# Migraine Genetics: An Update

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**Current Pain and Headache Reports** 2005, **9**:213–220
Current Science Inc. ISSN 1531-3433


A growing interest in genetic research in migraine has resulted in the identification of several chromosomal regions that are involved in migraine. However, the identification of mutations in the genes for familial hemiplegic migraine (FHM) forms the only true molecular genetic knowledge of migraine thus far. The increased number of mutations in the FHM1 (*CACNA1A*) and the FHM2 (*ATP1A2*) genes allow studying the relationship between genetic findings in both genes and the clinical features in patients. A wide spectrum of symptoms is seen in patients. Additional cerebellar ataxia and (childhood) epilepsy can occur in FHM1 and FHM2. Functional studies show a dysfunction in ion transport as the key factor in the pathophysiology of (familial hemiplegic) migraine that predict an increased susceptibility to cortical spreading depression—the underlying mechanism of migraine aura.

## Introduction

Migraine is a multifactorial neurovascular disorder, with an important genetic contribution to its cause. Unraveling the genetic causes of migraine likely will lead to better understanding of the mechanisms involved in the initiation of migraine attacks and thus also to the development of better prophylactic migraine treatment. Recent research has focused mainly on genes that are involved in familial hemiplegic migraine (FHM): *CACNA1A* in FHM1 and *ATP1A2* in FHM2. Both types of FHM are rare autosomal-dominant subtypes of migraine with aura [1•] in which migraine attacks are accompanied by hemiparesis. Although several chromosomal regions are reported to be involved in migraine, the identification of mutations in the genes for FHM1 and FHM2 form the only true molecular genetic knowledge of migraine thus far. Therefore, this article focuses on the research concerning these two genes.

## Familial Hemiplegic Migraine 1: *CACNA1A*

The chromosome 19-linked FHM gene *CACNA1A* was discovered in 1996 [2] and encodes the $Ca_v2.1$ pore-forming subunit of P/Q-type calcium channels. These channels are expressed throughout the brain and also are present at motor nerve terminals at the neuromuscular junction. A main function is to mediate transmitter release from synaptic nerve terminals [3].

Mutations in the *CACNA1A* gene cause FHM1 and other neurologic disorders with an autosomal-dominant inheritance pattern, including episodic ataxia type-2 (EA2) and spinocerebellar ataxia type-6 (SCA6). FHM, EA2, and SCA6 have considerably overlapping phenotypes [2,4]. The still-expanding clinical spectrum of *CACNA1A* mutations has a very complex genotype-phenotype correlation [5,6].

## *CACNA1A*: Familial Hemiplegic Migraine

Missense mutations in the *CACNA1A* gene are responsible for FHM1 [2,5–15,16•,17–21] (Fig. 1). Most of these mutations have been identified in one or two families only, but two mutations occur more frequently. The *T666M* mutation has been found in 20 families worldwide [2,5,6,11,12,14,17,18,20]. Patients with this mutation have a high frequency of hemiplegic migraine (98%), atypical attacks with coma (50%), and nystagmus (86%) [5]. One *T666M* patient was first diagnosed with EA2 because of ataxic symptoms during the attacks [14]. Patients with the *T666M* mutation also can show mental retardation [6] or attacks resembling acute confusional migraine.

The second recurrent mutation is *R583Q*, which has been described in six families [5,7,9,18]. Most patients have hemiplegic attacks with interictal ataxia, but some members of a large Portuguese family show cerebellar ataxia only [7], suggesting a reduced penetrance of the migraine attacks.

## *CACNA1A*: Fatal Brain Edema

Affected members of a family with a *CACNA1A S218L* mutation [15] had recurrent atypical attacks, often triggered by trivial head trauma. The proband of the family had, after a mild head trauma, a symptom-free period of several hours before she went into a coma. She died after 10 days because of severe cerebral edema. She had never

