J Headache Pain (2007) 8:190–195
DOI 10.1007/s10194-007-0389-4

TUTORIAL

Michael Bjørn Russell

Genetics in primary headaches

Received: 7 February 2007
Accepted in revised form: 8 March 2007
Published online: 11 June 2007

M.B. Russell (✉)
Head and Neck Research Group,
Akershus University Hospital,
Dr. Kobros vei 39,
NO-1474 Nordbyhagen, Oslo, Norway
e-mail: m.b.russell@medisin.uio.no
Tel.: +47-67-994402

M.B. Russell
Faculty Division Akershus University Hospital,
University of Oslo,
NO-1474 Nordbyhagen, Norway

M.B. Russell
Center of Research,
Akershus University Hospital,
NO-1478 Lørenskog, Norway

M.B. Russell
Department of Neurology,
Akershus University Hospital,
NO-1478 Lørenskog, Norway

Abstract This tutorial describes different methods and results of genetic studies of primary headaches. A positive family history is imprecise, because it does not specify the number of affected, family size or relation to the proband. Nor does it include an interview of the possibly affected family members. Calculation of the familial aggregation after confirmation of the diagnosis by a physician is more precise. Compared to the general population, first-degree relatives of probands with migraine without aura, migraine with aura, chronic tension-type headache and cluster headache has a significantly increased risk of the proband's disorder. These data are confirmed in twin studies. The primary headaches are caused by a combination of genetic and environmental factors. A major breakthrough was identification of 3 different genes all causing the rare autosomal dominant inherited familial hemiplegic migraine. The genes encode ion channels. So far no genes have been identified to cause the more common types of primary headaches.

Keywords Migraine • cluster • headache • tension-type headache • genetics • primary headache

Introduction

The diagnosis of primary headaches relies 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 minimise the diagnostic variability [1]. Genetic studies of primary headaches are further complicated by the high prevalence of migraine and tension-type headache [2, 3].

This tutorial describes different methods and results of genetic studies of primary headache.

Co-occurrence of primary headaches

Co-occurrence of migraine and tension-type headache is frequent, and both the prevalence and the frequency of tension-type headache are higher in those with than without migraine [3]. This confounding factor should be dealt with in genetic studies of migraine and tension-type headache. The prevalence of migraine in those with cluster headache corresponds to the prevalence of migraine in the general population, indicating that migraine and cluster headache are distinct primary headaches [2, 4].

Family history

A positive family history is imprecise, because it does not specify number of affected, family size or relation to the proband. An example: the lifetime prevalence of migraine is 16% in the general population [4]. This causes a positive family history simply by chance in >65% of the families, if the proband has six first-degree relatives (parents, siblings and children), and one or both parents are affected in >30% of the families. Furthermore, a positive family history does not include an interview of the relatives by a physician. This adds to the imprecision as probands only identify about half of their affected first-degree relatives with migraine [5].

Familial aggregation

The most precise calculation of familial occurrence can be assessed by estimating the population's relative risk of the disease in specified groups of relatives [6]. The risk is calculated according to the following equation:

$$\frac{\text{Prob(Relative is affected}|\text{Proband is affected)}}{\text{Prob(Random member of the population is affected)}}$$

A family aggregation is implied when this risk ratio significantly exceeds 1.

As the prevalence of the different primary headaches depends on age and gender, the value of the denominator is adjusted according to the distribution of age and gender in the group of relatives studied. Hence, this standardised population relative risk is estimated by dividing the observed number of affected first-degree relatives by the expected number according to the prevalence rates in the population. The expected number is calculated by adding the products of the current age- and gender-specific rates and the number of relatives within each corresponding age-gender category. Some studies calculate the familial aggregation by comparing the families of probands with and without disease.

Genetic epidemiological surveys

Table 1 shows the familial aggregation in family studies of migraine without aura, migraine with aura, chronic tension-type headache and cluster headache. All surveys except the one by Stewart et al. found that first-degree relatives of probands had a significantly increased risk of the proband's disorder as compared to the general population [7–15]. The study by Stewart et al. is biased because family members were interviewed only about their most severe type of headache by lay interviewers [10]. For an unerring diagnosis, interviews by physicians are preferred. Clinic populations are subject to selection bias. Thus, the study by Russell and Olesen conducted by one physician who was blinded to the diagnosis of the probands is probably the most precise genetic epidemiological survey on migraine [8]. Tension-type headache is far more prevalent than migraine and for that reason possible genetic mechanisms cannot be elucidated with a genetic epidemiological survey [3, 4]. The International Classification of Headache Disorders classifies tension-type headache as infrequent episodic, frequent episodic and chronic tension-type headache [1]. The frequency cut-off point is not based on scientific evidence, but is set arbitrarily. However, Østergaard et al. conducted a genetic epidemiological survey of chronic tension-type headache, as the prevalence is about 3% in the general population; for details see Table 1 [11]. The different results of genetic epidemiological surveys on cluster headache can at least partly be explained by methodological differences [12–15]. The survey by El Amrani et al. is

