

# Target Journal

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## Title

Adjusting for principal components can induce spurious associations in genome-wide association studies in admixed populations

## Authors and Affiliations

Kelsey E. Grinde,<sup>1\*</sup> Brian L. Browning,<sup>2</sup> Sharon R. Browning<sup>3</sup>

1. Department of Mathematics, Statistics, and Computer Science, Macalester College, Saint Paul, MN, 55105, USA
2. Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, WA, 98195, USA
3. Department of Biostatistics, University of Washington, Seattle, WA, 98195, USA

\* kgrinde@macalester.edu

## Abstract

Principal component analysis (PCA) is widely used to control for population structure in genome-wide association studies (GWAS). It has been shown that the top principal components (PCs) typically reflect population structure, but deciding exactly how many PCs to include in GWAS regression models can be challenging. Often researchers will err on the side of including more PCs than may be actually necessary in order to ensure that population structure is fully captured. However, through both analytic results and application to TOPMed whole genome sequence data for 1,888 and 2,676 unrelated African American individuals from the Jackson Heart Study (JHS) and Chronic Obstructive Pulmonary Disease Genetic Epidemiology Study (COPDGene), respectively, we show that adjusting for extraneous PCs can actually induce spurious associations. In particular, spurious associations arise when PCs capture local genomic features, such as regions of the genome with atypical linkage disequilibrium (LD) patterns, rather than genome-wide ancestry. In JHS and COPDGene, we show that careful LD pruning prior to running PCA, using stricter thresholds and wider windows than is often suggested in the literature, can resolve these issues, whereas excluding lists of high LD regions identified in previous studies does not. We also show that the rate of spurious associations can be appropriately controlled in these data when we simply adjust for either the first PC or a model-based estimate of admixture proportions. Our work demonstrates that great care must be taken when using principal components to control for population structure in genome-wide association studies in admixed populations.

# 1 Introduction

Considerable variability in global ancestry—the genome-wide proportion of genetic material inherited from each ancestral population—has been observed in many studies of admixed populations such as African Americans and Hispanics/Latinos<sup>1,2,3,4,5</sup>. It has been widely documented that heterogeneous global ancestry, as with other types of population structure, can lead to spurious associations in genome-wide association studies<sup>6,7,8,9</sup>. In fact, some authors have even cited the ancestral heterogeneity of admixed populations, and the statistical challenges it poses, as one of many reasons why these populations have been historically underrepresented in genome-wide association studies (GWAS)<sup>10,11,12,13,14</sup>. Spurious associations can arise in GWAS in ancestrally heterogeneous populations when global ancestry confounds the association between genotypes and the phenotype of interest (Figure 1). This confounding occurs when the genetic variant being tested differs in frequency across ancestral populations (i.e., global ancestry is associated with genotype) and global ancestry also has an effect on the phenotype via, for example, environmental factors or causal loci elsewhere in the genome that differ in frequency across ancestral groups.



Figure 1: Global ancestry ( $\pi$ ) confounds the association between the genotype at position  $j$  ( $g_j$ ) and the phenotype of interest ( $y$ ) if ancestry is associated with both the genotype (e.g., the allele frequencies differ across the ancestral populations) and the phenotype (e.g., there are environmental or other factors that affect the phenotype and differ across the ancestral populations).

A number of methods for detecting and controlling for ancestral heterogeneity in ge-

netic association studies have been proposed. Early approaches included restricting analyses to subsets of ancestrally homogeneous individuals<sup>15</sup>, performing a genome-wide correction for test statistic inflation due to ancestral heterogeneity via *genomic control*<sup>6</sup>, and using family-based designs<sup>16</sup>. More recently, approaches based on mixed models have been proposed<sup>17,18,19</sup>, using random effects to control for both close (e.g., due to family-based sampling) and distant (e.g., due to shared ancestry) relatedness across individuals. When studies do not include closely related individuals, a simpler approach is to include inferred global ancestry as a fixed effect in marginal regression models<sup>7,20</sup>. This fixed effects adjustment for global ancestry is currently used extensively throughout the literature, with global ancestry inferred using either model-based ancestry inference methods (e.g., `frappe`<sup>21</sup>, `STRUCTURE`<sup>22</sup>, `ADMIXTURE`<sup>23</sup>) or principal component analysis (e.g., `EIGENSTRAT`<sup>7</sup>, `SNPRelate`<sup>24</sup>, `PC-AiR`<sup>25</sup>).

Principal component analysis (PCA) is a widely-implemented unsupervised approach for inferring global ancestry that does not require reference panel data or pre-specification of the number of ancestral populations of interest and is capable of capturing sub-continental structure<sup>26</sup>. To infer global ancestry using PCA, we perform a singular value decomposition of the matrix of standardized genotypes (i.e.,  $\mathbf{X} = \mathbf{UDV}^\top$ ) or, equivalently, an eigenvalue decomposition of the genetic relationship matrix (i.e.,  $\mathbf{XX}^\top = \mathbf{UD}^2\mathbf{U}^\top$ ). It has been shown that top eigenvectors, or *principal components* (PCs),  $\mathbf{u}_1, \mathbf{u}_2, \dots$  tend to reflect global ancestry<sup>27,28</sup>. To adjust for ancestral heterogeneity, we choose some number of PCs to include as covariates in our GWAS regression models.

