Theoretical Interpretation of Genetic Studies in Admixed Populations

Hanbin Lee[1,2,§,†] and Moo Hyuk Lee[1,§]

[1]Department of Medicine, Seoul National University College of Medicine

[2]Department of Mathematical Sciences, Seoul National University

[§]These authors contributed equally.

[†]Corresponding Author: `hanbin973@snu.ac.kr`

Abstract

Admixed populations are formed through mixing of distant populations resulting in heterogeneous linkage disequilibrium patterns. This hampered the interpretation of genetic association studies followed by the development of various methods tailored for the purpose without clear guidance. In this work, we propose a unifying theory built upon population genetics and causal inference that brings a straightforward interpretation of GWAS findings in admixed populations. Furthermore, the theory establishes the connection between distinct methods in admixed GWAS. Finally, we propose two novel tests motivated by our theory that combine association and admixture signals.

1 Introduction

Populations that experienced recent admixture events provides an unique opportunity to understand the genetic basis of complex traits. When two or more populations are admixed, individuals inherit their genetic material from multiple ancestral populations. The more recent the admixture event is, the longer the range of blocks of genetic materials originating from the same ancestry is. Hence, using these blocks (hereafter, admixture blocks) for genome-wide scan remained popular until high-density single nucleotide polymorphism (SNP) markers became widely available.

Admixture mapping (ADM) measures the association between the number of haplotypes from a particular ancestry (or the *local ancestry*) at a region with the trait to localize genetic signals [1, 2]. When the underlying causal variant is more common compared to others, an individual is more likely to carry the causal variant with increasing number of haplotypes inheriting from that population. The approach has been successful in detecting disease loci associated from obesity to prostate cancer [3, 4].

Shortly after the success of genome-wide ADM, *genome-wide association study* (GWAS), a association mapping approach became popular [5]. As SNP LD blocks were generally shorter than admixture blocks, association mapping provided higher resolution in localizing the susceptibility loci compared to admixture mapping. However, GWAS have been performed predominantly on populations from single continental origins such as Europeans and East Asians [6, 7].

Despite the decline in diversity in genome-wide genetic studies, statistical methods for admixed populations have been steadily developed in the past decade. Pasaniuc and colleagues, together with a novel combined test for association and admixture, benchmarked various methods for detecting genetic signals in admixed populations [8]. As cohorts comprised of admixed populations (e.g. African Americans) gradually grew in the past years, methods such as Tractor has been proposed [9]. These methods differ in several ways. An important topic is whether to include local ancestry into the statistical model [10, 11, 12]. However, these arguments are largely based on simulations and no theoretical guarantees have been made. As a result, there have been no agreement in which method to use.

In this work, we propose a unifying theory built upon population genetics and causal inference that provides a general guidance for both association and admixture mapping in admixed populations. We assume that the population follows the admixture model and derive the target parameters (hereafter, estimands) of distinct methods proposed for admixed GWAS [13, 14]. The result provides provable interpretation of statistical estiamtes delivered from admixed populations. The interpretation gives a general guide on how to perform GWAS downstream analyses ranging from meta-analysis to genetic correlation and heritability inference. Furthermore, statistical efficiency and power are analyzed under

the asymptotic regime. Finally, we propose provably powerful tests designed using theory to perform admixed GWAS that combines association and admixture signals. To our knowledge, the novel tests are the first to combine the two designs in quantitative traits.

2 Results

Trait and population models

The central argument of this work is based on the distinction between the causal variants C_{ij} and the marker variants M_{ik}. $i = 1, \ldots, n_I$, $j = 1, \ldots, n_J$ and $k = 1, \ldots, n_K$ are the indices of individuals, causal variants and marker variants respectively. The boldface variables are the vector of variants $\mathbf{C}_i = \{C_{ij}\}_{j=1,\ldots,n_J}$ and $\mathbf{M}_i = \{M_{ik}\}_{k=1,\ldots,n_K}$. Y_i denotes the quantitative trait of an individual which is a linear function respect to the causal variants.

$$Y_i = \alpha_0 + \sum_{j=1}^{n_J} C_{ij}\alpha_j + \epsilon_i \tag{1}$$

where α_j is the causal effect size of variant j and ϵ_i is the random error such that $\mathbb{E}[\epsilon_i \mid \mathbf{C}_i] = 0$. We call this model the *causal additive model* (CAM) [15].

Suppose that there are n_L ancestral populations indexed by $l = 1, \ldots, n_L$. The admixture model we consider is determined by the ancestral reference allele frequency of markers g_{lk} and the individual's ancestral proportion P_{il} (or the *global ancestry*). $\mathbf{P}_i = \{P_{il}\}_{l=1,\ldots,n_L}$ is the random vector of global ancestry ($\sum_{l=1}^{n_L} P_{il} = 1$). For causal variants, we write f_{lj} for the reference allele frequencies. We define admixture blocks $b = 1, \ldots, n_B$ across the genome where each block has a ancestral origin called *local ancestry* $\mathbf{L}_{ib} = \{L_{ibl}\}_{l=1,\ldots,n_L}$. Here, L_{ibl} is the number of haplotypes of an individual inheriting from ancestral population l. For each variant j and k, they belong to a particular block b in which we write as $j, k \in b$ with a slight abuse of notation. Variables are often written respect to the parental origin (or haplotypes). For $\mathbf{L}_{ib}$, $\mathbf{C}_i$ and $\mathbf{M}_i$, the superscript $\mathbf{h} = \mathbf{m}, \mathbf{p}$ (maternal and paternal) denotes the haplotype. For example, $C_{ij}^{\mathbf{h}} = 0, 1$ is the reference allele count of the causal variant j at the $\mathbf{h}$-th haplotype.

The value at a given locus of an individual M_{ik} (or C_{ij}) is determined through a two step process. In the first step, an individual inherits its genetic material at the locus from a particular ancestral population according to its global ancestry. Next, the reference allele count is assigned according to the reference allele frequency of the selected ancestral population. This process is summarized in the following causal graph (**Figure 1**).
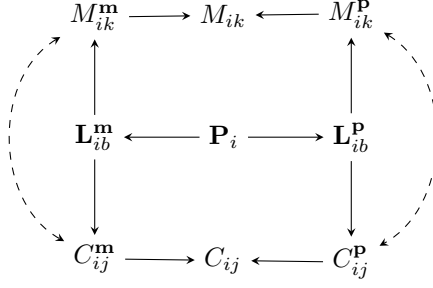
Figure 1: The causal graph of population genetic variables in admixed populations.

The bidirectional arrow denotes the linkage between M_{ik} and C_{ij}. The Pritchard-Stephens-Donnelly (PSD) model follows the described process with additional probabilistic assumptions [13].

Linkage disequilibrium and marginal effect sizes in admixed populations

Let h_{ljk} be the joint allele frequency of C_{ij} and M_{ik} in the ancestral population l. The *linkage disequilibrium* (LD) covariance is $D_{ljk} = h_{ljk} - f_{lj}g_{lk}$. Then the marginal effect size of marker M_{ik} restricted to an ancestral population l is the product of the LD covariance and the causal effect size [15].

$$\beta_{lk}^{\mathrm{anc}} = \sum_{j=1}^{n_J} \frac{D_{ljk}}{g_{lk}(1 - g_{lk})} \alpha_j \tag{2}$$

A natural question is whether the marginal effect sizes in admixed populations can be expressed similar formula (2). As formula (2) involves LD covariance, it is natural to analyze the LD in an admixed population.

