Migraine With Aura and Migraine Without Aura Are Not Distinct Entities: Further Evidence From a Large Dutch Population Study

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It is often debated whether migraine with aura (MA) and migraine without aura (MO) are etiologically distinct disorders. A previous study using latent class analysis (LCA) in Australian twins showed no evidence for separate subtypes of MO and MA. The aim of the present study was to replicate these results in a population of Dutch twins and their parents, siblings and partners (N = 10,144). Latent class analysis of International Headache Society (IHS)-based migraine symptoms resulted in the identification of 4 classes: a class of unaffected subjects (class 0), a mild form of nonmigrainous headache (class 1), a moderately severe type of migraine (class 2), typically without neurological symptoms or aura (8% reporting aura symptoms), and a severe type of migraine (class 3), typically with neurological symptoms, and aura symptoms in approximately half of the cases. Given the overlap of neurological symptoms and nonmutual exclusivity of aura symptoms, these results do not support the MO and MA subtypes as being etiologically distinct. The heritability in female twins of migraine based on LCA classification was estimated at .50 (95% confidence intervals [CI] .27 – .59), similar to IHS-based migraine diagnosis (h^2 = .49, 95% CI .19–.57). However, using a dichotomous classification (affected–unaffected) decreased heritability for the IHS-based classification (h^2 = .33, 95% CI .00–.60), but not the LCA-based classification (h^2 = .51, 95% CI .23–.61). Importantly, use of the LCA-based classification increased the number of subjects classified as affected. The heritability of the screening question was similar to more detailed LCA and IHS classifications, suggesting that the screening procedure is an important determining factor in genetic studies of migraine.

Migraine is a neurovascular disease characterized by a broad spectrum of symptoms, varying from headaches that are typically unilateral and have a pulsating quality, to various neurological symptoms such as nausea, increased sensitivity to light and sound (photophobia and phonophobia), and aura symptoms, which may consist of visual, sensory or motor disturbances (Headache Classification Committee of the International Headache Society, 2004).

A complicating factor in migraine research is the lack of clearly detectable biological markers that can help diagnose migraine. Therefore, diagnosis relies largely on symptomatology. The generally accepted diagnostic criteria for migraine are those published by the International Headache Society (Headache Classification Committee of the International Headache Society, 1988, 2004). These criteria were developed in order to standardize headache definitions and thereby facilitate comparisons between studies. The two main subtypes of migraine distinguished in these criteria are migraine without aura (MO) and migraine with aura (MA). However, it has been debated whether this distinction reflects true etiological differences between the disorders. Russell and Olesen (1995) found that first degree relatives of MA patients had a 3.8-fold risk of having MA, but no increased risk of having MO, suggesting distinct etiologies (Russell & Olesen, 1995). In a study published in 1996, Russell et al. report different precipitating factors for MO and MA, and a low co-occurrence (4%) of the two disorders (Russell et al., 1996). However, other studies report higher co-occurrence of MO and MA. Launer et al. (1999), who conducted a large population-based study of migraine, found that 13% of patients had both MO and MA, which corresponds to 42% of all MA patients (Launer et al., 1999). Kallela et al. (2001) report co-occurrence of MO and MA in 41% of all migraineurs (Kallela et al., 2001). However, these results may be biased due to the use of a clinical sample. Other evidence in support of MO and MA having shared etiologies is the fact that MO and MA are often found within the same family, and various types of migraine may be experienced by a single individual at different times in life (Ophoff et al., 1994). Thus, in spite of the traditional distinction

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between MO and MA, the frequent co-occurrence of the two types of attacks within families and within individuals suggests that a shared etiology may underlie MO and MA. Indeed, the recently updated International Headache Society (IHS) diagnostic criteria now include comments within the criteria for MA which state 'Many patients who have frequent attacks with aura also have attacks without aura (code as 1.2 *Migraine with aura* and 1.1 *Migraine without aura*)', and 'The majority of migraine auras are associated with headache fulfilling criteria for 1.1 *Migraine without aura*'.

Genetics of Migraine

Migraine has been shown to be under substantial genetic influence and is likely to be influenced by a large number of genes (Montagna, 2004). To date, three genes have been identified that are responsible for a rare autosomal dominant subtype of migraine with aura, called familial hemiplegic migraine (FHM). In 1996, various mutations were found in the calcium channel gene *CACNA1A*, located on chromosome 19p13, in five unrelated FHM families (Ophoff et al., 1996). In 2003, a second gene involved in FHM was identified on chromosome 1q23, the *ATP1A2* gene, which codes for the α2 subunit of the Na+/K+ pump (De Fusco et al., 2003). Dichgans et al. (2005) recently identified a third gene involved in FHM, located on chromosome 2q24. This gene, *SCN1A*, has previously been implicated in epilepsy. Some studies suggest that the *CACNA1A* gene may also play a role in the typical migraines (May et al., 1995; Nyholt et al., 1998; Terwindt et al., 2001), but negative findings have also been reported (Hovatta et al., 1994; Jones et al., 2001). Considering the clinical heterogeneity of migraine, and the fact that a variety of mutations in at least three different genes are implicated in a rare and specific subtype of migraine, it seems likely that many genes are involved in the pathogenesis of more common migraine types.

