

# Depression, migraine with aura and migraine without aura: their familiarity and interrelatedness

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## Cephalalgia

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Migraine is frequently comorbid with depression. There appear to be common aetiological factors for both disorders, but the aetiology of migraine within depressed patients, in particular the significance of aura, has been little studied. A large sample of concordantly depressed sibling pairs [the Depression-Network (DeNT) sample] was assessed as having migraine with aura (MA), migraine without aura (MoA), probable migraine or no migraine according to International Headache Society guidelines. Correlations between siblings' migraine status were used to assess the nature of familial liability to migraine. A multiple threshold isocorrelational model fit best, in which different syndromes are conceptualized as different severities of one underlying dimension rather than as having separate aetiologies. Thus, MA and MoA were found to be different forms of the same disorder, with MA occupying the more extreme end of the spectrum of liability. Implications for our understanding of the relationship between migraine and depression are discussed. □ *Migraine disorders, depression, genetics, comorbidity*

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### Contributions of authors

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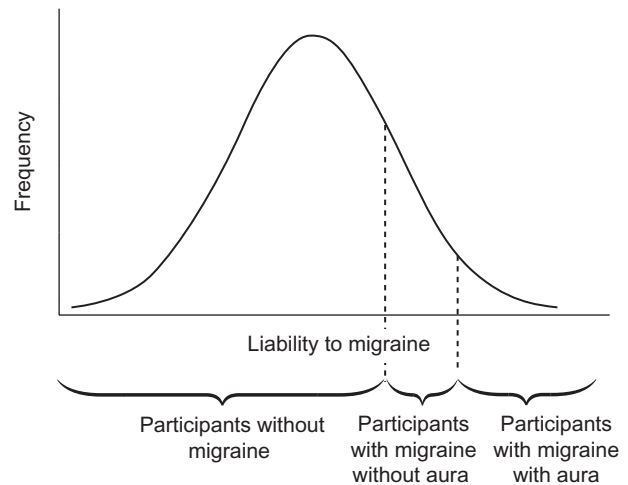
H.A.B. performed the model fitting analysis and wrote the first draft. Z.S. conceived the migraine component of the DeNT study, designed the migraine questionnaire and tested its reliability. A.E.F. and P.McG. were overall study Principal Investigators (PIs), designed the DeNT study and contributed to revising the draft; A.E.F. trained and supervised the interviewers. P.McG. wrote the TETCOR program and supervised the statistical analyses. S.B., L.M. and J.P. obtained the funding from Glaxo Wellcome, recruited site PIs and oversaw the quality of data collection, handling and analysis. The following authors were the individual site PIs in charge of all aspects of subject recruitment and data quality locally: OM Aarhus site, N.C., L.J. and I.J. (joint) Birmingham site, M.R. and W.M. (joint) Bonn site, A.K. and M.J.O. (joint) Cardiff site, M.G. Dublin site, M.P. Lausanne site, A.E.F. and P.McG. (joint) London site and J.R. St Louis site. All authors have read and approved the contents of the final manuscript.

## Introduction

The International Headache Society (IHS) operational criteria for migraine were first published in 1988 (1) and subsequently revised in 2004 (2). The criteria identify two main categories of migraine: migraine with aura (MA) and migraine without aura (MoA). The diagnostic criteria for MA are essentially those for MoA plus particular aura symptoms, therefore the aetiological mechanisms leading to MoA may also contribute to MA. However, the aura phenomenon may be the result of a different set of pathophysiological mechanisms. Family studies have shown generally higher than population incidence of migraine in relatives of migraineurs of the same type (i.e. higher incidence of MoA in the first-degree relatives of probands with MoA) (3, 4). Similarly, twin concordance of the same subtype of migraine is higher in monozygotic than in dizygotic twins (5, 6), suggesting that the familial similarity is due to genetic rather than family environmental reasons. Some studies have examined the cross-prevalence of MA and MoA (e.g. MA in probands and MoA in relatives)—such cross-prevalences could suggest an overlap in the aetiology of the two disorders. Two twin studies have supported this overlap in aetiology (7, 8), but earlier twin and family studies did not (4, 9). An overlap in aetiology is also suggested by the frequent co-occurrence of MA and MoA within the same individual (10) and within the same family (11).

