Views and Perspectives

Genetics of Migraine: Possible Links to Neurophysiological Abnormalities

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Key words: migraine, genetics, neurophysiology, *CACNA1A*, familial hemiplegic migraine

Abbreviations: MWOA migraine without aura, MWA migraine with aura, FHM familial hemiplegic migraine, EA2 episodic ataxia type 2, MRS magnetic resonance spectroscopy, CADASIL cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

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Migraine is a paroxysmal neurologic disorder affecting up to 12% of males and 24% of females in the general population. Two main types are distinguished: *migraine without aura* (MWOA) and *migraine with aura* (MWA), in which headache is preceded by transient focal neurologic symptoms (usually visual). Attacks of only MWOA are reported by about 70% of patients with migraine, while at least occasional attacks of MWA occur in about 30%.[1] Usually one type of attack prevails, but both types often coexist in the same patient.

Migraine frequently runs in families, but family and segregation studies have produced conflicting results with respect to a mode of inheritance.[2-5] At present, the only known monogenic subtype of migraine is familial hemiplegic migraine (FHM). The more common migraine phenotypes appear to be complex genetic disorders, wherein additive genetic effects (susceptibility genes) and environmental factors are interrelated.[6] The weight of genetic factors seems to be more pronounced in MWA than in MWOA.[7,8] Some studies suggest different susceptibility *loci* for migraine headache and aura.[7,8] For an overview on the mutations, polymorphisms, and linkage that are to be discussed, see Table 1.

Migraine is characterized by *recurrent* attacks. Genetic load can be seen as determining an inherent migraine threshold that itself is modulated by external and internal factors and, if exceeded, leads to brain and/or brain stem dysfunction, activation of the trigeminovascular system, and an attack. Depending on genetically derived susceptibility, the presence or absence of environmental influences, and the effect of any prophylactic therapy undertaken, some individuals will remain attack-free despite their genetic load, while others will continue to suffer. The genetic load also 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 is a rare autosomal dominant subtype of MWA (International Headache Society classification).[9] Patients with FHM have attacks of migraine which are associated with variable degrees of hemiparesis. The hemiparetic aura typically persists up to several days, much

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Table 1.—Migraine Genotypes*

DNA	Mutation	Polymorphism	Linkage	Source, y
CACNA1A	+ (n>16) FHM			Ophoff et al,[12] 1996 Ducros et al,[19] 2001
			± MWA>MWOA	Nyholt et al,[22] 1998 May et al,[23] 1995 Hovatta et al,[41] 1994 Terwindt et al,[24] 2001
		+ MWA		Ambrosini et al,[52] 2000
Notch 3	+ (Prolonged aura, 1 family)			Ceroni et al,[107] 2000
Chromosome 1q			+ FHM (1q21, 1q31)	Ducros et al,[84] 1997 (1q21-23) Echenne et al,[86] 1999 Gardner et al,[85] 1997 (1q31)
			+ MWA, MWOA (1q31)	Griffiths et al,[87] 2001
Chromosome Xq24-28			+ MWA, MWOA (and 1q, 1 family)	Nyholt et al,[89] 2000 Griffiths et al,[87] 2001
Chromosome Xp22			+ MWA, MWOA, FHM	Wieser et al,[90] 2001
Chromosome 3			+ MWOA, vascular retinopathy, and Raynaud (3p21)	Ophoff et al,[108] 2001
Chromosome 4			+ MWA	Wessman et al,[88] 2001
Dopamine D_2 receptor		+ MWA>MWOA		Peroutka et al,[91] 1997 Del Zompo et al,[92] 1998
Dopamine β hydroxylase		+ MWA, MWOA		Lea et al,[95] 2000
Angiotensin converting enzyme		+ MWA, MWOA		Paterna et al,[93] 2000
Serotonin transporter		+ MWA, MWOA		Ogilvie et al,[94] 1998
Tumor necrosis factor β		+ MWOA		Martelletti et al,[98] 2000
MTHF reductase	+ C677T, MWA, MWOA			Kowa et al,[100] 2000
Endothelin type A receptor (ETA-231 A/G)		+ MWOA, MWA		Tzourio et al,[96] 2001
Insulin receptor (ch 19p13.2/3)		+ (n=5) MWOA, MWA		White et al,[97] 2001
Mitochondrial DNA	+ Migraine and stroke			Bresolin et al,[112] 1991 Sano et al,[114] 1996 Ojaimi et al,[118] 1998
	− All other MWA, MWOA			Majamaa et al,[117] 1998

*FHM indicates familial hemiplegic migraine; MWA, migraine with aura; MWOA, migraine without aura; MTHF, methylenetetrahydrofolate.

longer than the 20 to 30 minutes expected for the more common aura forms. In addition, some families with FHM also experience ictal and/or progressive (interictal) cerebellar ataxia. Patients with FHM and their family members may also have attacks of "non-hemiplegic" migraine. Given this clinical background, it is plausible that FHM is most likely part of the migraine spectrum, and that genes involved in

FHM are candidate genes for "nonhemiplegic" migraine (especially migraine with prolonged aura [ie, longer than 60 minutes], migraine associated with vestibulocerebellar symptoms, or basilar migraine, the last of which may be clinically linked to FHM).[10,11]

Mutations in the Gene *CACNA1A*: FHM and Allelic Diseases.—The calcium channel gene, *CACNA1A* (formerly, *CACNL1A4*), is located on the short arm of chromosome 19 and codes for the pore-forming subunit (α_{1A}) of neuronal voltage-dependent P/Q-type calcium channels.[8] Some mutations on this gene cause FHM, while others cause episodic ataxia type 2 (EA2)[12]; CAG repeat expansions at the 3′ end cause spinocerebellar ataxia type 6.[13] Recent reports have indicated a *CACNA1A* point mutation (C5733T) introducing a premature stop codon (R1280stop) in one patient suffering from generalized epilepsy and ataxia and the involvement of one *CACNA1A* polymorphism in generalized epilepsy.[14,15]

Since the first report of 4 mutations in FHM,[8] at least 16 supplementary mutations have been found (Table 2).[8,16-19] Several of those mutations (especially T666M) also cause ataxia, while others (S218L, Y1385C) cause seizures and coma that can be triggered by trivial head trauma.[8,20-21] At present, the evidence that *CACNA1A* plays a role in the common forms of migraine is based on linkage studies and sib-pair analyses.[22-24]