Determining the number of PCs needed to capture global ancestry can be difficult. Numerous techniques have been proposed for selecting this number, including formal significance tests based on Tracy-Widom theory<sup>27,7</sup>, examining inflation factors<sup>29,5</sup> and/or the proportion of variance explained by each PC<sup>30,29,5</sup>, comparing PCs to self-reported race/ethnicity<sup>5</sup>, and keeping PCs that are significantly associated with the trait<sup>31,32</sup>. Typically, the number of PCs selected is on the order of one to ten<sup>33</sup>, but in practice it is not uncommon to see applications in which more than ten PCs are used—more even than may actually be necessary

to capture global ancestry. This could be due in part to work that has suggested that including higher-order PCs can provide the safeguard of removing “virtually all stratification”<sup>34</sup> at the cost of only “subtle” decreases in power<sup>35</sup>.

Another challenge that can arise in using PCA to adjust for ancestral heterogeneity involves ensuring that PCs actually reflect global ancestry and not some other features or artifacts of the data. Prior work has shown that PCs can capture relatedness across samples<sup>27,9,36,25</sup>, array artifacts or other data quality issues<sup>27,7,9,37</sup>, and/or small regions of the genome with unusual patterns of linkage disequilibrium (LD)<sup>27,7,38,39,40,9,37,41,42,36,43</sup>. To address this last issue, some authors have suggested running PCA on a reduced subset of variants after first performing *LD pruning*, using a program such as PLINK<sup>44</sup> to remove variants that are in “high” LD (e.g., pairwise-correlation  $r^2 > 0.2$ ) with nearby variants<sup>38,45,26,46,47,48,37,42,36,49,25,29,50,5,32</sup>, and/or excluding regions of the genome that are known to have extensive, long-ranging, or otherwise unusual patterns of LD<sup>38,45,26,40,48,37,30,5</sup>. A list of these previously-identified high LD regions and references that recommend their exclusion is provided in Table 1.

The above-cited suggestions regarding LD pruning and filtering are not universally implemented and the downstream implications of adjusting for PCs that capture features other than global ancestry are not fully understood. Furthermore, much of this work was conducted in populations of European ancestry, so recommendations on how best to implement principal component-based adjustment for ancestral heterogeneity in admixed populations are lacking. In this paper, we investigate the impact of LD filtering and pruning choices, as well as choices of the number of principal components to include in analyses, on genome-wide association studies in admixed populations. We conduct simulation studies using whole genome sequence data for African American individuals in the Trans-Omics for Precision Medicine (TOPMed) project and provide analytic results to show that including too many PCs can actually induce spurious associations in GWAS, particularly when those extraneous PCs capture local genomic features rather than genome-wide ancestry. — ADD WHI To

Chr	Start (bp)	End (bp)	References
chr1	48000000	52060567	48,40,37
chr2	85941853	100500000	48,40,37
chr2	129600000	140000000	40,26,37,30,5,51
chr2	182882739	190000000	48,40,37
chr3	47500000	50000000	48,40,37
chr3	83500000	87000000	48,40,37
chr3	89000000	97500000	40,37
chr3	163100000	164900000	51
chr5	44000000	51500000	45,48,40,37
chr5	98000000	100500000	40,37
chr5	129000000	132000000	48,40,37
chr5	135500000	138500000	40,37
chr6	23800000	39000000	45,48,40,26,37,30,5,51
chr6	57000000	64000000	48,40,37
chr6	140000000	142500000	48,40,37
chr7	55000000	66193285	48,40,37
chr8	6300000	13500000	45,48,40,26,39,37,30,5,51
chr8	43000000	50000000	48,40,37
chr8	112000000	115000000	48,40,37
chr10	37000000	43000000	48,40,37
chr11	45000000	57000000	45,40,37
chr11	87500000	90500000	48,40,37
chr12	33000000	40000000	48,40,37
chr12	109500000	112021663	40,37
chr14	46600000	47500000	51
chr17	37800000	42000000	26,5
chr20	32000000	34500000	48,40,37

Table 1: Regions of the genome with high, long-range, or otherwise unusual patterns of linkage disequilibrium (LD) that are often recommended for exclusion prior to running PCA. This list of regions was generated on the basis of an extensive literature review. Start and end physical (base pair) positions are provided with respect to genome build 36. Also available for download (in builds 36, 37, or 38) at <https://github.com/kegrinde/PCA/>.

conclude, we provide suggestions regarding best practice for appropriately controlling for ancestral heterogeneity in genome-wide association studies in admixed populations.

## 2 Material and Methods

**ADD WHI**

### 2.1 TOPMed Whole Genome Sequence Data

The Trans-Omics for Precision Medicine (TOPMed) Whole Genome Sequencing Project is an ongoing project sponsored by the National Heart, Lung, and Blood Institute (NHLBI) that is working to collect and analyze whole-genome sequences, other 'omics data, and rich phenotypic information for over 100,000 individuals from diverse backgrounds. Data are periodically released on dbGaP for analysis by the broader scientific community. Our analysis uses data from *freeze 4*, released in 2017, and *freeze 5b*, released in 2018. These two freezes include samples from a large number of contributing studies. We focus on two such studies: the Jackson Heart Study (JHS) (accession number: phs000964) and the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease Study (COPDGene) (accession number: phs000951). In total, the freeze 4 JHS dataset includes 3,406 African American individuals and the freeze 5b COPDGene dataset includes 8,742 African American and European American individuals.

For TOPMed freezes 4 and 5b, high coverage ( $\approx 30X$ ) whole genome sequencing was performed by several sequencing centers. Variant discovery and genotype calling was performed by the TOPMed Informatics Resources Center (IRC) using the GotCloud pipeline<sup>52</sup>. Quality control (QC) was performed by the sequencing centers, IRC, and TOPMed Data Coordinating Center, and only those samples and variants that passed these stages of QC are included in the VCF downloaded from dbGaP. Details on TOPMed sequencing and QC methods are available in Taliun et al.<sup>53</sup> and on the TOPMed website: <https://www.nhlbiwgs.org/data>.

sets.

