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ORIGINAL INVESTIGATION

Bayesian latent trait modeling of migraine symptom data

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Abstract Definition of disease phenotype is a necessary preliminary to research into genetic causes of a complex disease. Clinical diagnosis of migraine is currently based on diagnostic criteria developed by the International Headache Society. Previously, we examined the natural clustering of these diagnostic symptoms using latent class analysis (LCA) and found that a four-class model was preferred. However, the classes can be ordered such that all symptoms progressively intensify, suggesting that a single continuous variable representing disease severity may provide a better model. Here, we compare two models: item response theory and LCA, each constructed within a Bayesian context. A deviance information criterion is used to assess model fit. We phenotyped our population sample using these models, estimated heritability and conducted genome-wide linkage analysis using Merlin-qtl. LCA with four classes was again preferred. After transformation, phenotypic trait values derived from both models are highly correlated (correlation = 0.99) and consequently results from subsequent genetic analyses were similar. Heritability was estimated at 0.37, while multipoint linkage analysis produced genome-wide significant linkage to chromosome 7q31-q33 and suggestive linkage to chromosomes 1 and 2. We argue that such continuous measures are a powerful tool for identifying genes contributing to migraine susceptibility.

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Introduction

Research into the genetics of complex diseases often involves the identification of genes associated with groups of patients who exhibit different combinations of disease symptoms or phenotypes. This analysis depends crucially on the careful classification of patients. Commonly, the clustering of patients depends on the criteria established by medical societies, such as the International Headache Society (Headache Classification Committee of the International Headache Society 1988; Olesen and Steiner 2004; Silberstein et al. 2005) for migraine. Without doubt, these criteria are valuable for the diagnosis of diseases, but their effectiveness for genetic research is debatable (Hallmayer et al. 2003; Wessman et al. 2007) as discussed below.

Migraine is a hereditary disorder with estimated heritability between 34 and 57% (Ziegler et al. 1998; Mulder et al. 2003; Svensson et al. 2003, 2004; Nyholt et al. 2004, 2005). The two most common forms of migraine are

migraine without aura (MO) and migraine with aura (MA), where aura typically concerns a visual disturbance. The genetic research of migraine is mainly focused on these two subgroups. To date, except for CACNA1A, ATP1A2 and SCN1A—genes that contribute to a rare mendelian form of MA, familial hemiplegic migraine (FHM), no gene has been convincingly implicated in migraine (Table 1). This may be due to clinical and genetic heterogeneity of the disease. The phenotype defined by IHS criteria may oversimplify the complex variability among sufferers of this complex disease (Anttila et al. 2006; Wessman et al. 2007). Furthermore, there is overlap in the symptoms of MO and MA. Clinically, the symptoms of MA are a superset of the symptoms of MO. The work of Nyholt et al. 2004 and Ligthart et al. (2006) provides further support for the argument that MA and MO are not separate entities. Therefore, the development of an endophenotype or an alternative phenotype may give better insight into the genetics of common migraine.

There are currently two main types of method for investigating the phenotypic structure of symptom survey results, one based on the use of statistical methodologies to convert the symptoms to a unidimensional value and the other based on trait component analysis (TCA), which treats each individual symptom as a response variable for the purpose of linkage analyses. Nyholt et al. (2004) pioneered the use of latent class analysis (LCA) of the phenotype for migraine. The authors applied LCA to migraine symptomatic data in an Australian twin population sample and found that the best fit to the data was obtained using a model with three symptomatic latent classes; these correspond to a mild form of recurrent non-migrainous headaches, a moderately severe form of migraine and a severe form. Moreover, the estimated heritability using LCA was found to be slightly higher than the heritability estimated using IHS criteria. Nyholt et al. (2005) then applied this method for genome-wide linkage analysis and identified linkage to chromosome 5q21. They also replicated previously reported susceptibility loci on chromosomes 6p12.2-p21.1 and 1q21-q23.

Since migraine is a suite of symptoms and the subphenotype analysis in Nyholt et al. (2005) found that individual symptoms are associated with specific linkage peaks in their data, there have been several attempts to identify gene loci linked to individual symptoms (Anttila et al. 2006, 2008). This method is referred to as trait component analysis. Anttila et al. (2006) applied TCA to dissect the genetic susceptibility of migraine in a Finnish cohort. They found strong evidence that various migraine symptoms are linked to chromosome 4q24, including photophobia, phonophobia, intensity, unilaterality, nausea, vomiting and attack length. They also found that pulsation is linked to chromosome 17p3 and reported some suggestive linkage of the phonophobia trait to chromosome 10q22 and the "aggravation by physical exercise" trait to chromosomes 12q21, 15q14 and Xp21.

Besides LCA, other clustering methods have been applied to genetic research of diseases with complex aetiology. These include grade of membership (GoM), used to analyze schizophrenia (Hallmayer et al. 2003), mania (Cassidy et al. 2001) and Alzheimer's (Fillenbaum 1998; Corder and Woodbury 1993); model-based clustering, used to analyze anorexia nervosa (Devlin et al. 2002); and fuzzy clustering, used to analyze anxiety disorder (Kaabi et al. 2006). All these algorithms aim to identify homogenous classes/components in the data, based on specified traits of interest, and estimate the parameters associated with each class.

For some diseases composed of many individual symptoms, the data may be better modeled using a continuous representation. Indeed, in earlier analyses of multisymptom migraine data using LCA and GoM (Chen et al. 2009; Nyholt et al. 2004, 2005; Ligthart et al. 2006, 2008), the classes could be ordered in such a way that there was a gradual reduction in all symptoms, suggesting that there is a single latent continuous trait underlying the observed pattern of symptoms. It is therefore reasonable to hypothesize that the data may be modeled using a single continuous variable representing severity of the disease instead of classes.

