Genetic and Environmental Influences on Migraine: A Twin Study Across Six Countries

Elles J. Mulder[1], Caroline van Baal[1], David Gaist[2], Mikko Kallela[3], Jaakko Kaprio[7], Dan A. Svensson[4], Dale R. Nyholt[5], Nicholas G. Martin[5], Alex J. MacGregor[6], Lynn F. Cherkas[6], Dorret I. Boomsma[1], and Aarno Palotie[8]

[1] *Dept of Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands*
[2] *University of Southern Denmark, Odense & Dept of Neurology, Odense University Hospital, Denmark*
[3] *Helsinki University Central Hospital, Finland*
[4] *Karolinska Institutet Stockholm, Sweden*
[5] *The Queensland Institute of Medical Research, Brisbane, Australia*
[6] *Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, London, UK;*
[7] *Dept of Public Health, University of Helsinki & Dept of Mental of Health, National Public Health Institute, Helsinki, Finland;*
[8] *The Finnish Genome Center and the Department of Clinical Chemistry, University of Helsinki, Helsinki, Finland*

Migraine is a common neurovascular brain disorder that is manifested in recurrent episodes of disabling headache. The aim of the present study was to compare the prevalence and heritability of migraine across six of the countries that participate in GenomEUtwin project including a total number of 29,717 twin pairs. Migraine was assessed by questionnaires that differed between most countries. It was most prevalent in Danish and Dutch females (32% and 34%, respectively), whereas the lowest prevalence was found in the younger and older Finnish cohorts (13% and 10%, respectively). The estimated genetic variance (heritability) was significant and the same between sexes in all countries. Heritability ranged from 34% to 57%, with lowest estimates in Australia, and highest estimates in the older cohort of Finland, the Netherlands, and Denmark. There was some indication that part of the genetic variance was non-additive, but this was significant in Sweden only. In addition to genetic factors, environmental effects that are non-shared between members of a twin pair contributed to the liability of migraine. After migraine definitions are homogenized among the participating countries, the GenomEUtwin project will provide a powerful resource to identify the genes involved in migraine.

Migraine is considered to be a brain disorder of neurovascular origin that is manifested by recurrent episodes of disabling headache. These episodes last for about a day and the pain intensity is usually experienced as moderate or severe. Throbbing and pounding headache is typically accompanied by nausea, vomiting, and hypersensitivity to sound and light. In addition, about a third of migraine sufferers experience aura symptoms that are characterized by visual, sensory, motor or speech-related disturbances that precede the headache (e.g., Russell et al., 1996). Epidemiological studies indicate that the peak incidence is during adolescence, with a slightly later onset in females than in males (Steward et al., 1994). Lifetime prevalence is 15% in migraine without aura and 8% in migraine with aura. A two to threefold female preponderance in adult prevalence as well as associations with events of the female reproductive cycle, suggests a triggering effect of hormones (e.g., Massiou & Bousser, 2000).

Pathophysiology

As with most common complex diseases, migraine is thought to have a multifactorial basis. Although the pathogenesis has not yet been completely elucidated, some mechanisms have been proposed that could explain the migraine headache and aura symptoms. A key role is ascribed to the trigeminovascular system and associated brainstem nuclei. Aberrant activation of the brainstem gives rise to central transmission of pain and a cascade of biochemical events involving the release of neuropeptides, which leads to sterile neurogenic inflammation, vasodilation in the dura mater and vascular headache. The aura phenomena are explained by the theory of cortical spreading depression, a sustained neuronal depolarisation that starts at the posterior part of the brain, and then spreads across the cerebral cortex, generating a transient spike activity which is followed by a suppression that can last for minutes (Lauritzen, 1987, 1994).

How the aura relates to the headache is a matter of speculation, but the spreading depression is likely to be the key event for the episodic activation of the trigeminovascular system. A dysfunction of brainstem nuclei involved in the central control of pain might exert a permissive role by favouring central trigeminal hyperexcitability (Pietrobon & Striessnig, 2003). If the theory of spreading depression holds, the question emerges why the sufferer's brain is especially susceptible to it.

Address for correspondence: Elles J. Mulder, Dept of Biological Psychology, FPP, Vrije Universiteit. Van der Boechorststraat 1, Room 1F-58, 1081 BT, Amsterdam, the Netherlands.
Email: EJCM.Mulder@psy.vu.nl

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Various biochemical abnormalities have been described in migraine: chronically low systemic levels of serotonin (Ferrari & Saxena, 1993), mitochondrial defects (Barbirolli et al., 1992), magnesium deficiency (Welch & Ramadan, 1995), dysfunctional ion channels (Ophoff et al., 1996, 1997), increased membrane instability (Joutel et al., 1996; Welch, 1998), central sensitisation of trigeminal fibers (Burstein & Woolf, 2000), excessive excitation due to abnormal release of excitatory neurotransmitters, and reduced intracortical inhibition (see Pietrobon & Striessnig, 2003). Many of these findings seem to justify the hypothesis of a hyperexcitable brain in migraine.

