The Genetic Basis of Migraine: How Much Do We Know?

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ABSTRACT: Migraine with and without aura is thought to be genetically complex with aggregation in families due to a combination of environmental and genetic tendencies. Twin studies are most important in establishing the multifactorial nature of migraine with heritability approaching 50%. Familial hemiplegic migraine (FHM) on the other hand is an autosomal dominant, highly penetrant, though rare form of migraine with strong genetic tendency. Fifty percent of families with FHM are linked to chromosome 19p13 and mutations demonstrated for some in a brain expressed calcium channel alpha 1A subunit, CACNL1A4. Other FHM loci have been identified on chromosome 1q and further genetic heterogeneity is likely. The exact role of the mutated calcium channel in the pathway leading to hemiplegic migraine is yet to be established. Changes in the electrophysiologic properties of the mutated forms of the CACNL1A4 calcium channel expressed in heterologous systems help establish the functional significance of the mutations and suggest that chromosome 19p-linked FHM, an episodic disorder, represents a CNS channelopathy. Additional candidate genes causative for migraine might include other calcium channel subunits and related proteins important for neuronal membrane stability. Delineating the cascade of biochemical events leading to hemiplegic migraine will serve as a model for understanding the pathophysiology of more common forms of migraine. The evidence suggesting that some families of migraine with and without aura might also be related to the chromosome 19p locus, chromosome Xq28 locus, or DRD2 receptor polymorphisms is reviewed.

RÉSUMÉ: Les bases génétiques de la migraine: que sait-on? On pense généralement que la migraine avec et sans aura est complexe au point de vue génétique et que l'agrégation de cas dans les familles est due à une combinaison de tendances environnementales et génétiques. Les études sur les jumeaux sont très importantes pour établir la nature multifactorielle de la migraine dont l'héritabilité est de près de 50%. D'autre part, la migraine hémiplégique familiale (MHF), une maladie autosomale dominante dont la pénétrance est élevée, est une forme de migraine rare à forte tendance génétique. Chez cinquante pourcent des familles atteintes de MHF la maladie est liée au chromosome 19, en 19p13, et chez certaines familles, des mutations ont été démontrées dans la sous-unité 1A d'un canal calcique exprimé dans le cerveau, CACNL1A4. D'autres loci ont été identifiés sur le chromosome 1, en1q, et il existe sans doute une grande hétérogénéité génétique. Le rôle exact du canal calcique muté dans la voie qui est atteinte dans la MHF n'a pas encore été établi. Les changements dans les propriétés électrophysiologiques des formes mutées du canal calcique CACNL1A4 exprimé dans les systèmes hétérologues aident à établir la signification fonctionnelle des mutations et suggèrent que la MHF liée au chromosome 19, en 19p, un trouble épisodique, représente une canalopathie du SNC. Les gènes d'autres sous-unités de canaux calciques et de protéines associées, qui sont importants pour la stabilité de la membrane des neurones, pourraient être des gènes candidats dans l'étiologie de la migraine. La définition de la cascade d'événements biochimiques conduisant à la MHF servira de modèle pour comprendre la physiopathologie de formes plus communes de migraine. Les observations suggérant que dans certaines familles atteintes de migraine avec et sans aura la maladie pourrait également être liée aux loci sur le chromosome 19, en 19p, sur le chromosome X, en Xq28, ou aux polymorphismes du récepteur DRD2 sont revues.

Clinicians have long recognized the tendency for migraine to run in families, and twin studies have given us the most power to distinguish shared environment from shared genetic susceptibility as the cause for familial aggregation. Concordance rates in monozygotic twins suggest that up to 50% of the contribution to regular migraine is genetically based and indicates a multifactorial, genetically complex etiology.[1-3]

However, a rare subtype of migraine with aura, familial hemiplegic migraine (FHM), has a strong genetic basis with

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Table 1: Population based genetic epidemiology studies, regular migraine.