Functional Consequences of These Mutations.—Six functional subclasses of calcium 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).[25] Calcium channels are multiple-subunit complexes composed of a major transmembrane α1 unit and smaller auxiliary polypeptides which include a disulfide-linked α2δ 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.[26]

P/Q calcium channels are highly expressed in the cerebellum and known to control neurotransmitter release in the central (eg, serotonin) and peripheral nervous system (eg, acetylcholine at the neuromuscular junction).[27-31]

Table 2.—Familial Hemiplegic Migraine: Genotype-Phenotype Correlations*

	Ataxia/ Nystagmus	Notes
FHM 19p13 (*CACNA1A*)	+	~80%-90% penetrance with ictal coma/traumatic onset without epilepsy
R192Q	0	
R195K	0	
S218L	0	Coma/traumatic onset
T501M	0	
R583Q	+	Frequent
T666M	+	Most frequent, also sporadic
V714A	0	
D715E	+	Essential tremor
K1336E	0	
Y1385C	+	Sporadic; coma, epilepsy
R1668W	+	
L1682P	+	
W1684R	+	
V1696I	0	
I1811L	+	
V1457L	0	Putative
FHM 1 (1q21-23; 1q31)	0	~60% penetrance with ictal coma/traumatic onset; epilepsy present

*Modified from Montagna.[32]

In general, FHM is caused by missense mutations and EA2 by truncating mutations in *CACNA1A*, but in some families these clinical phenotypes may overlap.[17,32] Recently, missense mutations producing exclusively EA2 have been described, and in one patient EA2 was associated with nonhemiplegic migraine.[16,33] In EA2, loss-of-function mutations in *CACNA1A* can result in presynaptic failure of neuromuscular transmission.[34-36]

In vitro, the functional consequences of several of the FHM mutations were found to be rather complex: some mutations produce a gain of function, others a loss of function or functional instability.[37-39] Therefore, it appears that mutations producing different channel dysfunctions nonetheless may cause similar clinical phenotypes.

The mechanisms by which dysfunctioning P/Q-type calcium channels may cause disorders characterized by ictal phenomena such as EA2, FHM, and, possibly, "regular" migraine are still unknown. An in

vivo study showed that inhibition by alpha-eudesmol inhibits neurogenic plasma extravasation following electrical stimulation of rat trigeminal ganglion, as well as calcitonin gene-related peptide and substance P release.[40] By contrast, in another preliminary study, blockade of P/Q calcium channels in the periaqueductal gray facilitated trigeminal nociception in dorsal horn neurons.

POSSIBLE INVOLVEMENT OF *CACNA1A* IN NONHEMIPLEGIC MIGRAINE

Linkage Studies.—Although significant linkage was not found in one study,[41] linkage and sib-pair analyses suggest that the *CACNA1A* gene region 19p13 also is involved in MWA and MWOA.[22-24] This involvement seems to be more pronounced in MWA than in MWOA.[24]

Interictal Nervous System Dysfunction in Migraineurs.— *Subclinical Dysfunction of the Cerebellum and of Neuromuscular Transmission.*—In addition to direct evidence from studies of genetic epidemiology, there is indirect neurophysiological evidence suggesting an involvement of calcium channel genes in the common types of migraine. As previously indicated, mutations in the *CACNA1A* gene can cause FHM, cerebellar ataxia (or both), and P/Q-type calcium channels are highly expressed in the cerebellum.[27,28] We used a pointing paradigm and an infrared optoelectronic tracking system to search for impairment of motor control in migraineurs and found subclinical hypermetria and other subtle cerebellar signs in subjects with the common forms of migraine[42]; the cerebellar signs were more pronounced in MWA than in MWOA. These signs could reflect subtle dysfunctioning of genetically abnormal calcium channels in a central nervous system location which, at first glance, might not be thought involved per se in migraine pathogenesis. It is of interest, however, that during and between attacks, vertigo, dizziness, and episodes of dysequilibrium are frequent complaints of migraineurs, especially in those with MWA.[10,43] That the cerebellar signs were more pronounced in MWA than in MWOA is compatible with the stronger genetic influence in the former type.[44]

An example of a subclinical alteration in the peripheral nervous system of migraineurs seems to be the reduced safety factor at the neuromuscular junction recently found with single-fiber electromyography (EMG) in a subgroup of patients with MWA.[45-47] The abnormality was present mainly in patients with neurologic in addition to visual aura symptoms and in patients with prolonged auras.[45-47] P/Q calcium channels are known to control stimulation-induced acetylcholine release at the motor axon terminal.[48,49] As similar but more pronounced abnormalities of neuromuscular transmission were described in EA2 and in tottering mice, their presence in the common forms of migraine is compatible with mildly dysfunctioning P/Q-type calcium channels.[34,50] There is a significant correlation between cerebellar and neuromuscular junction performances in MWA supporting the hypothesis of a common cause for both types of subclinical dysfunction.[51]

