Genetic Analysis in Ancestrally Diverse Populations

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SCHOOL OF PUBLIC HEALTH
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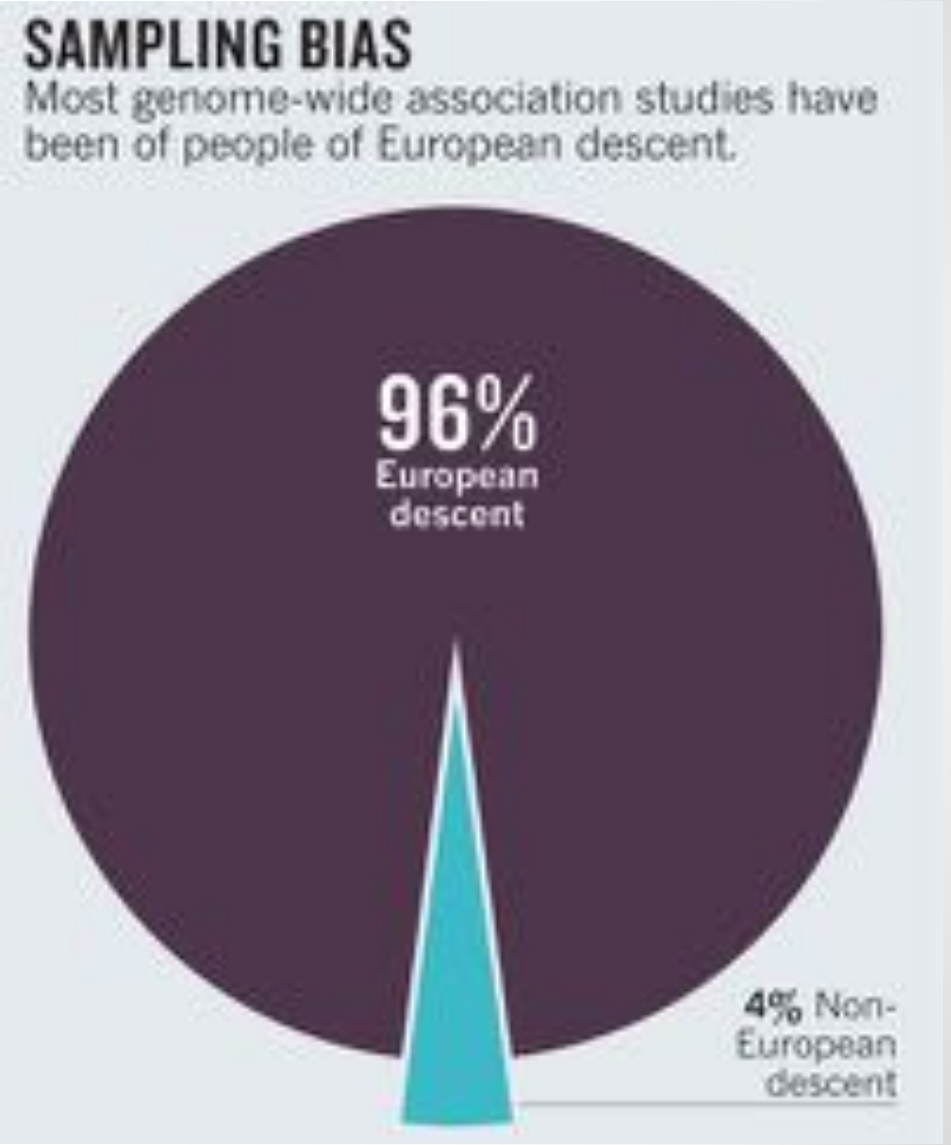
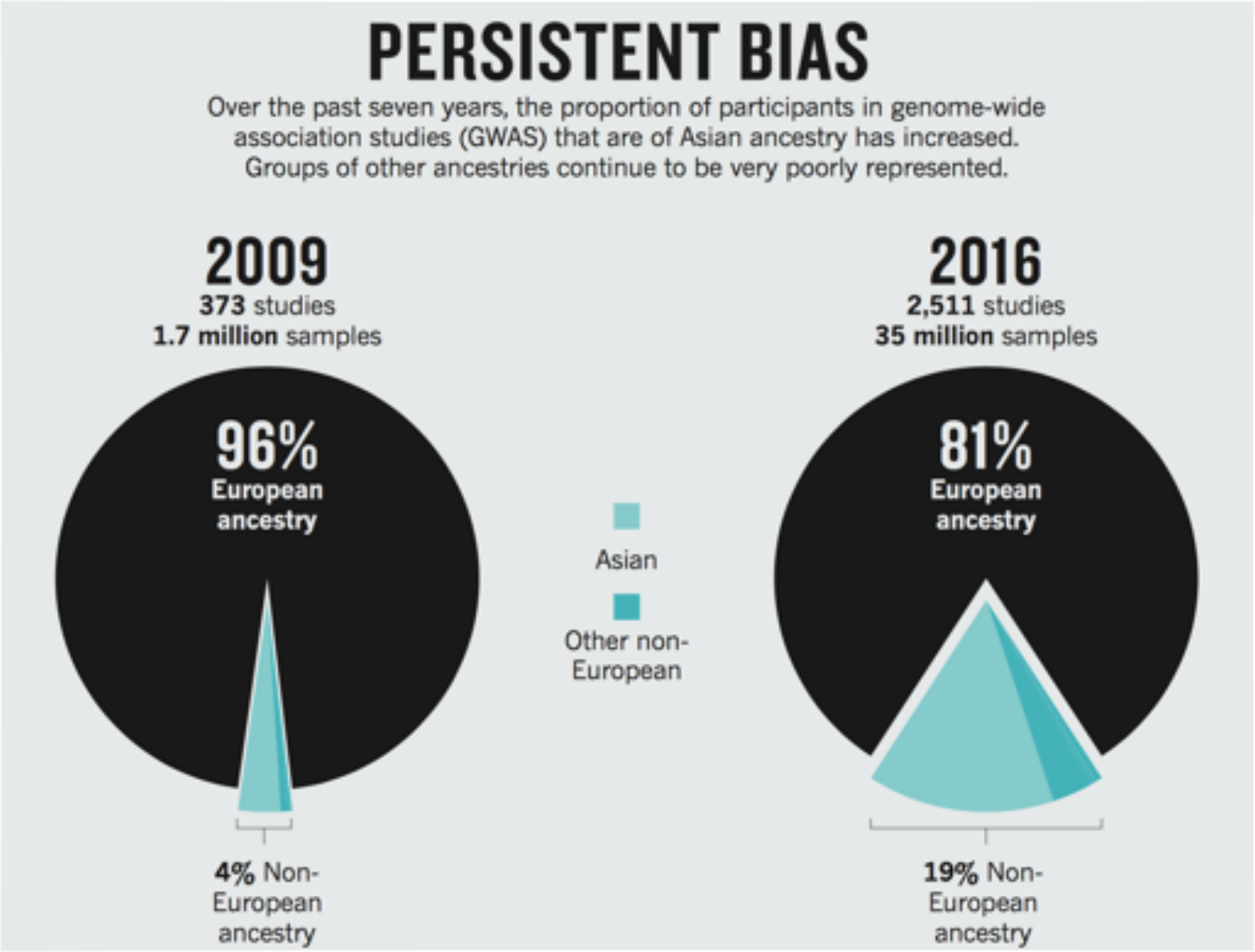
Introduction

- To date, tens of millions of individuals have been included in GWAS and sequencing association studies for the mapping of complex traits.
- The vast majority of these studies, however, have been conducted in populations of European ancestry



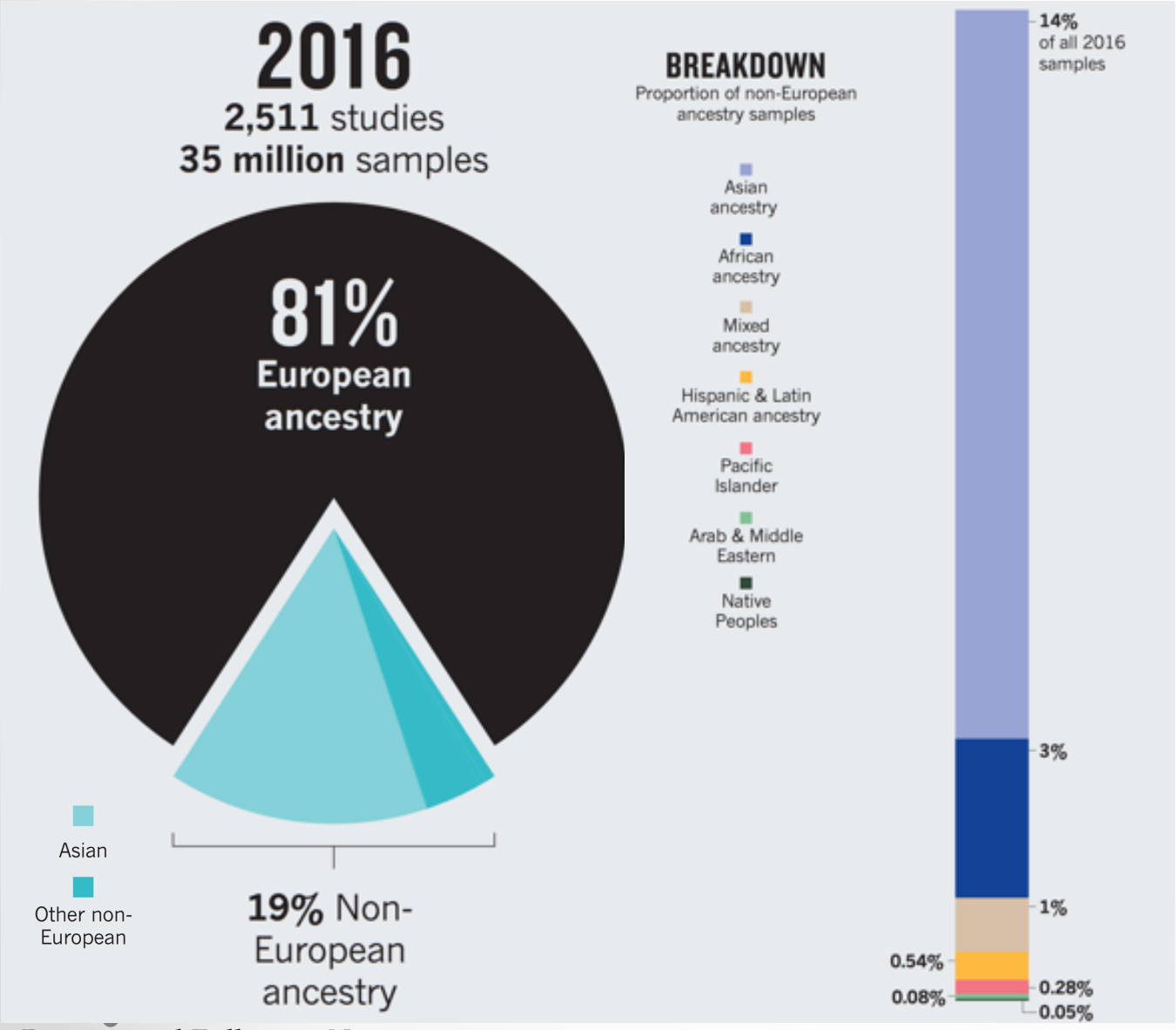
Bustamante et al. (Nature, 2011)

Current State of Affairs



Popejoy and Fullerton (Nature, 2016)

Over-representation of European Populations in Genetic Studies



- Biased understanding of which variants are important
- Potential for new health care inequalities

