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Genetic factors in migraine and chronic tension-type headache

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Abstract Pathophysiological studies have dominated migraine research for several years. However, these studies are difficult to interpret because it is difficult to decide whether the observed phenomena are primary or secondary to the migraine attack. For that reason it is important that future migraine research focus on studies that concern migraine etiology. Migraine is a paroxysmal disorder. It is most likely an ion-channel disorder like familial hemiplegic migraine. The present paper focuses on genetic factors in migraine and chronic tension-type headache.

Key words Migraine • Chronic tension type headache • Genetics

Family and twin studies of migraine

Positive family history

Transmission of migraine from parents to children was reported as early as the seventeenth century [1]. Since then, numerous studies have reported a positive family history for migraine [2]. A positive family history is imprecise, because it does not specify the number of affected, the family size, or the relation to the proband. The lifetime prevalence of migraine is 16%–21% in the general population [3, 4]. This causes a positive family history simply by chance in >80% of probands with six first-degree relatives (parents, siblings and children), and one or both parents are affected in >40% of families. Thus, a positive family history does not prove the presence of a genetic factor. Furthermore, a positive family history does not include an interview of the relatives by a physician. Migraine assessed by proband report compared to a clinical interview by a physician is not sufficiently precise, since the number of affected relatives is highly underestimated and often misclassified [5]. Thus, a clinical interview by a physician is indispensable in family studies of migraine.

Migraine without aura and migraine with aura

Clinical, epidemiological, pathophysiological and genetic differences suggest that migraine without aura (MO) and migraine with aura (MA) are distinct entities [6–10]. An important argument is that the observed number of people with cooccurrence of MO and MA is not significantly different from the expected number, i.e. the product of the prevalence of MO and MA [8, 10]. Cooccurrence of MO and MA is higher in clinic populations and other selected populations [11]. This can be explained by selection bias [12].

Migraine without aura

An increased familial risk can be caused by genetic as well as environmental factors. The risk among spouses can be used to evaluate this relation, because probands and spouses in part share a common environment, but differ in genetic constitution [13]. Thus, an increased risk among first-degree relatives and no increased risk among spouses favors importance of genetic factors, while no increased risk among first degree relatives and spouses favors importance of environmental factors. Table 1 shows the relative risk of MO in different genetic epidemiological surveys [9, 14, 15].

Studies of twin pairs are the classic method of investigating the relative importance of genetic and environmental factors. The majority of twin studies have been case reports or small series; larger samples are limited. Unfortunately, most studies have not discriminated between MO and MA. A Danish study included 1013 monozygotic and 1667 dizygotic twin pairs of the same gender, from a population-based twin register [16]. Table 2 shows the number of concordant and discordant twin pairs. The pairwise concordance rate was significantly higher among monozygotic than dizygotic twin pairs ($p<0.05$). Analyzing men and women separately showed a similar trend ($p=0.22$ and $p=0.08$). Women had slightly higher concordance rates than men, probably reflecting the higher prevalence in women. The significantly higher pairwise concordance rate among monozygotic than dizygotic twin pairs supports the importance of genetic factors. However, environmental factors also seem to play an important role, since the pairwise concordance rate in monozygotic twin pairs never reached 100%. The probandwise concordance rate was 31% among dizygotic twin pairs. This risk is comparable to the 30% recurrence risk in Danish siblings [9]. Thus, genetic epidemiological surveys and twin

Table 1 Participants in genetic epidemiological surveys of migraine without aura (MO) and migraine with aura (MA)

