Challenges and new approaches for whole genome analysis in multi-ethnic studies with pedigrees.

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New Statistical Methods for Family-Based Sequencing Studies

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SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

Motivation: Multi-Ethnic PAGE Study

- The Population Architecture using Genomics and Epidemiology (PAGE) study focuses on exploring the genetics of underrepresented populations.
- PAGE consists of **49,839** individuals of non-European ancestry from multi-ethnic studies,
- Individuals were genotyped using the approximately 1.3 million variants on the Multi-Ethnic Global Array (MEGA) imputed to 1000 Genomes Phase 3

Muti-Ethnic PAGE Study

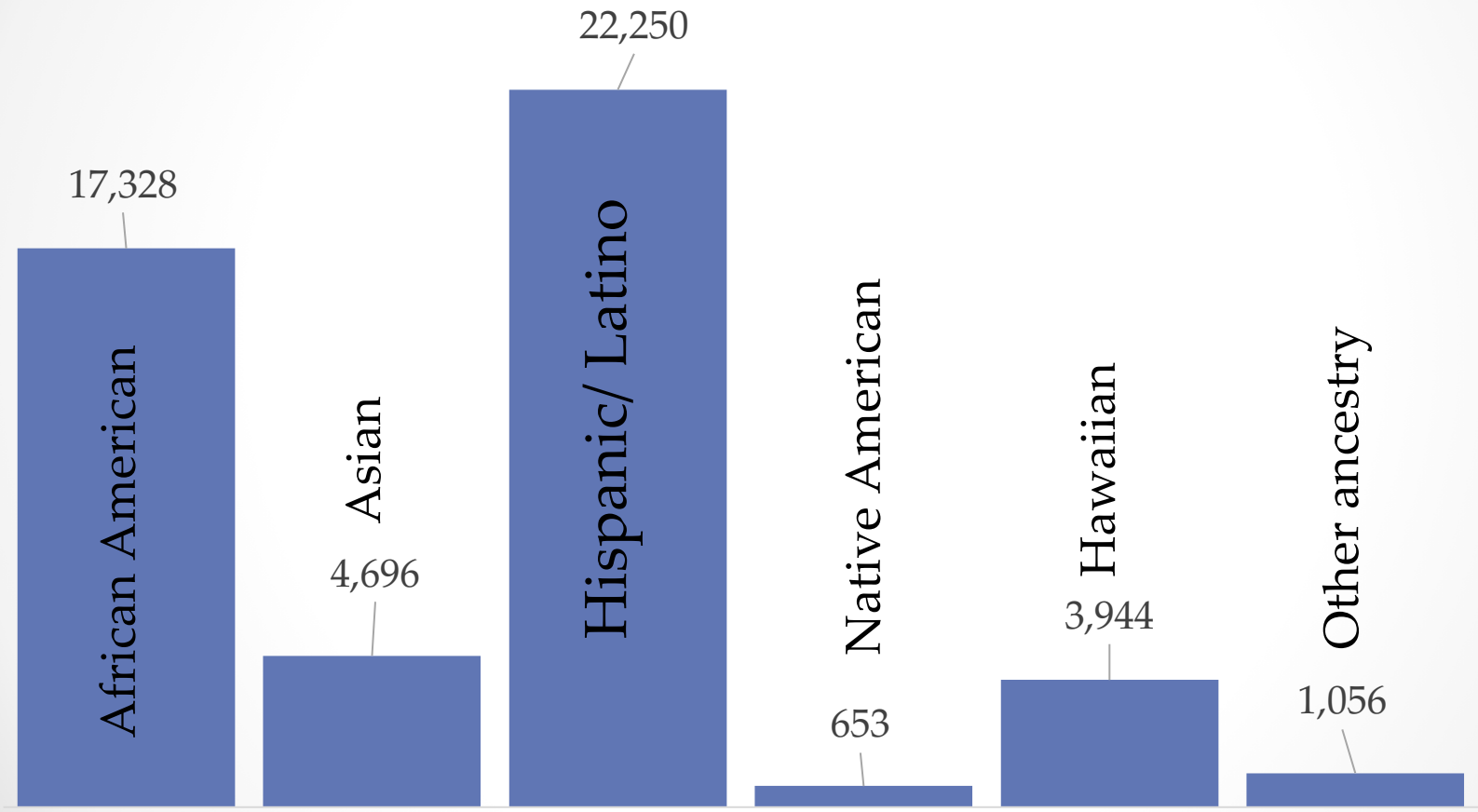


Figure Courtesy of TOPMed DCC

Muti-Ethnic PAGE Study

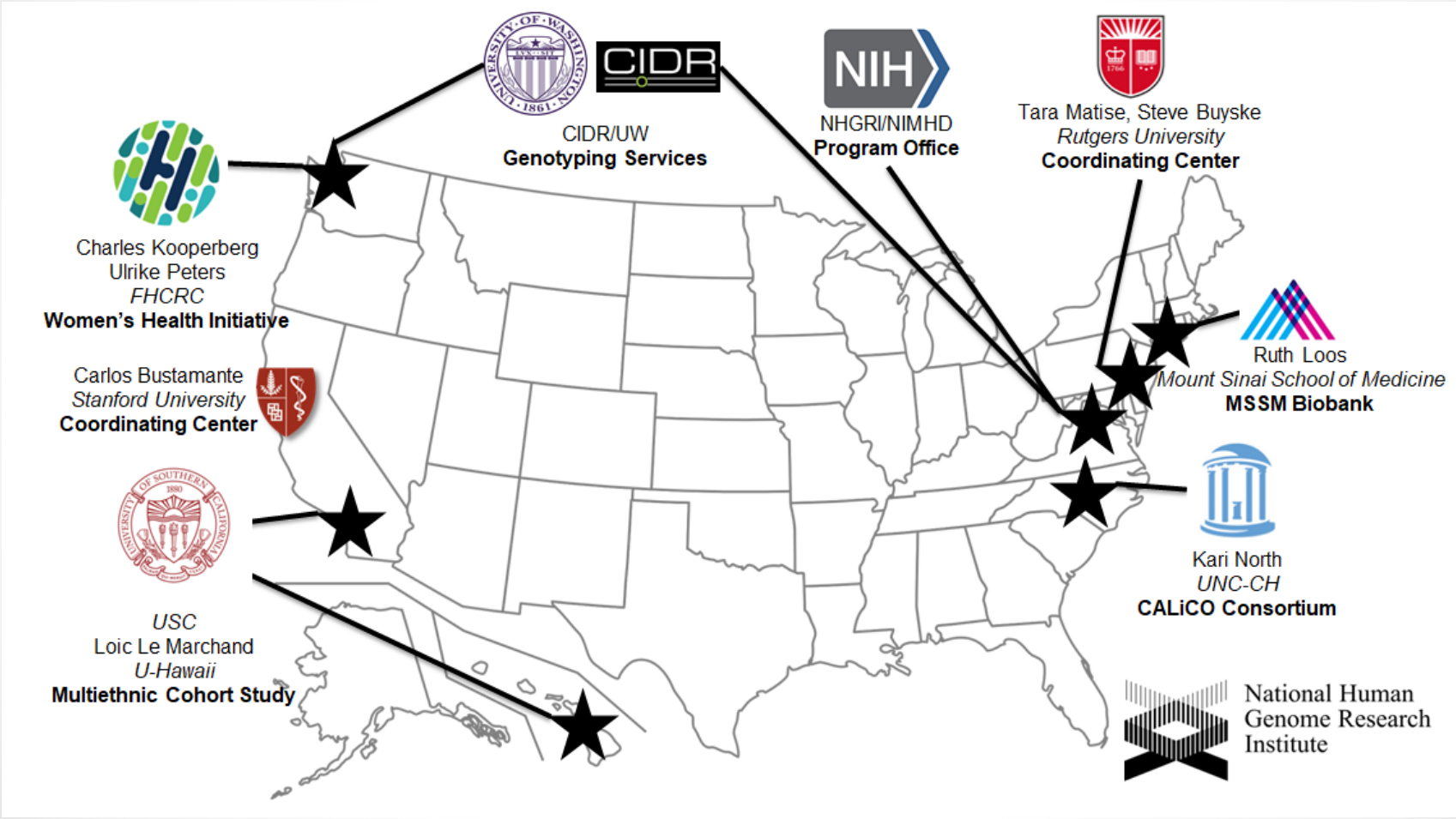


Figure Courtesy of Mariaelisa Graff (UNC Chapel Hill)

Motivation: TOPMed WGS Project

- NIH/NHLBI Trans-Omics for Precision Medicine (TOPMed) Whole-genome-sequence (WGS) project is generated deep whole genome sequencing data for more than **170,000 individuals.**
- Cohorts are from multi-ethnic populations with well-defined phenotypes and existing clinical outcomes data.

TOPMed WGS Project: Multi-Ethic Cohorts

- 30X coverage Illumina X-10 sequencing
- 4 sequencing centers with harmonized protocols

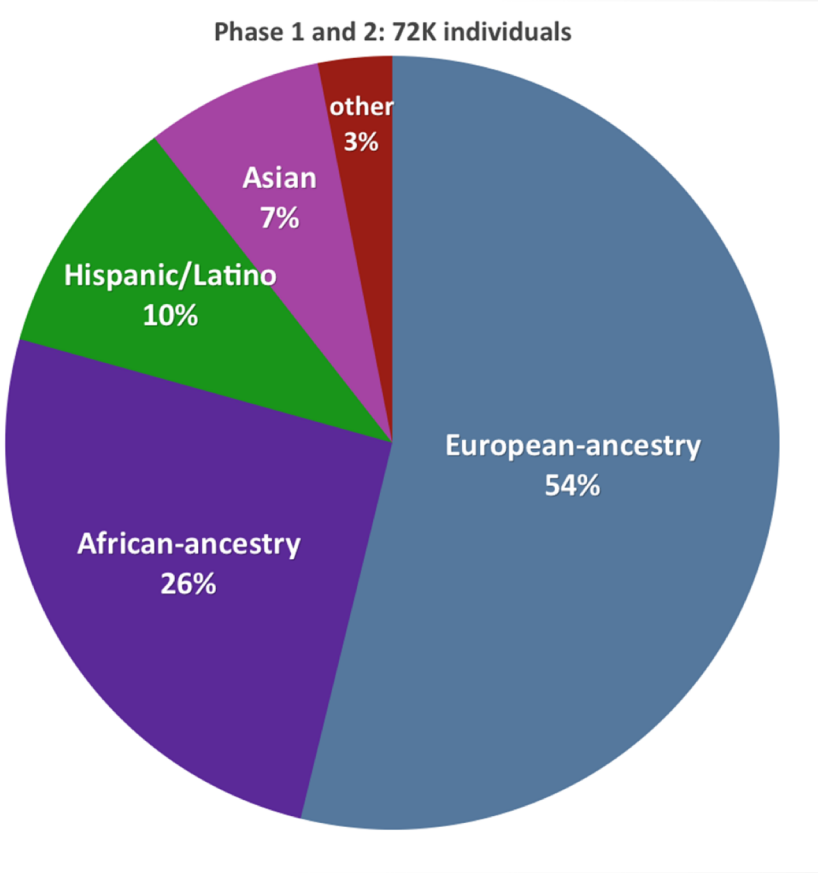


Chart from TOPMed DCC

PAGE and TOPMed and PAGE: Opportunities

- The PAGE and TOPMed WGS Project offer unprecedented opportunities for:
  - Identification of population-specific variants as well as novel low frequency and rare genetic variants underlying phenotypic diversity
  - Potential to provide new insights into human health and health disparities of minority populations for many complex diseases

TOPMed and PAGE : Challenges

- Challenges for analysis of PAGE and TOPMed whole genome data:
  - **Multi-ethnic populations and confounding due to highly heterogeneous genetic and environmental backgrounds within and across cohorts**
  - **Variety of study designs: case-control and cohort studies, family-based studies, founder populations (e.g., TOPMed includes the Framingham Heart Study, Jackson Heart Study, and Amish samples).**
  - Computational burden for analysis of deep whole genome sequence data for 120,000+ individuals (TOPMed) and 50,000 individuals with 1000 Genomes imputed genotypes (PAGE)

Linear Mixed Models

- Linear mixed models (LMMs) have emerged as a powerful and effective method of choice for genetic association testing in the presence of sample structure
- LMMs have been used to simultaneously account for both population structure, family structure, and/or cryptic relatedness