Through the years, various studies have investigated to what extent genes and environment influence migraine. The heritability of migraine is commonly estimated at 40 to 50% (Honkasalo et al., 1995; Larsson et al., 1995; Svensson et al., 2003). However, results have not always been consistent. Mulder et al. (2003) compared the prevalence and heritability of migraine in six different countries that participate in the GenomEUtwin project. Across countries, different questionnaires had been used to obtain data on migraine. The prevalence of migraine in females ranged from 10% in Finland to 34% in the Netherlands, and heritability estimates between 34% and 57% were found. In some countries evidence was found for nonadditive genetic effects, but this was significant in Sweden only (Mulder et al., 2003). This might be due to a lack of power to detect these effects, since very large samples are needed to detect nonadditive genetic effects (Martin et al., 1978). A combined analysis of data from all countries suggested that nonadditive effects might indeed play a role in migraine. However, demographic and ascertainment differences between countries might require to first consider measurement issues and testing of measurement invariance (Lubke et al., 2004).

In most migraine studies, potentially affected subjects are identified with a screening question, for example, 'Do you ever suffer from headache attacks, for instance migraine?' If participants answer this question with 'yes', they will be asked further questions concerning more detailed features of their headaches, such as duration, frequency and specific symptoms. Consequently, differences in screening procedure (e.g., wording differences) have potential to significantly influence estimations of prevalence and heritability. Furthermore, cultural/translation (Guillemin et al., 1993), dietary (Millichap & Yee, 2003) and climate (Prince et al., 2004) differences may also influence these estimates.

Latent Class Analysis

In a previous study, Nyholt et al. (2004) used latent class analysis (LCA) to study migraine symptomatology in an Australian twin population. LCA was used to empirically identify subgroups of migraine patients in a population-based twin sample, and to examine whether these subtypes reflected distinct etiologies or different levels of severity on a single dimension. The results did not support an etiological distinction between MO and MA, but rather suggested a continuum underlying both migraine subtypes. The aim of the present article is to test the stability of the results from the Australian twin study by applying LCA to data from a sample of Dutch twins and their parents, siblings and partners. Furthermore, we aim to compare the use of LCA and IHS-based migraine classifications and to evaluate the influence of the screening question. Prevalence and heritability estimates are compared for several classifications of migraine, based on latent class analysis, IHS diagnostic criteria, and the screening question alone.

Methods

Sample

Data on migraine symptoms were collected in a large sample of Dutch twins, their parents, partners and siblings. The data were collected in 2002, as part of an ongoing family study on health, lifestyle and personality. The participants were volunteer members of the Netherlands Twin Registry, kept by the department of Biological Psychology at the Vrije Universiteit in Amsterdam. Questionnaires were mailed to 7261 families. The response rate for twins, siblings and parents was approximately 30%. Sex was unknown for 10 subjects, who were consequently excluded from the analyses. Data from 10,144 participants were used; 4450 twins, 1446 siblings, 2743 parents, and 1505 partners. Of these 10,144 participants, 4239 (42%) were males and 5905 (58%) were females. The age of the participants ranged from 14.11 to 88.27 years,

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Table 1a

Diagnostic Criteria for Migraine Without Aura, as Published by the International Headache Society (IHS)

A.	At least 5 attacks fulfilling criteria B–D
B.	Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C.	Headache has at least two of the following characteristics:
	1. unilateral location
	2. pulsating quality
	3. moderate or severe pain intensity
	4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D.	During headache at least one of the following:
	1. nausea and/or vomiting
	2. photophobia and phonophobia
E.	Not attributed to another disorder

Table 1b

LCA Symptom Variables Based on IHS Criteria

Code	Abbreviation	Description
A	≥ 5 episodes	At least 5 episodes of migraine/headache during lifetime
B	4–72 hours	Headache attack usually lasts 4–72 hours
C2	Pulsating	The headache is usually pulsating
C3	Moderate or severe	The headache is usually moderate or severe
C4	Aggravation	Headache is aggravated by physical activity
D1	Nausea or vomiting	Headache is accompanied by nausea or vomiting
D2	Photophobia or phonophobia	Headache is accompanied by aversion of light or sound
Aura	Aura	Headache is accompanied by partial loss of vision, seeing flashes of light or zigzag patterns

