Generalized Admixture Mapping for Complex Traits

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Abstract

Admixture mapping is a popular tool to identify regions of the genome associated with traits in a recently admixed population. Existing methods have been developed primarily for identification of a single locus influencing a dichotomous trait within a case-control study design. We propose a generalized admixture mapping (GLEAM) approach, a flexible and powerful regression method for both quantitative and qualitative traits, which is able to test for association between the trait and local ancestries in multiple loci simultaneously and adjust for covariates. The new method is based on the generalized linear model and uses a quadratic normal moment prior to incorporate admixture prior information. Through simulation, we demonstrate that GLEAM achieves lower type I error rate and higher power than ANCESTRYMAP both for qualitative traits and more significantly for quantitative traits. We applied GLEAM to genome-wide SNP data from the Illumina African American panel derived from a cohort of black women participating in the Healthy Pregnancy, Healthy Baby study and identified a locus on chromosome 2 associated with the averaged maternal mean arterial pressure during 24 to 28 weeks of pregnancy.

Keywords

generalized linear model local ancestry mapping by admixture linkage disequilibrium quadratic normal moment prior quantitative traits

Admixture mapping, also known as mapping by admixture linkage disequilibrium, has become an important tool for localizing disease genes. A number of admixture mapping studies have successfully identified candidate loci associated with common complex traits and biomarkers (Reich et al. 2005; Zhu et al. 2005; Freedman et al. 2006; Kao et al. 2008; Yang et al. 2011).

As a genome-wide association approach, admixture mapping aims to identify susceptibility loci, which confer risk or are linked with other loci harboring risk variants, for complex traits that have different prevalences between ancestral populations (McKeigue 2005; Winkler et al. 2010). In recently admixed populations, such as African Americans or Hispanic Americans, the chromosome resembles a mosaic of ancestry blocks, with alleles inherited together from one ancestral population within each block. The ancestral populations have different risks for the trait, which is assumed to be due in part to frequency differences in risk variants. The block containing the risk variant is more likely to have originated from the high-risk ancestral population than the low-risk ancestral population. Hence, detecting the association between ancestry block and trait helps us to localize the susceptibility loci.

The ancestral status of a block at a specific genomic region, or local ancestry, is unobserved and can be estimated based on ancestry informative markers (AIMs), such as single-nucleotide polymorphisms (SNPs), which vary in frequency across ancestral populations. AIMs tag the status of an ancestry block, similar to that of tagSNPs, which are used to characterize common haplotypes in a chromosomal region. In the African-American population, the linkage disequilibrium due to admixture extends for a much wider region than the linkage disequilibrium between haplotypes (Smith et al. 2004; Patterson et al. 2004). Hence, compared with the tagSNP-based genome-wide association study, admixture mapping requires many fewer markers to tag the whole genome and therefore increases the detection power at a reduced resolution, which is still greater than linkage analysis (Patterson et al. 2004; Smith and O’Brien 2005). Moreover, admixture mapping is less vulnerable to allelic heterogeneity because it relies on local ancestry instead of alleles directly.

Given the local ancestries of each individual, several hypothesis testing-based approaches have been proposed to test, one locus at a time, the null hypothesis that the AIM is unlinked to the complex-trait/disease for a dichotomous trait within a case-control study design. McKeigue (1998) proposed a test for genetic disequilibrium between an AIM locus and the trait locus, conditional on the parental
admixture. Patterson et al. (2004) suggested a Bayesian likelihood ratio test, comparing the likelihood under the alternative hypothesis (a given AIM locus is associated with the trait) vs. the one under the null hypothesis, for cases and controls respectively. Zhu et al. (2004) described a Z-score statistic, similar to the one proposed by Montana and Pritchard (2004), for testing the estimated local ancestry proportion is equal to one under the null hypothesis for case-control and case-only studies.

In contrast, few methods are proposed for the quantitative traits and to consider multiple loci simultaneously while adjusting for other risk factors. To apply the aforementioned admixture methods primarily developed for a dichotomous trait, the common practice has been to dichotomize subjects with the least and greatest q% (e.g., 20%) of the quantitative trait value as cases and controls; The remaining subjects with in-between quantitative trait values are then discarded (Reich et al. 2007; Cheng et al. 2010; Scherer et al. 2010). In addition, ADMIXMAP (Hoggart et al. 2003) has been proposed for quantitative traits based on generalized linear model, which is also used by Basu et al. (2009) and Zhu et al. (2011) for one locus at a time. However, complex traits are commonly caused by joint effects of the multiple genes and other risk factors, such as age, sex, and smoking status. Investigating the association between AIM loci and a trait, one locus a time, without considering other loci or risk factors may capture a rather small proportion of joint effects and will possibly lead to inconsistent conclusions. Similar considerations have been addressed in association mapping using shrinkage priors (Wu et al. 2009; Guan and Stephens 2011).