Two regression estimators have been advocated in performing association studies in admixed populations. The first estimator regresses the trait Y_i with multiple reference allele counts for each ancestral population [8, 9]. Let M_{ikl} be the number of reference allele counts from ancestry l. Therefore, $M_{ik} = \sum_{l=1}^{n_L} M_{ikl}$. Together, local ancestry $\mathbf{L}_{ib}$ for $b \in k$ is included to the regression.

$$Y_i = \beta_0 + \sum_{l=1}^{n_L} M_{ikl}\beta_{lk} + \sum_{l=2}^{n_L} L_{ibl}\gamma_{lk} + \sum_{l=2}^{n_L} P_{il}\delta_{lk} + \zeta_{ik} \tag{3}$$

Note that the latter two summations start from $l = 2$ to avoid multicolinearity due to $\sum_{l=1}^{n_L} L_{ibl} = 2$ and $\sum_{l=1}^{n_L} P_{il} = 1$. Then,

$$\beta_{lk} = \beta_{lk}^{\mathrm{anc}} \tag{4}$$

Hence, regression (3) recovers the ancestry specific marginal effect sizes that would have been obtained had the regression been performed exclusively in a particular ancestral population. Therefore, the marginal effect size obtained from regression (3) does not contain any admixture signals. Furthermore, the coefficient of L_{ibl}, the local ancestry, is

$$\gamma_{lk} = \sum_{j \in b} \left(\frac{f_{lj} - h_{ljk}}{1 - g_{lk}} - \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} \right) \alpha_j \tag{5}$$

Thus, the local ancestry captures the effect of the causal variants that is missed by the marker. This is the term that captures the signal due to admixture that was missed by equation (3). We return to the issue on how marker and local ancestry capture the underlying signal later when discussing our novel estimator combining the both.

The second estimator does not separate the minor allele counts and does not include local ancestry [8, 10]. Only global ancestry is included as covariates. This regression is the usual one that is used in cohorts from a single continental origin without admixture.

$$Y_i = \beta_0^{\mathrm{agg}} + M_{ik}\beta_k^{\mathrm{agg}} + \sum_{l=2}^{n_L} P_{il}\delta_{lk}^{\mathrm{agg}} + \zeta_{ik}^{\mathrm{agg}} \tag{6}$$

This regression recovers a variance weighted mean of $\beta_k(\mathbf{P}_i)$

$$\beta_k^{\mathrm{agg}} = \frac{\mathbb{E}[\beta_k(\mathbf{P}_i)\mathrm{Var}(M_{ik} \mid \mathbf{P}_i)]}{\mathbb{E}[\mathrm{Var}(M_{ik} \mid \mathbf{P}_i)]} \tag{7}$$

where

$$\beta_k(\mathbf{P}_i) = \sum_{j \in b} \frac{\sum_l D_{ljk}P_{il} + \sum_l g_{lk}f_{lj}P_{il}(1 - P_{il}) - \sum_{l \neq l'} g_{lk}f_{l'k}P_{il}P_{il'}}{\sum_l g_{lk}(1 - g_{lk})P_{il} + \sum_l g_{lk}^2 P_{il}(1 - P_{il}) - \sum_{l \neq l'} g_{lk}g_{l'k}P_{il}P_{il'}} \alpha_j \tag{8}$$

Although equation (8) is complicated at glance, for an individual that inherits all of its genome from a single ancestral population, i.e. $P_{il} = 1$ and $P_{il'} = 0$ for $l \neq l'$, $\beta_k(\mathbf{P}_i) = \beta_{lk}^{\mathrm{anc}}$. Also, the numerator is the LD between the two variants right after admixture of n_L populations ignoring recombination [16]. Therefore, it can be said that regression (6), unlike (3), captures signals from admixture.

Finally, we discuss the admixture mapping (ADM). ADM in quantitative traits is the regression

$$Y_i = \beta_0^{\mathrm{adm}} + \sum_{l=2}^{n_L} L_{ibl}\gamma_{lk}^{\mathrm{adm}} + \sum_{l=2}^{n_L} P_{il}\delta_{lk}^{\mathrm{adm}} + \zeta_{ik}^{\mathrm{adm}} \tag{9}$$

This regression yields a very intuitive estimand, for $k \in b$,

$$\gamma_{lk}^{\mathrm{adm}} = \sum_{j \in b} (f_{lj} - f_{1j}) \alpha_j \tag{10}$$

which is the product of the underlying causal effect and the difference of reference allele frequencies between ancestral populations. That said, large allele frequency stratification leads to larger ADM signal.

Because regression (6) captures admixture signals, it has a close connection to ADM that holds when $n_L = 2$. When the marker is in LD with the causal variant only through admixture,

$$\beta_k^{\mathrm{agg}} = \frac{(g_{2k} - g_{1k})\mathbb{E}[P_1 P_2]}{g_1(1 - g_1)\mathbb{E}[P_1] + g_2(1 - g_2)\mathbb{E}[P_2] + (g_{2k} - g_{1k})^2 \mathbb{E}[P_1 P_2]} \cdot \gamma_{2k}^{\mathrm{adm}} \tag{11}$$

holds, which means that the two regresssion estimates essentially the same quantity that differs only up to a constant factor. Nevertheless, the efficiency of two approaches is different where ADM is strictly more powerful than regression (6) asymptotically.

The role of local ancestry

The inclusion of local ancestry has been a central discourse in association mapping of admixed populations [10, 11, 12]. We first analyze the effect of local ancestry on the interpretability of the marginal effect sizes. Recently, Hou et al. argued that excluding local ancestry from regression (3) is better in terms of power to detect marginal effect size heterogeneity across ancestries [12]. We show that this comes at the cost of lost interpretability. When the local ancestry is omitted in regression (3), β_{lk} is no more $\beta_{lk}^{\mathrm{anc}}$, and even worse, becomes a combination of parameters from multiple ancestries (see **Online Methods**). It has a closed form formula when $n_L = 2$ which is

$$
\begin{aligned}
\beta_{1k}^{\mathrm{nolanc}} &= \beta_{1k}^{\mathrm{anc}} + \sum_{j=1}^{n_J} \frac{g_{1k} g_{2k}(1 - g_{2k})\mathbb{E}[P_{i1}P_{i2}]\mathbb{E}[P_{i2}]}{\Lambda_{12}} \left(\frac{f_{1j} - h_{1jk}}{1 - g_{1k}} - \frac{f_{2j} - h_{2jk}}{1 - g_{2k}} \right) \alpha_j \\
\beta_{2k}^{\mathrm{nolanc}} &= \beta_{2k}^{\mathrm{anc}} + \sum_{j=1}^{n_J} \frac{g_{1k}(1 - g_{1k})g_{2k}\mathbb{E}[P_{i1}]\mathbb{E}[P_{i1}P_{i2}]}{\Lambda_{12}} \left(\frac{f_{2j} - h_{2jk}}{1 - g_{2k}} - \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} \right) \alpha_j
\end{aligned} \tag{12}
$$

As a result, comparing β_{lk} to conclude inter-ancestry difference becomes invalid. A test without local ancestry is valid provided the LD pattern in the ancestral populations are all identical.

Another important issue is statistical power. Earlier studies have found that inclusion of local ancestry alters the power of discovery. Three components are involved: (1) the estimand changes, (2) the variance of the estimator changes, and (3) the degree of freedom of the test changes due to the inclusion (or exclusion) of local ancestry. As shown in equation (4), adjusting local ancestry eliminates

the admixture LD from the estimation. Therefore, when admixture rather than linkage dominates the signal, local ancestry adjusted tests are likely to perform poorly. In this case, ADM is strictly more powerful than any association analysis like regression (3) and (6) (see **Online Methods**). In terms of the variance of the estimators, adjusting local ancestry is likely to be harmful because local ancestry directly affects the allele frequencies but not the trait [17]. For the degrees of freedom, it is evident that the larger the degrees of freedom becomes, the less powerful the test becomes.

Downstream analysis using summary statistics

Since regression (3) recovers ancestry specific effect sizes, the produced summary statistics can be used for downstream analysis such as heritability and genetic correlation estimation. However, care is required because the effective sample size is different from what is expected from a GWAS in a homogeneous population. The theory shows that the effective population size varies depending on the reference allele frequencies, and as a consequence, varies across loci. This invalidates these summary statistics as a valid input for downstream analysis such as the linkage disequilibrium score regression (LDSC) [18].

In practice, however, a convenient approximation can be used to overcome this problem. In cases like the UK Biobank, the ancestral proportions are concentrated in the vertices of the PCA plot making the locus-dependent terms in the effective sample size negligible (see **Methods**). As a result, the multiplying the overall ancestral proportion $\mathbb{E}[P_{il}]$ to the overall sample size can be used as a common effective sample size for estimating heritability and genetic correlation in the l-th ancestral population.

3   Discussion

In this work, we derive formal interpretation of regression coefficients of methods proposed for association studies in admixed population. The interpretation provides a clear guidance on when to include or exclude covariates such as local ancestry. Further characterization of the variance structure reveals the power properties of the methods. Finally, we propose powerful tests as extensions of existing methods based on the theoretical results we have derived.