with a mean age of 41.4 years for males (*SD* = 14.7) and 38.9 for females (*SD* = 14.0). All subjects were included in the latent class analyses. Due to the small numbers of male twins screening positive for headache, genetic analyses were performed using only data from the female twins. Individuals for whom zygosity was unknown were excluded, resulting in a sample of 928 complete female twin pairs and 590 female twin individuals from incomplete pairs. For 25% of the pairs, DNA was used to determine zygosity. For the remaining pairs, zygosity was determined by means of questionnaire data on physical similarity and confusion of the twins by relatives, friends and strangers, resulting in a correct classification in approximately 97% of the cases. The mean age of the female twins was 33.3 years (*SD* = 11.5, range 17–85). The majority (85%) were between 20 and 50 years of age.

Participants who screened positive for the question 'Do you ever experience headache attacks, for instance migraine?' answered a number of questions about the characteristics of their headache. These questions concerned the frequency and duration of the headaches, the quality of the headache (pounding, pressing or squeezing), and the severity. They were also asked whether any additional symptoms were present, such as sensitivity to light, sound or smell, nausea or vomiting, and aura symptoms, and whether the headache was aggravated by physical activity. This information was sufficient to obtain data on eight of the symptoms listed in the IHS criteria for migraine with and without aura, which allowed us to obtain migraine diagnoses consistent with IHS criteria (Tables 1a and 1b). Individuals satisfying IHS MO criteria also reporting visual aura symptoms were classified as having MA.

Latent Class Analysis

Latent class analysis (e.g., Lazarsfeld & Henry, 1968; McCutcheon, 1987) has been described as a 'categorical analog of factor analysis' (Kendler et al., 1996). A latent class cluster model describes the relationship between a set of observed variables and an unobserved, latent variable. The categories of this latent variable are called latent classes, or clusters. Given class membership, the observed variables are assumed to be independent. The parameters estimated in a latent class model are: (1) the prevalence of each class and (2) the probability, given class membership, that an individual will endorse a certain item. This results in a characteristic pattern of symptom endorsement for each of the classes. Each individual's most likely class membership is estimated based on his/her pattern of item endorsement. If the classes identified represent qualitatively different subtypes, we expect to find different patterns of symptom endorsement for different

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classes (i.e., symptom 1 might be more prevalent in class *x*, while symptom 2 might be more prevalent in class *y*). However, if there is one underlying continuous trait, classes will only differ by symptom severity (i.e., in class *y* all items are endorsed more frequently than in class *x;* Neuman et al., 1999). Because LCA is a model-based approach, it allows us to estimate the correct number of classes based on model fit and parsimony (e.g., Yeung et al., 2001). LCA can thus help us identify different classes of migraine patients within a sample, and give us an indication of whether these classes reflect separate migraine types with different etiologies, or merely different degrees of severity on the same dimension.

Latent class cluster models were tested using the Latent Gold 2.0 package (Statistical Innovations, Inc). The models utilized eight migraine symptom variables, each with three levels. For LCA of combined male and female data, sex was included as a covariate, to allow for differences in prevalence between males and females. Subjects who screened negative for the question: 'Do you ever experience headache attacks, for instance migraine?' were assigned a value of 0 for each symptom; subjects who screened positive were assigned a value of 1 if they did not have the symptom, and a value of 2 if they did. Latent Gold allows users to include cases with missing data on dependent variables. Under this option, data are assumed to be missing at random (Vermunt & Magidson, 2000). When running Latent Gold, up to 10,000 iterations of the EM algorithm were allowed, and the estimation algorithm was restarted 500 times with different starting values to ensure global maximum likelihood estimates were obtained. The requested output included the classification details for each individual, the endorsement probabilities for each item within each class and the bivariate residuals for each pair of variables, which indicate residual correlations between symptoms that are not explained by the latent class model. Model fits were compared using the Bayes Information Criterion (BIC; Schwarz, 1978), a measure of model fit that takes both sample size and model complexity into account. If the BIC of a more complex model fails to decrease, the simpler model (having the lower BIC) will be selected.