With these motivations, we propose regression-based generalized admixture mapping (GLEAM) for both quantitative and qualitative traits. The new approach is able to examine the association between the complex trait and single or multiple loci simultaneously while also adjusting for other risk factors. GLEAM is based on generalized linear models (GLMs) (McCullagh and Nelder 1989), with linear regression for continuous traits, logistic regression for binary (e.g., case-control) traits and Poisson regression for count traits. The predictors in GLM include local ancestries at the given AIM loci and other risk factors. The local ancestry is defined as the number of alleles from the high-risk ancestral population, for example, 0, 1, or 2 alleles from African ancestry at a given AIM locus. The association examined in GLEAM can be adjusted by other risk factors. We assume for complex genetic traits that most loci have no association with the trait, a few loci may have small to modest association (e.g., odds ratio <2 for binary traits), and the loci with greater proportions of disease-causing alleles from the high-risk population would possibly have stronger association with the traits. This prior knowledge is incorporated into GLEAM by using a quadratic normal moment (QNM) prior (Johnson and Rossell 2010) for the predictors in GLM (see Material and Methods) with the benefit of reducing the type I error while increasing the power, as demonstrated by the simulations in Results.

The number of AIMS (1500–3000) (Smith et al. 2004) is usually larger than the number of study subjects, and keeps increasing (>4000) (Tandon et al. 2011) with advances due to the HapMap project (The International Hapmap Consortium 2005) and commercially available genome-wide SNP arrays. It is not feasible to consider loci all together simultaneously due to the “curse of dimensionality” (Bellman 1961). Rather, we propose a two-stage approach: in the first stage, we examine the association between local ancestries with the trait for one locus at a time and select a small subset of susceptibility loci; in the second stage, the associations between the various combinations of these selected loci and the trait are evaluated and the most significant ones are reported. The associations in both steps are assessed by the Bayes factor (BF), the ratio between the likelihood of observed traits under the alternative hypothesis (presence of association between single or multiple loci with traits) and that under the null hypothesis (lack of association).

Different from the association mapping based on the SNPs that are directly measured, the local ancestries are unobserved and are inferred on the basis of the AIMs via use of the Hidden Markov Model (HMM) detailed in the Appendices. At each AIM locus, the number of alleles from the high-risk ancestral population is imputed multiple times for every subject, using a Markov chain Monte Carlo (MCMC) algorithm. By using the multiple imputed datasets of local ancestries, we are able to assess the association between the traits and local ancestries directly while taking imputation uncertainty into account through Bayesian averaging. Importantly, our multiple imputation approach preserves the admixture linkage disequilibrium between the AIM loci, which is crucial for multilocus admixture mapping in GLEAM. In addition, GLEAM can also use the local ancestries sampled by other local ancestry inferring methods, such as HAPMIX (Price et al. 2009).

MATERIAL AND METHODS

Generalized linear model with QNM prior

GLEAM is a regression method that extends the current approaches in various ways. The most obvious extension is to accommodate both quantitative and qualitative traits yi through a generalized linear model with the ability to adjust for covariates Ei = (Ei1, Ei2, . . . , Eip). Specifically, we use the linear model for continuous traits,

\[
y_i = \beta_0 + \beta'S_i + \alpha'E_i + \epsilon_i,
\]

and the logistic model for dichotomous traits,

\[
\logit\{\text{Prob}(y_i = 1)\} = \beta_0 + \beta'S_i + \alpha'E_i,
\]

where p local ancestries S_i = (S_{i1}, S_{i2}, . . . , S_{ip})' are considered and centered to have mean zero, \( \beta = (\beta_1, \beta_2, . . . , \beta_p)' \) and \( \alpha = (\alpha_1, \alpha_2, . . . , \alpha_p)' \) are the regression coefficients for \( S_i \) and \( E_i \) respectively, and \( \epsilon_i \sim N(0, \sigma^2) \). We use the Bayes factor to assess the admixture association between local ancestries and the trait of interest. The Bayes factor is the ratio of the marginal likelihoods under the alternative hypothesis, \( H_1: \beta_j \neq 0 \) for \( j = 1, \ldots , p \), and null hypothesis, \( H_0: \beta_j = 0 \) for \( j = 1, \ldots , p \). Marginal likelihoods remove the parameters from the likelihood by integrating over the prior distribution. The larger the Bayes factor, the stronger the evidence in favor of \( H_1 \).

As a prior distribution for \( \beta \) under \( H_1 \), we use the QNM prior having density

\[
f_{\text{QNM}}(\beta; \tau, \sigma^2, \Sigma) = \frac{\beta' \Sigma^{-1} \beta}{(1 + \tau \sigma^2) p} f_{\text{SNP}}(\beta, 0, 1, \tau \sigma^2, \Sigma),
\]

