Neurol Sci (2008) 29:S52–S54
DOI 10.1007/s10072-008-0887-4

HEADACHE CONTROVERSIES

Is migraine a genetic illness? The various forms of migraine share a common genetic cause

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Abstract Is migraine a genetic illness? This question was previously controversial, but today the answer *yes* is generally accepted. The scientific evidence is the significantly increased familial risk of migraine, and the significantly higher concordance rate of migraine in monozygotic than dizygotic twin pairs. Finally, the three identified ion-channel genes that can cause familial hemiplegic migraine provide very strong evidence of genetics. Mutations in these genes can also cause sporadic hemiplegic migraine. The next question is whether the different types of migraine, i.e. migraine without aura, migraine with aura, sporadic hemiplegic migraine and familial hemiplegic migraine share a common genetic cause. This question is at present controversial. However, the fact that all types of migraine are paroxystic in nature suggest that a common genetic cause could be mutations in ion channels, although a common mutation has not yet been identified in the more common types of migraine: migraine without aura and migraine with aura.

Keywords Migraine without aura · Migraine with aura · Hemiplegic migraine · Genetics

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The diagnosis of migraine relies exclusively on the headache history and exclusion of secondary causes. The lack of an objective marker applicable for usual clinical practice makes case definition a challenge. The International Classification of Headache Disorder provides explicit diagnostic criteria in order to maximise diagnostic precision [1]. Migraine without aura is defined by pain characteristics and accompanying symptoms. The majority of people with migraine without aura have never experienced an aura [2]. Migraine with aura is now subclassified according to headache characteristics and aura symptoms, while the first edition of the International Classification of Headache Disorders subclassified migraine with aura according to the aura symptoms alone [1, 3]. However, both the headache characteristics and aura symptoms usually vary from attack to attack [4]. Hemiplegic migraine includes motor aura and is subclassified into familial hemiplegic migraine and sporadic hemiplegic migraine depending on whether other first- and/or second-degree relatives have experienced motor aura or not. Migraine without aura and migraine with aura are common, affecting more than 10% of the general population, while familial hemiplegic migraine and sporadic hemiplegic migraine are relatively rare [5–8].

Is migraine a genetic illness?

A positive family history of migraine is imprecise, as probands only identify about half of their affected first-degree relatives with migraine [9]. Table 1 shows the familial aggregation in family studies of migraine without aura and migraine with aura. As compared to the general population, first-degree relatives had a significantly increased risk of the probands' disorder in all but the American survey [10–13]. The American survey is biased by family members interviewed only about their most severe type of headache by lay interviewers [13]. The diagnostic precision of lay interviewers is anticipated to be less precise than interviews by a physician, especially with regard to aura symptoms. The Italian and Greek surveys were based on clinic populations which may be subject to selection bias. Thus, the Danish survey conducted by one physician whom was blinded to the diagnosis of the probands is probably the most precise of the genetic epidemiological survey on migraine [11]. An increased familial risk of migraine can be caused by genetic and/or 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. Spouses to probands with migraine without aura had a slightly increased risk of migraine without aura, while spouses to probands with migraine with aura had no increased risk of migraine with aura [11]. Thus, the genetic epidemiological surveys of migraine without aura and migraine with aura support the importance of both genetic and environmental factors.

The literature provides information on several twin studies on migraine. The majority are based on questionnaires and lay interview [14]. The most precise survey was based on a population-based twin registry where the twin pairs were blindly interviewed by physicians [15, 16]. The probandwise concordance rate was significantly higher in monozygotic (MZ) than same gender dizygotic (DZ) twin pairs in both migraine without aura and migraine with aura (Table 2). The concordance rates in MZ twin pairs were less than 100%. The results support importance of both genetic and environmental factors.