Genes and Environment

It is quite a common event for anyone to have one or two migraine attacks sometime in life but it is the recurrence of attacks that is clinically relevant and qualifies migraine as a disease. Genes could predispose to this recurrence by setting the brainstem pain pathways in a hypersensitive state and thereby lowering the threshold for the manifestation of migraine. This could render a migraine sufferer sensitive to environmental factors, which could affect the frequency of attacks. Indeed, stress, weather changes, menstrual cycle, and excessive sunlight are leading trigger factors (Robbins, 1994), and lack of sleep and alcohol use can increase the number of attacks.

Migraine is under substantial genetic control as several lines of research indicate. A syndrome as diverse as migraine is unlikely to be a single gene disorder although a few rare autosomal migraine traits as well as extensive familial clustering have been described. Segregation studies have pointed towards a multifactorial inheritance for the common forms of migraine (Russell et al., 1995). Complicating factors in genetic epidemiological studies of migraine are the high prevalence (migraine might occur in several family members just by chance), the absence of simple markers for migraine, as well as the change and heterogeneity of the diagnostic criteria. Peroutka and Howell (1996) studied 255 patients who had migraine without aura according to the International Headache Society (IHS) criteria, and found that in 91% at least one of the parents had IHS migraine, suggesting a dominant mode of inheritance (Kalella, 2000).

A common finding in twin studies of migraine is that monozygotic (MZ) twins show roughly twice the concordance rates than dizygotic (DZ) twins (MZ: 32–48%; DZ: 12–31%; Kallela, 2000, p. 9) indicating the importance of genes. The fact that the concordance rate in MZ twins never reaches 100% illustrates an influence of the environment. Quantitative genetic modelling of twin data quantifies the contribution of genes and environment, showing that the relative importance of genes (heritability) to the liability of migraine is 40–60% and that the contribution of non-shared environmental factors is 35–55% but shared environmental factors seem to have no impact at all. (Gervil et al., 1999; Honkasalo et al., 1995; Larsson et al., 1995; Ulrich et al., 1999; Ziegler et al., 1998).

In recent years, molecular genetic studies have provided new and important information on the pathophysiology of migraine. In a rare, autosomal dominant form of migraine, Familial Hemiplegic Migraine (FHM) where attacks are preceded or accompanied with hemiparesis, two disease causing genes have been identified: CACNA1A on Chromosome 19p (Ophoff et al., 1994, 1996) and ATP1A2 on Chromosome 1q (DeFusco et al., 2003). The CACNA1A gene is brain-specific and codes for the α1A- subunit of neuronal calcium channels (Ophoff et al., 1996) and the ATP1A2 encodes the α2 subunit of the Na^+/K^+ pump. An intriguing fact is that both molecules associated with FHM are involved in ion transport, which stimulates the hypothesis that genes coding for similar cellular pathways are good candidates for the more common forms of migraine. The role of CACNA1A in more common types of migraine is, however, controversial and positive (May et al., 1995; Terwindt et al., 2001) as well as negative findings (Noble-Topham et al., 2002; Nyholt et al., 1998) have been reported.

GenomEUtwin and the Present Study

The GenomEUtwin project aims to study the population level significance and contribution of loci and genes identified in ascertained study samples. Eligible twin pairs that are affected by migraine as well as their family members will be approached for genotyping in eight countries, an effort that will yield significant power to identify new loci and susceptibility genes. As a first step, the present paper describes the screening instruments that have been used to define migraine in the participating countries as well as the data that are currently at our disposal. We report the number of MZ and DZ twin pairs and compare sex, age, prevalence, and heritabilities between the twin samples from Australia, Denmark, Finland, the Netherlands, Sweden, and the United Kingdom (UK). Finally, we summarize the available data and perform a simultaneous analysis to quantify genetic effects, and to test whether the size and nature of the genetic contribution is similar across the countries.

Methods

Only complete twin pairs with known zygosity were selected for the present study. Figure 1 contains a summary of the instruments that were used in the participating countries. Mean age and the numbers of twin pairs in each country are listed in Table 1.

Subjects and Migraine Classification

Australia. Migraine symptom data were obtained in the course of an extensive semi-structured telephone interview, designed to assess physical, psychological and social manifestations of alcoholism and related disorders, conducted with female and male twins born between 1964 and 1971 from the volunteer based Australian Twin Registry (Heath et al., 2001). The sample was unselected with regard to personal or family history of alcoholism or other psychiatric or medical disorders. Interviews relating to their headaches were conducted between 1996 and 2000 and participants answering "yes" to ever having "migraine or recurrent attacks of headache", then answered a number of questions based on the IHS diagnostic criteria. The interview yielded diagnostic criteria for migraine without aura and with aura, using visual prodromal symptoms as an index of migraine

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with aura. Individuals were diagnosed with or without migraine according to IHS criteria.