A notable character of our work is that regressions are proved rather than assumed at first place. We setup a trait model (the CAM) and the demographic model (the admixture model) and derive the estimators from scratch. This way, we were able to shed light on the properties of the estimators in the light of population genetics and causal inference. We hope that this approach becomes common in genetic methodology development which is likely to promote new findings and enhance interpretability of the results.

There are several limitations in this work. The current setup only considers population structure due to admixture. Therefore, other population processes such as inbreeding and assortative mating is not addressed [19]. Such processes breaks down the conditional independence between haplotypes which is central to our proofs. Nonetheless, our framework remains valid under ancestry-driven assortative mating because it is well-controlled by conditioning on the global ancestry [20, 21]. Trait-based assortative mating, however, remains a challenge. Second, this work targeted population designs, so the estimands of sibling designs should be addressed [22]. Further work should be made to address these issues.

Acknowledgements

Online Methods

Note that all vectors are column vectors unless mentioned otherwise.

The Admixture Model

As described in **Results**, the reference allele counts C_{ij} and M_{ik} are determined through a two step process in admixed populations (**Figure 1**). Therefore, the joint probability of $(\mathbf{P}_i, \mathbf{L}_{ib}, C_{ij}, M_{ik})$ obeys the following factorization.

$$\mathbb{P}(\mathbf{P}_i, \mathbf{L}_{ib}, C_{ij}, M_{ik}) = \mathbb{P}(\mathbf{P}_i) \cdot \mathbb{P}(\mathbf{L}_{ib} \mid \mathbf{P}_i) \cdot \mathbb{P}(C_{ij}, M_{ik} \mid \mathbf{L}_{ib}) \tag{M1}$$

$\mathbb{P}(\mathbf{P}_i)$ is the usually referred as the prior distribution of global ancestry. In the PSD model, this is given as the Dirichlet distribution [13].

$$\mathbf{P}_i \sim \text{Dirichlet}(\alpha_1, \ldots, \alpha_{n_L}) \text{ for } \alpha_1, \ldots, \alpha_{n_L} > 0 \tag{M2}$$

In this work, we mostly condition on $\mathbf{P}_i$ so the distribution of $\mathbf{P}_i$ does not alter the conclusions. Hence, we remain agnostic about the distribution of $\mathbf{P}_i$.

To determine $\mathbb{P}(\mathbf{L}_{ib} \mid \mathbf{P}_i)$, we must assume that the local ancestry of two haplotypes are independent given $\mathbf{P}_i$. In other words, we allow population structure by $\mathbf{P}_i$ but no assortative mating or inbreeding within a fixed $\mathbf{P}_i$. Given the independence, $\mathbb{P}(\mathbf{L}_{ib} \mid \mathbf{P}_i)$ follows a multinomial distribution with two trials and the probability of each choice given by the global ancestry $\mathbf{P}_i$.

$$\mathbf{L}_{ib} \mid \mathbf{P}_i \sim \text{Multinomial}(n = 2, p = \mathbf{P}_i) \tag{M3}$$

Determining the joint conditional probability $\mathbb{P}(C_{ij}, M_{ik} \mid \mathbf{L}_{ib})$ will be deferred to the next section when we derive the estimands of the regressions (3) and (6). Here, estimand stands for the target parameter in which the regression estimates [23]. Instead, we only write the marginal conditional expectations $\mathbb{E}[C_{ij} \mid \mathbf{L}_{ib}]$ and $\mathbb{E}[M_{ik} \mid \mathbf{L}_{ib}]$.

$$\mathbb{E}[C_{ij} \mid \mathbf{L}_{ib}] = \sum_{l=1}^{n_L} f_{lj} L_{ibl} \text{ and } \mathbb{E}[M_{ik} \mid \mathbf{L}_{ib}] = \sum_{l=1}^{n_L} g_{lk} L_{ibl} \tag{M4}$$

The conditional expectation conditional only on the global ancestry is also important. This is obtained

through the law of total expectation.

$$
\begin{aligned}
\mathbb{E}[C_{ij} \mid \mathbf{P}_i] &= \mathbb{E}_{\mathbf{L}}[\mathbb{E}[C_{ij} \mid \mathbf{P}_i, \mathbf{L}_{ib}] \mid \mathbf{P}_i] \\
&= \mathbb{E}_{\mathbf{L}}[\mathbb{E}[C_{ij} \mid \mathbf{L}_{ib}] \mid \mathbf{P}_i] \\
&= \mathbb{E}_{\mathbf{L}}\left[\sum_{l=1}^{n_L} f_{lj} L_{ibl} \,\middle|\, \mathbf{P}_i\right] \\
&= \sum_{l=1}^{n_L} f_{lj}\mathbb{E}_{\mathbf{L}}[L_{ibl} \mid \mathbf{P}_i] \\
&= 2\sum_{l=1}^{n_L} f_{lj} P_{il}
\end{aligned}
\tag{M5}
$$

and similarly $\mathbb{E}[M_{ik} \mid \mathbf{P}_i] = 2\sum_{l=1}^{n_L} g_{lk} P_{il}$. The second line follows from the conditional independence $C_{ij} \perp\!\!\!\perp \mathbf{P}_i \mid \mathbf{L}_{ib}$ encoded in **Figure 1**.

Models, Estimators and Regressions

Models and estimators are frequently conflated in literature as in the case of linear regression and a data generating process following a linear function. Although the confusion may not have notable consequences when the estimator is directly derived from the model, it is of central importance in our work because we have multiple estimators for a single model.

The model describes the data generating process. The causal additive model postulates that the quantitative trait of interest is generated in terms of an additive function of causal variants.

$$
Y_i = \alpha_0 + \sum_{j=1}^{n_J} C_{ij}\alpha_j + \epsilon_i
\tag{M6}
$$

This is an example of a data generating process that follows a linear functional relationship.

An estimator is an algorithm that estimates the parameter of a given model from data. If we had known which variants were the causal variants, it would have been possible to estimate $\boldsymbol{\alpha} = \{\alpha_j\}_{j=1,\dots,n_J}$ directly through the *ordinary least square* (OLS) estimator. Let $\mathbf{Y} = \{Y_i\}_{i=1,\dots,n_I}$ and $\mathbf{X} = \{\mathbf{X}_i\}_{i=1\dots,n_I}$ be the dependent and the explanatory variable respectively. The OLS estimator is

$$
(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}\mathbf{Y}
\tag{M7}
$$

When the model assumes that Y_i is linear respect to $\mathbf{X}_i$, then the OLS estimator is unbiased for the coefficients of $\mathbf{X}_i$. In the causal additive model, the OLS estimator produces a estimate $\widehat{\boldsymbol{\alpha}} = \widehat{\boldsymbol{\alpha}}(\{\mathbf{Z}_i\}_{i=1,\dots,n_I})$ (according to equation (M7)), a function of the data $\mathbf{Z}_i = (1, Y_i, \mathbf{C}_i)$, that estimates

the model parameter $\boldsymbol{\alpha}$ (here, 1 is the intercept). Explicitly, let $\mathbf{W}_i = (1, \mathbf{C}_i)$ and $\mathbf{W} = \{\mathbf{W}_i\}_{i=1,\dots,n_I}$. Then,

$$\widehat{\boldsymbol{\alpha}} = (\mathbf{W}^T\mathbf{W})^{-1}\mathbf{W}\mathbf{Y} \tag{M8}$$

Since $\widehat{\boldsymbol{\alpha}}$ is an unbiased estimator for $\boldsymbol{\alpha}$, people frequently write equation (M6) to denote the OLS estimator (M8).

In real data, the distinction between the model and the estimator becomes clearer. Causal variants are seldom observed themselves and usually the marker variants are observed. Therefore, regression is performed based on the observed markers as in regression (3) and (6). As the true model is equation (M6), the two regressions are not a description of the data generating process. Rather, they are referring to the OLS estimators, both with Y_i as the dependent variable, $(1, M_{ikl}, L_{ibl}, P_{il})$ and $(1, M_{ik}, P_{il})$ as the explanatory variables respectively. The formulas are given identical to equation (M7).

In summary, a model is the data generating process and an estimator is an algorithm that estimates the parameter of the model using data. Regression is frequently used as a substitute for estimator when the estimator can be expressed in a linear functional form. In practice, with an abuse of language, regression is often described as if it is a data generating process. Therefore, the readers should discern between a model and an estimator when the regression is described in such a way.