It has been suggested that the two syndromes are variants of one underlying liability continuum, with MA representing the more severe end of the continuum, rather than two distinct aetiologies. Two previous twin studies (7, 8) found that a multiple threshold model fit the data well (with MA being represented by a more extreme threshold than that for MoA) (Fig. 1). This implies that MA is a more extreme form of the migraine phenotype, although it does not necessarily imply that impairment is more extreme in MA compared with MoA. However, these studies focused on cases as defined using latent class analysis, rather than the stricter and well-defined criteria of the IHS.

The current study aimed to replicate and further characterize this finding of a single underlying phenotype, using the stricter IHS criteria for migraine, and examining migraine in the context of depression. A sample of siblings was used, who were concordant for lifetime depression. The high comorbidity between migraine and depression (12) also makes this a sample of convenience, as the high



**Figure 1** Two-threshold model for liability to migraine. Individuals with migraine without aura are those with a moderately high liability; individuals with migraine with aura have the highest liabilities.

prevalence of migraine gives more power to detect relationships than in a general population sample of the same size. Just under a half of migraineurs have had major depressive disorder (13–15), and the lifetime-ever risk of comorbidity is likely to be even higher given that the first onset of major depressive disorder may occur in mid to late adulthood (16). Thus, a history of or susceptibility to depression could well be the norm rather than the exception in migraineurs, and so examining migraine within the context of depression could be useful to determine if the same processes occur relative to migraineurs as a whole.

The comorbidity between migraine and depression suggests that there could be some aetiological risk factors shared between the two disorders, and this is further supported by a finding of a 'bidirectional' relationship (rather than one of the disorders usually preceding the other) (14). The overall hypothesis we aimed to test was that MA is the extreme end of the continuum of liability to migraine, rather than having a qualitatively different aetiology to MoA.

The current study tested the isocorrelational model (this is the basic form of the multiple threshold model, which posits that the familial correlations within both types of migraine are the same magnitude as the cross-correlations) (17). The current study also tested the 'environmental' or isoproportional model, which posits that the same genetic factors underlie the two phenotypes, but the level of non-familial environmental influence

or measurement inaccuracy differs in the two phenotypes.

## Methods

### Subjects

The study population comprised subjects from the Depression-Network (DeNT) study, an affected sibling pair genetic linkage study that has been described in detail elsewhere (18). Briefly, the sample consisted of sib pairs concordant for lifetime-ever International Classification of Diseases, 10th edn (19) and/or Diagnostic and Statistical Manual, 4th edn (20) operational criteria for recurrent unipolar depression (two or more episodes of at least moderate severity). Subjects were identified from eight different sites in Europe and North America and were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (21) to establish the diagnosis of depression. Pairs were excluded if either sibling had symptoms meeting criteria for mania, hypomania or schizophrenia, or if they had psychotic symptoms that were mood incongruent or present in the absence of mood disturbance. Other exclusion criteria were drug dependency, depression only in the context of alcohol use or secondary to medical illness or medication, or if any first-degree relatives of either sib had ever been diagnosed with bipolar disorder, schizophrenia, schizo-affective disorder or acute or transient psychotic disorders. All sites obtained ethical approval for the DeNT study within their own countries and institutions. All study participants gave written informed consent for participation.

As part of an investigation of the study participants' physical health, subjects were also interviewed using a migraine questionnaire designed to evaluate the lifetime ever occurrence of migraine and other types of headache, according to the criteria of the IHS (2004) (2). The majority were interviewed in person, but a few were interviewed by telephone. Subjects were assigned to one of the following IHS categories; MA, MoA, probable migraine (PM), non-migraine or tension headache (OH) and no headache (NH). The validating characteristics of the migraine interview were determined by comparing the headache diagnosis obtained from the interview with that of a Consultant Neurologist in 41 clinical subjects attending the City of London Migraine Clinic. Compared with a Consultant Neurologist diagnosis, the migraine interview had excellent specificity (1.00) and

modest sensitivity (0.66). In addition, for 20 of the depressed subjects, the test-retest reliability of the lifetime ever diagnosis of migraine was determined over a mean interval of 3 years (range 1–4 years). Spearman's correlation coefficient ( $\rho$ ) was 0.84 ( $P < 0.001$ ).

For the purposes of the present analyses, MA alone was considered as the narrow form of the phenotype, MA plus MoA plus PM were considered as the broad form of the phenotype, while OH plus NH were considered to indicate the absence of the phenotype. This ordinal classification balanced the need for sufficient participants in each category while assessing the status of aura as a marker of the aetiologically most extreme end of the migraine dimension.