Denmark. The main survey comprised 4314 twins identified from the population-based Danish Twin Registry (Skytthe et al., 2002). The twins were successfully home-interviewed by trained interviewers in 1998 using a structured interview (Gaist et al., 2000). The structured interview also contained the following questions screening for migraine (answer possibilities: Yes or No), which have previously been validated in a Danish twin population (Gervil et al., 1998): 1)Have you ever suffered from migraine? 2) Have you ever had visual disturbances of 5 to 60 minutes' duration followed by headaches? Twins who answered "Yes" to at least one of the questions were considered screening positive for migraine.

Finland. The selection procedures, determination of twinship and assessment of representativeness of the Finnish Twin Cohort Study are described in detail elsewhere (Kaprio & Koskenvuo, 2002). The twins were mailed a questionnaire on medical and psychosocial factors and a follow-up questionnaire including items on headache and migraine was sent out in 1981 (Honkasalo et al., 1995). The younger Twin Cohort (FinnTwin16), born between 1975 and 1979, was contacted within 2 months of their 16th birthday. In the older cohort assessed in 1981, twins were defined as having migraine if they responded affirmatively to the dichotomous question "Have you suffered from headache attacks during the previous year?", and if so, whether the attacks were associated specifically with any of the following three symptoms: visual disturbances, nausea or vomiting, and unilateral location, as described by Honkasalo et al. (1995). The younger twins of the FinnTwin16 study were asked whether a physician had ever told them they had had migraine.

The Netherlands. Twins were recruited from the Netherlands Twin and Family Register (NTR) that enrols twins and their spouses, siblings and parents. All receive biannual health and lifestyle questionnaires that address topics related to physical and mental health, smoking and drinking, personality and mood. The survey held in 2000 was used for the present study and items on recurrent headache and migraine were taken and translated from Gervil et al. (1998). A total of 6705 subjects (4613 twins, 1477 siblings, 705 spouses) filled out and returned the questionnaire. The sample was divided into a younger and an older cohort, and analysed for a "potential migraine" definition which was the same as in Denmark. If twins responded affirmatively either to the question: "Have you ever had migraine?" or to "Have you ever had visual disturbances for 5–60 minutes followed by headache?" they were considered potential migraineurs.

Sweden. All twins were recruited from the Swedish Twin Registry (Pedersen et al., 2002). As part of the Screening Across Lifespan of Twins (SALT) study, all twins born between 1886 and 1958 were invited to participate in a structured telephone interview concerning common health problems and health related factors. Headache questions were administered only to the twins born between 1935 and 1958. Data collection was made via Computer Assisted Telephone Interviews (CATI) performed by trained lay personnel between 1999 and 2002.

The International Headache Society classification of headache phenotypes was used to diagnose migraine (IHS, 1988). The structured migraine interview consisted of a series of brief questions to be answered "yes", "no", "do not know", or "refuse to answer". The sequence of diagnostic criteria for migraine was as follows: (a) recurrent headache not associated with infection, fever, or hangover (past or present); (b) headache attacks lasting somewhere between 4 hours and 3 days if no medication against the pain is taken; (c) at least two out of four pain features (moderate or severe intensity, one-sided location, pounding/throbbing quality, and aggravation by routine physical activity; and (d) at least one out of two accompanying symptoms (nausea and/or vomiting, and increased sensitivity to light and sound). A few respondents who declared that they did not know whether they had had headache attacks lasting from 4 hours to 3 days, but who fulfilled all other criteria, were also diagnosed as sufferers of migraine.

UK. All twins were enlisted with the St Thomas' UK Adult Twin Registry. This twin database was started in 1992 and

Table 1

Summary of Migraine Definitions and Instruments

	Migraine definition	Zygosity determination	Telephone interview to confirm migraine?
Australia	IHS	Questionnaire* partly confirmed by DNA from blood	Yes
Denmark	self reported migraine	Questionnaire*	Not used
Finland[3]	Physician diagnosis (self reported)	Questionnaire*, partly confirmed by DNA from blood	No
Finland[4]	Headache attacks with migrainous features	Questionnaire*, partly confirmed by DNA from blood	No
Netherlands[1,2]	self reported migraine	Questionnaire*, partly confirmed by DNA (blood and buccal swabs)	No
Sweden	IHS	Questionnaire*	Yes
UK	IHS	Questionnaire*, partly confirmed by DNA from blood	No

Note: All twin populations were unselected for migraine, headache or any other condition. [1]younger and [2] older Dutch cohorts; [3] younger cohort FinnTwin16; [4] older Finnish cohort Honkasalo (1995) data. *Childhood similarity questionnaires.

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twins were recruited by successive media campaigns without selecting for particular diseases and traits. In the present sample, all twins are female because the diseases initially focused on osteoporosis and osteoarthritis, which are more common in women. All twins receive a series of postal questionnaires and around half have been assessed in detail clinically. The UCSD Migraine Questionnaire (Tom et al., 1994) was incorporated in a larger questionnaire asking about a range of conditions. Migraine diagnoses were based on IHS criteria; namely: subject significantly bothered by recurrent (≥ 5) headaches, not due to a definite cause (e.g., tumour); pain free intervals between attacks, and if left untreated, headache would last 4–72 hours. Characteristics of headache include at least 2 of the following descriptions "pulsating", "unilateral", "severe enough to stop or decrease activities", "made worse by physical activity". In addition, headache is accompanied by at least 1 of the following "nausea or vomiting", "sensitivity to light", "sensitivity to noise" (IHS, 1988).