Item response theory (IRT), which is also known as latent trait analysis, is a popular statistical method for modeling psychological and educational survey responses. It assumes an underlying continuous latent value which has direct influence on the responses to items. Indeed, items are

Table 1 The chromosome regions associated with the common forms of migraine

Phenotype	Cohort	Chromosome	References
MO	Icelandic	4q21	Björnsson et al. (2003)
MO	Italian	14q21.2-q22.3	Soragna et al. (2003)
MA	Canadian	11q24	Cader et al. (2003)
MA	Finnish	4q24	Wessman et al.(2002)
MA	North American Caucasians	19q13	Jones et al.(2001)
TCA and LCA	Finnish and Australian	10q22-10q23	Anttila et al.(2008)

designed to capture this latent value. In this paper, the item variables are equivalent to the symptom variables. IRT has been found to be useful in behavioral genetics and genetic epidemiology, where the phenotype is often determined by the questionnaire or interview data. This method has been used for exploring the genetic and environmental influence on the timing of pubertal change (Eaves et al. 2004) and the analysis of multi-symptom genetic data (Eaves et al. 2005; Wray et al. 2008).

In this paper, we test the hypothesis proposed above by first introducing IRT for analyzing multi-symptom migraine data, then comparing this non-clustering method to LCA. Both the models are introduced in a Bayesian framework and compared using statistical measures that take into account goodness of fit and model complexity. The models are then compared further by assessing the utility of their resulting trait measures in genetic heritability and linkage analysis.

Methods

Data

Phenotype data

Data were collected by the Queensland Institute of Medical Research (QIMR) during the course of extensive and semi-structured telephone interview studies from 1993 to 2000. The surveys were primarily designed to assess physical, psychological, and social manifestations of alcoholism and related disorders. The sample was unselected with regard to personal or family history of alcoholism or other psychiatric or medical disorders. The data were collected over two periods, 1993–1995 and 1996–2000. The earlier interview was administered to Australian twins listed with the volunteer-based Australian Twin Registry who were born between 1902 and 1964 while the second interview was focused on twins born between 1964 and 1971. Participants of both cohorts were first asked the screening question:"Do you have recurrent attacks of headaches?" If the participant screened positive, then he/she was asked a number of questions which were developed by an experienced migraine researcher based on the IHS diagnosis criteria (Table 2). Although the wording of the questions is identical for both periods, the older cohort was not asked questions related to having at least five episodes of headaches, the duration of headaches (4–72 h) and the severity of the pain associated with headache ("moderate to severe").

There are 13,062 individuals from 6,764 families participating in this analysis, with 2,716 MZ twin pairs (63.6% females and 36.4% males), 3,399 DZ twin pairs (34.5% female twin pairs, 22.4% male twin pairs and 43.1% opposite sex twin pairs), 12 twins with unknown zygosity and 817 non-twin siblings. The mean age of participants was 37.5 years and ages ranged from 23 to 90 years at the time of survey. Details of the collection of the migraine data are provided by Nyholt et al. (2004, 2005).

Although it may be argued post-survey that it would have been more complete for all members of the cohort to be asked all symptom questions, this was considered to be an unacceptable impost by the survey designers. Possible ascertainment bias was considered and discounted since analysis showed little difference in prediction of LCA and IRT by including and excluding the "no" cohort. .

Genotype data

The genotypic data are composed of four smaller genome-wide linkage scans performed for other studies at the Queensland Institute of Medical Research (QIMR). Genotyping for the four studies was conducted at Gemini Genomics with 426 satellite markers, Sequana Therapeutics

Table 2 The survey questions based on IHS criteria

Notation	Abbreviation	Descriptions
a	≥5 episodes	Have at least five episodes of headache in your life time
b	4–72 h	Average headache last between 4 and 72 h
c1	Unilateral	Headache often occurs at one side of head
c2	Pulsating	Headache pain can be described as throbbing, pulsating or pounding
c3a	Moderate/severe	Headache pain can be described between moderate and severe
c3b	Prohibitive	Headache pain prohibits daily activities
d1	Nausea/vomiting	Headache associated with vomiting or feeling nausea
d2a	Photophobia	Enhance sensitivity to light
d2b	Phonophobia	Enhance sensitivity to sounds
Aura	Aura	Have visual problems such as light shower, blurring, blind spot or double vision

with 519 markers, the Center for Mammalian Genetics at Marshfield Clinic Research Foundation with 776 markers and the University of Leiden with 435 markers. The details of DNA collection, genotyping methods and data cleaning are discussed elsewhere (Zhu et al. 2004; Cornes et al. 2005).

Graphic Representation of Relationships (GRR) (Abecasis et al. 2001) and RELPAIR (Epstein et al. 2000; Duren et al. 2003) were applied for the examination of the pedigree structure and identification of inconsistencies between the genotypic data and self-reported pedigree relationships. The potential misspecification, incorrect zygosity labeling of twins and sample mix-ups were identified and corrected. A small number of cases with errors could not be corrected, so were excluded in further analysis. The SIB-PAIR version 0.99.9 program by Duffy (2002) was then implemented for identifying and cleaning the Mendelian inconsistencies in the genotype data.

Markers from four sources were included separately on the genetic map for the combined scan, separated by a small distance of 0.001 cM. Markers with genotypic data inconsistent between different genome scans were excluded and unlikely genotypes were identified by MERLIN (Abecasis et al. 2002) and omitted from further analysis. Potential map errors were identified by GENEHUNTER (Kruglyak et al. 1996) and MENDEL (Lange et al. 1988). Map positions were in Kosambi cM, which is estimated using locally weighted linear regression from the National Center for Biotechnology Information (NCBI) Build 34.3 physical map positions, as well as published deCODE and Marshfield genetic map positions (Kong et al. 2004). Where the results suggested inconsistencies between genetic map distance and recombination fraction, the primer sequences for all markers in the region were BLASTed against the entire human genome sequence (http://www.ensembl.org, NCBI build 34.3). The genetic map was then revised to include the updated physical positions of all markers in the problematic regions. The revised map and the original genotype data were cleaned of unlikely genotypes using MERLIN and map errors were resolved using GENEHUNTER. More details on the collapsing of markers is in Cornes et al (2005).

There are a total of 1,770 unique markers and the combined genome scan included 4,148 individuals from 919 families (143 MZ and 776 DZ twin pairs and some parent genotype).