## 2.2 Additional Quality Control and Filtering

Prior to principal component analysis, we perform additional variant- and sample-level filtering. We use `bcftools`<sup>54</sup> to remove indels and otherwise restrict our analyses to biallelic single nucleotide variants (SNVs). We also remove variants with low minor allele frequency (< 1%) and/or **high rates of missing calls (> 1%) — STILL NEEDS TO BE IMPLEMENTED**. After this filtering, a total of ??? SNVs remain in JHS and ??? SNVs remain in COPDGene.

At the sample level, we use the iterative procedure proposed by Conomos et al.<sup>55</sup> and implemented in the TOPMed Analysis Pipeline to identify a subset of mutually unrelated individuals using a kinship threshold of 0.044 (third degree relatives). We also perform an unsupervised `ADMIXTURE`<sup>23</sup> analysis with both  $K = 2$  and  $K = 3$  to identify admixed (African American) and non-admixed (European American) individuals; we restrict remaining analyses to admixed individuals only. Prior to both of these analyses we implement LD pruning/filtering as recommended in their respective user manuals. After exclusions, a total of ??? and ??? unrelated African Americans remain in JHS and COPDGene, respectively.

### 2.2.1 LD-Based Filtering

In addition to the filtering described above, we also implement different types of LD-based filtering. [... **Describe the different types of LD-based filtering we compared (see below).** ...] These analyses are also compared to a *naive* analysis that did not perform any LD-based filtering. The number of variants that remain after each type of filtering is presented in Table 2.2.1.

- Exclude
  - None
  - Lit Review (Table 1)

- Auto-Detect ([... using Prive package — implement or skip for now?? ...])
- Prune
  - None
  - Default 0.2
  - Stricter 0.1
  - [... Stricter 0.05 ??? ...]
  - [... Different window size ??? ...]

	Naive	Exclude	Prune	Stricter	Prune	Exclude + Stricter	Prune
JHS	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]
COPDGene	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]	[... ? ...]

Table 2: Single nucleotide variants that remained in Jackson Heart Study (JHS) and Genetic Epidemiology of COPD (COPDGene) datasets after varying levels of LD-based filtering.

- what filtering was performed, and how many variants left after filtering
  - JHS, ADMIXTURE: see above
  - JHS, PCA: exclude regions (TRUE/FALSE), r-squared (1, 0.1, 0.2, 0.05), window size (0, 0.5, 10), and MAF (0, 0.01)
    - \* no filtering: FALSE-1-0-0
    - \* MAF filtering: FALSE-1-0-0.01
    - \* exclude but no prune: TRUE-1-0-0.01
    - \* prune but no exclude: FALSE-0.1-0.5-0.01 and FALSE-0.1-10-0.01 and FALSE-0.2-0.5-0.01 and FALSE-0.05-0.5-0.01
    - \* prune and exclude: TRUE-0.1-0.5-0.01 and TRUE-0.1-10-0.01 and TRUE-0.2-0.5-0.01 and TRUE-0.05-0.5-0.01
  - COPD, ADMIXTURE: see above

- COPD, PCA: exclude regions (TRUE/FALSE), r-squared (1, 0.1, 0.2, 0.05), window size (0, 0.5, 10), MAF (0, 0.01)
  - \* no filtering: FALSE-1-0-0
  - \* MAF filtering: FALSE-1-0-0.01
  - \* exclude but no prune: TRUE-1-0-0.01
  - \* prune but no exclude: FALSE-0.1-0.5-0.01, FALSE-0.1-10-0.01, FALSE-0.2-0.5-0.01, FALSE-0.05-0.5-0.01
  - \* prune and exclude: TRUE-0.1-0.5-0.01, TRUE-0.1-10-0.01, TRUE-0.05-0.5-0.01, TRUE-0.2-0.5-0.01
- COPD, also ran SNPRelate on Europeans with different levels of filtering (FALSE-0.1-0.5-0.01, FALSE-0.2-0.5-0.01, FALSE-1-0-0.01, FALSE-1-0-0, TRUE-0.1-0.5-0.01, TRUE-0.2-0.5-0.01, TRUE-1-0-0.01)

## 2.3 Principal Component Analysis

We use the `SNPRelate` package in R to run principal component analysis using each of the subsets of SNVs described in Section 2.2. For each set of principal components, we also use the `SNPRelate` package to assess the contribution of each variant to each PC by calculating and plotting the correlation between genotypes and PCs. [... also look at loadings? shouldn't this give us the same picture as corr? ...]

## 2.4 Simulation Study to Investigate Rates of Spurious Associations

We implement a simulation study to explore the impact of different variant-level filtering choices, particularly with respect to linkage disequilibrium, on rates of spurious associations in genome-wide association studies using models that adjust for ancestral heterogeneity using principal components.

### 2.4.1 Simulated Traits

[...]

- find loading peaks from "naive" approach
- simulate trait that is  $\text{beta} * \mathbf{x} + \text{rnorm}(0, 1)$ , where  $\text{beta} = 1$  or  $2$  and  $\mathbf{x}$  = genotype at one of the peaks

...]

### 2.4.2 GWAS Models

To perform genome-wide association studies in samples of unrelated admixed individuals, we use marginal regression models, regressing the trait of interest on the genotype at each position across the genome. At a given position  $j$ , we quantify genotype  $g_{ij}$  as the number of copies (0, 1, or 2) of some pre-specified allele (e.g., the minor allele) carried by individual  $i$  at that position. Considering a quantitative trait  $y_i$ , we fit one linear regression model at each position ( $j = 1, \dots, m$ ):

$$E[y_i | g_{ij}, \mathbf{z}_i] = \beta_0 + \beta_j g_{ij} + \boldsymbol{\beta}_z \mathbf{z}_i,$$

where  $\mathbf{z}_i$  is a vector of additional covariates (e.g., potential confounding variables) that we want to include in the model. We test for an association between the trait and genotype by testing the null hypothesis  $H_0 : \beta_j = 0$  at each position  $j = 1, \dots, m$ .