Data Analyses

Migraine data from Australia, Denmark, Finland, the Netherlands, Sweden, and the UK were dichotomized (affected / unaffected) and summarized into 2 × 2 contingency tables for monozygotic males (MZM), dizygotic males (DZM), monozygotic females (MZF), dizygotic females (DZF), dizygotic opposite sex pairs with male born first and female second (DOS-MF), or with female born first (DOS-FM). Finland and the Netherlands provided two separate sets of contingency tables for their younger and older cohorts.

Mx 1.52 offers a maximum likelihood-based model fitting approach (Neale, 1997) for ordinal data and we used the appropriate scripts from the GenomEUtwin Mx script library to carry out the genetic analyses.[1] The analyses are based on liability models, which assume that the dichotomous distribution of migraine reflects an underlying continuous liability distribution, with a mean of 0 and a variance of 1. The threshold, which reflects the prevalence of the disease, is expressed as a *z*-value of the normal distribution, and divides the area under the curve into the proportions of affected and unaffected individuals. Each 2 × 2 contingency table has an underlying bivariate distribution that can be described by two thresholds (for twin 1 and for twin 2) and a correlation between the two liabilities. The tetrachoric correlation between migraine liability in twin 1 and in twin 2 in each sex by zygosity group is derived from the areas under the bivariate normal distribution (Neale & Cardon, 1992). If the tetrachoric correlations are larger for MZ than for DZ twins (this means a relatively larger proportion of concordant MZ than DZ pairs on the observed scale), then genetic influences will be important (see Posthuma, this issue), because monozygotic twins share all their genes, whereas dizygotic twins share on average 50% of their segregating genes.

We first calculated prevalences and tetrachoric correlations for each country from the sex by zygosity contingency tables and subsequently tested whether: (a) threshold of twin 1 = threshold of twin 2; (b) threshold of MZ twins = threshold of DZ twins; and (c) threshold of males = threshold of females. Next, genetic models were fitted to the available contingency tables of the sex by zygosity groups for each country. These genetic models included either additive genetic (A), common environmental (C) and non-shared environmental influences (E) or additive genetic, non-shared environmental and non-additive genetic influences (D). Note that an ADCE model is not identified if only the data from twins reared together are available, such as in the present samples. If twin correlations did not suggest shared environmental influences, model fitting results are shown for ADE models and reduced models only, and if twin correlations did not show evidence for non-additive genetic influences, we only give model fitting results for ACE and reduced models. The thresholds (i.e., prevalences) in the genetic models were equated for twin 1 and twin 2, as well as for MZ and DZ twins, but were different for males and females. Total variances (A + C + E or A + D + E) were always constrained to be 1.

We tested whether the same genes contribute to migraine in males and females by comparing models in which the correlation between the latent genetic factors in dizygotic opposite sex (DOS) twins was constrained at .5 with models in which this correlation was allowed to be smaller. If different genes influence the trait in males and females, this typically results in a lower genetic correlation than 0.5 in DOS twins. Next, we tested whether the relative influences of genes and environment were the same for males and females. Note that this is a test with 2 degrees of freedom (*df*): we constrained the total variance (additive and non-additive genetic variance plus environmental variance) of the liability scale to be 1 and consequently, equating two out of three sources of variance across the sexes implies that the third is equated as well. Next, ACE or ADE models (with and without sex differences) were further reduced to AE, CE and E models. The difference in χ^2 between the full and a reduced model is also a χ^2 and provides a likelihood-ratio test of the significance of the effect that was dropped.

Finally, all contingency tables from all countries were simultaneously analyzed. In this 56-group analysis, thresholds were allowed to differ between sexes and countries. We tested whether (i) broad heritabilities (i.e., the standardized estimate of the summed additive and non-additive genetic influences) were the same across countries, (ii) the proportion of non-additive genetic influences in broad heritable variation was the same across countries, and (iii) non-additive genetic influences could be omitted from the model.

Results

The total sample size across all participants added to a total number of 29,717 complete twin pairs who provided migraine data for the present study. The different samples show considerable variability in mean age, ranging from 24 years in Finland to 57 in Denmark (Table 1).