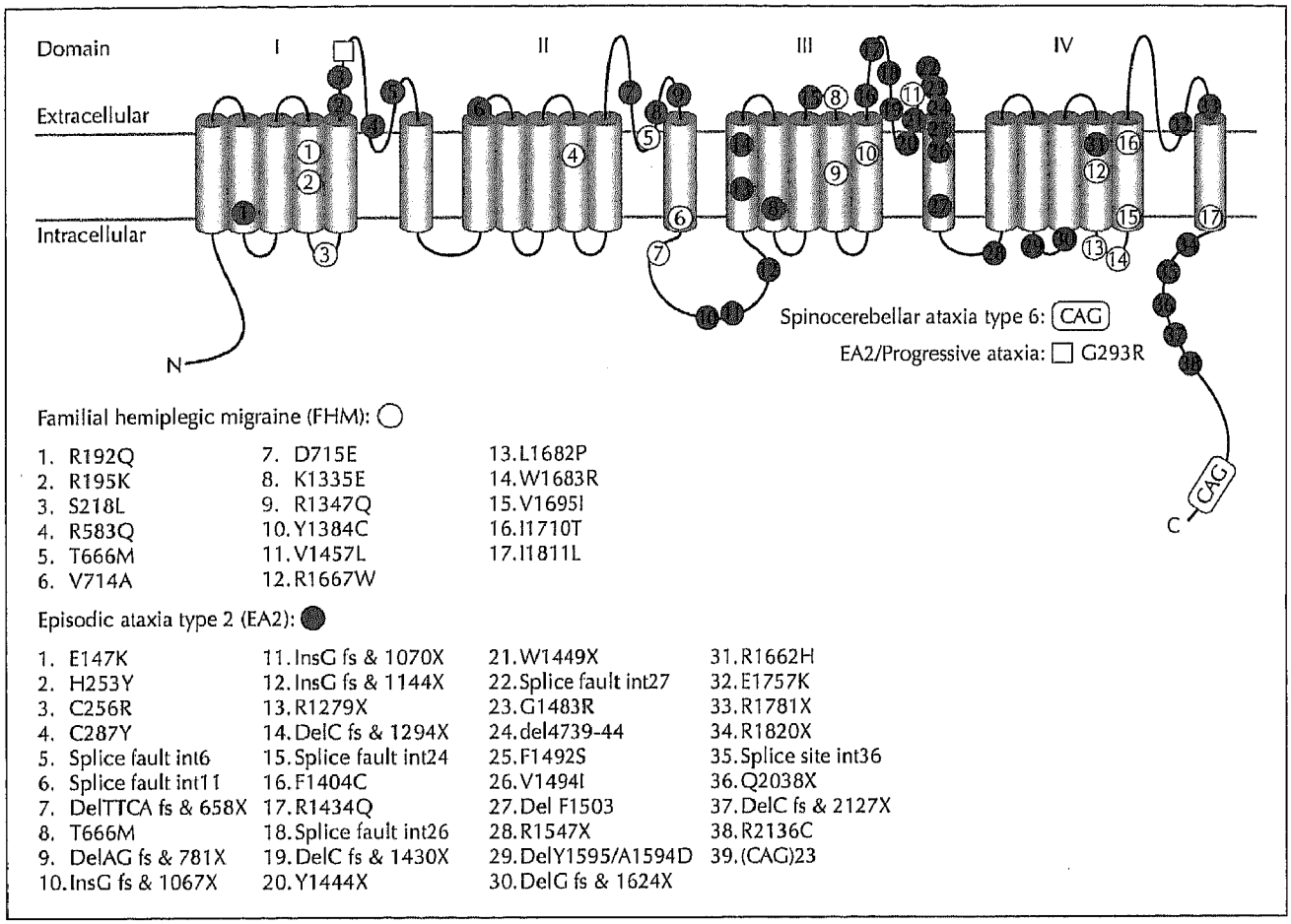


**Figure 1.** The *CACNA1A* gene with mutations. The Cav2.1 pore-forming subunit of the P/Q-type voltage-gated calcium channel is located in the neuron membrane and contains four repeated domains, each encompassing six transmembrane segments. Positions of mutations identified in this gene are given (*CACNA1A* ref. seq.: Genbank Ac. nr. X99897).

experienced attacks of (hemiplegic) migraine, unlike some of her family members. Since this description, several other unrelated patients with this mutation have been discovered, all of whom had transient neurologic symptoms after mild head trauma. Therefore, it seems that the *S218L* (and possibly other) *CACNA1A* mutations put patients at risk for cerebral edema, transient neurologic signs, and sometimes fatal coma after minor head trauma.