Estimands of Regressions

Now we prove equation (2), (5) and (7). The first two results are proved together by showing that

$$\begin{aligned}
\mathbb{E}[Y_i \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}, \mathbf{P}_i] = {}& \beta_0 \\
&+ \sum_{l=1}^{n_L} M_{ikl} \frac{D_{ljk}}{g_{lk}(1-g_{lk})}\alpha_j \\
&+ \sum_{l=2}^{n_L} L_{ibl} \left(\frac{f_{lj} - h_{ljk}}{1 - g_{lk}} - \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} \right)\alpha_j \\
&+ \sum_{l=2}^{n_L} P_{il}\delta_{lk}
\end{aligned} \tag{M9}$$

for some constant β_0, δ_{lk} and a vector variable $\mathbf{M}_{ik} = \{M_{ikl}\}_{l=1,\dots,n_L}$.

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Proof.

$$\mathbb{E}[Y_i \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}, \mathbf{P}_i] = \mathbb{E}\left[\alpha_0 + \sum_{j=1}^{n_J} C_{ij}\alpha_j + \epsilon_i \;\middle|\; \mathbf{M}_{ik}, \mathbf{L}_{ib}, \mathbf{P}_i\right]$$

$$= \alpha_0 + \sum_{j=1}^{n_J} \mathbb{E}[C_{ij} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}, \mathbf{P}_i]\alpha_j$$

$$= \alpha_0 + \sum_{j\in b} \mathbb{E}[C_{ij} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}, \mathbf{P}_i]\alpha_j + \sum_{j\notin b} \mathbb{E}[C_{ij} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}, \mathbf{P}_i]\alpha_j \qquad \text{(M10)}$$

$$= \alpha_0 + \sum_{j\in b} \mathbb{E}[C_{ij} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}]\alpha_j + \sum_{j\notin b} \mathbb{E}[C_{ij} \mid \mathbf{P}_i]\alpha_j$$

$$= \alpha_0 + \sum_{j\in b} \mathbb{E}[C_{ij} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}]\alpha_j + \sum_{j\notin b} \left[\sum_{l=1}^{n_L} 2f_{lj}P_{il}\right]\alpha_j$$

Now, it remains to compute $\mathbb{E}[C_{ij} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}]$ for $j, k \in b$.

$$\mathbb{E}[C_{ij} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}] = 2\mathbb{E}[C_{ij}^{\mathbf{h}} \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}]$$

$$= 2\mathbb{P}(C_{ij}^{\mathbf{h}} = 1 \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}) \qquad \text{(M11)}$$

$$= 2 \cdot \frac{\mathbb{P}(C_{ij}^{\mathbf{h}} = 1, \mathbf{M}_{ik} \mid \mathbf{L}_{ib})}{\mathbb{P}(\mathbf{M}_{ik} \mid \mathbf{L}_{ib})}$$

Since $\sum_{l=1}^{n_L} L_{ibl} = 2$, only two cases arise. It is either $L_{ibl} = 2$ for some l and $L_{ibl'} = 0$ for all $l' \neq l$, or $L_{ibl} = L_{ibl'} = 1$ for some l, l' and 0 otherwise. Therefore, it suffice to prove for the $n_L = 2$ case.

Case 1: $(L_{ib1}, L_{ib2}) = (2, 0)$**.** The possible combinations of (M_{ik1}, M_{ik2}) are $(0,0)$, $(1,0)$ and $(2,0)$.

$$2 \cdot \frac{\mathbb{P}(C_{ij}^{\mathbf{h}} = 1, \mathbf{M}_{ik} \mid \mathbf{L}_{ib})}{\mathbb{P}(\mathbf{M}_{ik} \mid \mathbf{L}_{ib})} = 2 \cdot \frac{\mathbb{P}(C_{ij}^{\mathbf{h}} = 1, M_{ik1} \mid \mathbf{L}_{ib})}{\mathbb{P}(M_{ik1} \mid \mathbf{L}_{ib})}$$

$$= \begin{cases} 2 \cdot \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} & : M_{ik1} = 0 \\ \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} + \frac{h_{1jk}}{g_{1k}} & : M_{ik1} = 1 \\ 2 \cdot \frac{h_{1jk}}{g_{1k}} & : M_{ik1} = 2 \end{cases} \qquad \text{(M12)}$$

$$= \frac{D_{1jk}}{g_{1k}(1 - g_{1k})}M_{ik1} + 2 \cdot \frac{f_{1j} - h_{1jk}}{1 - g_{1k}}$$

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Case 2: $(L_{ib1}, L_{ib2}) = (1, 1)$. The possible combinations of (M_{ik1}, M_{ik2}) are $(0, 0)$, $(1, 0)$, $(0, 1)$ and $(1, 1)$.

$$2 \cdot \frac{\mathbb{P}(C_{ij}^{\mathbf{h}} = 1, \mathbf{M}_{ik} \mid \mathbf{L}_{ib})}{\mathbb{P}(\mathbf{M}_{ik} \mid \mathbf{L}_{ib})} = 2 \cdot \frac{\mathbb{P}(C_{ij}^{\mathbf{h}} = 1, M_{ik1} \mid \mathbf{L}_{ib})}{\mathbb{P}(M_{ik1} \mid \mathbf{L}_{ib})}$$

$$= \begin{cases} \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} + \frac{f_{2j} - h_{2jk}}{1 - g_{2k}} & : (M_{ik1}, M_{ik2}) = (0, 0) \\[2mm] \frac{h_{1jk}}{g_{1k}} + \frac{f_{2j} - h_{2jk}}{1 - g_{2k}} & : (M_{ik1}, M_{ik2}) = (1, 0) \\[2mm] \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} + \frac{h_{2jk}}{g_{2k}} & : (M_{ik1}, M_{ik2}) = (0, 1) \\[2mm] \frac{h_{1jk}}{g_{1k}} + \frac{h_{2jk}}{g_{2k}} & : (M_{ik1}, M_{ik2}) = (1, 1) \end{cases} \tag{M13}$$

$$= \sum_{l=1,2} \frac{D_{ljk}}{g_{lk}(1 - g_{lk})} M_{ikl} + \sum_{l=1,2} \frac{f_{lj} - h_{ljk}}{1 - g_{lk}} L_{ibl}$$

Finally, substituting $L_{ib1} = 2 - L_{ib2}$ gives the desired result. $\qquad\square$

Formula (7) is proved in Lee and Lee [15]. Here, we prove equation (8).

Proof. Note that

$$\beta_k(\mathbf{P}_i) = \sum_{j=1}^{n_J} \frac{D_{jk}(\mathbf{P}_i)}{\operatorname{Var}[M_{ik} \mid \mathbf{P}_i]} \tag{M14}$$

where $D_{jk}(\mathbf{P}_i) = \mathbb{P}(M_{ik}^{\mathbf{h}} = 1, C_{ij}^{\mathbf{h}} = 1 \mid \mathbf{P}_i) - \mathbb{P}(M_{ik}^{\mathbf{h}} = 1 \mid \mathbf{P}_i) \cdot \mathbb{P}(C_{ij}^{\mathbf{h}} = 1 \mid \mathbf{P}_i) = \operatorname{Cov}[M_{ik}^{\mathbf{h}}, C_{ij}^{\mathbf{h}} \mid \mathbf{P}_i]$ [15]. The numerator can be computed using the law of total covariance.