where \( f_{\text{SNP}}(\cdot; m, V) \) is the p-dimensional multivariate normal distribution with the mean vector \( m \) and covariance matrix \( V \), and \( \tau \) is the dispersion parameter. The QNM prior is able to incorporate the case with a large number of loci of tiny effect. As shown in Figure 1A, the modes of the prior distribution will move toward zero when we reduce the value of \( \tau \). For illustration purposes, we only showed a particular value of \( \tau = 0.01 \), but as we decrease this value, tiny effects are accommodated. For data containing a large number of loci of tiny effect, the empirical Bayes approach should estimate a very small value, and the QNM prior will concentrate on very small effect sizes. Usual priors face major problems in distinguishing the signal from the noise, and we argue that nonlocal priors such as
the quadratic normal provide more accurate results for genetic effects on complex traits. Hence, The QNM prior increases the evidence in favor of both the true null and true alternative hypothesis, compared to other prior distributions (e.g., intrinsic and Cauchy priors) (Johnson and Rossell 2010). Moreover, we specify $\sigma^2 \Sigma$ as the covariance matrix of the (iterative weighted) least square estimation of $\beta$ in the GLM. This choice not only leads to convenient computation but also easily incorporates the prior knowledge about the effect of local ancestry on the trait. For example, when $S_1$ is orthogonal to $E_0$, $\Sigma = (S'S)^{-1}$ with $S = [S_1, S_2, \ldots, S_9]'$ in the linear model for the continuous trait. As illustrated by the right panel of Figure 1, the QNM prior with $\Sigma = (S'S)^{-1}$ suggests that for each locus, the greater the proportion of alleles from the high-risk population ($p_2$), on average the larger the risk effect of local ancestry. Such relationships are observed in admixture mapping but not in association mapping based on SNPs in general. More importantly, when we investigate multiple loci simultaneously, it is crucial to take the correlation (linkage disequilibrium, LD) between the local ancestries into consideration. Figure 2 plots several volcano-shaped bivariate QNM densities for various correlations between two local ancestries. It is clear that for two loci with admixture LD (as shown in Figure 2D), the greater the proportion of alleles from the high-risk population ($p_2$), on average the larger the risk effect of local ancestry. When we investigate multiple loci simultaneously, it is desirable to quantify the evidence for joint association of multiple loci with the trait. For this reason, in the second stage, we list all possible combinations of susceptibility loci selected in the first stage. For each set of susceptibility loci, we can again calculate the Bayes factors for the joint association at those loci simultaneously. The most significant ones are reported. The local ancestries at the AIM loci are unobserved and imputed from the HMM. The imputation uncertainty could be properly accounted for by calculating weighted average of the Bayes factors for each imputed local ancestry dataset, which is similar to the strategy used by Guan and Stephens (2008) in imputation-based association mapping for testing untyped variants.

Simulation studies

We carried out simulation studies to assess the performance of GLEAM in terms of type I error rate and power under various scenarios and compared it with the method based on Bayesian likelihood ratio (BLR) by Patterson et al. (2004), which is implemented by the software ANCESTRYMAP (http://genepath.med.harvard.edu/~reich/Software.htm) as well as regularized regression methods Lasso and elastic net (Tibshirani 1996; Zou and Hastie 2005; Friedman et al. 2010). GLEAM and ANCESTRYMAP use slightly different HMMs to impute the local ancestries and regularized regression methods require given local ancestries. Because of these differences, we assumed the true local ancestries were given and focused on evaluating the ability of localizing susceptibility loci instead of estimating local ancestries. Because of these differences, we assumed the true local ancestries were given and focused on evaluating the ability of localizing susceptibility loci instead of estimating local ancestries. Our simulations were based on empirical data of local ancestries for 1001 African-American subjects from the HPHB Study (Miranda et al. 2009), with 1296 AIM loci measured across the genome. The MATLAB codes for simulating and analyzing the data are included in a Supporting Information folder online.

We started by investigating the type I error rates for the local ancestries that were scattered around different regions of the genome and in linkage equilibrium. Under this scenario, the falsely localized
AIM locus would be in the region remote from the true disease causing locus, which leads to a false positive finding. We first randomly sampled 1000 AIM loci with replacement from 1296 AIM loci for 1000 subjects. At each AIM locus, we simulated the local ancestries measured by the number of alleles from the African ancestral population from their maximum a posteriori (MAP) frequency estimates under the assumption of Hardy-Weinberg equilibrium. Ten sets of trait data were then generated such that we were able to assess the type I error rates under the genome-wide threshold level, by using the following null model for continuous traits: $y_i = \alpha E_i + \varepsilon_i$ and for binary traits, $\logit(\text{Prob}(y_i = 1)) = \alpha E_i$; where the continuous risk covariate $E_i$ and the measurement error $\varepsilon_i$ followed standard normal distributions. We considered two situations whereby $\alpha = 0$ in the absence of a covariate effect and $\alpha = 1$ in the presence of a covariate effect.