Model

Latent class analysis

Suppose that there are n individuals and J observed (manifest) item response variables $(i = 1, \ldots, n; \quad j = 1, 2 \ldots, J)$. Let y_{ij} denote the binary response of the ith individual to symptom question j such that $y_{ij} = 1$ when the symptom j is present in person i, else $y_{ij} = 0$. Y_i is then the vector of the ith subject's responses to all symptoms. Assume that there are K latent classes embedded in the data. Let λ_{kj} be the probability of a positive response on variable j for a person in latent class $k (k = 1, \ldots, K)$. Then

$$P(Y_i|\lambda, p) = \sum_{k=1}^{K} p_k \prod_{j}^{J} (\lambda_{kj})^{y_{ij}} (1 - \lambda_{kj})^{1-y_{ij}}$$

where p_k denotes the probability that a randomly chosen individual belongs to latent class k. We used the following non-informative priors:

$$p_k \sim \text{Dirichlet}(1, \ldots, 1)_k$$
$$\lambda_{kj} \sim \text{Beta}(1, 1)$$

representing equal probability of membership to any of the k classes and equal probabilities of a 0 or 1 response for the jth variable in the kth class. The posterior probability that subject i belongs to class k is given by:

$$p_{ik} = \frac{p_k \prod_j f(Y_i|\lambda_k)}{\sum_k p_k \prod_j f(Y_i|\lambda_k)}$$

where λ_k is the expected probability of membership of the kth class and $f(Y_i|\lambda_k)$ represents the probability distribution for Y_i given this probability, that is,

$$f(Y_i|\lambda_k) = \prod_j (\lambda_{kj})^{y_{ij}} (1 - \lambda_{kj})^{1-y_{ij}}.$$

The parameter vectors p and λ are estimated by Markov Chain Monte Carlo (MCMC) simulations using WinBUGS1.4 (Spiegelhalter et al. 2006). Then the latent trait value for the ith subject is given by

$$\text{Phenotypic trait}_i = \sum_{k=1}^{k=K} \frac{\sum_{j=1}^{j=J} \lambda_{kj}}{J} \times p_{ik}. \quad (1)$$

Item response theory

As before, let y_{ij} denote the binary response of person i to variable j, $y_{ij} = \{0, 1\}, \quad i = 1, 2, \ldots, n$ and $j = 1, 2, \ldots, J$. Let θ_i denote the latent trait value of subject $i, \theta_i \in \mathbb{R}$ and $P_j(\theta_i)$ be the probability of observing a response score of 1 (symptom present) given the latent trait value $P_j(\theta_i) = P_j(y_{ij} = 1|\theta_i)$, which is called the item response function (IRF). Different types of IRF constitute the subtypes of IRT. Variations of the IRT model include the Rasch model, 2-parameter logistic model (2-PL), 3-PL model and the Birnbaum model.

In this paper, we adopt the 2-PL model, which is commonly implemented for phenotyping. The IRF for the 2-PL model is

$$P_j(\theta_i|a_j, b_j) = \frac{e^{a_j(\theta_i - b_j)}}{1 + e^{a_j(\theta_i - b_j)}} \quad (2)$$

where variables a_j and b_j are described in the education/psychology literature as the item discriminant parameter and item difficulty parameter. Higher values of a_j indicate that item j has higher correlation with the latent trait value. The item difficulty parameter represents the point on the latent trait scale at which the probability of having the symptom is 0.5.

The likelihood is thus

$$P(Y|\theta) = \prod_{i}^{n} \prod_{j=1}^{J} (p_j(\theta_i))^{y_{ij}} (1 - p_j(\theta_i))^{1-y_{ij}}.$$

As in the LCA model, noninformative priors are used for parameters θ_i, a_j and b_j:

$$\begin{aligned} &\theta_i \sim N(0,1), \quad \theta_i \in \mathbb{R} \\ &a_j \sim N(0, 10000) \\ &b_j \sim N(0, 10000). \end{aligned}$$

As for Bayesian LCA, estimation was carried out by Markov Chain Monte Carlo (MCMC) using WinBUGS1.4 (Spiegelhalter et al. 2006).

For both LCA and IRT models, MCMC chains were generated with 10,000 iterations. The initial 5,000 iterations were considered as burn-in and every fifth case of the remaining 5,000 (total of 1,000 cases) was extracted to build the marginal posterior distribution of the parameters. For the LCA model, a chain was generated for each value of K, $K = 2, \ldots, 7$.

Model comparison

The deviance information criterion (DIC) is a popular and useful method for assessing model fit and complexity for the purpose of comparing Bayesian models. The early DIC proposed by Spiegelhalter et al. (2002) is only suitable when the competing likelihood models have a closed form. It is not ideal for comparing models with missing values or mixture models (Celeux et al. 2006). Celeux et al (2006) suggested various alternative forms of DIC for these models and compared the performance of these criteria. Here we employ the DIC3 of their work to determine the optimum number of classes for the Bayesian LCA and compare Bayesian LCA and IRT models. DIC3 is defined as

$$\text{DIC} = -4\mathbb{E}_\theta[\log f(y|\eta)|y] + 2\log \hat{f}(y) \quad (3)$$

where y is observed data, η is a vector of model parameters and $\hat{f}(y)$ is the posterior expectation of model parameters. Further details on the calculation of DIC for Bayesian LCA and IRT can be found in Appendix.

Genetic analysis

Heritability of the quantitative phenotype values was estimated with the ACE model, which is well suited for twin studies.The ACE model assumes that phenotypic variation is due to additive genetic effect (A), shared environmental effect (C) and random (non-shared) environmental effect (E). The heritability is then the proportion of the total variance which is due to the additive genetic effect. The analysis was carried out using Mx (Neale et al. 1997). Mx applies a maximum likelihood method to estimate the variances and the corresponding heritability. The goodness of fit criterion used in Mx for assessing the ACE model is the Bayesian Information Criteria (BIC) (Schwarz 1978).

Non-parametric quantitative trait linkage analysis was carried out using Merlin-qtl. Merlin-qtl was developed under the general framework of Kong and Cox (1997) and Whittemore and Halpern (1994). The p_{ik} of LCA and the latent trait θ_i of IRT are treated as phenotypic traits for the genetic analysis.

Results

Bayesian LCA

Table 3 contains the DIC values for different values of $K, (K = 2, \ldots, 7)$. The DIC changes most dramatically when K changes from 2 to 3 but there is little improvement after $K = 4$. Therefore, the four-class model is preferred.