Disease in probands	Study population	Disease in first-degree relatives	Probands n	First-degree relatives		Relative risk[a]	Population relative risk[b]	95% Confidence interval
				Affected, n	Total, n			
MO								
Mochi et al. [14]	Clinic	MO	34	64	171	3.62		1.10–6.14
	MO			102			1.86	1.56–2.16
Russell and Olesen [9]	General		126		354			
	MA			42			1.44	1.03–1.85
	MO			30		1.43		0.83–2.47
Stewart et al. [15][c]	General		45		156			
	MA			10		2.36		0.87–6.38
MA								
Mochi et al. [14]	Clinic	MA	35	13	144	6.95		3.15–10.75
	MA			111			3.79	3.21–4.38
Russell and Olesen [9]	General		127		359			
	MO			56			1.02	0.77–1.26
Kalfakis et al. [29]	Clinic	MA	60	58	328	11.85		7.00–16.70
	MA			3		1.24		0.28–5.47
Stewart et al. [15]	General		28		87			
	MO			17		1.41		0.71–2.77

[a] First-degree relatives of probands with migraine compared with first-degree relatives of probands who had never had migraine

[b] First-degree relatives of probands with migraine compared with the risk of migraine in the general population

[c] Probands were interviewed by a physician, while first-degree relatives were interviewed by lay interviewers

Table 2 Concordant and discordant, same gender monozygotic (MZ) and dizygotic (DZ) twin pairs

	Men		Women		Overall	
	MZ	DZ	MZ	DZ	MZ	DZ
MO [16]						
Concordant pairs, n	8	6	30	41	38	47
Discordant pairs, n	39	69	60	141	99	210
Pairwise concordance rate, %	17	8	33	23	28	18
Proband-wise concordance rate, %	29	15	50	37	43	31
MA [35]						
Concordant pairs, n	12	10	14	6	26	16
Discordant pairs, n	21	48	30	70	51	118
Pairwise concordance rate, %	36	17	32	8	34	12
Proband-wise concordance rate, %	53	29	48	15	50	21

studies suggest that MO is caused by a combination of genetic and environmental factors.

An Italian study analyzed 34 pedigrees and excluded maternal and X-linked transmission [14]. The classic segregation analysis suggested an autosomal recessive kind of transmission, i.e. a single gene locus was involved. However, a classic segregation analysis only analyzes for autosomal dominant and recessive inheritance, while a complex segregation analysis also analyzes for multifactorial inheritance, as well as transmissible and non-transmissible environmental factors [17]. The Danish study analyzed 127 pedigrees with a complex segregation analysis [18]. The complex segregation analysis gave the sporadic model, no family resemblance, and a poor fit compared with the multifactorial model. There was no evidence of an intergenerational difference for multifactorial inheritance. None of the three models that incorporated a major locus explained the observed segregation pattern better than the multifactorial model. However, the results do not exclude that some families may have had a mitochondrial or Mendelian pattern of inheritance. Considering the high prevalence, a single gene is not likely to cause MO, since the gene has to be more common than any known disease-causing gene.

Migraine with aura

MA is subclassified into migraine with typical aura, migraine with prolonged aura, familial hemiplegic migraine, basilar migraine, migraine aura without headache, and migraine with acute-onset aura [19]. This subclassification may not be useful for separating possible etiologically different types of MA, because of the intraindividual variation of attacks [20–28]. Table 1 shows the relative risk of MA in different genetic epidemiological surveys [9, 14, 15, 29]. All the studies except the American [15] showed an increased risk of MA among first-degree relatives. The family members of the American study were only asked about their most severe type of headache by a lay interviewer [15]. The diagnosis of MA does not require specific headache characteristics [19]. However, the American study changed the diagnostic criteria, so that the headache characteristics were similar to those of MO. This may have causes an underestimation of MA since the headache in that type is often less severe than it is in MO [8, 10]. Furthermore, for an unerring diagnosis interviews by physicians are preferred. Thus, the American survey seems inconclusive. The Greek [29] and Italian [14] studies were based on clinic populations, which may have caused bias [12]. The Danish genetic epidemiological survey [9] found that, compared with the general population, first-degree relatives of probands with MA had a 3.8-fold increased risk of MO, while spouses of probands had no increased risk of MA [9].