To adjust for ancestral heterogeneity, we include inferred global ancestry in the vector  $\mathbf{z}_i$  of potential confounders in our regression models. We infer global ancestry using one of two techniques: model-based global ancestry inference or principal component analysis. [...  
describe which models we compare ...]

[...]

- for each of  $188^2$  simulated phenotypes

- for each set of PCs
- including 1, 4, or 10 PCs

[...]

#### 2.4.3 Evaluation

[... defining spurious associations ...]

### 2.5 Code and Data Availability

All code and data used throughout this paper are publicly available online:

- TOPMed Sequence Data: <https://www.ncbi.nlm.nih.gov/gap/>
- Code: <https://github.com/kegrinde/PCA>

## 3 Results

### 3.1 Ancestral heterogeneity in admixed populations

Inferred global ancestry proportions for TOPMed JHS African Americans, TOPMed COPDGene African Americans, WHI SHARe African Americans, and [... WHI SHARe Hispanic Americans ...] are presented in Figure 2. As has been the case in other studies of admixed populations, we observe considerable variability in the relative proportions of African and European (and, in the case of WHI SHARe Hispanic Americans, Native American) ancestry across these samples. This ancestral heterogeneity motivates the need to carefully adjust for global ancestry in genome-wide association studies in these, and other, admixed samples.

[... Barplots:

- JHS African Americans only (remove EA)

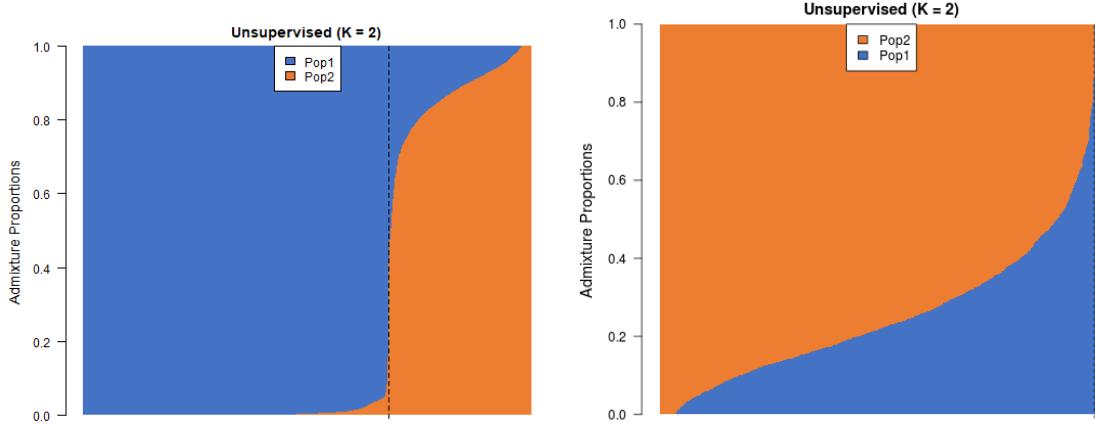


Figure 2: Barplots of estimated admixture proportions from unsupervised **ADMIXTURE** analyses with  $K = 2$  in TOPMed COPDGene African Americans (left panel) and JHS African Americans (right panel).

- COPDGene African Americans only (remove EA)
- WHI SHARe African Americans
- WHI SHARe Hispanic Americans

...]

### 3.2 Comparison of principal components and model-based admixture proportions

Comparing model-based admixture proportions generated by **ADMIXTURE** to principal components confirms that initial PCs are capturing genome-wide continental ancestry. In all three African American samples (Figure 3.2), the first PC is highly correlated with the inferred proportion of **African/European** ancestry, while later PCs show very little correlation with global ancestry. [... In WHI SHARe Hispanic Americans (Figure 3.2, we see ... ...)]

We observe similar patterns of correlation between PCs and inferred admixture proportions regardless of the type of LD filtering (or lack therof) performed prior to running PCA ([... see **Supplemental Figure ???** ...]). One might suspect that these later principal components may be capturing sub-continental structure, but, as we will see in Section 3.3, in many cases

these later PCs are driven by a small number of variants, suggesting that they are capturing local genomic features rather than genome-wide ancestry.

[... Scatterplot grids:

- AA: scatterplots of AFR admixture proportions vs the first four PCs (across columns) for each sample JHS/COPD/WHI (across rows)
- HA: scatterplots of admixture proportions AFR/EUR/NAM (across rows) vs the first four PCs (across columns)
- supplement: show that similar patterns arise even after strict LD pruning

...]