	RR, 1⁰ relatives	Number of patients	Study group
MA	3.8 (MA)		Denmark[18]
	~1 (MOA)		
		~1700	
MOA	1.4 (MA)		
	1.9 (MOA)		
MA	1.95		USA[17]
		~700	
MOA	1.42		

RR= relative risk, or the risk of disease recurrence in a group (such as first degree family members to a proband) above the population prevalence. A relative risk of 1 means that disease occurs no more frequently in relatives than it does in the general population. The greater the number above 1 for relative risk, the stronger the genetic tendency and the fewer sib pairs and families needed to establish linkage or association when evaluating candidate loci or genes for migraine.
MA = migraine with aura
MOA = migraine without aura

autosomal dominant inheritance and genetic heterogeneity involving at least three different loci on chromosome 19p,[4] chromosome 1q21-23,[5] and chromosome 1q31.[6] Chromosome 19p-linked FHM families have been associated with mutations in a brain expressed P/Q calcium channel subunit.[7] The complicated interactions of the calcium channel /alpha-1A subunit with other modulatory subunits, receptor mediated G proteins, protein kinases,[8] and presynaptic proteins[9] impact its overall role in secretion of neurotransmitters and gene transcription. Proteins making up these modulatory complexes potentially implicate additional candidate genes important for one hemiplegic migraine "channelopathy" pathway. Hemiplegic families linked elsewhere to two separate regions on chromosome 1q[5,6] await identification of the associated genes and mutations. One large family demonstrates significant linkage to both regions on chromosome 1q[10,11] and has a relatively pure phenotype of just hemiparetic attacks without other migraine types. This raises the possibility that the two loci interact and is reminiscent of the polygenic complexity we

expect to find in migraine with and without aura, hereafter referred to as "regular migraine". The full significance of this finding awaits further study. Some regular migraine families appear to be associated with the chromosome 19p calcium channel locus[12,13] and a new locus on Xq28 has been proposed for regular migraine with X dominant inheritance.[14] Association studies for dopamine D-2 receptor (DRD2) polymorphisms and regular migraine are reviewed[15,16] and the limitations of these genetic studies for regular migraine discussed.

REGULAR MIGRAINE, TWIN AND POPULATION BASED EPIDEMIOLOGIC STUDIES.

The familial aggregation of migraine has long been recognized in our clinic populations, which are perhaps naturally biased toward patients and families with greater familial tendency. One recent population based study correlated greater migraine disability in probands with higher risk of disease in family members.[17] This implies that clinic patients might have a greater familial tendency if we assume that they generally present with more severe disease. Results of population-based genetic epidemiological studies have shown mild to moderate evidence for genetic tendency in regular migraine by evaluating relative risk. Relative risk compares presence of disease in first or second degree family members of a proband with the prevalence of disease in the population. A relative risk of 1 means that disease occurs no more frequently in relatives than it does in the general population. The higher the relative risk, the stronger the likelihood of a genetic contribution for the disorder. The relative risk for migraine ranges from nonsignificant 1.42 for migraine without aura or mildly increased[17] to modestly increased 3.8 for migraine with aura[18] (Table 1). The validity of recent epidemiologic studies have been enhanced by the use of direct interviews, more uniform International Headache Society (I.H.S.) based criteria, and population based ascertainment. However, these studies cannot differentiate familial aggregation due to shared environment from shared genetic susceptibility.[19] Twin studies are most helpful in distinguishing environmental and genetic influences and several large studies of migraine in twins predict 40-50% heritability with multifactorial, polygenic inheritance (Table 2).[2,3,20]

On a more practical level, regular migraine is thought to be genetically complex because we cannot reliably define patterns of inheritance. A tendency for maternal transmission in many

Table 2: Twin studies, regular migraine.

	Twin monozygotic monozygotic concordance rate	Twin dizygotic concordance rate	Inheritance pattern, % genetic	Study group
Migraine (all types)	0.37 (37%)	0.21 (21%)		~5850, Australia[3]
	0.525 (52%)	0.155 (15%)	40-50%	~8200, Finland[20]
	0.48 (48%)	0.32 (32%)		~6500 **O**
	0.24 (24%)	0.11 (11%)		Sweden[2]
				~12,900 **Y**

O = older cohort
Y = younger cohort

Table 3. Clinical Features of Allelic CACNL1A4 Disorders and Chromosome 1q FHM families.

