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Latent Class and Genetic Analysis Does Not Support Migraine With Aura and Migraine Without Aura as Separate Entities

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Latent class and genetic analyses were used to identify subgroups of migraine sufferers in a community sample of 6,265 Australian twins (55% female) aged 25–36 who had completed an interview based on International Headache Society (IHS) criteria. Consistent with prevalence rates from other population-based studies, 703 (20%) female and 250 (9%) male twins satisfied the IHS criteria for migraine without aura (MO), and of these, 432 (13%) female and 166 (6%) male twins satisfied the criteria for migraine with aura (MA) as indicated by visual symptoms. Latent class analysis (LCA) of IHS symptoms identified three major symptomatic classes, representing 1) a mild form of recurrent nonmigrainous headache, 2) a moderately severe form of migraine, typically *without* visual aura symptoms (although 40% of individuals in this class were positive for aura), and 3) a severe form of migraine typically *with* visual aura symptoms (although 24% of individuals were negative for aura). Using the LCA classification, many more individuals were considered affected to some degree than when using IHS criteria (35% vs. 13%). Furthermore, genetic model fitting indicated a greater genetic contribution to migraine using the LCA classification (heritability, h^2=0.40; 95% CI, 0.29–0.46) compared with the IHS classification (h^2=0.36; 95% CI, 0.22–0.42). Exploratory latent class modeling, fitting up to 10 classes, did not identify classes corresponding to either the IHS MO or MA classification. Our data indicate the existence of a continuum of severity, with MA more severe but not etiologically distinct from MO. In searching for predisposing genes, we should therefore expect to find some genes that may underlie all major recurrent headache subtypes, with modifying genetic or environmental factors that may lead to differential expression of the liability for migraine.

Key words: headache continuum; etiology; twins; heritability

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INTRODUCTION

The classification of migraine has been impeded by the lack of pathognomonic markers for migraine, co-occurrence of migraine subtypes as well as migraine and tension-type headache within the same individual, and the lack of validity of inclusion criteria and thresholds for distinguishing disorder from nondisorder and the boundaries between migraine and other headache subtypes [Merikangas et al., 1993, 1994]. The nature of the association between two major subtypes of migraine defined by the International Headache Society (IHS) criteria [Headache Classification Committee of the International Headache Society, 1988], i.e., *migraine without aura* (MO) and *migraine with aura* (MA), was examined in several community, family, and twin studies. Russell and Olesen [1995] found that compared with the general population, the first-degree relatives of probands with MO had 1.86 (95% CI, 1.56–2.16) times the risk of MO and 1.44 (95% CI, 1.03–1.85) times the risk of MA, while the first-degree relatives of probands with MA had 3.79 (95% CI, 3.21–4.38) times the risk of MA and no increased risk of MO (1.02; 95% CI, 0.77–1.26). They concluded that MO and MA may have different etiologies and therefore different modes of inheritance. However, this conclusion is difficult to reconcile with the high

frequency of co-occurrence of MO and MA in the same individual and within the same families, as well as the tendency for age-dependent expression of variable symptoms within the migraine spectrum. A recent study found that 42% of active migraineurs with aura also reported having migraine attacks with no aura [Launer et al., 1999]. Moreover, MO and MA frequently coexist within the same family; a Headache Center in Italy reported that 45% of MA families also contained MO cases [Mochi et al., 1993], and the co-occurrence of the rare but severe familial hemiplegic form of migraine (FHM) and migraine with and without aura was reported in the same families [Joutel et al., 1994; Ophoff et al., 1994]. Furthermore, changes in the presenting symptoms of migraine attacks from hemiplegic to severe headache with or without aura in later life [Ophoff et al., 1994], as well as the development of aura among subjects with MO and the converse [Kallela et al., 2001; Ophoff et al., 1994], suggest common underlying genetic and/or environmental susceptibility factors.

To investigate the validity of implicitly separating migraine individuals with aura from individuals without aura, as with the IHS diagnostic criteria, the present study utilizes latent class analysis (LCA) (a statistical method for finding subtypes of cases (latent classes) from multivariate categorical data [Rindskopf and Rindskopf, 1986]) to investigate the presence and composition of migraine symptom groupings in a large young adult twin sample.

Relative risk and genetic analysis of the resulting empirically derived LCA subtypes of migraine and recurrent headache, and MO/MA classifications using conventional IHS criteria, were used to examine whether these diagnoses reflect different levels of severity on a single dimension, or distinct etiologies. This study takes advantage of the greater power of the twin study, compared to family study designs, for detecting a common underlying genetic susceptibility.

METHODS

SAMPLE AND ASSESSMENT

Migraine symptom data were obtained in the course of an extensive semistructured telephone interview, designed to assess physical, psychological, and social manifestations of alcoholism and related disorders, conducted with 3,462 (55.3%) female and 2,803 (44.7%) male twins born 1964–1971 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 were conducted between 1996–2000, and the mean age at interview for both males and females was 30.5 ± 2.5 years (range, 25–36). Participants answering ''yes'' to ever having ''migraine or recurrent attacks of headache'' (screening positive) then answered a number of questions developed by an experienced migraine researcher (K.R.M.) based on

TABLE IA. Diagnostic criteria for migraine without aura, excerpted from International Headache Society (IHS) classification of headache [Headache Classification Committee of the International Headache Society, 1988]

1.1	Migraine without aura
	A. At least five attacks fulfilling B–D
	B. Headache lasting 4–72 hr (untreated or unsuccessfully treated)
	C. Headache has at least two of the following characteristics:
	1. Unilateral location
	2. Pulsating quality
	3. Moderate or severe intensity (inhibits or prohibits daily activities)
	4. Aggravation by walking stairs or similar routine physical activity
	D. During headache at least one of the following:
	1. Nausea and/or vomiting
	2. Photophobia and phonophobia

TABLE IB. Ten symptom response variables based on IHS diagnostic criteria

Code	Abbreviation	Description
A	>5 episodes	At least five migraine/episodes of headache during lifetime
B	4–72 hr	Average typical migraine/headache lasts between 4–72 h
C1	Unilateral	Headache usually occurs on one side of head
C2	Pulsating	Usual headache pain is described as throbbing, pulsating, or pounding
C3a	Moderate/ severe	Pain associated with headache described as moderate or severe
C3b	Prohibitive	Headaches inhibit or prohibit daily activities
D1	Nausea/ vomiting	Associated and recurrent attacks of nausea, vomiting, or diarrhea
D2a	Photophobia	Photophobia (enhanced sensitivity to light)
D2b	Phonophobia	Phonophobia (enhanced sensitivity to noise)
Aura	Aura	Associated and recurrent visual problems such as blurring, showers of light, blind spots, or double vision

International Headache Society (IHS) diagnostic criteria [Headache Classification Committee of the International Headache Society, 1988] (Table Ia), relating to their headaches (see http://genepi.qimr.edu.au/general/daleN/MigraineQuestionairre.pdf). The interview yielded diagnostic criteria for migraine without aura and with aura, using visual prodromal symptoms as an index of migraine with aura.