A classical segregation analysis analyses for Mendelian inheritance, while a complex segregation analysis also analyses for multifactorial inheritance, as well as transmissible and non transmissible environmental

Table 1 Age and gender standardised risk of migraine without aura (*MO*) and migraine with aura (*MA*)

Disease in proband	Study population	Disease in first-degree relative	No. of affected relatives		Population relative risk (95% CI)
			Observed	Expected	
Migraine without aura					
Italy [10]	Clinic	MO	64	17.7	3.6 (1.1–6.1)
Denmark [11]	General	MO	102	54.8	1.9 (1.6–2.2)
		MA	42	29.2	1.4 (1.0–1.9)
USA [13]	General	MO	30	21.0	1.4 (0.8–2.5)
		MA	10	4.2	2.4 (0.9–6.4)
Migraine with aura					
Italy [10]	Clinic	MA	13	1.9	7.0 (3.2–10.8)
Denmark [11]	General	MA	111	29.3	3.8 (3.2–4.4)
		MO	56	54.9	1.0 (0.8–1.3)
Greece [12]	Clinic	MA	58	4.9	11.9 (7.0–16.7)
USA [13]	General	MA	3	2.4	1.2 (0.3–5.5)
		MO	17	12.1	1.4 (0.7–2.8)

The population relative risk is calculated by available data from the original articles by the Author
CI, confidence interval

Table 2 The probandwise concordance rates in monozygotic (*MZ*) and same gender dizygotic (*DZ*) twin pairs with migraine without aura and migraine with aura

	Men		Women		Total	
	MZ, % (95% CI)	DZ, % (95% CI)	MZ, % (95% CI)	DZ, % (95% CI)	MZ, % (95% CI)	DZ, % (95% CI)
Migraine without aura	29 (3–55)	15 (–19–49)	50 (41–59)	37 (31–43)	43 (37–49)	31 (26–36)
Migraine with aura	53 (35–71)	29 (15–43)	48 (32–64)	15 (4–26)	50 (38–62)	21 (12–30)

CI, confidence interval

factors [17]. A complex segregation analysis of migraine without aura and migraine with aura suggested multifactorial inheritance [18].

Familial hemiplegic migraine is a rare autosomal dominant inherited subtype of migraine with aura [19, 20]. At present three different genes have been identified to cause familial hemiplegic migraine, which is strong evidence of genetics in migraine [21–23].

The question *is migraine a genetic disorder?* was previously controversial, but today the answer *yes* is generally accepted regarding migraine without aura, migraine with aura and familial hemiplegic migraine.

Do the various forms of migraine share a common genetic cause?

The three familial hemiplegic migraine genes identified so far encode three different ion channels. The CACNA1A and SCNA1A genes encode the pore-forming α_1 subunits of the neuronal voltage-gated Ca^{2+} channels $Ca_v2.1$ and Na^+ channels $Na_v1.1$, and the ATP1A2 gene encodes the α_2 subunit of the Na^+,K^+ adenosinetriphosphatase [21–23]. Mutations in CACNA1A, ATP1A2 and SCNA1A genes cause familial hemiplegic migraine types 1, 2 and 3. The phenotypes are quite similar, with the exception that some type 1 families have permanent cerebellar symptoms in addition to familial hemiplegic migraine [20]. Due to the paroxystic nature of migraine it makes good sense that the familial hemiplegic migraine genes encode ion channels. However, are these genes important in other types of migraine? A systematic analysis of 39 patients with sporadic hemiplegic migraine identified one CACNA1A mutation, five ATP1A2 mutations and one SCN1A polymorphism [24]. The CACNA1A and ATP1A2 mutations were also carried by other family members with *non-hemiplegic* migraine with aura. This finding suggests that familial hemiplegic migraine, sporadic hemiplegic migraine and *non-hemiplegic* migraine with aura have a common genetic cause. However at present the three identified ion-channel genes cannot explain all cases of migraine with aura, and it is likely that several other ion-channel genes will be identified in the future. The next question is, what about migraine without aura? It is also a paroxystic disorder with a phenotype quite similar to that of migraine with aura, with the exception that aura is not present. It is likely that migraine without aura is also caused by mutations in ion-channel genes. Whether these possible mutations can cause both migraine without aura and migraine with aura is likely to be elucidated in the future.

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