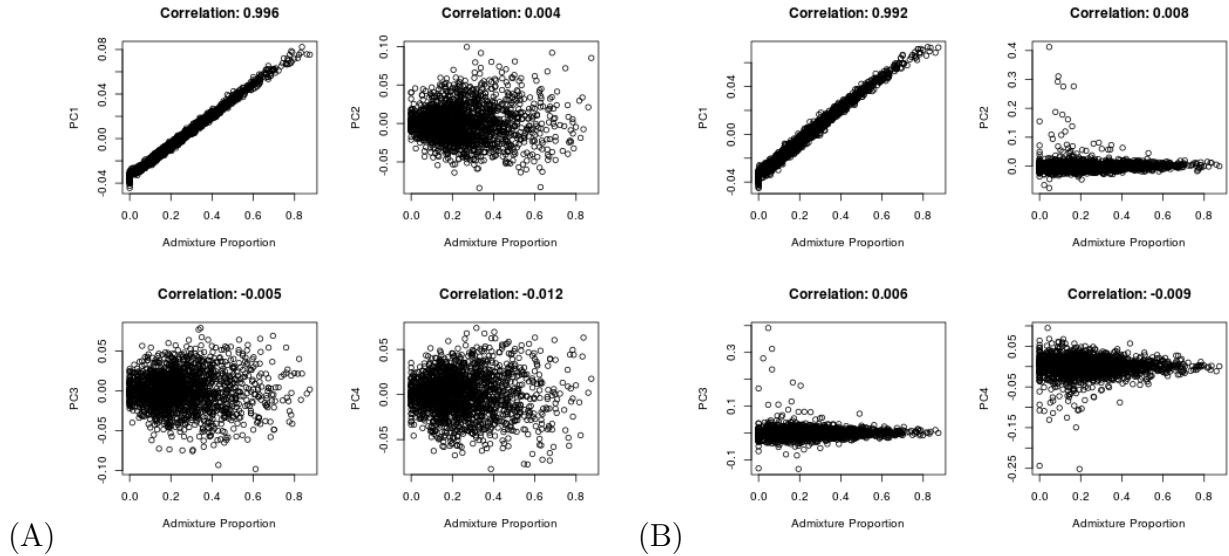


Figure 3: Comparison of model-based admixture proportions (from an unsupervised ADMIXTURE with  $K = 2$ ) and the first four principal components from various sets of PCs generated after different levels of LD filtering:

- (A) PCs generated in JHS African Americans without any LD filtering.  
 (B) PCs generated in JHS African Americans after excluding known high LD regions and pruning with an  $r^2$  threshold of 0.1 and window size of 10 Mb. — NEEDS UPDATING PER DIRECTIONS ABOVE

Figure 4: Comparison of model-based admixture proportions and the first four principal components in WHI SHARe Hispanic Americans. PCs were generated without any LD filtering.

### 3.3 Principal Component Analysis without Adequate Filtering Captures Multiple Local Genomic Features

- plots of SNP loadings and/or correlation for each set of PCs
  - JHS: Figures 3.3 and 3.3
  - COPD: Figures 3.3 and 3.3
- show that approaches that do not prune enough are picking up multiple local features
  - need smaller  $r^2$  threshold of 0.1 and larger window size of 10 Mb until peaks go away
  - in COPD is even this stricter pruning not enough??
- compare to European analyses that tend to pick up just one region at a time
  - one peak: Figure 3.3
  - weaker pruning fixes the problem

### 3.4 Principal Components Can Induce Spurious Associations

[... Part 1: how does FWER compare?

- manhattan plots for one or two simulated traits
- overall summary of rejection rates
- is it appropriate to use same significance threshold for all?

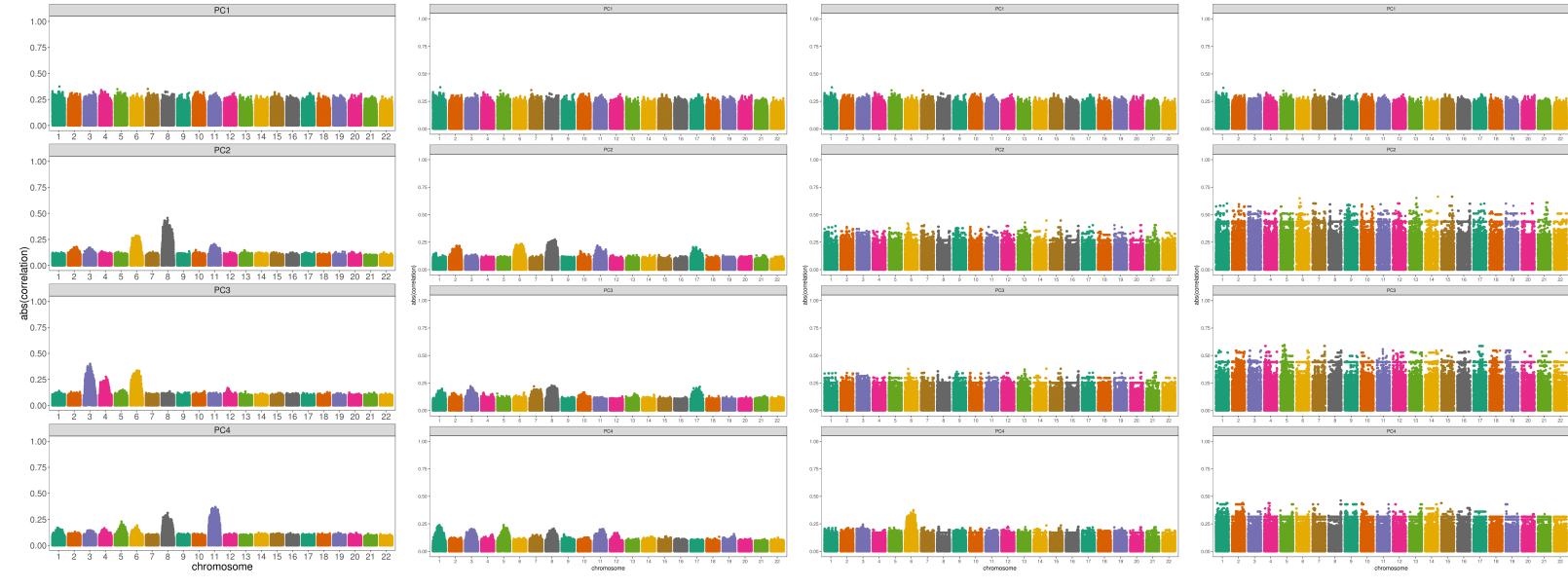


Figure 5: Correlation between the first four principal components and genotypes in Jackson Heart Study African Americans when previously-identified high-LD regions (Table 1) *are not* removed prior to analysis. From left to right, panels correspond to increasingly strict levels of LD pruning: no LD pruning, LD pruning with an  $r^2$  threshold of 0.2 and a window size of 0.5 Mb, LD pruning with an  $r^2$  threshold of 0.1 and a window size of 0.5 Mb, and LD pruning with an  $r^2$  threshold of 0.1 and a window size of 10 Mb.