The location of participants was as follows: Aarhus, Denmark,  $n = 54$ ; Birmingham, UK,  $n = 148$ ; Bonn, Germany,  $n = 154$ ; Cardiff, UK,  $n = 137$ ; Dublin, Ireland,  $n = 164$ ; Lausanne, Switzerland,  $n = 34$ ; London, UK,  $n = 91$ ; St Louis, MO, USA,  $n = 270$ . The English version of questionnaires was used, but for the 23% of participants in non-English speaking countries, it was translated into the local language.

Although a sibship with  $n$  affected members yields  $n(n-1)/2$  sib pairs, these are not statistically independent (22), and so utilizing all pairs overestimates the relative information contributed by large sibships. Therefore, we examined only  $n - 1$  pairs from each sibship (23) (effectively, taking this subset to be representative of all pairs in a family but giving a lower weighting to pairs in larger sibships), which is a sufficiently conservative approach for use in genetic analyses of affected sib pairs (24).

### Statistical analyses

The relationship between the narrow and broad forms of migraine was explored using a two-threshold model (17). A general model is fitted which estimates four correlations: between the narrow form in both sibs ( $r_{11}$ ), between the broad form in both sibs ( $r_{22}$ ) and between the narrow form in the first sib with the broad form in the second sib and vice versa ( $r_{12}$  and  $r_{21}$ ). An isocorrelational model (where all four correlations are set to be equal) should fit if both forms of the disorder are on the same continuum of liability, and if the narrow form simply represents the more extreme end of the continuum compared with the broad form. The isoproportional model (where  $r_{12}$  and  $r_{21}$  are set to be equal to one another, and equal to

**Table 1** Number of probands and siblings with different types of headache according to the International Headache Society criteria for migraine

Headache type	Probands	Siblings	Total
No recurrent headache (NH)	150 (30.3%)	179 (32.1%)	329 (31.3%)
Non-migraine headache (OH)	164 (33.1%)	172 (30.9%)	336 (32%)
Probable migraine (PM)	75 (15.2%)	106 (19%)	181 (17.2%)
Migraine without aura (MoA)	44 (8.9%)	44 (7.9%)	88 (8.3%)
Migraine with aura (MA)	62 (12.5%)	56 (10%)	118 (11.2%)
Total	495 (100%)	557 (100%)	1052 (100%)

the square root of the product of  $r_{11}$  and  $r_{22}$  should fit if the two forms represent the same continuum of liability but that one form is influenced more heavily by non-familial environment or measurement error. The independent model (in which  $r_{12}$  and  $r_{21}$  are set to zero) should fit if the narrow and broad forms are actually separate disorders in which there is no family-aetiological overlap.

The isocorrelational model, the isoproportional model and the independent model can be compared with the general model, by examining the increase in the  $\chi^2$  fit of the model relative to the degrees of freedom of the comparison. In addition, the isocorrelational model can be compared with the isoproportional model by means of a  $\chi^2$  comparison since the former is nested within, i.e. is a special case of, the latter: the isocorrelational model is a form of the isoproportional model in which the non-familial environment and measurement error 'are equally prominent in both forms' (17).

Model fitting was performed using TETCOR, a FORTRAN program written in-house that implements the models of Reich et al. (17). Polychoric correlations between siblings on the two-threshold migraine disorder were performed in the Stata statistical program (StataCorp LP, College Station, TX, USA) (25).

## Results

Recurrently depressed subjects [ $n = 1052$ ; 785 female (75%) and 267 male (25%)] from 495 White families participated in the migraine study. Because some families had more than two affected siblings (443 families had two affected siblings, 44 families had three, six families had four and two families had five), and because we utilised  $n - 1$  pairs from each sibship consisting of  $n$  affected members, there were 557 sibling pairs in total, comprising 321 female-female pairs, 44 male-male pairs and 192 mixed sex pairs.

The mean age of the participants was 45.6 years (S.D. 11.7, range 18.8–80.4 years); the probands' mean age was 46 years (S.D. 11.5, range 20.2–80.4 years) and siblings' mean age was 45.2 years (S.D. 11.9, range 18.8–78.4 years).