Linear Mixed Models

- A number of LMMs have been proposed including EMMAX proposed by Kang et al.[Nat Genet, 2010], GEMMA proposed by Zhou and Stephens [Nat Genet, 2012] and others:

LMMs for Genetic Association Testing

- Most LMM methods fit the following linear mixed model

$$\mathbf{Y} = \mathbf{g}_s\beta_s + \mathbf{X}\boldsymbol{\alpha} + \boldsymbol{\epsilon} \qquad \text{with} \qquad \boldsymbol{\epsilon} \sim \mathrm{N}\left(\mathbf{0}, \boldsymbol{\Sigma} \equiv \sigma_A^2\boldsymbol{\Psi} + \sigma_\epsilon^2\mathbf{I}\right)$$

where:

  - $\mathbf{Y}$ is the vector of phenotype values
  - $\mathbf{g}_s$ is the vector of genotypes at the SNP being tested,
  - β_s is the (scalar) association parameter of interest, measuring the effect of genotype on phenotype
  - $\mathbf{X}$ is a matrix of covariate values with vector $\boldsymbol{\alpha}$ of covariate effects
  - $\boldsymbol{\Psi}$ is an estimated genetic relationship matrix (GRM) capturing population structure and relatedness
  - σ_A^2 is the additive genetic variance for polygenic effects
  - $\mathbf{I}$ is the identity matrix
  - σ_ϵ^2 presents non-genetic variance due to non-genetic effects assumed to be acting independently on individuals

Standard GRM for LMMs

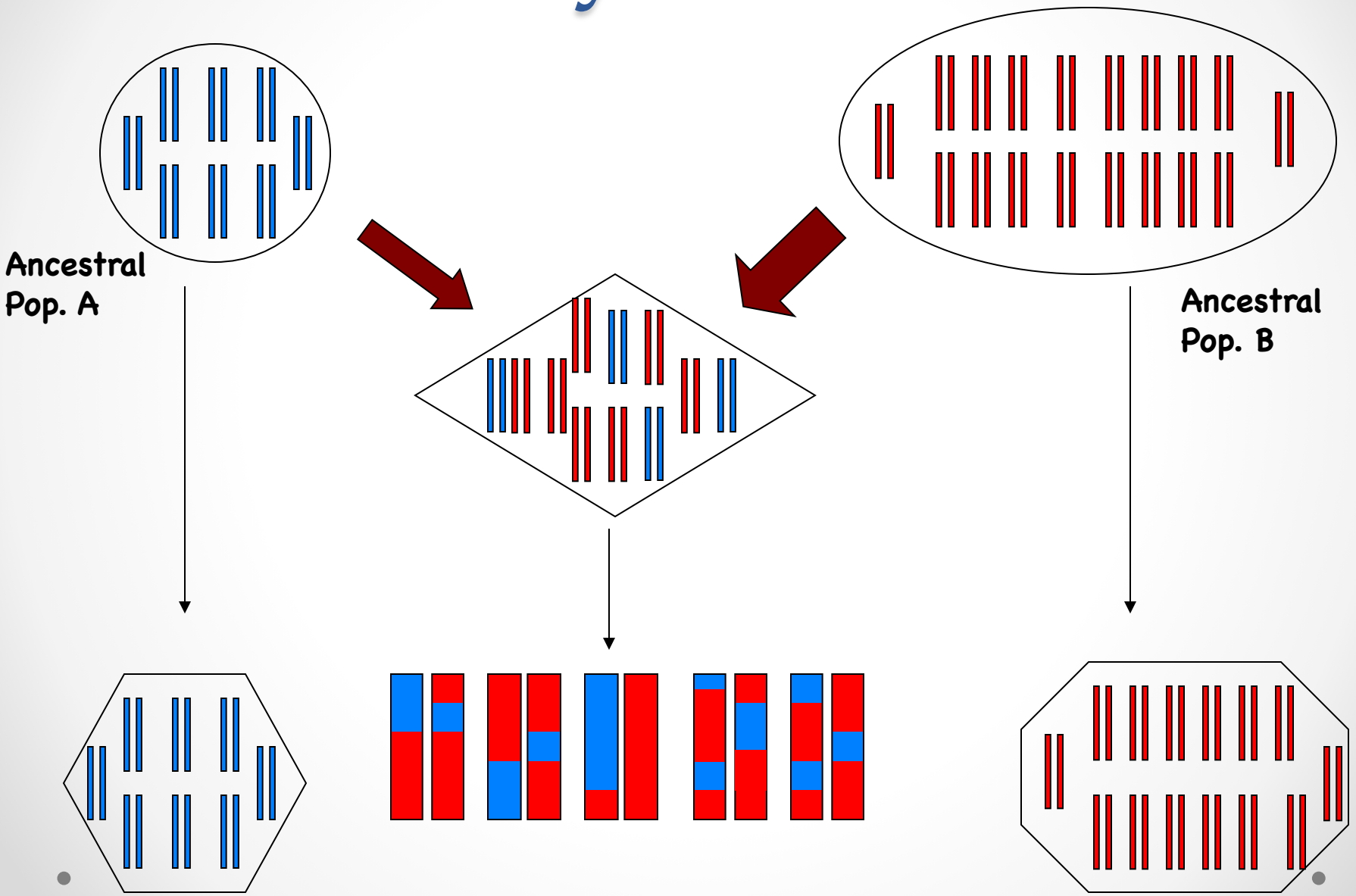
- Average genotypic correlations across the genome is summarized with a single genetic relatedness matrix (GRM)
- GRM entry for subjects *i* and *j* who have *M* genotyped markers across the autosomes:

$$\hat{\Psi}_{ij} = \frac{1}{M}\sum_{m=1}^{M}\frac{(g_{mi} - 2\hat{p}_m)(g_{mj} - 2\hat{p}_m)}{2\hat{p}_m(1-\hat{p}_m)}$$

Linear Mixed Models for Genetic Association Testing

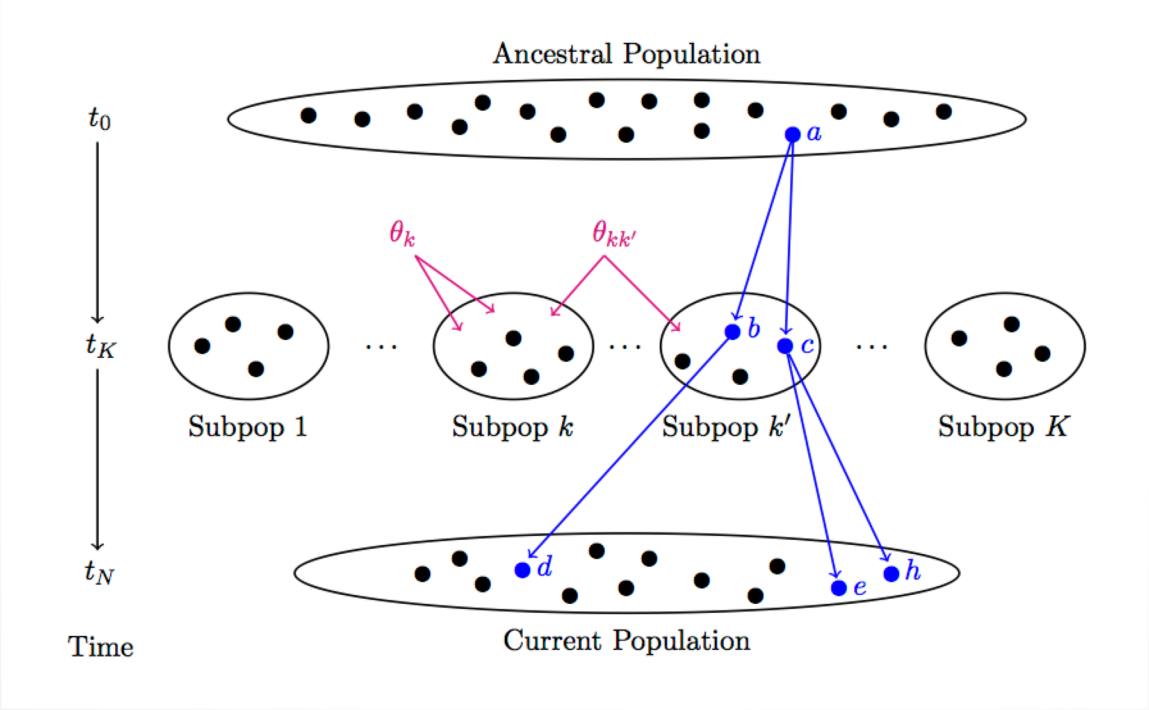
- LMMs have largely been evaluated in samples with relatively subtle population structure, e.g., European populations
- Existing LMMs methods use a single empirical genetic relationship matrix to model the entire genealogy of sampled individuals as part of the covariance structure of the phenotype.
- Samples from multi-ethnic cohorts often have complex genealogy due to ancestry admixture and both recent and distant genetic relatedness
- The genealogy of sampled individuals consists of:
  - Distant genetic relatedness, such as population structure
  - Recent genetic relatedness: pedigree relationships of close relatives

Ancestry Admixture



Recent versus Distant Genetic Relatedness

- Distinguishing familial relatedness from ancestry using genotype data in diverse populations is difficult, as both manifest as genetic similarity through the sharing of alleles.



Conomos et al. (AJHG, 2016)

Deconvolution of Genetic Relatedness

- Conomos et al., *Am J Hum Genet*, 2016

ARTICLE

Model-free Estimation of Recent Genetic Relatedness

Matthew P. Conomos,[1,*] Alexander P. Reiner,[2,3] Bruce S. Weir,[1] and Timothy A. Thornton[1,*]

- Conomos et al., Genet Epidemiology, 2015

RESEARCH ARTICLE

Genetic Epidemiology

OFFICIAL JOURNAL INTERNATIONAL GENETIC EPIDEMIOLOGY SOCIETY www.geneticepi.org

Robust Inference of Population Structure for Ancestry Prediction and Correction of Stratification in the Presence of Relatedness

Matthew P. Conomos,[1] Michael B. Miller,[2] and Timothy A. Thornton[1]*

- Thornton et al., *Am J Hum Genet*, 2012

ARTICLE

Estimating Kinship in Admixed Populations

Timothy Thornton,[1,*] Hua Tang,[2] Thomas J. Hoffmann,[3,4] Heather M. Ochs-Balcom,[5] Bette J. Caan,[6] and Neil Risch[3,4,6,*]

LMM-OPS for Multi-Ethnic Populations

- Matt Conomos PhD dissertation work developed LMM-OPS for association mapping in ancestrally diverse populations
- LMM-OPS, linear mixed models with orthogonal partitioned structure
- Appropriately accounts for the complex genealogy of ancestrally diverse samples by partitioning sample structure into two orthogonal components:
  1. a component for the sharing of alleles inherited identical by descent (IBD) from recent common ancestors, which represents familial relatedness
  2. and another component for allele sharing due to more distant common ancestry, which represents population structure.