Part 2: how does rate of spurious associations compare? (and alpha-adjusted spurious assoc?)

- manhattan plots for one or two traits
- overall summary of rejection rates

Part 3: why is this happening?

- are admixture proportions and PCs capturing similar information?
  - correlation between PCs and admixture proportions (PC1 highly correlated with admix prop)
  - correlation between PCs and genotypes (without pruning, later PCs highly correlated with genotypes in small regions)
- mathematical results

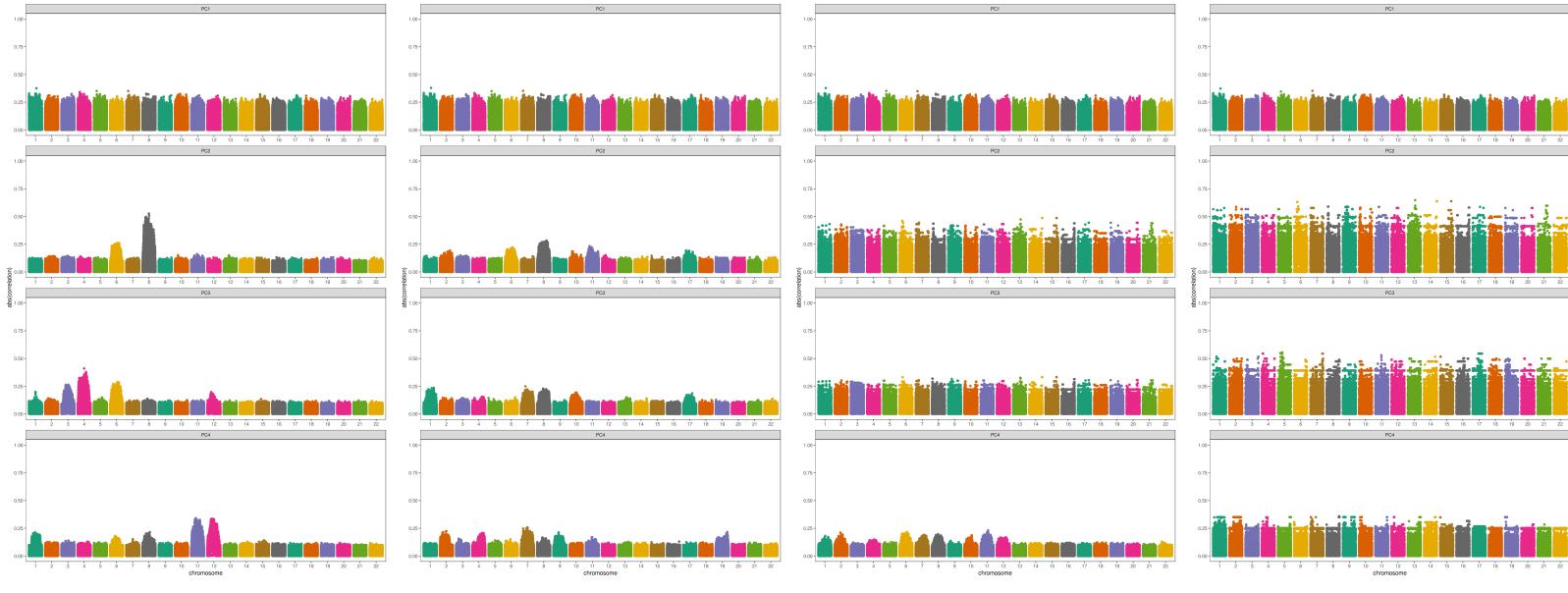


Figure 6: Correlation between the first four principal components and genotypes in Jackson Heart Study African Americans when previously-identified high-LD regions (Table 1) are removed prior to analysis. From left to right, panels correspond to increasingly strict levels of LD pruning: no LD pruning, LD pruning with an  $r^2$  threshold of 0.2 and a window size of 0.5 Mb, LD pruning with an  $r^2$  threshold of 0.1 and a window size of 0.5 Mb, and LD pruning with an  $r^2$  threshold of 0.1 and a window size of 10 Mb.

...]

## 4 Discussion

Global ancestry = confounder

- Summarize conditions under which global ancestry is a confounder
- Relate to current understanding in literature

Be careful with PCs!

- Summarize conditions under which PCs can be problematic
- Relate to current understanding in literature (what have others shown can happen if you include a PC that captures local LD? how are things different in admixed populations, where LD is more extensive?)