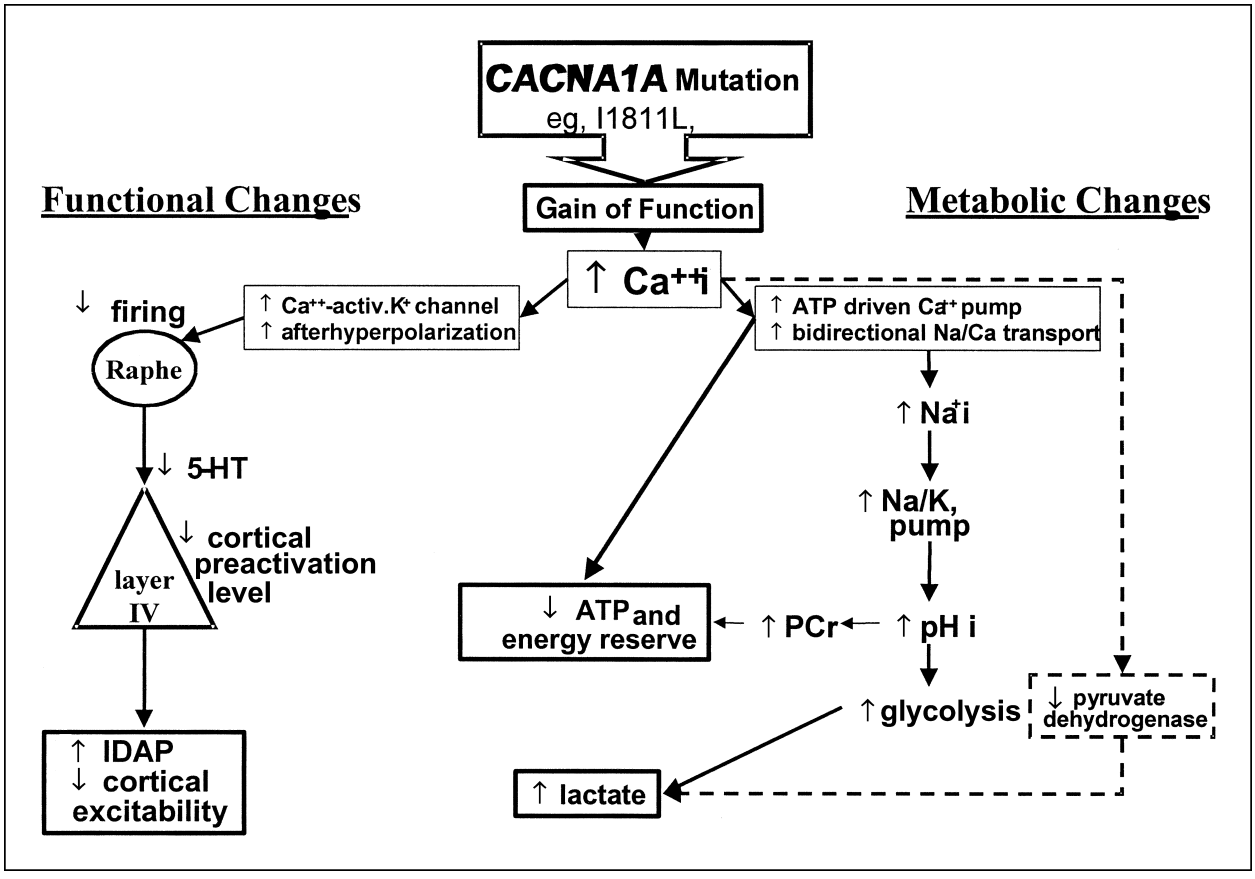
Other evidence for the involvement of P/Q-type calcium channels in the common forms of migraine comes from the favorable effect of acetazolamide on clinical symptoms in EA2, FHM, and migraine aura status and on single-fiber EMG abnormalities found in patients with nonhemiplegic migraine.[18,52-55] That no mutations have been identified up to now in the common forms of migraine, suggests that the calcium 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-fiber EMG was recently described in patients with MWA.[56]

Possible Involvement of the Cortex.—During the headache-free interval, abnormal functioning of the migrainous brain can be demonstrated by psychophysical, neurophysiological, and metabolic studies.

Sensitivity to environmental stimuli is enhanced interictally in migraineurs.[57] On psychophysical tests of visual functions, migraineurs differ from nonmigraineurs in being particularly intolerant to certain repetitive visual patterns.[58] Neurophysiological testing has shown that processing of cortical information in migraineurs is characterized by deficient habituation (or dishabituation) during repetition of the stimulation[59]; this has been demonstrated for both event-related and visual evoked potentials.[60-64] More-

over, intensity dependence of auditory evoked cortical potentials is increased in patients with migraine compared to normal controls, perhaps chiefly a consequence of similar dishabituation.[65,66] During prolonged visual stimulation, we found less habituation-like behavior of the BOLD signal in patients with MWA than in healthy volunteers, thus confirming with the method of functional magnetic resonance imaging a migraine-linked difference in cortical information processing.[67]

The precise cause of this cortical dysfunction is not known, but two independent studies have indicated that it is likely genetic in origin and may represent an "endophenotypic vulnerability marker."[68-70] Dysfunctioning P/Q-type calcium channels can change neuronal excitability and firing rate via changes in intracellular calcium 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 (Figure). We have shown in a recent study that dishabituation can be induced in the normal human brain by inhibiting the cortex with low-frequency repetitive transcranial magnetic stimulation, while habituation can be normalized in the migrainous brain by activating the cortex with high-frequency stimulation.[71] Another less obvious consequence of dysfunctioning calcium channels was demonstrated with magnetic resonance spectroscopy (MRS) in EA2, wherein an increase of intracellular lactate levels and pH suggested impairment of mitochondrial metabolism (Figure).[72] During prolonged visual stimulation in patients with MWA, we have found with functional MRS an abnormal increase of lactate levels within the visual cortices, perhaps representing the metabolic consequence of electrophysiological dishabituation, decreased mitochondrial energy reserve, or both.[73]



Putative functional and metabolic consequences of mutations in the α_{1A} calcium channel subunit gene *CACNA1A* (metabolic changes adapted from Sappey-Marinier et al[72]).

MOUSE MODELS OF MUTATIONS IN THE FHM GENE *CACNA1A*

There are four mouse mutants that can serve as a model for human diseases involving *CACNA1A* mutations: tottering, leaner, rolling Nagoya, and rocker.[74-78] A "knockout" mouse lacking the α_{1A} subunit also has been produced.[79]

The recessive tottering mice that have been studied as models for human epilepsy 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 calcium channel.[80] Its presence 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 EA2 families. The leaner mouse suffers from absencelike (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. The third mouse strain, the rolling Nagoya, presents an intermediate phenotype. Motor seizures do not occur, the ataxia is more severe than in the tottering mutant, and life span is normal. The recently described rocker mice, possessing a recessive missense mutation, exhibit a normal life span, ataxia, and intention tremor, but not seizures.[78] By contrast, the knock-out α_{1A}-null mice exhibit severe progressive ataxia, dystonia, and absence seizures; death normally occurs within 3 to 4 weeks.[79]

Tottering and leaner mice have an increased threshold for cortical spreading depression and attenuation of evoked increases of extracellular glutamate levels, suggesting a decrease in cortical excitability.[81] Could a similar lack of excitability be responsible for the abnormal cortical information processing found in migraineurs? In tottering mice, a cortical proliferation of noradrenergic terminals from the locus coeruleus is thought to be involved in the generation of seizures.[80] Interestingly, positron emission tomography studies have suggested that the brain stem area wherein the locus coeruleus and dorsal raphe nucleus reside may be of pathophysiological importance in migraine attacks.[82,83] As mentioned previously, tottering mice also exhibit clear abnormalities of acetylcholine release at the motor axon terminal,[50] another finding that indicates they may represent useful "channelopathy model" for certain migraine subtypes.