We next examined power under the single locus alternative models. We simulated 100 sets of traits. Each set included 1000 subjects and one disease associated local ancestry whose location was randomly sampled from 259 AIM loci, where the proportion of African ancestral population ranged from 0.8321 to 0.8817 and was on the top 20% percentile among 1296 AIM loci. Given the local ancestry $S$, continuous covariates $E$, and measurement error $\varepsilon_i$ generated same as that for the null model, continuous traits were simulated from $y_i = \alpha E_i + \beta S_i + \varepsilon_i$ and binary traits from $\logit(\text{Prob}(y_i = 1)) = \alpha E_i + \beta S_i$. Under both models, the $\beta$ was specified as $\beta = c \times$ proportion of African ancestral population which reflected the a priori observation that the locus with the larger proportion of the high-risk ancestral (here African American) population usually demonstrated stronger association with the traits. For continuous traits, we chose the values of effect size multiplier $c$ as 0.2, 0.25, 0.3, 0.35, and 0.4 respectively, with the largest possible effect size equal to 0.3527. Similarly, we picked the $c$ values as 0.4, 0.5, 0.6, 0.7, and 0.8 for binary traits with the largest possible odds ratio equal to 1.8537.

We further considered a multilocus alternative model where two local ancestries were associated with the traits and there existed admixture linkage disequilibrium. To do so, we generated an artificial chromosome composed of two pieces from chromosome 1 and chromosome 4 with the length 139.50 Mb and 114.88 Mb, respectively, for 1000 subjects, based on empirical data on local ancestries from HPHB study. In the middle of each chromosome piece with 51 loci,
there is one locus whose proportion of African ancestry population was among the highest in all 1296 AIM loci. In the simulations, those two loci are assumed to be associated with traits. We generated 100 sets of continuous and binary traits respectively, each of which was simulated similarly to the single locus alternative model except with two local ancestries involved and both effect size multiplier \( c \) values set at 0.7 for continuous traits and 0.35 for binary traits.

The simulated datasets were analyzed by the GLEAM and the BLR method. Because the BLR method was primarily developed for binary traits, the BLR method required transformation of continuous traits into binary ones, such as defining the subjects with top 20% traits as the cases and the one with bottom 20% traits as controls.

**RESULTS**

**Simulation studies**

Figure 3 presents the empirical type I error rates for both the binary and continuous traits, with or without covariate effects. For the GLEAM and the BLR methods, we chose a threshold of 2 for \( \log_{10}(BF(y)) \) to control the genome-wide type I error rates. The regularization parameters of Lasso and elastic net are chosen with the minimal cross validation error. The loci with nonzero regression coefficients are regarded as the ones associated with the traits. As illustrated in Figure 3A and Figure 3B, under the null model that all the local ancestries are in linkage equilibrium, the type I error rate is controlled at a low level with the median around \( 5 \times 10^{-4} \) for
GLEAM and $4.2 \times 10^{-3}$ for the BLR method. In both cases, those type I error rates seem overly conservative. However, in the application to real data, slight admixture linkage disequilibrium between the AIM loci will significantly inflate the type I error rate close to the nominal levels ($i.e.$, $\alpha = 0.05$ or 0.005), which is discussed in the later paragraphs. Comparing Figure 3A and Figure 3B reveals that the type I error rates of GLEAM are consistently smaller than those of the method based on BLR and are little affected by the presence of covariate effects when properly adjusted. The covariates are not considered by the BLR method and have a mixed effect on type I error rates, where the median is slightly reduced with the maximal type I error rates increased. For the regularized regression methods Lasso and elastic net, the type I errors are significantly inflated, as shown in Figure 3C and Figure 3D. In addition, when a nonzero covariate presents, the type I errors will further increase.

Power of the methods also was evaluated for binary and continuous traits under the single locus alternative model, with or without covariate effects. We considered various effect sizes of local ancestries with the results shown in Figure 4. For the binary trait, when the effect size is small, the BLR method performs better with larger power. With the increment of the effect sizes, GLEAM gradually outperforms the BLR method. For both methods, covariates have

\begin{figure}[h]
\centering
\begin{subfigure}{0.45\textwidth}
\includegraphics[width=\textwidth]{A.png}
\caption{Binary traits without covariate effect}
\end{subfigure}
\begin{subfigure}{0.45\textwidth}
\includegraphics[width=\textwidth]{B.png}
\caption{Binary traits with covariate effect}
\end{subfigure}
\begin{subfigure}{0.45\textwidth}
\includegraphics[width=\textwidth]{C.png}
\caption{Continuous traits without covariate effect}
\end{subfigure}
\begin{subfigure}{0.45\textwidth}
\includegraphics[width=\textwidth]{D.png}
\caption{Continuous traits with covariate effect}
\end{subfigure}
\caption{Powers for single locus alternative models. Power is calculated for each dataset with 100 replications total for the binary or continuous traits simulated under the single locus alternative model with or without covariate effect. The $\times$ indicates the median of powers by the GLEAM and $\bullet$ denotes the median of powers by the method based on Bayesian likelihood ratio; $\ast$ denotes the median of regularized regression with lasso; $\circ$ denotes the median of regularized regression with elastic net. The whiskers on each bar represent the minimal and maximal powers respectively. The effect sizes of local ancestries are equal to the multiplication of effect size multiplier $c$ and the proportion of African ancestry population. (A) Binary traits without covariate effect; (B) Binary traits with covariate effect; (C) Continuous traits without covariate effect; (D) Continuous traits with covariate effect.}
\end{figure}
Table 1 The frequency of identified loci for each locus or locus combination at different regions of the artificial chromosome