## *CACNA1A*: Migraine with and Without Aura

More than 50% of *CACNA1A* mutation carriers also have attacks of migraine with aura (MA) or without aura (MO), suggesting a role of the *CACNA1A* gene in more frequent types of migraine [5,22]. This is supported by a genetic study using sibling pairs with MA or MO, revealing an excess allele sharing of markers in the *CACNA1A* region [23]. This suggests that the *CACNA1A* gene may be involved in MO and MA, although the contribution to MA seems larger than to MO. No *CACNA1A* mutations were found in unselected groups of patients with MO or MA [24–26], nor in families with MO or MA [27]. A large Australian family showed linkage to the D19S1150 marker within *CACNA1A*, but no mutation was found in this family [28,29]. Other studies found no positive linkage results in migraine families using DNA markers adjacent to or within the *CACNA1A* gene, confirming genetic heterogeneity [30–32].

A recent Finnish study aimed to clarify the role of the *CACNA1A* locus in MA by analyzing 72 multigenerational Finnish MA families, the largest family sample thus far [33]. Polymorphic microsatellite markers surrounding the *CACNA1A* gene were genotyped on 757 individuals, but none showed evidence of linkage to MA under locus homogeneity or heterogeneity.

## *CACNA1A*: Episodic Ataxia Type-2 and Spinocerebellar Ataxia Type-6

Episodic ataxia type-2 patients present with early-onset attacks of imbalance or vertigo that lasts for hours to days [34]. The attacks can be provoked by a number of triggers, including physical exercise or emotional stress, and can be prevented by acetazolamide. Similar to FHM1, patients with EA2 can have interictal permanent cerebellar ataxia and the attacks can be associated with symptoms of

(basilar-type) migraine [35]. In some cases, generalized weakness is reported during ataxic spells; in others, episodic weakness can precede the attacks of ataxia [36,37]. Three patients with EA2 were reported with generalized epilepsy [38,39•,40]. Thus far, more than 30 missense mutations or mutations resulting in premature stops or affecting alternative splicing have been identified in patients with EA2 [2,14,37–51] (Fig. 1). There are considerable interfamilial differences and no clinical distinction can be made between the EA2 phenotype caused by truncating or missense mutations. In some families with symptoms indistinguishable from EA2, no *CACNA1A* mutation was identified, suggesting that mutations are missed or that genetic heterogeneity exists [52–54].

Spinocerebellar ataxia type-6 is characterized by a late onset and slowly progressive cerebellar ataxia, with oculomotor abnormalities, gait ataxia, mild upper limb ataxia, and dysarthria [4]. Eye-movement abnormalities, such as saccadic intrusions during smooth pursuit and nystagmus, are prominent and consistent early manifestations [55]. Some patients have ataxia combined with episodic headache or nausea. The permanent signs can be preceded by episodic manifestations [55]. SCA6 is caused by moderate stabile expansions of a CAG repeat in the *CACNA1A* gene.

## *CACNA1A*: Epilepsy

The involvement of the *CACNA1A* locus in epilepsy in humans is of interest in view of the epileptic phenotypes observed in *CACNA1A* mutant mice [2,56]. The first association was reported in a group of patients with idiopathic generalized epilepsy [57]. Of four single nucleotide polymorphisms (SNPs) and one microsatellite marker located within the *CACNA1A* gene, one SNP in exon 8 showed a significant association. Follow-up study showed that two SNPs in the immediate vicinity of exon 8 were responsible for the association with epilepsy [58]. The association was not limited to a specific epileptic syndrome or subgroup. An effect of these SNPs on expression or alternative splicing of the protein was suggested, but not investigated further. The presence of (childhood) seizures next to attacks of EA2 in *CACNA1A* mutation carriers further supports a role in epilepsy [38,40]. A family was described recently with a (novel) *CACNA1A* mutation, causing (childhood) epilepsy that occurred independently of FHM attacks [16•]. The same mutation caused status epilepticus during FHM attacks in another patient [21].

A family has been described with autosomal-dominant absence epilepsy and ataxia in three generations [39]. A *CACNA1A E147K* mutation seemed responsible for the symptoms, but hemiplegic migraine is not a part of the phenotype.