OTHER LOCI FOR MIGRAINE

Chromosomes 1, 4, 19, and X.—While the larger part of families with FHM have genetic abnormalities located on chromosome 19p13, some demonstrate no linkage to chromosome 19, but rather to a yet-to-be-identified gene on chromosome 1 or to other undetermined genetic loci.[84-86] Further analysis may disclose whether chromosome 1q harbors one or two FHM genes. Linkage to this chromosome (1q31) was recently found in nonhemiplegic forms of migraine, with some families having additional linkage to Xq24-28.[87] Some families with FHM cannot be linked to chromosomes 19 or 1, and at least a third gene consequently must be involved.[84] Significant linkage to chromosome 4 was described in MWA.[88] A new locus on chromosome 19 (19p13), distinct from the *CACNA1A* gene, recently was found to be linked to MWA.[89] The X chromosome also might be a candidate, as significant linkages have been shown both to chromosome Xq24-28 and Xp22 for familial hemiplegic and nonhemiplegic migraine.[90,91]

Polymorphisms.—The prevalence of various gene polymorphisms may be higher in migraineurs than in controls. This has been reported for the dopamine D_2 receptor, angiotensin converting enzyme, the serotonin transporter, dopamine β hydroxylase, the endothelin type A receptor, the insulin receptor, and the tumor necrosis factor β genes; the latter may reflect the decreased frequency of HLA class II DR2 antigen reported in MWOA. The role played by these various polymorphisms remains to be determined; some may not be specific to migraine, but still could increase susceptibility to the disorder and induce endophenotypic vulnerability markers. A recent study of 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.[100] No evidence has been found for an allelic association between migraine and a poly-

Table 3.—Mitochondrial DNA Studies in Migraine*

Negative studies	
Klopstock et al,[119] 1996	3243 MELAS, 8344 MERRF, mtDNA deletions absent in migraine with aura
Haan et al,[121] 1999	3243 MELAS, 3271, 11084, mtDNA deletions absent in matrilinear migraine
Russell et al,[120] 1997	11084 mutation absent in Danish migraineurs
Majamaa et al,[117] 1998	8344, 8993, 11778, mtDNA deletions absent in migraine stroke
Buzzi et al,[122] 2000	mtDNA A3243G MELAS mutation not associated with multigenerational female migraine
Positive studies	
Shimomura et al,[113] 1995	11084 mtDNA mutation in 25% of 53 Japanese migraineurs
Bresolin et al,[112] 1991	mtDNA deletion in one case with migraine stroke
Ojaimi et al,[118] 1998	4216 and 13708 LHON secondary mutations in juvenile stroke
Majamaa et al,[115] 1997	MELAS mutation in 6% of juvenile migraine stroke
Majamaa et al,[117] 1998	mtDNA U haplotype in migraine stroke
Boles et al,[116] 1997	8.1 Kb mtDNA deletion in cyclic vomiting syndrome

*Modified from Montagna.[32]

morphism in the inducible nitric oxide synthase gene, a result which may be relevant to the putative role of nitric oxide in migraine pathogenesis.[101]

OTHER CONDITIONS INCLUDING MIGRAINE AS A SYMPTOM

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL).—This is a disease with multifaceted symptomatology, including recurrent subcortical ischemic strokes, progressive vascular dementia, and mood disorders.[102] Remarkably, MWA occurs in many patients with CADASIL.[102-104] Typical FHM attacks have been described in one family with CADASIL.[105] In another family linked to the CADASIL locus, migraine and white matter lesions resembling typical CADASIL on MRI were reported.[102] A Notch 3 gene mutation has been identified as the cause of CADASIL.[106] It is unclear in CADASIL whether migraine attacks are directly related to the genetic abnormality or secondary to vascular changes. No further genetic data are, as yet, available from the families in which CADASIL is accompanied by migraine attacks typical of FHM. A mutation in the Notch 3 gene recently was found in an Italian family affected by migraine with prolonged aura but no other neurologic deficits.[107] In a family affected by migraine, hereditary vascular retinopathy, and Raynaud phenomenon, significant linkage occurred with a locus on chromosome 3 (3p21).[108]

Migraine and Mitochondrial Function.—Metabolic studies using MRS have demonstrated low mitochondrial phosphorylation potential in the brain and muscle of migraineurs.[109-111] Although mitochondrial DNA mutations have been reported in some migraineurs with strokelike episodes, none of the known mitochondrial mutations yet has been found in the more common forms of migraine (Table 3).[112,113,115-122] Even so, mitochondrial energy metabolism can be impaired by calcium channel dysfunction and by decreased magnesium levels, both of which may be present in migraine.[72,123-125] It has been hypothesized that the conjunction of 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 limb of the brain, the trigeminovascular system.[59] Preliminary re-

Table 4.—Phenotypic Aspects of Common Forms of Migraine Possibly Linked to Specific Genotypes

Trigger factors	Hereditary transmission patterns
Premonitory symptoms	Comorbid disorders
Presence of aura	Neuromuscular junction impairment
Prolonged aura	Subclinical cerebellar signs
Complex neurologic aura	Dishabituation on evoked potentials
Vertigo/imbalance	Interictal cognitive impairment

sults using functional MRS during prolonged visual stimulation suggest that the habituation deficit might suffice in certain migraineurs to produce an abnormal increase in cortical lactate levels.[73] It is still to be determined whether any mitochondrial abnormality found in migraine is an independent pathophysiological component or simply a consequence of other functional deficits.

CONCLUSIONS

Migraine is a complex disease wherein various genetic factors interact with environmental triggers. The challenge for future research is to establish better links between the clinical phenotype and the genotype. Hints may come from the known function and localization of some of the gene products found to be abnormal in or linked to migraine. The recently described subclinical cerebellar and neuromuscular junction dysfunctions could be due to abnormal calcium channels, but direct proof is still missing. Other phenotypic aspects of migraine, be they clinical, electrophysiologic, or metabolic, may have a genetic basis (Table 4). There clearly is a need to explore their potential correlation with the genetic profile of subgroups of migraineurs, down to the level of single nucleotide polymorphisms.