Five pairs of monozygotic twins were concordant [30–33], and one pair of monozygotic twins was discordant for MA [34]. However, case records are subject to selection bias. For example, the discordant twin pair was one of a series of articles about discordant monozygotic twins [34]. The results of the Danish population-based twin survey are shown in Table 2 [35]. The pairwise concordance rate was significantly higher among monozygotic than dizygotic twin pairs ($p<0.001$). Analyzing each gender separately showed a significant difference in women and a similar trend in men ($p=0.002$ and $p=0.07$). The significantly higher pairwise concordance rate among monozygotic than dizygotic twin pairs supported the importance of genetic factors. However, environmental factors also played an important role, since the pairwise concordance rate in monozygotic twin pairs never reached 100%. Thus, genetic epidemiolog-

ical surveys and twin studies suggest that MA is caused by a combination of genetic and environmental factors.

Five studies have included direct interviews by physicians of probands and their relatives [14, 18, 29, 35, 36]. A detailed description of the study designs is provided in the genetic epidemiological surveys and twin sections above. The Italian study analyzed 35 pedigrees and excluded maternal and X-linked transmission [14]. The classic segregation analysis suggested an autosomal recessive kind of transmission. The Greek study included 60 families [29]. A classic segregation analysis suggested multifactorial inheritance, but the contribution of a major gene could not be excluded. The Danish study analyzed 126 families with a complex segregation analysis [18]. The complex segregation analysis gave the best fit to the multifactorial model without generational differences. The results do not exclude that some families have a mitochondrial or Mendelian pattern of inheritance. From that point of view it is interesting that another Danish study analyzed the mode of inheritance in high-risk families with MA [36]. The 31 nuclear families consisted of one affected and one unaffected parent and at least one affected and one unaffected child. The nuclear families were expanded with other first-degree relatives as well as second-degree relatives in case the first-degree relatives were affected. An analysis of the families suggested multifactorial inheritance even in these high-risk families. Until now only familial hemiplegic migraine had been shown to have an autosomal dominant mode of inheritance. MA most likely has a multifactorial mode of inheritance.

Linkage and association studies of migraine

MO and MA are associated with many disorders. However, caution is necessary due to the high prevalence of both types of migraine, which means that spurious associations frequently occur. Single families with cosegregation of two disorders can supply important information, but the generalizability of the results must subsequently be established in the general population. All linkage and association studies should in general be regarded as preliminary evidence until independently confirmed.

The CACNA1A gene

A German-Dutch affected sib-pair analysis of 28 families found that the CACNA1A gene on chromosome 19p13 is involved in MO and MA [37]. The maximum multipoint lod score was 1.29 (p~0.013), but the major contribution was made by one large family. The results were inconclusive with respect to the relative importance in MO and MA. Subsequently, in a second larger and independent affected sib-pair analysis involving 36 extended Dutch families with migraine with and without aura, significant increased sharing of the marker alleles in sibs with MA was confirmed [38]. A Dutch genotype-phenotype relation study found the I1811L familial hemiplegic migraine mutation in patients with familial hemiplegic migraine and in two unaffected family members with "non-hemiplegic" migraine [39]. This result suggests that the I1811L mutation might be involved in non-hemiplegic migraine. However, it might as well be two unaffected carriers of familial hemiplegic migraine. Two classic linkage studies have been performed. Finnish researchers did not find linkage to chromosome 19 in four multigenerational families with MO and MA, but they used the unlikely single gene assumption model [40]. An Australian study included several multigenerational families [41]. One large family showed both cosegregation and significant allele sharing for markers situated within or adjacent to the familial hemiplegic migraine locus. Other families showed neither cosegregation nor excess allele sharing to chromosome 19 markers. An American family with dominantly inherited migraine, episodic vertigo and essential tremor that responded to acetazolamide did not link to chromosome 19p13 [42]. Thus, it seems likely that in a minority of families, MO or MA is caused by mutation in one or more gene(s) on chromosome 19p13, while in the majority of families this is not the case. This is in line with family studies of MO and MA [9, 14, 15, 18, 29]. Future direct mutation analysis of persons with MO and MA will establish the precise role of the calcium channel gene in these conditions. MO and MA have remarkably many characteristics in common with established neurological channelopathies. These include a paroxysmal presentation with attacks which can be provoked by both endogenous and exogenous stimuli, which may last from minutes to hours or days, and which may come in a frequency ranging from once in a lifetime to once per day. Onset is usually at puberty, amelioration and complete remission may occur after age 40 years, and penetrance and expression are gender-related. Thus, there is also clinical evidence, though still circumstantial, supporting the notion that migraine is a cerebral ion channelopathy.