## *CACNA1A*: Functional Studies

Several FHM mutations have been analyzed with electrophysiologic techniques in neuronal and non-neuronal cells [38,39•,59–63]. Although EA2 truncating and missense mutations show a dramatic decrease or even complete loss of current density, FHM mutations cause different effects on channel conductance, kinetics, or expression in transfected cells. The most consistent change found with FHM mutations seems to be a hyperpolarizing shift of approximately 10 mV of the activation voltage. Although this effect in theory will lead to easier opening of the channels in neurons, the overall change in calcium influx is difficult to predict because it will be determined by a delicate interplay of effects of a particular mutation on the different channel properties and the cellular environment.

Some phenomena may contribute to the episodic nature of symptoms because calcium influx will be altered, especially during high neuronal activity. Mutant *T666M* and *V714A* channels have a low conductance mode that sometimes switches to the wild type state. For other FHM mutations, such as *R583Q* and *D715E*, accumulation of inactivated channels was observed during repetitive stimulation.

## *CACNA1A*: Mouse Models

Several mouse *CACNA1A* mutants with symptoms of ataxia and epilepsy are available. The main effect of *tottering, leaner,* and *rolling Nagoya* mutated P/Q-type channels appears to be a reduction of calcium current density [64–67]. Furthermore, *leaner* and *rolling Nagoya* channel kinetics are changed [64–66]. Two *CACNA1A-null*-mutant (knock-out) mice show a lethal phenotype at a young age [68,69]. Total calcium current density in cerebellar cells was found decreased. P/Q-type currents were abolished and apparently partly compensated by N- and- L-type current. Cerebellar granule cells of heterozygous mice from one of the two *null*-mutants displayed a 50% reduction in P/Q-type current density [68,69], whereas no reduction was observed in the other model [68,69]. The fact that for the latter mutant, targeting was performed in exon 4 whereas exon 16 was targeted in the former raises the interesting possibility that compensation is dependent on whether truncated protein is made.

It is generally accepted that migraine aura is caused by cortical spreading depression, a depolarization wave associated with temporary disturbance of ion balances [70]. *CACNA1A* mutations may very well influence cortical spreading depression because P/Q-type calcium channels mediate glutamate release and an altered glutamate was reported in *tottering* and *CACNA1A* knockout mice [69,71,72]. Experimentally induced cortical spreading depression in *tottering* and *leaner* mice was found altered, in parallel with a reduced release of cortical glutamate [73].

A knock-in mouse model was generated, carrying the human pure FHM1 *R192Q* mutation [74••]. Unlike the natural *CACNA1A* mutant mouse models, transgenic *R192Q* mice exhibit no overt phenotype. However, multiple gain-of-function effects were found, including increased $Ca^{2+}$ influx in cerebellar neurons, increased

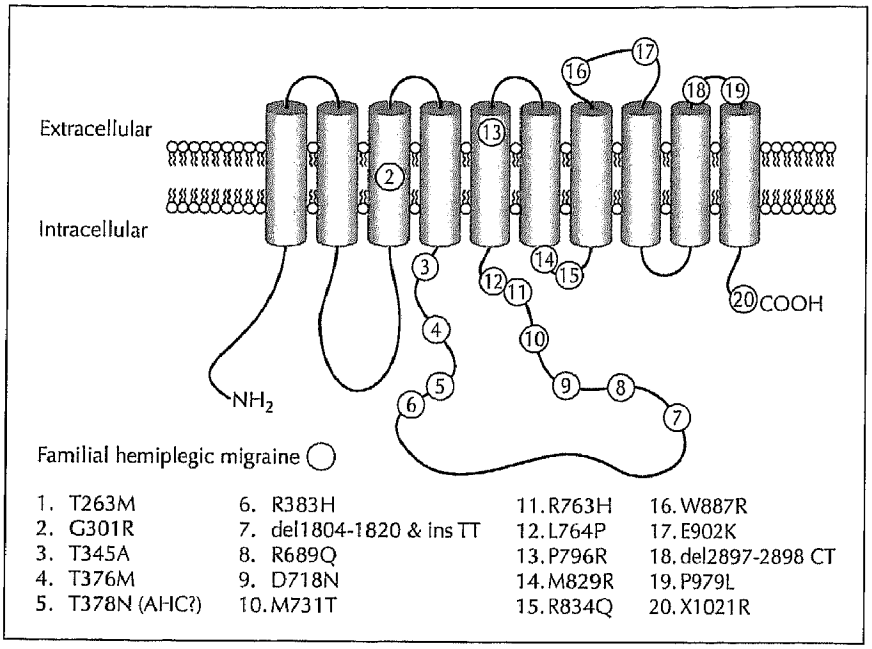


**Figure 2.** The *ATP1A2* gene with mutations. The α2 subunit of sodium potassium pumps is located in the plasma membrane and contains 10 transmembrane segments. Positions of mutations identified in this gene are given. AHC—alternating hemiplegia of childhood (*ATP1A2* ref. seq.: Genbank Ac.nr. NM_000702).