Table 1 Age and gender standardised risk of migraine without aura (MO), migraine with aura (MA), cluster headache (CH) and chronic tension-type headache (CTTH). The population relative risk is calculated by available data from the original articles by the author. The revised population relative risks on CH were calculated assuming the prevalence of cluster headache is 200 per 100.000 inhabitants [16]. CI denotes confidence intervals

Disease in proband	Study population	Disease in first-degree relative	No. of affected relatives		Population relative risk (95% CI)
			Observed	Expected	
Migraine without aura					
Mochi et al. [7]	Clinic	MO	64	17.7	3.6 (1.1–6.1)
Russell and Olesen [8]	General	MO	102	54.8	1.9 (1.6–2.2)
		MA	42	29.2	1.4 (1.0–1.9)
Stewart et al. [10]	General	MO	30	21.0	1.4 (0.8–2.5)
		MA	10	4.2	2.4 (0.9–6.4)
Migraine with aura					
Mochi et al. [7]	Clinic	MA	13	1.9	7.0 (3.2–10.8)
Russell and Olesen [8]	General	MA	111	29.3	3.8 (3.2–4.4)
		MO	56	54.9	1.0 (0.8–1.3)
Kalfakis et al. [9]	Clinic	MA	58	4.9	11.9 (7.0–16.7)
Stewart et al. [10]	General	MA	3	2.4	1.2 (0.3–5.5)
		MO	17	12.1	1.4 (0.7–2.8)
Chronic tension-type headache					
Østergaard et al. [11]	Clinic	CTTH	71	22.6	3.1 (2.5–3.9)
Cluster headache					
Russell et al. [12]	Clinic	CH	26	5.40	4.7 (3.1–6.9)
		CH *	10	13.20	0.8 (0.4–1.4)
Kudrow and Kudrow [13]	Clinic	CH	41	2.70	15.2 (11.1–21.1)
Leone et al. [14]	Clinic	CH	39	2.97	13.1 (9.0–17.3)
		CH *	18	6.69	2.7 (1.5–3.9)
El Amrani et al. [15]	Clinic	CH	22	1.25	17.6 (10.2–24.9)

*Second-degree relatives

the most accurate, because all first-degree relatives were directly interviewed by a physician [15]. Russell et al. and Leone et al. probably underestimated the risk of cluster headache, as only those possibly affected were interviewed [12, 14]. The survey by Kudrow and Kudrow either under- or overestimated the risk of cluster headache, depending on the balance between underestimation and misclassification by the probands [13]. A diagnosis of cluster headache was confirmed in only 57%, while the remaining 43% had migraine in the cluster headache survey by Russell et al. [12].

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. 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 [8]. Spouses to probands with chronic tension-type headache had no increased risk of chronic tension-type headache [11]. Thus, the epidemiological surveys of migraine without aura, migraine with aura and chronic tension-type headache suggest the importance of genetic factors. The increased familial risk of cluster headache strongly suggests a genetic cause. Theoretically, a shared environment can produce relative risks of the magnitude observed for cluster headache only under extreme conditions [17].

Table 2 The probandwise concordance rates in monozygotic (MZ) and same gender dizygotic (DZ) twin pairs with migraine without aura, migraine with aura and tension-type headache without co-occurrence of migraine. The concordance rates are in percentage and the 95% confidence intervals are in parenthesis. n.s. denotes not significant

	Men		Women		Total	
	MZ	DZ	MZ	DZ	MZ	DZ
Migraine without aura						
Gervil et al. [19]	29 (3–55)	15 (–19 to 49)	50 (41–59)	37 (31–43)	43 (37–49)	31 (26–36)
Migraine with aura						
Ulrich et al. [18]	53 (35–71)	29 (15–43)	48 (32–64)	15 (4–26)	50 (38–62)	21 (12–30)
Tension-type headache No						
Russell et al. [22]	50 (43–57)	40 (33–48)	51 (40–62)	33 (20–46)	50 (45–56)	38 (32–45)
p-values	<0.001		<0.001		<0.001	
Infrequent episodic						
Russell et al. [22]	75 (73–78)	74 (71–76)	78 (76–81)	71 (68–74)	77 (75–79)	73 (71–74)
p-values	n.s.		<0.001		<0.001	
Frequent episodic						
Russell et al. [22]	34 (21–48)	18 (2–34)	50 (43–57)	37 (29–45)	46 (39–52)	32 (25–39)
p-values	<0.001		<0.001		<0.001	
Chronic						
Russell et al. [22]	0 (–)	0 (–)	15 (–52 to 83)	12 (–50 to 73)	10 (–47 to 67)	9 (–45 to 63)
p-values	–		n.s.		n.s.	