To summarize the clustering of migraine symptoms, odds ratios (OR) with 95% confidence intervals (CI) between symptoms were computed after combining individuals answering ''no'' to ever having ''migraine or recurrent attacks of headache'' (i.e., screening negative) with individuals screening positive but negative for symptom, using SPSS 10.0.5 (SPSS, Inc). Relative risks (RR) for individual zygosity groups were calculated relative to individuals screening negative, with 95% CIs computed from the ratio of two independent binomial probabilities [Miettinen and Nurminen, 1985]. For the total like-sexed MZ and DZ data, Mantel-Haenszel weighted relative risks and 95% confidence intervals were obtained using Epi-Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA).

LATENT CLASS ANALYSIS

Latent class analysis is a statistical technique (best characterized as a ''categorical analog'' of factor analysis) that models associations (covariation) between observed variables that imperfectly measure a nonobservable (latent) variable [McCutcheon, 1987]. By assessing the symptom profile of individual patients, LCA produces mutually exclusive groups (classes) of *patients* based on their patterns of symptoms.

Latent class cluster models were fitted to 10 trichotomous symptom response variables (i.e., negative to screening question, screening positive but negative for symptom, and screening positive and positive for symptom) (Table Ib), based on IHS diagnostic criteria (Table Ia) using the Latent GOLD 2.0 package (Statistical Innovations, Inc.). For each Latent GOLD run, up to 10,000 iterations of the EM algorithm were allowed, using a convergence criterion of 1×10^{-10}. Each LCA solution was restarted at least 100 times with new starting values to find the maximum likelihood estimates for the parameters.

Classification information was requested for latent class cluster models. For each symptom profile, the classification output contains the associated probabilities of belonging to each cluster. Also, bivariate residuals were obtained, which identify correlations between symptom pairs that are not adequately explained by the model.

Although estimates of class membership and symptom endorsement probabilities ignored the twin structure of the data, which may result in the likelihood-ratio chi-square (χ^2) test overestimating the significance of adding an extra class, as in traditional factor analysis [Neale and Cardon, 1992], estimates of symptom endorsement and class membership probabilities will remain statistically unbiased [Madden et al., 1997]. Subsequently, and as recommended for large sample sizes, the comparative fits of LCA models were assessed by evaluating the Bayes information criterion (BIC) [Schwarz, 1978] where, if the BIC of a more complex model fails to decrease, the simpler model (having the lower BIC) will be selected.

GENETIC ANALYSIS

A major goal of the genetic analysis was to test the multiple threshold model [Kendler, 1993; Reich et al., 1972], which posits that different syndromes reflect different levels of severity on a single dimension, rather than distinct etiologies. These thresholds can be regarded as the z-value of the normal distribution that divides the area under the curve in such a way that it gives the right proportion of individuals in each (diagnostic) group, thus reflecting the prevalence of each group [Neale and Cardon, 1992]. For each of the five zygosity groups, the fit of a multiple threshold model was tested by calculating the polychoric correlation for the IHS and LCA classifications, using PRELIS 2.30 [Jöreskog and Sörbom, 1999] or POLYCORR (http://ourworld.compuserve.com/homepages/jsuebersax/xpc.htm). The polychoric correlation, also termed the ''correlation of liability,'' assumes that underlying the observed polychotomous distribution of affection status, there exists a continuous, normally distributed latent liability [Kendler, 1993]. That is, the polychoric correlation is an estimate of the correlation between two latent variables, where each latent variable is assumed to have a bivariate normal distribution. A χ^2 goodness-of-fit test is used to test whether the multiple threshold model provides a good fit to the observed data (i.e., compares the observed frequencies to those predicted by the model). Calculation of 95% CIs

for polychoric correlations, the comparison of threshold values within twin pairs and across zygosity groups, and genetic model fitting by maximum likelihood univariate analysis of raw data were performed using the Mx program [Neale et al., 1999].

Genetic model fitting used structural equation modeling (SEM) to estimate parameters of a model that included additive genetic effects (A), nonadditive genetic effects (i.e., dominance or epistasis) (D) or shared family environment (C), and random or unique environment (E) [Neale and Cardon, 1992]. Sex-specific genetic (or shared environmental) effects (i.e., effects not shared by males and females), and then sex-differences in the magnitudes of genetic and environmental effects (sex-limitation), were tested for. These sex-specific and sex-limitation models were then compared to a model which did not allow for sex effects. For each model, we obtained: a χ^2 goodness-of-fit statistic (-2LL) and calculated the Akaike information criterion (AIC) [Akaike, 1987], which indexes the fit of the model and its parsimony. Nested models were compared using the likelihood ratio (χ^2 difference) test ($\Delta-2$LL), a significant χ^2 value indicating a deterioration in model fit, and by examining the change in AIC (better-fitting models produce lower values of AIC). Likelihood-based 95% confidence intervals for estimates of genetic and environmental parameters were then computed using Mx [Neale et al., 1999].

RESULTS

IHS MIGRAINE AND SYMPTOM PREVALENCE

Of the total sample of 3,438 females responding to the question ''Have you ever had migraine or recurrent attacks of headaches?'', 1,777 (51.7%) screened positive, while 888 (32.0%) of 2,774 males screened positive. A total of 703 (20.4%) females and 250 (9.0%) males satisfied the IHS criteria for MO. Four hundred and thirty-two (12.6%) females and 166 (6.0%) males who satisfied the MO criteria also met our index of MA criteria by reporting a visual ''aura,'' described as recurrent attacks of visual problems such as blurring, showers of light, blind spots, or double vision associated with headaches.

Odds ratios for the associations between individual IHS migraine symptoms ranged in magnitude from 7.78 (C1 with Aura) to 140.32 (C3a with C3b), with all symptom-symptom combinations being statistically significant. This highlights the substantial interrelationships among IHS symptoms in migraine.

LATENT CLASS ANALYSIS

Although LCA models were initially fitted to the male and female data separately, when the male and female data were combined, with sex included in the model as a covariate to allow for the increased prevalence in females, the combined data set provided a more parsimonious fit (producing smaller BIC values) compared to the separate male and female analyses, suggesting that male and female migraine symptoms are quantitatively but not qualitatively different. For the combined data set, comparative fits of LCA models determined a four-class model to be the best solution, producing a minimum BIC value of -4164346 (three-class model, BIC$=-4164306$; five-class model, BIC$=-4164226$). Profile plots for the four-class solution in the male and female data set (Fig. 1) show the similarity in endorsement probabilities (the proportion of individuals in each class presenting with each symptom) across sex.

The four classes derived from the most parsimonious solution may be described as follows (Fig. 1). The first class, latent class 0 (CL0), consists principally of participants reported to have no symptoms (mean, 0.00). Latent class 1 (CL1) is ''minimally symptomatic,'' with a mean of 2.97 symptoms, representing a mild form of recurring (typically) pulsating headache, with endorsement frequency $>50\%$ only for symptoms ''A (>5 episodes)'' and ''C2 (pulsating).'' Class 2 (CL2), with a mean of 5.94 symptoms, represents a moderately severe form of migraine typically *without* ''aura,'' loading on all of the nine remaining MO symptoms except ''C1 (unilateral)'' and ''D1 (nausea/vomiting).'' Class 3 (CL3), with a mean of 8.72 symptoms, represents a form of severe migraine typically *with* ''aura,'' loading on all IHS symptoms.