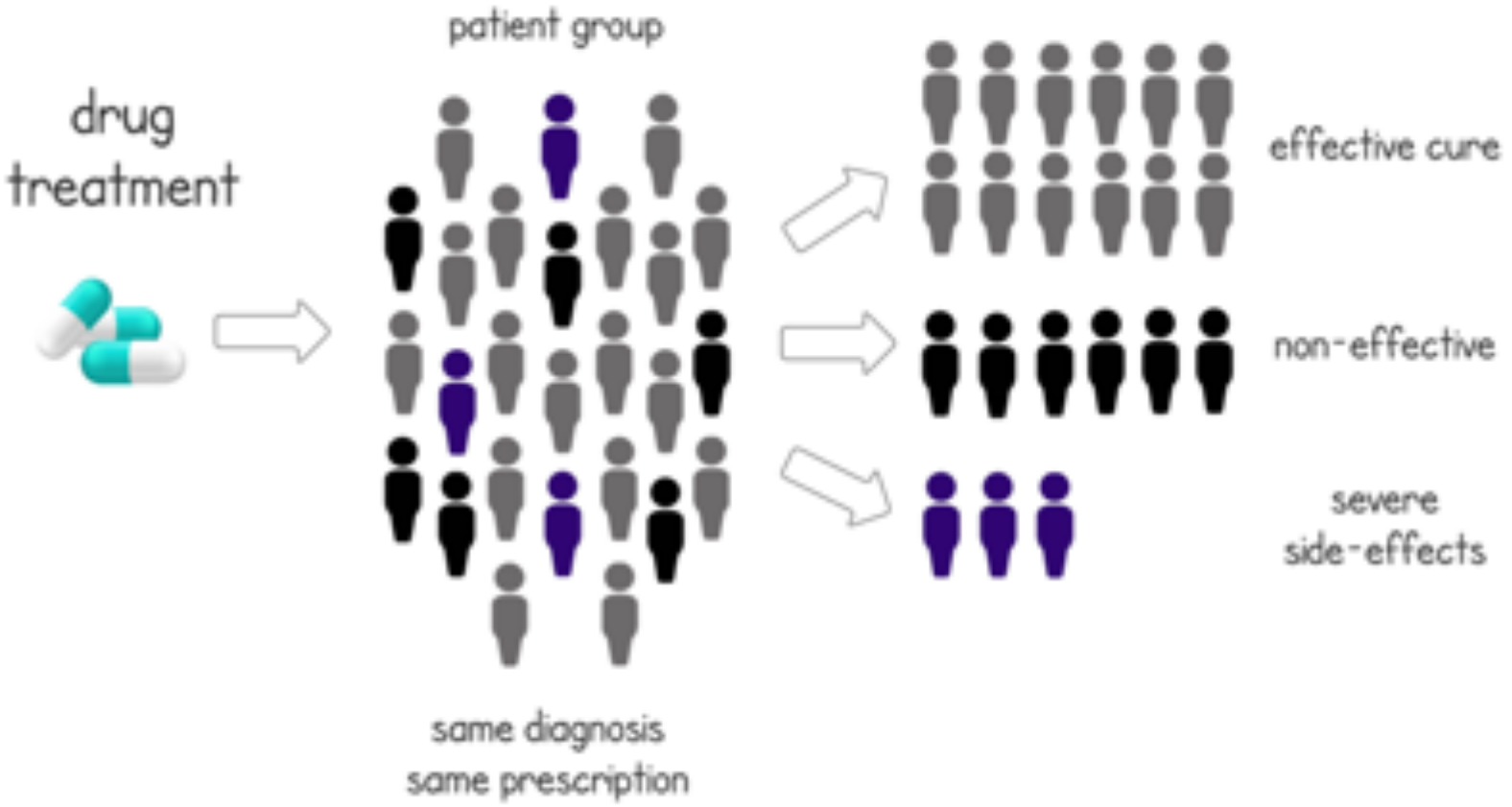
Popejoy and Fullerton. *Nature*, 2016

Need for Genetic Studies in Diverse Populations

- Medical genomics has focused almost entirely on those of European descent.
- Other race and ethnic groups must be studied to ensure that more people benefit

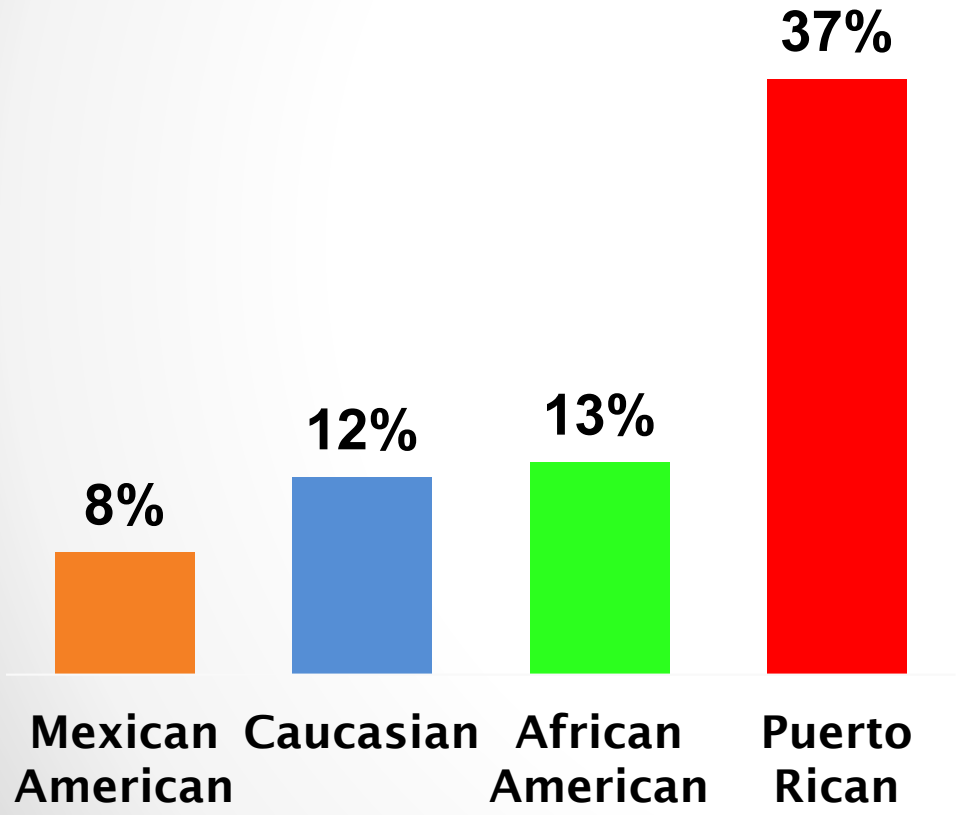
Bustamante et al. (Nature, 2011)

Health Disparities: Personalized Medicine



Example: Asthma Affects ~334M Globally

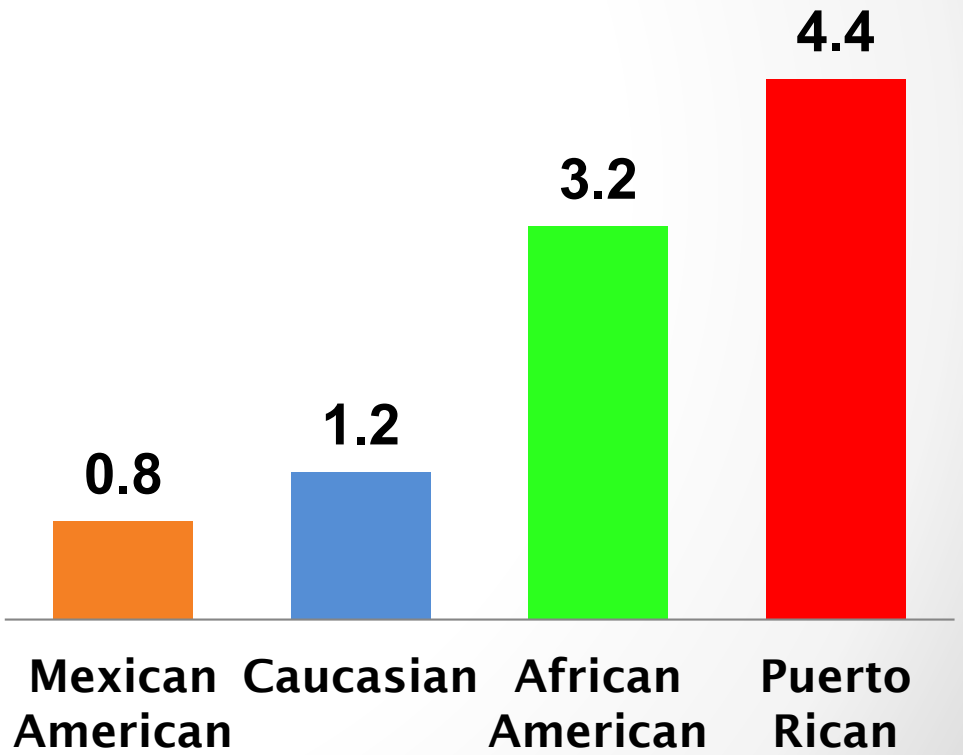
Prevalence



NHLBI Study of Latinos (SOL)

Barr et. ai., *AJRCCM* 2016

Mortality

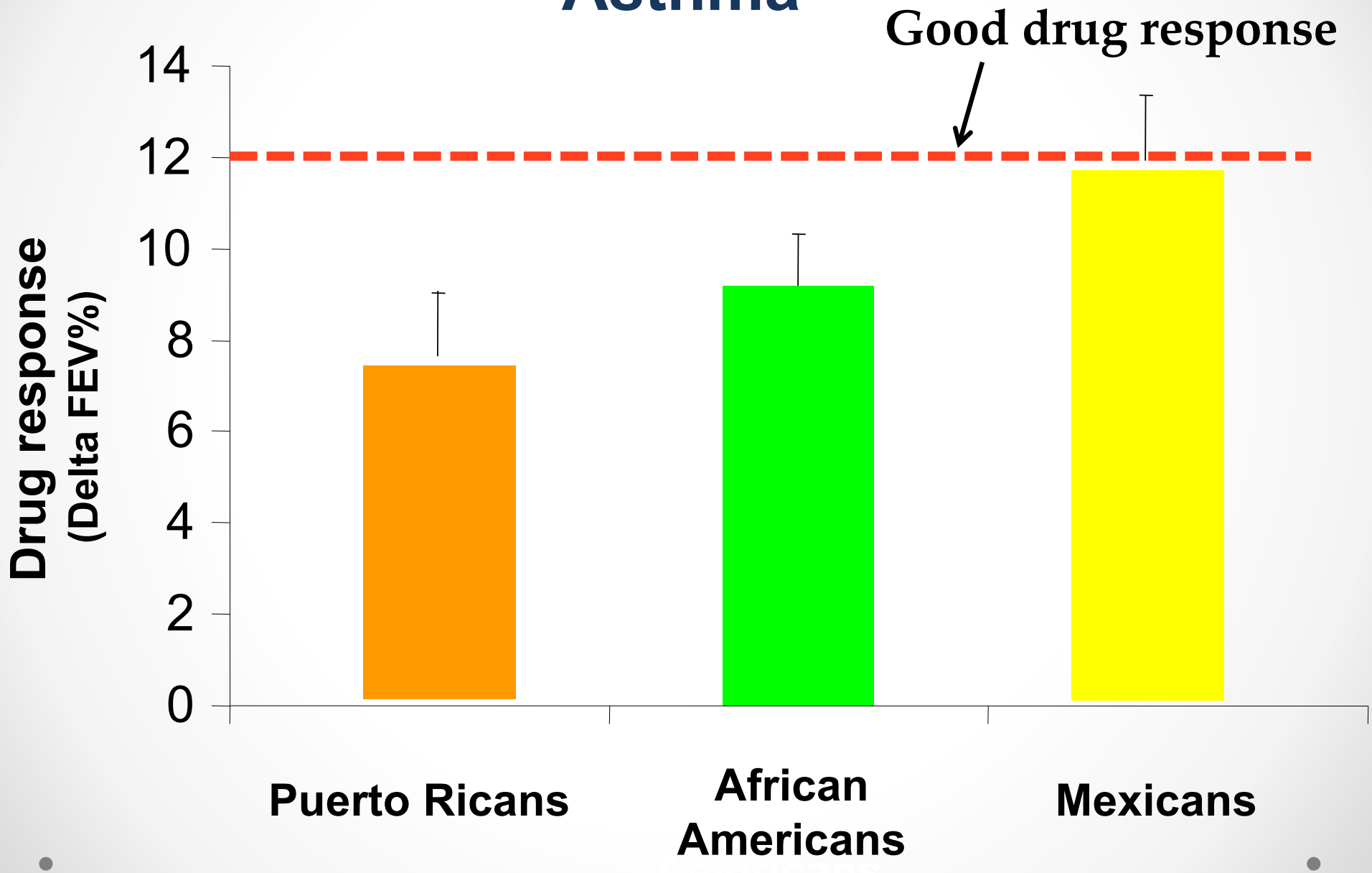


Akinbami L. CDC/NCHS

Example: Asthma Health Disparities

- These disparities extend to asthma mortality, which is 3- to 4-fold higher in Puerto Ricans and African Americans compared to Whites and Mexicans.
- Albuterol is the most commonly prescribed asthma medication in the world.
- Dr. Esteban Burchard (UCSF) and colleagues leading Genetics of Asthma in Latino Americans (GALA) and Study of African Americans, Asthma, Genes, & Environments (SAGE)
  - **Marked differences in drug response to Albuterol between racial and ethnic groups, which contribute to health disparities in asthma morbidity and mortality.**

GALA: Children with Moderate-to-Severe Asthma



Naqvi, M, *J. of Asthma*, 2007

Courtesy of Dr. Esteban Burchard; UCSF

Salmeterol tiny Black Box Warning

- Salmeterol is used in moderate-to-severe persistent asthma following previous treatment with a short-acting β_2 adrenoreceptor agonist(SABA) such as salbutamol (albuterol).
- However, African Americans, beware!