Genetic Analysis

The statistical program PRELIS 2.53 (Jöreskog & Sörbom, 1999) was used to test the fit of a multiple threshold model to the class membership data derived from the latent class analysis. A multiple threshold model assumes that the ordinal data are an imprecise measurement of an underlying normal distribution of liability (Neale & Cardon, 1992). The thresholds (expressed as *z* values) are the values that discriminate between categories. The area under the curve between thresholds thus represents the proportion of people in that category. Polychoric correlations for the twins were calculated using PRELIS, for each zygosity separately. A χ^2 goodness-of-fit test was used to assess the fit of the threshold model. A good fit of a multiple threshold model to the data would support the hypothesis that the categories reflect degrees of severity on a single dimension. Ninety-five per cent confidence intervals (CI) for the polychoric correlations were estimated in Mx 1.54 (Neale et al., 2003). Mx was also used for genetic model fitting. We first tested whether thresholds were equal in first- and second-born twins and in monozygotic (MZ) and dizygotic (DZ) twins. Using structural equation modeling, the variance of a trait can be decomposed into an additive genetic component (A), a shared environmental (C) or nonadditive genetic (D) component, and a nonshared environmental component (E). Since the use of data from twins reared together does not allow us to estimate C and D simultaneously, separate ACE and ADE models were tested and compared. The significance of the variance components A, C and D was assessed by testing whether dropping them from the model resulted in a deterioration of fit. Model fit can be assessed using the –2 log likelihood (–2LL), which is χ^2 distributed. Nested models were compared using likelihood ratio tests (Δ–2LL), a significant increase in –2LL indicating a deterioration of model fit. Genetic models are also typically compared using the Akaike Information Criterion (AIC), a goodness-of-fit measure based on model fit and parsimony (AIC = –2LL minus two times the degrees of freedom). A lower AIC indicates a better model fit.

Results

Latent Class Analysis

Of the total sample of 10,144 subjects, 2951 (29%) screened positive for the question: 'Do you ever experience headache attacks, for instance migraine?' Seven hundred and seventy-three (26%) of these were males, and 2178 (74%) were females. Within the 2951 individuals screening positive, 2579 reported having headaches at least several times a year, 1593 participants had headaches lasting between 4 and 72 hours, and 1526 participants reported that their headache had a pulsating quality. Moderate or severe pain intensity was reported by 2639 individuals, and 1911 individuals reported aggravation of the headache by physical activity. Nausea or vomiting during a headache attack was reported by 1264 participants; photo- or phonophobia was reported by 1787 participants; and finally, 902 participants reported having visual aura symptoms during a headache attack (partial loss of vision, seeing flashes of light or zig-zag patterns). The prevalence of each symptom in males and females is listed in Table 2.

Latent class analysis was performed for the combined male and female data, followed by separate analyses for males and females. The latent classes identified were very similar across sex, suggesting that there were no qualitative sex differences in migraine symptoms (Figure 1). Three- and four-class models provided a similar fit to the data when parsimony was

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Table 2

Symptom Prevalence and LCA Classification by Sex

	Females (*N* = 5905)		Males (*N* = 4239)	
	N	%	*N*	%
Screening question	2178	36.9%	773	18.2%
≥ 5 episodes (A1)	1921	32.5%	658	15.5%
4–72h (B)	1219	20.6%	374	8.8%
Pulsating (C2)	1129	19.1%	397	9.4%
Moderate / severe (C3a)	2002	33.9%	637	15.0%
Aggravation (C4)	1476	25.0%	435	10.3%
Nausea and/or vomiting (D1)	1045	17.7%	219	5.2%
Photo- and/or phonophobia (D2)	1414	23.9%	373	8.8%
Aura	707	12.0%	195	4.6%
Class 0	3730	63.2%	3469	81.8%
Class 1	120	2.0%	202	4.8%
Class 2	730	12.4%	333	7.9%
Class 3	1325	22.4%	235	5.5%

taken into account (producing BIC values of –608,726.55 and –608,725.83, respectively). However, unlike the three-class model, the four-class model produced no nominally significant ($p < .05$) bivariate residuals, thus indicating it provides a better explanation for the observed symptom correlations. For the four-class model, the combined analysis resulted in a more parsimonious fit (BIC = –608,726) than the separate analyses for males (BIC = –225,357) and females (BIC = –337,972), which sum to a comparatively larger BIC value of –563,329. Two- and five-class models provided a worse fit to the data, with substantially higher BIC values (–607,558 for a two-class model and –608,635 for a five-class model).

The four classes derived from the most parsimonious model may be described as follows (Figure 1). Class 0 (not shown) describes subjects who screened negative and/or reported no migraine symptoms. Class 1 consists of subjects who have a mild form of non-migrainous headache, usually with moderate or severe pain intensity. These subjects typically do not have any of the other symptoms (i.e., the endorsement probabilities, which represent the proportion of individuals in each class presenting with each symptom, are less than 50%). Class 2 describes a moderately severe type of migrainous headache, typically without aura. It generally lasts 4 to 72 hours, is mostly pulsating, characterized by moderate or severe pain intensity, and aggravated by physical activity. Participants in class 2 usually do not have any of the neurological or aura symptoms (with endorsement probabilities of 18%, 34% and 6% for nausea/vomiting, photophobia/ phonophobia and aura, respectively). Finally, class 3 describes a severe type of migraine, which typically includes all IHS migraine symptoms. However, although the endorsement frequency for 'aura' is higher for class 3 than for any of the other classes, it is still only 49%. Interestingly, the endorsement frequency for 'aura' is higher in class 1 than in class 2, suggesting that there is a group of patients who have relatively mild headaches without neurological symptoms, but who experience visual aura symptoms.

