

Report

A New Susceptibility Locus for Migraine with Aura in the 15q11-q13 Genomic Region Containing Three GABA-A Receptor Genes

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Migraine is the most common type of chronic episodic headache. Several population-based family studies have suggested a strong genetic predisposition to migraine, especially migraine with aura (MA). Although several susceptibility loci have been identified, none of the numerous studies performed to date have led to the identification of a gene responsible for the more common forms of migraine. GABA-A receptors and their modulator sites seem to be involved in the pathophysiological events that underlie migraine. We report on clinical and molecular data from a total of 10 families with MA, in which MA segregates as an autosomal dominant trait and presents with homogeneous clinical features. After excluding linkage with the known candidate loci, we used a functional candidate approach and genotyped these families with markers from the 15q11-q13 genomic region, which contains the genes encoding GABA-A receptor subunits. Evidence of linkage was obtained with a parametric two-point linkage analysis (maximum LOD score of 5.56 at a recombination fraction of 0.001 for marker *GABRB3*) and was supported by multipoint analysis (maximum LOD score of 6.54 between markers *D15S113* and *D15S1019*). The critical region spanned 3.6 Mb. These results provide the basis for further investigation of the hypothesized relationship between a GABA-A receptor dysfunction and migraine.

Migraine is the most common type of chronic episodic headache, affecting 11% of the general population of Western Europe and the United States (Goadsby et al. 2002). Up to 31% of migraine patients have an aura consisting of transient (usually <60 min in duration) neurological symptoms, whereas 5% have an aura without headache (Goadsby et al. 2002). On the basis of clinical manifestations, two types of migraine can be distinguished: migraine with aura (MA) and migraine without aura (Rasmussen and Olesen 1992).

Several population-based family studies have suggested a strong genetic predisposition to migraine, especially to MA (Russel and Olesen 1995; Ziegler et al. 1998), although the mode of inheritance remains unclear. Most likely, the two types of migraine are inherited as multifactorial traits, with the exception of a few fam-

ilies that display an autosomal dominant pattern of inheritance (Russel 2001). In any case, the genetic factors are likely to act by determining a constitutional migraine threshold modulated by external and internal triggers (Pietrobon and Striessnig 2003). Although several susceptibility loci have been identified—on chromosomes 1q (*MGR6* [MIM 607516]) (Ducros et al. 1997; Gardner et al. 1997), 4q24-q28 (*MGR1* [MIM 157300]) (Wessman et al. 2002), Xq24-q28 (*MGR2* [MIM 300125]) (Nyholt et al. 2000), 19p13 (*MGR5* [MIM 607508]) (Jones et al. 2001), and 14q21-q22 (*MGR4* [MIM 607501]) (Soragna et al. 2003)—none of the numerous studies performed to date have led to the identification of a gene responsible for the most common forms of migraine. The only exception is familial hemiplegic migraine (MIM 141500), a rare autosomal dominant subtype of migraine (Joutel et al. 1993) that is caused by mutations in a gene on chromosome 19 encoding a calcium-channel alpha subunit (*CACNA1A* [MIM 601011]) (Ophoff et al. 1996).

Little progress has been made toward understanding the neurobiology of migraine. Activation of the trigeminovascular system is thought to be responsible for the

