Migraine – advances in genetic research and possible link to neurophysiological abnormalities

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Summary

Sándor PS, Agosti RM, Schoenen J. Migraine – advances in genetic research and possible link to neurophysiological abnormalities. Schweiz Arch Neurol Psychiatr 2001;152:183–93.

Some important steps forward were achieved in recent years in migraine research. A number of mutations were described in the monogenic subtype of migraine with aura, familial hemiplegic migraine, partly with some clinical overlap to the allelic disorders, episodic ataxia type 2 and spinocerebellar ataxia type 6.

Migraine is now considered a neuro-vascular headache disorder and genetic studies point towards migraine in part as a central channelopathy, but also as a complex genetic disorder where genetic and environmental factors are interrelated.

There is evidence that certain neurophysiological abnormalities, like deficient cortical information processing and diminished mitochondrial energy reserve, may be interictal endophenotypic markers of the genetic vulnerability to migraine; it remains to be proven that they also are of pathophysiological importance. Other neurophysiological abnormalities, such as subclinical impairment of cerebellar function and of neuromuscular transmission, are unlikely to play a causative role in migraine. If they are due, as suspected, to dysfunctioning neuronal ion channels, they could be useful for the selection of patients for genetic analyses by better defining the phenotype of subgroups of migraineurs. In future studies correlations between neurophysiological and genetic data need to be emphasised.

Keywords: migraine; genetics; neurophysiology; CACAN1A; familial hemiplegic migraine

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Zusammenfassung

In den letzten Jahren machte die Erforschung der Migräne wichtige Fortschritte. Mehrere Mutationen wurden für die familiäre hemiplegische Migräne (FHM) beschrieben. Die familiäre hemiplegische Migräne ist ein monogener Subtyp der Migräne mit Aura, der sich klinisch teilweise mit den allelischen Erkrankungen, episodischer Ataxie Typ 2 und spinozerebellärer Ataxie Typ 6, überschneidet.

Migräne gilt mittlerweile als neurovaskuläreres Kopfschmerzsyndrom. Genetische Studien legen eine Einstufung der Migräne einerseits als Ionenkanalerkrankung, anderseits aber auch als komplexe genetische Erkrankung nahe, bei der genetische und Umweltfaktoren eine Rolle spielen.

Es gibt Hinweise dafür, dass bestimmte neurophysiologische Abnormitäten, wie z.B. eine gestörte kortikale Informationsverarbeitung sowie eine verminderte mitochondriale Energiereserve, endophänotypische Marker einer genetisch bedingten Anfälligkeit für Migräne sein könnten; es ist jedoch noch unklar, inwieweit ihnen eine pathophysiologische Bedeutung zukommt. Es ist unwahrscheinlich, dass die subklinischen Störungen zerebellärer Funktion und neuromuskulärer Übertragung eine kausale Rolle bei der Migäne spielen. Falls die oben genannten Störungen, wie vermutet, auf eine Fehlfunktion neuronaler Ionenkanäle zurückzuführen sind, könnten sie nützlich sein, um Patienten für genetische Analysen auszuwählen, da man mit ihrer Hilfe den Phänotyp einiger Untergruppen besser definieren könnte.

Schlüsselwörter: Migräne; Genetik; Neurophysiologie; CACAN1A; familiäre hemiplegische Migräne

Introduction

Migraine is an episodic neurological disorder, affecting up to 12% of males and 24% of females in the general population. Two main types are

Table 1 Mutations, polymorphisms and linkage in migraine.

