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Molecular genetics and migraine

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Abstract Migraine carries a significant hereditary determination. Familial hemiplegic migraine (FHM) has been recently linked to mutations in the CACNA1A gene on chromosome 19. CACNA1A codes for a subunit of a neural calcium channel. Other linkage loci on chromosome 1q21-23 and 1q31 have been reported. Several linkage and association studies have been performed to determine the role of the CACNA1A gene, and of other candidate genes implicated in the metabolism of serotonin and dopamine, in the more common types of migraine. Co-morbidity of migraine with vascular events has been analysed versus genetic prothrombotic factors and mitochondrial DNA, and genes involved in the inflammatory cascade have been explored. Though no definite conclusions have emerged from these studies as yet, molecular genetics of migraine can be expected to unravel the complex aetiologies of these fascinating diseases.

Key words Migraine • Headache • Genetics • Serotonin • Dopamine • Mitochondria

Introduction

Pedigree and twin studies have demonstrated that migraine carries a significant hereditary risk, but the precise hereditary transmission modalities are unclear and controversial. The high prevalence of migraine among the general population, the lack of any laboratory marker for the disease, the variability of the phenotypic characteristics according to sex and age, all compound to make genetic studies of migraine difficult. Migraine is most likely a multifactorial disease, not conforming to standard mendelian transmission as a single hereditary trait. In such a setting, linkage studies are unlikely to identify genetic loci of interest because of the likelihood of phenocopies, the uncertainty in genetic transmission models and the difficulties in ascertaining affected versus nonaffected family members.

Association studies explore the co-segregation of markers - usually polymorphic DNA repeats - with known genomic localization in migraine patients in comparison to a control population. These studies are powerful means to detect loci for genetic susceptibility in multifactorial diseases, especially when the genetic background variability is reduced in genetic isolates. There is, however, one type of migraine that conforms to simple mendelian transmission: familial hemiplegic migraine (FHM), a subtype of migraine with aura (MA), has long been known to be transmitted as an autosomal dominant disease. Indeed, linkage analysis has been successful in unravelling the molecular genetics of FHM. At least three genes are implicated in the aetiology of FHM, and one of the genes involved and its mutations have been identified. FHM is a rare disease with an unknown prevalence in the general population. On the basis of these successful genetic studies, FHM has been proposed as a model for the other more common types of migraine, the so-called typical migraines with aura (MA) and without aura (MO). Accordingly, linkage and association studies have been performed to demonstrate the involvement of the

known FHM gene in the typical migraines, but with controversial results to date. Other linkage and association studies performed with candidate genes, chosen on the basis of the current fashionable pathogenetic hypotheses of migraine, have likewise remained controversial. These studies shall be reviewed here.

Molecular genetics of familial hemiplegic migraine

Familial hemiplegic migraine (FHM) is characterized by hemiparesis or hemiplegia arising at the onset of a typical migraine attack as an aura phenomenon, or more rarely during the attack itself. The attacks are usually self-resolving. Detailed clinical analysis of the pedigrees disclosed that in some but not all families, FHM was associated with signs of cerebellar involvement in the form of progressive ataxia and nystagmus. Other clinical characteristics associated with FHM in other pedigrees were epileptic seizures, sometimes at the onset of the attack, coma and mental retardation.

Linkage analysis performed in a series of families with hemiplegic migraine disclosed linkage to several markers located at 19p13 in 4 of 9 families [1]. Genetic heterogeneity of FHM was implied. FHM also mapped to a different locus and was thus clearly differentiated from CADASIL, another familial condition with autosomal dominant transmission of migrainous attacks and strokes which can mimic FHM during early stages when dementia has not yet set in. More recently, other linkages have been found in FHM, to 1q31 in a multi-generational American family [2] and to 1q21–23 in three French [3] and one Italian [4] family. It is still unclear whether these loci on chromosome 1 are one or multiple sites, due to difficulties with the linkage analysis. Since some families with FHM do not link to either chromosome 19 or 1 (either 1q31 or 1q21–23), some other genes must be involved. This means that at least three and probably more genes are responsible for FHM.

Refinement of the localization site on chromosome 19 has led to the identification of the gene involved, which proved to code for a subunit of a neuronal calcium channel of the P/Q type. This gene, called CACNA1A (also defined as CACNL1A4), is expressed throughout the neural axis in a pre-synaptic localization, especially in Purkinje cells of the cerebellum, but also at the pre-synaptic endings of neuromuscular synapses [5]. The functional role of this calcium channel, apart from regulating calcium entry into the cell, is not completely clear. It does appear, however, to be regulated by the release of other neurotransmitters such as serotonin. It is also modulated by several regulatory proteins, so that it is difficult to extrapolate a simple pathogenetic explanation for FHM.