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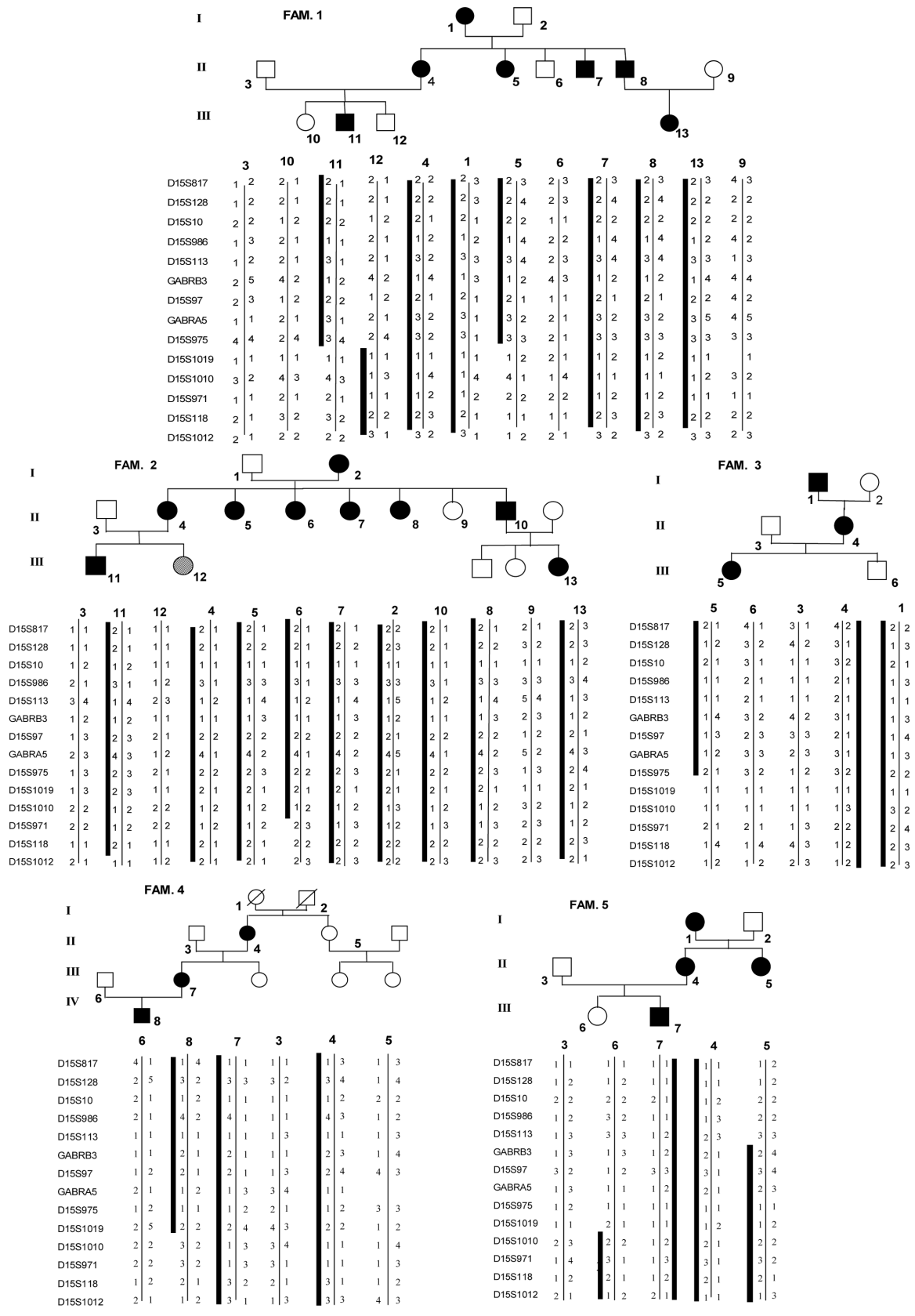


Figure 1 Haplotypes and pedigrees of the five families with MA in linkage with the 15q11-q13 genomic region. The gray shading of the symbol representing individual III-12 of family 2 indicates an MA-like phenotype (see text for discussion).