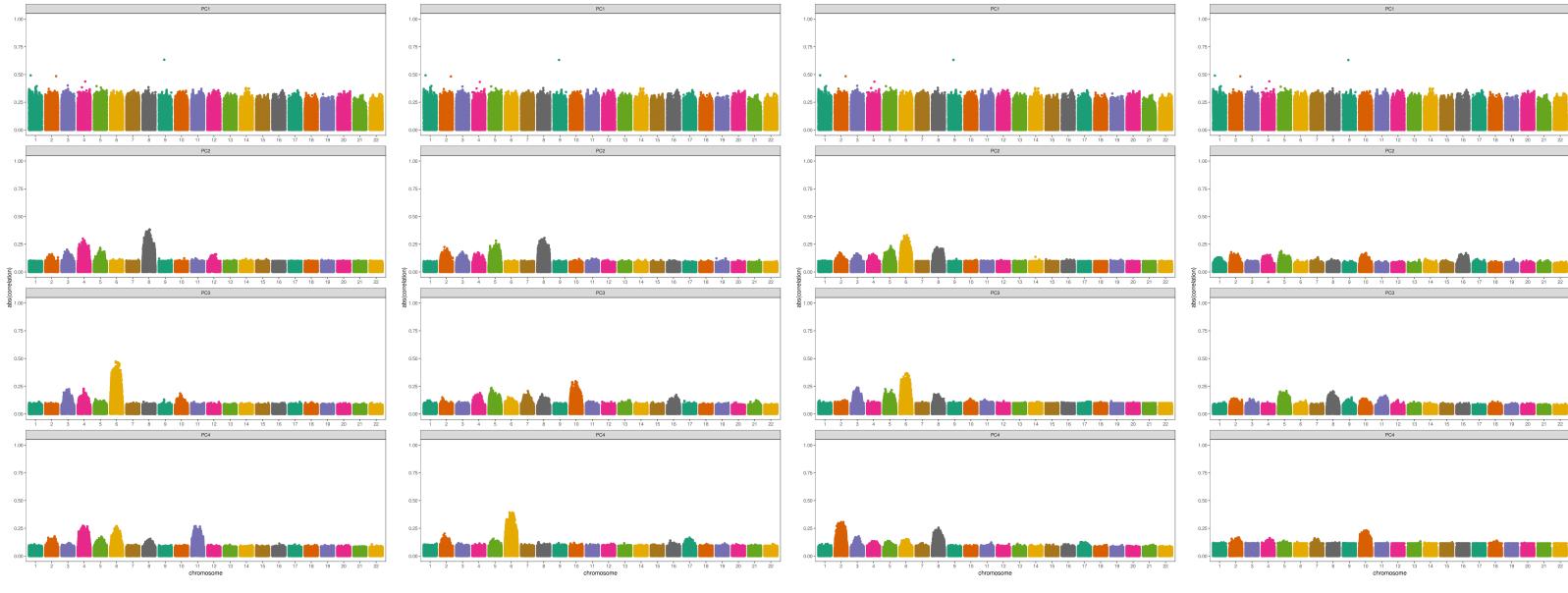


Figure 7: Correlation between the first four principal components and genotypes in COPDGene African Americans when previously-identified high-LD regions (Table 1) *are not* removed prior to analysis. From left to right, panels correspond to increasingly strict levels of LD pruning: no LD pruning, LD pruning with an  $r^2$  threshold of 0.2 and a window size of 0.5 Mb, LD pruning with an  $r^2$  threshold of 0.1 and a window size of 0.5 Mb, and LD pruning with an  $r^2$  threshold of 0.1 and a window size of 10 Mb.

- Relate to concept of collider bias
- Suggested diagnostics

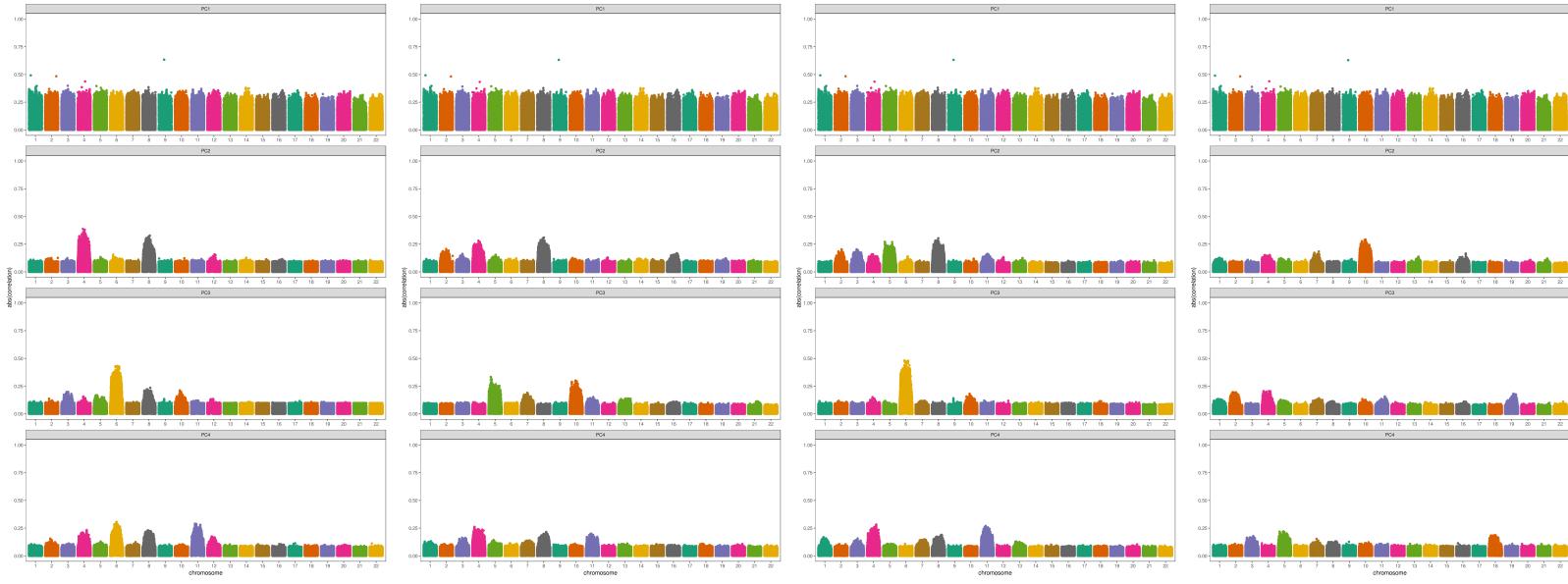


Figure 8: Correlation between the first four principal components and genotypes in COPDGene African Americans when previously-identified high-LD regions (Table 1) *are* removed prior to analysis. From left to right, panels correspond to increasingly strict levels of LD pruning: no LD pruning, LD pruning with an  $r^2$  threshold of 0.2 and a window size of 0.5 Mb, LD pruning with an  $r^2$  threshold of 0.1 and a window size of 0.5 Mb, and LD pruning with an  $r^2$  threshold of 0.1 and a window size of 10 Mb.

