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REVIEW

Migraine, ataxia and epilepsy: a challenging spectrum of genetically determined calcium channelopathies

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Clinical and genetic heterogeneity as well as influence of environmental factors have hampered identification of the genetic factors which are involved in episodic diseases such as migraine, episodic ataxia and epilepsy. The study of rare, but clearly genetically determined subtypes, may help to unravel the pathogenesis of the more common forms. Recently, different types of mutation in the brain-specific P/Q type calcium channel α_{1A} subunit gene (CACNA1A) on chromosome 19p13 were shown to be involved in three human disorders: familial hemiplegic migraine (FHM), episodic ataxia type 2 (EA2), and chronic spinocerebellar ataxia type 6 (SCA6). In addition, evidence is accumulating that the same gene is also involved in the common forms of migraine with and without aura. In the tottering and leaner mouse, which are characterised by epilepsy and ataxia, similar mutations were identified in the mouse homologue of the calcium channel α_{1A} subunit gene. These findings add to the growing list of episodic (and now also chronic) neurological disorders, which are caused by inherited abnormalities of voltage-dependent ion channels. The findings in migraine illustrate that rare, but monogenic variants of a disorder, may be successfully used to identify candidate genes for the more common, but genetically more complex, forms.

Keywords: migraine; familial hemiplegic migraine (FHM); episodic ataxia type 2 (EA2); spinocerebellar ataxia type 6 (SCA6); CADASIL; epilepsy; CACNA1A; P/Q type calcium channel

Gene Mapping Approaches to Multifactorial Disorders

The search for genetic risk factors for multifactorial diseases is complex. This is particularly true of episodic disorders. When family material is abundant and candidate genes are scarce, random genome screening for linkage is the method of choice, although there are clear views on the optimal statistical approach.[1–4] Linkage findings, after independent confirmation, may point to *positional* candidate genes as opposed to *functional* candidates based on pathophysiological hypotheses.

A third approach is to localise genes which cause rare Mendelian variants of a specific multifactorial disorder.

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These *phenotypic* candidate genes can then be evaluated as possible susceptibility loci, under the assumption that mutations which convey susceptibility to a complex disease are allelic to more serious gene defects leading to Mendelian segregation. Since the rare variants usually have a clear inheritance pattern, candidate loci can be identified by using regular lod score analyses. This approach has proved to be successful in the search for genes implicated in migraine.

Migraine, a Multifactorial Disorder

Migraine is an episodic neurological disorder, affecting up to 12% of males and 24% of females in the general population.[5] Two main types are distinguished

(i) migraine without aura, typically characterised by attacks of severe unilateral pulsating headache, nausea, vomiting, and photo- and phonophobia, and

(ii) migraine with aura, in which the headache attacks are preceded by transient focal neurological, usually visual, aura symptoms.

The visual symptoms may include scintillating scotoma, blurred vision, flickering, dark spots. Both types of migraine attacks may coexist in the same patient but usually one type prevails. Attacks of migraine without aura are found in 67% of patients and attacks of migraine with aura in 33%.[6] Migraine frequently runs in families, but family and segregation studies have produced conflicting results with respect to the mode of inheritance.[7–10] From a large proband-oriented clinical study[6] it was inferred that migraine with aura is largely or exclusively determined by genetic factors, whereas migraine without aura seems to be caused by a combination of both genetic and environmental factors. Thus migraine is a multifactorial disorder.

Familial Hemiplegic Migraine

Clinical Features and Linkage Data

Familial hemiplegic migraine (FHM) is a rare autosomal dominantly inherited subtype of migraine with aura.[11] Patients with FHM have attacks of migraine with aura which are also associated with hemiparesis or hemiplegia (one-sided weakness of the body). Otherwise symptoms of headache and aura phase are similar to those of 'non-hemiplegic' migraine with aura, but may be much longer. In addition, some FHM families are associated with progressive permanent ataxia (disturbance of coordination of movements). Patients with FHM may also have attacks of 'non-hemiplegic' migraine and in families with FHM, both individuals with FHM and individuals with 'non-hemiplegic' migraine are to be found. These observations strongly suggest that FHM is part of the migraine spectrum, and that genes involved in FHM are candidate genes for 'non-hemiplegic' migraine with and without aura.