| Trait | Method | REG1 | REG2 | REG3 | Locus1 | Locus2 | Locus1/2* |
|-------|--------|------|------|------|--------|--------|-----------|
| Binary | BLR    | 0.103| 0.047| 0.025| 0.000  | 0.000  | 1.000     |
|        | GLEAM1*| 0.013| 0.014| 0.003| 0.020  | 0.020  | 0.960     |
|        | GLEAM2*| 0.002| 0.003| 0.001| 0.030  | 0.030  | 0.940     |
|        | Lasso  | 0.030| 0.025| 0.017| 0.000  | 0.000  | 1.000     |
|        | Elastic net | 0.045| 0.038| 0.025| 0.000  | 0.000  | 1.000     |
| Continuous | BLR | 0.035| 0.018| 0.011| 0.030  | 0.400  | 0.560     |
|        | GLEAM1 | 0.021| 0.017| 0.004| 0.030  | 0.000  | 0.970     |
|        | GLEAM2 | 0.004| 0.003| 0.002| 0.040  | 0.000  | 0.960     |
|        | Lasso  | 0.039| 0.031| 0.023| 0.000  | 0.000  | 1.000     |
|        | Elastic net | 0.049| 0.037| 0.029| 0.000  | 0.000  | 1.000     |

a Applying the combination of Locus 1 and Locus 2.
b Applying first step of generalized admixture mapping procedure only.
c Applying both steps of generalized admixture mapping procedure.

BLR, Bayesian likelihood ratio; GLEAM, generalized admixture mapping.

DISCUSSION

When the admixture linkage disequilibrium is used, admixture mapping is an indispensable tool to localize the alleles that are associated with the qualitative or quantitative traits and diseases that vary in prevalence across the ancestral populations. In this article, we propose a flexible and powerful generalized admixture mapping strategy that allows for the identification of loci with high power. The approach, known as GLEAM, incorporates the admixture linkage disequilibrium effect in the admixture mapping model. This strategy significantly improves the power of admixture mapping compared to traditional methods, which typically assume Hardy-Weinberg equilibrium and ignore the admixture linkage disequilibrium.

The proposed GLEAM approach was applied to a dataset to identify the local ancestry associated with the averaged maternal MAP, a continuous trait, while we adjusted for mother’s age. The local ancestries were multiply imputed based on the HMM. We first examined the marginal association between the trait and local ancestries, one locus at a time. The results are summarized in Figure 5, where one local ancestry on the chromosome 2 was identified with its log_10(Bayes factor) = 2.05 exceeding the threshold 2. With only one local ancestry localized, the second step of the generalized admixture mapping procedure was unnecessary. The same data were analyzed by the BLR method, which treated the subjects with averaged maternal MAP more than 93.67 (top 20% quantile) as cases and the ones with averaged maternal MAP less than 79.33 (bottom 20% quantile) as control. No local ancestry was identified as being associated with the averaged maternal MAP with this approach, presumably due to its relatively low power compared with the GLEAM approach.
approach, which is based on the generalized linear model and is able to incorporate admixture prior information by using the quadratic normal moment prior and to adjust for covariates. The proposed method is applicable to both qualitative and quantitative traits with satisfactory power while controlling the type I error rates at a low level, and is able to be easily implemented as we demonstrated with our HPHB example.

In addition to the flexibility to handle different types of traits, other attractive generalizations include consideration of multiple loci simultaneously. It is known that admixture linkage disequilibrium extends much further than haplotype linkage disequilibrium. Consequently, if we only examine one locus at a time, the local ancestries which are highly correlated to the true disease associated local ancestry tend to be identified as significant ones as well. As demonstrated by the simulations, those false positives can be significantly reduced by considering multiple susceptible loci simultaneously, which reduce the type I error rates and improve the mapping resolution. In addition, GLEAM specifies a hidden Markov model treating the recombination rates varying across the genome, which allows us to infer the recombination “hotspots” in admixture population. Moreover, within the generalized linear model framework, it is straightforward to extend the current method to populations with more than to two ancestral populations, such as Hispanic populations, by adding extra ancestry population covariates. It is also easy to consider the interaction between the local ancestries and covariates with the properly specification of the priors on interaction coefficients.

ACKNOWLEDGMENTS
This work was supported by Award Number R01ES017436 from the National Institute of Environmental Health Sciences, by funding from the National Institutes of Health (5P2O-RR020782-O3), and the U.S. Environmental Protection Agency (RD-83329301-0) and by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Bethesda, Maryland. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Environmental Health Sciences, the National Institutes of Health, or the U.S. Environmental Protection Agency.