REFERENCES

1. Russell MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex-ratio of the subtypes of migraine. *Int J Epidemiol.* 1995;24:612-618.
2. Mochi M, Sangiorgi S, Cortelli P, et al. Testing models for genetic determination in migraine. *Cephalalgia.* 1993;13:389-394.
3. Russell MB, Olesen J. The genetics of migraine without aura and migraine with aura. *Cephalalgia.* 1993;13:245-248.
4. Stewart WF, Staffa J, Lipton RB, Ottman R. Familial risk of migraine: a population-based study. *Ann Neurol.* 1997;41:166-172.
5. Haan J, Terwindt GM, Ferrari MD. Genetics of migraine. *Neurol Clin.* 1997;15:43-60.
6. Nappi G, Costa A, Tassorelli C, Santorelli FM. Migraine as a complex disease: heterogeneity, comorbidity and genotype-phenotype interactions. *Funct Neurol.* 2000;15:87-93.
7. Russell MB, Olesen J. Increased familial risk and evidence of genetic factor in migraine. *BMJ.* 1995; 311:541-544.
8. Diriong S, Lory P, Williams ME, Ellis SB, Harpold MM, Taviaux S. Chromosomal localization of the human genes for alpha 1A, alpha 1B, and alpha 1E voltage-dependent Ca^{2+} channel subunits. *Genomics.* 1995;30:605-609.
9. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia.* 1988;8(suppl 7): 1-96.
10. Neuhauser H, Leopold M, von Brevern M, Arnold G, Lempert T. The interrelations of migraine, vertigo, and migrainous vertigo. *Neurology.* 2001;56: 436-441.
11. Haan J, Terwindt GM, Ophoff RA, et al. Is familial hemiplegic migraine a hereditary form of basilar migraine? *Cephalalgia.* 1995;15:477-481.
12. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{2+} channel gene *CACNL1A4. Cell.* 1996;87:543-552.
13. Jodice C, Mantuano E, Veneziano L, et al. Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the *CACNA1A* gene on chromosome 19p. *Hum Mol Genet.* 1997;6:1973-1978.
14. Jouvenceau A, Eunson LH, Spauschus A, et al. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. *Lancet.* 2001;358: 801-807.
15. Chioza B, Wilkie H, Nashef L, et al. Association between the $alpha_{1a}$ calcium channel gene *CACNA1A* and idiopathic generalized epilepsy. *Neurology.* 2001;56:1245-1246.
16. Friend KL, Crimmins D, Phan TG, et al. Detection of a novel missense mutation and second recurrent mutation in the *CACNA1A* gene in individuals with EA-2 and FHM. *Hum Genet.* 1999;105:261-265.
17. Jen J, Yue Q, Nelson SF, et al. A novel nonsense mutation in *CACNA1A* causes episodic ataxia and hemiplegia. *Neurology.* 1999;53:34-37.
18. Battistini S, Stenirri S, Piatti M, et al. A new *CACNA1A* gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia. *Neurology.* 1999;53:38-43.
19. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated

with mutations in a neuronal calcium channel. *N Engl J Med.* 2001;345:17-24.
20. Vahedi K, Denier C, Ducros A, et al. *CACNA1A* gene de novo mutation causing hemiplegic migraine, coma, and cerebellar atrophy. *Neurology.* 2000;55:1040-1042.
21. Kors EE, Terwindt GM, Vermeulen FL, et al. Delayed cerebral edema and fatal coma after minor head trauma: role of the *CACNA1A* calcium channel subunit gene and relationship with familial hemiplegic migraine. *Ann Neurol.* 2001;49:753-760.
22. Nyholt DR, Lea RA, Goadsby PJ, Brimage PJ, Griffiths LR. Familial typical migraine: linkage to chromosome 19p13 and evidence for genetic heterogeneity. *Neurology.* 1998;50:1428-1432.
23. May A, Ophoff RA, Terwindt GM, et al. Familial hemiplegic migraine locus on 19p13 is involved in the common forms of migraine with and without aura. *Hum Genet.* 1995;96:604-608.
24. Terwindt GM, Ophoff RA, van Eijk R, et al. Involvement of the *CACNA1A* gene containing region on 19p13 in migraine with and without aura. *Neurology.* 2001;56:1028-1032.
25. Catterall WA. Structure and function of voltage-gated ion channels. *Annu Rev Biochem.* 1995;64: 493-531.
26. Dunlap K, Luebke JI, Turner TJ. Exocytotic Ca^{2+} channels in mammalian central neurons. *Trends Neurosci.* 1995;18:89-98.
27. Stea A, Tomlinson WJ, Soong TW, et al. Localization and functional properties of a rat brain alpha 1A calcium channel reflect similarities to neuronal Q- and P-type channels. *Proc Natl Acad Sci U S A.* 1994;91:10576-10580.
28. Randall A, Tsien RW. Pharmacological dissection of multiple types of Ca^{2+} channel currents in rat cerebellar granule neurons. *J Neurosci.* 1995;15:2995-3012.
29. Craig PJ, McAinsh AD, McCormack AL, et al. Distribution of the voltage-dependent calcium channel $alpha_{1A}$ subunit throughout the mature rat brain and its relationship to neurotransmitter pathways. *J Comp Neurol.* 1998;397:251-267.
30. Katz E, Protti DA, Ferro PA, Rosato Siri MD, Uchitel OD. Effects of Ca^{2+} channel blocker neurotoxins on transmitter release and presynaptic currents at the mouse neuromuscular junction. *Br J Pharmacol.* 1997;121:1531-1540.
31. Westenbroek RE, Hoskins L, Catterall WA. Localization of Ca^{2+} channel subtypes on rat spinal motor neurons, interneurons, and nerve terminals. *J Neurosci.* 1998;18:6319-6330.
32. Montagna P. Molecular genetics of migraine headaches: a review. *Cephalalgia.* 2000;20:3-14.
33. Denier C, Ducros A, Durr A, Eymard B, Chassande B, Tournier-Lasserve E. Missense *CACNA1A* mutation causing episodic ataxia type 2. *Arch Neurol.* 2001;58:292-295.
34. Jen J, Wan J, Graves M, et al. Loss-of-function EA2 mutations are associated with impaired neuromuscular transmission. *Neurology.* 2001;57:1843-1848.
35. Guida S, Trettel F, Pagnutti S, et al. Complete loss of P/Q calcium channel activity caused by a *CACNA1A* missense mutation carried by patients with episodic ataxia type 2. *Am J Hum Genet.* 2001; 68:759-764.
36. Maselli RA, Jen J, Graves MC, Baloh RW, Wollmann RL. Patients with *CACNA1A* mutations and associated myasthenic weakness have presynaptic failure of neuromuscular transmission [abstract]. *Neurology.* 2001;56(suppl 3):A60.
37. Hans M, Luvisetto S, Williams ME, et al. Functional consequences of mutations in the human alpha1A calcium channel subunit linked to familial hemiplegic migraine. *J Neurosci.* 1999;19:1610-1619.
38. Kraus RL, Sinnegger MJ, Glossmann H, Hering S, Striessnig J. Familial hemiplegic migraine mutations change alpha1A Ca^{2+} channel kinetics. *J Biol Chem.* 1998;273:5586-5590.
39. Kraus RL, Sinnegger MJ, Koschak A, et al. Three new familial hemiplegic migraine mutants affect P/Q-type Ca^{2+} channel kinetics. *J Biol Chem.* 2000; 275:9239-9243.
40. Asakura K, Kanemasa T, Minagawa K, et al. Alpha-eudesmol, a P/Q-type Ca^{2+} channel blocker, inhibits neurogenic vasodilation and extravasation following electrical stimulation of trigeminal ganglion. *Brain Res.* 2000;873:94-101.
41. Hovatta I, Kallela M, Farkkila M, Peltonen L. Familial migraine: exclusion of the susceptibility gene from the reported locus of familial hemiplegic migraine on 19p. *Genomics.* 1994;23:707-709.
42. Sandor PS, Mascia A, Seidel L, de Pasqua V, Schoenen J. Subclinical cerebellar impairment in the common types of migraine: a three-dimensional analysis of reaching movements. *Ann Neurol.* 2001; 49:668-672.

