family, we did not find linkage to 19p13, but the two-point lod scores (Zmax=1.81) were positive for markers of chromosome 1q21-23 (D1S2707 and ApoA2), in the same region as that reported by Ducros et al. [7]. Even though a Zmax <3 is considered not statistically significant, 1.81 represents nonetheless an interesting value since all family members were not recombinants (Fig. 1). Two-point lod score with marker CACNA1A3 in 1q32 (Table 1) was lower (Zmax=0.90) because a recombination event was detected in one family member: therefore we consider an FHM locus in 1q32 more unlikely in this fam-

Table 1 Two-point lod scores between FHM and chromosome 1 markers. Full penetrance

	Recombination fraction (θ)				
Locus	θ=0	θ=0.01	θ=0.10	θ=0.20	θ=0.30
D1S2707	1.81	1.77	1.44	1.04	0.60
ApoA2	1.81	1.77	1.44	1.04	0.61
CACNL1A3	0.90	0.88	0.68	0.43	0.20

Table 2 Two-point lod scores between FHM and chromosome 1 markers. Penetrance, 0.90

	Recombination fraction (θ)				
Locus	θ=0	θ=0.01	θ=0.10	θ=0.20	θ=0.30
D1S2707	1.71	1.68	1.36	0.97	0.56
ApoA2	1.71	1.68	1.36	0.97	0.56
CACNL1A3	0.85	0.83	0.63	0.40	0.19

ily. Our results suggest linkage of FHM to chromosome 1q21-23 also in an Italian kindred, as found by Ducros et al. [7] in 3 French families.

We wish, also, to emphasize the clinical features of this family: three individuals showed cerebellar involvement in the form of gaze-evoked nystagmus and scanning speech; gait ataxia was, however, absent and brain MRI did not show cerebellar atrophy. Also, one individual was retarded, one was epileptic and one had attacks triggered by mild head trauma. Cerebellar involvement, progressive or episodic, has been considered until now a feature unique or typical of FHM linked to chromosome 19 [5, 8]. The present family indicates that subtle cerebellar signs may also be found in FHM unlinked to chromosome 19 and probably linked to 1q21-23.

Sommario *Descriviamo una famiglia italiana affetta da emicrania emiplegica familiare (EEF), lievi segni cerebellari e probabile linkage al cromosoma 1. L'EEF è geneticamente eterogenea; circa il 50% delle famiglie presenta mutazioni nel gene CACNA1A sul cromosoma 19. Altre famiglie presentano linkage al cromosoma 1q31 e 1q21-23, ed altre ancora né al cromosoma 19, né all'1. L'EEF con linkage al cromosoma 19 può presentare nistagmo e atassia cerebellare. I membri affetti di questa famiglia vennero esaminati neurologicamente, e venne effettuato studio di linkage con marcatori per 19p13, 1q21-23 e 1q32. Cinque familiari erano affetti da EEF, e 3 mostrarono in più segni cerebellari (voce scandita e nistagmo). In un familiare l'EEF era scatenata da trauma cranico anche lieve, ed epilessia e ritardo mentale erano presenti ciascuno in un caso. Il linkage a 19p13 risultò negativo, mentre il massimo lod score per 1q21-23 risultò 1.81. Questa famiglia con EEF associata a lievi segni cerebellari, epilessia e ritardo mentale, mostra probabile linkage a 1q21-23.*

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