DNA	mutations	polymorphisms	linkage
CACNA1A	+ (n >14) (FHM)		+/– (MA, MO)
Notch3	+ (prolonged aura; one family)		
chromosome 1			+ (FHM: 2 loci)
chromosome X			+ (MA, MO)
dopamine D2 receptor		+ (MA, MO)	
dopamine β hydroxylase		+ (MA, MO)	
angiotensin converting enzyme		+ (MA, MO)	
serotonin transporter		+ (MA, MO)	
tumour necrosis factor β		+ (MO)	
MTHF reductase	+ (C677T: MA, MO)		
mitochondrial DNA	+ (Japan, migraine and stroke) – (all other MA, MO)		

MTHF = methylenetetrahydrofolate; FHM = familial hemiplegic migraine; MA = migraine with aura; MO = migraine without aura

distinguished: *migraine without aura*, typically characterised by attacks of severe unilateral pulsating headache accompanied by nausea or vomiting, photo- and phonophobia, and *migraine with aura*, in which the headache is preceded by transient focal neurological (usually visual) symptoms. Attacks of migraine without aura are found in about 70% of migraine patients and attacks with aura in about 30% [1]. Usually one type of attacks prevails, however, both types may coexist in the same patient.

Migraine frequently runs in families, but family and segregation studies have produced conflicting results with respect to the mode of inheritance [2–5]. Up to now, the only known monogenic subtype of migraine is familial hemiplegic migraine (FHM). The more common migraine phenotypes appear to be complex genetic disorders, where additive genetic effects (susceptibility genes) and environmental factors are interrelated [6]. The weight of genetic factors seems to be more pronounced in migraine with aura than in migraine without aura [7]. Some studies suggest different liability loci for migraine headache and aura [7]. For an overview on mutations, polymorphisms and linkage, which are discussed below, see table 1.

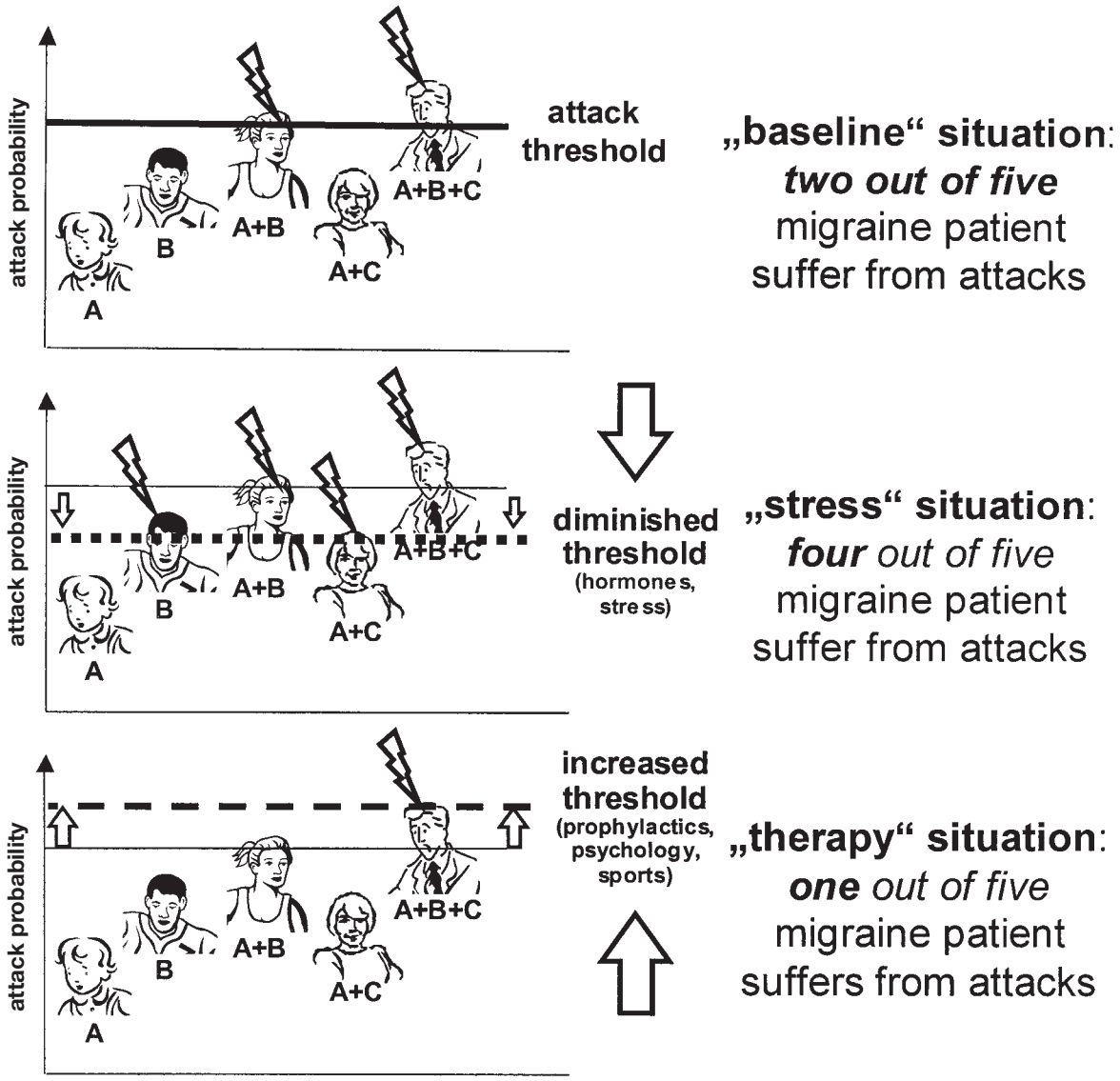
Migraine is characterised by *recurrent* attacks. Genetic load can be seen as determining on the one hand a critical migraine threshold that is modulated by external as well as internal factors and, if reached, leads via a brain and/or brainstem dysfunction to an attack (see fig. 1). On the other hand, genetic load may be responsible for interictal nervous system dysfunction that can produce subtle subclinical signs.