"In African Americans, asthma-related deaths occurred at a higher rate in patients treated with Salmeterol than those treated with placebo (..relative risk: 7.26..)…"

"And that's why we're here today.
Because something called ***Precision Medicine*** … gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen."

State of the Union Address
January 20, 2015

Precision Medicine Initiative

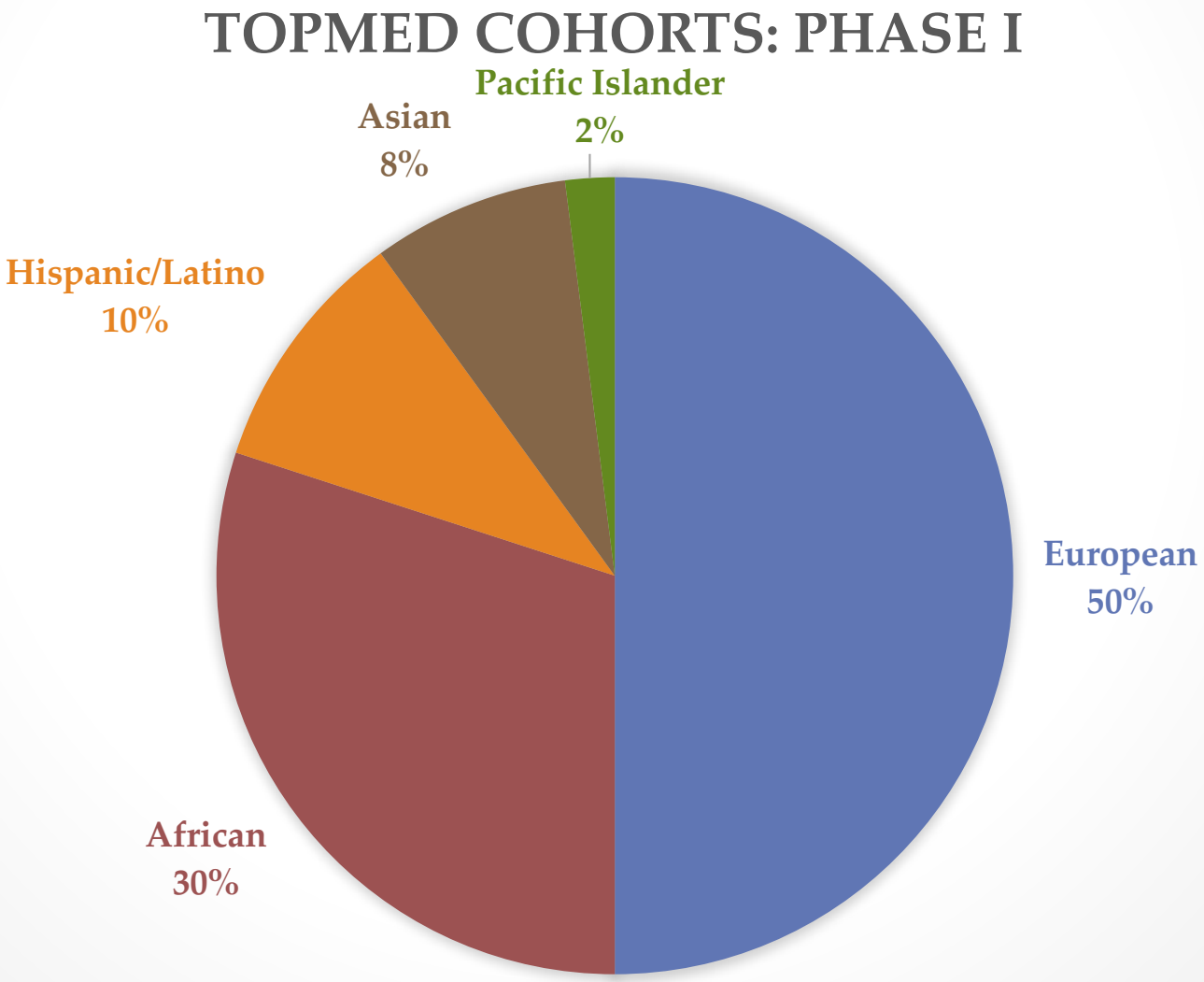
- NIH launched the Precision Medicine Initiative (PMI) in 2015
  - PMI Cohort Program will build a large research cohort of **one million or more** Americans
  - Goal is to support and advance the targeted prevention and treatment strategies that take an individual's unique characteristics into account, **including individual genome sequences**, environmental factors and lifestyles.

TOPMed WGS Project

- NIH/NHLBI Trans-Omics for Precision Medicine (TOPMed) Program is a component of the PMI
- TOPMed Whole-genome-sequence (WGS) project currently generating deep WGS data for over **120,000 individuals**
- More than 30 cohorts studies with well-defined phenotypes and existing clinical outcomes data, many with cognitive function measures
- Primary aims is to identify genetic variants for increased or decreased risk of disease, as well as those that help define disease subtypes.
- To date, over 70,000 whole genome sequences have been completed
- **University of Washington Genetic Analysis Center** is the Data Coordinating Center for the TOPMed WGS Project

Multi-ethnic TOPMed Cohorts

- Concerted effort to be reflective of the diverse ancestries of the U.S. population.



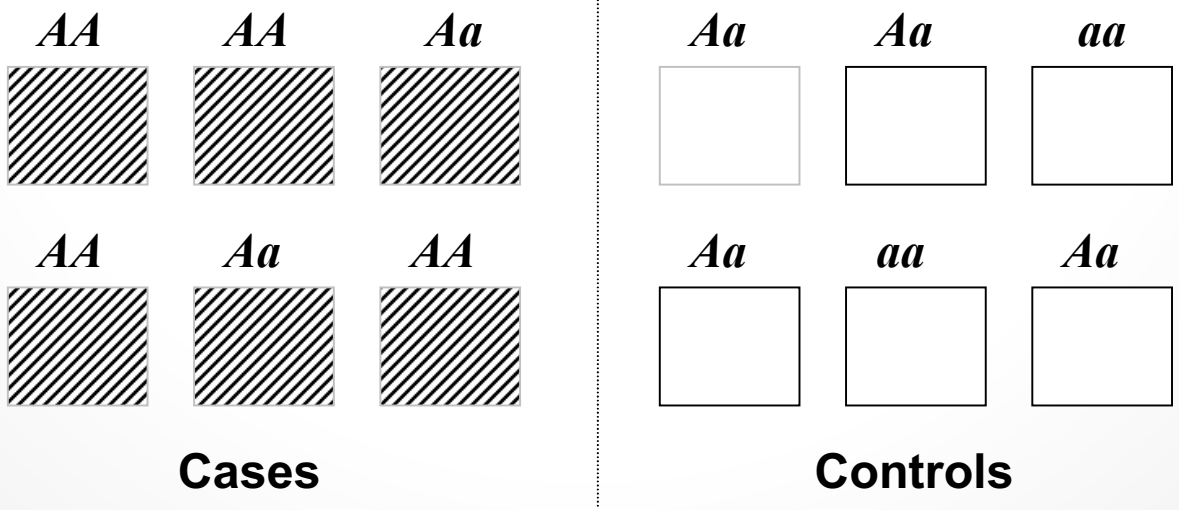
Genetics Studies in Diverse Populations:

Opportunities and Challenges

- Opportunities:
  - Identification of novel genetic variants underlying phenotypic diversity between populations.
  - Potential to provide new insights for health disparities of minority populations for many complex diseases
- Challenges for complex trait mapping:
  - Heterogeneous genetic background
  - **Confounding due to ancestry/population structure**
  - **Population structure inference and correction**
  - Familial structure and/or cryptic relatedness

Case-Control Association Testing

- Below is a simple example to illustrate association testing at a genetic marker with two allelic types labeled **A** and **a**
- Statistics for identifying an association could either compare allele or genotype frequencies between the cases controls

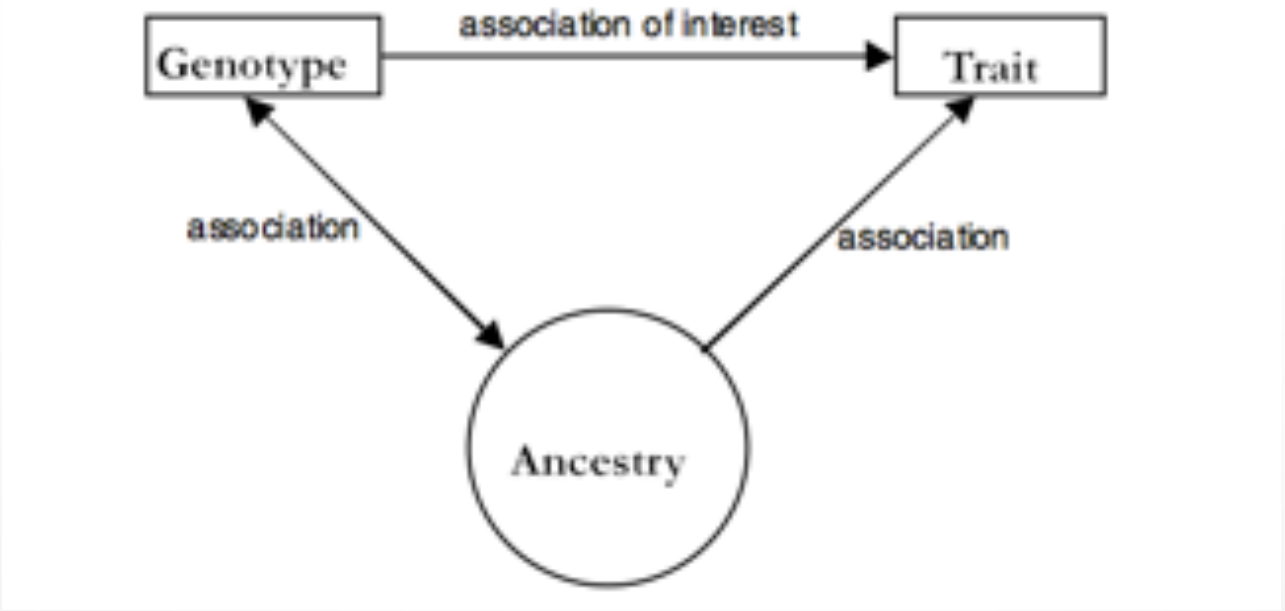


Case-Control Association Testing

- The observations in genetic association studies can be confounded by population structure
  - **Population structure**: the presence of subgroups in the population with ancestry differences
- Neglecting or not accounting for ancestry differences among sample individuals can lead to **false positives** or **spurious associations!**
- This is a serious concern for all genetic association studies

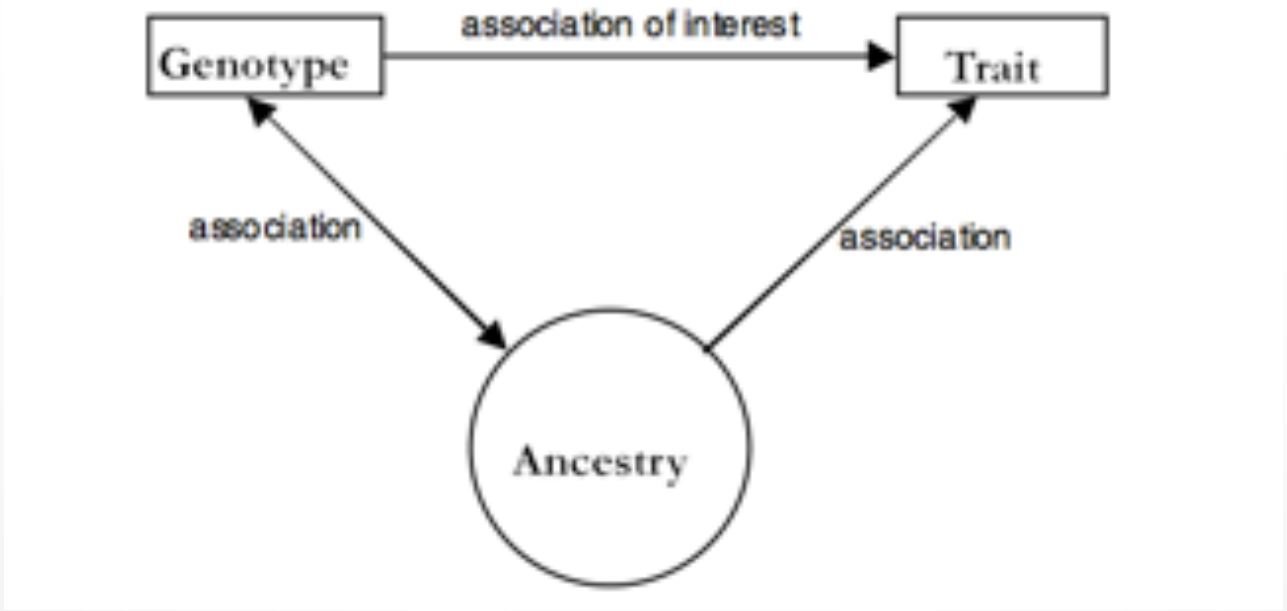
Confounding due to Ancestry Differences

- In statistics, a **confounding variable** is an extraneous variable that correlates with both the outcome variable and the predictor variable of interest.