With K equal to 4, the deviance stabilized after 5,000 iterations with an approximately normal distribution, a mean of 49,062.91 and standard deviation of 126.315. The posterior marginal distributions for the majority of parameters were also approximately normal, with the exceptions of the conditional probabilities of classes 1 and 4, which are bounded by the values 0 and 1, respectively. Table 4 lists the posterior mean values and the credible intervals (analogous to frequentist confidence intervals) of all parameters of Bayesian LCA for $K = 4$.

Table 3 DIC and deviance values for $K = 2, \ldots, 7$ and Bayesian IRT model

Model	K	DIC value	Deviance
LCA	2	60,801.19	60,721.39
	3	51,390.08	51,097.95
	4	49,442.02	49,062.91
	5	48,531.12	47,577.47
	6	47,236.32	45,910.07
	7	46,687.76	45,120.79
IRT	–	51,718.36	51,370.00

Table 4 The posterior statistics of LCA model parameters and its credible interval

K	1 (CI)	2 (CI)	3 (CI)	4 (CI)
P_k	0.55 (0.55–0.56)	0.10 (0.09–0.12)	0.20 (0.19–0.22)	0.14 (0.12–0.2)
$\lambda_{k,1}$	0.00 (0.00–0.01)	0.76 (0.73–0.81)	0.72 (0.69–0.75)	0.94 (0.92–1.0)
$\lambda_{k,2}$	0.00 (0.00–0.00)	0.43 (0.39–0.48)	0.70 (0.67–0.74)	0.90 (0.88–0.9)
$\lambda_{k,3}$	0.00 (0.00–0.00)	0.34 (0.30–0.37)	0.43 (0.41–0.46)	0.71 (0.68–0.7)
$\lambda_{k,4}$	0.00 (0.00–0.00)	0.65 (0.62–0.69)	0.78 (0.76–0.80)	0.92 (0.90–0.9)
$\lambda_{k,5}$	0.00 (0.00–0.00)	0.56 (0.50–0.62)	0.93 (0.90–0.95)	1.00 (0.99–1.0)
$\lambda_{k,6}$	0.00 (0.00–0.00)	0.20 (0.15–0.26)	0.76 (0.72–0.80)	0.98 (0.97–1.0)
$\lambda_{k,7}$	0.00 (0.00–0.00)	0.18 (0.14–0.22)	0.51 (0.47–0.54)	0.93 (0.90–1.0)
$\lambda_{k,8}$	0.00 (0.00–0.00)	0.16 (0.12–0.20)	0.70 (0.66–0.75)	1.00 (0.99–1.0)
$\lambda_{k,9}$	0.00 (0.00–0.00)	0.30 (0.26–0.34)	0.70 (0.66–0.74)	0.96 (0.94–1.0)
$\lambda_{k,10}$	0.00 (0.00–0.00)	0.19 (0.16–0.23)	0.48 (0.45–0.52)	0.84 (0.81–0.9)

We observed a gradual increase in the probability of each symptom across the four classes. Class 1 is composed of participants with limited symptoms (Fig. 1). In contrast, class 4 is a collection of participants with all symptoms. Except for symptoms related to the location of the pain (unilateral, C3 of Table 2, 74%), more than 84% of individuals in this class have all other symptoms. Nearly all members in this class described their headache pain as moderate to severe, experienced sensitivity to light as the headache occurred and described the headache attacks as inhibiting their daily activities (c1: moderate/severe, $\lambda_{4,5} = 0.997$; d2a: photophobia, $\lambda_{4,8} = 0.996$; c3b: prohibitive, $\lambda_{4,6} = 0.983$, Table 4).

The main difference between the two intermediate classes 2 and 3 lies in five symptoms: duration of headache, severity of pain associated with headache, ability to carry out daily activities and the physical reactions associated with headache such as nausea/vomiting, sensitivity to light and sound and visual problems (b, c3a, c3b, d1, d2a, d2b, aura of Table 2). Members in class 3 showed higher probability of these symptoms than members in class 2. The only item experienced by more individuals in class 2 is '>5 headaches occurring in your lifetime'. Individuals in class 2 exhibited a higher frequency of headache episodes. Class 1 is the largest class with more than 55% of the total 13,062 participants. The second largest class is class 3 which contained 20% of participants followed by class 4 (14%) and class 3 (10%) (Table 4).

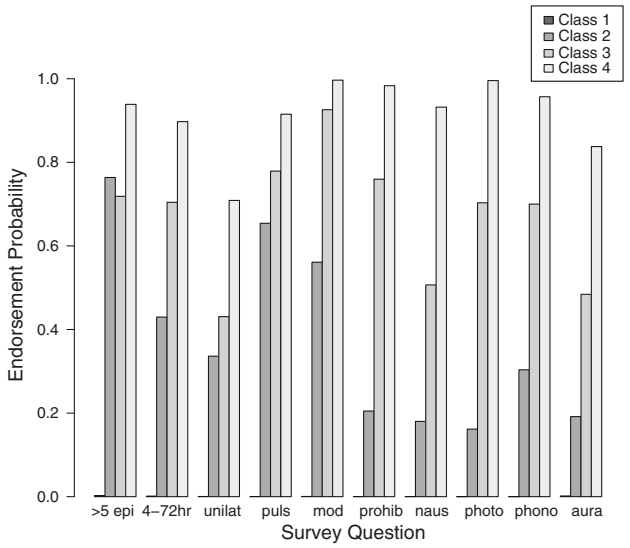

Fig. 1 Barplot showing the symptomatic characteristics of each class under the four-class model

Bayesian IRT

Because of the very large number of parameters in this model, the MCMC analysis required a large amount of computational memory and a long computational time. The marginal distributions of the item discriminant parameters and item response parameters (parameters a and b of Eq. 2) were approximately normal, with posterior mean values and credible intervals as listed in Table 5. Figure 2 displays results for each symptom, using the 2-PL model. The x-axis is the latent trait value; the y-axis is the probability of having the symptom and each line represents one symptom. Given a trait value, symptoms on the right side of Fig. 2 are less likely to be described by subjects than the symptoms on the left. For instance, nearly all subjects with latent value of 1 described the headache as moderate to severe but only 60% described the headache as unilateral (Fig. 2). Overall, the results indicate that the symptom "unilateral" is the least prevalent, followed by aura and nausea/vomiting. The other symptoms have similar values of item response probability (6, Table 5) ranging from 0.43 to 0.65.