LMM-OPS for Multi-Ethnic Populations

- With LMM-OPS, a score test for association is calculated based on the following linear mixed model:

$$\mathbf{Y} = \mathbf{g}_s\beta_s + \mathbf{X}\boldsymbol{\alpha} + \mathbf{V}\boldsymbol{\gamma} + \boldsymbol{\epsilon} \qquad \text{with} \qquad \boldsymbol{\epsilon} \sim \mathrm{N}\left(\mathbf{0}, \boldsymbol{\Sigma} \equiv \sigma_A^2\boldsymbol{\Phi} + \sigma_\epsilon^2\mathbf{I}\right)$$

where:

- $\boldsymbol{\Phi}$ is an genetic relatedness matrix adjusted for ancestry admixture (via the PCs) with PC-Relate
- $\mathbf{V}$ is a matrix with PCs from PC-AiR, and γ is a vector (unknown) ancestry effects on the phenotype
- $\mathbf{X}$ is a matrix of covariate values with vector α of covariate effects

PC-Relate GRMs for LMM-OPS

Two possible GRMs we have considered for LMM-OPS are as follows, with the following entries for subjects *i* and *j who have M genotyped markers*.

$$\hat{\Phi}^{1}_{ij} = \frac{1}{M}\sum_{m=1}^{M}\frac{(g_{mi}-2\hat{p}_{mi})(g_{mj}-2\hat{p}_{mj})}{\sqrt{2\hat{p}_{mi}(1-\hat{p}_{mi})}\sqrt{2\hat{p}_{mj}(1-\hat{p}_{mj})}}$$

$$\hat{\Phi}^{2}_{ij} = \frac{\frac{1}{M}\sum_{m=1}^{M}(g_{mi}-2\hat{p}_{mi})(g_{mj}-2\hat{p}_{mj})}{\frac{1}{M}\sum_{m=1}^{M}\sqrt{2\hat{p}_{mi}(1-\hat{p}_{mi})}\sqrt{2\hat{p}_{mj}(1-\hat{p}_{mj})}}$$

Both use **individual specific allele** frequencies, $\hat{p}_{mi}$, calculated from a regression analysis with the PCs from PC-AiR included as predictors of genotype

Simulations with Admixture: Genomic Control Inflation Evaluation

Method	Genome-Wide	Highly[a] Differentiated	Moderately[b] Differentiated	Weakly[c] Differentiated
LMM-OPS	1.000 (0.0002)	0.999 (0.0007)	1.001 (0.0004)	1.001 (0.0003)
EMMAX	1.001 (0.0002)	**1.098 (0.0011)**	**1.016 (0.0004)**	**0.979 (0.0003)**
GEMMA	1.004 (0.0002)	**1.110 (0.0011)**	**1.020 (0.0005)**	**0.980 (0.0003)**
Linear Reg. with PCs	**1.026 (0.0006)**	**1.025 (0.0009)**	**1.027 (0.0007)**	**1.026 (0.0006)**

[a] Highly differentiated SNPs: $D_s \geq 0.4$ between the two populations
[b] Moderately differentiated SNPs: $0.4 > D_s \geq 0.2$ between the two populations
[c] Weakly differentiated SNPs: $D_s < 0.2$ between the two populations

Applications and Discoveries in Hispanic/Latino Populations

ARTICLE

Genetic Diversity and Association Studies in US Hispanic/Latino Populations: Applications in the Hispanic Community Health Study/Study of Latinos

Matthew P. Conomos,[1,14,*] Cecelia A. Laurie,[1,14] Adrienne M. Stilp,[1,14] Stephanie M. Gogarten,[1,14] Caitlin P. McHugh,[1] Sarah C. Nelson,[1] Tamar Sofer,[1] Lindsay Fernández-Rhodes,[2] Anne E. Justice,[2] Mariaelisa Graff,[2] Kristin L. Young,[2] Amanda A. Seyerle,[2] Christy L. Avery,[2] Kent D. Taylor,[3] Jerome I. Rotter,[3] Gregory A. Talavera,[4] Martha L. Daviglus,[5] Sylvia Wassertheil-Smoller,[6] Neil Schneiderman,[7] Gerardo Heiss,[2] Robert C. Kaplan,[6] Nora Franceschini,[2] Alex P. Reiner,[8] John R. Shaffer,[9] R. Graham Barr,[10] Kathleen F. Kerr,[1] Sharon R. Browning,[1] Brian L. Browning,[11] Bruce S. Weir,[1] M. Larissa Avilés-Santa,[12] George J. Papanicolaou,[12] Thomas Lumley,[13] Adam A. Szpiro,[1] Kari E. North,[2] Ken Rice,[1] Timothy A. Thornton,[1] and Cathy C. Laurie[1,*]

ORIGINAL ARTICLE

Genetic Associations with Obstructive Sleep Apnea Traits in Hispanic/Latino Americans

Brian E. Cade[1,2], Han Chen[3], Adrienne M. Stilp[4], Kevin J. Gleason[1], Tamar Sofer[4], Sonia Ancoli-Israel[5,6,7], Raanan Arens[8], Graeme I. Bell[9], Jennifer E. Below[10], Andrew C. Bjonnes[11], Sung Chun[11,12], Matthew P. Conomos[4], Daniel S. Evans[13], W. Craig Johnson[4], Alexis C. Frazier-Wood[14], Jacqueline M. Lane[1,2,15,16], Emma K. Larkin[17], Jose S. Loredo[18], Wendy S. Post[19], Alberto R. Ramos[20], Ken Rice[4], Jerome I. Rotter[21], Neomi A. Shah[22], Katie L. Stone[13], Kent D. Taylor[21], Timothy A. Thornton[4], Gregory J. Tranah[13], Chaolong Wang[3,23], Phyllis C. Zee[24], Craig L. Hanis[10], Shamil R. Sunyaev[11,12,16], Sanjay R. Patel[1,2,25], Cathy C. Laurie[4], Xiaofeng Zhu[26], Richa Saxena[1,15,16], Xihong Lin[3], and Susan Redline[1,2,25]

ARTICLE

Genome-wide Association Study of Platelet Count Identifies Ancestry-Specific Loci in Hispanic/Latino Americans

Ursula M. Schick,[1,2,3,16] Deepti Jain,[4,16] Chani J. Hodonsky,[5,16] Jean V. Morrison,[4] James P. Davis,[6] Lisa Brown,[4] Tamar Sofer,[4] Matthew P. Conomos,[4] Claudia Schurmann,[2,3] Caitlin P. McHugh,[4] Sarah C. Nelson,[4] Swarooparani Vadlamudi,[6] Adrienne Stilp,[4] Anna Plantinga,[4] Leslie Baier,[7] Stephanie A. Bien,[1] Stephanie M. Gogarten,[4] Cecelia A. Laurie,[4] Kent D. Taylor,[8,9] Yongmei Liu,[10] Paul L. Auer,[11] Nora Franceschini,[5] Adam Szpiro,[4] Ken Rice,[4] Kathleen F. Kerr,[4] Jerome I. Rotter,[8] Robert L. Hanson,[7] George Papanicolaou,[12] Stephen S. Rich,[13,14] Ruth J.F. Loos,[2,3,15] Brian L. Browning,[4] Sharon R. Browning,[4] Bruce S. Weir,[4] Cathy C. Laurie,[4] Karen L. Mohlke,[6] Kari E. North,[5,16] Timothy A. Thornton,[4,16] and Alex P. Reiner[1,16,*]

ARTICLE

Control for Population Structure and Relatedness for Binary Traits in Genetic Association Studies via Logistic Mixed Models

Han Chen,[1,8] Chaolong Wang,[1,2,8] Matthew P. Conomos,[3] Adrienne M. Stilp,[3] Zilin Li,[1,4] Tamar Sofer,[3] Adam A. Szpiro,[3] Wei Chen,[5] John M. Brehm,[5] Juan C. Celedón,[5] Susan Redline,[6] George J. Papanicolaou,[7] Timothy A. Thornton,[3] Cathy C. Laurie,[3] Kenneth Rice,[3] and Xihong Lin[1,*]

ASSOCIATION STUDIES ARTICLE

Genome-wide association study of dental caries in the Hispanic Communities Health Study/Study of Latinos (HCHS/SOL)

Jean Morrison[1], Cathy C. Laurie[1], Mary L. Marazita[2,3,4], Anne E. Sanders[5], Steven Offenbacher[6], Christian R. Salazar[7,8], Matthew P. Conomos[1], Timothy Thornton[1], Deepti Jain[1], Cecelia A. Laurie[1], Kathleen F. Kerr[1], George Papanicolaou[9], Kent Taylor[10], Linda M. Kaste[11], James D. Beck[5] and John R. Shaffer[2,*]

ASSOCIATION STUDIES ARTICLE

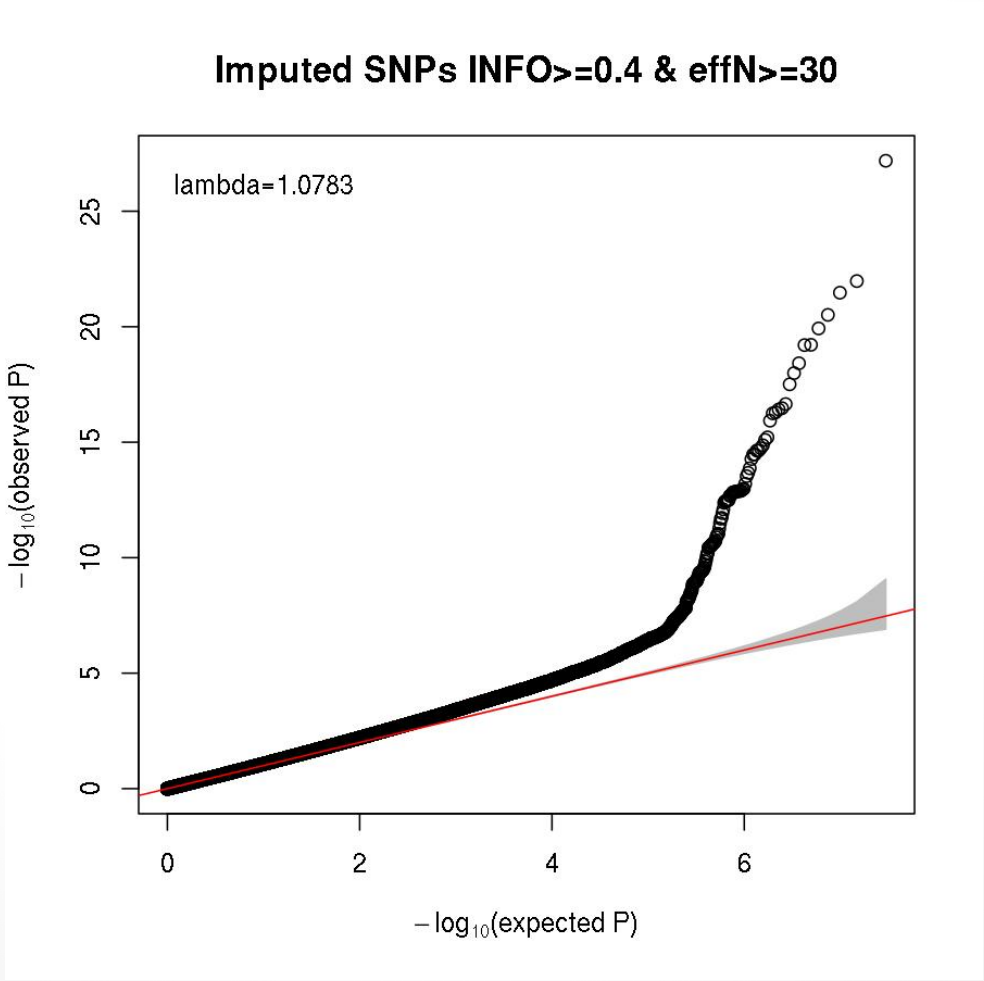
Genome-wide association study of iron traits and relation to diabetes in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL): potential genomic intersection of iron and glucose regulation?