If we consider that calcium is a cation implicated in the regulation of the membrane excitability of neurons, FHM can be conceived as a disorder of neuronal excitability. This concept may explain the co-morbidity of FHM with epilepsy and episodic ataxia. Indeed, the CACNA1A gene is also responsible for episodic ataxia type 2 (EA2), a paroxysmal form of cerebellar ataxia unassociated with myokymia [5], and for spinocerebellar ataxia type 6 (SCA6), a progressive ataxia of adulthood associated with cerebellar atrophy [6]. FHM, EA2 and SCA6 are therefore considered allelic diseases of CACNA1A, but are due to different types of mutations: missense mutations (at least 16 of them) are found in FHM pedigrees, whereas triplet CAG repeat expansions account for the SCA6 phenotype and mutations altering the reading frame of the gene account for EA2 [7]. Increasingly, however, clinical overlap between these three allelic conditions and especially between EA2 and SCA6 is evident. Moreover, differing clinical expression is also found within the many missense mutations responsible for FHM, some being associated or not with progressive cerebellar ataxia or with essential tremor [8, 9]. In particular, the T666M mutation which represents the most common FHM mutation, is associated with cerebellar involvement. A few sporadic cases with hemiplegic migraine have also been found to harbour CACNA1A mutations. The reasons why only some CACNA1A mutations are associated with cerebellar ataxia remain obscure, but do not seem to be related directly to the alterations in neurophysiological functioning of the channel (gain or loss of function) as brought forth by studies in embryonic cells or Xenopus oocytes [10, 11]. The pathogenic cascade of FHM likewise remains a mystery, despite experimentation in animal models such as the leaner and tottering mice, which express mutated murine CACNA1A [12].

The phenotypic variability of CACNA1A mutations is becoming increasingly complex, since a pre-synaptic myasthenic syndrome of the Eaton-Lambert type has been associated with EA2 in a family with a codon 1404 mutation [13]. This observation indicates that the neuromuscular localization of this protein also has relevant clinical effects. Moreover, an association study of the CACNA1A gene and idiopathic generalised epilepsy has shown significant differences with a polymorphism in exon 8 of the gene, possibly indicating that mutations in CACNA1A confer some susceptibility to epilepsy [14].

While FHM with linkage to chromosome 19 shows cerebellar involvement, FHM linked to chromosome 1 instead displays epileptic seizures but not overt cerebellar ataxia. Subtle cerebellar signs (e.g. scanning speech and nystagmus), while not overt cerebellar atrophy, have, however, been found in an Italian family with possible linkage to 1q21–23 [4], and again may indicate some clinical overlap. FHM linking to chromosome 1 does not otherwise differ from FHM linked to CACNA1A, except for a reduced penetrance.

The identification of the CACNA1A gene as being responsible for FHM has unleashed a series of studies aimed at detecting whether this gene is also implicated in the more

common types of migraine (so-called typical migraines). The evidence here is controversial, since studies performed in Finnish [15] and Italian [16] families gave negative results, while some positive linkage was found by others in a single family [17] or by means of sib-pair analysis [18]. Extensive sequencing of the gene in families with migraine, paroxysmal vertigo and an autosomal dominant pattern failed, however, to demonstrate abnormalities in the CACNA1A gene [19]. Therefore, CACNA1A is unlikely to play a major role in the pathogenesis of the typical migraines.

To date, CACNA1A remains the only migraine gene known. This may warrant the concept of migraine as a calcium channelopathy, with co-morbidity with epilepsy and paroxysmal ataxia as a corollary [20].

Linkage and genetic association studies in typical migraine

The only linkage study of typical migraine to have generated positive findings detected excessive allele sharing to Xq [21] in some pedigrees. While this result is surprising in view of the female preponderance of migraine, it may explain the increased risk of migraine in relatives of male probands. Linkage studies with CACNA1A, as mentioned earlier, gave mixed results. Association studies have been performed with the assumption that migraine pathogenesis stems at least in part from dysfunction in serotonergic or dopaminergic receptors. Thus, positive results were obtained by Ogilvie et al. [22] in a sample of MA and MO patients with the serotonin uptake receptor gene 5HT-SERT. This pre-synaptic receptor is responsible for the reuptake of serotonin after its release into the synaptic fissure. It is also the site of action of selective serotonin reuptake inhibitors (SSRIs) that act as antidepressants and are useful in the prophylactic treatment of migraine.

MA patients showed increased frequencies of some alleles, different from those increased in MO, a finding which implies genetic differences between MA and MO. However, other linkage and sib-pair studies with 5HT-SERT were negative [16]. Uniformly negative have been several studies with the serotonin receptor genes 5HT1D, 5HT1B, 5HT1F, 5HT2A and 5HT2C [16, 23–27], performed on the evidence of the efficacy of triptans in the treatment of migraine attacks and the preventive efficacy of tricyclic antidepressants.