$$\begin{aligned} \operatorname{Cov}[M_{ik}^{\mathbf{h}}, C_{ij}^{\mathbf{h}} \mid \mathbf{P}_i] &= \mathbb{E}[\operatorname{Cov}(M_{ik}^{\mathbf{h}}, C_{ij}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}, \mathbf{P}_i) \mid \mathbf{P}_i] \\ &\quad + \operatorname{Cov}[\mathbb{E}(M_{ik}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}, \mathbf{P}_i), \mathbb{E}(C_{ij}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}, \mathbf{P}_i) \mid \mathbf{P}_i] \\ &= \mathbb{E}[\operatorname{Cov}(M_{ik}^{\mathbf{h}}, C_{ij}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}) \mid \mathbf{P}_i] \\ &\quad + \operatorname{Cov}[\mathbb{E}(M_{ik}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}), \mathbb{E}(C_{ij}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}) \mid \mathbf{P}_i] \\ &= \mathbb{E}\left[\sum_{l=1}^{n_L} D_{ljk} L_{ibl}^{\mathbf{h}} \,\middle|\, \mathbf{P}_i\right] + \operatorname{Cov}\left[\sum_{l=1}^{n_L} g_{lk} L_{ibl}^{\mathbf{h}}, \sum_{l'=1}^{n_L} f_{l'k} L_{ibl}^{\mathbf{h}} \,\middle|\, \mathbf{P}_i\right] \\ &= \sum_{l=1}^{n_L} D_{ljk} \mathbb{E}[L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i] + \sum_{l,l'} g_{lk} f_{l'j} \operatorname{Cov}[L_{ibl}^{\mathbf{h}}, L_{ibl'}^{\mathbf{h}} \mid \mathbf{P}_i] \end{aligned} \tag{M15}$$

Since $\mathbf{L}_{ib}^{\mathbf{h}}$ follows a multinomial distribution with $n = 1$ and probability given by $\mathbf{P}_i$, $\mathbb{E}[L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i] = P_{il}$. Also, $\operatorname{Cov}[L_{ibl}^{\mathbf{h}}, L_{ibl'}^{\mathbf{h}} \mid \mathbf{P}_i]$ is $P_{il}(1 - P_{il})$ if $l = l'$ and $-P_{il} P_{il'}$ if $l \neq 1'$ respectively. Substituting these to equation (M15) gives the numerator as desired.

The denominator can be computed similarly using the law of total variance.

$$\begin{aligned}
\mathrm{Var}[M_{ik}^{\mathbf{h}} \mid \mathbf{P}_i] &= \mathbb{E}[\mathrm{Var}(M_{ik}^{\mathbf{h}} \mid \mathbf{L}_{ib}) \mid \mathbf{P}_i] + \mathrm{Var}[\mathbb{E}(M_{ik}^{\mathbf{h}} \mid \mathbf{L}_{ib}) \mid \mathbf{P}_i] \\
&= \mathbb{E}\left[\sum_{l=1}^{n_L} g_{lk}(1-g_{lk})L_{ibl}^{\mathbf{h}} \,\middle|\, \mathbf{P}_i\right] + \mathrm{Var}\left[\sum_{l=1}^{n_L} g_{lk}L_{ibl}^{\mathbf{h}} \,\middle|\, \mathbf{P}_i\right] \\
&= \sum_{l=1}^{n_L} g_{lk}(1-g_{lk})\mathbb{E}[L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i] + \sum_{l,l'} g_{lk}g_{l'k}\mathrm{Cov}[L_{ibl}^{\mathbf{h}}, L_{ibl'}^{\mathbf{h}} \mid \mathbf{P}_i]
\end{aligned} \tag{M16}$$

Using the covariance formula of the multinomial distribution as the numerator finishes the proof.

$\square$

Exclusion of Local Ancestry and Interpretability

Proof. Obtaining the coefficient of M_{ikl} without L_{ibl} requires computing $\mathcal{P}[L_{ibl} \mid \mathbf{M}_{ik}, \mathbf{P}_i]$. Here, $\mathcal{P}$ is the linear projection [24]. The coefficient of M_{ikl} of this projection is the bias term. Following the Frisch-Waugh-Lovell (FWL) theorem, the coefficient is equal to the coefficient of $\mathcal{P}[L_{ibl} \mid \mathbf{M}_{ik} - \mathbb{E}(\mathbf{M}_{ik} \mid \mathbf{P}_i)]$ [24, 25]. By the definition of linear projection, this coefficient is

$$\mathrm{Var}[\mathbf{M}_{ik} - \mathbb{E}(\mathbf{M}_{ik} \mid \mathbf{P}_i)]^{-1}\mathrm{Cov}[\mathbf{M}_{ik} - \mathbb{E}(\mathbf{M}_{ik} \mid \mathbf{P}_i), L_{ibl}] \tag{M17}$$

This hold because $\mathbb{E} = \mathcal{P}$ when $\mathbb{E}$ is linear respect to the conditional variables.

We first compute $\mathrm{Var}[\mathbf{M}_{ik} - \mathbb{E}(M_{ik} \mid \mathbf{P}_i)]$. The l-th diagonal element is

$$\begin{aligned}
\mathrm{Var}[M_{ikl} - \mathbb{E}(M_{ikl} \mid \mathbf{P}_i)] &= \mathbb{E}[\mathrm{Var}(M_{ikl} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Var}(M_{ikl}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Var}(\mathbb{E}[M_{ikl}^{\mathbf{h}} \mid \mathbf{L}_{ibl}^{\mathbf{h}}] \mid \mathbf{P}_i) + \mathbb{E}(\mathrm{Var}[M_{ikl}^{\mathbf{h}} \mid \mathbf{L}_{ibl}^{\mathbf{h}}] \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Var}(g_{lk}L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i) + \mathbb{E}(g_{lk}[1-g_{lk}]L_{bil}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[g_{lk}^2\mathrm{Var}(L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i) + g_{lk}(1-g_{lk})\mathbb{E}(L_{bil}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[g_{lk}^2 P_{il}(1-P_{il}) + g_{lk}(1-g_{lk})P_{il}] \\
&= 2g_{lk}^2\mathbb{E}[P_{il}(1-P_{il})] + 2g_{lk}(1-g_{lk})\mathbb{E}[P_{il}]
\end{aligned} \tag{M18}$$

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and the value at (l, l') is

$$
\begin{aligned}
\mathrm{Cov}[M_{ikl} - \mathbb{E}(M_{ikl} \mid \mathbf{P}_i), M_{ikl'} - \mathbb{E}(M_{ikl'} \mid \mathbf{P}_i)] &= \mathbb{E}[\mathrm{Cov}(M_{ikl}, M_{ikl'} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Cov}(M_{ikl}^{\mathbf{h}}, M_{ikl'}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2g_{lk}g_{l'k}\mathbb{E}[\mathrm{Cov}(L_{ibl}^{\mathbf{h}}, L_{ibl'}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2g_{lk}g_{l'k}\mathbb{E}[-P_{il}P_{il'}] \\
&= -2g_{lk}g_{l'k}\mathbb{E}[P_{il}P_{il'}]
\end{aligned}
\tag{M19}
$$

due to $\mathrm{Cov}[M_{ikl}^{\mathbf{h}}, M_{ikl'}^{\mathbf{h}} \mid \mathbf{L}_i^{\mathbf{h}}] = 0$ if $l \neq l'$. The inverse matrix is complicated for general l but can be computed in the $l = 2$ case. The formula is provided at the end of the section.

Next, we compute $\mathrm{Cov}[\mathbf{M}_{ik} - \mathbb{E}(\mathbf{M}_{ik} \mid \mathbf{P}_i), L_{ibl}]$. The l'-th element is

$$
\begin{aligned}
\mathrm{Cov}[M_{ikl'} - \mathbb{E}(M_{ikl'} \mid \mathbf{P}_i), L_{ibl}] &= \mathbb{E}[\mathrm{Cov}(M_{ikl'}, L_{ibl} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Cov}(M_{ikl'}^{\mathbf{h}}, L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Cov}(g_{l'k}L_{ibl'}^{\mathbf{h}}, L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2g_{l'k}\mathbb{E}[\mathrm{Cov}(L_{ibl'}^{\mathbf{h}}, L_{ibl}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= \begin{cases} 2g_{l'k}\mathbb{E}[P_{il}(1 - P_{il})] & \text{if } l = l' \\ -2g_{l'k}\mathbb{E}[P_{il}P_{il'}] & \text{if } l \neq l' \end{cases}
\end{aligned}
\tag{M20}
$$

$\square$

For general n_L, it is hard to derive the closed form solution of this result. Nevertheless, $n_L = 2$ case can be computed using the inverse formula of 2×2 matrices. Additionally, further simplification can be made by $P_{i1} + P_{i2} = 1$.