Familial hemiplegic migraine – a monogenic subtype of migraine with aura and allelic channelopathies

Phenotype

Familial hemiplegic migraine (FHM) is a rare autosomal dominant subtype of migraine with aura (IHS Headache Classification 1988). FHM patients have attacks of migraine which are associated with hemiparesis. Typically, the hemiparetic aura persists up to several days, much longer than the 20 to 30 minutes expected for the more common aura forms. In addition, some FHM families are associated with ictal and/or progressive (interictal)

Figure 1 A threshold model of migraine.



Threshold model:

Migraine is a complex genetic disorder. Genetic load ("migraine" susceptibility genes A, B, C) can be cumulative and determines a probability to suffer from recurrent attacks. There is a critical attack threshold. This can be modulated by external (prophylactic medication, psychosocial environment,...) as well as internal factors (estrogen changes, stress) and, if reached, leads via a brain and/or brainstem dysfunction to activation of the trigeminovascular system. Certain subjects can be attack-free or suffer from frequent attacks, depending on their susceptibility and threshold level. Some subjects (child on the left) will remain attack-free despite their genetic load, while others (man on the right), will continue to suffer in spite of therapeutic intervention. In addition to the above-mentioned threshold-modulating factors, attacks can be triggered e.g. by food (alcohol), particularly at a time when the threshold is lowered.

cerebellar ataxia. Patients with familial hemiplegic migraine and their family members may also have attacks of "non-hemiplegic" migraine. On this background it is plausible that familial hemiplegic migraine is most likely part of the migraine spectrum, and that genes involved in familial hemiplegic migraine are candidate genes for "non-hemiplegic" migraine, especially migraine with prolonged aura (i.e. longer than 60 min) and migraine associated with vestibulo-cerebellar symptoms [8].

FHM mutations in the gene CACNA1A

The calcium channel gene CACNA1A is located on the short arm of chromosome 19 and codes for the alpha-1 subunit of a neuronal P/Q Ca^{2+} channel. Some mutations on this gene cause familial hemiplegic migraine while others cause episodic ataxia type 2 (EA-2); CAG repeat expansions at the 3′ end cause spinocerebellar ataxia type 6. Since the first report of 4 mutations in familial hemiplegic migraine [7] at least 13 supplementary mutations have been found (cf. fig. 2; e.g. [9–11]). Several of those mutations, especially T666M, also cause ataxia [12]; others (T1385C) cause seizures and coma that can be triggered by trivial head trauma [13]. At present, the evidence that CACNA1A plays a role in the common forms of migraine is based on linkage studies and sib-pair analyses [14, 15].