In approximately 50% of the reported families, FHM has been assigned to chromosome 19p13.[12,13] Recently two groups also found linkage to chromosome 1.[14,15] An American group showed, in one large family, a lod score of 3.04 at $\Theta = 0.09$ with marker D1S249 on chromosome 1q31,[15] whereas a French group showed linkage to chromosome 1q21–q23 in three FHM families.[14] Further analysis has yet to disclose whether chromosome 1q harbours one or two FHM genes. There remain some FHM families unlinked to chromosome 19 or chromosome 1, indicating at least a third gene involved.[14]

So far very few clinical differences between the FHM families linked to chromosome 19 and the non-chromosome 19 linked families have been found except for cerebellar ataxia that appears in approximately 50% of the chromosome 19 linked but in none of the unlinked FHM families.[12,13,16–20] Presumably, FHM and cerebellar degeneration reflect defects in the same gene in chromosome 19 linked FHM families.[10,20] In addition, patients from families linked to chromosome 19 are more likely to have attacks triggered by minor head trauma or attacks associated with coma in comparison with patients from families not linked to this chromosome.[18]

FHM: a Channelopathy

Molecular Biology of Calcium Channels

Six functional subclasses of calcium channels have so far been defined by electrophysiological and pharmacological criteria. The classes fall into two major categories: low-voltage activated (T type) and high-voltage activated channels (L, N, P, Q, R type).[21–24] Calcium channels are multiple-subunit complexes composed of a major transmembrane α_1 unit and smaller auxiliary polypeptides which include a β subunit and the disulphide-linked $\alpha_2\delta$ subunit. In skeletal muscle a γ subunit may also form part of the channel complex. The α_1 subunit is the most important component and acts as

a voltage sensor and forms the ion-conducting pore modified by the other subunits.[25]

Six genes (*A, B, C, D, E* and *S*) have been identified that encode α_1 subunits (see Table 1).[22–24,26] The α_1 subunit topology is very similar to the structure seen in voltage-dependent Na^+ and K^+ channels.[22] The α_1 subunit consists of four internal homologous repeats (I–IV), each containing six putative α-helical membrane spanning segments (S1–S6) and one pore-forming (P) segment between S5 and S6 that spans only the outer part of the transmembrane region.[27] The S4 segment contains a positively charged amino acid in every third or fourth position and is the voltage sensor for the voltage-gated ion channels.[23]

The β subunits are cytoplasmic proteins capable of modulating current amplitude, activation and inactivation kinetics, and voltage dependence when coexpressed with α_1 subunits.[28] β subunits are encoded by four different genes, all expressed in brain (Table 1).

The $\alpha_2\delta$ subunit is encoded by a single gene (Table 1) and consists of glycosylated α_2 and δ proteins linked together by disulphide bonds with δ as the transmembrane protein anchor and α_2 extracellular.

Additional molecular diversity arises from alternative splicing of the α, β and $\alpha_2\delta$ transcripts.[24,28] The characteristics of the different calcium channel types are primarily correlated with the different α_1 isoforms.[29] The α_{1A} subunit encodes P and Q type calcium channels which were originally identified in cerebellar Purkinje cells[30] and granule cells.[31] P and Q type calcium channels differ in inactivation kinetics possibly due to α_{1A} subunit splice variants,[32] post-translational modification, or the influence of an auxiliary subunit.[33]

Mutations in the P/Q Type Calcium Channel α_{1A} Subunit Gene in FHM

Using exon trapping, a human cDNA highly homologous to a brain-specific rabbit and rat voltage gated P/Q type calcium channel α_{1A} subunit gene was identified.[34–36] The human gene was designated CACNL1A4,[37] but according to a newly proposed nomenclature the gene is called CACNA1A.[29] The gene is transcribed specifically in cerebellum, cerebral cortex, thalamus and hypothalamus.