## 5 Appendices

### 5.1 Regions Removed Prior to PCA

- a list of all "high-LD" regions removed prior to running PCA

### 5.2 Mathematical Derivations

- theoretical results
- proofs
- simulations validating theory

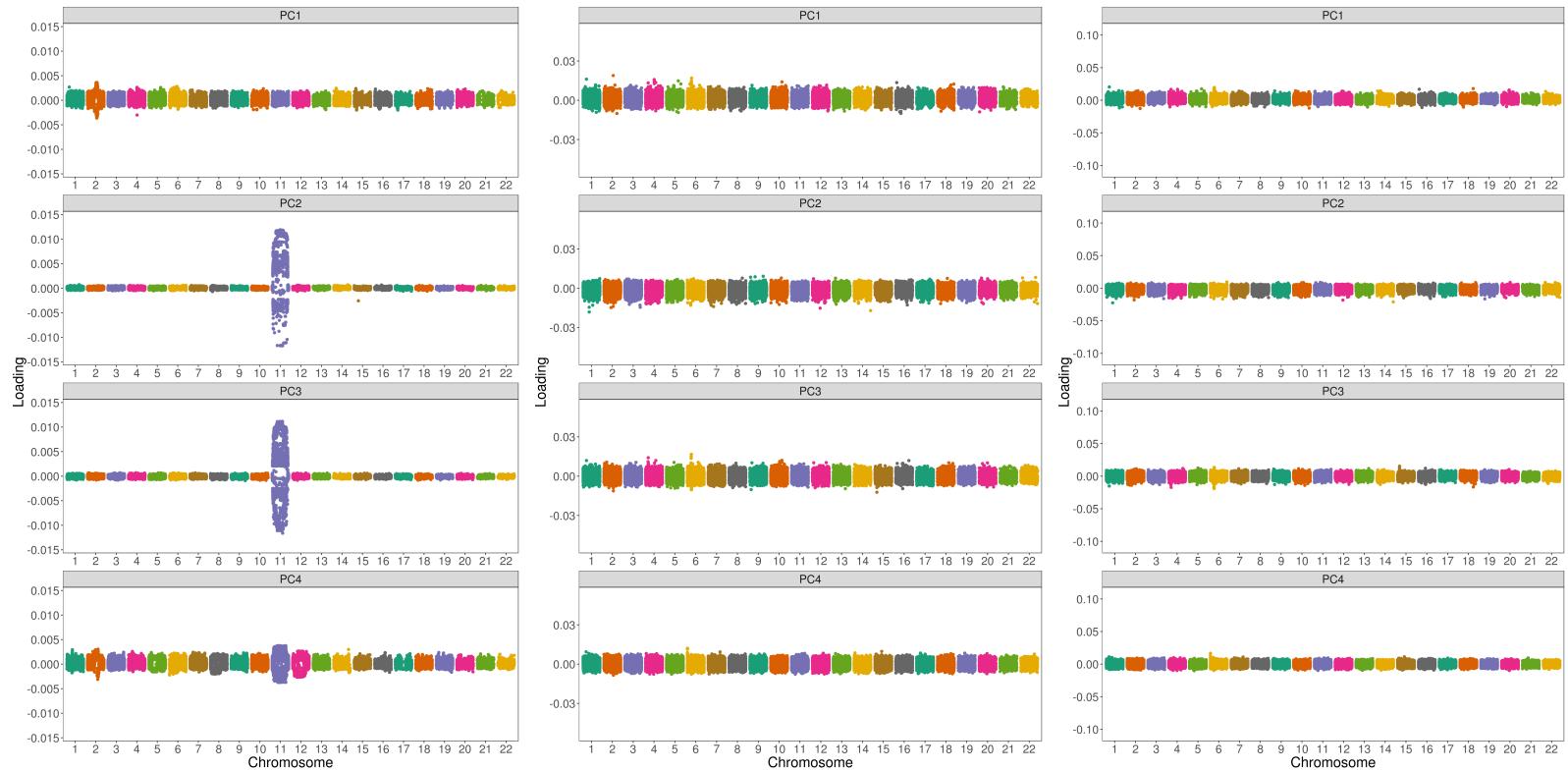


Figure 9: SNP loadings for the first four principal components in COPDGene European Americans when previously-identified high-LD regions (Table 1) are not removed prior to analysis but increasingly strict levels of LD pruning are performed. From left to right, columns correspond to no LD pruning, LD pruning with an  $r^2$  threshold of 0.2 and a window size of 0.5 Mb, and LD pruning with an  $r^2$  threshold of 0.1 and a window size of 0.5 Mb. [... Change to look at correlation instead of loadings ...]

## **Supplemental Data**

Supplemental Data include [... ?? ...] figures and [... ?? ...] tables.

## **Declaration of Interests**

The authors declare no competing interests.

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## **Web Resources**

[GitHub Repository](#): lists of regions to exclude, code for LD pruning, excluding, and plotting loadings

## **Data and Code Availability**

## References

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## **Figure Titles and Legends**

## **Tables**