Association Analysis with Linear Mixed Models

- LMM-OPS worked well for WHI-SHARe Hispanics and the Hispanic Community Health Study / Study of Latinos
- Applied LMM-OPS and standard LMM to PAGE and TOPMed traits
- Very perplexing results for many phenotypes!
- One phenotype with badly behaved results if fasting glucose

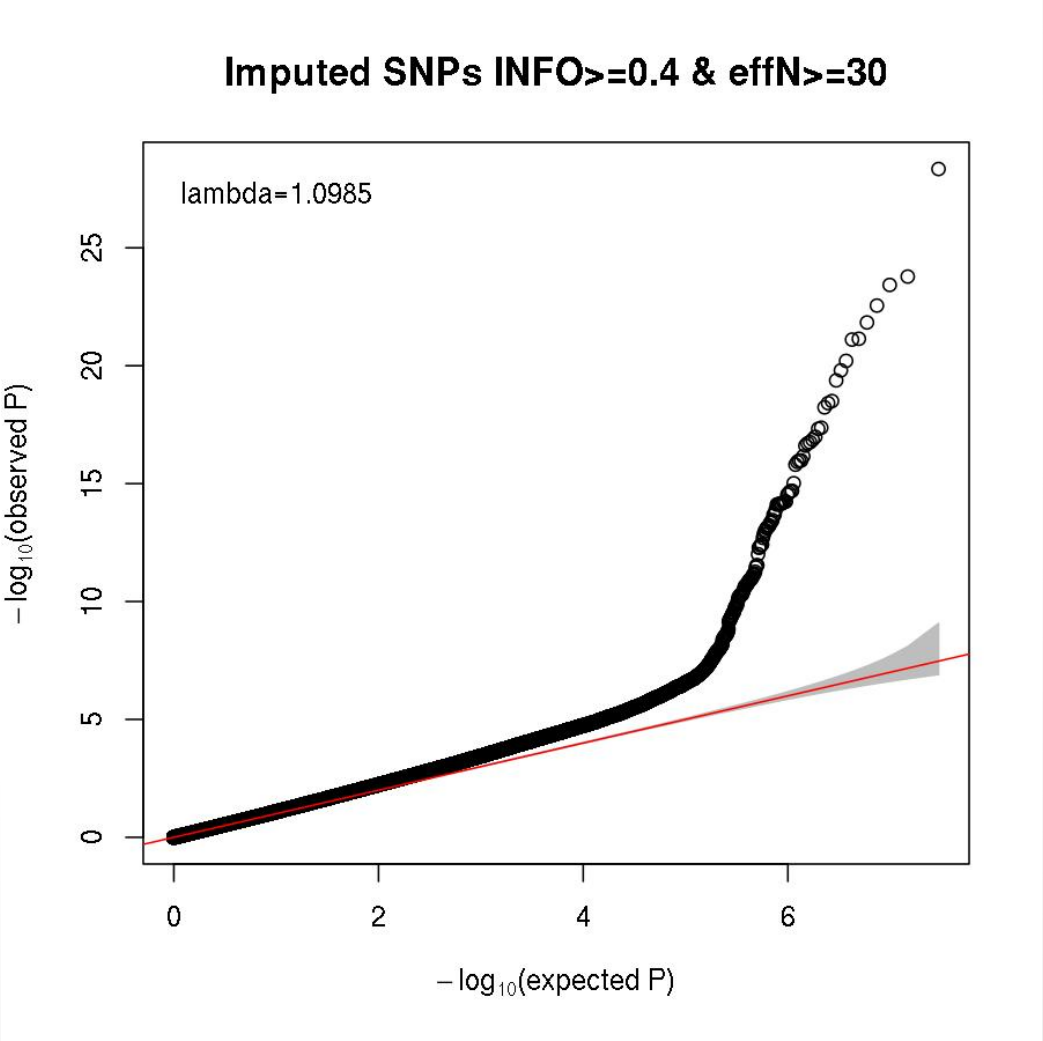
PAGE Analysis: Standard LMM (EMMAX/GCTA)

- Results for PAGE fasting glucose with adjustment for BMI



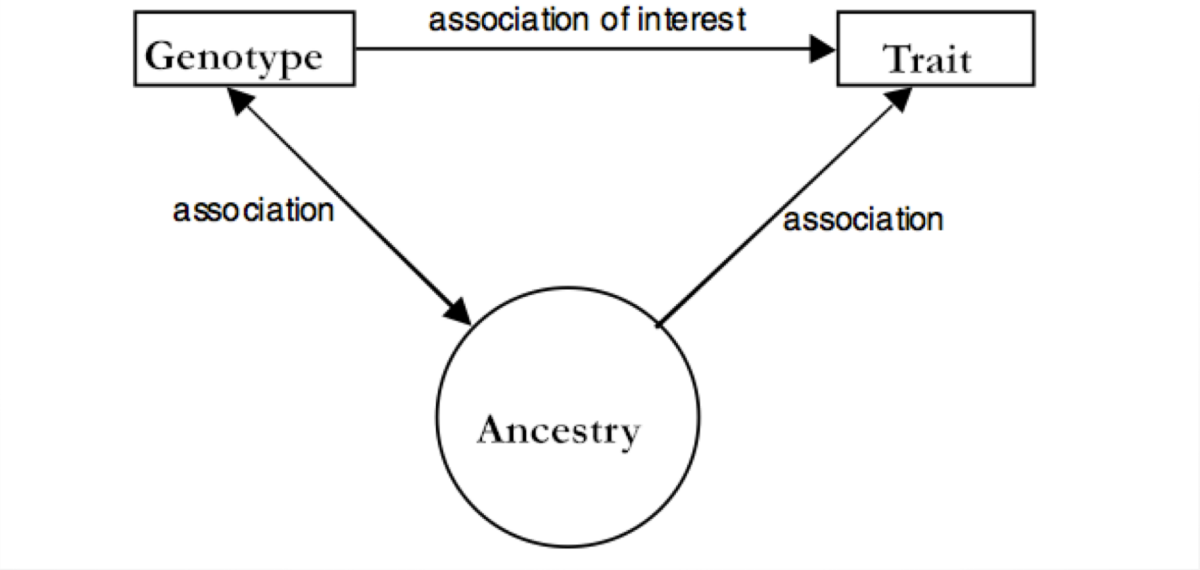
PAGE Analysis: LMM-OPS

- LMM-OPS Results for fasting glucose with adjustment for BMI in PAGE

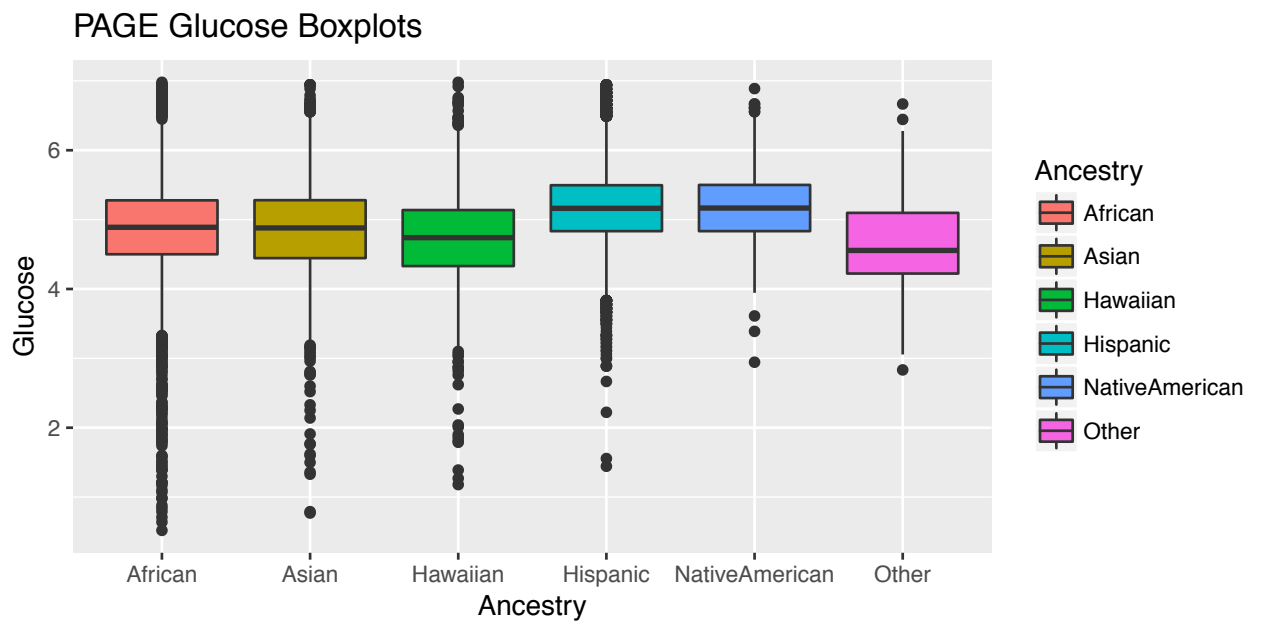


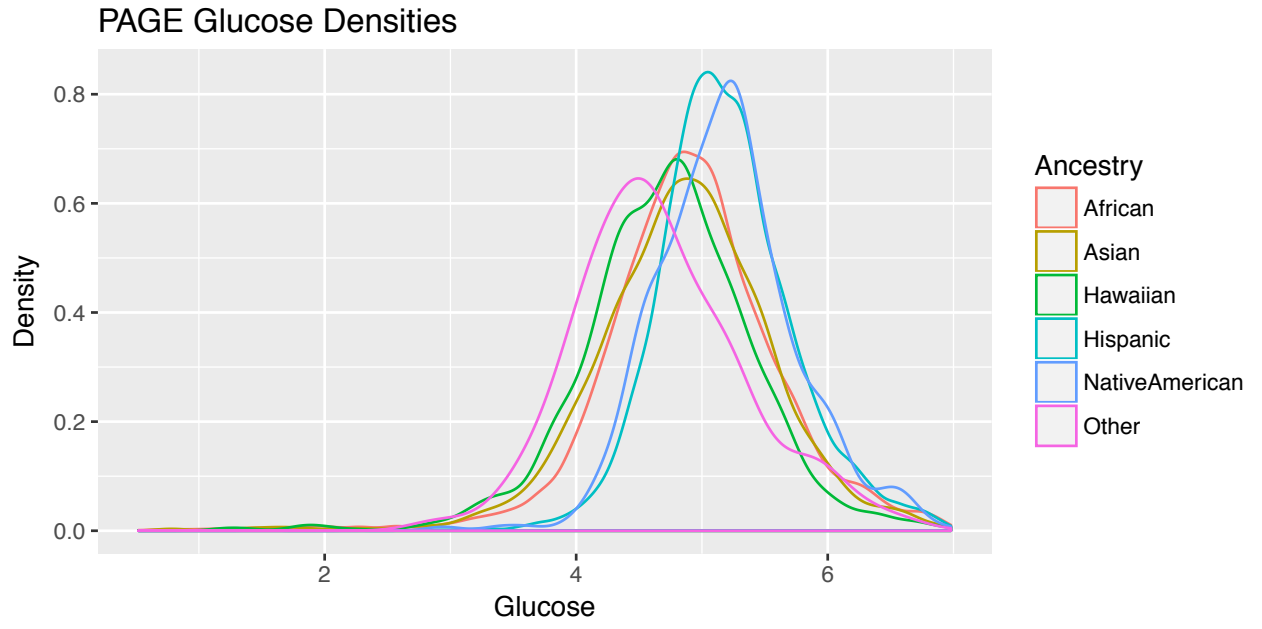
Problems? Confounding due to combining samples form multi-ethnic populations

- Ethnic groups (and subgroups) often share distinct dietary habits and other lifestyle characteristics that result in traits of interest having **different distributions** that are correlated with genetic ancestry and/or ethnicity.



PAGE Glucose by Race/Ethnicity





PAGE Principal Components Analysis

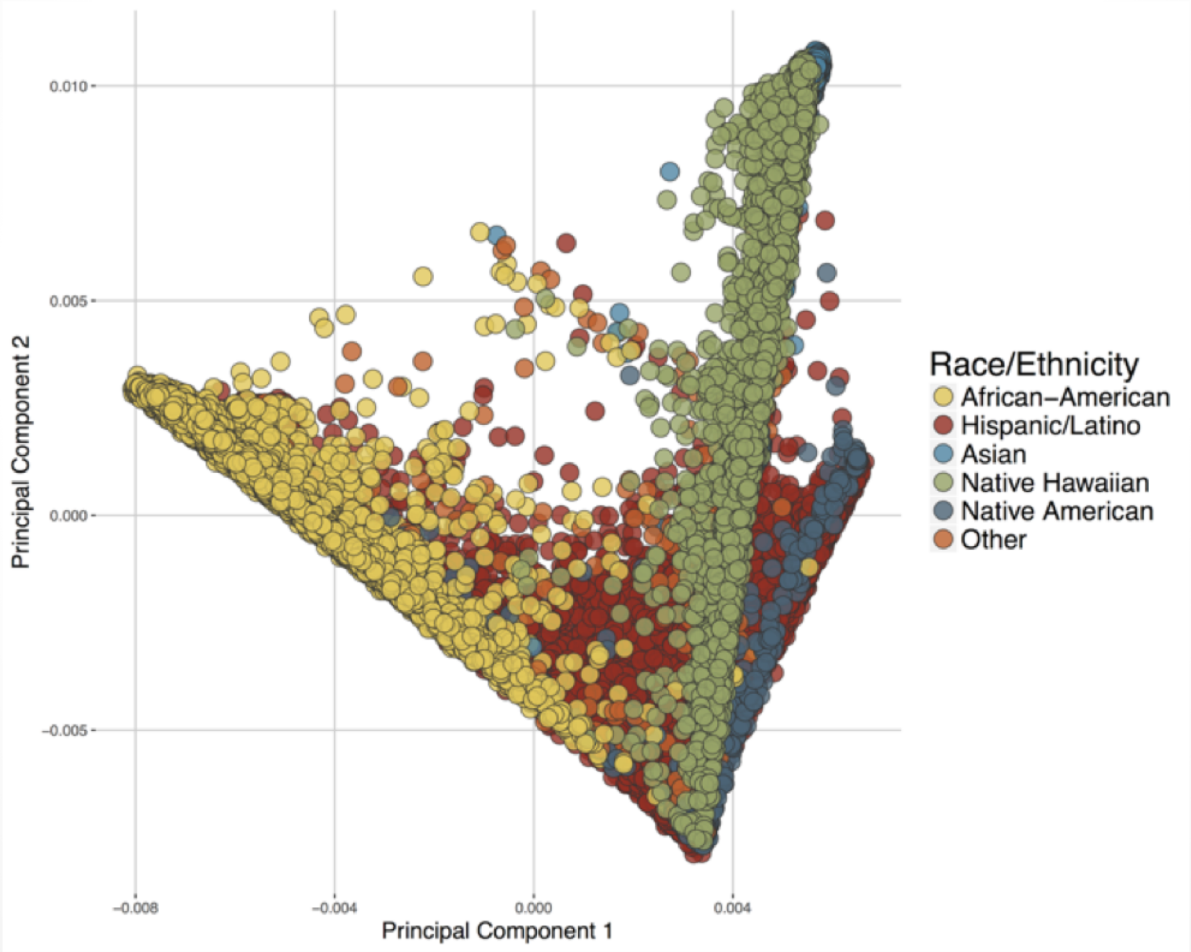


Figure Courtesy of Mariaelisa Graff (UNC Chapel Hill)