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APPENDICES

Hidden Markov Model

For a population-based design, suppose we have $I$ unrelated subjects, each of which has the same set of $J$ AIMs recorded. The local ancestry is measured by $S_{ij} \in \{0, 1, 2\}$, the number of alleles from the high-risk population $A$ (e.g., African) for the $i$th subject and the $j$th AIM. $S_{ij}$ is unknown and will be imputed using the HMM. For African Americans with African and European ancestral populations, HMM assumes that given the $S_{ij}$, the distribution of $X_{ij} \in \{0, 1, 2\}$, the number of variant alleles, is independent of other $S_{ij}$ and $X_{ij}$ with $j' \neq j$ and is specified by the observation probability mass matrix $P_j = [p_j(m, n)]_{3 \times 3}$ with $p_j(m, n) = \text{Prob}(X_{ij} = n | S_{ij} = m)$ and

$$P_j = \begin{pmatrix} X_{ij} = 0 & X_{ij} = 1 & X_{ij} = 2 \\ S_{ij} = 0 & (1 - p^B)^2 & 2p^B (1 - p^B) & p^B (1 - p^B) \\ S_{ij} = 1 & (1 - p^A)^2 & (1 - p^A)(1 - p^B) & 2p^A (1 - p^A) \\ S_{ij} = 2 & (1 - p^A)(1 - p^B) & (1 - p^A)(1 - p^B) & p^A (1 - p^B) \end{pmatrix},$$

where $p^A$ is the minor allele probability at loci $j$ in the high-risk population $A$ and $p^B$ is the corresponding probability in the low-risk population $B$.

The latent states $S = [S_{ij}]_{I \times J}$ tagging the status of the ancestry blocks, are unobserved and modeled by a Markov chain which considers the genetic recombination events. Let $\rho_i$ denote the genome-wide proportion of alleles from the high-risk population $A$ for subject $i$, $Q_{ij} = [(1 - \rho_j)^2, 2\rho_j(1 - \rho_j), \rho_j^2]$ initial state vector, $R_{ij} \in \{0, 1, 2\}$ the number of recombination events between AIM loci $j - 1$ and $j$, $Q_{ij}^{(r)} = [q_{ij}^{(r)}(m, n)]_{3 \times 3}$ the conditional state transition matrix given $r$ recombination events between the neighboring AIM loci with $q_{ij}^{(r)}(m, n) = \text{Prob}(S_{ij} = n | S_{ij-1} = m, R_{ij} = r)$. The Markov chain $S$ is governed by the state transition matrix $Q_j = [Q_{ij}(m, n)]_{3 \times 3}$ with $q_{ij}(m, n) = \text{Prob}(S_{ij} = n | S_{ij-1} = m)$. $Q_j = \sum_{r=0}^{R_{ij}} Q_{ij}^{(r)} \text{Prob}(R_{ij} = r)$, where $Q_{ij}^{(0)}$, $Q_{ij}^{(1)}$ and $Q_{ij}^{(2)}$ are specified as...
\[ Q_{ij}^{(0)} = S_{ij}^{(j-1)} = 0 \begin{pmatrix} 1 & 0 & 0 \ 0 & 1 & 0 \ 0 & 0 & 1 \end{pmatrix}, \quad Q_{ij}^{(1)} = S_{ij}^{(j-1)} = 1 \begin{pmatrix} 1 - \rho_i & \rho_i & 0 \ \frac{1}{2} (1 - \rho_i) & \frac{1}{2} \rho_i & \frac{1}{2} \rho_i \ 0 & 1 - \rho_i & \rho_i \end{pmatrix}, \]

and \( R_{ij} \sim \text{Bin}(2, \gamma_j) \) a binomial distribution with \( \gamma_j \) the probability that a recombination event occurs between the neighboring AIM loci in a single chromosome. Consequently, we can get,

\[ Q_{ij} = S_{ij}^{(j-1)} = 0 \begin{pmatrix} S_{ij} = 0 & 2 \gamma_j \rho_i (1 - \gamma_j \rho_i) & \gamma_j \rho_i \left( 1 - \gamma_j (1 - \rho_i) \right) \\
\gamma_j (1 - \rho_i) & (1 - \gamma_j (1 - \rho_i)) & \gamma_j (1 - \gamma_j (1 - \rho_i)) \end{pmatrix} \]

\[ S_{ij} = 1 \begin{pmatrix} S_{ij} = 1 & 2 \gamma_j \rho_i (1 - \gamma_j \rho_i) & \gamma_j \rho_i \left( 1 - \gamma_j (1 - \rho_i) \right) \\
\gamma_j (1 - \rho_i) & (1 - \gamma_j (1 - \rho_i)) & \gamma_j (1 - \gamma_j (1 - \rho_i)) \end{pmatrix} \]

\[ S_{ij} = 2 \begin{pmatrix} S_{ij} = 2 & 0 \end{pmatrix} \]