Table 1

Clinical Features of Patients

FAMILY AND PATIENT	SEX	AGE (years)		PRESENCE OF FEATURE ^a						HEADACHE SIDE ^b	HIGHEST ATTACK FREQUENCY	
		At Study	At Onset	Visual Disturbance	Language Disturbance	Sensory/Motor Disturbance	Confusion	Ataxia	Dizziness			
1:												
III-11	M	17	13		+	+	+			L	10/mo	
III-13	F	20	12	+						R-L alternating	2-3/mo	
II-4	F	43	10		+	+	+			R	3-4/mo	
II-5	F	45	8	+						R-L alternating	1-2/mo	
II-7	M	48	9	+					+	R-L alternating	1-2/mo	
II-8	M	50	8	+						R-L alternating	2/mo	
I-1	F	80	<18	+	+	+	+			R-L alternating	2/mo	
2:												
III-11	M	13	13	+						L	2/year	
II-4	F	46	8	+	+	+				L	2-3/mo	
II-5	F	48	7	+						R-L alternating	2/mo	
II-6	F	50	8	+						R-L alternating	1-2/mo	
II-7	F	53	9	+						R-L alternating	2/mo	
II-10	M	59	10	+		+				R-L alternating	1-2/mo	
II-8	F	55	7	+						R-L alternating	2/mo	
3:												
III-5	F	16	10							+	Bilateral	Daily
I-1	M	75	<18							+	Bilateral	4/mo
II-4	F	55	<18							+	Bilateral	3-4/year
4:												
IV-8	M	15	14	+		+	+				Bilateral	5-6/year
III-7	F	35	12	+							R-L alternating	2-3/mo
II-4	F	38	10	+			+				R-L alternating	2/mo
5:												
III-7	M	10	6	+					+	+	Bilateral	2-3/year
II-4	F	28	8	+							R-L alternating	2/mo
II-5	F	35	7	+							R-L alternating	2-3/mo
I-1	F	50	12	+							R-L alternating	1/mo

^a A plus sign (+) indicates presence of clinical feature.

^b R = right; L = left.

pain, whereas cortical spreading depression (CSD) seems to underlie the aura symptoms (Pietrobon and Striessnig 2003). In a recent study, Bolay et al. (2002) showed that CSD activates trigeminal afferents that cause inflammation of the pain-sensitive meninges, generating a headache. These data point to CSD as a critical event in the mechanisms of MA and support the emerging notion that CSD is a valid therapeutic target (Iadecola 2002).

An increase in excitability could explain the predisposition of the brain to episodes of CSD (Parsons 1998). The mechanisms that underlie the cortical excitability and its periodicity remain unclear. A possible cause is an abnormal release of excitatory neurotransmitters or, alternatively, a reduced intracortical inhibition (Pietrobon and Striessnig 2003). With regard to the latter alternative, several studies demonstrate a very likely involvement of GABAergic circuits through deficient intracortical inhibitory processes, especially in patients with MA (Aurora et al. 1998; Palmer et al. 2000).

Moreover, it is currently thought that the neuronal mechanisms underlying headache may work similarly in healthy individuals and individuals with migraines, but, because of central neuronal hyperexcitability in patients with migraine, headache is more easily triggered in these individuals. In recent years, the concept of migraine as a result of CNS hyperexcitability has led to the use of GABAergic anticonvulsant medications as the first line of therapy for prevention of migraine (Silberstein 2004). In particular, GABA-A receptors and their modulator sites seem to be involved in the pathophysiological events that underlie migraine, mainly at the trigeminovascular-complex level (Cutrer and Moskowitz 1996; Storer et al. 2001, 2004).

Therefore, we hypothesized that genes encoding GABA-A receptor subunits should be good candidate genes and performed linkage analysis in 10 families with MA by use of markers from the 15q11-q13 genomic region, which harbors three genes encoding three GABA-A receptor subunits. The genotyping of 10 families with