A lower value of the item discrimination parameter a indicates a weaker correlation between the symptom and underlying latent trait. Of all ten symptoms, the estimated

Table 5 The posterior statistics of item response probability and item discrimination parameters

Item	Mean	SD	2.5%	25%	Median	75%	97.5%
a-a	4.074	0.12	3.844	3.992	4.073	4.154	4.311
a-b	4.245	0.135	3.983	4.152	4.244	4.336	4.518
a-c1	2.874	0.073	2.73	2.824	2.874	2.922	3.021
a-c2	4.454	0.109	4.24	4.38	4.453	4.525	4.672
a-c3a	8.368	0.361	7.688	8.117	8.36	8.598	9.095
a-c3b	6.562	0.217	6.164	6.415	6.553	6.702	7.003
a-d1	4.646	0.136	4.392	4.551	4.644	4.739	4.919
a-d2a	6.608	0.219	6.194	6.46	6.601	6.755	7.047
a-d2b	5.263	0.148	4.981	5.164	5.258	5.359	5.567
a-Aura	3.732	0.104	3.54	3.659	3.728	3.799	3.943
b-a	0.493	0.015	0.464	0.482	0.492	0.502	0.524
b-b	0.618	0.015	0.59	0.608	0.618	0.627	0.647
b-c1	0.936	0.016	0.907	0.925	0.936	0.947	0.969
b-c2	0.49	0.013	0.466	0.48	0.489	0.499	0.516
b-c3a	0.427	0.014	0.401	0.418	0.427	0.436	0.454
b-c3b	0.61	0.013	0.585	0.601	0.609	0.618	0.635
b-d1	0.781	0.014	0.756	0.771	0.781	0.79	0.807
b-d2a	0.648	0.012	0.625	0.64	0.648	0.656	0.673
b-d2b	0.623	0.013	0.6	0.615	0.623	0.632	0.648
b-Aura	0.845	0.014	0.818	0.835	0.845	0.854	0.872

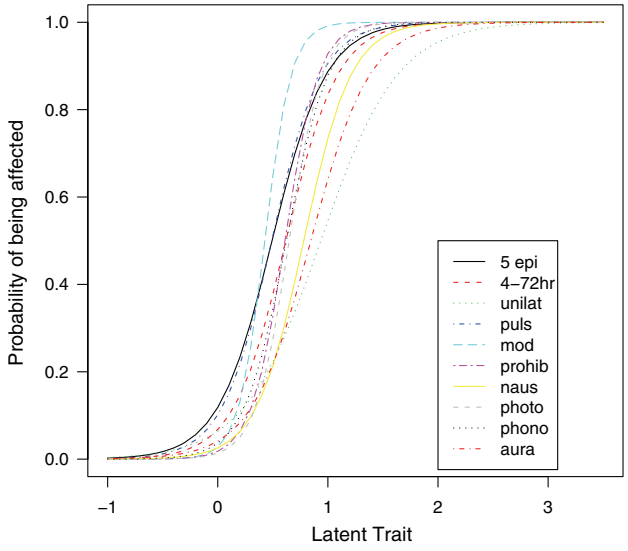

Fig. 2 Plot showing the relationship between the latent trait and each symptom for IRT model

latent value correlates most strongly with the severity of pain during the headache, followed by the symptoms 'prohibitive of daily activities', photophobia and phonophobia (indicated by the posterior mean discrimination parameters of 8.368, 6.608, 6.562 and 5.263 respectively; Table 5). Location of pain ('unilateral') and aura correlated least strongly with the latent value.

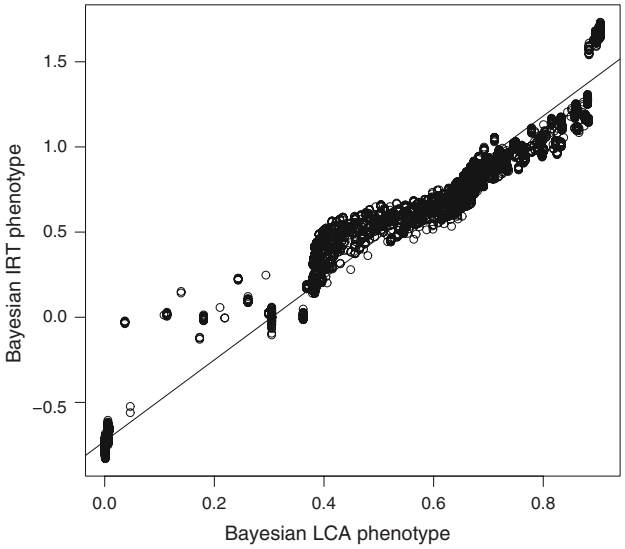

Fig. 3 Scatter plot showing the relationship between predicted continuous phenotypic values by Bayesian LCA and Bayesian IRT model. The continuous phenotypic trait is bounded between 0 and 1, where 1 represented a severe type of common migraine and 0 indicated no evidence of common migraine. The *straight line* is the predicted linear relationship between these two phenotypes. The correlation between the phenotypic traits is 0.99

Model comparison

The DIC estimated for the Bayesian IRT model of the migraine symptomatic data is 51718.36 (Table 3). This value is slightly higher than the equivalent value of 49,442.02 for the best LCA model ($K = 4$). This suggests that, by this criterion, Bayesian LCA with $K = 4$ classes provides a slightly better model for these data than the Bayesian IRT model.

The models were also compared using deviance, which is $-2\times$log-likelihood and measures the fit of a model but not its complexity. Although the difference in the deviance values between LCA with $K = 4$ and IRT is less than for DIC, lower deviance is still observed for LCA with $K = 4$ (Table 3). This supports the observation that LCA with $K = 4$ is a slightly better model for these data.

Figure 3 is a scatter plot showing the relationship between the phenotype trait values estimated using Bayesian LCA and Bayesian IRT. There is a strong correlation between phenotype values estimated with the two models (correlation = 0.99).