PAGE Principal Components Analysis

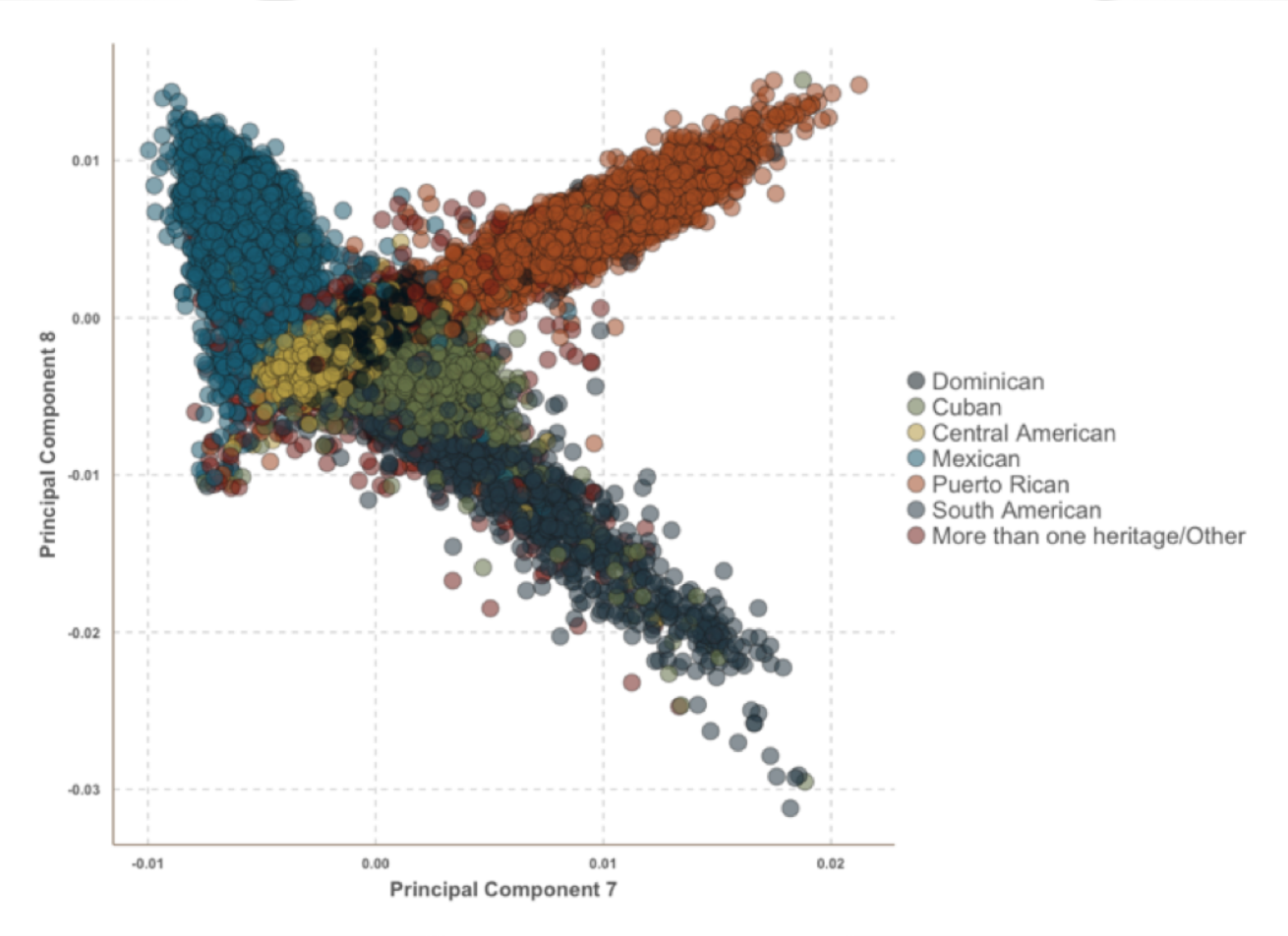


Figure Courtesy of Mariaelisa Graff (UNC Chapel Hill)

PAGE Analysis: Standard LMM (EMMAX/GCTA)

- Recall the standard LMM model

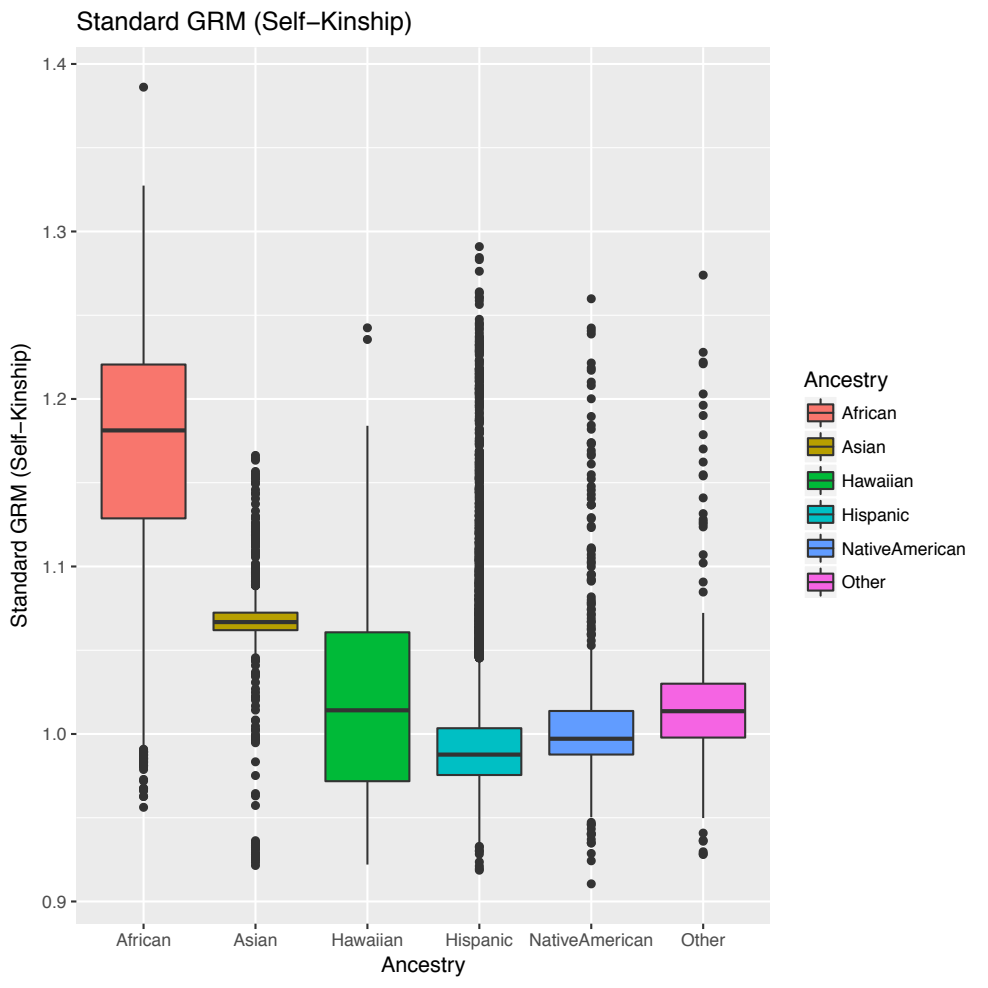
$$\mathbf{Y} = \mathbf{g}_s\beta_s + \mathbf{X}\boldsymbol{\alpha} + \boldsymbol{\epsilon} \qquad \text{with} \qquad \boldsymbol{\epsilon} \sim \mathrm{N}\left(\mathbf{0}, \boldsymbol{\Sigma} \equiv \sigma_A^2\boldsymbol{\Psi} + \sigma_\epsilon^2\mathbf{I}\right)$$

- For glucose with BMI adjustment, variance components were estimated
- Residual variance component: $\hat{\sigma}^2_\epsilon = 0.258$
- Additive genetic variance component: $\hat{\sigma}^2_A = 0.063$

$$\hat{\Psi}_{ij} = \frac{1}{M}\sum_{m=1}^{M}\frac{(g_{mi} - 2\hat{p}_m)(g_{mj} - 2\hat{p}_m)}{2\hat{p}_m(1-\hat{p}_m)}$$

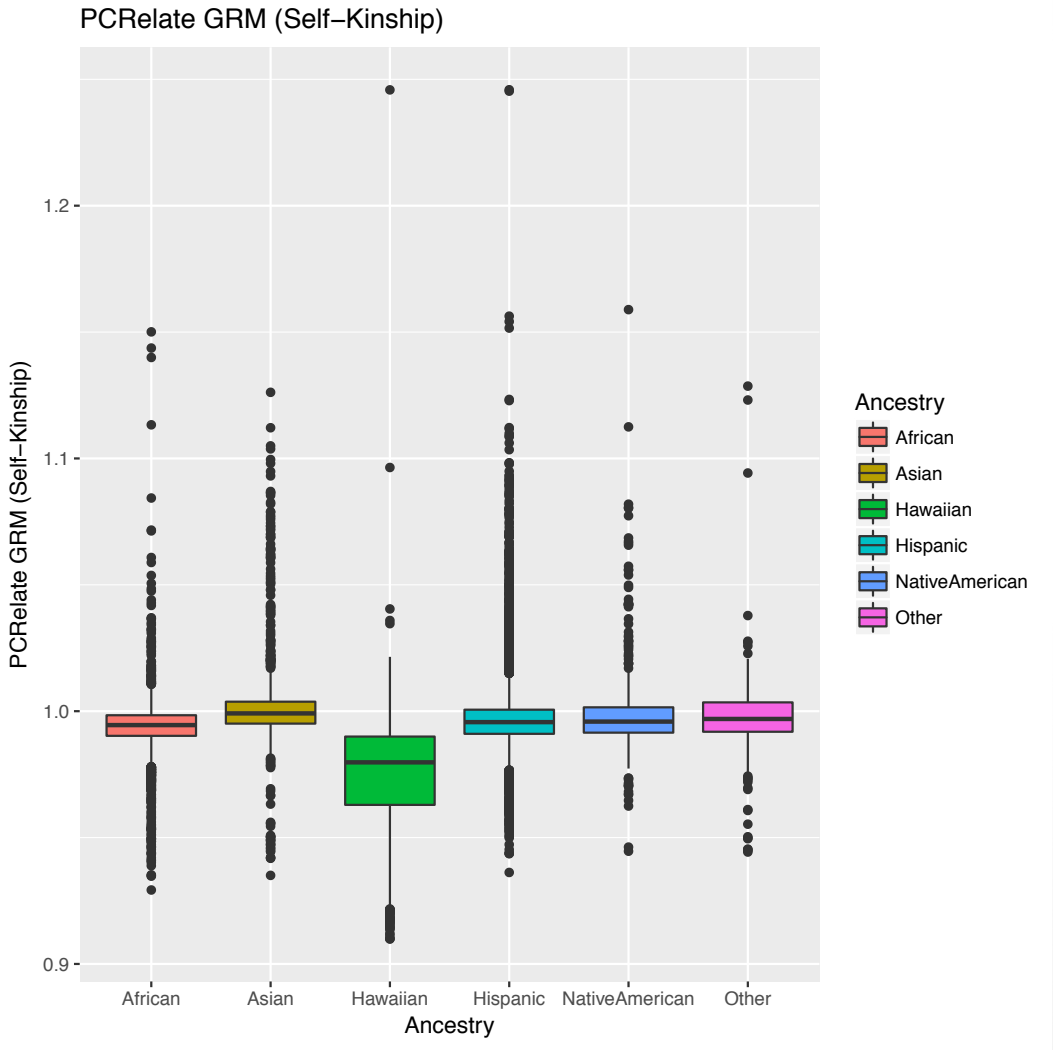
Standard GRM for PAGE

- Below is a figure of the diagonal elements of the standard GRM for PAGE.



