Genetic loading in familial migraine with aura

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

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 family history of MA and as importantly, affected siblings were not a criteria for inclusion (fig 1).

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.

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. Of the 108 participating probands, 54 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).
and forty one of the siblings were interviewed and 29 (20.1%) of MA probands had a total of 154 siblings. One hundred and eighteen point five (18.5%).

The 54 MA probands were referred for: changes to the complexity of their aura (n=2; 3.7%), increased frequency of MA medication (n=16; 29.6%), reactivation of dormant MA at p=0.433).

There is no difference in the sex distribution (χ²=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 (11.7) 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 complexity of their aura (n=16; 29.6%), reactivation of dormant MA at menopause (n=5; 9.3%), occurrence of aura alone after years of MA episodes (n=2; 3.7%), increased frequency of MA (n=6; 11.1%), or MA identified as part of history taking for another headache type or other neurological disorder (n=10; 18.5%).

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. In contrast, two generation and three generation families have substantially higher risks to siblings compared with the general population.

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.

Table 1: Statistical comparison of risk to siblings of probands, and age at onset and aura type of probands stratified by family history of migraine with aura

<table>
<thead>
<tr>
<th>(A) Risk to siblings (MA siblings [n]/total siblings [n])</th>
<th>Two generation</th>
<th>Three generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>one generation [3/39; 7.8%]</td>
<td>NS</td>
<td>χ²=9.95, p=0.002</td>
</tr>
<tr>
<td>two generations [7/51; 13.7%]</td>
<td>↑</td>
<td>χ²=6.24, p=0.0125</td>
</tr>
<tr>
<td>three generations [19/51; 37.3%]</td>
<td>↑</td>
<td>↑</td>
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<tr>
<th>(B) Mean (SD) age at onset (AO) of MA probands</th>
<th>Two generation</th>
<th>Three generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>one generation [26.1 (11.7)]</td>
<td>NS</td>
<td>F=1.138, p=0.300</td>
</tr>
<tr>
<td>two generation [21.7 (8.7)]</td>
<td>↑</td>
<td>NS</td>
</tr>
<tr>
<td>three generation [17.6 (8.1)]</td>
<td>↑</td>
<td>↑</td>
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<tr>
<th>(C) Aura type of MA probands (probands with visual aura [n] plus*/ total probands [n])</th>
<th>Two generation</th>
<th>Three generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>one generation [13/19; 68.4%]</td>
<td>NS</td>
<td>χ²=4.44, p=0.035</td>
</tr>
<tr>
<td>two generation [11/20; 55.0%]</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>three generation [14/15; 93.3%]</td>
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*Visual aura plus refers to proband report of visual plus one of aphasic, sensory or motor aura; NS, not significant; †no comparison performed; SD, standard deviation.

Statistical analyses
The crude recurrence risk was calculated as the number of siblings with MA/total number of siblings. A χ² 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 (χ²=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 (11.7) 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 complexity of their aura (n=15; 27.8%), required more efficacious medication (n=16; 29.6%), reactivation of dormant MA at menopause (n=5; 9.3%), occurrence of aura alone after years of MA episodes (n=2; 3.7%), increased frequency of MA (n=6; 11.1%), or MA identified as part of history taking for another headache type or other neurological disorder (n=10; 18.5%).

Genetic load and risk to siblings
The 54 MA probands had a total of 154 siblings. One hundred and forty one of the siblings were interviewed and 29 (20.1%) had MA by IHS criteria. The remaining 112 unaffected siblings were all older than 30 years of age and 82% (n=92) were older than 40 years of age. Fifty three (98.1%) of the MA probands were greater than 30 years of age and 70.4% (n=38) were greater than 40 years of age. There was no difference in the mean current age of the MA probands and the unaffected probands (26.1 (11.7)) (F=5.138, p=0.303). 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 (χ²=6.24, p=0.0125). The range of aura type was comparable for the one generation and two generation MA families (χ²=0.076, p=0.783).

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. In contrast, two generation and three generation families have substantially higher risks to siblings compared with the general population.

Age at onset was also examined as a measure of the severity of MA as a younger 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 generation MA families reported a broader range of aura type 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 corresponds 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.27

In this study, we identified 192 MA probands from coded patient records and interviewed 108 probands and available first degree relatives. The referral practices of family physicians and the modest participation rate (56.3%) of the identified MA probands in this study are potential sources for selection bias. We found no difference in the sex ratio or mean current age of the 108 participants and the 84 non-participants. We also determined that all 54 MA probands sought specialised care because of medical needs, as adults (39.2 (10.9) years) about 17 years after their initial episode.

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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 Coder, D A Distefano, C Ebers, Department of Clinical Neurology, University of Oxford, Oxford, UK
G C Ebers, Department of Clinical Neurology, University of Oxford

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