Genetic analysis

The ACE model was fitted to the latent trait value θ of the Bayesian IRT model and the converted continuous estimate derived from Bayesian LCA (Eq. 1), to estimate the heritability of common migrainous headache. Although the trait values derived from the Bayesian LCA model are

preferable (as indicated by the smaller BIC value in Table 6), there is little difference in the heritability between the traits (component A of Table 6) due to the high correlation in the phenotypic trait values of the two models. The estimated heritability for both models is 0.37 (CI 0.34–0.40). The non-shared environmental factor is the main contributor to the variation in the twin migraine status (62%, component *E* of Table 6). Interestingly, the common shared environment in twins has negligible effect on the variation of migraine "severity" (as measures by our latent trait measures) between twin pairs.

Figure 4 summarizes the results of linkage analysis using the phenotypic measures derived from Bayesian LCA with four classes using MERLIN-qtl. The black solid line of Fig. 4 shows the LOD score of the trait derived from the posterior mean of the model parameters using Eq. 1. Strong evidence for linkage was observed at 7q31-q33 where LOD scores are between 2.37 and 3.54. The highest LOD score (3.54) was observed for marker D7S640 on chromosome 7, followed by a nearby marker, GATA43C11 (LOD = 3.33). Besides chromosome 7, there is some suggestive evidence of linkage on chromosomes 1 and 2. The LOD scores for the area around marker ATA73A08 (153–157 cM) on chromosome 1 are between 2.14 and 2.23. Marker GATA194A05 on chromosome 2 also has a LOD score above 2.0 (LOD = 2.04). The next highest peak is on chromosome 8 at 86.314cM, with a LOD score of 1.85. Figure 5 presents similar results for trait values derived from Bayesian IRT; the black solid line shows the LOD score for the posterior mean trait. Linkage to the posterior mean values of Bayesian IRT indicates a maximum LOD score on chromosome 7 at 136 cM. This coincides with the maximum LOD score linking to the trait estimated using the Bayesian LCA model. Similarly, the loci with the second and third highest LOD scores in the Bayesian LCA are also identified under the Bayesian IRT analysis [marker ATA73A08 (LOD = 2.2) and GATA194A05 (LOD = 1.99)].

Table 6 The parameters of ACE model estimated using Mx, where A is the variation due to genetic variation and C is the variability due to environmental effect

Model	BIC	Component	Mean	Lower CI	Upper CI
Bayesian LCA	−48,290.53	A	0.3719	0.3413	0.4017
		C	0.0000	0.0000	0.0000
		E	0.6281	0.5983	0.6587
Bayesian IRT	−39,159.34	A	0.3760	0.3475	0.4037
		C	0.0000	0.0000	0.0000
		E	0.6240	0.5963	0.6525

In this analysis, sex is included as a covariate

Discussion

This paper aimed to compare two latent variable models in describing the phenotype of migraine and investigate the impact of model choice on the subsequent genetic analysis. Whereas the LCA model assumes that the subject population comprises multiple distinct subgroups or subtypes of migraine, the IRT model assumes a single continuous latent value for each subject. Both models were fitted within the Bayesian framework. Based on DIC, the LCA model with four classes provides a better fit to the data than the IRT model, but the classes could be ordered in such a way that there was a clear progression from minimum symptoms ('non-affected') in the first class through to nearly all symptoms (the most severe type of migrainous headache) in the last class. Members of the non-affected class in the Bayesian LCA model also had the lowest latent trait values under the Bayesian IRT model, compared with other classes. The two intermediate classes differ in the last five symptoms, which may be related to individual reaction during the headache episodes. An exception to the increasing progression of symptoms was the frequency of headache, which was larger in class 2 than class 3. The importance of this symptom as an indicator of the severity of migraine has been questioned by Ligthart et al. (2006) in a Dutch cohort.

The characteristics of the classes identified using Bayesian LCA in this analysis are very similar to those reported by Nyholt et al. (2004), but quite different from those found by Ligthart et al. (2006) . The latter authors observed that except for the items related to the severity of pain and sensitivity to light and sound, the prevalence of other symptoms was much lower in their least severe class compared with the finding here. Moreover, the differences we observed here for classes 2 and 3 were not present in their cohort, with their classes 1 and 2 (corresponding to our classes 2 and 3) both composed of individuals with low physical reaction during the headaches.

A potential problem with the LCA model is that the classes identified via this method may be influenced by the composition of the population or the method of sampling-factors which have nothing to do with the etiology of the disease. For instance, when the data are dominated by individuals with moderate migrainous headache and only a small proportion of subjects have the severe type of headache, classes derived from LCA may not represent "affected" and "non-affected" disease status. Therefore, as for all clustering approaches, the results of LCA need to be interpreted with a degree of caution and ideally with reference to clinical criteria.

Although the IRT model fit less well with respect to the DIC and is less parsimonious than its LCA counterpart in terms of the number of parameters, it provides a valuable