43. Baloh RW. Neurotology of migraine. *Headache.* 1997;37:615-621.
44. Ulrich V, Gervil M, Kyvik KO, Olesen J, Russell MB. Evidence of a genetic factor in migraine with aura: a population-based Danish twin study. *Ann Neurol.* 1999;45:242-246.
45. Ambrosini A, de Noordhout AM, Alagona G, Dalpozzo F, Schoenen J. Impairment of neuromuscular transmission in a subgroup of migraine patients. *Neurosci Lett.* 1999;276:201-203.
46. Ambrosini A, Maertens de Noordhout A, Schoenen J. Neuromuscular transmission in migraine: a single-fiber EMG study in clinical subgroups. *Neurology.* 2001;56:1038-1043.
47. Ambrosini A, de Noordhout AM, Schoenen J. Neuromuscular transmission in migraine patients with prolonged aura. Another suggestion of the possible involvement of P/Q Ca^{2+}-channels in common forms of migraine? *Acta Neurol Belg.* 2001;101:166-170.
48. Uchitel OD, Protti DA, Sanchez V, Cherksey BD, Sugimori M, Llinas R. P-type voltage-dependent calcium channel mediates presynaptic calcium influx and transmitter release in mammalian synapses. *Proc Natl Acad Sci U S A.* 1992;89:3330-3333.
49. Wessler I, Dooley DJ, Lohr B. P-type Ca^{2+} channels trigger stimulus-evoked [3H]acetylcholine release from mammalian motor endplates. *Eur J Pharmacol.* 1995;278:83-86.
50. Plomp JJ, Vergouwe MN, Van den Maagdenberg AM, Ferrari MD, Frants RR, Molenaar PC. Abnormal transmitter release at neuromuscular junctions of mice carrying the tottering $alpha_{1A}$ Ca^{2+} channel mutation. *Brain.* 2000;123(pt 3):463-471.
51. Ambrosini A, Sandor PS, De Pasqua V, Schoenen J. Correlation between performances in cerebellar function and neuromuscular transmission in migraineurs: congruent evidence for P/Q Ca^{2+} channel involvement in common forms of migraine [abstract]? *Neurology.* 2001;56(suppl 3):A393.
52. Ambrosini A, Santorelli FM, Martini B, et al. Correlation between single fibre EMG findings and *CACNA1A* gene polymorphisms in migraine [abstract]. *Cephalalgia.* 2000;20:275-276.
53. Griggs RC, Moxley RT III, Lafrance RA, McQuillen J. Hereditary paroxysmal ataxia: response to acetazolamide. *Neurology.* 1978;28:1259-1264.
54. Athwal BS, Lennox GG. Acetazolamide responsiveness in familial hemiplegic migraine. *Ann Neurol.* 1996;40:820-821.
55. Haan J, Sluis P, Sluis LH, Ferrari MD. Acetazolamide treatment for migraine aura status. *Neurology.* 2000;55:1588-1589.
56. Ambrosini A, Pierelli F, Buzzi MG, Schoenen J. Acetazolamide improves SFEMG abnormalities in migraine patients [abstract]. *Cephalalgia.* 2001;21:387-388.
57. Hay KM, Mortimer MJ, Barker DC, Debney LM, Good PA. 1044 women with migraine: the effect of environmental stimuli. *Headache.* 1994;34:166-168.
58. Sand T, Vingen JV. Visual, long-latency auditory and brainstem auditory evoked potentials in migraine: relation to pattern size, stimulus intensity, sound and light discomfort thresholds and preattack state. *Cephalalgia.* 2000;20:804-820.
59. Schoenen J. Cortical electrophysiology in migraine and possible pathogenetic implications. *Clin Neurosci.* 1998;5:10-17.
60. Maertens de Noordhout A, Timsit-Berthier M, Timsit M, Schoenen J. Contingent negative variation in headache. *Ann Neurol.* 1986;19:78-80.
61. Kropp P, Gerber WD. Is increased amplitude of contingent negative variation in migraine due to cortical hyperactivity or to reduced habituation? *Cephalalgia.* 1993;13:37-41.
62. Schoenen J, Wang W, Albert A, Delwaide PJ. Potentiation instead of habituation characterizes visual evoked potentials in migraine patients between attacks. *Eur J Neurol.* 1995;2:115-122.
63. Afra J, Cecchini AP, De Pasqua V, Albert A, Schoenen J. Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. *Brain.* 1998;121(pt 2):233-241.
64. Wang W, Wang GP, Ding XL, Wang YH. Personality and response to repeated visual stimulation in migraine and tension-type headaches. *Cephalalgia.* 1999;19:718-724,697-698.
65. Wang W, Timsit-Berthier M, Schoenen J. Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? *Neurology.* 1996;46:1404-1409.
66. Siniatchkin M, Kropp P, Neumann M, Gerber W, Stephani U. Intensity dependence of auditory evoked cortical potentials in migraine families. *Pain.* 2000;85:247-254.
67. Sandor PS, Dydak U, Schoenen J, et al. Functional magnetic resonance imaging during sustained visual stimulation: less habituation-like changes of the

