Migraine with aura (MA) is a common neurological disorder in the general population with a lifetime population prevalence of less than 10%. Population based segregation analyses, family, and twin studies support an underlying genetic susceptibility to MA and this susceptibility is generally recognised as arising from a combination of genetic and environmental factors. In the general population, there is a broad range of MA family types with varying degrees of family history or genetic loading. Given that MA probably segregates as a complex trait with incomplete penetrance, phenocopies, and locus heterogeneity, strategies to reduce the genetic heterogeneity within a sample will be of importance in identifying the MA susceptibility genes.

The aim of this study is to develop a rationale for selecting MA families for genetic studies. We have therefore examined the sibling risk, age at onset, and complexity of the aura between 54 three generation Canadian families stratified by the number of generations of vertical transmission of MA.

METHODS
Selection and headache classification of study participants
The probands (63 male, 167 female) for this study were coded as MA from clinic records (GPAR 1994–1998, JDB 1991–1998). These patients with MA were first examined by their family physician who then decided whether to refer based on clinical presentation. Study participants were interviewed by telephone using a semi-structured headache questionnaire that identified headache pain characteristics, the frequency and age of onset of the headaches, the presence of accompanying autonomic disturbances, and type of aura symptoms. Parents, siblings, and offspring of the MA probands were interviewed using the same questionnaire regardless of whether they reported having headaches. Participants were classified as MA, MO, MA and MO or no migraine based on the International Headache Society (IHS) classification for migraine. Interviews were conducted by a qualified neurologist who was blinded to the stratification strategy. The catchment area for study participants and their families included London, Canada and surrounding communities. Written consent was obtained from all study participants.

Categorisation of families based on family history of MA
Two hundred and thirty subjects were coded with a diagnosis of MA. After review of the clinic records and an initial telephone call, 108 probands (47.0%) agreed to participate in the study, 84 probands (36.5%) were determined to be non-participants because they declined participation (n=39) or could not be located (n=45), and 38 probands (16.5%) were determined to have MA caused by associated disorders and were therefore excluded. Of the 108 participating probands, 54 probands (50.0%) were eligible for the study as the migraine status of the proband’s parents, spouse, siblings, and offspring could be ascertained. A total of 392 first degree relatives were interviewed. The 54 remaining interviewed probands were ineligible for the study as 45 (41.7%) probands did not have any offspring and could not be classified as a two generation or three generation MA family and nine (8.3%) probands were a conjugal MA/MA or MA/MO mating pair. Probands and family members with MA could also have a co-occurrence of MO.

The 54 MA probands were categorised by family history of MA as follows: (1) an affected parent and at least one affected offspring (three generation; n=15; 27.8%), (2) an affected parent or at least one affected offspring (two generation; n=20, 37.0%), and (3) neither an affected parent nor an affected offspring (one generation; n=19, 35.2%). For this stratification scheme, the proband was always in the second generation and as importantly, affected siblings were not a criteria for inclusion (fig 1).
The crude recurrence risk was calculated as the number of siblings with MA/total number of siblings. A chi^2 analysis was performed to test for the significance of the comparison of the proportions. The comparisons of mean age were performed using single factor analysis of variance.

### RESULTS

#### MA probands

There is no difference in the sex distribution (chi^2=0.076, p=0.78) or mean (SD) current age (F=2.28, p=0.13) of the 108 participating MA probands (41.3 (11.6) years) and the 84 non-participants (44.2 (11.1) years). The female to male gender ratios were 3.0:1.0 for the participants and 2.5:1.0 for the non-participants.

The 54 MA probands were referred for: changes to the com-

#### Aura and genetic load

The severity of MA, as measured by type of aura, was assessed in the 54 MA probands. Participants were categorised as having visual aura only or as having visual aura plus at least one other type of aura (aphasic, sensory, or motor) for a minimum of one aura episode (table 1C). The probands from the three generation MA families (14 of 15; 93.3%) reported a broader range of aura type than either the two generation (11 of 20; 55.0%) or one generation (13 of 19; 68.4%) MA families and MA probands with both an MA parent and an MA child were significantly more likely to exhibit visual plus other aura types than MA probands with either an MA parent or an MA child only (chi^2=4.44, p=0.035). The range of aura type was comparable for the one generation and two generation MA families (chi^2=0.283, p=0.595).

### DISCUSSION

The siblings of MA probands have a significantly 2.7-fold higher crude recurrence risk to siblings in three generation than in the two generation MA families and a significantly higher 4.8-fold risk in three generation than in one generation families. The risk to siblings in the one generation MA families, a family type that corresponds to phenotypically sporadic MA cases in the general population, is similar to a reported population prevalence of MA.