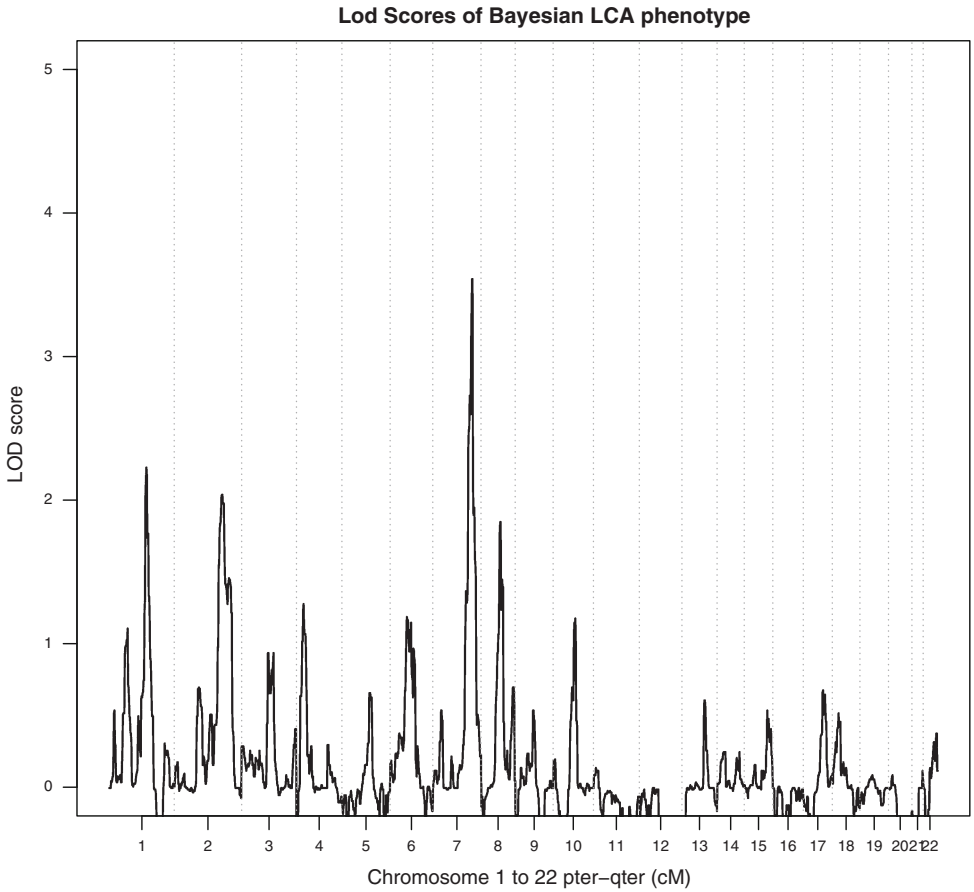

Fig. 4 Linkage plot of phenotype derived using Bayesian LCA

insight into the relationship between individual symptoms and the underlying latent value which is not directly available in the LCA model. The analysis of the Bayesian IRT revealed that the symptom 'unilateral' is less important in prediction of migraine status. This finding is supported by the Bayesian LCA with low prevalence of this symptom in all classes. This may be due to the participants' understanding of this item, or difficulty in remembering the location of the pain during the time of the survey. Surprisingly, the symptom 'aura' was reported to be the second least correlated variable to the latent trait of the Bayesian IRT model, yet this is the major symptom used in the IHS criteria in separating subjects into two subtypes, MA and MO. As much as LCA and IRT are different methods, these two models complement each other and together provide a better investigation, interpretation and explanation of these data than either can provide by itself.

In our previous work (Chen et al. 2009), we found that the results of genetic analysis using traits derived from grade of membership (GoM; Woodbury et al. 1978) are very different from those obtained using traits derived from LCA and fuzzy clustering (Fanny, Fanny; Kaufman and Rousseeuw 1990). Based on information criteria, LCA outperformed the GoM model for these migraine symptom data. The current study demonstrates that a fourth model, IRT, produces similar results to LCA and therefore Fanny, leaving GoM as the odd method out. Further research is suggested to confirm whether the GoM model is suitable for data analyses such as those reported here.

Currently, linkage analysis is designed for either dichotomous or continuous traits and multinomial traits can only be analyzed by introducing a threshold value or by conversion. As an example of the former, Nyholt et al. (2005) fitted migraine symptom data using LCA with four classes, then separated the subjects into "affected" and "non-affected" based on the predicted allocation to the first two and last two classes, respectively.

Here, we employed a simple conversion function to convert the multinomial trait to a continuous measure. This simple conversion included the clustering feature of LCA, as well as the uncertainty of belonging to multiple classes. Without any other manipulation, this continuous measure has a high correlation with the latent trait of the IRT model; therefore, with some confidence, this converted value is representative of migraine "severity".

Indeed, more advanced methods could be considered for the conversion of the clustering output of LCA to a continuous phenotypic trait. Factor mixture analyses (McLachlan et al. 2005) which provides a general framework for combining LCA and factor analysis, is one such method.

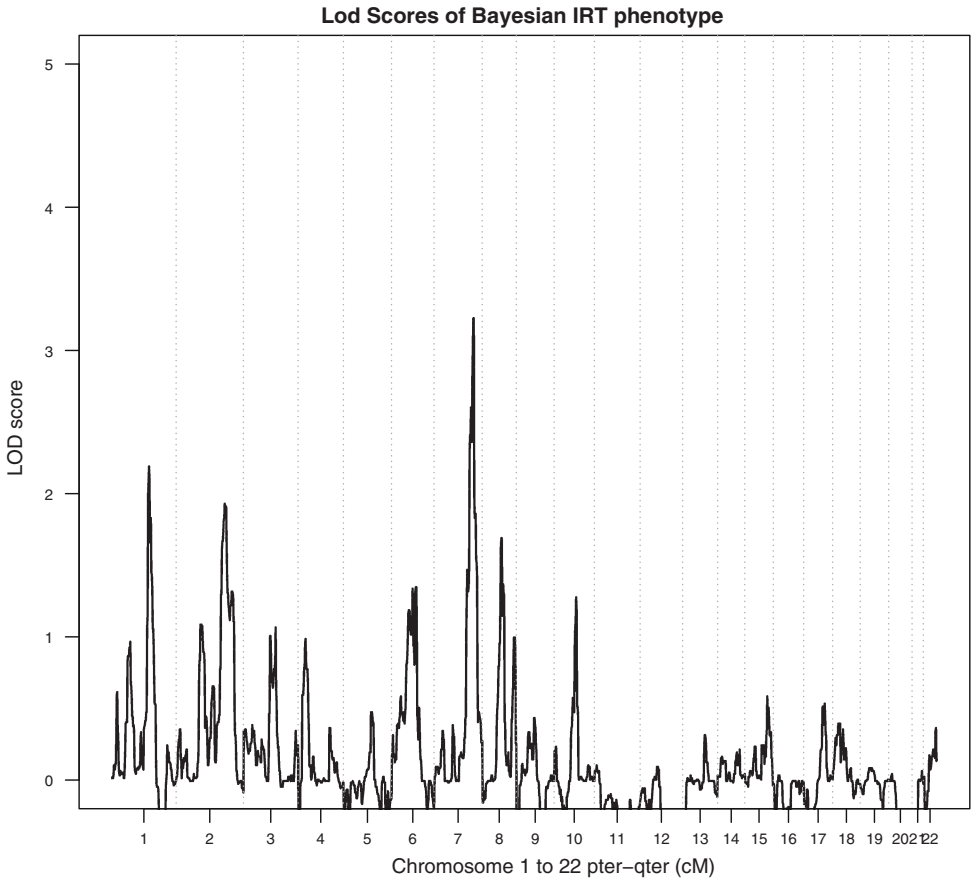

Fig. 5 Linkage plot of phenotype derived using Bayesian IRT

As expected, the high correlation in the trait values of the two models resulted in minimal differences in the results from genetic analyses. Interestingly, the heritability of both traits is 0.37, which is comparable to the heritability estimated in an Australian cohort when the status is determined by the IHS criteria (h^2 = 0.34, Mulder et al. 2003; h^2 = 0.36, Nyholt et al. 2004], despite these values being derived from substantially different data.