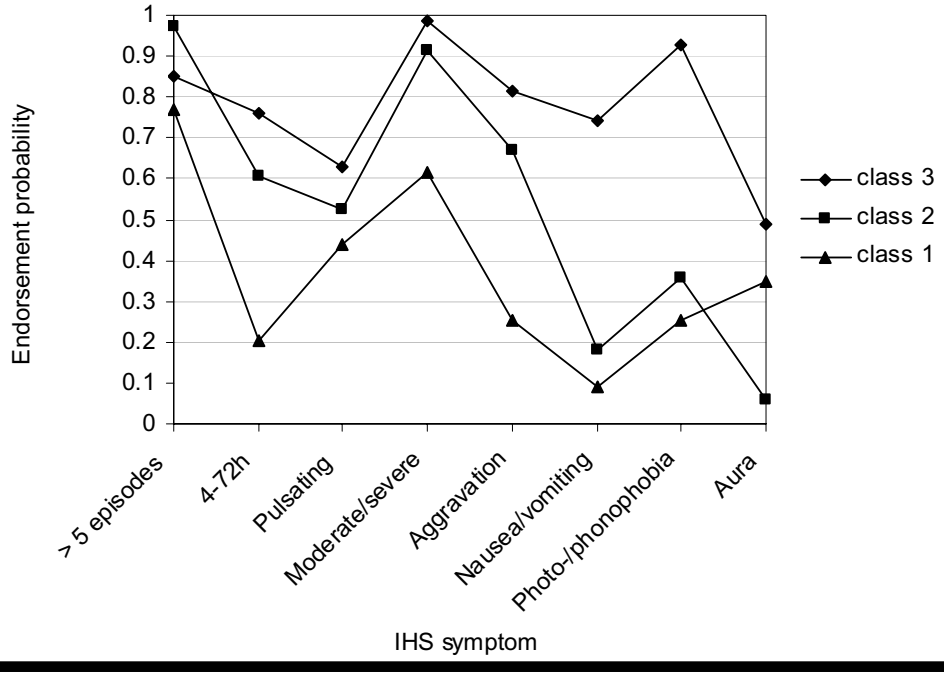

Figure 1

Symptom prevalence within each latent class.
All endorsement probabilities in class 0 were zero (not shown).

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Table 3

Polychoric Correlations (*r*) and Variance Components for 4- and 2-Group LCA and IHS Classifications, and for Screening Question

Classification	*r*	95% CI	A (95% CI)	C (95% CI)	E (95% CI)	A (95% CI)	D (95% CI)	E (95% CI)
LCA 4-group								
MZ	.52	(.42–.60)	.50	.00	.50	.25	.27	.48
DZ	.19	(.03–.34)	(.27–.59)	(.00–.20)	(.41–.59)	(.00–.58)	(.00–.60)	(.40–.58)
IHS 4-group								
MZ	.49	(.40–.57)	.49	.00	.51	.43	.06	.51
DZ	.23	(.08–.37)	(.19–.57)	(.00–.27)	(.43–.60)	(.00–.60)	(.00–.56)	(.43–.59)
LCA 2-group								
MZ	.53	(.42–.62)	.51	.00	.49	.22	.31	.47
DZ	.19	(.00–.37)	(.23–.61)	(.00–.25)	(.39–.59)	(.00–.60)	(.00–.62)	(.38–.58)
IHS 2-group								
MZ	.46	(.29–.60)	.33	.13	.54	.47	.00	.53
DZ	.29	(.04–.52)	(.00–.60)	(.00–.51)	(.40–.71)	(.00–.60)	(.00–.58)	(.40–.69)
SQ								
MZ	.53	(.42–.62)	.52	.00	.48	.28	.25	.47
DZ	.20	(.02–.38)	(.22–.61)	(.00–.26)	(.39–.58)	(.00–.61)	(.00–.62)	(.38–.58)

Note: Full ACE and ADE models and confidence intervals are shown. A = additive genetic factors; C = shared environmental factors; D = nonadditive genetic factors; E = nonshared environmental factors; SQ = screening question.