In total, 1,661 (48.3%) females and 1,886 (68.0%) males were estimated to be in CL0, 203 (5.9%) females and 204 (7.4%) males in CL1, 781 (22.7%) females and 486 (17.5%) males in CL2, and 793 (23.1%) females and 198 (7.1%) males in CL3. Although the most parsimonious LCA model combined female and male data, the prevalence of some migraine-associated neurological symptoms differed between females and males for the

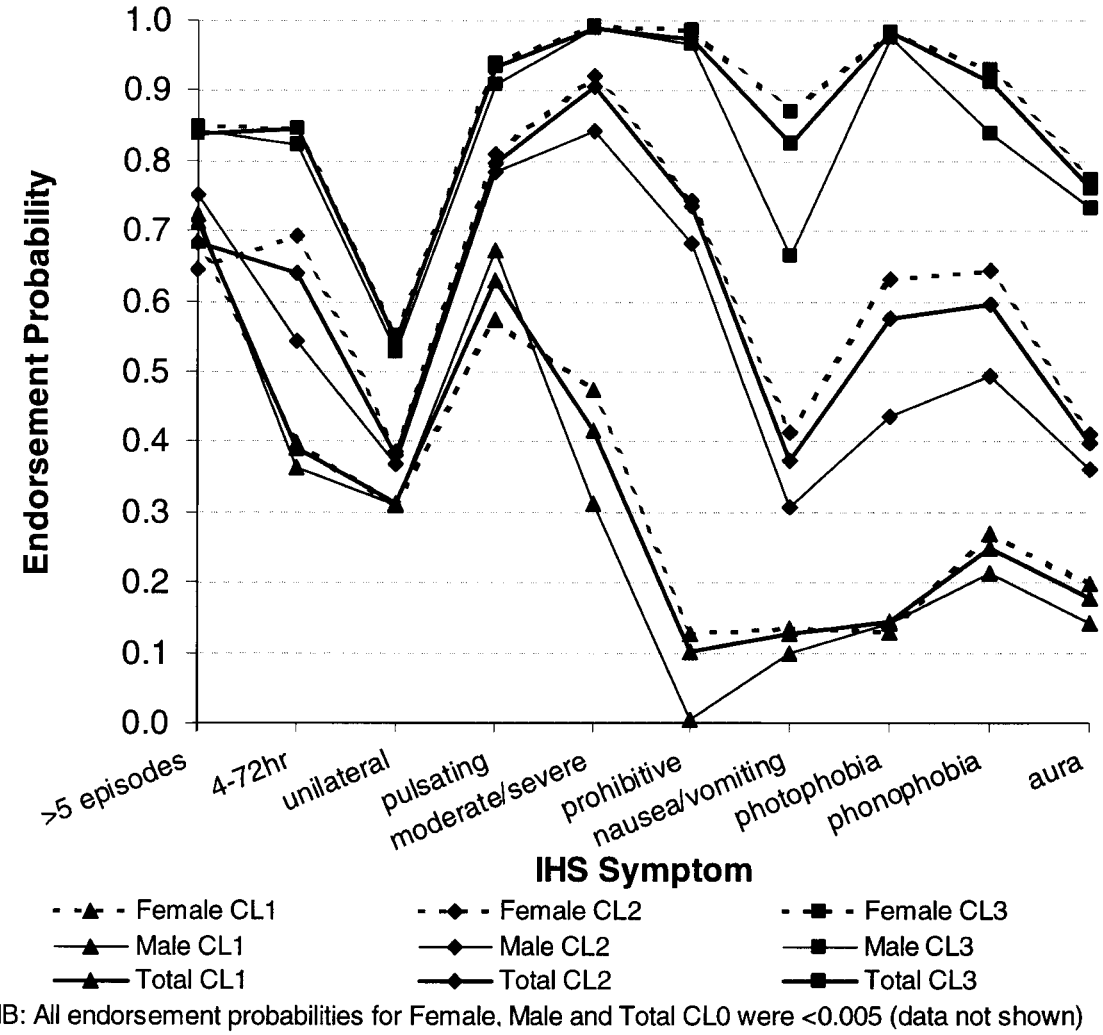

Fig. 1. Profile plot for three symptomatic classes under four-class model. Endorsement probabilities indicate proportion of individuals in each class presenting with each symptom.

latent classes. After correcting for 40 comparisons, significant differences ($P<0.05$) were observed in CL1, with more females compared to males positive for symptom "C3b (prohibitive)" (12.7% vs. 0.5%). In CL2, significantly more females reported symptom "D2a (photophobia)" (63.3% vs. 43.8%) and "D2b (phonophobia)" (64.4% vs. 49.6%). In CL3, significantly more females were positive for symptom "D1 (nausea/vomiting)" (87.2% vs. 66.7%). Summing across all four classes, significantly more females were positive for symptom "D1 (nausea/vomiting)" (35.4% vs. 26.8%) and "D2b (phonophobia)" (46.1% vs. 38.7%).

A nominally significant ($P<0.05$) bivariate residual was obtained between symptoms "A (>5 episodes)-sex," indicating that, controlling for class membership, females were more likely to have had at least five migraine/episodes of headache. Also, a nominally significant residual correlation between "C3a (moderate/severe)-C2 (pulsating)" indicates that if the pain associated with headache is described as throbbing, pulsating, or pounding, the headache pain is more likely to be described as moderate or severe. The residual correlation between "D2a (photophobia)-D2b (phonophobia)" suggests that enhanced light and sound sensitivity co-occur. However, no bivariate residuals remain significant after correcting for 55 correlations.

Finally, to ensure we had not biased LCA results away from traditional IHS categories by underestimating the significance of adding an extra class, exploratory latent class modeling fitting up to 10 classes was performed. However, these

analyses still did not identify classes corresponding to either the IHS MO or MA classification.

COMPARISON OF LCA WITH IHS DIAGNOSES

Comparing the four-category IHS-based (''no'' IHS-ve, ''yes'' IHS-ve, MO, and MA) diagnosis to latent class (CL0, CL1, CL2, and CL3) membership (Table II), all individuals satisfying IHS criteria (i.e., MO or MA) are also considered affected in the latent class analysis (i.e., CL2 or CL3). However, the most striking result shown in Table II concerns the large number of individuals considered affected under the LCA scheme compared with the IHS scheme. Specifically, 1,305 (21.0%) individuals (25.3% female, 15.7% male) not satisfying IHS MO or MA criteria are considered affected under the LCA classification (i.e., CL2 or CL3).

RELATIVE RISK AND GENETIC ANALYSES

Polychoric correlations (with 95% CIs) for the four-group IHS and LCA classifications are shown in Table III. None of the multiple-threshold model goodness-of-fit tests (one for each zygosity group; see Table IV for an example) were significant at the 5% level (data not shown). Therefore, these results support the validity of the liability threshold model for both the IHS and LCA classification schemes, and indicate that the migrainous latent class 2 (CL2) and class 3 (CL3), and IHS MO and MA, can be conceptualized as different levels of severity on a single dimension of liability (Fig. 2), and are therefore not etiologically distinct from each other.

Although the female and male thresholds were consistent within sex across zygosity groups, there were significant differences ($P < 0.001$) between female and male thresholds; females had considerably lower thresholds (i.e., higher prevalences) than males (Fig. 2). The best-fitting threshold model constrained female thresholds to be equal across zygosity and produced female thresholds of −0.04, 0.83, and 1.15 for IHS ''yes''-ve, MO, and MA, and −0.04, 0.11, and 0.74 for LCA CL1, CL2, and CL3, respectively. Analogously, constraining male thresholds to be equal across zygosity produced male thresholds of 0.47, 1.34, and 1.56 for IHS ''yes''-ve, MO, and MA, and 0.47, 0.69, and 1.47 for CL1, CL2, and CL3, respectively.