We further specify informative prior distributions for the parameters \( p_h^A, p_h^B, \gamma_j \) and \( \rho_i \) involved in the HMM. Although the \( p_h^A \) of the high-risk population A is unknown, we have information on \( p_h^B \), the proportion of the variant allele \( j \) in a subpopulation of high-risk population A (e.g. YRI for African), from the HapMap or 1000 genome projects. Hence, we expect that \( p_h^A \) would be close to \( p_h^B \) and specify \( p_h^A \sim \text{Beta}(\tau^A \rho_h^B, \tau^A (1 - \rho_h^B)) \) with the expectation \( E(p_h^A) = p_h^B \) and \( \tau^A \sim [50, 1000] \) a uniform distribution to reflect the uncertainty in borrowing the subpopulation information. A similar specification is chosen for \( p_h^B \) based on the proportion of the variant allele \( j \) in a subpopulation of low-risk population B (e.g. CEU for European). As for \( \gamma_j \), it is well known that the recombination probability is roughly proportional to \( d_i \) the genetic distance between \( (j - 1) \)th and \( j \)th AIM loci. A common choice is \( \gamma_j = 1 - \exp(-\lambda d_i) \) with \( \lambda = 6 \) the number of recombination events per Morgan since admixture (Falush et al. 2003; Patterson et al. 2004). However, recombination “hotspots” can occur along the chromosomes where the recombination probabilities are much greater than the other regions (Myers et al. 2005). For this reason, we avoid the aforementioned parametric specification of \( \gamma_j \). Instead, we let \( \gamma_j = \text{Beta} (\tau^\gamma \gamma_{ij}, \tau^\gamma (1 - \gamma_{ij})) \) with the expectation \( E(\gamma_j) = \gamma_{ij} = 1 - \exp(-\lambda d_i) \). Hence, on average the probability of recombination is proportional to the genetic distance while allowing significant deviation (e.g. “hotspots”) from the average. The deviation is measured by \( \tau^\gamma \) with \( \text{Var}(\gamma_j) = \frac{\mu_{ij}^\gamma - \gamma_{ij}^2}{\tau^\gamma} \). In addition, for the admixed population, we often know about the proportions of ancestral populations at the population level. For example, the African American population in general consists of 80% African ancestral population and 20% European ancestral population (Smith and O’Brien, 2005; Winkler et al. 2010). We borrow this population level information to specify \( \rho_i \), the subject specific proportion of high-risk population A, by letting \( \rho_i = \text{Beta} (\tau^\rho \rho_0, \tau^\rho (1 - \rho_0)) \) with \( \rho_0 \) (e.g. 0.8 for African American) and \( \text{Var}(\rho_i) = \frac{\mu_i^\rho - \rho_i^2}{\tau^\rho} \).

We use an MCMC algorithm to sample the local ancestries \( S_i \) for \( i = 1, 2, \ldots, l \), along with other parameters. The details of MCMC are given as follows.

**MCMC algorithm for HMM**

We propose an MCMC algorithm for posterior computation of HMM as follows.

(1) Impute the missing AIM \( X_{ij}^m \). Given the \( P_i \) and \( S_{ij}, X_{ij}^m \in \{0, 1, 2\} \) can be easily sampled with probability mass \( p_i(S_{ij}, X_{ij}^m) \).

(2) Update the latent states \( S_i \) for \( i = 1, 2, \ldots, l \). Given the \( Q_{ij} \) and \( \mathbf{R}_i = [R_{ij}]_{1 \leq j \leq p} \) we will use the forward filtering backward sampling (FFBS) algorithm (Scott 2002) to sample the \( S_i \) in one block. The FFBS algorithm mixes more rapidly compared to the direct Gibbs sampler which samples one \( S_{ij} \) a time conditional on the remains of \( S_i \). Let \( X_{ij} = [X_{ij1}, X_{ij2}, \ldots, X_{ijn}] \) and \( \mathbf{R}_i = [R_{ij1}, R_{ij2}, \ldots, R_{ijn}] \). We begin the FFBS algorithm by calculating \( Q_{ij}^{(0)} = (q^{(m)}_{ij}(m, n))_{3 \times 3} \) with \( q^{(m)}_{ij}(m, n) = \text{Prob}(S_{ij} = m, S_j = n | X_{ij}^m, \mathbf{R}_i) \) recursively for \( j = 1, 2, \ldots, f \). As

\[ q^{(m)}_{ij}(m, n) = \frac{\text{Prob}(S_{ij} = m, S_j = n | X_{ij}^m, \mathbf{R}_i)}{\text{Prob}(X_{ij}^m | X_{ij1}^{m-1}, \mathbf{R}_i)} = \frac{q^{(m-1)}_{ij}(m, n)p_j(n, X_{ij})}{\text{Prob}(X_{ij}^m | X_{ij1}^{m-1}, \mathbf{R}_i)}, \]
where \( q^F(m) = Q_{m0}, \) \( \text{Prob}(X_{ij}|X_{i-1}^{j-1}, R_i) = \sum_{m=0}^{2} m \sum_{n=0}^{2} \text{Prob}(S_{ij-1} = m, S_{ij} = n, X_{ij}|X_{i-1}^{j-1}, R_i), \) and \( q^F(n) = \sum_{m=0}^{2} q^F(m, n). \)

We can then sample the \( S_i \) backward from \( S_{ij} \) to \( S_{i1} \) with

\[
\text{Prob}(S_i|X_i, R_i) = \text{Prob}(S_{ij}|X_i, R_i) \prod_{j=1}^{I-1} \text{Prob}(S_{ij-j}|S_{ij-j+1}, X_i, R_i),
\]

where

\[
\text{Prob}(S_{ij}|X_i, R_i) = q^F(S_{ij}),
\]

\[
\text{Prob}(S_{ij-j}|S_{ij-j+1}, X_i, R_i) = \frac{q^F(S_{ij-j+1}) (S_{ij-j}, S_{ij-j+1})}{q^F(S_{ij-j}) (S_{ij-j+1})}.
\]

The initial state \( S_0 \) will be sampled with \( \text{Prob}(S_0|S_1, X_i, R_i) = \frac{q^F(S_0, S_1)}{q^F(S_1)} \).