Age at onset was also examined as a measure of the severity of MA as a younger age at onset of disease is a hallmark of the familial form of many disorders in the general population such as early onset breast cancer and early onset Alzheimer's disease.

Sibling risk increases with a decreasing age at onset of the proband for multiple sclerosis and breast cancer.

More significantly, stratification of relatively prevalent disorders by age at onset made it possible to identify linkage in multiplex families with apparent autosomal dominant mode of inheritance and ultimately, to identify the causative genes (BRCA1, pre-senilin-1). In our data, there is an observable downward trend in mean age at onset of the proband that corresponds with an increasing degree of genetic loading. The probands from three generation MA families were significantly younger than the MA probands from the one generation MA families. Age at onset should therefore be an additional consideration for selecting MA families for genetic studies.
As almost all people with MA have visual aura, we used the presence of non-visual types of aura as a measure of severity of MA. Ninety three per cent of probands from three generations reported a broader range of aura types than probands from two generation (55.0%) and one generation (68.4%) MA families. The broader range of aura described by the probands of the three generation MA families is consistent with the greater genetic load that contributes to a higher risk to siblings and the lower age at onset in this type of family. In a Finnish clinic population of MA or MA and MO probands with family history of migraine, a broader range of aura types was also reported for at least 50% of the probands. However, in this study we are comparing sibling risk, age at onset, and complexity of the aura between three groups likely to be biased in the same way. Although we believe that the lower age at onset and increased sibling risk in MA families when MA is vertically transmitted through three generations is probably applicable to MA in the general population, these results need to be confirmed in a population based cohort.

MA arises from a combination of genetic and environmental factors and it has been suggested that MA be considered a complex trait for genetic studies. The spectrum of MA family types, ranging from phenotypically sporadic MA through varying degrees of family history, contributes to an overall complex picture for the genetic susceptibility to MA, but the complexity can be reduced by stratifying MA families by family history. For example, the proportion of MA siblings in our three generation MA families is consistent with an autosomal dominant mode of inheritance with reduced penetrance. Parametric linkage analysis of such enriched multiplex families may be a rewarding strategy as demonstrated by the identification of the early onset breast cancer and early onset Alzheimer's disease susceptibility genes. The significant linkage of MA to 4q24 supports the utility of parametric linkage analysis of large, multiplex families enriched for MA. By selecting for MA families with a high penetrance of MA and age at onset in the mid-teenage to late teenage years, we should be selecting for families with a greater genetic load and fewer confounding factors attributable to environmental effects and ultimately, a more homogenous MA cohort.

The stratification of three generation families into those with one, two, or three generations of family history of MA has allowed us to evaluate MA with respect to genetic loading and risk to siblings, age at onset, and type of aura. The significant difference in genetic loading and earlier age at onset in the three generation MA families adds further evidence for a genetic basis for MA and the heterogeneity illustrated by the increased sibling risk in subtypes of MA probands emphasises the complexity of MA in the general population.

ACKNOWLEDGEMENT

The authors appreciate the voluntary participation of the families in this study, the assistance of Roopa Ganapathy, Pam Schoffer, and Tracey Bentall for contacting the families and Dr Dean Wingerchuk and Dr Patti Mandalfino with confirmation of ascertainment.

Authors' affiliations

S E Noble-Topham, Lawson Health Research Institute, London Health Sciences Centre, London, Canada
G P A Rice, J D Brown, Department of Clinical Neurological Sciences, London Health Sciences Centre, London, Canada
M Z Cader, D A Dyment, G C Ebers, Department of Clinical Neurology, University of Oxford, Oxford, UK
G C Ebers, Department of Clinical Neurology, University of Oxford

Competing interests: none declared.

Correspondence to: Dr G C Ebers, Department of Clinical Neurology, University of Oxford Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK; george.ebers@clin.ox.ac.uk

Received 4 November 2002
In revised form 1 January 2003
Accepted 11 February 2003

REFERENCES

Genetic loading in familial migraine with aura

S E Noble-Topham, M Z Cader, D A Dyment, G P A Rice, J D Brown and G C Ebers

*J Neurol Neurosurg Psychiatry* 2003 74: 1128-1130
doi: 10.1136/jnnp.74.8.1128

Updated information and services can be found at:
http://jnnp.bmj.com/content/74/8/1128

These include:

**References**
This article cites 17 articles, 7 of which you can access for free at:
http://jnnp.bmj.com/content/74/8/1128#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Headache (including migraine) (459)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/