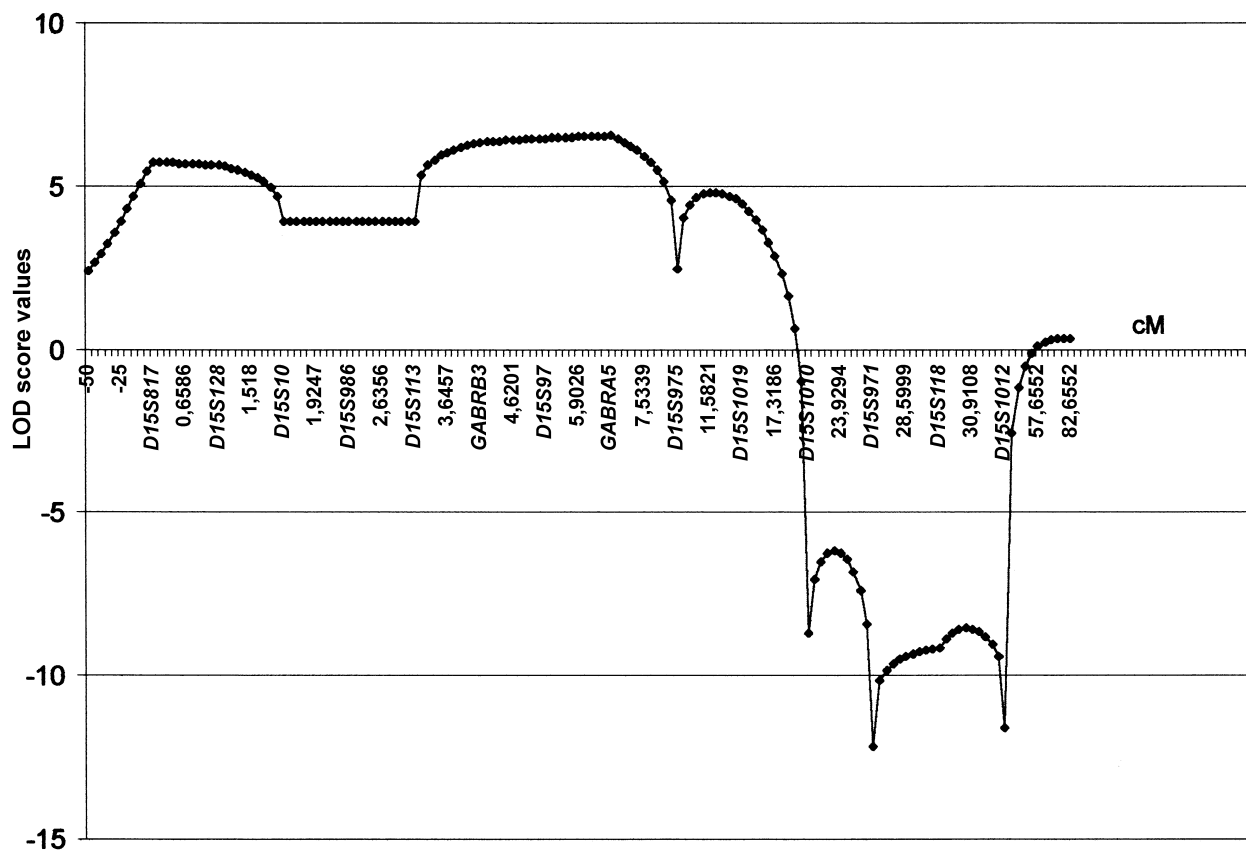


Figure 2 Graphic representation of the results of multipoint linkage analysis

MA by use of microsatellite markers from candidate regions identified elsewhere (19p13, 1q21-q23, 1q31, 4q24, and 14q24) showed several recombinations in affected individuals. Multipoint analysis did not support linkage with these loci, clearly showing negative LOD score values (data not shown).

On the contrary, microsatellite analysis with markers from the 15q11-q13 region showed no recombinants in affected individuals from five families with MA. In the other five families with MA, we did not observe cosegregation of haplotypes with the disease. Haplotypes and pedigrees of the five linked families are shown in figure 1. Clinical data from 25 affected members of these families are reported in table 1. In a linkage analysis (by use of LINKAGE 5.1 software [Lathrop et al. 1984]), the highest two-point values were obtained with markers *GABRB3* ($Z_{\max} = 5.56$ at $\theta_{\max} = 0.001$) and *D15S97* ($Z_{\max} = 5.31$ at $\theta_{\max} = 0.001$), under the assumption of 100% penetrance (table 2). The two-point score values, under the assumption of 80% penetrance, are shown in table 3. The highest Z_{\max} values for the same two markers were 5 and 4.75, respectively, at $\theta_{\max} = 0.001$. Multipoint linkage analysis (by use of SIMWALK 2.89 software [Sobel and Lange 1996]) provided strong

evidence of linkage between markers *D15S113* and *D15S1019*, with a maximum LOD score of 6.54 for marker *GABRA5* (fig. 2), confirming the results of the two-point analysis. The genomic region within proximal and distal recombinants spanned 3.6 Mb (fig. 3).