Migraine Prevalence

The threshold that divides the liability distribution into affected and unaffected subjects was the same for first- and second born twins (twin 1 and twin 2), as well as for MZ twins and DZ twins. In every country, the thresholds were

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Table 1

Age and Numbers of Discordant and Concordant Twin Pairs for Migraine in GenomEUtwin

	Age mean	Age range	MZ (dis)	MZ (con)	MZ (non)	DZ (dis)	DZ (con)	DZ (non)	OS (dis)	OS (con)	OS (non)	Total Pairs
Australia	30	22–39	242	55	860	217	34	658	156	20	476	2718
Denmark	57	46–68	141	70	451	173	39	391	218	50	349	1882
Finland[3]	24	23–27	91	17	528	103	10	518	103	5	537	1912
Finland[4]	41	24–94	257	57	2376	594	58	4845	0	0	0	8187
Netherlands[1]	25	18–35	118	50	412	87	20	216	61	9	166	1139
Netherlands[2]	47	36–68	51	31	100	32	10	49	18	4	35	330
Sweden	52	41–64	450	107	2673	750	84	3590	824	49	3594	12121
UK	48	31–62	196	76	430	238	53	435	0	0	0	1428
Total			1377	382	7318	2075	278	10437	1301	124	4956	29,717

Note: Age mean, age range, and number of complete monozygotic (MZ), dizygotic (DZ), and dizygotic opposite sex (OS) twin pairs that are discordant affected (dis), concordant affected (con), or none affected (non) for survey-based migraine. DZ group only includes same sex pairs. Dutch sample was split in two age groups: [1]18–35, [2]36–68; [3]younger cohort FinnTwin16; [4]older Finnish cohort Honkasalo (1995) data.

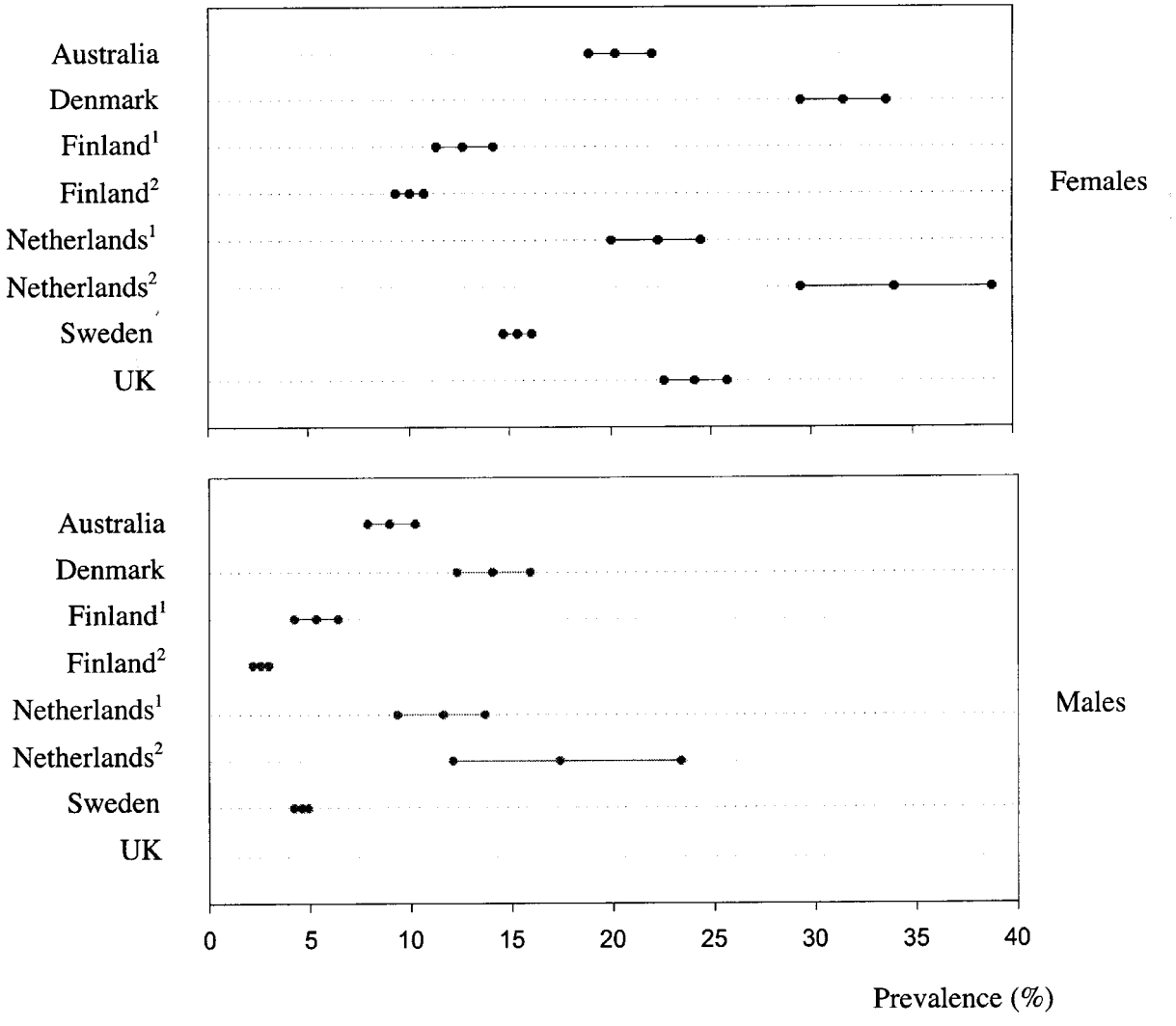

Figure 2

Prevalences in males and females for survey-based migraine. Each country shows three dots of which the middle denotes the mean and the flanking dots denote the 95% confidence interval. [1]younger and [2]older Dutch cohorts; [3] younger cohort FinnTwin16; [4] older Finnish cohort Honkasalo (1995) data. UK provides females only.