Twin studies

The literature provides information on several twin studies on migraine. The majority is based on questionnaires and lay interview [2]. The most precise survey was based on a population-based twin registry where the twin pairs were blindly interviewed by physicians [18, 19]. 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 the importance of both genetic and environmental factors. Cluster headache has been reported in five concordant monozygotic twin pairs [16]. This indicates the importance of genetic factors, although publication itself introduces selection bias [20]. In a single large twin survey based on the Swedish Twin Registry and the Swedish Inpatient Registry, the two monozygotic and nine dizygotic twin pairs were all discordant for cluster headache and had been discordant for 10–31 years [21]. The twin data on cluster headache support the importance of both genetic and environmental factors. Tension-type headache, with exception of its chronic form, is not suited for a genetic epidemiological survey due to its high prevalence, but a twin study can be helpful. As migraine is a confounding factor, it is important to exclude twin pairs with co-occurrence of migraine in such a study. Table 2 shows the results of a population-based twin survey [22]. It seems that genetic factors play a role in no and frequent episodic tension-type headache, while infrequent episodic tension-type headache is caused primarily by environmental factors. The result regarding chronic tension-type headache was inconclusive.

Mode of inheritance

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 factors [23]. A complex segregation analysis of migraine without aura, migraine with aura and chronic tension-type headache suggested multifactorial inheritance [24, 25]. An analysis of cluster headache suggested that an autosomal dominant gene has a role in some families [26]. An analysis of a single Italian pedigree suggested autosomal recessive inheritance in that particular family [27].

Molecular genetic studies

Sporadic and familial hemiplegic migraine are rare sub-

types of migraine with aura, the latter having autosomal dominant inheritance [28, 29]. At present three different genes have been identified to cause familial hemiplegic migraine, i.e., locus heterogeneity [30–32]. The genes all encode ion channels, which makes good sense due to the paroxysmal nature of migraine. At present these genes have not been shown to be involved in the common types of migraine, nor have other genes causing migraine been identified. However, it is likely that migraine without aura and migraine with aura also are ion channel disorders. So far no genes have been identified for tension-type headache or cluster headache. The migraine and cluster headache literature provides information on several linkage and association studies. So far it is not possible to draw firm conclusion about the results, and many of the association studies suffer from lack of power as well as contradictory results [28].

Pharmacogenetic

The variability of therapeutic effect and adverse events depend on both environmental and genetic factors. An example is the intraindividual variability of migraine with aura attacks, which is likely to be caused by environmental factors as the genetic constitution remains the same [33]. The efficacy and adverse events both show intra- and interindividual variability, even though the medication is given subcutaneously. Intraindividual variability is likely to be caused mainly by environmental factors, while interindividual variability is likely to be caused by a combination of genetic and environmental factors. Most primary headaches have multifactorial inheritance and a precise description of the pathogenesis is lacking. This constitutes a major challenge for future pharmacogenetic research, a research field that hopefully will expand in the future for the benefit of patients.

Conclusions

Our knowledge about genetics in primary headache disorders has improved rapidly since linkage was first demonstrated in familial hemiplegic migraine at the International Headache Society congress in Paris 1993 [34]. The genetics of migraine without aura, migraine with aura, tension-type headache and cluster headache are considered to be complex and identification of genes is anticipated to be a difficult task. So we still have a long way to go before we can fully elucidate the aetiology in the more common types of primary headache.