According to the University of California–Santa Cruz (UCSC) database, this critical region harbors the following genes: *GABRB3* (MIM 137192; GenBank accession number NM_021912), *GABRA5* (MIM 137142), *GABRG3* (MIM 600233), *OCA2* (MIM 203200), *HERC2* (MIM 605837), *APB2*, and *NDNL2* (MIM 608243).

We focused on the three genes encoding GABA-A receptor subunits and sequenced the coding region in affected and unaffected individuals from the five linked families. We did not detect any significant mutation; rather, we detected a polymorphism, C75T, in the first exon of the *GABRB3* gene in all affected members of family 1.

We detected a significant linkage between the MA phenotype and markers within the 15q11-q13 genomic region, thus providing strong evidence of the existence of an MA susceptibility locus on the proximal chromosome 15q. Evidence of linkage was obtained by parametric two-point linkage analysis and was supported by mul-

Table 2
Two-Point LOD Scores under the Assumption of 100% Penetrance

MARKER	LOD AT $\theta =$							θ_{max}	Z_{max}
	.001	.01	.05	.1	.2	.3	.4		
<i>D15S817</i>	-1.95	-.96	-.30	-.06	.11	.17	.14	.3	.17
<i>D15S128</i>	1.73	2.65	3.02	2.88	2.27	1.47	.59	.05	3.02
<i>D15S10</i>	.78	1.57	1.98	1.93	1.50	.93	.35	.05	1.98
<i>D15S986</i>	-.41	1.36	2.40	2.56	2.23	1.58	.78	.1	2.56
<i>D15S113</i>	-.05	1.72	2.76	2.92	2.56	1.84	.91	.1	2.92
<i>GABRB3</i>	5.56	5.47	5.04	4.48	3.32	2.10	.87	.001	5.56
<i>D15S97</i>	5.31	5.22	4.80	4.26	3.12	1.94	.78	.001	5.31
<i>GABRA5</i>	3.16	4.07	4.34	4.08	3.20	2.10	.92	.05	4.34
<i>D15S975</i>	.74	1.67	2.02	1.88	1.31	.80	.36	.05	2.02
<i>D15S1019</i>	4.48	4.41	4.07	3.63	2.71	1.71	.69	.001	4.48
<i>D15S1010</i>	-7.44	-3.59	-.88	.13	.75	.71	.35	.2	.75
<i>D15S971</i>	-13.62	-7.64	-3.59	-1.99	-.69	-.22	-.06	.4	-.06
<i>D15S118</i>	-11.80	-5.88	-2.02	-.65	.26	.37	.16	.3	.37
<i>D15S1012</i>	-14.11	-8.14	-4.08	-2.46	-1.05	-.43	-.14	.4	-.14

NOTE.—The highest values for each marker are shown in bold.

tipoint analysis (Lander and Kruglyak 1995). We could use this type of analysis because, in the families we studied, MA segregates as an autosomal dominant trait and presents with homogeneous clinical features. The only exception was individual III-12 in family 2 (see fig. 1), who suffered from a single hemiplegic attack, unprecedented in her family, resembling a form of sporadic hemiplegic migraine (SHM), which is considered to be a separate diagnostic entity from typical MA (Headache Classification Subcommittee of the International Headache Society 2004). This patient did not share the affected haplotype, which confirms that she is affected by a different condition—that is, SHM. Alternatively, her condition can be interpreted as a phenocopy. The pres-

ence of phenocopies is not an uncommon phenomenon in families with MA (Soragna et al. 2003).