BOLD signal in migraine with aura [abstract]. *Cephalalgia.* 2001;21:398.
68. Sandor PS, Afra J, Proietti-Cecchini A, Albert A, Schoenen J. Familial influences on cortical evoked potentials in migraine. *Neuroreport.* 1999;10:1235-1238.
69. Kropp P, Kirbach U, Detlefsen JO, Siniatchkin M, Gerber WD, Stephani U. Slow cortical potentials in migraine: a comparison of adults and children. *Cephalalgia.* 1999;19(suppl 25):60-64.
70. Siniatchkin M, Kropp P, Gerber WD. Contingent negative variation in subjects at risk for migraine without aura. *Pain.* 2001;94:159-167.
71. Bohotin V, Fumal A, Vandenheede M, et al. Effects of repetitive transcranial magnetic stimulation on visual evoked potentials in migraine. *Brain.* In press.
72. Sappey-Marinier D, Vighetto A, Peyron R, Broussolle E, Bonmartin A. Phosphorus and proton magnetic resonance spectroscopy in episodic ataxia type 2. *Ann Neurol.* 1999;46:256-259.
73. Sandor PS, Dydak U, Schoenen J, et al. On the search of a metabolic equivalent of electrophysiologic dyshabituation: cortical lactate changes during prolonged visual stimulation in migraine with aura, studied by functional magnetic resonance spectroscopy imaging (f-MRI-SI) [abstract]. *Neurology.* 2001;56(suppl 3):A392.
74. Fletcher CF, Lutz CM, O'Sullivan TN, et al. Absence epilepsy in tottering mutant mice is associated with calcium channel defects. *Cell.* 1996;87:607-617.
75. Hess EJ. Migraines in mice? *Cell.* 1996;87:1149-1151.
76. Doyle J, Ren X, Lennon G, Stubbs L. Mutations in the *CACNL1A4* calcium channel gene are associated with seizures, cerebellar degeneration, and ataxia in tottering and leaner mutant mice. *Mamm Genome.* 1997;8:113-120.
77. Mori Y, Wakamori M, Oda S, et al. Reduced voltage sensitivity of activation of P/Q-type Ca^{2+} channels is associated with the ataxic mouse mutation rolling Nagoya (tg(rol)). *J Neurosci.* 2000;20:5654-5662.
78. Zwingman TA, Neumann PE, Noebels JL, Herrup K. Rocker is a new variant of the voltage-dependent calcium channel gene *CACNA1A*. *J Neurosci.* 2001;21:1169-1178.
79. Jun K, Piedras-Renteria ES, Smith SM, et al. Ablation of P/Q-type Ca^{2+} channel currents, altered synaptic transmission, and progressive ataxia in mice lacking the $alpha_{1A}$-subunit. *Proc Natl Acad Sci U S A.* 1999;96:15245-15250.
80. Kostopoulos GK. The tottering mouse: a critical review of its usefulness in the study of the neuronal mechanisms underlying epilepsy. *J Neural Transm Suppl.* 1992;35:21-36.
81. Ayata C, Shimizu-Sasamata M, Lo EH, Noebels JL, Moskowitz MA. Impaired neurotransmitter release and elevated threshold for cortical spreading depression in mice with mutations in the alpha1A subunit of P/Q type calcium channels. *Neuroscience.* 2000;95:639-645.
82. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med.* 1995;1:658-660.
83. Bahra A, Matharu MS, Buchel C, Frackowiak RS, Goadsby PJ. Brainstem activation specific to migraine headache. *Lancet.* 2001;357:1016-1017.
84. Ducros A, Joutel A, Vahedi K, et al. Mapping of a second locus for familial hemiplegic migraine to 1q21-q23 and evidence of further heterogeneity. *Ann Neurol.* 1997;42:885-890.
85. Gardner K, Barmada MM, Ptacek LJ, Hoffman EP. A new locus for hemiplegic migraine maps to chromosome 1q31. *Neurology.* 1997;49:1231-1238.
86. Echenne B, Ducros A, Rivier F, et al. Recurrent episodes of coma: an unusual phenotype of familial hemiplegic migraine with linkage to chromosome 1. *Neuropediatrics.* 1999;30:214-217.
87. Griffiths LR, Lea RA, Curtain RP, Quinlan S, Chappell J, MacMillan JC. Localization of migraine susceptibility genes to chromosomes 1q, 19p and Xq. *Am J Hum Genet.* 2001;69(suppl):2007.
88. Wessman M, Kallela M, Oswell G, et al. A genome-wide scan identifies a genetic locus for migraine with aura. *Am J Hum Genet.* 2001;69(suppl):190.
89. Nyholt DR, Curtain RP, Griffiths LR. Familial typical migraine: significant linkage and localization of a gene to Xq24-28. *Hum Genet.* 2000;107:18-23.
90. Wieser T, Pascual J, Barmada M, Soso M, Oterino A, Gardner K. Genetic analysis of chromosome X in migraine families. *Am J Hum Genet.* 2001;69(suppl):2171.
91. Peroutka SJ, Wilhoit T, Jones K. Clinical susceptibility to migraine with aura is modified by dopamine D2 receptor (DRD2) NcoI alleles. *Neurology.* 1997;49:201-206.