References

1. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders. Cephalalgia 24[Suppl 1]:9–160
2. Russell MB (1997) Genetic epidemiology of migraine and cluster headache. University of Copenhagen. Cephalalgia 17:683–701
3. Russell MB (2005) Tension-type headache in 40-year-olds: a Danish population-based sample of 4000. J Headache Pain 6:441–447
4. Rasmussen BK, Jensen R, Schroll M, Olesen J (1991) Epidemiology of headache in a general population – a prevalence study. J Clin Epidemiol 44:1147–1157
5. Russell MB, Fenger K, Olesen J (1996) The family history of migraine. Direct versus indirect information. Cephalalgia 16:156–160
6. Weiss KM, Chakraborty R, Majumder PP, Smouse PE (1982) Problems in the assessment of relative risk of affected individuals. J Chronic Dis 35:539–551
7. Mochi M, Sangiorgi S, Cortelli P et al (1993) Testing models for genetic determination in migraine. Cephalalgia 13:389–394
8. Russell MB, Olesen J (1995) Increased familial risk and evidence of genetic factor in migraine. Br Med J 311:541–544
9. Kalfakis N, Panas M, Vassilopoulos D, Malliara Loulakaki S (1996) Migraine with aura: segregation analysis and heritability estimation. Headache 36:320–322
10. Stewart WF, Staffa J, Lipton RB, Ottman R (1997) Familial risk of migraine: a population based study. Ann Neurol 41:166–172
11. Østergaard S, Russell MB, Bendtsen L, Olesen J (1997) Comparison of first degree relatives and spouses of people with chronic tension type headache. Br Med J 314:1092–1093
12. Russell MB, Andersson PG, Thomsen LL (1995) Familial occurrence of cluster headache. J Neurol Neurosurg Psychiatry 58:341–343
13. Kudrow L, Kudrow DB (1994) Inheritance of cluster headache and its possible link to migraine. Headache 34:400–407
14. Leone M, Russell MB, Rigamonti A et al (2001) Familial risk of cluster headache: a study of Italian families. Neurology 56:1233–1236
15. El Amrani M, Ducros A, Boulan P et al (2002) Familial cluster headache: a series of 186 index patients. Headache 42:974–977

16. Russell MB (2004) Epidemiology and genetics of cluster headache. Lancet Neurol 3:279–283
17. Khoury MJ, Beaty TH, Liang K-Y (1988) Can familial aggregation of diseases be explained by familial aggregation of environmental risk factors? Am J Epidemiol 127:674–683
18. Ulrich V, Gervil M, Kyvik KO et al (1999) Evidence of a genetic factor in migraine with aura: a population-based Danish twin study. Ann Neurol 45:242–246
19. Gervil M, Ulrich V, Kyvik KO et al (1999) Migraine without aura: A population based twin study. Ann Neurol 46:606–611
20. Motulsky AG (1978) Biased ascertainment and the natural history of diseases. N Engl J Med 298:1196–1197
21. Svensson D, Ekbom K, Pedersen NL et al (2003) A note on cluster headache in a population-based twin registry. Cephalalgia 5:376–380
22. Russell MB, Saltyte-Benth J, Levi N (2006) Are infrequent episodic, frequent episodic and chronic tension-type headache inherited? A population-based study of 11 199 twin pairs. J Headache Pain 7:119–126
23. Lalouel JM, Morton NE (1981) Complex segregation analysis with pointers. Hum Hered 31:312–321
24. Russell MB, Iselius L, Olesen J (1995) Investigation of inheritance of migraine by complex segregation analysis. Hum Genet 96:726–730
25. Russell MB, Iselius L, Østergaard S, Olesen J (1998) A complex segregation analysis of chronic tension-type headache. Hum Genet 102:138–140
26. Russell MB, Andersson PG, Thomsen LL, Iselius L (1995) Cluster headache is an autosomal dominant inherited disorder in some families. A complex segregation analysis. J Med Genet 32:954–956
27. De Simone R, Fiorillo C, Bonuso S, Castaldo G (2003) A cluster headache family with possible autosomal recessive inheritance. Neurology 61:578–579
28. Ducros A, Tournier-Lasserve E, Bousser MG (2002) The genetics of migraine. Lancet Neurol 1:285–293
29. Thomsen LL, Ostergaard E, Romer SF et al (2003) Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. Neurology 60:595–601
30. Ophoff RA, Terwindt GM, Vergouwe MN et al (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{2+} channel gene CACNL1A4. Cell 87:543–552
31. De Fusco M, Marconi R, Silvestri L et al (2003) Haploinsufficiency of ATP1A2 encoding the Na^+/K^+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 33:192–196
32. Dichgans M, Freilinger T, Eckstein G et al (2005) Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 366:371–377
33. Russell MB, Olesen J (1996) A nosographic analysis of the migraine aura in the general population. Brain 119:355–361
34. Joutel A, Bousser MG, Biousse V (1993) A gene for familial hemiplegic migraine maps to chromosome 19. Nat Genet 5:40–45