As illustrated in figure 3, the MA critical region spans 3.6 Mb and is defined by the proximal marker *D15S113* and the distal marker *D15S1019*. A number of genes map to this interval. Among these, *GABRB3*, *GABRG3*, and *GABRA5*—encoding β_3 , γ_3 , and α_5 GABA-A receptor subunits, respectively—can be considered the best candidates. Two imprinted genes, maternally expressed, are located in the proximity of the centromeric boundary of the critical region: *UBE3A* (MIM 601623) (Matsuura et al. 1997) and the more closely located *ATP10A* (MIM 605855) (Meguro et al. 2001). Since we observe an excess of maternal transmission of the disease in these fam-

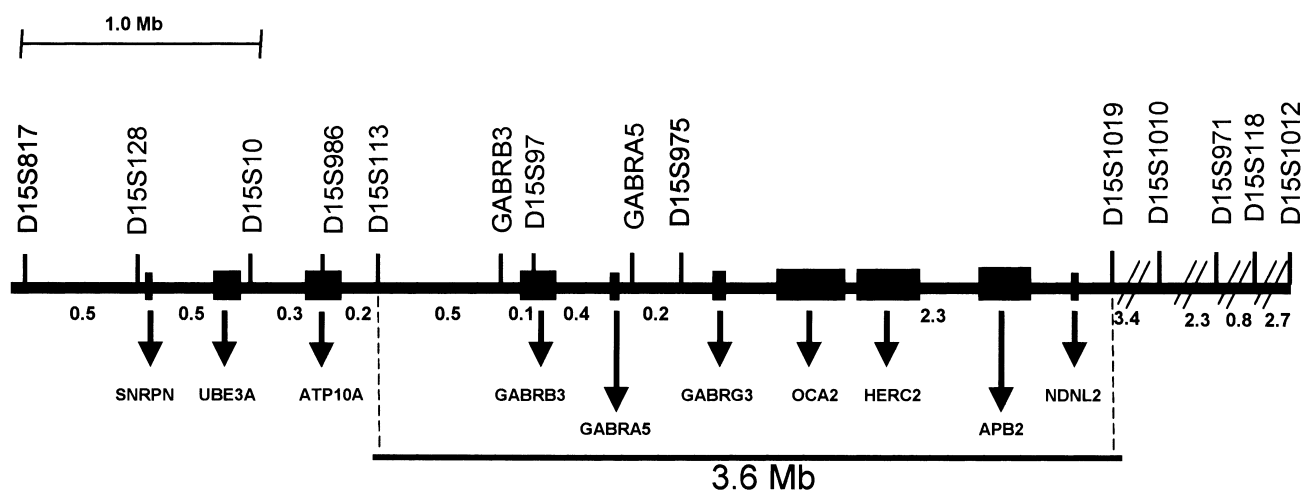


Figure 3 Map of the critical region for MA. The microsatellite markers used for genotyping are indicated at top. Distances between markers are as given in the UCSC database. Known genes are indicated at bottom. The critical region between markers *D15S113* and *D15S1019* is boxed.