Functional consequences of these mutations

Six functional subclasses of Ca^{2+} channels have been defined by electrophysiological and pharmacological criteria. They fall into two major categories: low-voltage activated (T type) and high-voltage activated channels (L, N, P, Q, R type) [16]. Ca^{2+} channels are multiple-subunit complexes composed of a major transmembrane α_1 unit and smaller auxiliary polypeptides which include a disulphide-linked α_2 subunit and the β subunit. The α_{1A} subunit, which is encoded by the CACNA1A gene, is the most important component of P and Q type channels; it acts as a voltage sensor and forms the ion-conducting pore [17].

In general, familial hemiplegic migraine is caused by missense mutations and episodic ataxia type 2 by truncating mutations in CACNA1A, but in some families these clinical phenotypes may overlap (e.g. [10], for review [18]).

The functional consequences of several of the FHM mutations were characterised in vitro. They were found to be rather complex: some mutations produced a gain of function, others a loss of functions and again others functional instability [19–21]. It therefore appears that mutations producing different channel dysfunctions may nonetheless cause similar clinical phenotypes.

In the cerebellum P/Q Ca^{2+} channels are highly expressed [22, 23] and known to control neurotransmitter release in the central (e.g. serotonin, [24]) and peripheral nervous system (e.g. acetylcholine at the neuromuscular junction [25, 26]).

Possible involvement of CACNA1A in non-hemiplegic migraine

Linkage studies

Linkage and sib-pair analyses suggest that the CACNA1A gene region 19p13 is also involved in the common forms of migraine with and without aura [15, 27] although significant linkage was not found in one study [28].

Interictal nervous system dysfunction in migraineurs

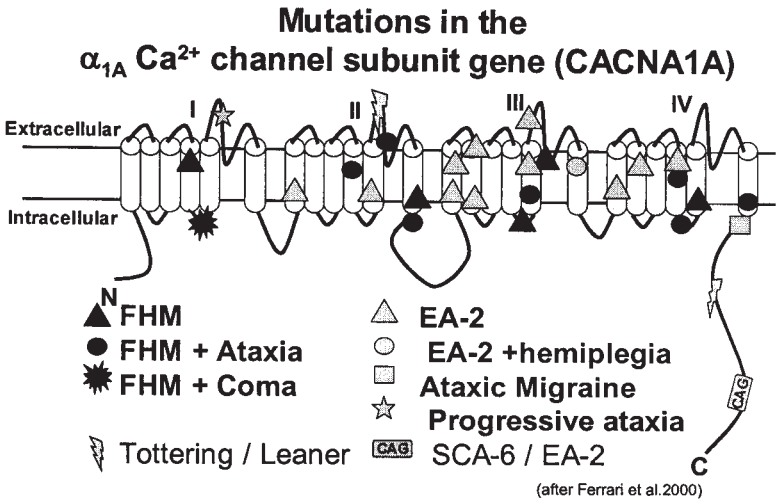
Subclinical dysfunction of the cerebellum and of neuromuscular transmission

In addition to the direct evidence from studies of genetic epidemiology there is indirect neurophysiological evidence suggesting an involvement of Ca^{2+}-channel genes in the common types of migraine. Mutations in the CACNA1A gene can cause familial hemiplegic migraine and/or cerebellar ataxia. As P/Q Ca^{2+} channels are highly expressed in the cerebellum, we used a pointing paradigm and an infra-red opto-electronic tracking system to search for an impairment of motor control in migraineurs and found subclinical hypermetria as well as other subtle cerebellar signs in the common forms of migraine [29a]. These cerebellar signs were more pronounced in migraine with than without aura and could reflect subtle dysfunctioning of genetically abnormal Ca^{2+} channels in a CNS location which at first sight is not involved per se in migraine pathogenesis. It is of interest, however, that during and between attacks, vertigo, dizziness and episodes of dysequilibrium are frequent in migraineurs, especially in those suffering from migraine with aura [8, 29b]. That the abnormalities are more pronounced in migraine with than in migraine without aura is compatible