Four different missense mutations in five unrelated FHM families have been identified (see Figure 1).[36] A transition from G to A was identified resulting in an arginine to glutamine substitution (R192Q) within the fourth segment of the first membrane spanning domain (IS4). The highly conserved S4 segment is thought to be part of the voltage sensor. The second mutation

Table 1 Calcium channel subunits

Subunit	*Nomenclature*	*Channel type*	*Pharmacology (blockers)*	*Location*	*Distribution*	*Human disorders*	*Mouse models*
1A	CACNA1A	P/Q	-Agatoxin IVA -Conotoxin MVIIC	19p13	neuronal, endocrine	FHM, EA2, SCA6	Tottering (tg) Leaner (tg[a])
1B	CACNA1B	N	-Conotoxin GVIA -Conotoxin MVIIA	9q34	neuronal		
1C	CACNA1C	L	Dihydropyridines	12p14.3	cardiac and smooth muscle, neuronal		
1D	CACNA1D	L	Dihydropyridines	3p14.3	neuronal, endocrine		
1E	CACNATE	R/T	?	1q25–q31	neuronal		
1S	CACNA1S	L	Dihydropyridines	1q31–q32	skeletal muscle	HypoKK, MHS2	
1	CACNB1			17q11.2–q22	skeletal muscle, neuronal		
2	CACNB2			10p12	heart, aorta, neuronal		
3	CACNB3			12q13	neuronal, aorta, trachea, lung, heart, skeletal muscle		
4	CACNB4			2q22–q23	neuronal		Lethargic (Ih)
2	CACNA-2			7q21–q22	skeletal muscle, heart, vascular and intestinal smooth muscle, neuronal		
	CACNG			17q24	skeletal muscle		

FHM = Familial Hemiplegic Migraine; EA2 = Episodic Ataxia type 2; SCA6 = SpinoCerebellar Ataxia type 6; HypoKK = Hypokalemic Periodic Paralysis; MHS2 = Malignant Hyperthermia susceptibility2; see Ref Nos 110, 111.

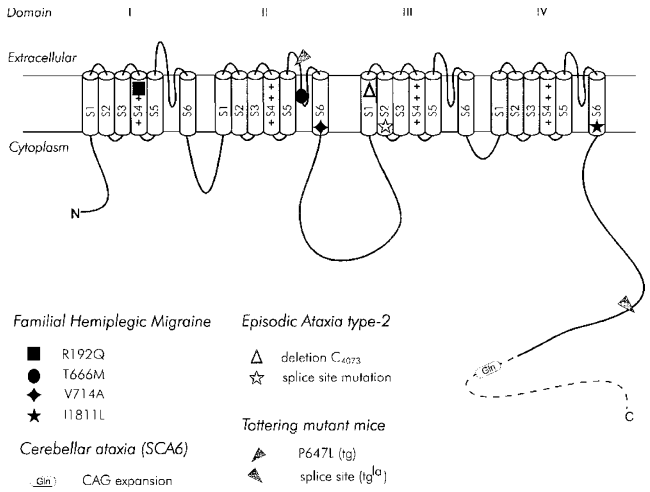

Figure 1 *Membrane topology of α_{1A} subunit of the P/Q type Ca^{++} channel, CACNA1A. The α_{1A} subunit consists of four internal homologous repeats (I-IV), each containing six putative α-helical membrane spanning segments S1–S6 and one pore-forming (P) segment between S5 and S6 that spans only the outer part of the transmembrane region. The S4 segment contains a positively charged amino acid in every third or fourth position and is the voltage sensor for the voltage-gated ion channels. The location and amino acid substitutions are indicated for mutations that cause familial hemiplegic migraine (FHM), episodic ataxia type 2 (EA2), tottering mouse (tg), leaner mouse (tg^{la}, and spinocerebellar ataxia type 6 (SCA6).*