Since the relative risks (RR) from Russell and Olesen [1995] provide the best empirical evidence supporting MO and MA as distinct entities, we only present cross-tabulations of twin pairs diagnosed according to IHS criteria (Table V). However, RRs and 95% confidence intervals (CI) in same-sex female and male MZ and DZ twin pairs, of a twin being in a certain category given the category of the cotwin, using both IHS and LCA schemes, are presented in Table VI. Relative risks and 95% CIs in total same-sex MZ and DZ, and opposite-sex twin pairs, are shown in Table VII.

Except for the increased risk of CL2 in male MZ cotwins of male probands with CL2 (RR=2.71; 95% CI, 1.79–4.04), compared to female MZ cotwins of female probands with CL2 (RR=1.33; 95% CI, 0.95–1.84) (Breslow-Day chi-square test for homogeneity of odds ratios; $\chi^2_1 = 6.53$, P=0.01), there were no significant gender differences in RRs within same-sex twin pairs. However, male cotwins of male probands consistently had higher RRs than female cotwins of female probands for both the IHS and LCA classifications.

The RRs for same-sex female and male MZ twin pairs provide compelling evidence for a shared etiology between MO and MA. Specifically, the increased risk of MA for cotwins of probands with MO in females (RR=2.76; 95% CI, 1.31–5.58) and

TABLE II. IHS vs. LCA Diagnoses: Cross tabulation[a]

	IHS diagnosis			
LCA diagnosis	''No'' IHS-ve	''Yes'' IHS-ve	MO	MA
Class 0	3,547			
Class 1		407		
Class 2		1,010	182	75
Class 3		295	173	523

[a]''No''/''Yes''=response to screening item, ''have you ever had migraine or recurrent attacks of headache?'' Consequently, individuals who answered ''no'' gave no symptom data.

TABLE III. Polychoric correlations for liability to migraine, using IHS and LCA classification[a]

Model	Zygosity	rPC	95% CI
IHS (4-group)	MZ F-F	0.35	0.26–0.43
	MZ M-M	0.41	0.29–0.52
	DZ F-F	0.16	0.05–0.26
	DZ M-M	0.22	0.20–0.36
	DZ F-M	0.12	0.02–0.22
LCA (4-group)	MZ F-F	0.42	0.34–0.50
	MZ M-M	0.42	0.30–0.52
	DZ F-F	0.23	0.12–0.33
	DZ M-M	0.21	0.06–0.35
	DZ F-M	0.09	0.00–0.19

[a]Polychoric correlations (r_{PC}) and 95% Cls were calculated using Mx with thresholds set equal within sex, regardless of zygosity.

TABLE IV. Multiple threshold model goodness-of-fit test for MZ female-female twin pairs[a]

		Twin 2				
Number of pairs	Twin1	"No" IHS-ve	"Yes" IHS-ve	MO	MA	Total
Observed	"No" IHS-ve	200	92	11	20	323
	"Yes" IHS-ve	93	77	16	41	227
	MO	22	17	8	7	54
	MA	21	33	10	18	82
	Total	336	219	45	86	686
Predicted under threshold model	"No" IHS-ve	196.94	90.65	14.66	21.53	323.78
	"Yes" IHS-ve	98.94	79.45	16.75	31.32	226.46
	MO	18.51	19.64	4.79	10.44	53.38
	MA	21.79	29.78	8.44	22.37	82.38
	Total	336.18	219.52	44.64	84.66	686

[a]With four category variables, chi-square (χ^2) test has 8 degrees of freedom (df), obtained as difference of 15 parameters in unrestricted multinomial model for 16 cells (observed frequencies) and 3+3+1=7 parameters in normality (threshold) model (3 thresholds for each variable, and 1 polychoric correlation). Latter model is nested within former. Also, twin1 and twin2 thresholds may be set equal resulting in an 11-df test. Goodness-of-fit test for above data produces Pearson χ^2 value of 10.36; P=0.24 (8 df); P=0.50 (11 df). Hence, multiple threshold model fits data well, supporting a single liability dimension (SLD) model for migraine, with MO not etiologically distinct from MA.

males (RR=5.22; 95% CI, 1.50–15.47), and the increased risk of MO in cotwins of probands with MA in females (RR=2.02; 95% CI, 0.92–4.33) and males (RR=4.66; 95% CI, 1.20–16.97), do *not* support MO and MA as distinct entities. Combining female and male MZ data further support a shared etiology between MO and MA, producing an RR of 3.11 (95% CI, 1.64–5.92) for MA in cotwins of probands with MO, and an RR of 2.35 (95% CI, 1.18–4.69) for MO in cotwins of probands with MA.

Using the IHS classification, for the total like-sex DZ population (applicable to first-degree relatives in the general population), the RR of MO and MA was 1.53 (95% CI, 0.61–3.83) and 1.42 (95% CI, 0.68–3.00), respectively, in cotwins of probands with MO. Meanwhile, in cotwins of probands with MA, the RR of MO and MA was 1.46 (95% CI, 0.65–3.27) and 1.77 (95% CI, 1.00–3.13), respectively. The RR of being diagnosed with either MO or MA was 1.59 (95% CI, 1.09–2.32) in cotwins of probands with MO/MA.

Using the LCA classification, for the total like-sex DZ population, the RR of CL2 and CL3 was 1.40 (95% CI, 1.03–1.90) and 1.22 (95% CI, 0.82–1.82), respectively, in cotwins of probands with CL2. Meanwhile, in cotwins of probands with CL3, the RR of CL2 and CL3 was 1.01 (95% CI, 0.69–1.46) and 2.18 (95% CI, 1.57–3.03), respectively. The RR of being diagnosed with either CL2 or CL3 was 1.42 (95% CI, 1.20–1.69) in cotwins of probands with CL2/CL3.

The observed difference between female and male thresholds/prevalence (Fig. 2) is reflected in the different pattern of relative risks for the IHS and LCA diagnoses in opposite-sex twin pairs (Table VII). That is, sisters of males with MO have an increased chance (RR=1.50; 95% CI, 0.58–3.40) of having MA, yet sisters of males with MA have a greater chance (RR=1.80; 95% CI, 0.74–4.13) of having MO. Meanwhile, sisters of males in CL2 have an increased chance (RR=1.39; 95% CI, 0.99–1.92) of being in CL3, and sisters of males in CL3 do *not* have an increased chance (RR=0.81; 95% CI, 0.40–1.55) of being in CL2. In other words, unlike the IHS classification, the LCA scheme seems to account for the increase in liability to migraine in females compared to males. Hence, consistent with the threshold model, sisters of male migraine sufferers tend to have more severe symptoms than their brothers.

Although an RR>1 signifies familial aggregation, it does not provide unequivocal evidence for a genetic contribution, because environmental influences may also produce familial aggregation. However, the consistently higher RRs within same-sex MZ twin pairs compared to DZ pairs *do* suggest a genetic effect. The presence of a genetic contribution to migraine was further supported from the results of fitting genetic models to the twin data, using structural equation modeling.