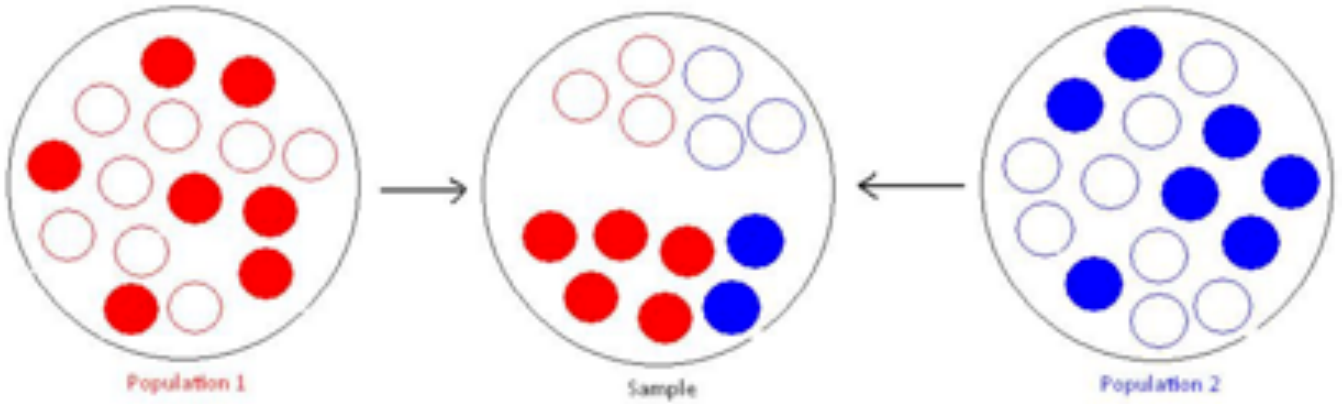
Confounding due to Ancestry Differences

- Ethnic groups (and subgroups) often share distinct genetic variation, dietary habits and other lifestyle characteristics that leads to many traits of interest being correlated with ancestry and/or ethnicity.



Spurious Associations: Case-Control Studies

- Case/Control association test
  - Comparison of allele frequency between cases and controls.
- Consider a sample from 2 populations:



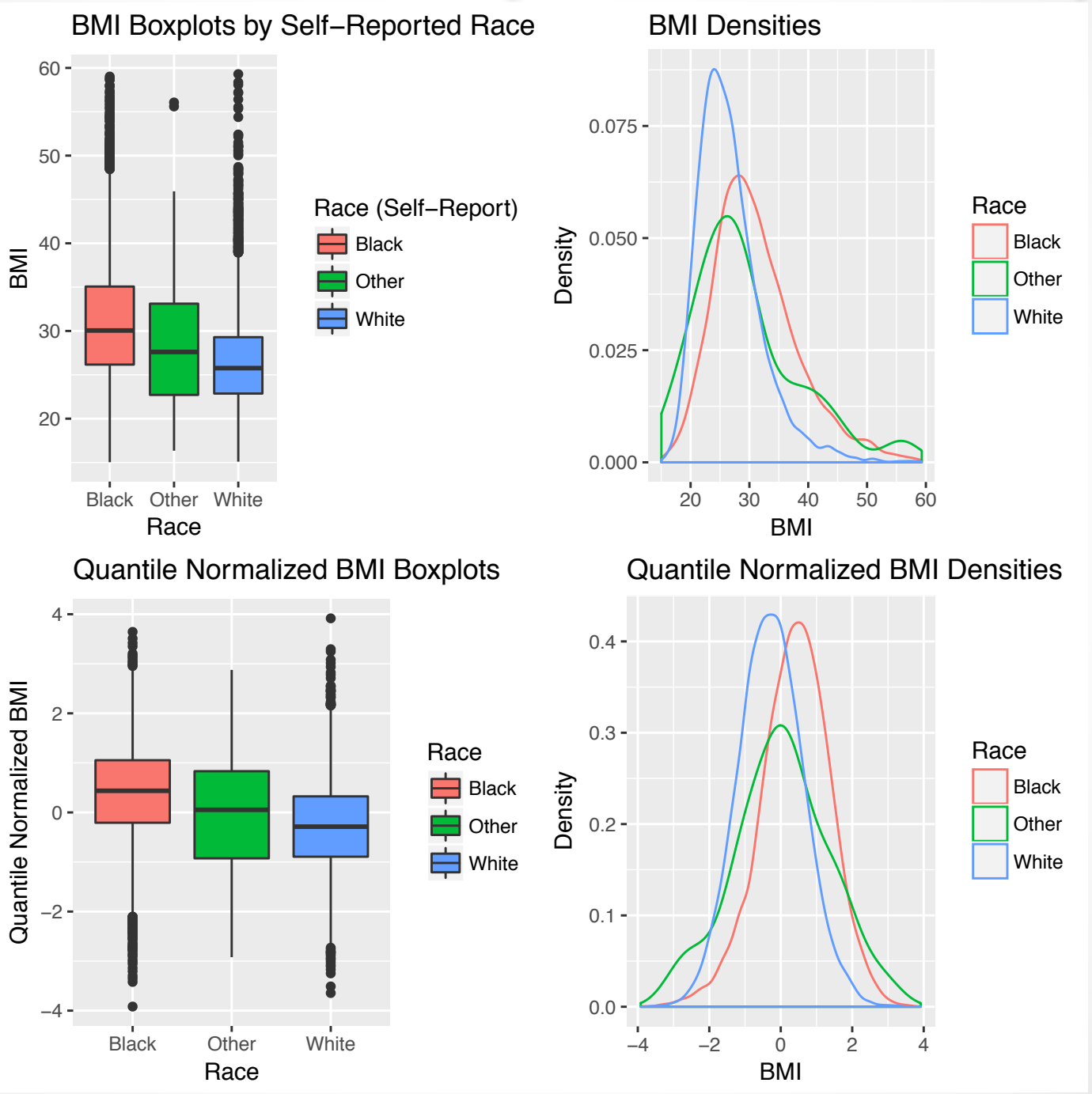
  - Red population overrepresented among cases in the sample.
  - Genetic markers that are not influencing the disease but with significant differences in allele frequencies between the populations $\Longrightarrow$ spurious association between disease and genetic marker

Spurious Associations: Quantitative Trait Studies

- Quantitative trait association test
  - Test for association between genotype and trait value
- Consider sampling from 2 populations:

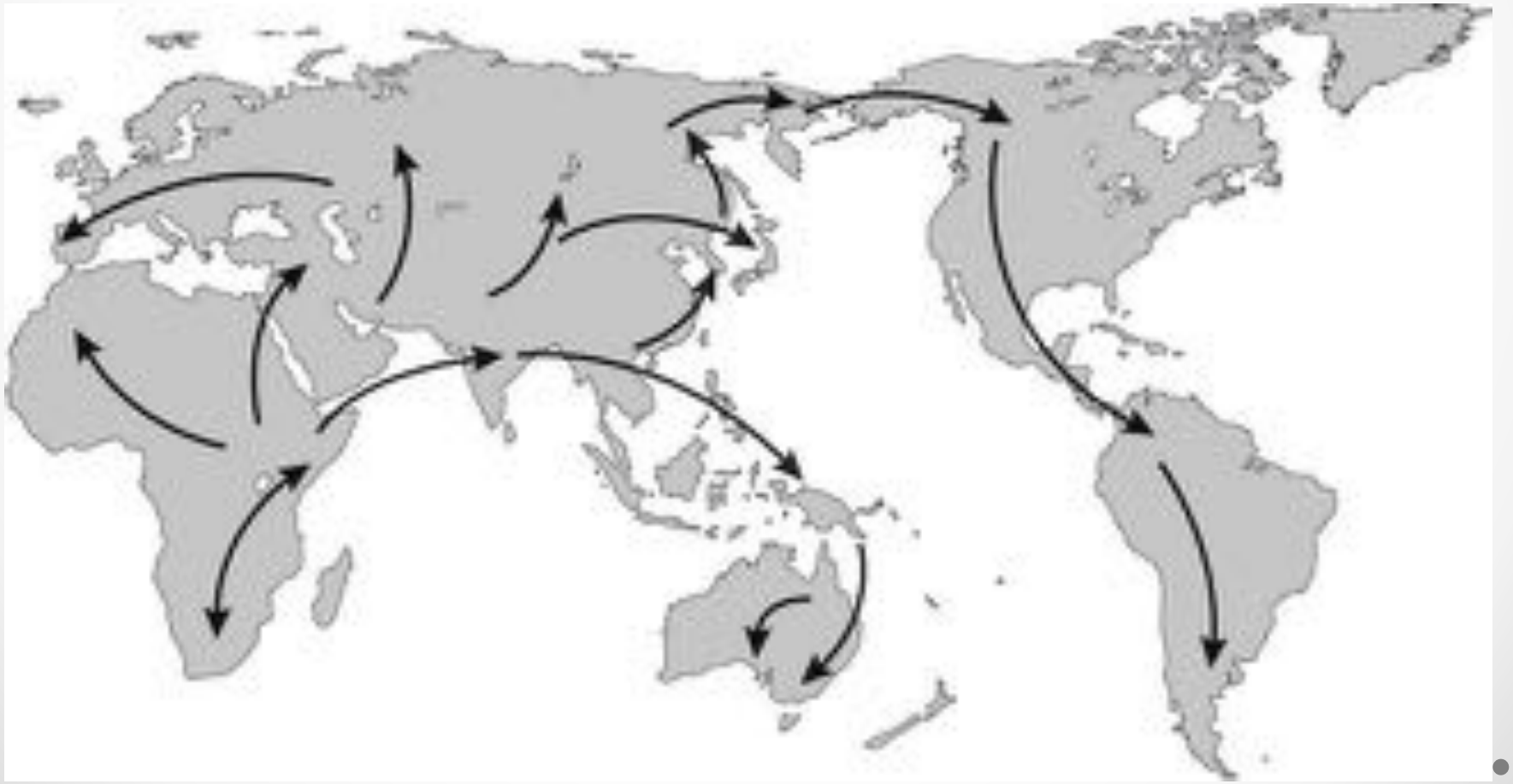
  - Blue population has higher trait values.
  - Different allele frequency in each population
    $\Longrightarrow$ spurious association between trait and genetic marker if one population is overrepresented in the sample

TOPMed BMI: Self-reported Race/Ethnicity



Background: Population Structure

- Humans originally spread across the world many thousand years ago out of Africa
- Migration and genetic drift led to genetic diversity between isolated groups.



Population Structure Inference

- Inference on genetic ancestry differences among individuals from different populations, or **population structure**, has been motivated by a variety of applications:
  - population genetics
  - genetic association studies
  - personalized medicine
  - forensics
- Advancements in array-based genotyping and sequencing technologies have largely facilitated the investigation of genetic diversity at remarkably high levels of detail
- A variety of methods have been proposed for the identification of genetic ancestry differences among individuals in a sample using high-density genome-screen data.

Inferring Population Structure with PCA

- Principal Components Analysis (PCA) is the most widely used approach for identifying and adjusting for ancestry difference among sample individuals
- PCA applied to genotype data can be used to calculate **principal components** (PCs) that explain differences among the sample individuals in the genetic data
- The top PCs are viewed as continuous axes of variation that reflect genetic variation due to ancestry in the sample.
- Individuals with "similar" values for a particular top principal component are expected to have "similar" ancestry for that axes.

PCA for Population Structure Inference

- PCA is an unsupervised learning tool for dimension reduction in multivariate analysis.
- Widely used in genetics community to infer population structure from genetic data.
  - Premise is that top principal components (PCs) will reflect population structure in the sample.
- Orthogonal linear transformation to a new coordinate system
  - PCA sequentially identifies linear combinations of genetic markers that explain the greatest proportion of variability in the data
  - these define the axes (PCs) of the new coordinate system
  - each individual has a value along each PC
- EIGENSOFT (Price et al., 2006) is a popular implementation of PCA

Data Structure for PCA

- Sample of N individuals, indexed by $i = 1, 2, \ldots, N$.
- Genome screen data on M genetic autosomal markers, indexed by $m = 1, 2, \ldots, M$.
- At each marker, for each individual, we have a genotype value, g_{im}.
- Here we consider bi-allelic markers, so g_{im} takes values 0, 1, or 2, corresponding to the number of reference alleles.
- We center and standardize these genotype values:

$$z_{im} = \frac{g_{im} - 2\hat{p}_m}{\sqrt{2\hat{p}_m(1-\hat{p}_m)}}$$

where $\hat{p}_m$ is an estimate of the reference allele frequency for marker m.