Figure 2 The CACNA1A gene, familial hemiplegic migraine and migraine as a channelopathy.

The CACNA1A gene

The gene **CACNA1A** is located on the short arm of **chromosome 19** and codes for the alpha-1 subunit of a neuronal P/Q calcium channel. Some mutations on this gene cause FHM while others cause episodic ataxia type 2; CAG repeat expansions at the 3' end cause spinocerebellar ataxia type 6. Since the first report of four mutations in FHM by Ophoff et al. (1996) a number of supplementary mutations have been found. Several mutations found in FHM families, especially T666M, also cause ataxia; others (T1385C) cause seizures and coma that can be triggered by trivial head trauma. At present, the evidence that CACNA1A plays a role in the common forms of migraine is based on linkage studies and sib-pair analyses.



Migraine - a channelopathy

The P/Q calcium channels that are functionally impaired by the known CACNA1A mutations (Hans et al. 1999, Kraus et al. 1999, Kraus et al. 2000) are highly expressed in the cerebellum and known to control neurotransmitter release in the central (e.g.5-HT) and peripheral nervous system (e.g. acetylcholine at the neuromuscular junction). This might explain recent evidence for subclinical abnormalities in cerebellar function (Sándor et al. 2001) and neuromuscular transmission (Ambrosini et al. 1999) in subgroups of migraineurs. Another argument for the involvement of P/Q-channels comes from the favourable effect of acetazolamide on aura status (Haan & Ferrari 2000) and on neuromuscular dysfunction (Ambrosini et al. 2001).

Familial hemiplegic migraine : genotype-phenotype correlations

(modified from Montagna 2000)

	Ataxia/nystagmus	Notes
FHM 19p13 (CACNA1A)	+	80~90% penetrance with ictal coma/ traumatic onset without epilepsy
R192Q	0	
R195K	0	
T501M	0	
R583Q	+	frequent
T666M	+	**most frequent; also sporadic**
V714A	0	
D715E	+	Essential tremor
K1335E	0	
Y1384C	+	Sporadic
R1546X		EA2
R1667W	+/0	
L1682P	+	
W1683R	+	
V16951	0	
I1811L	+	
V1457L	0	Putative
FHM 1 (1q21-23, 1q 31)	0	60% penetrance with ictal coma/ traumatic onset epilepsy present

with the stronger genetic influence in the former migraine type [30, 31].

An example for a subclinical alteration in the peripheral nervous system of migraineurs seems to be the neuromuscular transmission abnormality recently found in a subgroup of migraine with aura patients [32]. A similar abnormality was described also in tottering mice, a CACNA1A mutant ([33], vide infra). P/Q Ca^{2+} channels are known indeed to control stimulation-induced acetylcholine release at the motor axon terminal [25, 26].

No mutations have been identified up to now in the common forms of migraine but the Ca^{2++} channels could be functionally impaired because of alterations in channel kinetics due to more subtle genetic changes such as gene polymorphisms. A correlation between a CACNA1A single nucleotide polymorphism and neuromuscular transmission assessed by single fibre EMG was recently described in migraine with aura patients [31, 34]. Another argument for the involvement of P/Q channels comes from the favourable effect of acetazolamide on neuromuscular dysfunction.

Possible involvement of the cortex

During the headache-free interval, an abnormal functioning of the migrainous brain can be demonstrated by psychophysical, neurophysiological and metabolic studies. Sensitivity to environmental stimuli is enhanced interictally in migraineurs [35]. On psychophysical tests of visual functions responses differ from normal in migraine patients who are particularly intolerant to certain visual patterns (see review in [36]).