Genetic model-fitting indicated no sex-specific genetic effects for either the IHS ($\chi^2_1 = 0.71$, P=0.40) or LCA ($\chi^2_1 = 2.47$, P=0.12) four-group classification. There was also no significant difference in the magnitude of heritability between the sexes for either the IHS ($\chi^2_2 = 1.71$,

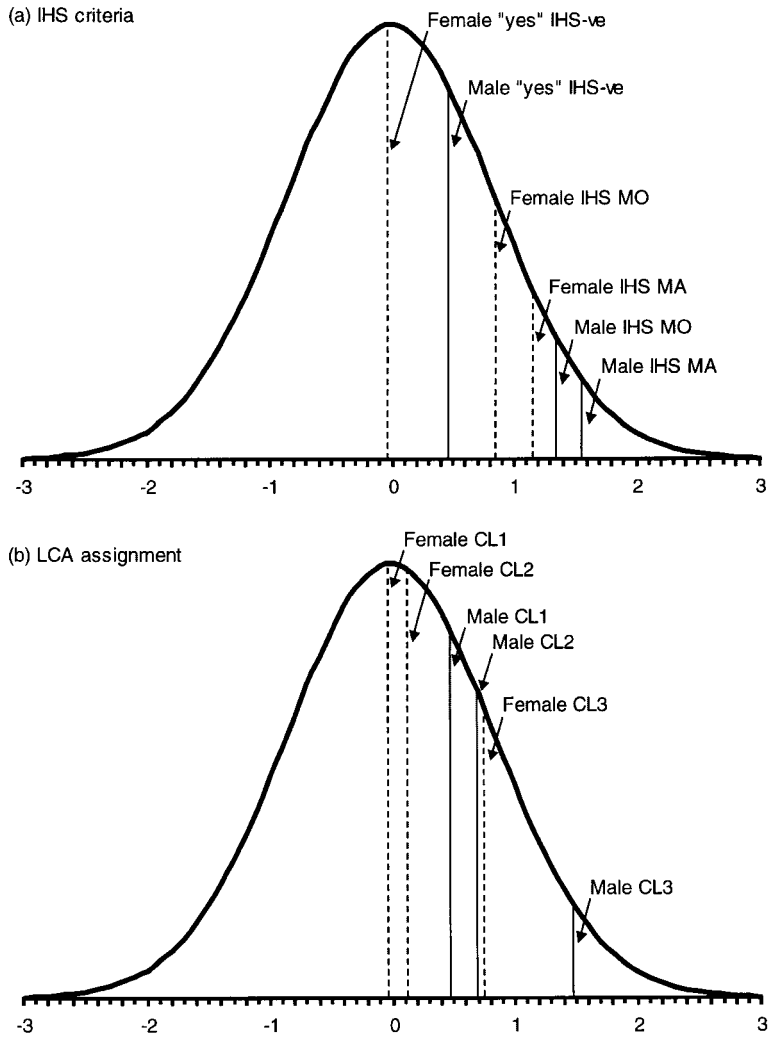

Fig. 2. Multiple threshold model for level of severity of migraine symptoms in men and women. Thresholds (vertical lines) can be regarded as z-values of normal distribution that divides area under the curve such that it gives correct proportion of individuals in each diagnostic group, thus reflecting prevalence of each group [Neale and Cardon, 1992].

P=0.42) or LCA ($\chi^2_2 = 2.52$, P=0.28) classification. For the IHS classification, additive genetic effects (A), shared family environment (C), and random or unique environment (E) were estimated to be 0.36 (95% CI, 0.22–0.42), 0.00 (95% CI, 0–0.10), and 0.64 (95% CI, 0.58–0.71), respectively. For the LCA classification, the corresponding components of variance were 0.40 (95% CI, 0.29–0.46), 0.00 (95% CI, 0–0.09), and 0.60 (95% CI, 0.54–0.66), respectively.

In support of the multiple threshold model, these values do not significantly change after grouping the individuals screening negative (CL0) with the latent class 1 (CL1) category, producing a heritability estimate of 0.43 (95% CI, 0.29–0.50). This strategy makes conceptual sense, as we would not expect individuals screening negative for "migraine or recurrent attacks of headache" to experience diagnostic criteria sufficient for inclusion in CL2/CL3. Moreover, the precision of the heritability estimate for the three-group LCA scheme remains similar to that for the four-group LCA scheme, suggesting no loss of genetic information.

In contrast, grouping individuals screening negative ("no" IHS-ve) with the "yes" IHS-ve category produced a heritability estimate of 0.31 (95% CI, 0–0.41) and a decrease in the precision of the heritability estimate (as reflected in the expanded CI) compared to the four-group IHS scheme. This suggests a poorer correspondence between genetic risk and IHS groupings.

TABLE V. Twin-Pair IHS diagnoses: Cross-tabulations[a]

		Cotwin (twin2)				
Zygosity group	Proband (twin1)	"No" IHS-ve	"Yes" IHS-ve	MO	MA	Total
MZ female-female	"No" IHS-ve	200.0	92.5	16.5	20.5	329.5
	"Yes" IHS-ve	92.5	77.0	16.5	37.0	223.0
	MO	16.5	16.5	8.0	8.5	49.5
	MA	20.5	37.0	8.5	18.0	84.0
MZ male-male	"No" IHS-ve	250.0	56.5	6.0	11.5	324.0
	"Yes" IHS-ve	56.5	35.0	4.0	9.0	104.5
	MO	6.0	4.0	1.0	2.5	13.5
	MA	11.5	9.0	2.5	6.0	29.0
DZ female-female	"No" IHS-ve	126.0	69.5	16.5	25.5	237.5
	"Yes" IHS-ve	69.5	47.0	18.0	23.5	158.0
	MO	16.5	18.0	4.0	7.0	45.5
	MA	25.5	23.5	7.0	11.0	67.0
DZ male-male	"No" IHS-ve	198.0	57.5	6.0	11.5	273.0
	"Yes" IHS-ve	57.5	33.0	1.5	6.0	98.0
	MO	6.0	1.5	1.0	0.5	9.0
	MA	11.5	6.0	0.5	3.0	21.0
DZ female-male	"No" IHS-ve	244.0	66.0	13.0	18.0	341.0
	"Yes" IHS-ve	127.0	39.0	6.0	10.0	182.0
	MO	29.0	12.0	1.0	5.0	47.0
	MA	50.0	18.0	4.0	10.0	82.0
DZ male-female	"No" IHS-ve	244.0	127.0	29.0	50.0	450.0
	"Yes" IHS-ve	66.0	39.0	12.0	18.0	135.0
	MO	13.0	6.0	1.0	4.0	24.0
	MA	18.0	10.0	5.0	10.0	43.0

[a]For same-sex twin pairs, tables were made symmetrical by averaging over using either twin1 or twin2 as proband. Relative risks (RR) (see Tables VI and VII) were calculated relative to twin1 answering "no" to ever having "migraine or recurrent attacks of headache" ("no" IHS-ve). For example, RR for MA-MA in MZ female-female twins=(18/84)/(20.5/329.5)=3.44.

Higher heritability was still observed for the latent class compared to the IHS scheme when a clinically relevant "unaffected-affected" dichotomy was used (i.e., grouping IHS "no"-ve with "yes"-ve, and MO with MA; and grouping LCA CL0 with CL1, and CL2 with CL3), with similar (two-group) heritability estimates of 0.33 (95% CI, 0.05–0.44) and 0.41 (95% CI, 0.23–0.49) for the IHS and LCA scheme, respectively.