Locus	Disorder	Gene	Mutations	Phenotype
Chromosome19p13[4] (50% of FHM families)	FHM	CACNL1A4 (calcium channel alpha-1A subunit)[7]	Missense, V 714A R192Q	Hemiplegic migraine attacks
			19p disease haplotype	Occasional essential tremor, cerebellar signs[45]
			T666M, I1811L[44]	ataxia<50%
	EA-2		Truncating; nt 4073, del C nt 4270+1, G ->A nt 4410, C->T[48]	Episodic ataxia interictal nystagmus +/- mild progressive ataxia +/-regular migraine
			missense, G293R[49]	mod-severe progressive ataxia
	SCA6(37)		CAG expansion	Late onset, progressive cerebellar ataxia
			Borderline expanded	+/- episodic ataxia
Chromosome1q21-23[5]	FHM	unknown	unknown	Hemiplegic migraine attacks rare seizure +/- MA, MOA
Chromosome1q25-31[6] and Chromosome1q21-23[10]	FHM	unknown	unknown	Single large family linked to both regions on chromosome 1q Hemiplegic migraine attacks with prominent sensory component Rare migraine with aura

FHM= familial hemiplegic migraine   EA-2= episodic ataxia type 2   SCA6=spinocerebellar ataxia type 6
MA = migraine with aura   MOA= migraine without aura

families has long been recognized yet some families are more suggestive of dominant or even recessive inheritance. Our difficulty in establishing inheritance pattern for an individual family is due to lower and age-related disease penetrance, phenocopies (alternative causes, including nongenetic, for the disorder other than a particular gene of interest), disease in both sides of the family, and reliance on history for diagnosis of migraine. Because of this inherent ambiguity, large numbers of sibpairs and nuclear families are required for nonparametric linkage analysis and family controlled association studies of regular migraine. Statistical formulas predict the numbers needed to find linkage[21] or disease association,[22] using relative risk established by the population based epidemiologic studies.

FAMILIAL HEMIPLEGIC MIGRAINE

Clinical features and differential diagnosis

J.M. Clark first described hemiplegic migraine in 1910[23] and more than 40 families have since been described and reviewed by Whitty.[24,25] The identification of hemiplegic loci and the chromosome 19p gene described below have allowed our first phenotype-genotype correlations in those families large enough to be evaluated with linkage analysis or with mutational analysis of the calcium channel CACNL1A4 gene in the chromosome 19p families (Table 3). The clinical features of hemiplegic migraine are very similar regardless of locus involved with the exception of additional progressive ataxia in up to 50% of only chromosome 19p families[26] and rare seizures seen with severe attacks in chromosome 1q21-23 families.[5] There is variability of attack severity and side of involvement for most patients, and a spectrum of neurologic deficit ranging from coma and brain stem signs to visual scotoma, hemisensory loss, aphasia, confusion, and hemiparesis. CSF pleocytosis, meningitic signs, cerebral edema, and EEG slowing are possible additional features.[25]

To make the diagnosis of hemiplegic migraine, International Headache Society criteria call for two or more attacks, hemiparesis during aura, and similar attacks in at least one first degree relative in accordance with the known autosomal dominant inheritance and high penetrance seen with the disorder.[27] Therefore migraineurs who have hemiparetic aura but lack similarly affected relatives are not considered hemiplegic migraineurs but instead categorized by length of aura. We do not yet know how many of these patients will represent sporadic mutations in the hemiplegic genes, reflect an uninformative family history, or are simply not related to hemiplegic genes. These migraineurs with prolonged aura are appropriately

evaluated first for possible transient ischemic attack, often requiring extensive workup since they usually present at a young age. Note that reports of definite stroke with hemiplegic migraine are rare, atypical,[28] and should raise the possibility of other disorders if family history is positive for migraine or stroke. In migraineurs with hemiparetic aura and completed stroke, especially when confirmed on imaging studies, family history should be carefully evaluated for possible maternal inheritance given that mitochondrial disorders are strongly associated with migraine that might include hemiparetic aura, especially mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).[29] CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)[30] should also be considered in the differential, especially in the setting of progressive multi-infarct dementia, white matter disease, and positive family history that can include paternal transmission. Additionally, a role for one or several coagulation factor and apolipoprotein mutations or polymorphisms[31-33] may ultimately have to be considered in any type of migraine associated with stroke, pending future clarification of complex stroke genetics.