release of neurotransmitters, and, in the intact animal, a reduced threshold and increased velocity of cortical spreading depression. It seems that whole-animal studies are necessary to dissect the effects of mutations and understand the integrated physiology of the disease.

## Familial Hemiplegic Migraine Type-2: *ATP1A2*

Although linkage studies identified the FHM2 locus on chromosome 1 in 1997, it took another 6 years to identify mutations in the *ATP1A2* gene, encoding the α2 subunit of sodium potassium pumps [75,76].

### *ATP1A2*: Familial hemiplegic migraine

Missense mutations were identified in two Italian families with pure FHM (without ataxia) [75]. Since then, several other FHM families with similar mutations have been described (Fig. 2). A *M731T* mutation was identified in a small Dutch family with pure FHM [77] and a *T345A* mutation caused FHM attacks and coma in a Scandinavian family [78]. A screening in 27 FHM families, in which *CACNA1A* mutations were excluded, revealed six novel *ATP1A2* mutations [79•]. Three other novel mutations (and another three possible mutations) were found in German FHM families [80]. Another Italian group reported a *G301R* mutation in a family with FHM, seizures, coma, and sensory deficits, but also transient and permanent cerebellar signs [81•]. Therefore, the phenotypic spectrum of FHM2 expands beyond migraine, similar to that of FHM1.

## *ATP1A2*: Migraine with and Without Aura

In a recent study, no *ATP1A2* mutations were found in probands of families with common types of migraine (MO and MA) [27]. However, in several of the published families with *ATP1A2* mutations, there are mutation carriers with "non-hemiplegic" migraine (*eg*, the Italian families described in the first publication [75]). The true contribution of the *ATP1A2* gene to MO and MA remains unclear.

## *ATP1A2*: Epilepsy

Three subjects in the Italian families of the first publication on *ATP1A2* [75] reported a history of epileptic seizures resembling the migraine-triggered seizures observed in FHM1 patients. The association of *ATP1A2* mutations and epilepsy was confirmed by the finding of a *R689Q* mutation in a large Dutch-Canadian family with FHM and benign familial infantile convulsions (BFIC) [77,82]. BFIC is a rare autosomal-dominant benign form of epilepsy with strictly partial nonfebrile convulsions that begin between 3 an 12 months of age and disappear after the first year of life. In the *R689Q* family, all BFIC patients tested had the missense mutation, but BFIC and FHM only partially cosegregated. It seems that, in this family, migraine and epilepsy have partially overlapping mechanisms related to dysfunction of ion transport.

A further association of an *ATP1A2* mutation (*G301R*) and epilepsy was found by an Italian group in a family with FHM, seizures, coma, sensory deficits, and transient and permanent cerebellar signs [81•]. Epileptic seizures were present in German *D719N* and *P979L* mutation carriers [80].

## *ATP1A2*: Alternating Hemiplegia of Childhood?

Alternating hemiplegia of childhood (AHC) is a rare brain disorder, characterized by repeated periods of hemiplegia involving either side of the body at least in some attacks;

episodes of bilateral hemiplegia or quadriplegia starting as generalization of a hemiplegia episode or bilateral from the start; other paroxysmal phenomena, including tonic/dystonic attacks, choreoathetotic movements, nystagmus, strabismus, dyspnea, and autonomic phenomena, occurring during hemiplegic attacks or in isolation; immediate disappearance of all of the symptoms on going to sleep, with recurrence 10 to 20 minutes after awakening in long-lasting attacks; and evidence of developmental delay, mental retardation, and permanent neurologic abnormalities including choreoathetosis, dystonia, or ataxia. Age at onset generally is before 18 months [83]. AHC often has been regarded as being related to migraine, but some of its aspects are clearly distinct, including choreoathetosis and dystonic posturing and a progressive course associated with mental deterioration