92. Del Zompo M, Cherchi A, Palmas MA, et al. Association between dopamine receptor genes and migraine without aura in a Sardinian sample. *Neurology.* 1998;51:781-786.
93. Paterna S, Di Pasquale P, D'Angelo A, et al. Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. *Eur Neurol.* 2000;43:133-136.
94. Ogilvie AD, Russell MB, Dhall P, et al. Altered allelic distributions of the serotonin transporter gene in migraine without aura and migraine with aura. *Cephalalgia.* 1998;18:23-26.
95. Lea RA, Dohy A, Jordan K, Quinlan S, Brimage PJ, Griffiths LR. Evidence for allelic association of the dopamine beta-hydroxylase gene (DBH) with susceptibility to typical migraine. *Neurogenetics.* 2000;3:35-40.
96. Tzourio C, El Amrani M, Poirier O, Nicaud V, Bousser MG, Alperovitch A. Association between migraine and endothelin type A receptor (ETA - 231 A/G) gene polymorphism. *Neurology.* 2001;56: 1273-1277.
97. White NJ, Hosford DA, Humphrey PP, et al. Single nucleotide polymorphism (SNP) alleles in the insulin receptor (INSR) gene are associated with migraine [abstract]. *Cephalalgia.* 2001;21:280.
98. Martelletti P, Brioli G, Lulli P, Morellini M, Giacovazzo M, Trabace S. Tumor necrosis factor B gene polymorphism contributes to susceptibility to migraine without aura. *J Headache Pain.* 2000;2: 119-122.
99. Martelletti P, Lulli P, Morellini M, et al. Chromosome 6p-encoded HLA-DR2 determination discriminates migraine without aura from migraine with aura. *Hum Immunol.* 1999;60:69-74.
100. Kowa H, Yasui K, Takeshima T, Urakami K, Sakai F, Nakashima K. The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. *Am J Med Genet.* 2000;96:762-764.
101. Lea RA, Curtain RP, Shepherd AG, Brimage PJ, Griffiths LR. No evidence for involvement of the human inducible nitric oxide synthase (iNOS) gene in susceptibility to typical migraine. *Am J Med Genet.* 2001;105:110-113.
102. Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet.* 1995;346:934-939.
103. Verin M, Rolland Y, Landgraf F, et al. New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent clinical feature. *J Neurol Neurosurg Psychiatry.* 1995;59:579-585.
104. Jung HH, Bassetti C, Tournier-Lasserve E, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a clinicopathological and genetic study of a Swiss family. *J Neurol Neurosurg Psychiatry.* 1995;59:138-143.
105. Hutchinson M, O'Riordan J, Javed M, et al. Familial hemiplegic migraine and autosomal dominant arteriopathy with leukoencephalopathy (CADASIL). *Ann Neurol.* 1995;38:817-824.
106. Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature.* 1996;383:707-710.
107. Ceroni M, Poloni TE, Tonietti S, et al. Migraine with aura and white matter abnormalities: Notch3 mutation. *Neurology.* 2000;54:1869-1871.
108. Ophoff RA, DeYoung J, Service SK, et al. Hereditary vascular retinopathy, cerebroretinal vasculopathy, and hereditary endotheliopathy with retinopathy, nephropathy, and stroke map to a single locus on chromosome 3p21.1-p21.3. *Am J Hum Genet.* 2001;69:447-453.
109. Welch KM, Levine SR, D'Andrea G, Schultz LR, Helpern JA. Preliminary observations on brain energy metabolism in migraine studied by in vivo phosphorus 31 NMR spectroscopy. *Neurology.* 1989;39:538-541.
110. Barbiroli B, Funicello R, Ferlini A, Montagna P, Zaniol P. Muscle energy metabolism in female DMD/BMD carriers: a 31P-MR spectroscopy study. *Muscle Nerve.* 1992;15:344-348.
111. Montagna P, Cortelli P, Monari L, et al. 31P-magnetic resonance spectroscopy in migraine without aura. *Neurology.* 1994;44:666-669.
112. Bresolin N, Martinelli P, Barbiroli B, et al. Muscle mitochondrial DNA deletion and 31P-NMR spectroscopy alterations in a migraine patient. *J Neurol Sci.* 1991;104:182-189.
113. Shimomura T, Kitano A, Marukawa H, Takahashi K. Mutation in platelet mitochondrial gene in patients with migraine [abstract]. *Cephalalgia.* 1995; 15(suppl 14):10.

114. Sano M, Ozawa M, Shiota S, Momose Y, Uchigata M, Goto Y. The T-C(8356) mitochondrial DNA mutation in a Japanese family. *J Neurol.* 1996;243: 441-444.
115. Majamaa K, Turkka J, Karppa M, Winqvist S, Hassinen IE. The common MELAS mutation A3243G in mitochondrial DNA among young patients with an occipital brain infarct. *Neurology.* 1997;49:1331-1334.
116. Boles RG, Chun N, Senadheera D, Wong LJ. Cyclic vomiting syndrome and mitochondrial DNA mutations. *Lancet.* 1997;350:1299-1300.
117. Majamaa K, Finnila S, Turkka J, Hassinen IE. Mitochondrial DNA haplogroup U as a risk factor for occipital stroke in migraine. *Lancet.* 1998;352: 455-456.
118. Ojaimi J, Katsabanis S, Bower S, Quigley A, Byrne E. Mitochondrial DNA in stroke and migraine with aura. *Cerebrovasc Dis.* 1998;8:102-106.
119. Klopstock T, May A, Seibel P, Papagiannuli E, Diener HC, Reichmann H. Mitochondrial DNA in migraine with aura. *Neurology.* 1996;46:1735-1738.
120. Russell MB, Diamant M, Norby S. Genetic heterogeneity of migraine with and without aura in Danes cannot be explained by mutation in mtDNA nucleotide pair 11084. *Acta Neurol Scand.* 1997;96:171-173.
121. Haan J, Terwindt GM, Maassen JA, Hart LM, Frants RR, Ferrari MD. Search for mitochondrial DNA mutations in migraine subgroups. *Cephalalgia.* 1999;19:20-22.
122. Buzzi MG, Di Gennaro G, D'Onofrio M, et al. mtDNA A3243G MELAS mutation is not associated with multigenerational female migraine. *Neurology.* 2000;54:1005-1007.
123. Ramadan NM, Halvorson H, Vande-Linde A, Levine SR, Helpern JA, Welch KM. Low brain magnesium in migraine. *Headache.* 1989;29:590-593.
124. Schoenen J, Sianard-Gainko J, Lenaerts M. Blood magnesium levels in migraine. *Cephalalgia.* 1991;11: 97-99.
125. Mazzotta G, Sarchielli P, Alberti A, Gallai V. Intracellular Mg++ concentration and electromyographical ischemic test in juvenile headache. *Cephalalgia.* 1999;19:802-809.