Neurophysiological methods show that cortical information processing in migraineurs is characterised by a deficient habituation during repetition of the stimulation [37]. This has been demonstrated for event-related [38–40]and visual evoked potentials [41–43]. Moreover, intensity dependence of auditory evoked cortical potentials is increased in migraine patients compared to normal controls [44, 45]. During prolonged visual stimulation we found less habituation-like behaviour of the BOLD signal in migraine with aura patients, confirming with the method of functional MRI a difference in cortical information processing (Sándor unpublished observations).

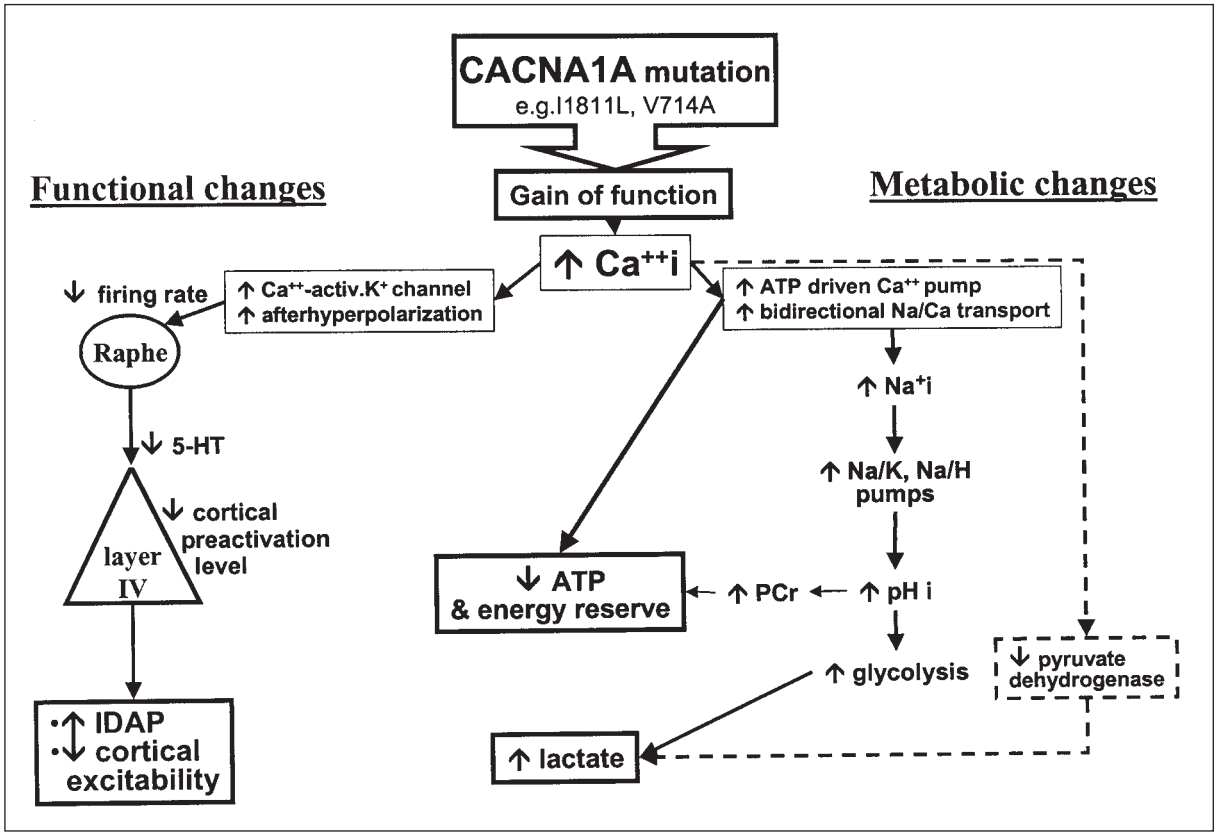
The precise cause for this cortical dysfunction is not known. However, it is likely to be genetically determined as shown by two independent studies [46, 47] and may represent an "endophenotypic vulnerability marker". It is likely on the one hand that an abnormal function of P/Q Ca^{2+} channels can change neuronal excitability and firing rate via changes in intracellular Ca^{2+} levels. Since the excitability of sensory cortices is known to be strongly modulated by subcortical aminergic neurons, a decreased firing rate of the latter might be responsible for the observed electrophysiological abnormalities (see fig. 3). On the other hand, a less obvious consequence of dysfunctioning Ca^{2+} channels has recently been demonstrated with NMR spectroscopy in episodic ataxia type 2: an increase in intracellular lactate levels and pH suggesting a disturbed mitochondrial metabolism (fig. 3) [48]. During prolonged visual stimulation in patients suffering from migraine with aura, we have found with functional magnetic resonance spectroscopy (MRS) an abnormal increase in lactate levels in the visual cortices which may be the metabolic consequence of the electrophysiological dishabituation or of a decreased mitochondrial energy reserve, or of both.