Of the 5905 women, 3730 (63.2%) were estimated to be in class 0, 120 (2.0%) in class 1, 730 (12.4%) in class 2 and 1325 (22.4%) in class 3. Of the 4239 men, 3469 (81.8%) were estimated to be in class 0, 202 (4.8%) in class 1, 333 (7.9%) in class 2 and 235 (5.5%) in class 3 (Table 2). Although combining the data of males and females resulted in the most parsimonious fit and the LCA symptom profiles were similar across sex, separate analysis of males and females indicated that within the latent classes the prevalence of some migraine symptoms differed for males and females. After a correction for 32 comparisons, a number of symptoms showed significant ($p \leq .05$) sex differences within classes. In class 1 more males (24%, $N = 52$) than females (2%, $N = 3$) had attacks lasting 4 to 72h. Headache accompanied by nausea was more common in females (19%, $N = 28$) than in males (4%, $N = 8$), as was headache with photo- or phonophobia (females 39%, $N = 59$; males 16%, $N = 34$). Females also had a higher prevalence of visual aura symptoms (61%, $N = 93$) than men (25%, $N = 55$). In class 2, more males (47%, $N = 148$) than females (28 %, $N = 205$) had photo- or phonophobia during headache, and more females (8%, $N = 60$) than males (1%, $N = 4$) had visual aura symptoms. In class 3 more females (87%, $N = 633$) than males (74%, $N = 235$) had had at least five episodes of headache or migraine, and headache lasting 4 to 72 hours was also more prevalent in females (78%, $N = 570$) than in males (64%, $N = 204$).

Heritability

Our next step was to perform genetic analyses on the LCA classification data for the twins. We obtained LCA classifications for 637 MZ and 291 DZ female twin pairs. Data for the males were available for only 236 MZ and 100 DZ pairs. As a result, we observed only two male–male DZ pairs where both twins screened positive. Consequently, we restricted our genetic analyses to the female population.

Polychoric twin correlations and 95% confidence intervals (95% CI) for the LCA classification are shown in table 3. A χ^2 goodness-of-fit test for a multiple threshold model was performed on the twin correlations for the MZ and DZ twins separately (data not shown). None of these tests reached the nominal significance level of 5%, indicating that a multiple threshold model provides a good fit to the data. Thresholds were equal across zygosity and for first- and second-born twins. In the best fitting model the thresholds were estimated at .32, .44 and .85.

Results of testing an ACE model on the LCA four-class scheme indicated substantial influence of genetic factors, but no evidence for shared environmental influences. In an AE model, additive genetic factors explained 50% (95% CI = 41–59) of the variance. In an ADE model, the contribution of additive genetic effects was estimated at 25%, while nonadditive genetic effects explained 27% of the variance (Table 3). Although the 95% CI for both the A and D components included zero, dropping both of them from the model resulted in a significant deterioration in fit (Δ–2LL = 95.441, 2*df*, $p < .001$).

The four-group IHS classification produced very similar polychoric twin correlations to the four-group LCA classification, resulting in similar overall heritabilities under the ACE model of .49 (95% CI = .19–.57) and 0.50 (95% CI = .27–.59), respectively. This indicates that use of the LCA classification does not lead to a loss of genetic information, compared

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Table 4

Cross-Tabulation of LCA and IHS Diagnoses for Female Twins ($N = 2446$)

	IHS SQ–	IHS SQ+	IHS SQ+, MO	IHS SQ+, MA
LCA Class 0 (SQ–)	1530	0	0	0
LCA Class 1	0	108	0	0
LCA Class 2	0	279	45	0
LCA Class 3	0	222	140	122

Note: SQ+ = screening positive; SQ– = screening negative; MO = migraine without aura, based on IHS criteria; MA = migraine with aura, based on IHS criteria.

to the IHS classification. Interestingly, the contribution of nonadditive effects was substantially lower for the IHS classification.

The four-group LCA and IHS classifications were then compared to clinically relevant two-group classifications (affected vs. unaffected). Table 3 shows results for the two-group LCA classification (treating class 0 and 1 as unaffected and class 2 and 3 as affected) and the two-group IHS classification (migraine vs. no migraine). The two-group LCA classification produces results very similar to the four-class scheme, whereas use of the two-group IHS classification resulted in a decrease in both the magnitude and precision (as reflected in the wider confidence intervals) of the heritability estimates compared to the four-group IHS scheme. This suggests a poorer correspondence between genetic risk and IHS groupings compared to the LCA groupings. Furthermore, as can be seen in Table 4, a substantial number (62%) of the individuals classified as LCA class 2 or 3, do not satisfy the criteria for IHS migraine.

Finally, we analyzed the heritability of the screening question alone. This two-group classification produced polychoric correlations and heritability estimates very similar to those of the other classifications, suggesting that the screening question is a very important determining factor for the genetic analyses performed on the more detailed symptom data and subsequent endpoint diagnoses.