The serotonin system

Serotonin is implicated in migraine pathophysiology [43]. An Australian study tested three large multigenerational pedigrees for the Mspl polymorphism in the human 5-HT2A

receptor gene [44]. In the association analyses, no significant difference was found between the MO and control populations. The subsequent linkage analysis was not informative. A Danish-British association study on allelic variation in codon 23 on the 5-HT2C receptor gene indicated that it did not contribute to the genetic predisposition to MO and MA [45]. An American study found no evidence of linkage to the 5-HT2A and 5-HT2C receptor genes [46]. Mutation analysis indicated that DNA-based mutations in the 5-HT2A and 5-HT2C receptors are not generally involved in the pathogenesis of migraine. A Danish-Scottish association study investigated the role of allelic variation of the human serotonin transporter gene in susceptibility to migraine [47]. The results support that susceptibility to MO and MA has a genetic component, that these disorders are distinct and that genetic susceptibility may in some cases be associated with a locus at or near the serotonin transporter gene.

Nitric oxide synthase genes

Nitric oxide has been implicated in the pathophysiology of migraine [48]. An Australian study investigated the endothelial nitric oxide synthase (NOS) polymorphism [49]. No evidence of association or linkage was found. No data are available on the importance of the other NOS genes.

Dopamine D2 receptor gene

An American study investigated the dopamine D2 receptor gene [50]. Individuals with MA have significantly increased frequency (0.84) of the dopamine D2 Ncol C allele compared with controls (0.71) and individuals with MO (0.70). MA was present in 27% of the C/C individuals, 16% of the C/T individuals, and 5% of the T/T individuals. These data suggest that activation of the dopamine D2 receptor plays a modifying role in the pathophysiology of MA.

The X chromosome

The female preponderance in MO and MA suggests that genes on the X chromosome are important in the etiology. An Australian study investigated three large multigenerational migraine pedigrees and found evidence of significant excess allele sharing of chromosome Xq markers in two families [51]. Overall analysis of data from all three pedigrees gave significant evidence in support of linkage to chromosome Xq. Confirmation in other families and sporadic cases is important as is analyzing MO and MA separately.

Mitochondrial disorders

Mitochondrial proteins function in the oxidative pathways and are encoded by both the mitochondrial and the nuclear genomes. Diseases caused by alterations of the mitochondrial genome have a maternal inheritance, because mitochondrial DNA is transmitted from mothers to children. Migraine has been associated with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and less frequently with MERRF (mitochondrial disease, myoclonic epilepsy with ragged-red fibers). MELAS is caused by a point mutation at base pair 3243 and MERRF is caused by a point mutation at base pair 8344. However, neither of the two base pair point mutations nor large scale deletions were found in 23 Germans with MA [52], excluding a significant role of this mutation in Caucasians. A point mutation in mitochondrial nucleotide pair 11 084 was reported in Japanese migraineurs [53]. Twenty-five percent (13 of 53) of Japanese migraineurs had this mutation, while none of 39 normal and 60 tension-type headache sufferers did [53]. The mutation was not detected in Danes [54]. Thus, mitochondrial mutations might explain some cases of migraine in Japanese, but confirmation of the result is necessary.

The future

Other familial hemiplegic migraine genes are likely to be identified in the near future. These genes are suspected to encode ion channels. MO and MA also have many clinical characteristics in common with established neurological channelopathies. It is likely, therefore, that these types of migraine will also prove to be channelopathies. The identification of genes for MO and MA is expected to be difficult, because of the complex mode of inheritance and the relatively strong influence of environmental factors.

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