Genetic Correlation Estimation

- Create an N x M matrix, $\mathbf{Z}$, of centered and standardized genotype values, and with $\mathbf{Z}$ we can obtain an N x N genetic relatedness matrix (GRM) for all possible pairs in the sample:

$$\widehat{\mathbf{\Psi}} = \frac{1}{M}\mathbf{Z}\mathbf{Z}^T$$

- The (i, j)th element of this matrix is

$$\widehat{\mathbf{\Psi}}_{ij} = \frac{1}{M}\sum_{m=1}^{M}\frac{(g_{im} - 2\hat{p}_m)(g_{jm} - 2\hat{p}_m)}{2\hat{p}_m(1-\hat{p}_m)},$$

where $\widehat{\mathbf{\Psi}}_{ij}$ can be viewed as an estimate of the genome-wide average genetic correlation between individuals i and j.

Individuals from the same ancestral population are expected to have genotypic values that are more correlated than individuals from different ancestral populations.

Principal Components Analysis

- PCA is performed by obtain the eigen-decomposition of $\widehat{\mathbf{\Psi}}$; that is, we find **eigenvectors** and **eigenvalues** such that $\widehat{\mathbf{\Psi}} = \mathbf{V}^T\mathbf{L}\mathbf{V}$ where
  - $\mathbf{V} = [\mathbf{V}_1, \mathbf{V}_2, \ldots, \mathbf{V}_N]$ is a N x N matrix consisting of N eigenvectors, each of length N
  - $\mathbf{L}$ is a diagonal matrix of N eigenvalues, $(\lambda_1 > \lambda_2 > \ldots > \lambda_N)$, that are in decreasing order, i.e.,

$$\mathbf{L} = \begin{bmatrix} \lambda_1 & 0 & \ldots & 0 \\ 0 & \lambda_2 & & \vdots \\ \vdots & & \ddots & \\ 0 & \ldots & 0 & \lambda_N \end{bmatrix}$$

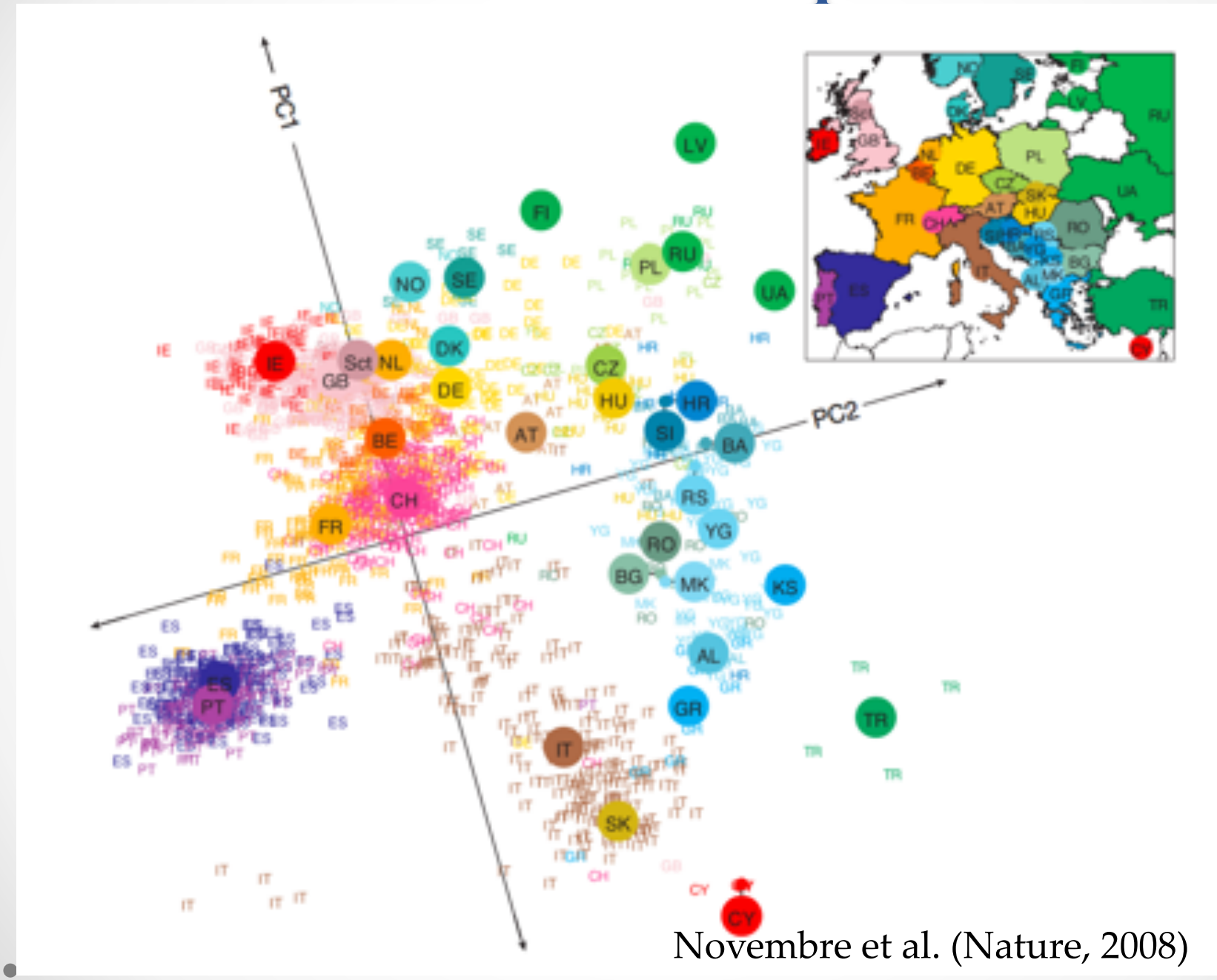
Principal Components Analysis

- The d^{th} principal component (eigenvector) corresponds to eigenvalue λ_d, where λ_d is proportional to the percentage of variability in the genome-screen data that is explained by $\mathbf{V}_d$.
- The top principal components are viewed as continuous axes of variation that reflect genetic variation that best explain genotypic variability amongst the N sample individuals.
- Individuals with "similar" values for a particular top principal component are expected to have "similar" ancestry for that axes.
- As a result, eigenvectors (PCs) are often used as surrogates for ancestry (or population structure).

PCA of Europeans

- In a very influential paper for modern genetic studies, an application of PCA to genetic data from European samples, Novembre et al. (Nature, 2008) illustrated that among Europeans for whom all four grandparents originated in the same country, the first two principal components computed using 200,000 SNPs could map their country of origin quite accurately in a plane

PCA of Europeans

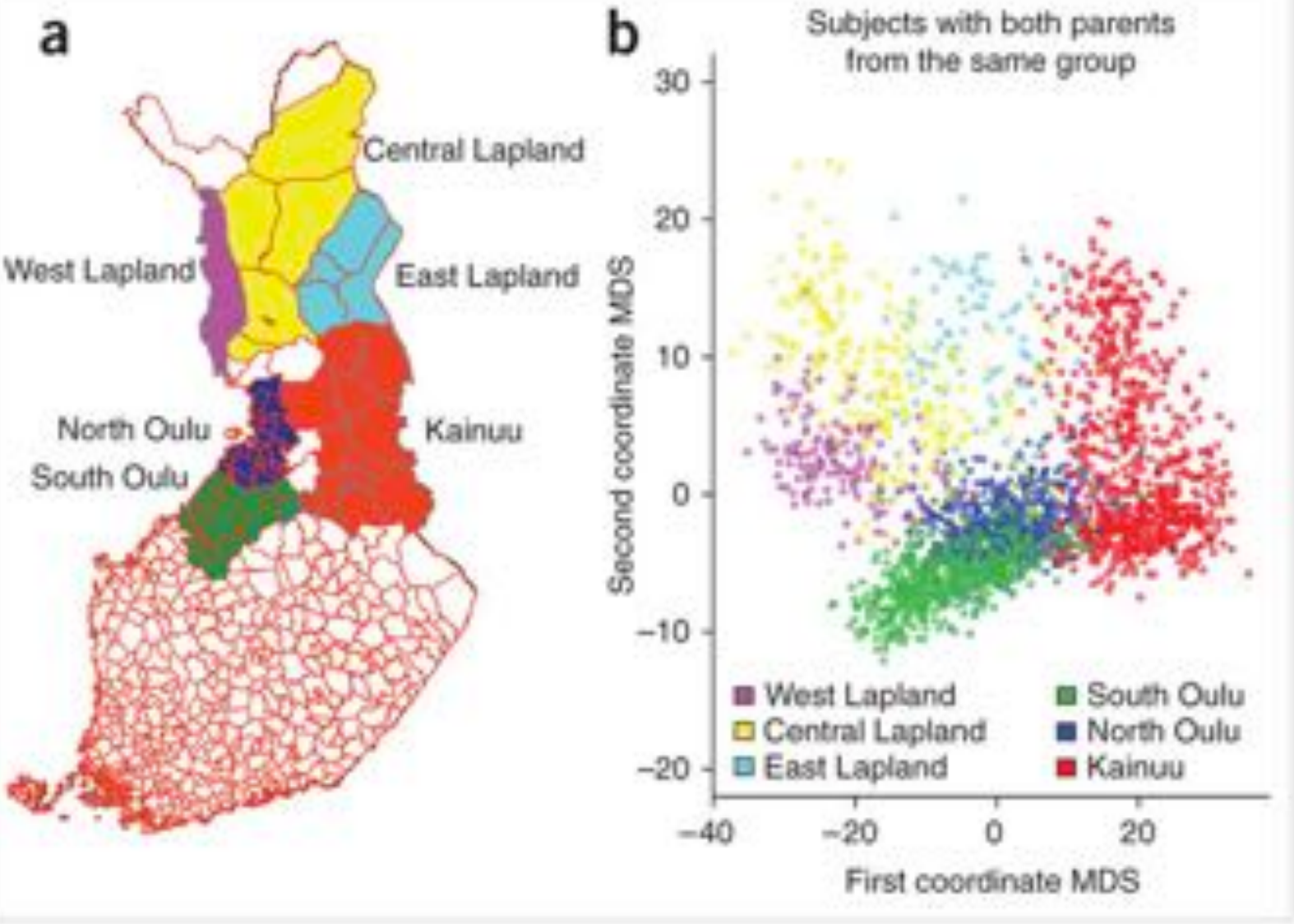


Novembre et al. (Nature, 2008)

PCA in Finland

- here can be population structure in all populations, even those that appear to be relatively "homogenous"
- An application of principal components analysis to genetic data from Finland samples (Sabatti et al., 2009) identified population structure that corresponded very well to geographic regions in this country.

PCA in Finland



Sabatti et al. (Nature Genetics, 2009)

Correcting for Population Structure with PCA

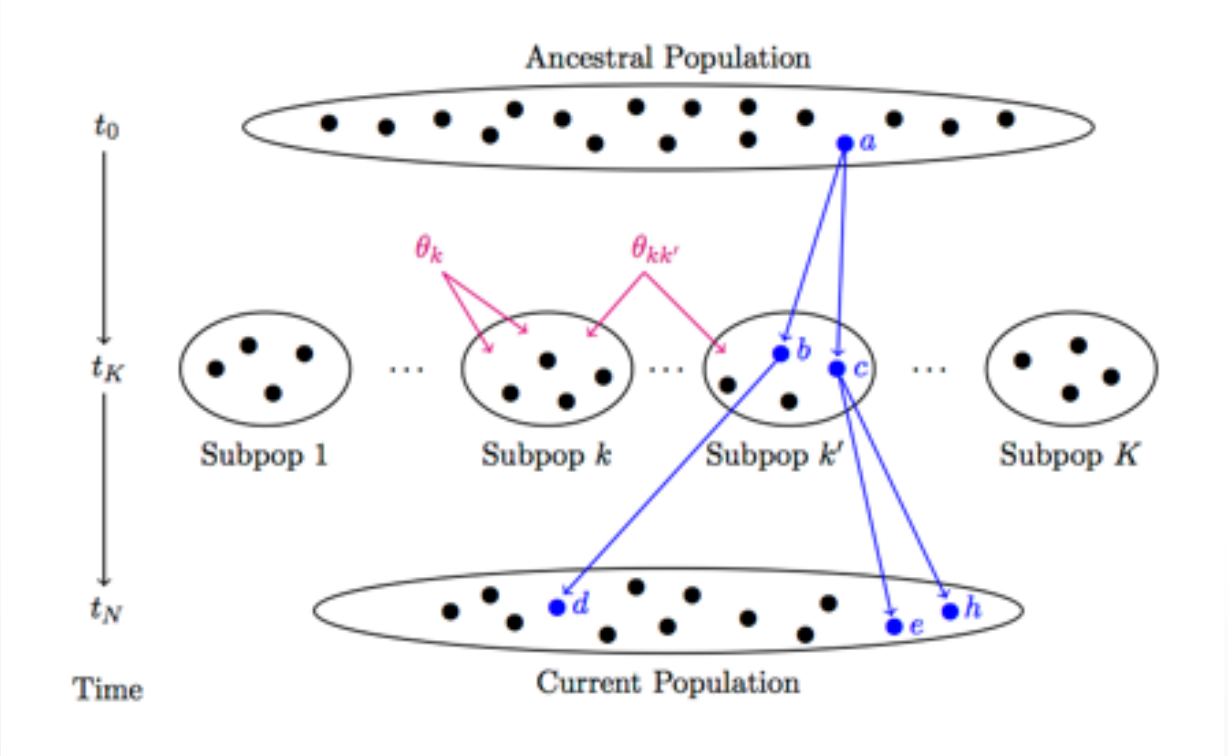
- Price et al. (2006) proposed corrected for structure in genetic association studies by applying PCA to $\hat{\Psi}$.
- They developed a method called EIGENSTRAT for association testing in structured populations where the top principal components (highest eigenvalues)
- EIGENSTRAT essentially uses the top principal components from the PCA as covariates in a multi-linear regression model to correct for sample structure.