Discussion

Analogous to the results of Nyholt et al. (2004) utilizing Australian migraine data, latent class analysis of Dutch migraine data suggests the existence of four classes based on IHS migraine criteria: a subgroup of individuals who screened negative for the question 'Do you ever experience headache attacks, for instance migraine?' and/or reported no IHS symptoms (class 0), a subgroup of participants who had a mild form of nonmigrainous headache (class 1), a subgroup with a moderately severe type of migrainous headache, typically without neurological symptoms or aura (class 2), and a subgroup with a severe type of migraine, typically including all IHS migraine symptoms, and in approximately 50% of the cases, aura symptoms. These results do not support the MO and MA subtypes as being etiologically distinct. Although the frequency of aura is very low in class 2 and highest in class 3, more than 50% of patients in class 3 do not report aura symptoms. Our data suggest that it is the severity, number and combination of symptoms (in particular the presence of neurological symptoms) that distinguishes between classes, rather than the simple presence of aura symptoms.

The heritability of four-class LCA migraine in female twins was estimated at 50%. Nonshared environment explained the remaining 50% of variance, and no evidence was found for shared environmental influences. This estimate remained relatively stable across a variety of classifications, utilizing both LCA and IHS-based diagnosis. However, using a two-group IHS classification (migraine vs. no migraine) resulted in a decrease of the heritability estimate (33%), suggesting a poorer correspondence between genetic risk and IHS groupings, compared to LCA groupings. A similar decrease in heritability was observed by Nyholt et al. (2004).

Overall, results are similar for the Dutch and Australian populations. However, there are some interesting differences. Table 5 lists the positive screening rates, and the prevalence of individual symptoms and endpoint diagnoses for the Dutch and Australian twin samples. In the Dutch study, individuals were screened for potential migraine using the question: 'Do you ever experience headache attacks, for instance migraine?' This resulted in 37% of females and 19% of males screening positive. The screening question used in the Australian study was 'Have you ever had migraine or recurrent attacks of headaches?', resulting in 52% of females and 32% of males screening positive. The number of participants diagnosed as having LCA or IHS migraine is also lower in the Dutch population, probably as a consequence of the lower number of participants screening positive.

Interestingly, a relatively low prevalence of aura and pulsating headache was found in the Dutch population, whereas the number of individuals reporting at least five headache episodes was relatively high. These discrepancies may possibly be explained by differences in ascertainment.

In the Australian study, aura symptoms were described as 'visual problems such as blurring, showers of light, blind spots or double vision', whereas in the Dutch questionnaire they were described as 'partial loss of vision, seeing flashes of light or (zigzag) patterns'. This difference in the definition of visual aura symptoms might be responsible for the lower reported prevalence of visual aura in the Dutch population.

Furthermore, in the Australian study the participants were asked how many attacks of headache they had had in their lifetime. In the Dutch study, participants were asked how often their attacks occurred (i.e., the number of attacks per week/month/year).

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Table 5

Comparison of Dutch and Australian Twin Samples: Number of Individuals Positive for Screening Question, Symptom or Endpoint Diagnosis, Percentage of Total, and Percentage of Those Screening Positive

	Dutch sample (*N* = 4448*)						Australian sample (*N* = 6212)					
	Females			Males			Females			Males		
	N	% of *N*	% of *N*s	*N*	% of *N*	% of *N*s	*N*	% of *N*	% of *N*s	*N*	% of *N*	% of *N*s
Total (*N*)	3031			1417			3438			2774		
Screening question (*N*s)	1124	37.1%	—	270	19.1%	—	1777	51.7%		888	32.0%	
A1 ≥ 5 episodes	996	32.9%	88.6%	232	16.4%	85.9%	1294	37.6%	72.8%	689	24.8%	77.6%
B 4–72h	607	20.0%	54.0%	128	9.0%	47.4%	1053	30.6%	59.3%	444	16.0%	50.0%
C2 Pulsating	579	19.1%	51.5%	151	10.7%	55.9%	1465	42.6%	82.4%	708	25.5%	79.7%
C3a Moderate/severe	1026	33.9%	91.3%	226	15.9%	83.7%	1576	45.8%	88.7%	708	25.5%	79.7%
C4 Aggravation	776	25.6%	69.0%	164	11.6%	60.7%	—	—	—	—	—	—
D1 Nausea and/or vomiting	507	16.7%	45.1%	79	5.6%	29.3%	980	28.5%	55.1%	344	12.4%	38.7%
D2 Photo- and/or phonophobia	718	23.7%	63.9%	120	8.5%	44.4%	1013	29.5%	57.0%	356	12.8%	40.1%
Aura	359	11.8%	31.9%	53	3.7%	19.6%	924	26.9%	52.0%	394	14.2%	44.4%
MO	380	12.5%	33.8%	53	3.7%	19.6%	703	20.4%	39.6%	250	9.0%	28.2%
MA[1]	146	4.8%	13.0%	15	1.1%	5.6%	432	12.6%	24.3%	166	6.0%	18.7%
IHS-migraine	380	12.5%	33.8%	53	3.7%	19.6%	703	20.4%	39.6%	250	9.0%	28.2%
CL2	397	13.1%	35.3%	127	9.0%	47.0%	781	22.7%	44.0%	486	17.5%	54.7%
CL3	600	19.8%	53.4%	69	4.9%	25.6%	793	23.1%	44.6%	198	7.1%	22.3%
LCA-migraine	997	32.9%	88.7%	196	13.8%	72.6%	1574	45.8%	88.6%	684	24.7%	77.0%

Note: *N*t = total; *N*s = number of individuals screening positive. *Does not include the twins' parents, siblings and partners.