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lower in females, reflecting the fact that migraine prevalence is higher in females than in males. More specifically, prevalence is about twice as high in females as in males in most countries but it is threefold in Sweden and even fourfold in the older Finnish cohort (Figure 2).

Twin Correlations

Correlations show some variability between the countries (Table 2), but the pattern is the same: MZ correlations are at least twice the size of the DZ correlations. This is a first indication of a contribution of genes to the liability to migraine. Genetic non-additivity is suggested by MZ correlations that are more than twice as high as the DZ correlations, which is the case in Denmark and the young sample of the Netherlands, and also in Sweden and Finland where MZ correlations are even more than threefold the DZ correlations (Table 2). Sex differences in twin correlations seem rather modest but may play a role in some countries. For instance, the younger Finnish cohort exhibits very high MZM and low MZF values. Opposite sex correlations and DZ same sex correlations were within a similar range, which suggests that the same set of migraine-related genes is expressed in males and females. There seems little evidence for shared family environment on the resemblance in migraine between twins.

Sex Differences in Variance Components

We did not find evidence for different genes between males and females in the liability to migraine, as the correlation between latent genetic factors was not significantly different from 0.5 in opposite sex twins. For each country, the estimates for additive genetic (a^2), non-additive genetic (d^2) and non-shared environmental variance (e^2) were the same for males and females (maximum χ^2 difference between these models was 3.41, $df = 2$) except for the younger Finnish twins (Table 3) where additive genetic effects were larger in females and non-additive genetic effects were larger in males.

Table 2

Twin Correlations for Survey-based Migraine

	MZM	DZM	MZF	DZF	DOSMF	DOSFM	MZ	DZ
Australia	.45	.29	.30	.09	.10	.25	.34	.15
Denmark	.61	.24	.53	.13	.25*	—	.56	.21
Finland[3]	.74	.08	.26	.19	.06*	—	.41	.12
Finland[4]	.54	.06	.50	.25	—	—	.51	.22
Netherlands[1]	.32	–.09	.57	.34	.16	.08	.53	.22
Netherlands[2]	.41	.37	.55	.24	.46	.07	.52	.28
Sweden	.33	.06	.46	.15	.04	.17	.44	.13
UK	—	—	.42	.17	—	—	.42	.17

Note: Tetrachoric correlations given for monozygotic (MZ), dizygotic (DZ) same sex pairs and dizygotic opposite sex pairs (DOS) separated for males (M) and females (F). DOSMF: male born first; DOSFM: female born first. Last two columns denote mean MZ and DZ (including OS) correlations. Dutch sample was split in two age groups: [1] 18–35, [2] 36–68; [3] younger cohort FinnTwin16; [4] older Finnish cohort Honkasalo (1995) data. * DOS pairs were always ordered as male-female, regardless of birth order.

Table 3

ADE Models with Sex Differences for Survey-based Migraine

		χ^2	*df*	*p*	AIC	a^2m	a^2f	d^2m	d^2f	e^2m	e^2f	T_{males}	$T_{females}$
Australia	ADE	12.18	12	1	–11.82	.46	.19	.01	.10	.53	.71	1.35	0.83
	$\Delta\chi^2$	2.43	2										
Denmark	ADE	13.05	9	1	–4.95	.42	.24	.20	.29	.38	.48	1.08	0.48
	$\Delta\chi^2$	0.89	2										
Finland[3]	ADE	2.48	9	1	–15.52	.02	.28	.71	.00	.27	.72	1.62	1.14
	$\Delta\chi^2$	6.84*	2										
Finland[4]	ADE	0.88	6	0.99	–11.12	.00	.49	.53	.01	.47	.50	1.96	1.28
	$\Delta\chi^2$	1.66	2										
NL[1]	ADE	16.35	12	1	–7.65	.08	.57	.21	.00	.70	.43	1.19	0.76
	$\Delta\chi^2$	3.41	2										
NL[2]	ADE	5.74	12	1	–18.26	.44	.55	.00	.00	.56	.45	0.95	0.41
	$\Delta\chi^2$	.19	2										
Sweden	ADE	18.01	12	1	–5.99	.04	.13	.29	.33	.67	.54	1.69	1.02
	$\Delta\chi^2$	2.1	2										

Note: Models with sex differences and with different prevalences (m = males; f = females). χ^2 differences are given between ADE models with and without sex differences. Genetic correlation fixed at 0.5 for opposite sex twins. NL: Dutch sample was split in two age groups: [1] 18-35, [2] 36–68; [3] younger cohort FinnTwin6; [4] older Finnish cohort Honkasalo (1995) data; T = threshold (in Z-values); * significant χ^2 difference. UK provided females only and is not included.