occurred within the pore-forming (P) hairpin loop of the second domain replacing a threonine residue for methionine (T666M). These conserved P segments, located between each S5 and S6, are involved in the ion-selectivity of ion channels and present binding sited for toxins.[27] Two other mutations were located in the sixth transmembrane spanning segment of repeats II and IV. The IIS6 mutation was a T-to-C transition at codon 714, resulting in a valine-to-alanine substitution (V714A). The IVS6 mutation was an A-to-C transversion at codon 1811 that resulted in substitution of isoleucine for leucine (I1811L) and was found in two independent FHM families. The S6 mutations do not actually change the neutral-polar nature of the amino acid residues, but the original residues are conserved in all calcium channel α_1 subunit genes described.[26] Residues in the S6 transmembrane segments may be of influence in the inactivation of the calcium channel.[38] The missense mutations in FHM suggest a molecular mechanism similar to what is found in other human channelopathies. Both alleles are likely to be expressed with the allele harbouring the missense mutation resulting in gain-of-function variants of the P/Q type calcium channels. Such mutations have been described in the α subunit of the skeletal muscle sodium channel resulting in hyperkalemic periodic paralysis, paramyotonia congenita, and the sodium channel myotonias (Table 2).[39,40]

Interestingly, the second FHM locus on chromosome 1q is located near a brain-specific R/T calcium channel α_{1E} subunit gene (*CACNA1E*). Mutation analysis has yet to disclose whether this *CACNA1E* gene is involved in chromosome 1-linked FHM families.

Table 2 Heritable neurological disorders of ion channels

Disorder	*Ion channel gene*	*Chromosomal location*
Hyperkalemic periodic paralysis	*SCNA4* (skeletal muscle sodium channel)	17q23–25
Paramyotonia congenita	,,	,,
Pure myotonias (fluctuans, permanens, acetazolamide-responsive)	,,	,,
Hypokalemic periodic paralysis	*CACNA1S* (skeletal muscle calcium channel)	1q31–32
Malignant hyperthermia susceptibility2	,,	,,
Familial hemiplegic migraine	*CACNA1A* (neuronal calcium channel)	19p13
Episodic ataxia2	,,	,,
Spinocerebellar ataxia6	,,	,,
Episodic ataxia1	*KCNA1* (neuronal potassium channel)	12p14
Malignant hyperthermia susceptibility1	*RYR1* (ryanodine calcium channel)	19p13.1
Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4* (neuronal nicotinic acetylcholine receptor)	20q13.2–q13.3
Hyperekplexia	*GLRA1* (neuronal glycine receptor)	5q33–35
Thomsen's myotonia congenita	*CLCN1* (skeletal muscle chloride channel)	7q35
Becker's myotonia congenita	,,	,,
Myotonia levior	,,	,,

All disorders have an autosomal dominant inheritance except for Becker's myotonia congenita which has autosomal recessive inheritance[26, 112, 113].

Involvement of the P/Q type Calcium Channel Gene on Chromosome 19 in 'non-Hemiplegic' Migraine