$$
\begin{aligned}
&\begin{bmatrix} g_{1k}^2\mathbb{E}[P_{i1}(1 - P_{i1})] + g_{1k}(1 - g_{1k})\mathbb{E}[P_{i1}] & -g_{1k}g_{2k}\mathbb{E}[P_{i1}P_{i2}] \\ -g_{1k}g_{2k}\mathbb{E}[P_{i1}P_{i2}] & g_{2k}^2\mathbb{E}[P_{i2}(1 - P_{i2})] + g_{2k}(1 - g_{2k})\mathbb{E}[P_{i2}] \end{bmatrix}^{-1} \\
&= \frac{1}{\Delta_{12}} \begin{bmatrix} g_{2k}^2\mathbb{E}[P_{i2}(1 - P_{i2})] + g_{2k}(1 - g_{2k})\mathbb{E}[P_{i2}] & g_{1k}g_{2k}\mathbb{E}[P_{i1}P_{i2}] \\ g_{1k}g_{2k}\mathbb{E}[P_{i1}P_{i2}] & g_{1k}^2\mathbb{E}[P_{i1}(1 - P_{i1})] + g_{1k}(1 - g_{1k})\mathbb{E}[P_{i1}] \end{bmatrix}
\end{aligned}
\tag{M21}
$$

where

$$
\begin{aligned}
\Delta_{12} &= g_{1k}(1 - g_{1k})g_{2k}^2\mathbb{E}[P_{i1}]\mathbb{E}[P_{i1}P_{i2}] \\
&\quad + g_{1k}^2g_{2k}(1 - g_{2k})\mathbb{E}[P_{i1}P_{i2}]\mathbb{E}[P_{i2}] \\
&\quad + g_{1k}(1 - g_{1k})g_{2k}(1 - g_{2k})\mathbb{E}[P_{i1}]\mathbb{E}[P_{i2}]
\end{aligned}
\tag{M22}
$$

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Then we multiply the inverse matrix to the second term.

$$
\begin{bmatrix} g_{2k}^2\mathbb{E}[P_{i2}(1-P_{i2})] + g_{2k}(1-g_{2k})\mathbb{E}[P_{i2}] & g_{1k}g_{2k}\mathbb{E}[P_{i1}P_{i2}] \\ g_{1k}g_{2k}\mathbb{E}[P_{i1}P_{i2}] & g_{1k}^2\mathbb{E}[P_{i1}(1-P_{i1})] + g_{1k}(1-g_{1k})\mathbb{E}[P_{i1}] \end{bmatrix}
$$

$$
\times
$$

$$
\begin{bmatrix} -g_{1k}\mathbb{E}[P_{i1}P_{i2}] \\ g_{2k}\mathbb{E}[P_{i1}P_{i2}] \end{bmatrix} \tag{M23}
$$

$$
= \begin{bmatrix} -g_{1k}g_{2k}(1-g_{2k})\mathbb{E}[P_{i1}P_{i2}]\mathbb{E}[P_{i2}] \\ g_{1k}(1-g_{1k})g_{2k}\mathbb{E}[P_{i1}]\mathbb{E}[P_{i1}P_{i2}] \end{bmatrix}
$$

Therefore, gathering the terms gives

$$
\beta_{1k}^{\text{nolanc}} = \beta_{1k}^{\text{anc}} + \sum_j \frac{g_{1k}g_{2k}(1-g_{2k})\mathbb{E}[P_{i1}P_{i2}]\mathbb{E}[P_{i2}]}{\Delta_{12}} \left(\frac{f_{1j} - h_{1jk}}{1 - g_{1k}} - \frac{f_{2j} - h_{2jk}}{1 - g_{2k}} \right) \alpha_j \tag{M24}
$$

and

$$
\beta_{2k}^{\text{nolanc}} = \beta_{2k}^{\text{anc}} + \sum_j \frac{g_{1k}(1-g_{1k})g_{2k}\mathbb{E}[P_{i1}]\mathbb{E}[P_{i1}P_{i2}]}{\Delta_{12}} \left(\frac{f_{2j} - h_{2jk}}{1 - g_{2k}} - \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} \right) \alpha_j \tag{M25}
$$

The Impact of Local Ancestry on Precision

Let $\widetilde{M}_{ik} = M_{ik} - \mathbb{E}[M_{ik} \mid \mathbf{P}_i]$ and $\widetilde{\mathbf{M}}_{ik} = \mathbf{M}_{ik} - \mathbb{E}[M_{ik} \mid \mathbf{L}_{ib}]$. We borrow the results of Ding (2021) and Buja et al. (2014) [25, 26].

$$
\sqrt{n_I} \left(\widehat{\boldsymbol{\beta}}_k - \boldsymbol{\beta}_k \right) \xrightarrow[n_I \to \infty]{} \mathcal{N} \left(\mathbf{0}, \mathbb{E}\left[\widetilde{\mathbf{M}}_{ik}\widetilde{\mathbf{M}}_{ik}^T \right]^{-1} \mathbb{E}\left[\zeta_{ik}^2 \widetilde{\mathbf{M}}_{ik}\widetilde{\mathbf{M}}_{ik}^T \right] \mathbb{E}\left[\widetilde{\mathbf{M}}_{ik}\widetilde{\mathbf{M}}_{ik}^T \right]^{-1} \right)
$$

$$
\sqrt{n_I} \left(\widehat{\beta}_k^{\text{agg}} - \beta_k^{\text{agg}} \right) \xrightarrow[n_I \to \infty]{} \mathcal{N} \left(\mathbf{0}, \mathbb{E}\left[\widetilde{M}_{ik}^2 \right]^{-2} \mathbb{E}\left[(\zeta_{ik}^{\text{agg}})^2 \widetilde{M}_{ik}^2 \right] \right) \tag{M26}
$$

where ζ_{ik} and ζ_{ik}^{agg} are the residuals appearing in regression (3) and (6) respectively. The expectations in the right hand side are difficult to compute. The calculations can be greatly eased by assuming that the variance explained by the causal variants linked to variant k is small relative to the total genetic variance [27]. Furthermore, we must assume that ϵ_i has constant variance. Then,

$$
\sqrt{n_I} \left(\widehat{\boldsymbol{\beta}}_k - \boldsymbol{\beta}_k \right) \xrightarrow[n_I \to \infty]{} \mathcal{N} \left(\mathbf{0}, \mathbb{E}\left[\widetilde{\mathbf{M}}_{ik}\widetilde{\mathbf{M}}_{ik}^T \right]^{-1} \mathbb{E}\left[\eta_i^2 \right] \right)
$$

$$
\sqrt{n_I} \left(\widehat{\beta}_k^{\text{agg}} - \beta_k^{\text{agg}} \right) \xrightarrow[n_I \to \infty]{} \mathcal{N} \left(\mathbf{0}, \mathbb{E}\left[\widetilde{M}_{ik}^2 \right]^{-1} \mathbb{E}\left[\eta_i^2 \right] \right) \tag{M27}
$$

where $\eta_i = \epsilon_i + \sum_{j=1}^{n_J} [C_{ij} - \sum_{l=1}^{n_L} 2f_{lj}P_{il}]$.

Now, the expectations appearing the limit distributions can be expressed in terms of population genetic parameters. $\mathbb{E}\left[\widetilde{\mathbf{M}}_{ik}\widetilde{\mathbf{M}}_{ik}^T\right] = \mathrm{Var}[\mathbf{M}_{ik} - \mathbb{E}(\mathbf{M}_{ik} \mid \mathbf{P}_i)]$ so the diagonal elements are given by equation (M18) and the non-diagonal elements are given by equation (M19). The remaining terms are