The frequency of headache in the depressed sibling pairs is shown in Table 1: 37% of the probands and the siblings had had migraine (MA + MoA + PM). Female subjects showed a higher prevalence of migraine (42%) compared with male subjects (22%) ( $z = 5.85$ ,  $P < 0.001$ ). The sibling concordance rates are shown in Table 2. When the probands had the narrow form of the disorder there were more siblings affected by the narrow form (MA) and more siblings affected overall (i.e. broad form: MA + MoA + PM). Thus, when a non-parametric test for trend across ordered groups was conducted in Stata, with the siblings in mutually exclusive categories (MA/MoA + PM/NH + OH), the result was highly significant ( $z = 3.62$ ,  $P < 0.001$ ) in the hypothesized direction. This pattern is consistent with the broad and narrow forms being on the same continuum of genetic liability, but with the narrow form being at the more extreme end of the distribution. This was then formally tested using model fitting (below).

### Model fitting

The results of model fitting are shown in Table 3. The independent model revealed a poor fit ( $P < 0.01$ ), indicating that there are common aetiological influences on both forms of the disorder (MoA and MA). The isoproportional and the isocorrelational models both fit the data well ( $\chi^2$  difference = 2.76, d.f. = 2,  $P = 0.25$ ;  $\chi^2$  difference = 3.49, d.f. = 3,  $P = 0.33$ , respectively), indicating that the two forms of migraine fit a model in which the narrow form is simply the result of the more extreme end of the genetic liability distribution compared with the broad form. The isocorrelational model is preferred because it is more

**Table 2** Sibling concordance for migraine in the DeNT sample

		Sibling		NH + OH: No migraine (%)	Total N
		MA + MoA + PM (broad form)			
Proband*		MA: narrow form (%)	MoA + PM (%)		
MA + MoA + PM (broad form)	MA: Narrow form	13 (18)	25 (35)	33 (46)	71
	MoA + PM	11 (8)	45 (33)	79 (59)	135
NH + OH: No migraine		32 (9)	80 (23)	239 (68)	351
Total N		56	150	351	557

\*The 557 probands are 495 individuals, 62 of whom are counted more than once in order to include analyses between the proband and extra siblings.

MA, migraine with aura; MoA, migraine without aura; PM, probable migraine; NH, no headache; OH, non-migraine or tension headache.

**Table 3** Results of two-threshold model fitting to determine the nature of the relationship between the broad and narrow forms of migraine

Model*	$\chi^2$ of model compared with general model			$\chi^2$ of model compared with model 2		
	d.f.	P		d.f.	P	
1. Independent	15.71	2	0.0004	–	–	–
2. Isoproportional	2.76	2	0.2516	–	–	–
<b>3. Isocorrelational</b>	<b>3.49</b>	<b>3</b>	<b>0.3221</b>	<b>0.73</b>	<b>1</b>	<b>0.3929</b>

\*The general model estimates the correlations between broad and narrow forms of the disorder in probands and siblings; the independent model fixes the cross-correlations (between broad and narrow forms) to zero; the isoproportional and isocorrelational models allow cross-correlations such that the narrow form has a higher familial loading than the broad form, but in addition the isoproportional model allows for different non-familial or measurement error contributions to the two forms of the disorder.

Bold indicates best fitting model.

parsimonious and not a significantly worse fit than the isoproportional model ( $\chi^2$  difference = 0.72, d.f. = 1,  $P = 0.39$ ).

The polychoric sib correlation for migraine, when assuming a two-threshold model as supported by the above models, was 0.22 [95% confidence interval (CI) 0.12, 0.32]. We cannot calculate variance components as the sample comprises full sibs only. However, if we assume this familial resemblance is best explained by only additive genetic rather than shared family environmental effects, as has been found in previous twin studies (5, 6, 19), then this would correspond to an additive genetic effect (heritability) of 44%.

In order to examine the effect of sex, the analyses were repeated in the female–female sib pairs ( $N = 321$ ). The results of the model fitting were the same. The polychoric sib correlation for female–female pairs assuming a two-threshold model was 0.30 (95% CI 0.16, 0.44); thus, it was higher than the correlation estimated using all sex sib pairs, but not significantly so.