Chromosome 19p hemiplegic migraine

The first migrainous disorder linked to chromosome 19 was CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy) in 1993 by a group in France.[34] The same group quickly found linkage to a neighbouring region at chromosome 19p13 for hemiplegic migraine[4] and for what is now called episodic ataxia type 2,[35] using the CADASIL locus as a candidate for these disorders because of similar episodic clinical features, including migraine. The causative gene for CADASIL associated with multi-infarct dementia, migraine, and leukoencephalopathy has since been described with missense mutations in the NOTCH 3 gene, involved in cell cycle and development.[36] In 1996, the chromosome 19p13 gene for allelic disorders (different mutations, same gene) hemiplegic migraine and episodic ataxia type 2 was described as a P/Q voltage-gated, brain expressed, calcium channel alpha-1A pore-forming subunit.[7] Four missense mutations in three different families were associated with hemiplegic migraine and truncating mutations were found responsible for episodic ataxia type 2. Shortly thereafter, another allelic disorder associated with the channel was described as spinocerebellar ataxia type 6 (SCA6), due to minor expansions in a CAG repeat found in the 3' end of coding sequence of certain isoforms.[37] There is some clinical or phenotypic overlap of these allelic disorders, especially with respect to ataxia, as outlined in Table 3.

The alpha-1A subunit (Figure) forms the pore through which the calcium ion passes and is made up of four domains, each containing six transmembrane segments, with segments five and six thought to form the actual pore.[38] The P/Q channels are widely expressed in brain, especially cerebellum, and heavily concentrated at presynaptic nerve terminals.[39] Presumably they play a significant role in synaptic transmission[40] via exocytosis of dopamine and glutamate into nerve terminals.[41] Channel function is controlled by a complex of additional molecules that surround the pore-forming alpha-1A subunit, including receptor mediated G protein[42] complexed with the βγ regulatory subunits. This G protein-βγ complex binds the domain I-II cytosolic linker of the alpha-1A subunit and together they inhibit the channel.[8] Alternatively the receptor mediated G protein-βγ complex may be upregulated by protein kinase C, though these effects occur most prominently in a related N type calcium channel, often co-expressed with the P/Q channel at presynaptic sites.[8] The domain II-III linker binds presynaptic proteins syntaxin and SNAP-25 which participate in fusion of neurotransmitter filled vesicles with the cell membrane and exocytosis.[9] In summary, we are beginning to more precisely define the modulation, protein interactions, and immediate effects of the P/Q channel. The more "remote" effects of the activated channel and the signaling cascade leading to gene transcription are yet to be determined.

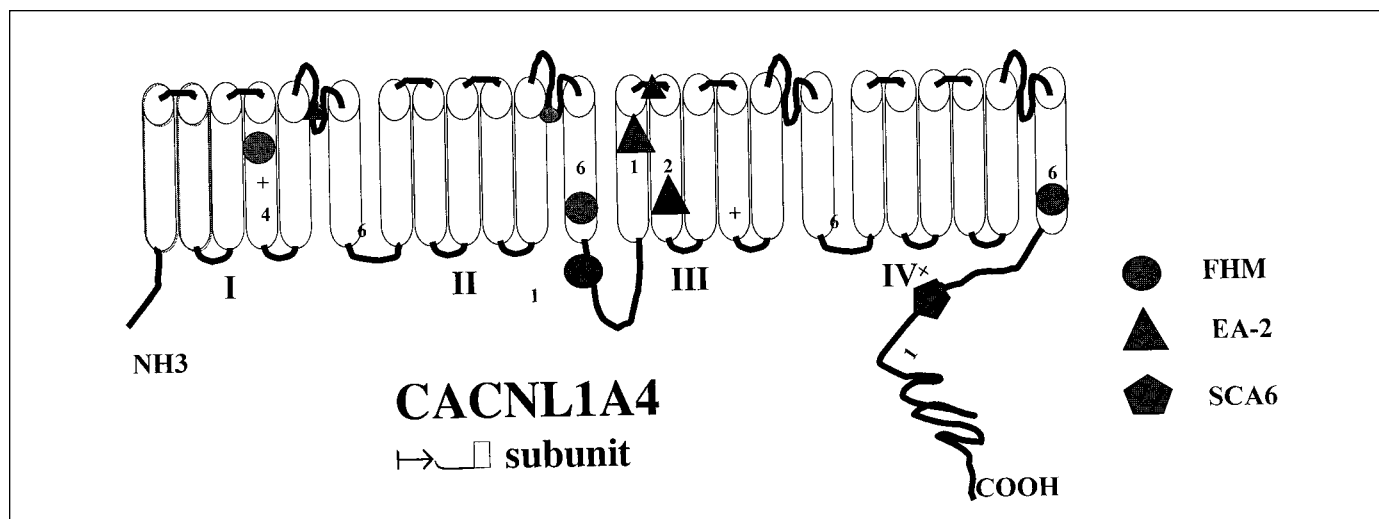The FHM mutations occur in highly conserved trans-