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Table 4
ADE and AE Models Without Sex Differences for Survey-based Migraine

		χ^2	*df*	*p*	AIC	a^2	d^2	e^2	h^2
Australia	ADE	14.61	14	.41	–13.39	.27 (.00–.44)	.07 (.00–.45)	.66 (.55–.77)	.34 (.45–.23)
	AE	14.68	15	.47	–15.32	.33 (.23–.43)	—	.67 (.57–.77)	.33 (.43–.23)
Denmark	ADE	13.94	11	.24	–8.06	.30 (.00–.61)	.27 (.00–.65)	.44 (.33–.56)	.56 (.67–.44)
	AE	15.15	12	.23	–8.85	.53 (.42–.63)	—	.47 (.37–.58)	.53 (.63–.42)
Finland[3]	ADE	9.32	11	.59	–12.68	.09 (.00–.51)	.32 (.00–.57)	.59 (.43–.78)	.41 (.57–.22)
	AE	10.02	12	.61	–13.98	.37 (.21–.52)	—	.63 (.48–.79)	.37 (.51–.21)
Finland[4]	ADE	2.54	8	.96	–13.46	.38 (.02–.57)	.12 (.00–.52)	.49 (.41–.59)	.51 (.59–.41)
	AE	2.91	9	.97	–15.09	.49 (.41–.57)	—	.51 (.43–.59)	.49 (.57–.41)
NL[1]	ADE	19.76	14	.14	–8.24	.33 (.00–.63)	.20 (.00–.65)	.47 (.35–.61)	.53 (.65–.39)
	AE	20.07	15	.17	–9.93	.52 (.39–.63)	—	.48 (.37–.61)	.52 (.63–.39)
NL[2]	ADE	5.93	14	.97	–22.07	.52 (.00–.69)	.00 (.00–.68)	.48 (.31–.68)	.52 (.69–.32)
	AE	5.93	15	.98	–24.07	.52 (.32–.69)	—	.48 (.31–.68)	.52 (.69–.32)
Sweden	ADE	20.11	14	.13	–7.89	.07 (.00–.31)	.37 (.09–.51)	.56 (.49–.64)	.44 (.51–.36)
	AE	26.75	15	.03	–3.25	.38 (.31–.45)	—	.62 (.55–.69)	.38 (.45–.31)
UK[5]	ADE	1.96	3	.58	–4.04	.26 (.00–.51)	.15 (.00–.52)	.58 (.47–.70)	.42 (.53–.30)
	AE	2.23	4	.69	–5.77	.41 (.29–.51)	—	.59 (.49–.71)	.41 (.51–.29)

Note: Models without sex differences and with different prevalences. Estimates and 95% confidence intervals are given for a^2, d^2, e^2, and h^2 (1-e2). Genetic correlation fixed at 0.5 for opposite sex twins; Dutch sample was split in two age groups: [1] 18–35, [2] 36–68; [3] younger cohort FinnTwin16; [4] older Finnish cohort Honkasalo (1995) data; [5] females only.

Non-additive Genetic Variance

We proceeded with the models without sex differences in genetic architecture for every country. We subsequently tested for non-additive genetic influences, which were larger than zero in all samples except for the older Dutch cohort. The AE model appeared to be most appropriate for almost every sample but the ADE model fitted best to the Swedish data (Table 4). The total genetic effects (broad heritability) range from 34% (Australia) to 57% (Denmark). Within this broad heritability, 0% (older Dutch twins) to 84% (Sweden) is accounted for by non-additive effects.

Simultaneous Analysis

An analysis was performed on all available contingency tables simultaneously to test whether heritabilities were the same across the countries and to increase the probability to detect effects of non-additive genetic variance. The ADE model was fitted to the data for 29,717 twin pairs from all countries. Migraine prevalences appeared different across countries and across sexes in the univariate analyses (see confidence intervals in Figure 2), so this was maintained in the simultaneous analysis. Broad heritabilities could be equated across countries (χ^2_7 = 10.76, p = 0.15). None of the estimates from the individual countries differed significantly from the broad heritability point estimate of 46%. If non-additive genetic influences were omitted from the model, the fit was significantly worse (χ^2_1 = 8.30). The proportions of non-additive genetic effects in broad heritability were not significantly different across the countries (χ^2_7 = 5.25, p = 0.63). Overall, additive heritability is 21% (CI = 6–36%) and non-additive heritability is 25% (CI = 8–42%).

The power to detect non-additive genetic effects (size of 25%) is very low (12–32%) in each country given its sample size and migraine prevalence. It appeared unlikely to detect non-additivity of this magnitude in any country except Sweden where the power is reasonable (59%). The power to detect non-additive effects of this magnitude rises to over 90% in the total sample size.

Discussion

The aim of GenomEUtwin is to identify loci and susceptibility genes that are involved in migraine. The main purpose of the present study was, therefore, to describe the migraine instruments and twin samples that are currently available from Australia, Denmark, Finland, the Netherlands, Sweden, and the UK, and to compare prevalences and heritabilities before standardisation. The number of complete twin pairs that were at our disposal for the present study added to a total of 29,717.