Table 3
Two-Point LOD Scores under the Assumption of 80% Penetrance

MARKER	LOD AT $\theta =$							θ_{\max}	Z_{\max}
	.001	.01	.05	.1	.2	.3	.4		
<i>D15S817</i>	−1.62	−.87	.27	−.05	.11	.16	.13	.3	.16
<i>D15S128</i>	1.55	2.35	2.72	2.62	2.07	1.34	.54	.05	2.72
<i>D15S10</i>	.35	1.13	1.57	1.55	1.21	.74	.27	.05	1.57
<i>D15S986</i>	−.64	.92	1.96	2.16	1.92	1.37	.68	.1	2.16
<i>D15S113</i>	−.28	1.36	2.40	2.58	2.28	1.64	.80	.1	2.58
<i>GABRB3</i>	5.00	4.91	4.52	4.01	2.95	1.85	.76	.001	5.00
<i>D15S97</i>	4.75	4.67	4.28	3.78	2.75	1.69	.67	.001	4.75
<i>GABRA5</i>	2.83	3.61	3.89	3.67	2.87	1.88	.81	.05	3.89
<i>D15S975</i>	2.57	2.51	2.25	1.90	1.19	.65	.27	.05	2.57
<i>D15S1019</i>	4.14	4.07	3.75	3.34	2.48	1.56	.62	.001	4.14
<i>D15S1010</i>	−6.76	−3.69	−1.11	−.11	.55	.56	.27	.2	.56
<i>D15S971</i>	−8.62	−5.40	−2.68	−1.53	−.56	−.19	−.05	.4	−.05
<i>D15S118</i>	−9.44	−4.97	−1.78	−.61	.17	.27	.11	.3	.27
<i>D15S1012</i>	−10.41	−7.01	−3.71	−2.31	−1.05	−.47	−.16	.4	−.16

NOTE.—The highest values for each marker are shown in bold.

ilies, we cannot rule out the existence of an imprinting effect on the MA phenotype, even though the sequencing of the *ATP10A* gene did not detect any mutation (data not shown). In addition, we performed a mutational analysis of the coding sequences of three GABA-A receptor genes in at least one affected member from each family, but we did not detect any significant sequence variation. Only a single polymorphism (C75T) in the first exon of *GABRB3* was found in family 1. Even though we failed to detect significant mutations, we cannot rule out the possibility that dysfunctional activity of these GABA receptor subunits is due either to polymorphisms, such as C75T, that have functional effect or to mutations in noncoding regulatory sequences.

Given the ubiquitous expression and the vital function of the GABA-A receptors, which ligate a neurotransmitter widely distributed throughout the CNS, we expected to find not clear pathogenetic mutations in patients with MA but, rather, variants with a mild effect on protein function. However, we cannot exclude the possibility that mutations in regulatory sequences located outside the coding region might have strong biochemical effects, similar to what would be expected for an autosomal dominant condition. In addition, there are several lines of evidence suggesting that GABAergic drugs modulate biochemical and physiological events involved in the pathophysiology of migraine, particularly via GABA-A receptor-mediated mechanisms.

It has been proposed elsewhere that an increase in inhibitor GABAergic neurotransmission may suppress the abnormal cortical events underlying the migraine aura (Cutrer et al. 1997). The GABAergic migraine prophylactic drugs may restore a normal cortical inhibitory potential by elevating cortical threshold for spreading depression propagation in patients with migraines (Pal-

mer et al. 2000). Valproic acid blocks neurogenic inflammation within the meninges via GABA-A receptor-mediated mechanisms (Cutrer et al. 1997). Other studies underline the specific importance of GABA-A receptors in modulating trigeminovascular nociceptive neurotransmission (Cutrer et al. 1995, 1997; Storer et al. 2001, 2004). It is also very interesting that an anaesthetic agent, propofol, acting in a well-documented manner at GABA-A receptor subtypes, may represent a rapid and highly effective form of abortive headache treatment (Krusz et al. 2000).

Our study also confirmed the role of GABAergic medications. During the period of clinical observation, individuals II-7 and II-8 of family 1 needed prophylactic therapy for the worsening of migraine. Within 2 wk of administration, sodium valproate completely abolished their headaches.

This result further supports the link between the patients' conditions, drug response, and genetic findings in the families we studied. In conclusion, our results may provide the basis for further investigation of the hypothesized relationship between a possible GABA-A receptor dysfunction and migraine (Cutrer and Moskowitz 1996).

Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

GenBank, <http://www.ncbi.nih.gov/Genbank/> (for *GABRB3* [accession number NM_021912])

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for *MGR6*, *MGR1*, *MGR2*, *MGR5*, *MGR4*, familial hemiplegic migraine, *CACNA1A*,

GABRB3, *GABRA5*, *OCA2*, *HERC2*, *NDNL2*, *UBE3A*, and *ATP10A*)

UCSC, <http://www.genome.ucsc.edu>

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