$$Y = \beta_0 + \beta_1 X + \beta_2 PC_1 + \beta_3 PC_2 + \beta_4 PC_3 + \cdots + \epsilon$$

  - $H_0 : \beta_1 = 0$ vs. $H_a : \beta_1 \neq 0$

Caution: Familial Relatedness Confounds standard PCA

- 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)

PCA in Related Samples

RESEARCH ARTICLE

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]*

Genetic Epidemiology

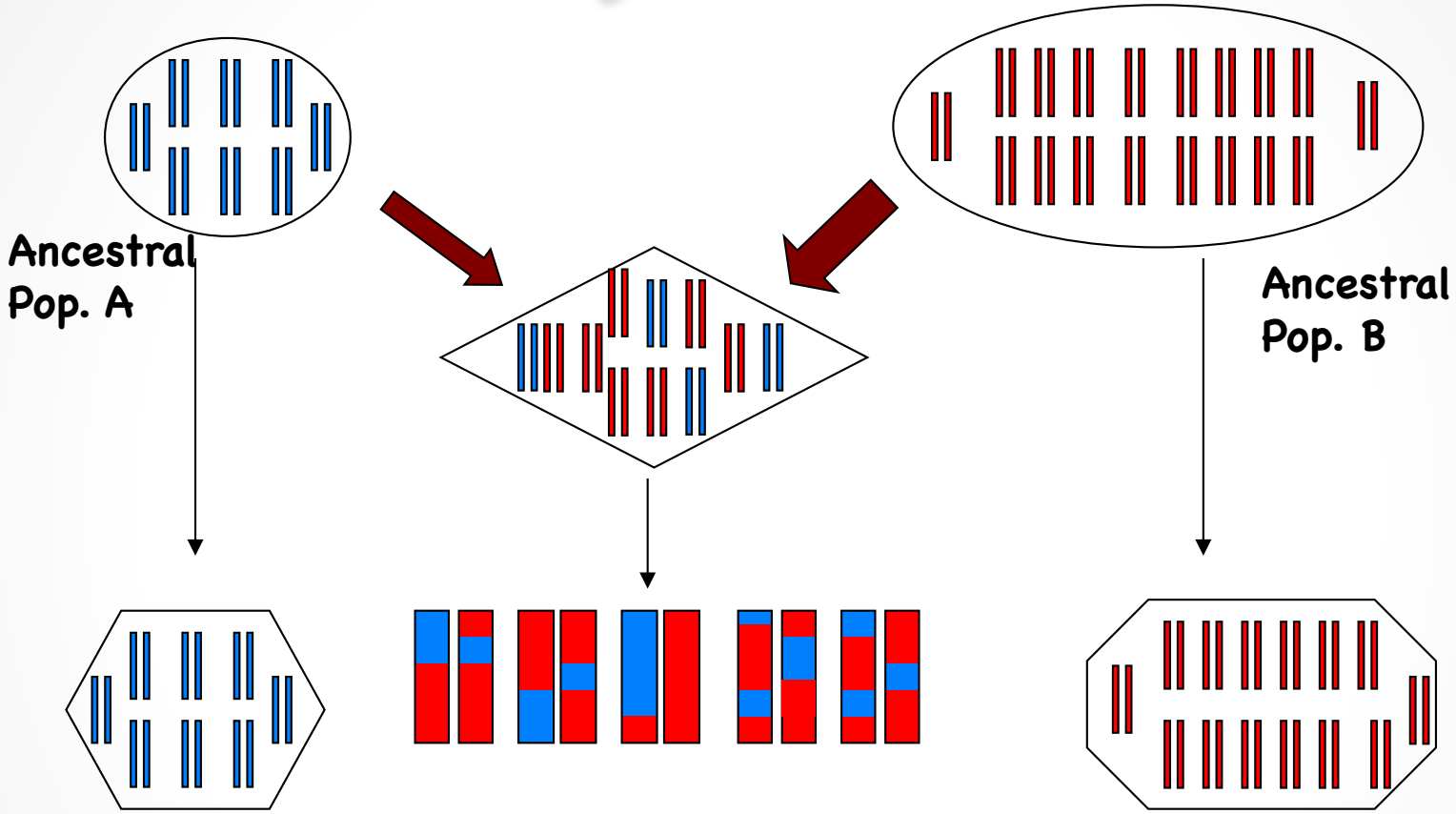
OFFICIAL JOURNAL INTERNATIONAL GENETIC EPIDEMIOLOGY SOCIETY

- Developed the PC-AiR method for performing a **P**rincipal **C**omponents **A**nalysis **i**n **R**elated samples.

Admixed Populations

- A number of recent large-scale genetic studies include sampled individuals from **admixed populations**:
  - populations characterized by ancestry derived from two or more ancestral populations that were reproductively isolated.
- Admixed populations have arisen in the past several hundred years as a consequence of historical events such as the transatlantic slave trade, the colonization of the Americas and other long-distance migrations.
- Examples of admixed populations include
  - African Americans and Hispanics in the U.S
  - Latinos from throughout Latin America
  - Uyghur population of Central Asia
  - Cape Verdeans
  - South African "Coloured" population

Ancestry Admixture



- The chromosomes of an admixed individual represent a mosaic of chromosomal blocks from the ancestral populations..

Recently Admixed Populations

- There can be substantial genetic heterogeneity among individuals in admixed populations
- Admixed populations are ancestrally admixed and thus have population structure.
- Statistical method for estimating admixture proportions from genetic data

Supervised Learning of Ancestry Admixture

- Methods, such as ADMIXTURE (Alexander et al., 2009), have recently been developed for supervised learning of ancestry proportions for an admixed individuals using high-density SNP data.
- Most use either a hidden Markov model (HMM) or an Expectation-Maximization (EM) algorithm to infer genome-wide or global ancestry
- Other methods, such as RFMix (Maples et al., 2013) have been implemented to infer local ancestry of admixed individuals, i.e., ancestry at specific locations on the genome.

Admixture Inference

- Example: We are interested in identifying the ancestry proportions for an admixed individual
- Suppose the observed sequence on a chromosome for an admixed individual is:

...TATACGTGCACCTGGATTACAGATTACAGATTACAGATTACATTGCATCGATCGAA...

- Assume that we have a suitable reference panel with diverse ancestries, and a similar sequence is observed in samples from one of the "homogenous" reference populations:

...TGATCCTGAACCTAGATTACAGATTACAGATTACAGATTACAATGCTTCGATGGAC...

...AGATCCTGAACCTAGATTACAGATTACAGATTACAGATACCAATGCTTCGATGGAC...

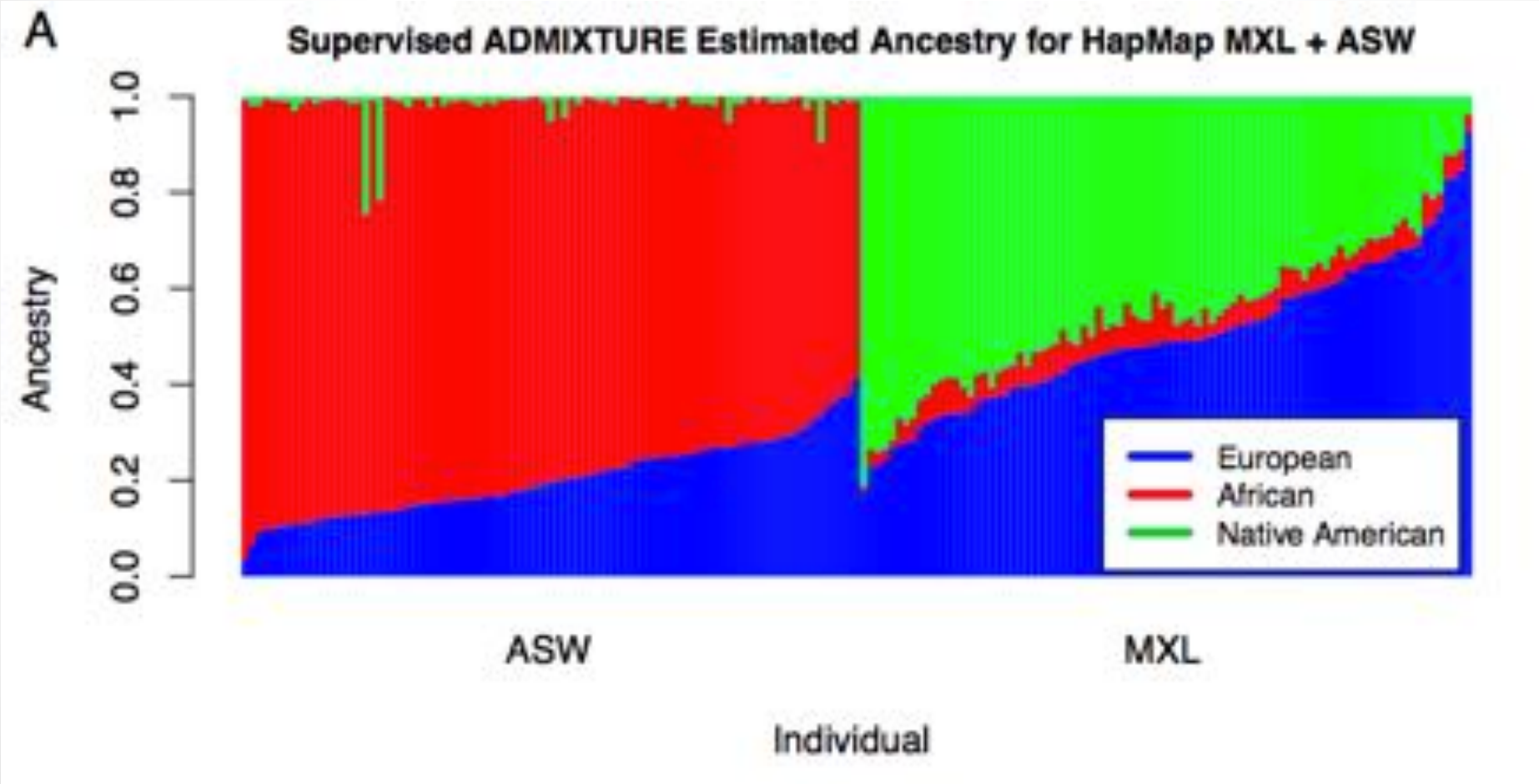
...CGATCCTGAACCTAGATTACAGATTACAGATTTGCGTATACAATGCTTCGATGGAC...

Can infer the likelihood of the observed sequence in the admixed individuals being derived from each of the reference population samples. This can be performed across the genome.

Admixture: HapMap ASW and MXL

- Genome-screen data on 150,872 autosomal SNPs was used to estimate ancestry
- Estimated genome-wide ancestry proportions of every individual using the ADMIXTURE (Alexander et al., 2009) software
- A supervised analysis was conducted using genotype data from the following reference population samples for three "ancestral" populations
  - HapMap YRI for West African ancestry
  - HapMap CEU samples for northern and western European ancestry
  - HGDP Native American samples for Native American ancestry.