Figure: Symbols listed at top right for each of the three allelic disorders (FHM, EA-2, SCA6) associated with different mutations in the calcium channel alpha1A subunit, CACNL1A4 are used to identify the relative location for known mutations in the alpha1A subunit diagram. FHM = familial hemiplegic migraine, EA-2 = episodic ataxia type 2, SCA6 = spinocerebellar ataxia type 6.

membrane segments or loops associated with either the ion pore or the voltage-sensing S4 segment. The highly homologous rabbit alpha-1A calcium channel subunit has been mutated, expressed in *Xenopus* oocytes, and electrophysiologic studies performed for the four human FHM mutations.[43] Compared to wild type, relatively mild changes were observed with prolonged inactivation of the channel being the most prominent finding in three of the mutations, and no abnormality found in the R192Q mutation of the S4 voltage sensor segment. During high frequency stimulation the I1811L and V714A mutant channels allowed excess calcium influx, suggesting a change in function under certain "trigger" conditions. However, calcium influx decreased for the T666M mutation during high frequency stimulation. Interestingly, despite opposite effects on calcium influx, the T666M and I1811L mutations have both been associated with the additional FHM phenotypic feature of progressive cerebellar neurodegeneration.[44] The significance of this seeming discrepancy between specific mutation, calcium influx and neurodegeneration (ataxia component seen in some families) is unknown. Understanding the complexity of channel interactions and function will be especially challenging *in vivo* but necessary for clarification of P/Q channel activity and its role in the pathophysiology of chromosome 19p hemiplegic migraine with and without ataxia.

Chromosome 1q hemiplegic migraine

There is evidence for two additional hemiplegic loci at separate regions on chromosome 1 at cytogenetic regions 1q21-23[5] and at 1q31.[6] Among the 24 affected members from three French families linked to chromosome 1q21-23 hemiplegic attacks were typical, not distinguishable from the chromosome 19p families, except for two patients who had seizure associated with a single severe attack. Ataxia is not a clinical feature. Penetrance was lower at 76% compared with 89-90% penetrance for chromosome 19p families. A fair number of their chromosome 1q21-23 and chromosome 19 hemiplegic migraineurs among 13 French families had additional migraine headache types, 16% suffering migraine with aura and 34% migraine without aura, demonstrating the spectrum of migraine found in hemiplegic families.[45]

We found linkage in a large family with hemiplegic migraine, prominent hemisensory complaints, and rare other headache types at chromosome 1q31 with multipoint LOD score 3.3, using a candidate locus approach and searching specifically for another brain calcium channel, CACNL1A6, thought to reside in that region.[6] The CACNL1A6 calcium channel was subsequently mapped more proximally, prompting evaluation of the 1q21-23 hemiplegic locus where we found a second region of linkage in the same family.[10] With the addition of new affected members we narrowed both regions and found multipoint LOD scores of 5.5 in the proximal region at chromosome 1q21-23 and LOD 4.95 in the distal region at chromosome 1q31. A two-locus model favored a contribution from each locus with combined LOD score of 6.1.[11] Study is underway to exclude an alternative explanation for two regions of significant linkage in a single family, such as genetic inversion not evident with high resolution karyotyping. The full significance of this finding with respect to regular or hemiplegic migraine, especially at the distal locus chromosome 1q31, awaits identification of the genetic mutation(s). The possibility that two genes contribute to a

relatively pure hemiplegic phenotype in this family is reminiscent of the genetic complexity we expect to find with regular migraine and disturbs the notion that "monogenic" disorders are truly simple.

REGULAR MIGRAINE LINKAGE AND ASSOCIATION STUDIES

Complex genetic disorders require different methods of analysis for establishing genetic linkage or association than the maximum likelihood comparison of marker and disease which generates LOD scores for monogenic disorders. Nonparametric linkage methods are emphasized instead because "parameters" such as inheritance patterns and penetrance are not well defined in complex disorders. These methods rely on the principle that each person carries two alleles or copies of each gene or "marker" allele, with one allele inherited from each parent. Only one of these alleles is then passed to a child, for instance allele A from the father, and with each child subsequently born there is a fifty percent chance of passing allele A from the father. Among siblings therefore we expect 50% allele sharing for a particular gene or marker allele. Sibpair based nonparametric methods use this expected fifty percent allele sharing as a comparison among affected siblings by looking for a marker allele associated with disease more often than 50% of the time.