Mouse models of mutations in the FHM gene CACNA1A

There are three main mouse mutants that can serve as a model for human diseases with CACNA1A mutations: *tottering*, *leaner* and *rolling Nagoya* [49–51]. The recessive *tottering* mice that have been studied extensively as models for human epilepsy [52] carry a missense mutation that is very similar to one of the FHM mutations, and most likely affects the pore function of the P/Q-type Ca^{2+} channel. It results in intermittent convulsions similar to human absence epilepsy, motor seizures, and mild ataxia. The more severely affected *leaner* mouse is associated with a mutation producing an aberrant intracellular terminus and resembling the mutations found in two EA-2 families. The leaner mouse suffers from absence-like (but not motor) seizures, is severely ataxic and typically dies early in life. Purkinje- and granule cell loss throughout the anterior cerebellum and reduced cerebellar size are found in this mutant. For the third mouse strain, the *rolling Nagoya*, which presents an intermediate phenotype, no mutation has yet been identified. Motor seizures do not occur, the ataxia is more severe than in the tottering mutant, and these mice have a normal life span [49].

It was shown that tottering mice have a modified threshold for cortical spreading depression [53], which is a phenomenon most likely involved in the pathophysiology of migraine aura. In the tottering mouse a cortical proliferation of noradrenergic axons from the locus coeruleus is considered to be involved in the generation of seizures [52]. Interestingly, positron emission tomography studies suggested brain stem structures in the re-

Figure 3 Putative functional and metabolic consequences of mutations in the α_{1A} Ca^{2+} channel subunit gene (CACNA1A).



gion of the locus coeruleus and the dorsal raphe nucleus to be of pathophysiological importance in migraine attacks [54]. As mentioned above, tottering mice have clear abnormalities of acetylcholine release at the motor axon terminal [33]. In addition to serving as model for epilepsy and ataxia, the tottering mouse may therefore serve also as a channelopathy model for migraine.

Other loci for familial hemiplegic migraine

Chromosomes 1 and X

While approximately 50% of FHM families have been assigned to chromosome 19p13 [55,56], about one third of families are not linked to chromosome 19, but to a yet to be identified gene on chromosome 1 [12, 57, 58] or to other undetermined genetic loci. Further analysis has to disclose whether chromosome 1q harbours one or two FHM genes. Some FHM families cannot be linked to chromosomes 19 or 1. Therefore, at least a third gene must be involved [57]. The X chromosome might be a candidate as in a study of familial typical migraine significant linkage to chromosome Xq24-28 was found [59].