Admixture: HapMap ASW and MXL

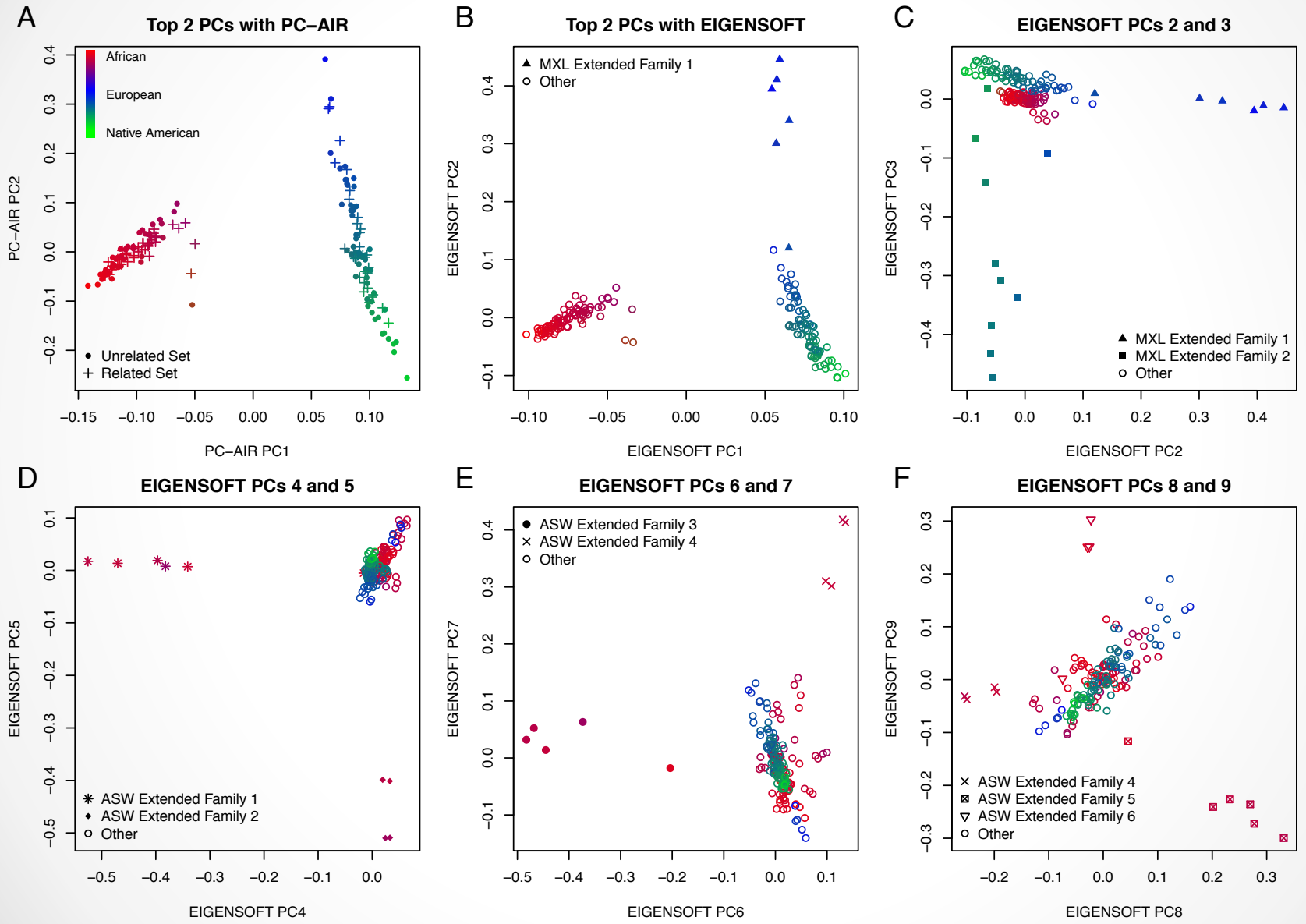


Admixture: HapMap ASW and MXL

Table: Average Estimated Ancestry Proportions for HapMap African Americans and Mexican Americans

	Estimated Ancestry Proportions (SD)		
Population	European	African	Native American
MXL	49.9% (14.8%)	6%(1.8%)	44.1% (14.8%)
ASW	20.5% (7.9%)	77.5% (8.4%)	1.9% (3.5%)

PCA: HapMap ASW and MXL

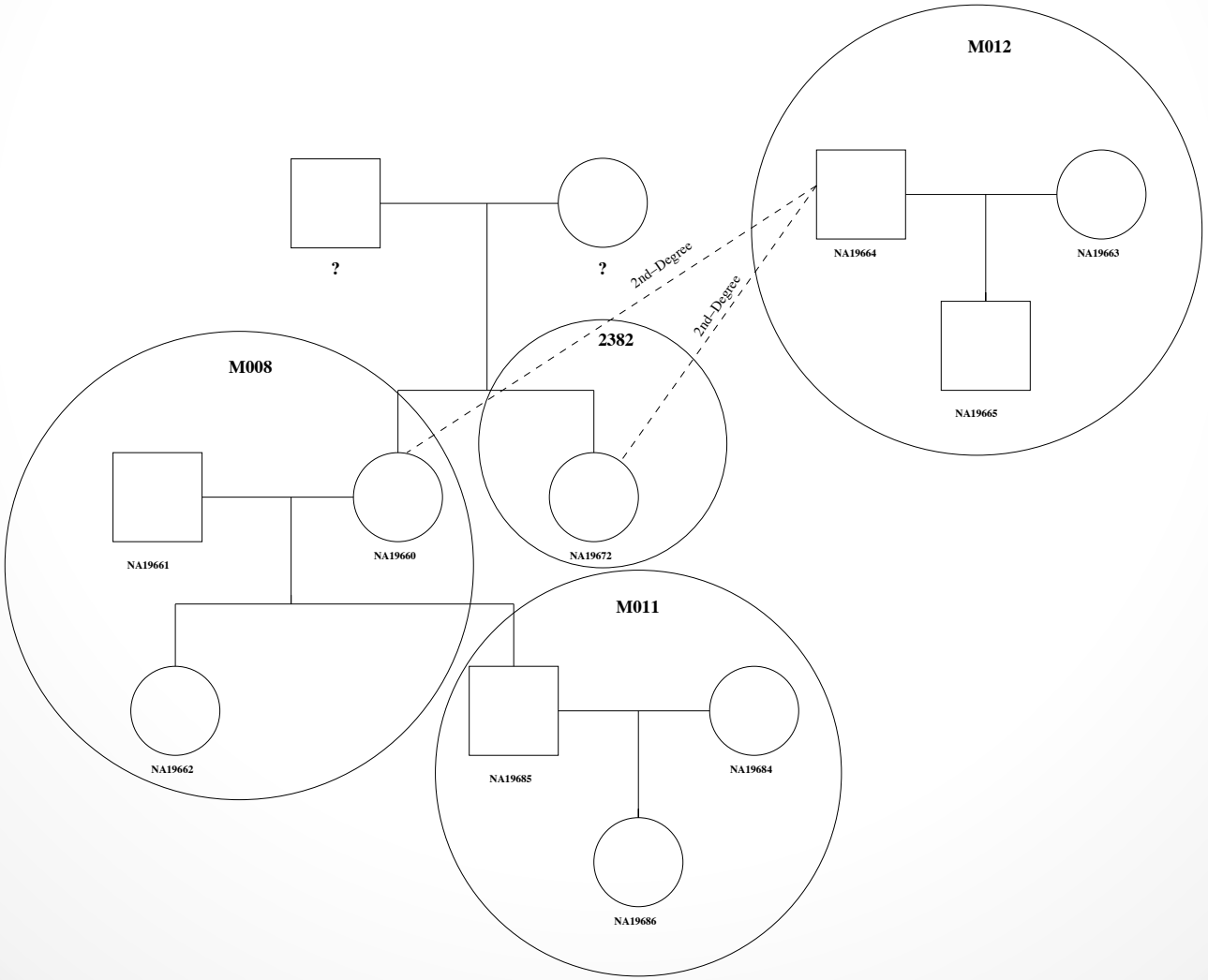


Unexpected Relatedness in HapMap MXL

ARTICLE

Estimating Kinship in Admixed Populations

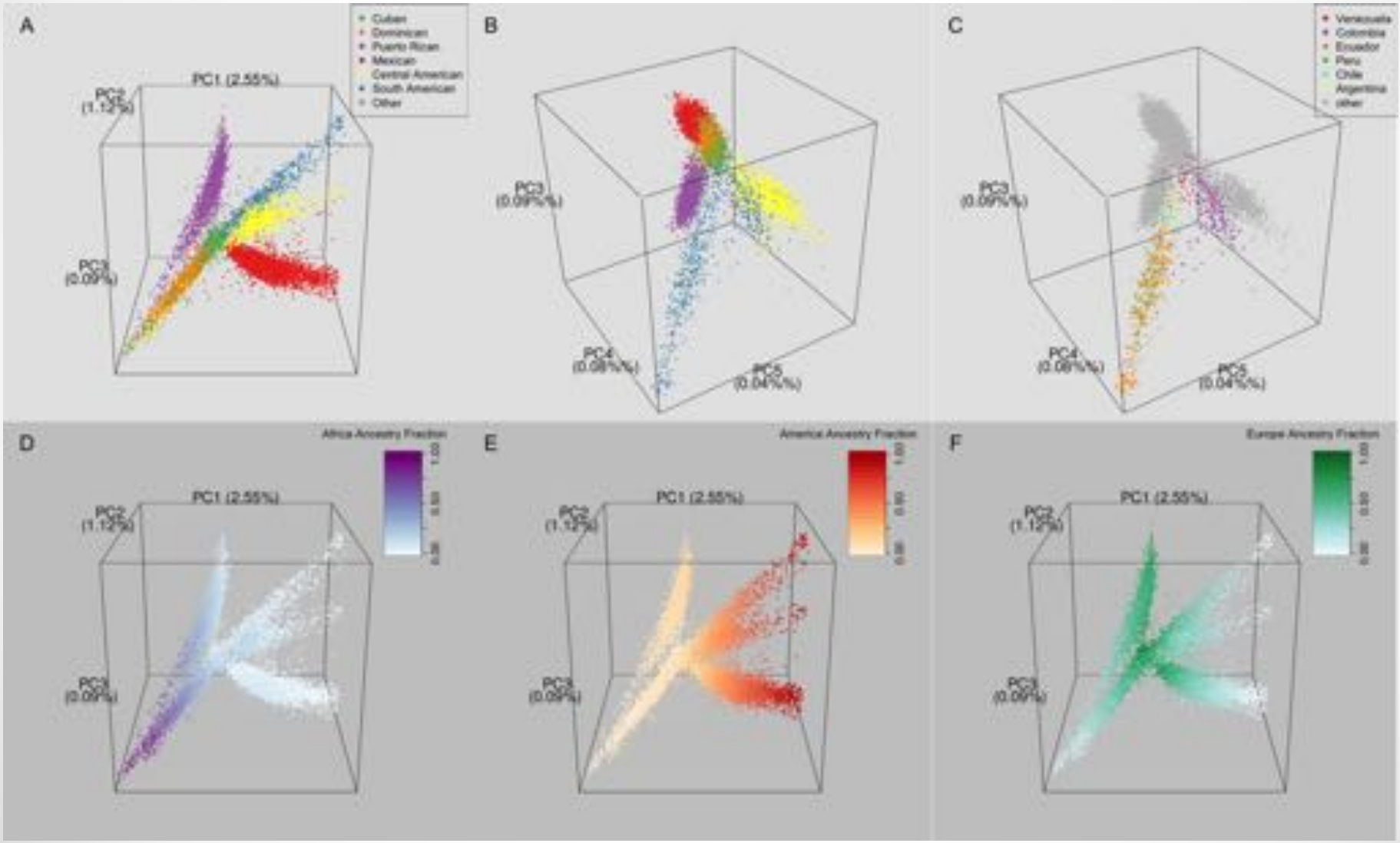
Timothy Thornton,[1,*] Hua Tang,[2] Thomas J. Hoffmann,[3,4] Heather M. Ochs-Balcom,[5] Bette J. Caan,[6] and Neil Risch[3,4,6,*]



Example: HCHS/SOL

- The Hispanic Community Heath Study / Study of Latinos (HCHS/SoL) is the largest genetic study of Hispanics/Latinos
- Goal is to identify genetic risk factors for a variety of health conditions: heart, lung and blood disorders, kidney and liver function, diabetes, cognitiive function, dental conditions, hearing disorders, etc.
- 13,065 self-identified Hispanic or Latino men and women, aged 18-74 years, consented to have DNA extracted for genetic studies.