DISCUSSION

Our primary goals were to 1) identify empirically derived subtypes of migraine and recurrent headache based on IHS symptom criteria and subtype overlap, based on the pattern of clustering of these symptoms using latent class analysis in an unselected community sample of twins; and 2) determine whether these empirically derived symptom groupings, and the IHS MO and MA classifications, reflect different levels of severity on a single dimension, or distinct etiologies.

PREVALENCE

There was a high lifetime prevalence of migraine symptoms, ranging from 18.0% for unilateral location to 36.8% for severity of pain associated with headache. The interrelationships among symptoms were quite complex and did not parallel clearly the subtypes defined by the IHS. The sex-specific lifetime prevalence rates of migraine without aura (i.e., female, 20.4%; and male, 9.0%) are similar to those reported in other large epidemiologic studies in Western populations [Stewart et al., 1992], including a recent Australian population-based questionnaire study (n=3,654) which found that 22% of women and 9.6% of men satisfied the IHS criteria for MO

TABLE VI. Relative risks (95% Cl) and number of proband-cotwin pairs [n] in same-sex twin pairs[a]

	Zygosity			
Proband-cotwin	MZ female-female RR (95% CI) [n]	MZ male-male RR (95% CI) [n]	DZ female-female RR (95% CI) [n]	DZ male-male RR (95% CI) [n]
IHS-ve-IHS-ve	1.23 (0.96–1.58) [77]	1.92 (1.33–2.73) [35]	1.02 (0.74–1.38) [47]	1.60 (1.11–2.37) [33]
IHS-ve-MO	1.48 (0.77–2.83) [16.5]	2.07 (0.63–6.67) [4]	1.64 (0.87–3.07) [18]	0.70 (0.14–3.41) [1.5]
IHS-ve-MA	2.67 (1.61–4.43) [37]	2.43 (1.06–5.48) [9]	1.39 (0.82–2.32) [23.5]	1.45 (0.57–3.64) [6]
MO-IHS-ve	1.19 (0.75–1.76) [16.5]	1.70 (0.68–3.41) [4]	1.35 (0.87–1.98) [18]	0.79 (0.19–2.44) [1.5]
MO-MO	3.23 (1.47–6.84) [8]	4.00 (0.64–21.73) [1]	1.27 (0.45–3.34) [4]	5.06 (0.81–25.67) [1]
MO-MA	2.76 (1.31–5.58) [8.5]	5.22 (1.50–15.47) [2.5]	1.43 (0.66–2.96) [7]	1.32 (0.13–9.96) [0.5]
MA-IHS-ve	1.57 (1.15–2.09) [37]	1.78 (0.95–3.02) [9]	1.20 (0.81–1.72) [23.5]	1.36 (0.64–2.51) [6.5]
MA-MO	2.02 (0.92–4.33) [8.5]	4.66 (1.20–16.97) [2.5]	1.50 (0.65–3.36) [7]	1.08 (0.11–10.01) [0.5]
MA-MA	3.44 (1.92–6.10) [18]	5.83 (2.34–13.67) [6]	1.53 (0.79–2.86) [11]	3.39 (1.05–9.87) [3]
IHS-ve-MO/MA	2.14 (1.46–3.13) [53.5]	2.30 (1.17–4.48) [13]	1.49 (1.02–2.16) [41.5]	1.19 (0.53–2.64) [7.5]
MO/MA-IHS-ve	1.43 (1.08–1.86) [53.5]	1.75 (1.03–2.82) [13]	1.26 (0.92–1.71) [41.5]	1.19 (0.59–2.15) [7.5]
MO/MA-MO/MA	2.87 (1.94–4.22) [43]	5.23 (2.67–9.85) [12]	1.46 (0.96–2.19) [29]	2.60 (1.03–6.07) [5]
CL1-CL1	1.94 (0.78–4.55) [5]	1.88 (0.60–5.39) [3]	1.39 (0.44–4.05) [3]	1.86 (0.75–4.30) [5]
CL1-CL2	1.21 (0.66–2.06) [10]	1.98 (0.98–3.68) [7.5]	0.85 (0.39–1.68) [6]	1.46 (0.69–2.84) [7]
CL1-CL3	0.88 (0.35–2.04) [4.5]	1.1 (0.24–4.58) [1.5]	1.21 (0.58–2.30) [7]	0.95 (0.25–3.38) [2]
CL2-CL1	0.98 (0.48–2.00) [10]	1.66 (0.74–3.65) [7.5]	0.76 (0.31–1.83) [6]	1.41 (0.63–3.05) [7]
CL2-CL2	1.33 (0.95–1.84) [43]	2.71 (1.79–4.04) [29]	1.28 (0.87–1.84) [33]	1.69 (0.98–2.82) [15]
CL2-CL3	1.97 (1.33–2.90) [39.5]	1.42 (0.56–3.50) [5.5]	1.20 (0.77–1.85) [25.5]	1.28 (0.50–3.19) [5]
CL3-CL1	0.45 (0.33–0.57) [4.5]	0.82 (0.18–3.41) [1.5]	0.86 (0.37–1.96) [7]	0.91 (0.24–3.13) [2]
CL3-CL2	1.24 (0.88–1.74) [39.5]	1.26 (0.55–2.65) [5.5]	0.95 (0.62–1.43) [25.5]	1.28 (0.54–2.74) [5]
CL3-CL3	3.60 (2.59–5.02) [71]	7.62 (3.85–14.51) [12]	2.09 (1.47–2.97) [46]	2.90 (1.15–6.79) [5]
CL1-CL2/CL3	1.09 (0.68–1.62) [14.5]	1.75 (0.93–2.98) [9]	1.01 (0.62–1.50) [13]	1.3 (0.69–2.27) [9]
CL2/CL3-CL1	0.72 (0.38–1.36) [14.5]	1.42 (0.66–3.00) [9]	0.81 (0.40–1.62) [13]	1.26 (0.60–2.58) [9]
CL2/CL3-CL2/CL3	1.85 (1.56–2.22) [193]	2.54 (1.85–3.45) [52]	1.36 (1.12–1.65) [130]	1.63 (1.11–2.36) [30]

[a][n] may not be a whole number, as RRs were obtained by averaging over using either twin1 or twin2 as proband; see Table V.

[Wang et al., 1997]. The 12.6% female and 6.0% male prevalence rates of the index of migraine with aura observed in our study are also similar to those previously reported [Rasmussen and Olesen, 1992; Russell et al., 1995].

ARE MO AND MA ETIOLOGICALLY DISTINCT ENTITIES?

Latent class analysis indicated that four classes best fit the data, ranging from asymptomatic (CL0) to severe migraine (CL3). Of particular note, although aura was predominantly found in CL3, 23.9% of CL3 individuals did not report aura, and 39.9% of CL2 individuals reported aura. Further exploratory latent class modeling, fitting up to 10 classes, did not identify classes corresponding to either the IHS MO or MA classification. Thus, our latent class analysis did not confirm the conventional distinction between *migraine without aura* and *migraine with aura* (interestingly, 69 individuals, all in CL3, had all symptoms, except ''aura''). Rather, the LCA classifications were determined by the severity and combination of symptoms.