3. Update the recombination count \( R_i = [R_{ij}]_{1 \times I} \) for \( i = 1, 2, \ldots, I \). \( R_{ij} \) is sampled with full conditional probability mass function

\[
\text{Prob}(R_{ij}|S_{ij-1} = m, S_{ij} = n, Q_{i}^{(0)}, Q_{i}^{(1)}, Q_{i}^{(2)}, \gamma_j) = \frac{q^F_{ij} (m, n) \left( \frac{2}{R_j} \right) ^{\gamma_j} \left( 1-\gamma_j \right) ^{-R_j}}{\sum_{r=0}^{2} q^F_{ij} (m, n) \left( \frac{2}{2-r} \right) ^{r} \left( 1-\gamma_j \right) ^{2-r}}.
\]

4. Update recombination probability \( \gamma_j \) from Beta(\( \tau^\gamma \gamma_j + \sum_{i=1}^{I} R_{ij} \tau^\gamma (1-\gamma_j) + 2I - \sum_{i=1}^{I} R_{ij} \) for \( j = 1, 2, \ldots, I \).

5. Update the proportion ancestry from population A \( p_i \) from Bin(\( \tau^\rho \rho_0 + n_{01}^{(1)} + n_{01}^{(2)} + n_{11}^{(1)} + n_{11}^{(2)} + 2n_{12}^{(1)} + 2n_{22}^{(1)} + n_{12}^{(2)} + n_{22}^{(2)} + 2n_{21}^{(2)} + 2n_{21}^{(1)} \), where \( n_{ij}^{(1)} = \sum_{j=1}^{I} I(S_{ij-1} = k \text{ and } S_{ij} = l \text{ and } R_{ij} = 1) \) and \( n_{ij}^{(2)} = \sum_{j=1}^{I} I(S_{ij-1} = k \text{ and } S_{ij} = l \text{ and } R_{ij} = 2) \).

6. Update \( Q_{i}^{(0)}, Q_{i}^{(1)}, Q_{i}^{(2)} \) and \( Q_{00} \) based on last \( p_i \) for \( i = 1, 2, \ldots, I \).

7. Update \( p_j^A \) and \( p_j^B \) for \( j = 1, 2, \ldots, I \). Let \( n_{ij} = \sum_{j=1}^{I} I(S_{ij} = k \text{ and } X_j = l) \) and \( n_{ij}^{VA} \) denotes the case that the allele from population A is variant allele when \( S_{ij} = 1 \) and \( X_j = 1 \). \( n_{ij}^{VA} \) is unobserved and can be imputed from Bin(\( n_{ij-1}^{(1)} + n_{ij-1}^{(2)} + 2n_{ij}^{(1)} + 2n_{ij}^{(2)} + 2n_{ij}^{(3)} + 2n_{ij}^{(4)} \)). \( p_j^A \) is then sampled from Beta(\( \tau^\alpha p_j^A + n_{22} + 2n_{21} + n_{21}^{VA}, \tau^A (1-p_j^A) + n_{21} + 2n_{20} + n_{11} - n_{ij}^{VA} \)) and \( p_j^B \) is sampled from Beta(\( \tau^\alpha p_j^B + n_{01} + 2n_{01} + n_{11} - n_{ij}^{VA}, \tau^A (1-p_j^B) + n_{01} + 2n_{00} + n_{11} - n_{ij}^{VA} \)).

8. Update \( \tau^A \) and \( \tau^B \) using Random-Walk Metropolis-Hasting. For \( \tau^A \), we propose the new \( \tau^A + \epsilon \) where \( \epsilon \sim N_1(0, \sigma_{\tau^A}^2) \). The posterior distribution of \( \tau^A f(\tau^A|p_j^A) \propto \prod_{j=1}^{I} \text{Beta}(p_j^A|\tau^A p_j^A, \tau^A (1-p_j^A)) I(50 < \tau^A < 1000) \). Then, \( \tau(\tau^A + \epsilon) - \min\left(\frac{\tau^A + \epsilon}{\tau^A}, 1\right) \). We draw \( \tau^A \sim U[0, 1] \). If \( \mu^A < \alpha(\tau^A, \tau^A) \), then \( \tau^A \) is replaced by \( \tau^A \); otherwise, \( \tau^A \) is unchanged. Similar update is conducted for \( \tau^B \).