PCA in HCHS/SOL

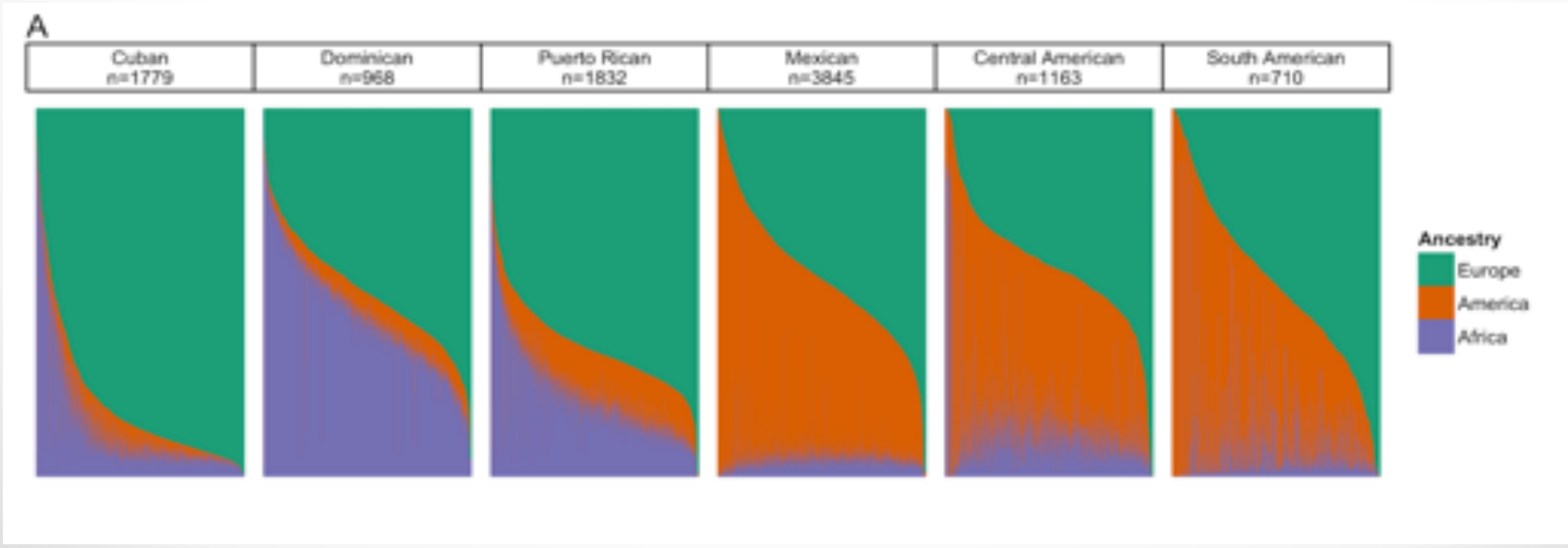


Genetic Diversity in HCHS/SOL

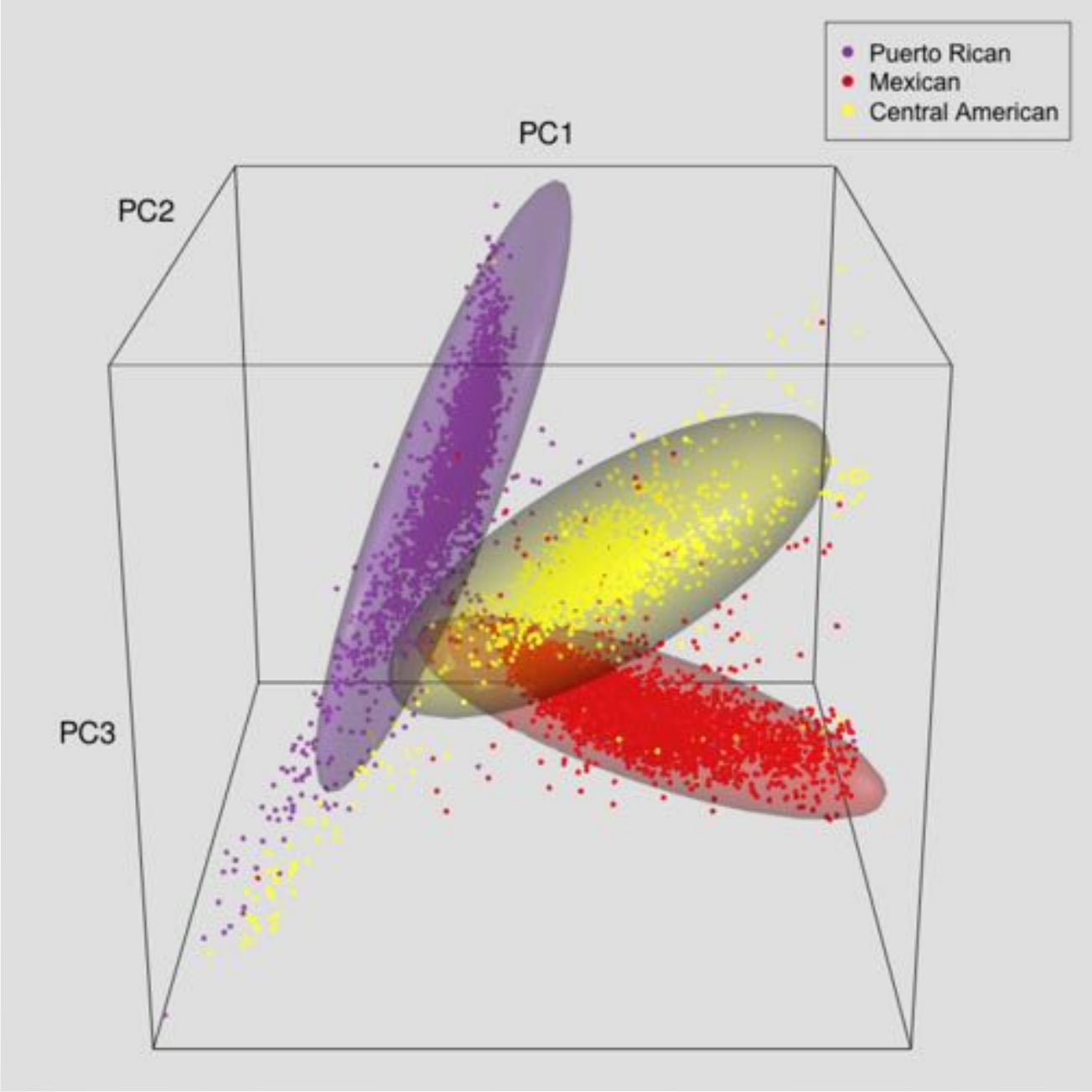
ARTICLE

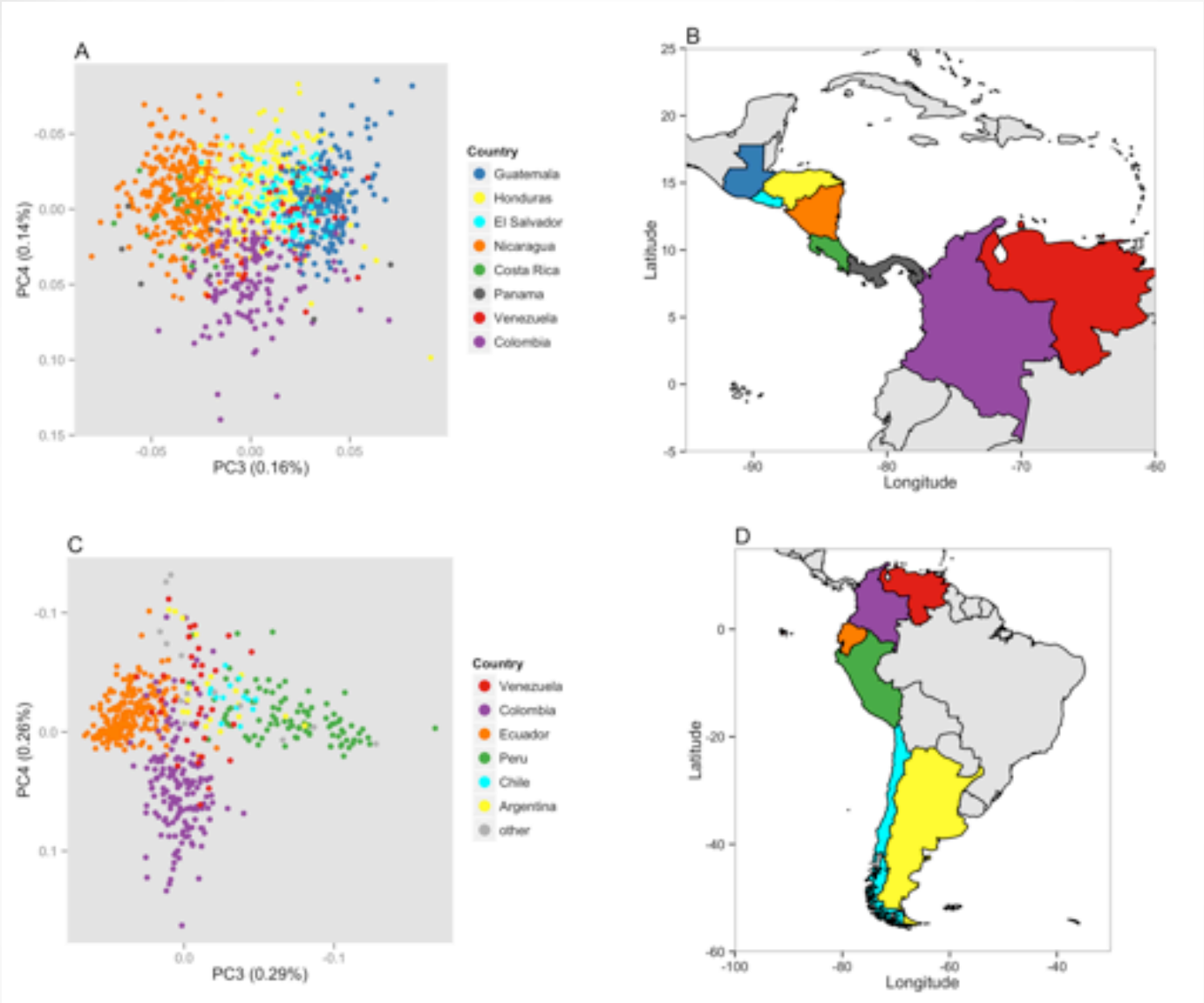
Genetic Diversity and Association Studies in US Hispanic/Latino Populations: Applications in the Hispanic Community Health Study/Study of Latinos

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,*]



PCA in HCHS/SOL





- Genetic differentiation among individuals is associated with the geography of their countries of grandparental origin.
- Plots of PCs from analyses using individuals for whom all four grandparents were born in a specific country in Central or South America show geographic structure

Applications and Novel 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

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ORIGINAL ARTICLE

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

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ARTICLE

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

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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?

Alzheimer's Disease Studies in Diverse Populations

ELSEVIER

Alzheimer's & Dementia 12 (2016) 233-243

Alzheimer's & Dementia

Featured Article

Global and local ancestry in African-Americans: Implications for Alzheimer's disease risk

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ELSEVIER

Alzheimer's & Dementia 13 (2017) 727-738

Alzheimer's & Dementia

Featured Article

Transethnic genome-wide scan identifies novel Alzheimer's disease loci

Gyungah R. Jun[a,b], Jaeyoon Chung[b], Jesse Mez[c], Robert Barber[d], Gary W. Beecham[e], David A. Bennett[f], Joseph D. Buxbaum[g,h,i], Goldie S. Byrd[j], Minerva M. Carrasquillo[k], Paul K. Crane[l], Carlos Cruchaga[m,n], Philip De Jager[o,p], Nilufer Ertekin-Taner[k], Denis Evans[q], M. Danielle Fallin[r], Tatiana M. Foroud[s], Robert P. Friedland[t], Alison M. Goate[g], Neill R. Graff-Radford[k], Hugh Hendrie[u,v], Kathleen S. Hall[v,w], Kara L. Hamilton-Nelson[e], Rivka Inzelberg[x], M. Ilyas Kamboh[y], John S. K. Kauwe[z], Walter A. Kukull[aa,bb], Brian W. Kunkle[e], Ryozo Kuwano[cc], Eric B. Larson[p,dd], Mark W. Logue[b,f,ee], Jennifer J. Manly[ff,gg], Eden R. Martin[e], Thomas J. Montine[hh], Shubhabrata Mukherjee[l], Adam Naj[ii], Eric M. Reiman[ij,kk,ll,mm], Christiane Reitz[nn,oo,pp], Richard Sherva[b], Peter H. St. George-Hyslop[qq,rr], Timothy Thornton[l], Steven G. Younkin[k], Badri N. Vardarajan[ff,gg,nn], Li-San Wang[ij], Jens R. Wendlund[ss], Ashley R. Winslow[ss], Alzheimer's Disease Genetics Consortium, Jonathan Haines[tt], Richard Mayeux[ff,gg,nn,oo,pp], Margaret A. Pericak-Vance[e], Gerard Schellenberg[ij], Kathryn L. Lunetta[uu], Lindsay A. Farrer[b,c,uu,vv,ww,*]

ORIGINAL CONTRIBUTION

Variants in the ATP-Binding Cassette Transporter (*ABCA7*), Apolipoprotein E ε4, and the Risk of Late-Onset Alzheimer Disease

GENESIS Software

- GENESIS: Statistical methods for analyzing genetic data from samples with population structure and/or relatedness
- R software package is available from Bioconductor:
  - https://bioconductor.org/packages/release/bioc/html/GENESIS.html

Conomos et al. (AJHG, 2016)

Friday Harbor Admixture Session

https://faculty.washington.edu/tathornt/FridayHarbor.html