## Discussion

Consistent with previous studies that used general population samples and different criteria to identify cases (7, 8), the present study supports the hypothesis that MA represents the extreme end of a continuum of migraine familial liability, even when examined in depressed participants. Therefore, these results contradict studies (4, 9) that present MA and MoA as two separate disorders with separate aetiologies. However, latent class analysis has shown that presence or absence of aura did not strongly correspond to the severity of the migraine or neurological symptoms (7, 8). The conceptualization of MA as the most extreme form of the disorder in terms of aetiology is still consistent with evidence that the actual migraines are reported as being more severe in MoA (26).

The present study has demonstrated that the continuum of liability to migraine is also a valid hypothesis when strict IHS criteria are used, and within a depressed population. Although the

selection of our sample limits the extent to which our findings can be extrapolated to migraineurs as a whole, the phenotypes of migraine are similar in depressed people to those in the general population, excepting the higher prevalence seen in the context of depression (12). This may be consistent with the hypothesis that the comorbidity between migraine and depression is due to shared aetiological risk factors, with depressed people having more of those risk factors than the general population. That is, on top of the familial factors that predispose to depression, which we have over-ascertained in this sample of concordantly depressed sib pairs, there are familial influences on the continuum of liability to migraine.

It is also possible that, in the general population, the same factors that confer familial liability to depression also confer familial liability to migraine. If there are such common liability factors, we would expect to find a stronger association with depression in aetiologically more severe cases of migraine. Indeed, a recent case-control comparison found a stronger association of lifetime-ever major depression with MA than with MoA (27). If these familial liability factors are genetic (as suggested by the lack of familial-environmental influences on either depression (28) or migraine (29)), then by concentrating on aetiologically more severe migraineurs (who can be approximately indexed by the presence of aura), we may achieve the greatest power to detect genes in molecular studies. Furthermore, where genes are identified as contributing to migraine, some may also influence liability to depression.

### Limitations

The participants in this study may not be fully representative of the whole depressed population, because they have a similarly affected sibling. However, past research has not supported the hypothesis that there is a 'genetic' subtype of depression that is aetiologically different from a 'non-genetic' subtype (30). Comorbidity between anxiety and depression could mean that anxiety is acting as a confounding factor in the prevalence rate of migraine in this sample. However, past research has suggested that although anxiety levels are higher in migraineurs than in non-migraineurs, there appears to be no relationship between anxiety and the presence or absence of aura (31), so the particular relationships tested in this study are unlikely to be affected. The exclusion criteria (e.g. mania, psychosis, drug dependency) mean that our

sample does not reflect all possible presentations of depression, and so these exclusions may have led to some confounding of the prevalence rate of migraine; however, these exclusions give us a relatively homogeneous sample in which to test our hypotheses concerning the aetiology of migraine in the context of unipolar depression. Furthermore, this study can only indirectly (in combination with previous reports of comorbidity in population-based samples) tell us about the relationship between migraine and depression because the current sample contains only those who have had depression.

Another limitation of the study was the use of a questionnaire-based interview rather than clinical opinion; nonetheless, the interview was found to have reasonable test-retest reliability, and specificity and sensitivity when judged against the diagnoses of an expert neurologist. The questionnaire-based method on average resulted in a narrower definition of migraine. However, this would tend to reduce power to distinguish between models rather than create false-positive findings.

In conclusion, this study suggests that MA is typically the result of a greater dose of the same causal risk factors that lead to MoA. Some of these risk factors are shared within families and are likely to be genetic. This was found even within the current depressed sample, which shows that (i) similar aetiological processes are involved in the general population of migraineurs as in those who also have experiences of depression, and (ii) the relationship between MA and MoA is not explained by confounding by depression. The higher prevalence of migraine within depressed samples, and the more extreme aetiological position of migraine with than without aura, suggests that future research looking for specific causal risk factors (genetic or otherwise) for any of these three disorders may achieve the greatest power by focusing on patients comorbid for depression and MA.

### Competing interests

M.J.O. and N.C. have acted as consultants to GlaxoSmith-Kline (GSK) and have received honoraria for academic talks from Eli Lilly, Astra Zeneca and GSK. A.K. has received research grants from GSK and Synthelabo-Sanofi and has received honoraria from Eli Lilly. A.E.F. has received honoraria for presentations and chairing meetings from Eli Lilly, GSK and Wyeth and is a consultant for GSK. P.McG. has received honoraria from Eli Lilly and GSK and has acted as a consultant in the recent past for GSK and Astra Zeneca.

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