LMM-OPS GRM for PAGE

$$\mathbf{Y} = \mathbf{g}_s\beta_s + \mathbf{X}\boldsymbol{\alpha} + \mathbf{V}\boldsymbol{\gamma} + \boldsymbol{\epsilon} \qquad \text{with} \qquad \boldsymbol{\epsilon} \sim \mathrm{N}\left(\mathbf{0}, \boldsymbol{\Sigma} \equiv \sigma_A^2\boldsymbol{\Phi} + \sigma_\epsilon^2\mathbf{I}\right)$$



Heterogeneity in Phenotypic Variances

- For multi-ethnic population samples, we should expect confounding due to traits having different means and variances.
- Developed **HEMMAT**: Heterogenous Effects Mixed Model Association Test.
- HEMMAT is an extension of LMM-OPS to allow for multiple random effects to be included in the model, in addition to the PC-adjusted GRM.
- HEMMAT incorporates additional **random effects to allow for heterogeneous variances** by self-reported race/ethnicity or by study (or any other discrete classification)

Real Phenotype Data for Methods Comparison

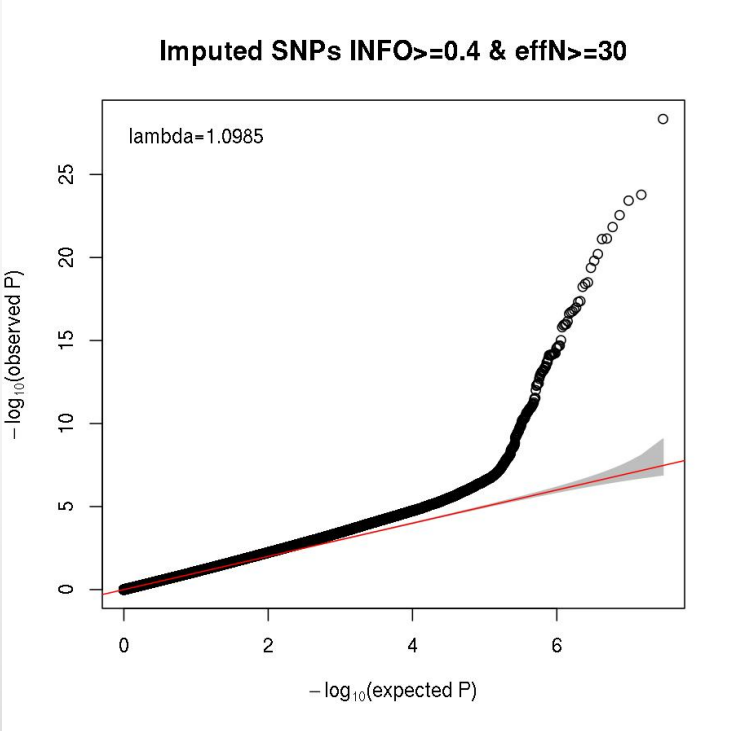
- Variance components were estimated for BMI adjusted fasting glucose
- Additive genetic variance component is .032
- Residual variance components for each race/ethnicity:

Race/Ethnicity	Sample Size	Residual Variance
AA	6457	0.41
HS	13556	0.20
AS	1918	0.40
HI	1400	0.43
NA	412	0.24
Other	168	0.35

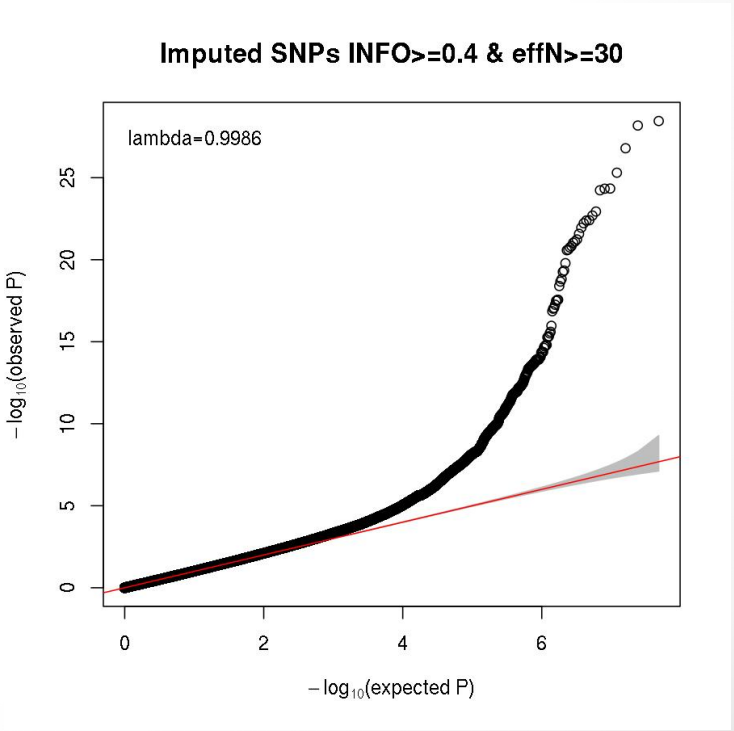
HEMMAT Association Analysis Results

- HEMMAT results for fasting glucose with adjustment of BMI

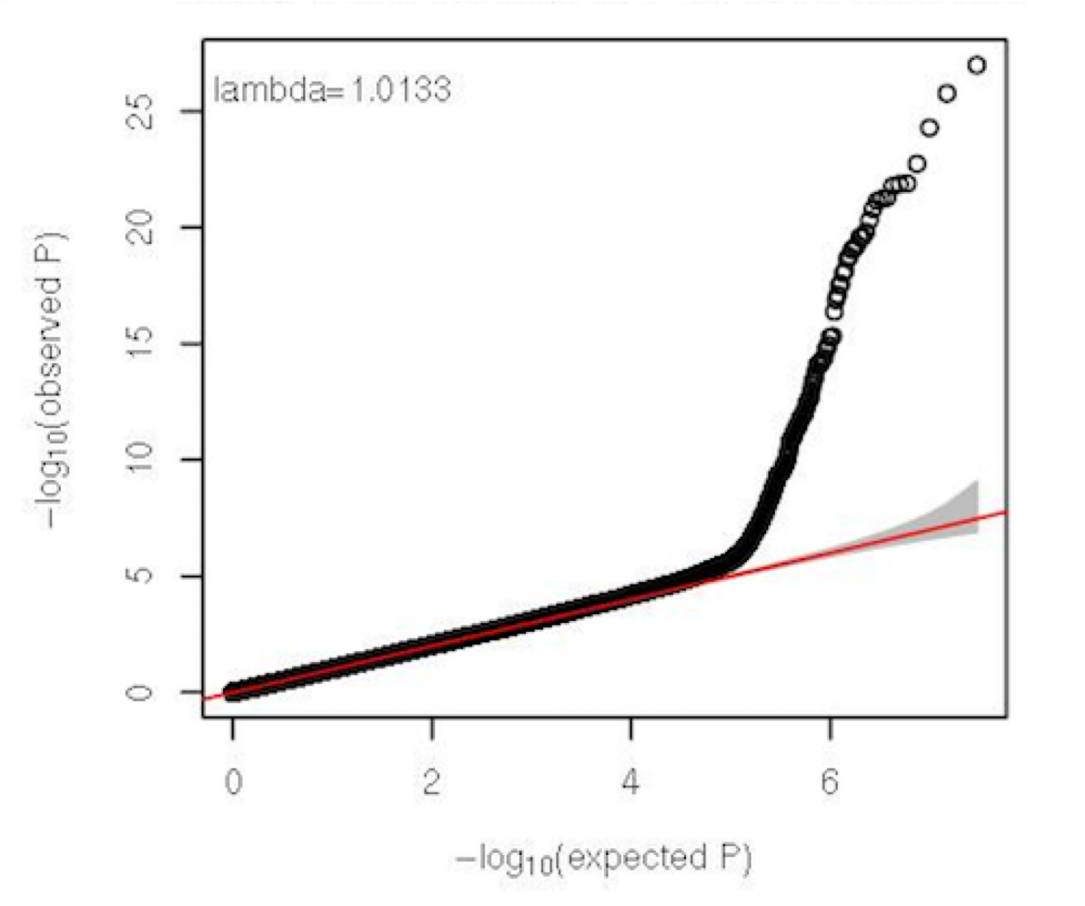
Homogenous Trait Variance



Heterogeneous Trait Variance by Ethnicity/Race



Linear Mixed Model with Standard GRM and Heterogenous Variances



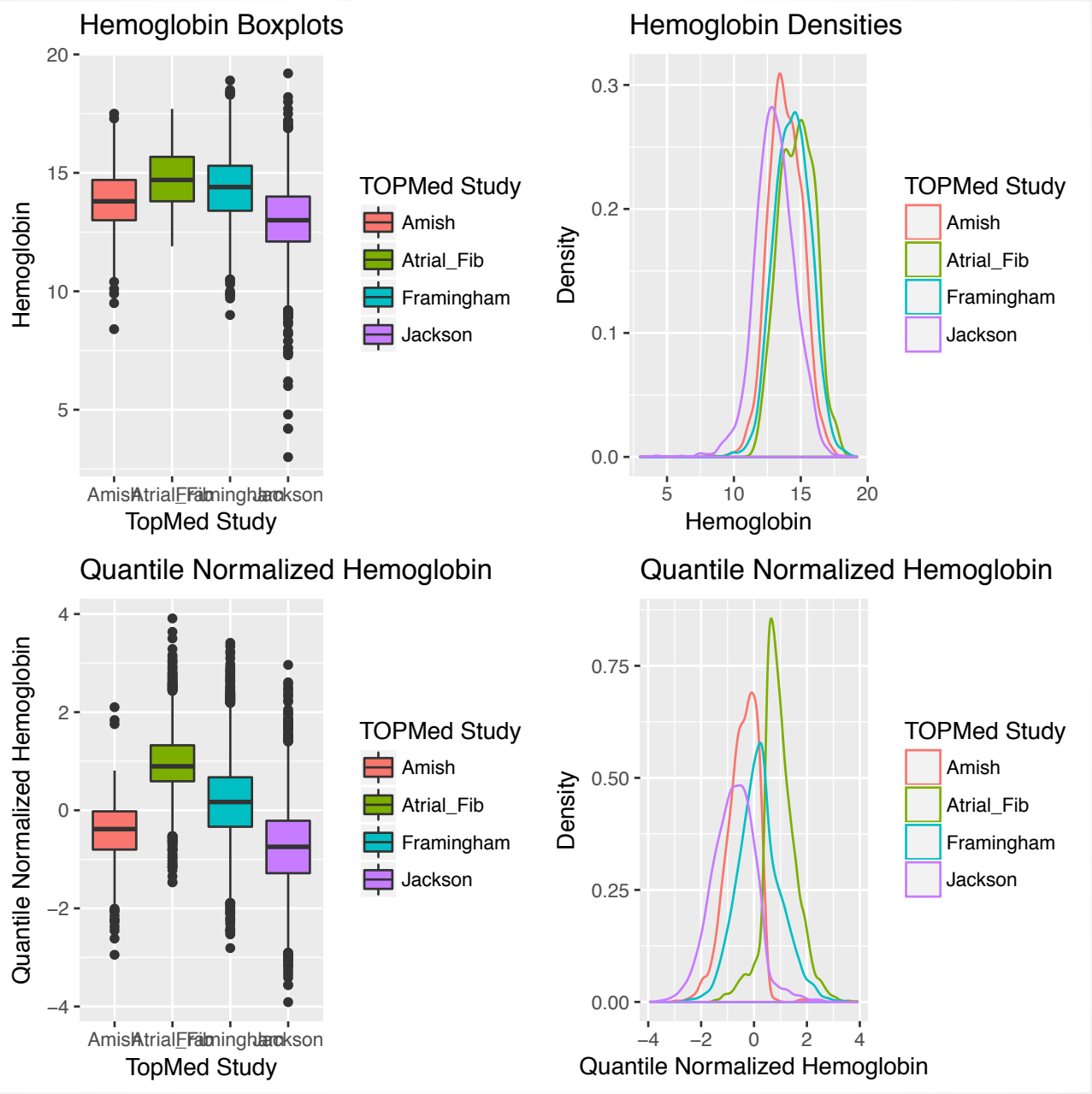
Comparison of HEMMAT and Standard LMM with Heterogenous Variance