As to the dopaminergic receptors, Peroutka et al. [28, 29] found a higher frequency of the NcoI C allele of the dopamine receptor 2 (DRD2) in MA but not in MO, again implying genetic differences between the two conditions. These authors also found an increased incidence of MA associated with depression and anxiety in individuals sharing the NcoI C/C genotype. These results were not, however, confirmed by Dichgans et al. [30]. A significantly different distribution of the DRD2 NcoI allele was found by Del Zompo et al. [31] in MO patients with nausea and yawning during the migraine attack (so-called dopaminergic group), although there were no differences for the migraine group as a whole; DRD3 and DRD4 genes were not significantly associated. My colleagues and I did not find any significant association between migraine and the DRD2 and DRD3 receptors or the MAO-A and COMT genes, all implicated in the metabolism of dopamine [32]. The association of migraine with genes regulating serotonergic or dopaminergic metabolism remains therefore unproven.

Migraine is associated with an increased risk of stroke and other thrombotic events, and this has suggested that the pathogenetic relationship be explored at the genetic level. Significant associations of MA with the prothrombotic factor V Leiden at codon 506 (which represents a risk factor for venous thromboembolism) and with protein S deficiency were reported by D'Amico et al. [33]. However, Haan et al. [34], Corral et al. [35] and Soriani et al. [36] failed to find any association of migraine with the Leiden V factor mutation.

Paterna et al. recently rerported an association between MO and angiotensin-converting enzyme (ACE) gene polymorphisms implicated in cardiovascular events [37].

In some pedigrees harbouring mutations of mitochondrial DNA (mtDNA), migraine figures prominently in carriers of the mutation, especially the MELAS type. Therefore searches have been made for mtDNA mutations in typical migraine patients, with occasionally positive results [38–40]. These results have, however, been subsequently disproved. The 11084 mtDNA mutation has been shown, for instance, to represent a normal polymorphism in the Japanese population [41]. These studies also often lack adequate testing in large samples of patients. There is no evidence for an association between migraine and the mtDNA mutations 3243 and 3271 MELAS, 8344 MERRF, 8993 Narp, 11778 Leber hereditary optic neuropathy (LHON), and other common mtDNA deletions, even in families with a matrilinear transmission [42–45]. Therefore there seems to be no role for mtDNA in the genetic determination of typical migraine, and MELAS patients may be thought of as phenocopies. Interestingly though, an increased prevalence of mtDNA mutations (the "secondary" 4216 and 13708 LHON mutations and the MELAS mutation) and an increased prevalence of the mtDNA haplogroup U have been noted in patients with migraine stroke [44, 46, 47], possibly explaining the co-morbidity of migraine with vascular accidents. Children with cyclic vomiting syndrome, considered to be a migraine equivalent, may display ragged-red fibres on muscle biopsy and have an 8.1-kb mtDNA deletion [48]. These findings await verification in larger samples of patients.

Finally, some studies have explored the association between migraine and the genes implicated in the cascade of inflammation events. In particular, Griffiths et al. [49] excluded the endothelial NO synthase gene NOS3, and Peroutka et al. [50] found no association between migraine and the complement C3 protein involved in acute inflammation. Martelletti et al. [51] reported that HLA class II DR2 antigens are decreased in frequency in MA compared to MO and the control population, and, more recently, that the frequency of tumour necrosis factor B allele 2 is significantly associated with MO [52]. If confirmed, these findings establish a genetic association of migraine with cytokine genes involved in the inflammatory cascade.

Conclusions

Molecular genetic studies of migraine headaches have just started, leading to the exciting discovery of the first gene implicated in FHM. Even though FHM is a rare disease not really representative of typical migraines, and linkage and association studies have been negative or controversial in the more common types of migraine to date, migraine has joined other diseases in the molecular age. It is therefore likely that positive results should come in the near future, leading to substantial strides forward in the understanding of the pathogenetic aspects of the disease, now still largely hypothetical, and in its treatment. Procedures which may foster genetic analysis should be looked for and applied, for instance the incorporation into genetic characterization of patients and families of some neurophysiological abnormalities already known in migraineurs (such as alterations in evoked and cognitive potentials, and single fiber electromiography (SFEMG) abnormalities) and which might represent the missing laboratory marker of disease. Association studies need to be performed in populations selected because of reduced genetic variability – e.g. genetically isolated groups – and also in sufficiently large subgroups of migraineurs, chosen because of specific clinical or pharmacological characteristics (menstrual migraine is a particularly interesting subgroup). We envisage that molecular genetic studies shall unravel the aetiology of these fascinating diseases and open new insights into their pathogenetic mechanisms and the functioning of the brain.

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