$$
\begin{aligned}
\mathbb{E}\left[\widetilde{M}_{ik}^2\right] &= \mathbb{E}[\mathrm{Var}(M_{ik} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Var}(M_{ik}^{\mathbf{h}} \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}[\mathrm{Var}(\mathbb{E}[M_{ik}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}] \mid \mathbf{P}_i) + \mathbb{E}(\mathrm{Var}[M_{ik}^{\mathbf{h}} \mid \mathbf{L}_{ib}^{\mathbf{h}}] \mid \mathbf{P}_i)] \\
&= 2\mathbb{E}\left[\mathrm{Var}\left(\sum_{l=1}^{n_L} g_{lk} L_{ibl}^{\mathbf{h}} \,\middle|\, \mathbf{P}_i\right) + \mathbb{E}\left(\sum_{l=1}^{n_L} g_{lk}(1-g_{lk})L_{bil}^{\mathbf{h}} \,\middle|\, \mathbf{P}_i\right)\right] \\
&= 2\mathbb{E}\left[\sum_{l,l'} g_{lk}g_{l'k}\mathrm{Cov}\left(L_{ibl}^{\mathbf{h}}, L_{ibl'}^{\mathbf{h}} \mid \mathbf{P}_i\right) + \sum_{l=1}^{n_L} g_{lk}(1-g_{lk})\mathbb{E}\left(L_{bil}^{\mathbf{h}} \mid \mathbf{P}_i\right)\right] \\
&= 2\mathbb{E}\left[\sum_{l=1}^{n_L} g_{lk}^2 P_{il}(1-P_{il}) + \sum_{l\neq l'} g_{lk}g_{l'k}(-P_{il}P_{il'}) + \sum_{l=1}^{n_L} g_{lk}(1-g_{lk})P_{il}\right] \\
&= 2\sum_{l=1}^{n_L} g_{lk}^2 \mathbb{E}[P_{il}(1-P_{il})] - 2\sum_{l\neq l'} g_{lk}g_{l'k}\mathbb{E}[P_{il}P_{il'}] + 2\sum_{l=1}^{n_L} g_{lk}(1-g_{lk})\mathbb{E}[P_{il}]
\end{aligned}
\tag{M28}
$$

and

$$
\begin{aligned}
\mathbb{E}[\eta_i^2] &= \mathbb{E}[\mathrm{Var}(Y_i \mid \mathbf{P}_i)] \\
&= \mathrm{Var}[Y_i] - \mathrm{Var}[\mathbb{E}(Y_i \mid \mathbf{P}_i)]
\end{aligned}
\tag{M29}
$$

which is the variance of Y_i subtracted by the variance explained by $\mathbf{P}_i$. The relative efficiency of regression (3) and (6) is not affected by this term. Note that $\mathbb{E}[Y_i \mid \mathbf{P}_i]$ is the mean polygenic score given $\mathbf{P}_i$ as $\mathbb{E}[\epsilon_i \mid \mathbf{P}_i] = 0$.

We focus on the Wald test because the test, log-likelihood test (LRT) and F-test are all asymptotically equivalent at the true parameter [28]. Regression (3) tests $\boldsymbol{\beta}_k = \mathbf{0} \in \mathbb{R}^{n_L}$ and regression (6) tests $\beta_k^{\mathrm{agg}} = 0$. The corresponding test statistics asymptotically ($n_I \to \infty$) obeys

$$
\begin{aligned}
T_n &= \sqrt{n_I}\left(\widehat{\boldsymbol{\beta}}_k - \boldsymbol{\beta}_k\right)^T \left(\mathbb{E}\left[\widetilde{\mathbf{M}}_{ik}\widetilde{\mathbf{M}}_{ik}^T\right]^{-1}\mathbb{E}\left[\eta_i^2\right]\right)^{-1}\sqrt{n_I}\left(\widehat{\boldsymbol{\beta}}_k - \boldsymbol{\beta}_k\right) \sim \chi_{n_L}^2 \\
T_n^{\mathrm{agg}} &= \sqrt{n_I}\left(\widehat{\beta}_k^{\mathrm{agg}} - \beta_k^{\mathrm{agg}}\right)\left(\mathbb{E}\left[\widetilde{M}_{ik}^2\right]^{-1}\mathbb{E}\left[\eta_i^2\right]\right)^{-1}\sqrt{n_I}\left(\widehat{\beta}_k^{\mathrm{agg}} - \beta_k^{\mathrm{agg}}\right) \sim \chi_1^2
\end{aligned}
\tag{M30}
$$

Note that we used the asymptotic variances themselves instead of the estimator. Also, we assumed that the inverted matrices are non-singular.

A similar argument gives an identical statement for ADM.

$$\sqrt{n_I} \left(\widehat{\boldsymbol{\gamma}}_k^{\text{adm}} - \boldsymbol{\gamma}_k^{\text{adm}} \right) \xrightarrow[n_I \to \infty]{} \mathcal{N} \left(\mathbf{0}, \mathbb{E}\left[\widetilde{\mathbf{L}}_{ib(-1)} \widetilde{\mathbf{L}}_{ib(-1)}^T \right]^{-1} \mathbb{E}\left[\eta_i^2 \right] \right) \tag{M31}$$

where $\boldsymbol{\gamma}_k = \{\gamma_{lk}\}_{l=2,\ldots,n_L}$ and $\widetilde{\mathbf{L}}_{ib} = \mathbf{L}_{ib} - \mathbb{E}[\mathbf{L}_{ib} \mid \mathbf{P}_i]$. The corresponding Wald statistic is

$$T_n^{\text{adm}} = \sqrt{n_I} \left(\widehat{\boldsymbol{\gamma}}_k^{\text{adm}} - \boldsymbol{\gamma}_k^{\text{adm}} \right)^T \left(\mathbb{E}\left[\widetilde{\mathbf{L}}_{ib(-1)} \widetilde{\mathbf{L}}_{ib(-1)}^T \right]^{-1} \mathbb{E}\left[\eta_i^2 \right] \right)^{-1} \left(\widehat{\boldsymbol{\gamma}}_k^{\text{adm}} - \boldsymbol{\gamma}_k^{\text{adm}} \right) \sim \chi_{n_L-1}^2 \tag{M32}$$

Comparing the two test statistics T_n^{agg} and T_n^{adm} under the only-admixture LD scenario with $n_L = 2$ shows that

$$\frac{T_n^{\text{adm}}}{T_n^{\text{agg}}} \xrightarrow[n_I \to \infty]{} \frac{g_{1k}(1 - g_{1k})\mathbb{E}[P_{i1}] + g_{2k}(1 - g_{2k})\mathbb{E}[P_{i2}] + (g_{1k} - g_{2k})^2 \mathbb{E}[P_{i1}P_{i2}]}{(g_{2k} - g_{1k})^2 \mathbb{E}[P_{i1}P_{i2}]} > 1 \tag{M33}$$

Hence, ADM is strictly powerful than regression (6) asymptotically.

Combining Association and Admixture Signals

We prove equation (**??**) and (**??**).

Proof. When $M_{ik} = C_{ij}$ and variant j is the only causal variant (in block b), $f_{ljk} = f_{lj} = g_{lk}$ and $D_{ljk} = g_{lk} - g_{lk}g_{lk} = g_{lk}(1 - g_{lk})$. Substituting the above equation to equation (8) gives

$$
\begin{aligned}
\beta_k(\mathbf{P}_i) &= \frac{\sum_l D_{ljk} P_{il} + \sum_l g_{lk} f_{lj} P_{il}(1 - P_{il}) - \sum_{l \neq l'} g_{lk} f_{l'k} P_{il} P_{il'}}{\sum_l g_{lk}(1 - g_{lk}) P_{il} + \sum_l g_{lk}^2 P_{il}(1 - P_{il}) - \sum_{l \neq l'} g_{lk} g_{l'k} P_{il} P_{il'}} \alpha_j \\
&= \frac{\sum_l g_{lk}(1 - g_{lk}) P_{il} + \sum_l g_{lk}^2 P_{il}(1 - P_{il}) - \sum_{l \neq l'} g_{lk} g_{l'k} P_{il} P_{il'}}{\sum_l g_{lk}(1 - g_{lk}) P_{il} + \sum_l g_{lk}^2 P_{il}(1 - P_{il}) - \sum_{l \neq l'} g_{lk} g_{l'k} P_{il} P_{il'}} \alpha_j \\
&= \alpha_j
\end{aligned}
\tag{M34}
$$

As a result,

$$
\begin{aligned}
\beta_k^{\text{agg}} &= \frac{\mathbb{E}[\beta_k(\mathbf{P}_i) \text{Var}(M_{ik} \mid \mathbf{P}_i)]}{\mathbb{E}[\text{Var}(M_{ik} \mid \mathbf{P}_i)]} \\
&= \frac{\mathbb{E}[\alpha_j \text{Var}(M_{ik} \mid \mathbf{P}_i)]}{\mathbb{E}[\text{Var}(M_{ik} \mid \mathbf{P}_i)]} \\
&= \alpha_j \frac{\mathbb{E}[\text{Var}(M_{ik} \mid \mathbf{P}_i)]}{\mathbb{E}[\text{Var}(M_{ik} \mid \mathbf{P}_i)]} \\
&= \alpha_j
\end{aligned}
\tag{M35}
$$

Hence, we proved equation (**??**).