Previously, tentative evidence that the FHM locus on chromosome 19p13 is involved in 'non-hemiplegic' migraine with and without aura has been found.[41] However, the results were inconclusive as to the magnitude of the involvement and the relative importance of migraine with aura and migraine without aura. A second affected sib pair analysis was performed in an independent additional sample of 36 extended Dutch families, with migraine with aura and migraine without aura.[42] Significant increased sharing of the marker alleles in sibs with migraine with aura (maximum multipoint lod score (MLS) was 1.29 corresponding with $P = 0.013$ approximately) was confirmed. No such increased sharing was found for migraine without aura. A combined analysis for both migraine types, including sib pairs in which one had migraine with aura and the other migraine without aura, resulted in an even more significant increased sharing (MLS = 1.69 corresponding approximately with $P = 0.005$). The relative risk ratio for a sib (λ_s) to suffer from migraine with aura, defined as the increase in risk of the trait attributable to the 19q13 locus, was $\lambda_s = 2.4$. When combining migraine with and without aura, λ_s was 1.25. When the results obtained in the study including Dutch families and those obtained in our previous study, mainly including German families,[41] were combined with maximum multipoint lod score raised to 2.27 ($P = 0.001$ approximately). These two studies provide independent evidence of the involvement of the region on chromosome 19q13 containing the P/Q type calcium channel α_{1A} subunit gene in the etiology of migraine; the contribution to migraine with aura, however, seems stronger. Mutation analysis in patients with migraine has yet to reveal when the known FHM mutations contribute to the etiology of migraine or other specific variants of this gene are involved in migraine with and without aura.

Role of Calcium Channels in the Pathophysiology of Migraine

Physiologically, calcium acts as an intracellular second messenger by initiating or regulating numerous biochemical and electrical events in the cell. Calcium ions are implicated in the regulation of several enzymes and for the control of the activity of several other ion channels.[43] They also control many neuronal events such as neurotransmitter release,[25,44–47] synaptogenesis, and neurite outgrowth.[43] P/Q type calcium channels seem to be more effective at modulating neurotransmitter release than other channel types.[48]

Most current models of migraine suggest that serotonin (5-hydroxytryptamine, 5-HT) has a central role in migraine pathophysiology.[49] Effective specific acute anti-migraine drugs all share the ability to stimulate neuronal and vascular 5-HT_1 receptors, thereby (among other effects) inhibiting release of vasoactive neuropeptides.[50,51] Remarkably, P type neuronal Ca^{2+} channels mediate neurotransmitter release including 5-HT.[52,53] Conversely, serotonin acts at 5-HT_{2c} receptors to increase intracellular calcium activity in choroid plexus epithelial cells, both by liberating Ca^{2+} from intracellular stores and by activating a Ca^{2+} influx pathway.[54] In rat motorneurones serotonin inhibits N and P type calcium currents.[55]

In the pathophysiology of migraine, cortical spreading depression may initiate migraine attacks.[56] Calcium and other ion channels are important in the mechanism of cortical spreading depression.[56,57] Therefore impaired function of cerebral calcium channels may facilitate initiation of attacks.

There is also evidence of involvement of Mg^{2+} in the pathophysiology of migraine. Magnetic resonance spectroscopy studies suggest that intracellular brain magnesium is reduced in migraine patients and that the regional distribution of brain magnesium is altered in patients with FHM.[58,59] Preliminary clinical trial data suggest that chronic administration of magnesium may reduce migraine attack frequency.[60] Interestingly, Mg^{2+} is known to interfere with Ca^{2+} channels.[61,62]

Hormones seem to be of importance in migraine because there is a female preponderance among migraine patients, and in females attacks may be affected by menstruation and pregnancy. An influence of hormones on ion channels has been considered in hypokalemic and hyperkalemic periodic paralysis.[63,64] Joëls and Karst[65] investigated the effects of oestradiol and progesterone on voltage-gated calcium and potassium conductances in rat C_{A1} hippocampal neurons and concluded that long-term modulation with these hormone levels alters the calcium but not the potassium currents.