- Both HEMMAT and LMM with a standard GRM and heterogenous variances have proper control of genomic inflation for fasting glucose in PAGE
- HEMMAT: 168 genome-wide significant variants ($p<5e-08$) for fasting glucose identified
- LMM with standard GRM and heterogenous variance: 146 genome-wide significant variants for fasting glucose identified

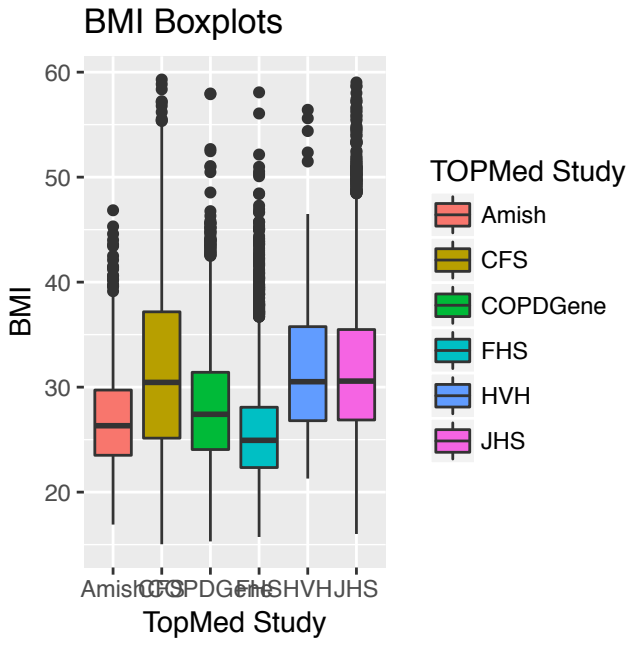
Comparison of HEMMAT to LMM with Heterogenous Variance

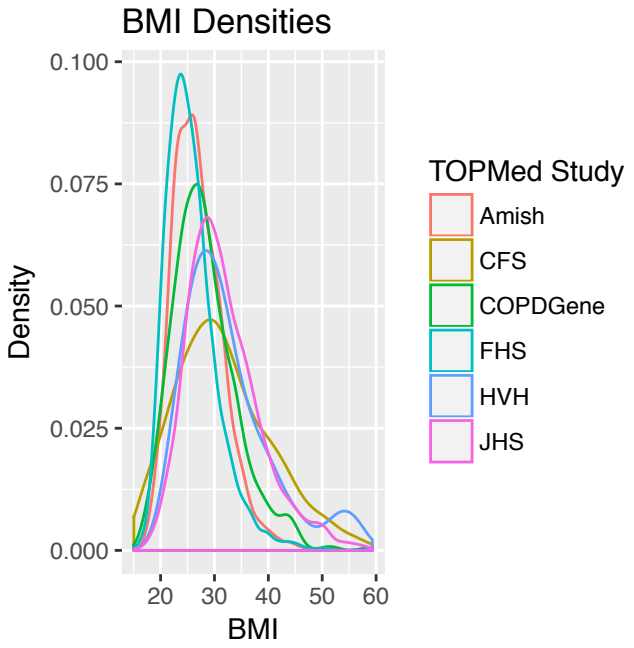
LOCUS	Chr	Position	HEMMAT	LMM with Standard GRM and Heterogenous Variances
GCKR rs780093	2	27742603	1.03E-11	1.48e-10
ABCB11 rs563694	2	169774071	5.85e-25	1.64e-22
GCK rs1799884	7	44229068	3.94e-23	7.35e-22
TCF7L2 rs7903146	10	114758349	2.78e-08	1.47e-07
MTNR1B rs10830963	11	92708710	3.50e-29	4.48e-28
FOXA2 rs3833331	20	22562326	3.24e-12	3.83e-11

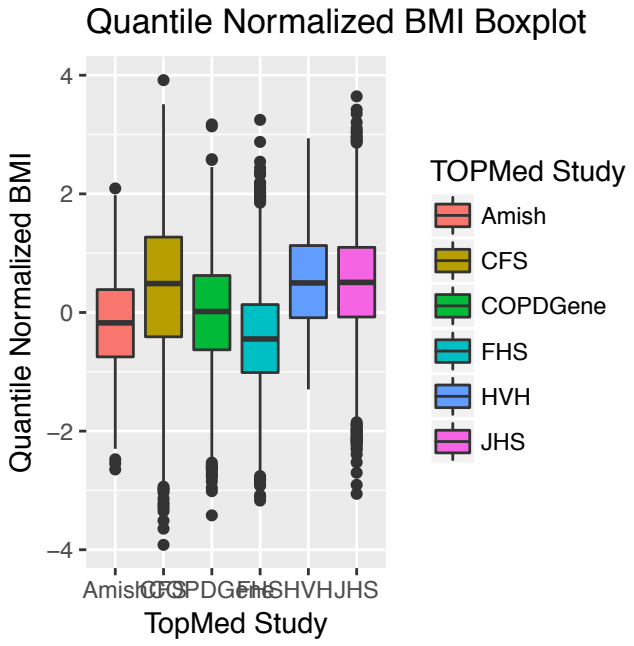
TOPMed Hemoglobin Distributions by Study

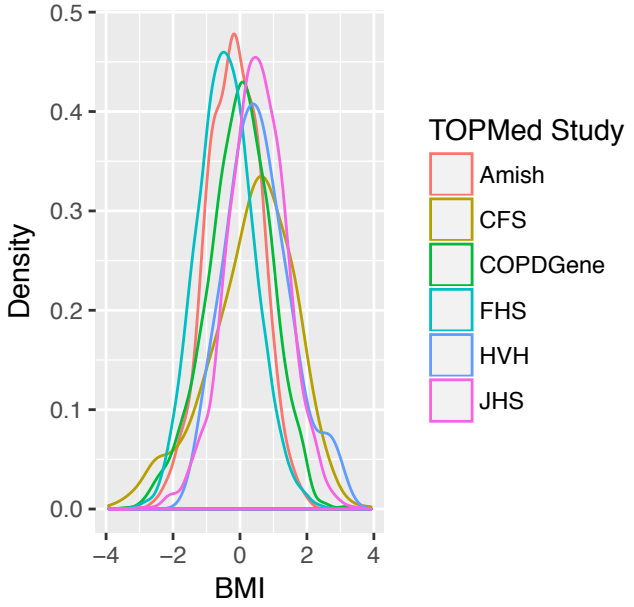


TOPMed BMI Distributions by Study





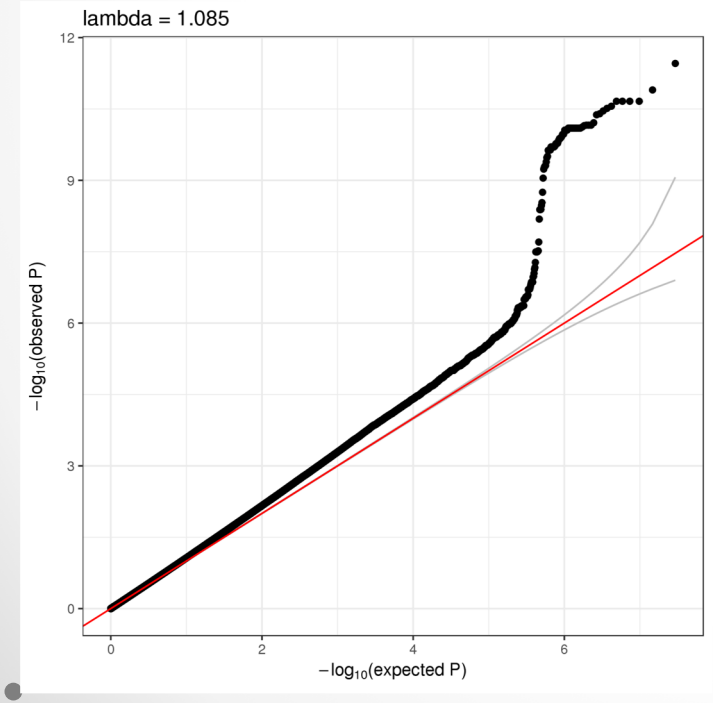




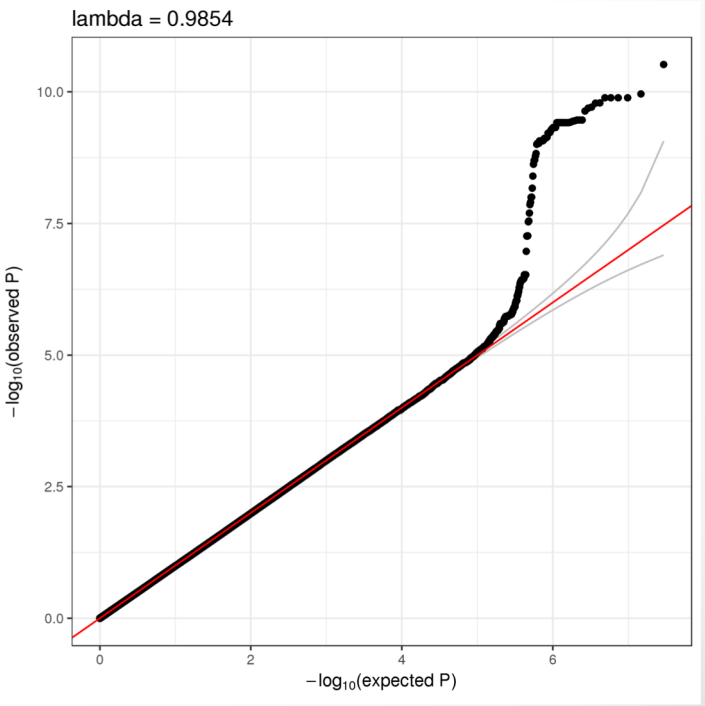
Heterogeneity in Hemoglobin Phenotypic Variances: By Study

- HEMMAT results for hemoglobin: heterogeneous phenotypic variances

Homogenous Residual Variance



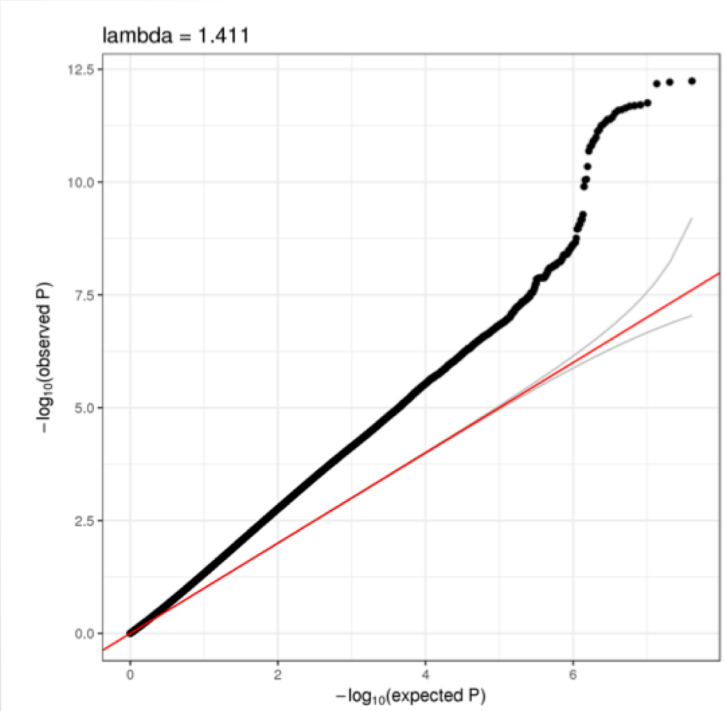
Heterogeneous Residual Variances by Study