Utilizing χ^2 goodness-of-fit tests to compare observed contingency tables to tables predicted under the multiple threshold model, we found that a multiple threshold model gave a good fit to the observed twin data, under both IHS and LCA classification schemes. Given that such contingency-table comparisons are known to be sensitive to even small deviations, these results strongly support the validity of the threshold model for both the IHS and LCA classification schemes, and indicate that the migrainous latent class 2 (CL2) and class 3 (CL3), and IHS MO and MA, can be conceptualized as different levels of severity on a single dimension of liability (Fig. 2), and are therefore not etiologically distinct from each other.

To further clarify, the multiple threshold model predicts that the distribution of liability can be approximated by a continuous, normally distributed trait that is determined by multiple genetic and environmental influences; individuals whose liability exceeds a certain threshold manifest the disorder, with more severely affected individuals assumed to have a higher liability than less severely affected individuals. In other words,

TABLE VII. RR (95% Cl) and number of proband-cotwin pairs [n] in total MZ, DZ, and opposite-sex twin pairs[a]

	Zygosity			
Proband-cotwin	Total MZ RR (95% CI) [n]	Total same-sex DZ RR (95% CI) [n]	DZ female-male RR (95% CI) [n]	DZ male-female RR (95% CI) [n]
IHS-ve-IHS-ve	1.42 (1.16–1.74) [112]	1.23 (0.97–1.55) [80]	1.11 (0.78–1.57) [39]	1.02 (0.75–1.37) [39]
IHS-ve-MO	1.59 (0.89–2.84) [20.5]	1.46 (0.81–2.64) [19.5]	0.86 (0.34–2.16) [6]	1.38 (0.73–2.58) [12]
IHS-ve-MA	2.61 (1.68–4.05) [46]	1.41 (0.89–2.22) [29.5]	1.04 (0.50–2.16) [10]	1.20 (0.72–1.96) [18]
MO-IHS-ve	1.27 (0.86–1.86) [20.5]	1.27 (0.86–1.90) [19.5]	1.32 (0.76–2.16) [12]	0.89 (0.42–1.63) [6]
MO-MO	3.31 (1.59–6.92) [9]	1.53 (0.61–3.83) [5]	0.56 (0.09–3.14) [1]	0.65 (0.11–3.28) [1]
MO-MA	3.11 (1.64–5.92) [11]	1.42 (0.68–3.00) [7.5]	2.02 (0.79–4.87) [5]	1.50 (0.58–3.40) [4]
MA-IHS-ve	1.61 (1.24–2.10) [46]	1.23 (0.88–1.73) [29.5]	1.13 (0.71–1.76) [18]	0.82 (0.46–1.37) [10]
MA-MO	2.35 (1.18–4.69) [11]	1.46 (0.65–3.27) [7.5]	1.28 (0.44–3.59) [4]	1.80 (0.74–4.13) [5]
MA-MA	3.89 (2.37–6.38) [24]	1.77 (1.00–3.13) [14]	2.31 (1.11–4.69) [10]	2.09 (1.12–3.66) [10]
IHS-ve-MO/MA	2.18 (1.56–3.04) [66.5]	1.43 (1.01–2.01) [49]	0.97 (0.55–1.70) [16]	1.27 (0.87–1.82) [30]
MO/MA-IHS-ve	1.50 (1.18–1.90) [66.5]	1.25 (0.94–1.66) [49]	1.20 (0.82–1.74) [30]	0.85 (0.53–1.29) [16]
MO/MA-MO/MA	3.25 (2.32–4.55) [55]	1.59 (1.09–2.32) [34]	1.71 (1.01–2.85) [20]	1.70 (1.10–2.52) [20]
CL1-CL1	1.92 (0.93–3.95) [8]	1.65 (0.80–3.39) [8]	2.35 (0.95–5.39) [5]	2.68 (1.07–6.29) [5]
CL1-CL2	1.46 (0.94–2.25) [17.5]	1.10 (0.65–1.85) [13]	1.42 (0.69–2.69) [7]	1.00 (0.51–1.80) [8]
CL1-CL3	0.93 (0.42–2.06) [6]	1.14 (0.60–2.16) [9]	0.00 [0]	0.59 (0.25–1.27) [5]
CL2-CL1	1.22 (0.71–2.10) [17.5]	1.04 (0.57–1.91) [13]	0.95 (0.44–2.02) [8]	1.26 (0.56–2.80) [7]
CL2-CL2	1.71 (1.33–2.21) [72]	1.40 (1.03–1.90) [48]	1.33 (0.86–2.01) [26]	1.09 (0.74–1.59) [26]
CL2-CL3	1.87 (1.30–2.68) [45]	1.22 (0.82–1.82) [30.5]	0.76 (0.34–1.67) [7]	1.39 (0.99–1.92) [35]
CL3-CL1	0.52 (0.23–1.22) [6]	0.88 (0.42–1.81) [9]	0.53 (0.21–1.31) [5]	0.00 [0]
CL3-CL2	1.25 (0.91–1.71) [45]	1.01 (0.69–1.46) [30.5]	1.59 (1.08–2.32) [35]	0.81 (0.40–1.55) [7]
CL3-CL3	3.99 (2.96–5.38) [83]	2.18 (1.57–3.03) [51]	1.16 (0.60–2.22) [12]	1.32 (0.77–2.11) [12]
CL1-CL2/CL3	1.28 (0.90–1.81) [23.5]	1.11 (0.78–1.60) [22]	0.96 (0.47–1.79) [7]	0.79 (0.48–1.19) [13]
CL2/CL3-CL1	0.94 (0.58–1.54) [23.5]	0.99 (0.59–1.65) [22]	0.72 (0.38–1.39) [13]	0.93 (0.41–2.07) [7]
CL2/CL3-CL2/CL3	2.01 (1.72–2.34) [245]	1.42 (1.20–1.69) [160]	1.31 (1.00–1.72) [80]	1.20 (0.99–1.45) [80]

[a][n] may not be a whole number, as RRs were obtained by averaging over using either twin1 or twin2 as proband; see Table V.

our data do *not* support the existence of a distinct aura or MA etiologic factor per se, but instead suggest the existence of multiple causative factors (possibly interacting genes with numerous environmental triggers) contributing to migraine susceptibility and severity, with increased risk of aura associated with increased severity.

Besides supporting the concept of a migraine continuum, these results provide valuable insight into the co-occurrence of migraine symptoms (Fig. 1). The observed symptom correlations provide clues regarding associations between and among symptoms that could be informative for the classification system. In particular, IHS group D selection criteria (photophobia, phonophobia, and nausea and/or vomiting) are more likely to occur with aura. This suggests that *migraine without aura* could perhaps be based on IHS symptoms A–C alone. Nonetheless, as clearly shown in Figure 1, whether using the IHS or LCA classification, the migraine classes have many symptoms in common. To further dissect the co-occurrence of these symptoms, work is currently underway utilizing multivariate genetic analyses to investigate whether the same or different genetic factors influence the occurrence and co-occurrence of individual migraine symptoms.

Interestingly, a recent study by Kallela et al. [2001], which attempted to separate individuals with MO, individuals with MA, and individuals suffering from both kinds of attacks (MO+MA), suggested the possibility of "a continuum with pure MA at the neural and pure MO at the headache end of the spectrum, and MO+MA lying in between the two." Although our current data do not allow differentiation between MO, MA, and MO+MA, our latent class and genetic analysis results do not support this hypothesis. Moreover, our data suggest that there may be another repetitive and typically pulsating headache subtype (CL1) that may map onto tension-type headache that falls on the same continuum as subtypes of MA/MO and CL2/CL3.