Episodic Ataxia Type 2

Clinical Features and Linkage Data

Episodic ataxia (EA) is characterised by recurrent attacks of generalised ataxia and other signs of cerebellar dysfunction.[66] The disease is heterogeneous and at least two autosomal dominantly inherited types are distinguished. Episodic ataxia type 1 (EA1) is characterised by brief episodes of ataxia and dysarthria (disturbed articulation) lasting seconds to minutes and is associated with interictal myokymia (twitching of small muscles).[66] EA1 is caused by missense mutations in a potassium channel gene (*KCNA1*) on chromosome 12p14.[67] Episodic ataxia type 2 (EA2) is also called acetazolamide responsive paroxysmal cerebellar ataxia (APCA), paroxysmal vestibulocerebellar ataxia (PVCA), or hereditary paroxysmal cerebellar ataxia (HPCA).[68–71] EA2 is characterised by attacks of generalised ataxia, usually associated with an interictal nystagmus (eye movement disturbance). Treatment with acetazolamide is very effective in preventing attacks. Attacks typically last a few hours and can be precipitated by emotional stress, exercise, or alcohol. Clinical onset generally occurs in childhood or early adulthood.[66]

Episodic ataxia 2 was linked to the same interval on chromosome 19p as FHM.[68–71] Notwithstanding the clinical differences between EA2 and FHM there are also some similarities. Both are episodic disorders, patients with EA2 may show migraine-like features,[68,71–74] and in both disorders there may be progressive ataxia and dysarthria and cerebellar atrophy on magnetic resonance imaging.[16,17,75]

Mutations in the P/Q Type Calcium Channel α_{1A} Subunit Gene

Because of the clinical and genetic similarities between FHM and EA2, families with EA2 were included in the mutation analysis of the *CACNA1A* gene. Until now two different truncating mutations were identified in EA2 families (see Figure 1).[36] One mutation is a nucleotide deletion (deletion C_{4073}) causing a frame shift and a premature stop. The other mutation affects the first invariant G nucleotide of the intron consensus sequence leading to aberrant splicing. Both mutations result in truncated α_{1A} subunits which are unlikely to form functional calcium channels and may either degrade resulting in haploinsufficiency, or negatively influence channel assembly in the membrane.

Spinocerebellar Ataxia6 and the P/Q Type Calcium Channel α_{1A} Subunit Gene

The autosomal dominant cerebellar ataxias (SCA) are a clinically and genetically heterogeneous group of disorders with many possible accompanying features in addition to the ataxia, such as ophthalmoplegia, pyramidal and extrapyramidal signs, neuropathy, dysarthria, amyotrophy, and pigmentary retinopathy.[76] Genes are located on chromosomes 6p22–p23 (SCA1),[77,78] 12q23–24.1 (SCA2),[79] 14q13.1 (SCA3/Machado-Joseph disease,[80,81] 16q24-ter (SCA4),[82] 11 (SCA5),[83] and 3p12–p21.1 (SCA7).[84–86] For SCA1, 2, 3, and 7 the disease-causing mutations have been identified as expanded and unstable CAG trinucleotide repeats.[87–92] For SCA4 and 5 the disease-causing genes are still to be identified.

Recently, six different cDNA isoforms of the *CACN1A1* gene have been reported of which three contained a 5-nucleotide insertion prior to the previously described stop codon, resulting in a shift of the open reading frame in which the CAG repeat is predicted to encode a polyglutamine stretch.[36,93] Small triplet expansions of the intragenic CAG repeat ranging from 21 to 30 repeat units were observed in patients with autosomal dominant cerebellar ataxia (SCA6),[93–95] whereas normal chromosomes displayed 4–20 repeats.[36,93–96] The CAG repeat length is inversely correlated with age at onset.[94–96] Anticipation of the disease was observed clinically[94] but no detectable intergenerational allele size change was seen in contrast to other disease-causing repeats (eg in other SCAs and Huntington disease). The occurrence of the SCA6 mutation was estimated to be 10% of SCA patients in Germany,[95] whereas in Japan SCA6 comprised 30% of the examined ataxia patients and one homozygous case was found suggesting a founder effect.[94]

Interestingly, both chromosome 19 linked FHM families and EA2 families may develop progresive cerebellar ataxia and atrophy.[12,13,16–20,75] Screening for CAG repeat expansion in FHM and EA2 families with chronic cerebellar ataxia has to be performed to answer the question whether the FHM and/or EA2 mutations

cause chronic progressive cerebellar ataxia independent of the number of CAG repeats.