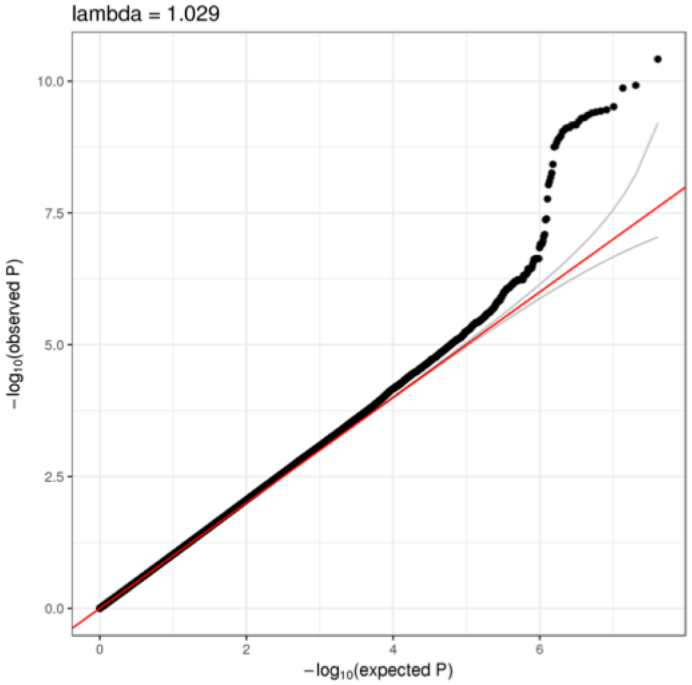
Heterogeneity in BMI Phenotypic Variances

- HEMMAT Association results for BMI: heterogeneous phenotypic variances

Homogenous Residual Variance



Heterogeneous Residual Variances by Study



Heterogenous residual variances for BMI

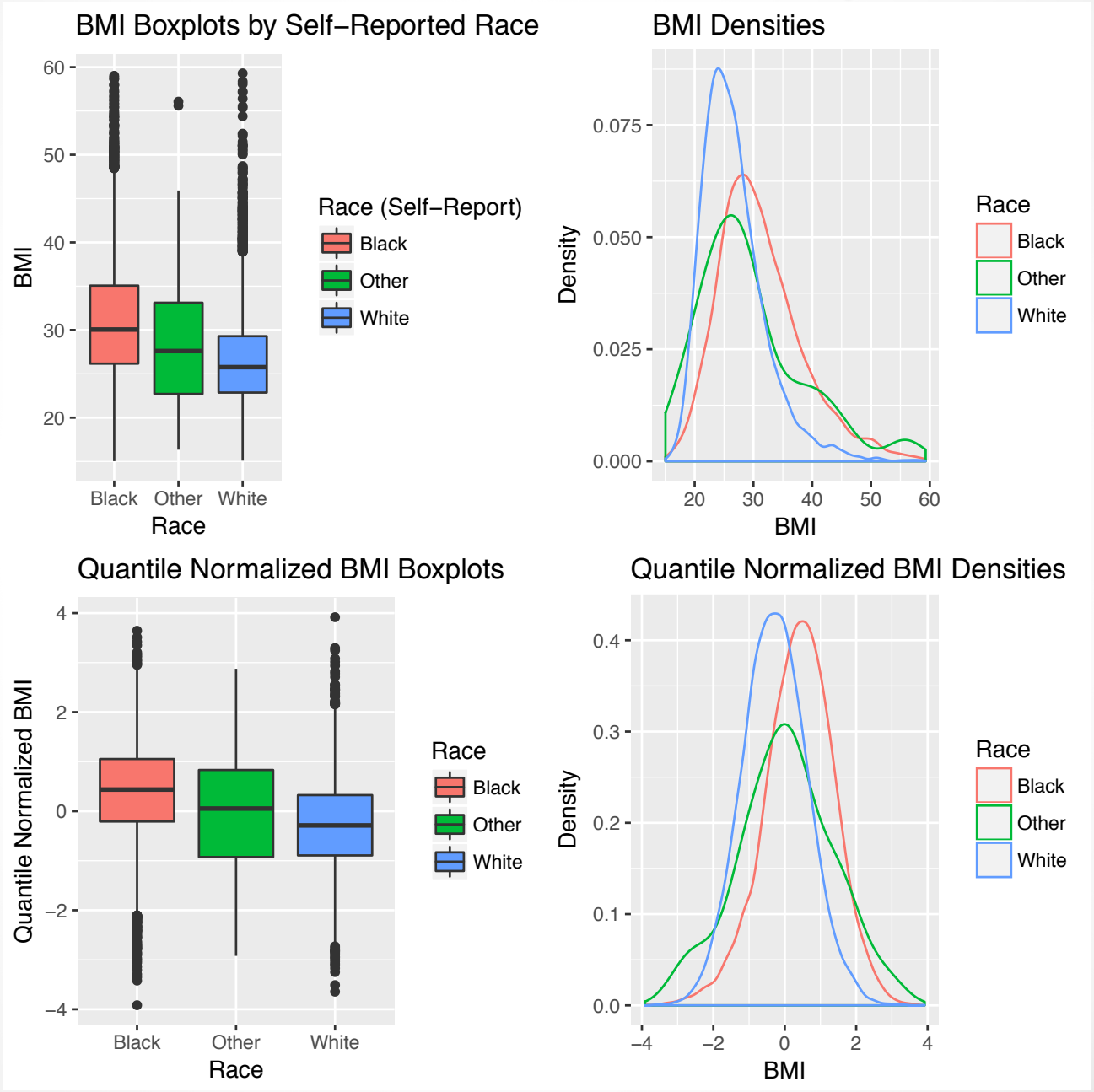
- Residual variance components of BMI for a few studies in TOPMed

TopMed Cohort Study	Phenotypic Residual Variances
Jackson Heart Study	35.44
CFS	52.33
Framingham Heart Study	13.14
Amish	12.19
COPDGene	26.61
HVH	61.31

Allowing for heterogeneity in variances: By Self-Reported Race

- There are limitations with modeling heterogenous variances by study in TOPMed.
- A number of TOPMed studies have multiple ethnicities/ancestries.
- Also explored the differences in BMI distribution by self-reported race.

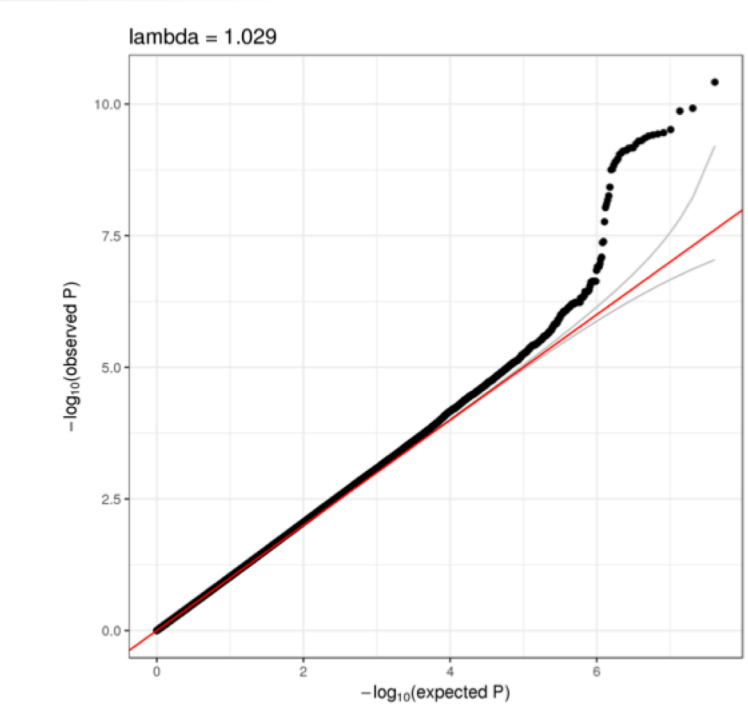
TOPMed BMI Distributions: By Race



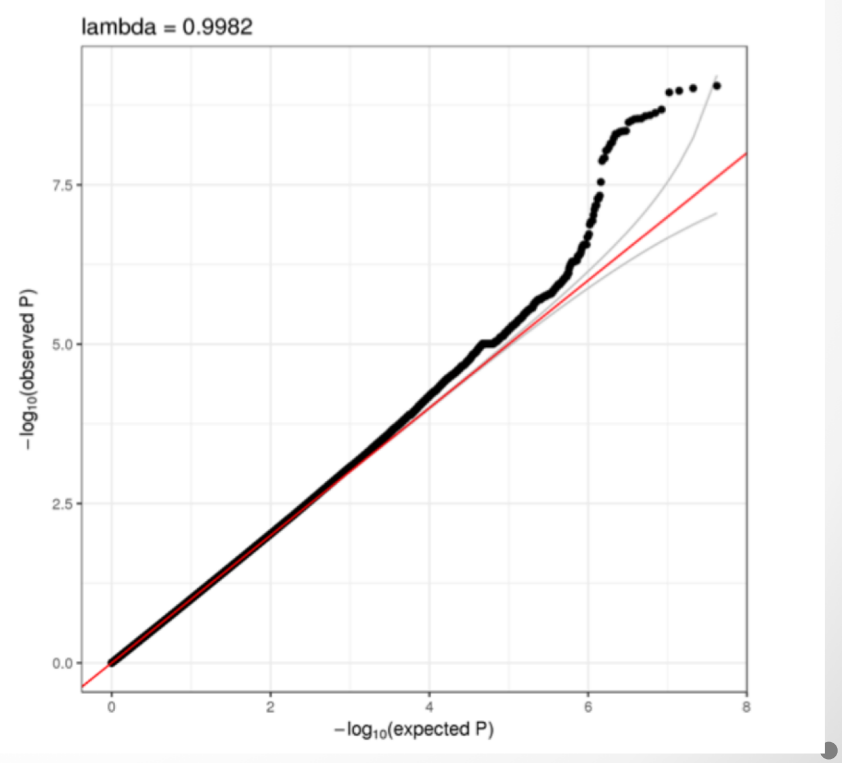
BMI Heterogeneity: Study vs. Self-Reported Race

- HEMMAT Association results for BMI: heterogeneous phenotypic variances

Heterogenous Residual Variance by Study



Heterogenous Residual Variance by Race



Novel Discoveries in Multi-Ethnic PAGE Study

- Conducted a GWAS of 26 clinical and behavioral phenotypes in 49,839 non-European individuals.
- Allowed for heterogenous variances across all phenotypes
- 574 GWAS catalog variants across these traits were confirmed in PAGE
- 28 novel loci were identified.
- Manuscript submitted to *Nature*. *Currently* is in revision and will be re-submitted soon.

GENESIS SOFTWARE

- **GENESIS**: R software package is available from Bioconductor
- Installation in R:
  - **source("https://bioconductor.org/biocLite.R")**
  - **biocLite("GENESIS")**
- Current release of GENESIS:
  - **PC-AiR**
  - **PC-Relate**
  - **LMM-OPS**
  - **HEMMAT (for multi-ethnic populations with heterogenous variances)**
  - **Burden and SKAT tests have been extended, allow for population structure/relatedness and heterogenous variances**

Current/Future Work: X Chromosome analyses

HIGHLIGHTED ARTICLE
GENETICS | INVESTIGATION

Detecting Heterogeneity in Population Structure Across the Genome in Admixed Populations

Caitlin McHugh, Lisa Brown, and Timothy A. Thornton[1]
Department of Biostatistics, University of Washington, Seattle, Washington 98195

McHugh et al., ***Genetics, 2016***

Current/Future Work: X Chromosome analyses in TOPMed and PAGE

- Relatedness and population structure on the X-chromosome is quite difference than the autosomes in multi-ethnic populations
- Dr. Caitlin McHugh has been developing extension of mixed methods for appropriate association testing (single variant and testing multiple variants simultaneously) on the X in multi-ethnic populations.
- Currently implementing the methods in GENESIS and will be applying to TOPMed and PAGE.

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