[1] = MA individuals also fulfill criteria for MO.

Individuals who had attacks at least several times a year were assumed to fulfil the criterion of having had at least five attacks in a lifetime. However, since this would be expected to be a conservative cut-off, the high prevalence resulting from this procedure is unexpected.

The question concerning pulsating headache was phrased similarly in both studies. The Dutch participants were asked if their headache was usually 'throbbing or stabbing', whereas the Australian participants were asked if their headaches were usually experienced as 'throbbing, pulsating or pounding — like being stabbed with a sharp knife'. A possible explanation for the lower prevalence of this symptom in the Dutch population is that in the Dutch study a questionnaire was used, whereas in the Australian study, data were obtained through a telephone interview. Indeed, we expect data collected via telephone interview to be more accurate, as it allows subjects to ask the interviewer for a clarification of a question or description. Thus, this difference in data collection could also explain other prevalence differences between the two studies.

Finally, for the Dutch cohort, no data were collected on whether headache was unilateral or whether it prohibited daily activities. The Australian study, on the other hand, did not include data on aggravation of headache by physical activity, whereas the present study did. However, considering the high correlations between the reporting of these individual migraine symptoms (Nyholt et al., 2004), these differences are unlikely to significantly alter the LCA results.

Despite differences in the data collection procedures used, the populations examined, and the age range of the subjects, both latent class and genetic analyses yielded similar results for the present (Dutch) and Australian study. Our findings support earlier evidence that migraine is influenced by genetic factors (with some indication for nonadditive effects) and nonshared environment, but not by shared environment. In addition, our LCA results further support the hypothesis that MO and MA are not etiologically distinct disorders.

Furthermore, our results indicate that in questionnaire-based migraine research, it is of vital importance to use an appropriate and sensitive screening question. The heritability of the screening question was very similar to the heritability of two-group LCA- and IHS-migraine, suggesting that the screening question is an important determining factor for the results of genetic analyses performed on the more detailed symptom data and endpoint diagnoses. A closer look at the contingency tables for the screening question, two-group LCA-migraine and two-group IHS-migraine (Table 6) shows that the large number of concordant unaffected pairs is likely to significantly influence the tetrachoric/polychoric correlations on which the genetic analyses are based.

A related issue is the influence of the screening question on findings regarding migraine prevalence.

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Table 6

Concordance Rates for Two-Group LCA-Migraine, Two-Group IHS-Migraine and the Screening Question in Female Twins

Screening question					IHS-migraine					LCA-migraine				
	MZ		DZ			MZ		DZ			MZ		DZ	
	–	+	–	+		–	+	–	+		–	+	–	+
–	308	90	120	61	–	505	50	223	29	–	339	87	136	60
+	103	136	59	51	+	56	26	29	10	+	97	114	55	40

Note: + = affected; — = unaffected; MZ = monozygotic twin pairs; DZ = dizygotic twin pairs.

The different prevalence found in the Dutch and Australian populations (Table 5) may in part reflect real differences in migraine prevalence between Australia and the Netherlands, caused by cultural, environmental or genetic factors. For example, one would expect MA individuals would similarly answer yes to either the Australian and Dutch screening questions. However, even within the Dutch population large differences in positive screening rate are found between two questionnaires that used different screening questions. An earlier questionnaire-based Dutch twin study, conducted in 1991, used the screening question: 'Do you ever suffer from headaches?' This resulted in a positive screening rate of 66%, whereas in the present study (which used the question, 'Do you ever experience headache attacks, for instance migraine?') only 29% screened positive. Using a screening question that excludes too many potential migrainous headache sufferers will lead to unnecessary loss of valuable symptom data and bring into question the validity of an unaffected status.

Finally, analogous to the results of Nyholt et al. (2004), the LCA-based approach resulted in a larger number of migrainous headache patients being classified, and a higher heritability, compared to the IHS-based approach. This suggests that the use of an LCA-based approach has the potential to increase power in genetic studies of migraine. Indeed, two recent genome-wide linkage scans (Lea et al., 2005; Nyholt et al., 2005) found significantly increased evidence for linkage utilizing an LCA-based migrainous headache definition compared to migraine diagnosed according to strict IHS criteria.

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