P/Q Type Calcium Channel α_{1A} Subunit Gene in Mice with Epilepsy and Ataxia

Simultaneously with the identification of mutations in FHM and EA2, mutations in the *CACNA1A* gene were found in the tottering (tg) and leaner mouse (tg^{la}) phenotypes (Figure 1).[97–98] These recessive tottering mice have been studied extensively as models for human epilepsy.[100] The mutation in the tottering mouse is a missense mutation close to the pore-forming P loop of the second transmembrane domain, very similar to one of the FHM missense mutations, and most likely affects the pore function of the P/Q type calcium channel. The more severe leaner mouse is associated with a splice site mutation producing an aberrant intracellular terminus and resembles the mutations found in two EA2 families. Mutations at the mouse tottering locus result in intermittent convulsions similar to human absence epilepsy, motor seizures, and mild ataxia. The leaner (tg^{la}) mouse suffers from absence seizures, but no motor seizures. The tg^{la} mutants are more ataxic and often do not survive past weaning. The profound chronic ataxia is associated with pervasive Purkinje- and granule cell loss throughout the anterior cerebellum and reduced cerebellar size. A third mouse strain, the rolling Nagoya (tg^{rol}) presents an intermediate phenotype; the ataxia is more severe than in the tg mouse, motor seizures do not occur, and they have a normal life span.[97] No mutation for the tg^{rol} mouse has yet been identified.

It has been demonstrated that tottering mutant mice have a significantly increased threshold for cortical spreading depression [unpublished data], which is a phenomenon thought to be involved in the pathophysiology of migraine. In the tottering mouse a proliferation of noradrenaline axons arising from the locus coeruleus is considered to be one of the neuronal mechanisms underlying the generation of absence seizures.[100] Interestingly, positron emission tomography studies in acute migraine attacks suggested the locus coeruleus and the dorsal raphe nucleus to be the 'migraine centre' in man.[101] The tottering mice may therefore not only serve as a model for epilepsy and ataxia, but also for migraine.

Interestingly, it was recently shown that a mutation in the calcium channel β4 subunit gene is associated with ataxia and seizures in the lethargic mouse (1h).[102] Homozygotes of the 1h mouse are characterised by ataxia, lethargic behaviour, motor seizures and seizures resembling absence seizures of human petit mal epilepsy.[102]

CADASIL: Clinical but no Genetic Overlap with Migraine

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare disorder caused by mutations in a *Notch3* gene on chromosome 19p[103,104] and characterised by recurrent subcortical ischaemic strokes, progressive vascular dementia, mood disorders with severe depression,[105] and in 30% of patients by migraine with aura.[105–107] One CADASIL family has been described with typical FHM attacks,[108] and another family, linked to the CADASIL locus, with migraine and CADASIL-like white matter lesions on magnetic resonance imaging.[109] All these observations contributed to the clinical spectrum of migraine-FHM-CADASIL. Further study of this intriguing relation is needed.

Discussion and Conclusions

So far, different sets of mutations in the P/Q type calcium channel gene seem to be associated with specific clinical phenotypes although these phenotypes may show some clinical overlap. The mechanism in which these mutations produce both episodic and chronic disorders is not yet understood. Presumably, these mutations permit proper cell function until extra- or intracellular conditions exacerbate the molecular pathology, leading to episodic failure of the channel function. In the long term, mutations may lead to impairment of inactivation of the calcium channel and a chronic disturbance of calcium homeostasis. The inability to restore the resting intracellular calcium levels may then induce a slow but progresive apoptotic neuronal cell death and a chronic progressive phenotype.

In summary, the identification of the P/Q type calcium channel in migraine, epilepsy, and ataxia is a leap forward in the understanding of neurological channelopathies. Furthermore, the identification of calcium channels involved in the pathophysiology of

these disorders opens new avenues for the development of prophylactic treatment.

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