Finally, our finding of elevated relative risks for both MO and MA, regardless of whether the proband had MO or MA, replicates the results of Stewart et al. [1997] and contradicts the findings of Russell and Olesen [1995]. Given that the findings of Russell and Olesen [1995] are typically referenced in support of MO and MA being

etiologically distinct, our relative risk results provide particularly important and compelling evidence against MO and MA being distinct entities.

GENETIC INFLUENCE AND SEX-LIMITATION

Latent class analysis identified many more individuals as affected (i.e., CL2 or CL3) than did the IHS criteria. In total, 1,305 individuals not satisfying IHS MO or MA criteria were considered affected under the LCA classification. Moreover, 240 DZ twin pairs are concordant *affected* under the LCA scheme, compared with only 54 pairs using the IHS criteria. While 66% more individuals were classified in the severe LCA CL3 category compared with the severe IHS MA category, the relative risk (RR) for CL3 (RR=2.18; 95% CI, 1.57–3.03; n=51 pairs) in cotwins of DZ probands with CL3 was larger than the risk for MA (RR=1.77; 95% CI, 1.00–3.13; n=14 pairs) in cotwins of DZ probands with MA. This suggests that the LCA classification may capture more of the genetic contribution to migraine susceptibility than the comparable IHS category. Genetic model-fitting confirmed that more of the genetic variation in liability to migraine is captured using the LCA classification (four-group h^2=0.40) compared to the IHS classification (h^2=0.36); however, this difference was not very large.

Although we failed to find evidence for shared environmental effects, the power to detect such effects is known to be low when additive genetic effects are also present; therefore, it is possible that shared environmental effects (C) accounting for as much as 11% of variance are also present, but undetectable [Martin et al., 1978]. Also, although not statistically significant from expectation under a model ignoring sex-specific genetic effects, the reduced polychoric correlations for opposite-sex twin pairs (Table III) suggest that genetic sex-specific effects (i.e., effects expressed in one sex but not the other) might be detected in larger samples. We also did not find significant gender differences in the magnitude of genetic influences (sex-limitation) on risk of migraine. Nevertheless, given the known difference in prevalence and risk of migraine in females compared to males, our results indicate that sibling-pair genetic linkage studies should focus on sex-specific associations, excluding affected sister-unaffected brother pairs, whereas all other concordant affected and discordant same-sex and opposite-sex pairs should prove useful.

With the absence of sex-specific genetic effects, environmental factors (e.g., sex hormones) conceivably play a pivotal role in the increased vulnerability to migraine among women and reduced polychoric correlations for opposite-sex twin pairs. A number of findings provide support for a relationship between hormonal variations and migraine. These include evidence indicating that many women with migraine report worsening of their headaches around the time of menstruation [Edelson, 1985; Greene, 1967; Lance and Anthony, 1966]. In fact, menstrual migraine (i.e., 90% of attacks of MO occur in association with menstruation) is experienced by 24–25% of females with MO [Rasmussen, 1993; Russell et al., 1996]. Indeed, although not directly assessed, since our sample is aged 25–36 (mean, 30.5 ± 2.5), menstrual migraine is likely to represent a major component of female migraine in our sample.

Further support for a relationship between hormonal variations and migraine includes reports of the oral contraceptive pill precipitating a first attack of migraine, or worsening or improving the frequency and severity of existing attacks [Dalton, 1976; Kudrow, 1975; Larson-Cohn and Lundberg, 1970; Mears and Grant, 1962; Phillips, 1968; Ryan, 1978; Whitty et al., 1966]. In addition, many women with migraine have fewer attacks during pregnancy [Callaghann, 1968; Nattero, 1982; Somerville, 1972], although the condition may be exacerbated in the postpartum period [Stein, 1981]. Also, some women have fewer attacks or cease to have attacks after menopause [Martin et al., 1971].

Finally, the prevalence of migraine has generally been shown to be equal in boys and girls before puberty, but to increase at a greater rate in girls as adolescence approaches, so that by adulthood, the female to male ratio has increased to 3:1 [Lance, 1982; Welch et al., 1984]. It was postulated that this age-dependent increase in female prevalence could be the result of hormonal fluctuations triggering a primary predisposition [Dennerstein et al., 1978; Greene, 1969].

STRENGTHS AND LIMITATIONS

This is the largest single population-based study of familial aggregation of migraine symptoms utilizing IHS criteria. Although migraine diagnosis is preferably performed via direct

communication between physician and patient (which is impractical for 6,265 subjects spread throughout Australia), our study obtained similar symptom information and level of detail as other migraine studies, which were repeatedly found to be a valid diagnostic tool for migraine [Gervil et al., 1998; Rasmussen et al., 1991; Russell et al., 1995]. Furthermore, our combined use of questionnaire and interview increases the reliability of symptom data. For example, using a similar screening approach, Stewart et al. [1997] obtained a 92.6% positive predictive value of their telephone interview diagnosis compared with their clinical examination. Moreover, our study design minimizes the effect of different symptom interpretations by clinicians.

The power to detect independent genetic effects on risk of aura would be somewhat modest for the sample sizes available in the present study, unless the heritability of aura was substantial. To address this issue, we conducted power calculations based on asymptotic theory, using noncentral chi-square distribution. We generated expected four-way twin-pair contingency tables under the strong hypothesis of independent genetic determinants of liability to migraine, and of liability to experience aura in those who developed migraine, using prevalence estimates corresponding to those observed in women, and assuming 36% heritability of the first ''migraine'' liability dimension, and either 36%, 50%, or 64% heritability of the conditional ''aura'' liability dimension. Power to reject the hypothesis of a single underlying normal liability distribution at alpha=0.05 was 42%, 79%, and 98%, respectively. Since univariate genetic analysis produced a heritability estimate of 0.47 (95% CI, 0.07–0.60) for visual aura in our data (not shown), we estimate this sample to have 75% power to truly detect a difference in showing the multiple threshold model to fail.

CONCLUSIONS

Consistent with previous studies, our results indicate a moderate (to high) heritability of migraine [Gervil et al., 1999; Honkasalo et al., 1994; Larsson et al., 1995; Ulrich et al., 1999], and at least a 50% greater risk of migraine in first-degree relatives of migraine probands than in relatives of unaffected probands [Russell and Olesen, 1995; Stewart et al., 1997]. In searching for genes predisposing individuals to migraine, genetic studies should endeavor to reduce the degree of genetic heterogeneity by reducing the clinical (diagnostic) heterogeneity. To this end, given the higher diagnostic specificity, higher heritability, and potential for larger sample sizes, we favor our LCA approach over the IHS classification. We should note, however, that both classification schemes are possible using the symptoms of our IHS-based interview, and that sensible researchers will analyze their data using both classification schemes. We predict that our scheme will be no less sensitive than that currently favored, and may prove more illuminating.

Future research to examine the extent to which a continuum conceptualization provides a better characterization than current dichotomous classification of migraine symptoms, using validity indicators such as longitudinal stability, familial aggregation, and biologic markers, is strongly indicated by these findings.

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