Polymorphisms

The prevalence of various gene polymorphisms may be higher in migraineurs than in controls. This was reported for the dopamine D2 receptor [60], the angiotensin converting enzyme [61], the serotonin transporter [62], the dopamine β hydroxylase [63] and the TNFβ genes [64]. The latter may be related to the decreased frequency of HLA Class II DR2 antigen reported in migraine without aura [65]. The role played by these various polymorphisms remains to be determined; some of them may not be specific to migraine, but they could increase susceptibility to the disorder and induce endophenotypic vulnerability markers (see above). A recent study in Japanese migraineurs showed a higher incidence of the homozygous C677T mutation of the methylenetetrahydrofolate reductase gene, which is associated with increased homocysteine levels and thrombosis. No evidence was found for an allelic association with migraine of a polymorphism in the inducible nitric oxide synthase gene [63], which may be relevant for the putative role of NO in migraine pathogenesis.

Table 2 mtDNA studies in migraine (modified from Montagna P. Molecular genetics of migraine headaches: a review. Cephalalgia 2000;20:3–14).

negative studies	
Klopstock et al. 1996	3243 MELAS, 8344 MERRF, mtDNA deletions absent in MA
Haan et al. 1999	3243 MELAS, 3271, 11084, mtDNA deletions absent in matrilinear migraines
Russel et al. 1997	11084 mutation absent in Danish migraineurs
Majamaa et al. 1998	8344, 8993, 11778, mtDNA deletions absent in migraine stroke
Buzzi et al. 2000	mtDNA A3243G MELAS mutation not associated with multigenerational female migraine

positive studies	
Shimomura et al. 1995	11084 mtDNA mutation in 25% of 53 Japanese migraineurs
Bresolin et al. 1991	mtDNA deletion in one case with migraine stroke
Ojaimi et al. 1998	4216 and 13708 LHON secondary mutations in juvenile stroke
Majamaa et al. 1997	MELAS mutation in 6% of juvenile migraine stroke
Majamaa et al. 1998	mtDNA U haplotype in migraine stroke
Ohno et al. 1998	tRNA Giu and 12SrRNA mutations in matrilinear FHM

Other conditions including migraine as a syndrome

CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a disease with a multifaceted symptomatology, including recurrent subcortical ischaemic strokes, progressive vascular dementia, and mood disorders [66]. Remarkably, migraine with aura occurs in many patients with CADASIL [66–68]. Typical FHM attacks have been described in one CADASIL family [69] and migraine with white matter lesions resembling typical CADASIL on MRI in another family linked to the CADASIL locus [66]. A Notch3 gene mutation was identified to be cause of CADASIL [70]. It is not clear whether in CADASIL migraine attacks are directly related to the genetic abnormality or secondary to the vascular changes. Up to now, no further genetic data are available on the families, in which CADASIL occurs together with FHM-like migraine attacks. Interestingly, a mutation in the Notch3 gene was recently found in an Italian family affected by migraine with prolonged aura but no other neurological deficits [71].

Migraine and mitochondrial function

Metabolic studies using MRS have shown a low mitochondrial phosphorylation potential in the brain and muscles of migraineurs (fig. 3) [72–74]. Although mitochondrial DNA mutations were reported in some migraineurs with stroke-like episodes [75–78], none of the known mitochondrial mutations was found up to now in the common forms of migraine [79–81]. Mitochondrial energy metabolism can, however, be impaired by Ca^{2+}-channel dysfunction (see above and fig. 3) [82] and by decreased magnesium levels both of which may be involved in migraine [83–85]. It has been hypothesised that the conjunction of a decreased mitochondrial energy reserve and a deficit in habituation of cortical information processing, known to protect against overstimulation and lactate accumulation, might lead to activation of the major pain-signalling system of the head, the trigeminovascular system [41].

Preliminary results using functional MRS during prolonged visual stimulation (vide supra) suggest that the habituation deficit might suffice to produce an abnormal increase in cortical lactate levels. It is still to be determined whether the mitochondrial abnormality is an independent pathophysiological component or rather a consequence of other functional deficits.

Acknowledgements:
We thank Mrs Ulli Sänger for excellent technical assistance.

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