Alternatively, marker allele frequencies associated with disease are compared with matched case control allele frequencies or with other family member (control) allele frequencies in association studies. The association studies are potentially more efficient than sibpair studies though they are also more susceptible to false positives due to stratification of alleles among different populations and ethnic groups. The association studies also rely heavily on the likelihood that the candidate allele (polymorphism) / gene of interest is truly related to disease or very tightly linked. This often requires a difficult biochemical explanation for how a DNA polymorphism (usually thought to represent normal variation in DNA sequence) can result in disease.

Linkage studies and regular migraine

Linkage studies for regular migraine using both parametric and nonparametric analysis for evaluation of the chromosome 19p hemiplegic locus have thus far shown mixed results. Some families appear not to be linked[46] while other families are more or less suggestive of linkage,[12,13] with much of the statistical power in each study coming from one or several families. This is what we might expect from a complex disorder presumed to be genetically heterogeneous.

A new locus for regular migraine was proposed on Xq28, based on suggestion of linkage in two of three large multigenerational Australian families.[14] An X dominant pattern of inheritance was postulated and the general idea is enhanced by the excessive number of women migraineurs not fully explained by hormonal factors.[47] However, male-to-male transmission of migraine was noted in one of the reported families with the discrepancy attributed to incoming gene from a spouse.[14] The possibility of different migraine genes contributed by spouses and "nonpenetrant" or unaffected family members carrying disease genes will always make the linkage and association analysis of regular migraine more difficult, requiring larger study groups to confirm findings.

DRD2 receptor association studies

Association studies for regular migraine have suggested that dopamine type 2 receptor (DRD2) polymorphisms may play some role in certain migraine subgroups. Polymorphisms are thought to represent normal variation in DNA sequence without obvious change, for instance, in coded proteins. However, there is growing suspicion that the additive effects of minor functional changes induced by polymorphisms in one or more genes could be important in the pathophysiology of complex genetic disorders.

Different methods and populations were used in studies looking at two different marker alleles or polymorphisms in exon 6 and intron 1. A case controlled study found an association with an exon 6, NcoI restriction site polymorphism in migraine with aura.[15] A family controlled transmission dysequilibrium test in a relatively isolated Sardinian population found an association between an intron 1, TG repeat polymorphism and a subgroup of "dopaminergic" migraineurs without aura.[16]

The functional significance of the DRD2 receptor and migraine is attributed to the clinical observation of vegetative "dopaminergic" symptoms that often accompany migraine attack and because DRD2 antagonist pharmacotherapy is often effective in providing relief for the acute attack. Establishing the functional significance at a biochemical level, however, will be more difficult, especially if the polymorphism itself must be implicated. It will likely be easier to interpret the findings of our association studies in regular migraine once a single migraine pathway is fully established, such as the hemiplegic chromosome 19p calcium channel pathway.

CONCLUSION

Rare hemiplegic migraine families have the strongest genetic basis of all migraine types and have the greatest potential for contributing to an understanding of migraine pathophysiology using molecular genetic techniques. Chromosome 19p-linked hemiplegic migraine families have been associated with mutations in a brain expressed P/Q calcium channel subunit CACNL1A4, important in neurotransmitter release at presynaptic nerve terminals and with effects on gene transcription yet to be described. Delineation of the signaling pathways for this calcium channel will further our understanding of one genetically based migraine disorder thought to represent a CNS "channelopathy". It will require work in orthologous mammalian systems, and has potential for identifying important new candidate genes for regular migraine. Identification of new hemiplegic genes has equal potential for establishing migraine pathways and collectively we expect them to shed light on the pathophysiology of all migraine and vascular headache disorders.

Sibpair and association studies in regular migraine may ultimately broaden our understanding of regular migraine against the framework of hemiplegic migraine pathways. However, the genetic complexity and heterogeneity of regular migraine hamper, the immediate usefulness of linkage studies in the search for new genes, requiring large study groups and improved methods for identifying candidate genes. Likewise, association studies for regular migraine are limited by technical concerns regarding population stratification among case controls, identification of strong candidate genes, and our current inability to establish the functional significance of DNA polymorphisms or to find the nearby causative mutation in a genetically heterogenous test group of regular migraineurs.

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