To prove equation (**??**), we consider the case when variant j is the only causal variant (in block

b), and marker k is unlinked to j. Then $\beta_{lk} = 0$ for all l and $f_{lj} - h_{ljk} = f_{lj} - f_{lj}g_{lk} = f_{lj}(1 - g_{lk})$. Substituting the latter equation to equation (5) gives

$$
\begin{aligned}
\gamma_{lk} &= \left(\frac{f_{lj} - h_{ljk}}{1 - g_{lk}} - \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} \right) \alpha_j \\
&= \left[\frac{f_{lj}(1 - g_{lk})}{1 - g_{lk}} - \frac{f_{1j}(1 - g_{1k})}{1 - g_{1k}} \right] \alpha_j \\
&= (f_{lj} - f_{1j})\alpha_j
\end{aligned}
\tag{M36}
$$

as desired. $\qquad\square$

Based on the above two results, we formulate a Z-estimator combining the association and admixture [28]. We first define two composite random vectors

$$
\mathbf{W}_i = (1, M_{ik}, \mathbf{P}_{i(-1)}) \text{ and } \mathbf{Z}_i = (1, \mathbf{N}_{ib(-1)}, \mathbf{P}_{i(-1)})
\tag{M37}
$$

where $\mathbf{N}_{ib} = \{(f_{lj} - f_{1j})L_{ibl}\}_{l=1,\ldots,n_L}$ and the subscript (-1) stands for the omission of the first element. The corresponding coefficients are

$$
\boldsymbol{\beta}_{\mathbf{W},(-1)} = (\beta_0^{\text{agg}}, \alpha_j, \boldsymbol{\delta}_{k(-1)}^{\text{agg}}) \text{ and } \boldsymbol{\beta}_{\mathbf{Z},(-1)} = (\beta_0, \underbrace{\alpha_j, \ldots, \alpha_j}_{(n_L-1)\text{-copies}}, \boldsymbol{\delta}_{k(-1)})
\tag{M38}
$$

The moment function $\boldsymbol{\psi}$ is

$$
\boldsymbol{\psi}(\mathbf{W}_i, \mathbf{Z}_i ; \boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)}) = \begin{bmatrix} \mathbf{W}_i \left(Y_i - \mathbf{W}_i^T \boldsymbol{\beta}_{\mathbf{W},(-1)} \right) \\ \mathbf{Z}_i \left(Y_i - \mathbf{Z}_i^T \boldsymbol{\beta}_{\mathbf{Z},(-1)} \right) \end{bmatrix} \in \mathbb{R}^{3n_L \times 1}
\tag{M39}
$$

which obeys $\mathbb{E}\left[\boldsymbol{\psi}(\mathbf{W}_i, \mathbf{Z}_i ; \boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)}) \right] = \mathbf{0}$. As a result, we have total n_L-constraints on α_j. Note that considering only the first $(n_L + 1)$ components $\mathbf{W}_i^T \left(Y_i - \boldsymbol{\beta}_{\mathbf{W},(-1)} \mathbf{W}_i \right)$ are identical to OLS. Augmenting additional $(2n_L - 1)$ constraints is at least as asymptotically efficient as the OLS [29, 30, 31]. The latter constraints only is simply the admixture mapping.

The estimators of $\boldsymbol{\beta}_{\mathbf{W},(-1)}$ and $\boldsymbol{\beta}_{\mathbf{Z},(-1)}$ of defined as

$$
\begin{aligned}
&\left(\boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)} \right) \\
&= \underset{\boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)}}{\operatorname{argmin}} \left[\sum_{i=1}^{n_I} \boldsymbol{\psi}_i \left(\boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)} \right) \right]^T \boldsymbol{\Omega} \left[\sum_{i=1}^{n_I} \boldsymbol{\psi}_i \left(\boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)} \right) \right]
\end{aligned}
\tag{M40}
$$

for some positive definite weighting matrix $\boldsymbol{\Omega} \in \mathbb{R}^{3n_L \times 3n_L}$, and due to space constraints, we write

$$\psi_i \left(\boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)} \right) = \psi \left(\mathbf{W}_i, \mathbf{Z}_i \; ; \; \boldsymbol{\beta}_{\mathbf{W},(-1)}, \boldsymbol{\beta}_{\mathbf{Z},(-1)} \right).$$

Non-constant causal effect

The causal effect of a variant can vary depending on the genetic backgroud (gene-by-gene interaction, G×G) and the environment (gene-by-environment, G×E) in which the individual is exposed to. A researcher might want to estimate the effect of these phenomenons while avoiding confounding due to these effects.

A classic approach to estimate G×G and G×E was to include interactions to the regression and interpret the coefficients of the interaction terms as such effects. However, interactions terms can have multiple interpretations depending on the context. For example, interaction can mean either joint treatment effect or effect modification where each entity generally have different identification conditions [32, 33]. Under the G×G and the G×E paradigm, it is usually the effect modification that is of interest to the researcher.

To avoid such complication while maintaining a simple regression framework, we propose a extension of regression (3) that allows the causal effect α_j to vary across the genetic background (in this case, the global ancestry) and the environment (such as biological sex). Then, we can express $\alpha_j = \alpha_j + \mathrm{A} \left(\mathbf{C}_{i(-b)}, \mathbf{E}_i \right)$ as a function of remaining causal variants $\mathbf{C}_{i(-b)}$ and the environment $\mathbf{E}_i$. To maintain the average causal effect interpretation of α_j, we constrain A to satisfy $\mathbb{E} \left[\mathrm{A} \left(\mathbf{C}_{i(-b)}, \mathbf{E}_i \right) \right] = 0$ without loss of generality.

Let $\mathbf{E}_i$ be the environmental variable. Then the regression (3) generalizes to

$$
\begin{aligned}
\mathbb{E}[Y_i \mid \mathbf{M}_{ik}, \mathbf{L}_{ib}, \mathbf{P}_i] = \beta_0 & \\
& + \sum_{l=1}^{n_L} M_{ikl} \frac{D_{ljk}}{g_{lk}(1 - g_{lk})} \left(\alpha_j + \mathbb{E} \left[\mathrm{A} \left(\mathbf{C}_{i(-b)}, \mathbf{E}_i \right) \mid \mathbf{P}_i, \mathbf{E}_i \right] \right) \\
& + \sum_{l=2}^{n_L} L_{ibl} \left(\frac{f_{lj} - h_{ljk}}{1 - g_{lk}} - \frac{f_{1j} - h_{1jk}}{1 - g_{1k}} \right) \left(\alpha_j + \mathbb{E} \left[\mathrm{A} \left(\mathbf{C}_{i(-b)}, \mathbf{E}_i \right) \mid \mathbf{P}_i, \mathbf{E}_i \right] \right) \\
& + \sum_{l=2}^{n_L} P_{il} \delta_{lk}
\end{aligned}
\tag{M41}
$$

Although additional assumptions should be imposed in most cases, several notable examples do not require any assumption on the function $\mathrm{A} \left(\mathbf{C}_{i(-b)}, \mathbf{E}_i \right)$ because $\mathbf{E}_i$ is discrete and can be expressed in terms of dummy indicators. Gene-by-sex interaction is one such example [34]. If we denote $Z_i = 0, 1$ to be the biological sex, $\mathrm{A} \left(\mathbf{C}_{i(-b)}, \mathbf{E}_i \right) = \eta \left(Z_i - \frac{1}{2} \right)$ where η is a constant and $\frac{1}{2}$ is the mean of Z_i. This means that one only requires to include the interactions of M_{ikl} and L_{ibl} with $Z_i - \frac{1}{2}$ to incorporate the effect modification of a variant by sex. Of course, the mean can be obtained from

census data or simply replaced by a sample mean $\overline{Z} = \frac{1}{n_I} \sum_{i=1}^{n_I} Z_i$. The subtraction by the mean of Z_i is necessary to maintain the average effect interpretation of α_j [35, 36]. If one further assumes that $A\left(\mathbf{C}_{i(-b)}, \mathbf{E}_i\right)$ is a linear function respect to $\mathbf{C}_{i(-b)}$ and $\mathbf{E}_i$, interacting both M_{ikl} and L_{ibl} with $\mathbf{P}_i$ and $\mathbf{E}_i$ will suffice.

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