Two separate groups found a *ATP1A2 T378N* mutation in two (or one and the same?) families with (presumed) AHC [84•,85•]. In both studies, the familial occurrence was remarkable because AHC generally is considered a sporadic disease. Therefore, the authors of both studies questioned whether the correct diagnosis in the affected patients was AHC or FHM. These findings are of some importance because they expand the number of families with *ATP1A2* mutations (AHC or not), but only the discovery of *ATP1A2* mutations in sporadic AHC patients could confirm the importance of this gene in this rare disease. In two previous studies from our laboratory, no *CACNA1A* or *ATP1A2* mutations were found in sporadic AHC patients [86,87]. In another study of eight sporadic AHC patients and patients from five small families with presumed AHC, no *ATP1A2* mutations were found [85•].

## *ATP1A2*: Functional Studies

The *ATP1A2* gene encodes the α2 subunit of a $Na^+,K^+$ pump ATPase. This catalytic subunit binds $Na^+$, $K^+$, and ATP and uses ATP hydrolysis to extrude $Na^+$ ions. $Na^+$ pumping provides the steep $Na^+$ gradient essential for the transport of glutamate and $Ca^{2+}$. The gene is predominantly expressed in neurons at the neonatal age and in glial cells at the adult age. Functional analysis of mutated proteins revealed inhibition of pump activity and decreased affinity for $K^+$ [75,84•,88]. Both functional phenotypes fit nicely into the current concepts of (hemiplegic) migraine pathophysiology; clearance of synaptic glutamate and $K^+$ is slowed, either because of $Na^+,K^+$ ATPase haploinsufficiency or reduced $K^+$ affinity, resulting in increased susceptibility to cortical spreading depression [89•].

## *ATP1A2*: Mouse Models

Two groups have generated α2-subunit-deficient mice [90,91]. In homyzygous *ATP1A2-null*, 18.5-day-old fetuses, selective neuronal apoptosis in the amygdala and piriform cortex in response to neural hyperactivity was observed [90]. *ATP1A2-null* mice in both models died immediately after birth because of severe motor deficits that also abolish respiration [90,91]. Additional studies have indicated that lack of spontaneous respiratory activity in these mice can be attributed to defects of brain stem respiratory neurons because of disturbed Cl-homeostasis in these neurons and excess extracellular GABA [90]. In line with the observed epilepsy in patients, *ATP1A2-null* mice on 129-sv genetic background display frequent and generalized seizures, but die within 24 hours after birth [92].

Heterozygous $ATP1A2^{+/-}$ mice are viable and the heart showed a hypercontractile state with positive inotropic response and resembles what typically is seen after the administration of cardiac glycosides [91]. In addition, $ATP1A2^{+/-}$ mice revealed enhanced fear/anxiety behaviors after conditioned, likely because of the observed neuronal hyperactivity in the amygdala and piriform cortex [90].

## Sporadic Hemiplegic Migraine

Patients with hemiplegic migraine are not always clustered in families. Sporadic patients, without affected family members, are seen often. It was shown that the clinical symptoms of patients with SHM were more similar to FHM than MA, which resulted in the inclusion of sporadic hemiplegic migraine (SHM) as a separate diagnostic entity in the second edition of the diagnostic criteria, apart from migraine with typical aura [1•,93]. Some of the sporadic patients are the first 'FHM patient' in the family, as was shown by the identification of *CACNA1A* mutations in two of 27 patients undergoing mutation analysis [18]. However, the greater part seem to have no mutation in any of the known FHM genes, defining SHM as an heterogeneous disease of unknown genetic origin. This was confirmed by the observation that first-degree relatives of SHM probands had an increased risk of MO and typical MA, whereas first-degree relatives of probands with SHM exclusively had no increased risk of MO, but an increased risk of typical MA. SHM probands had a highly increased risk of typical MA only [94].

## Conclusions

Investigation of FHM is an important part of migraine genetics research based on the assumption that FHM is part of the migraine spectrum. This has been confirmed by several family studies. The recent identification of the second FHM gene, *ATP1A2*, confirmed that dysfunction in ion transport is a key factor in the pathophysiology of familial hemiplegic migraine. New loci for the common forms of migraine have been reported (on chromosomes 4, 6, 11, and 14), but the responsible gene alterations have not been found. These findings underline the complex genetic nature of MO and MA and indicate that much research is still needed.

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