Migraine was ascertained using questionnaires that differed between most countries. Sweden, the UK, and Australia had IHS-based migraine, Finland used headache attacks with migraine features in the older cohort, self-reported "having ever received a migraine diagnosis by a physician" in the younger cohort, and Denmark and the Netherlands used self-reported "ever had migraine", or "ever had headache attacks with visual prodroma". Interpretation of inter-country differences with respect to prevalence and heritability has to be tempered by the fact that these results are confounded to some extent by differences in diagnostic accuracy, age, and cultural differences in the reporting of pain. Despite these differences, the questionnaires have in common that subjects that screened positive are at risk for migraine.

Denmark and the Netherlands used the same, and most liberal, criteria and showed the highest prevalences in females (32% and 34%, respectively), whereas the lowest prevalence was found in the younger and older Finnish

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cohorts (13% and 10%, respectively). Prevalence is known to reach its maximum in mid-life (Breslau & Rasmussen, 2001), and in line with this we demonstrated a 10% rise when comparing the younger with the older Dutch cohort. All samples showed a prevalence that is more than twice as high in females as in males, which is a common finding (Breslau & Rasmussen, 2001). It must be emphasized that, from a mathematical point of view, incidence of a trait in the population provides no information about its heritability (Lynch & Walsh, 1998, p. 735).

Non-shared environment and genes contribute significantly to the liability to migraine, as has been shown by many other studies. The AE model yielded the best fit in every country but there was also some indication of genetic dominance. This was only significant in Sweden where the ADE model provided the best fit. Environmental effects were substantial, ranging from just under 50% (Denmark and both Dutch cohorts) to 66% (Australia). Diet or lower temperatures might be protective against the manifestation of migraine in countries with low prevalence such as Finland and Sweden. Summed additive and non-additive genetic effects (broad heritability) ranged from 34% to 57%, with lowest estimates in Australia, and highest estimates in the older cohort of Finland, the Netherlands, and Denmark. It is interesting to note that migraine instruments of Denmark and Netherlands were characterized by high prevalence as well as high heritability, whereas Finland and Sweden have low prevalences and heritabilities. Further analyses by GenomEUtwin may resolve whether differences in the estimated prevalence and heritability of the liability to migraine across nations is because of measurement error, environmental exposures, or variation in allele frequencies.

The proportion of non-additivity in broad heritability ranged from zero (older Dutch twins) to 0.84 in Sweden where the power to detect dominance is by far the largest (0.59) followed by the older Finnish cohort (0.32). It became even less likely to detect non-additive genetic influences in other countries. We performed a simultaneous analysis on all available data, resulting in significant additive genetic effects (21%), non-additive genetic effects (25%) and non-shared environmental effects (54%). We did not detect differences in the size and nature of genetic effects between the countries, although it should be noted that insufficient power might contribute to this.

Non-additive genetic variation results from interaction effects of either the two homologous alleles that define the genotype at a locus (dominance) or between genotypes at separate loci (epistasis). The presence of non-additive genetic effects could have implications for linkage analyses (see Posthuma, this issue) as only twin pairs with IBD-status = 2 will be informative. Although the validity of simultaneously analyzing such heterogenous migraine definitions might be questionable, we argue that it at least provides information on migraine risk. The presence of non-additivity should be confirmed, however, after migraine is defined with the same instrument in every country.

To gain optimally from the large number of the twin pairs that are available, GenomEUtwin will need to homogenize the migraine definition and use a validated migraine instrument to screen for migraine with and without aura in the general population. Non-specified migraine was analysed in the present study, but in the future the two migraine subtypes will be distinguished. We hope to make a significant contribution to the active discussion as to whether these subtypes belong to the same pathogenic entity. Clinical, laboratory, radiological or other tests to confirm the diagnosis are not available and it is hugely impractical to arrange face-to-face interviews between patients and neurologists to obtain a uniform clinical examination and diagnosis in a population of the magnitude represented by our combined sample. We will therefore have to use questionnaires that might be supported by telephone interviews.

IHS criteria are widely used to diagnose migraine and represent the expert opinion of clinicians on what characterises migraine. These criteria have been shown to be exhaustive and valid in clinical practice (Iversen et al., 1990; Rasmussen et al., 1991), but they certainly are not flawless (Blau, 1993). Still, the IHS criteria have been a huge step forward in migraine research and they will be the starting point in harmonizing and defining migraine across countries. It is large population-based genetic studies, such as GenomEUtwin, that will be able to determine the true inherited core of these criteria and may contribute to their future refinement.

GenomEUtwin aims to identify susceptibility loci and underlying genes in migraine with and migraine without aura after defining and homogenizing the diagnostic criteria. The initial genome scan will be carried out first in concordant DZ twin pairs, and twins including monozygotic twins and their family members will be added. A large population-based genetic study such as GenomEUtwin provides a great opportunity to fine tune the diagnostic IHS criteria and identify the genes that are involved in complex diseases such as migraine.

Endnote

1 Mx scripts can be retrieved from the GenomEUtwin Mx script library (www.psy.vu.nl/mxbib).

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