Analogous to the heritability results, linkage to the latent trait values from the IRT model is also nearly identical to that of the LCA continuous trait. There is strong evidence for linkage to chromosome 7q31-q33, which has not been previously identified by other studies. In addition, markers ATA73A08 and GATA194A on chromosomes 1 and 2, respectively are reported in other studies. Marker ATA73A08 is close to the familial hemiplegic migraine (FHM)-implicated ATP1A2 gene (De Fusco et al. 2003; Vanmolkot et al. 2003) and GATA194A on chromosome 2 is close to the SCN1A FHM3 gene (Dichgans et al. 2005). The other interesting locus identified here is on chromosome 10q22.3. Recent work by Anttila et al. (2008) applied both LCA and TCA to Australian and Finnish cohorts and successfully identified this locus linked to migraine.

Building upon our earlier work on the empirical clustering of migraine symptomatology, the results from our Bayesian latent trait modeling indicate that migraine symptom data may be modeled using a single continuous variable representing severity of the disease. The purpose of such quantitative measures is not to diagnose migraine but to provide new research tools for geneticists. For example, as in other complex diseases, the use of quantitative traits such as lipid values in hyperlipidaemia or allergy-related phenotypes in asthma provides an option for refined analysis. We therefore propose that the use of such continuous measures, which directly reflect migraine severity, provides a powerful and useful approach to identify genes contributing to migraine susceptibility.

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Appendix 1

DIC3 is the difference between twice the posterior mean deviance and the deviance of estimated η

$$\mathrm{DIC} = 2\overline{D(\eta)} - D(\tilde{\eta}) \tag{4}$$

In the DIC3 proposed by Celeux et al. (2006), when the likelihood has a closed form, the first term can be approximated using M simulated values, $\eta^{(1)}, \ldots, \eta^{(M)}$, where $\eta^{(m)} = (p^m, \lambda^m)$ from an MCMC chain.

$$\begin{aligned}\overline{D(\eta)} &= \mathbb{E}_\eta[-2\log f(y|\eta)|y] \\ &\approx -\frac{2}{M}\sum_{m=1}^{M}\log f(y|\eta^{(m)})\end{aligned} \tag{5}$$

The second term of Eq. 3 we used here is the posterior expectation, $\mathbb{E}[f(y|\eta)|y]$ which is also approximated using the parameters of an MCMC chain.

$$\begin{aligned}D(\tilde{\eta}) &= -2\log\hat{f}(y) = -2\log\mathbb{E}_\theta[f(y|\eta)|y] \\ &\approx -2\log\frac{1}{M}\sum_{m=1}^{M} f(y|\eta^{(m)})\end{aligned} \tag{6}$$

From Eqs. 5 and 6, Eq. 3 is the expanded form of Eq. 4. In the Bayesian LCA model, $f(y|\eta^{(m)})$ is

$$f(y|\lambda^{(m)}, p^{(m)}) = \sum_{k=1}^{K} p_k^{(m)} \prod_i^n \prod_j^J \left(\lambda_{kj}^{(m)}\right)^{y_{ij}} \left(1-\lambda_{kj}^{(m)}\right)^{1-y_{ij}}$$

and the posterior mean deviance is

$$\overline{D(p,\lambda)} = -\frac{2}{M}\sum_{m=1}^{M}\log\sum_{k=1}^{K} p_k^{(m)} \prod_i^n \prod_j^J \left(\lambda_{kj}^{(m)}\right)^{y_{ij}} \left(1-\lambda_{kj}^{(m)}\right)^{1-y_{ij}}$$

and $D(\hat{\eta})$ is

$$\begin{aligned}D(\hat{p},\hat{\lambda}) = -2\log\Bigg\{&\frac{1}{M}\sum_{m=1}^{M}\sum_{k=1}^{K} p_k^{(m)} \prod_i^n \prod_j^J \left(\lambda_{kj}^{(m)}\right)^{y_{ij}} \\ &\times \left(1-\lambda_{kj}^{(m)}\right)^{1-y_{ij}}\Bigg\}.\end{aligned}$$

For the Bayesian IRT model, the likelihood is

$$f(y|\theta,a,b) = \prod_i^n \prod_{j=1}^J \left[\frac{e^{a_j(\theta_i-b_j)}}{1+e^{a_j(\theta_i-b_j)}}\right]^{yij} \left[1-\frac{e^{a_j(\theta_i-b_j)}}{1+e^{a_j(\theta_i-b_j)}}\right]^{1-yij}$$

therefore $\overline{D(\eta)}$ is

$$\begin{aligned}\overline{D(\theta,a,b)} = -\frac{2}{M}\sum_{m=1}^{M}\log &\prod_i^n \prod_{j=1}^J \left[\frac{e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}{1+e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}\right]^{yij} \\ &\times \left[1-\frac{e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}{1+e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}\right]^{1-yij}\end{aligned}$$

and $D(\hat{\eta})$ is

$$\begin{aligned}D(\hat{\theta},\hat{a},\hat{b}) = -2\log\Bigg\{&\frac{1}{M}\sum_{m=1}^{M}\prod_i^n \prod_{j=1}^J \left[\frac{e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}{1+e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}\right]^{yij} \\ &\times \left[1-\frac{e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}{1+e^{a_j^{(m)}(\theta_i^{(m)}-b_j^{(m)})}}\right]^{1-yij}\Bigg\}.\end{aligned}$$

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