

# Impact of Demographic History and Natural Selection on Human Genomic Diversity

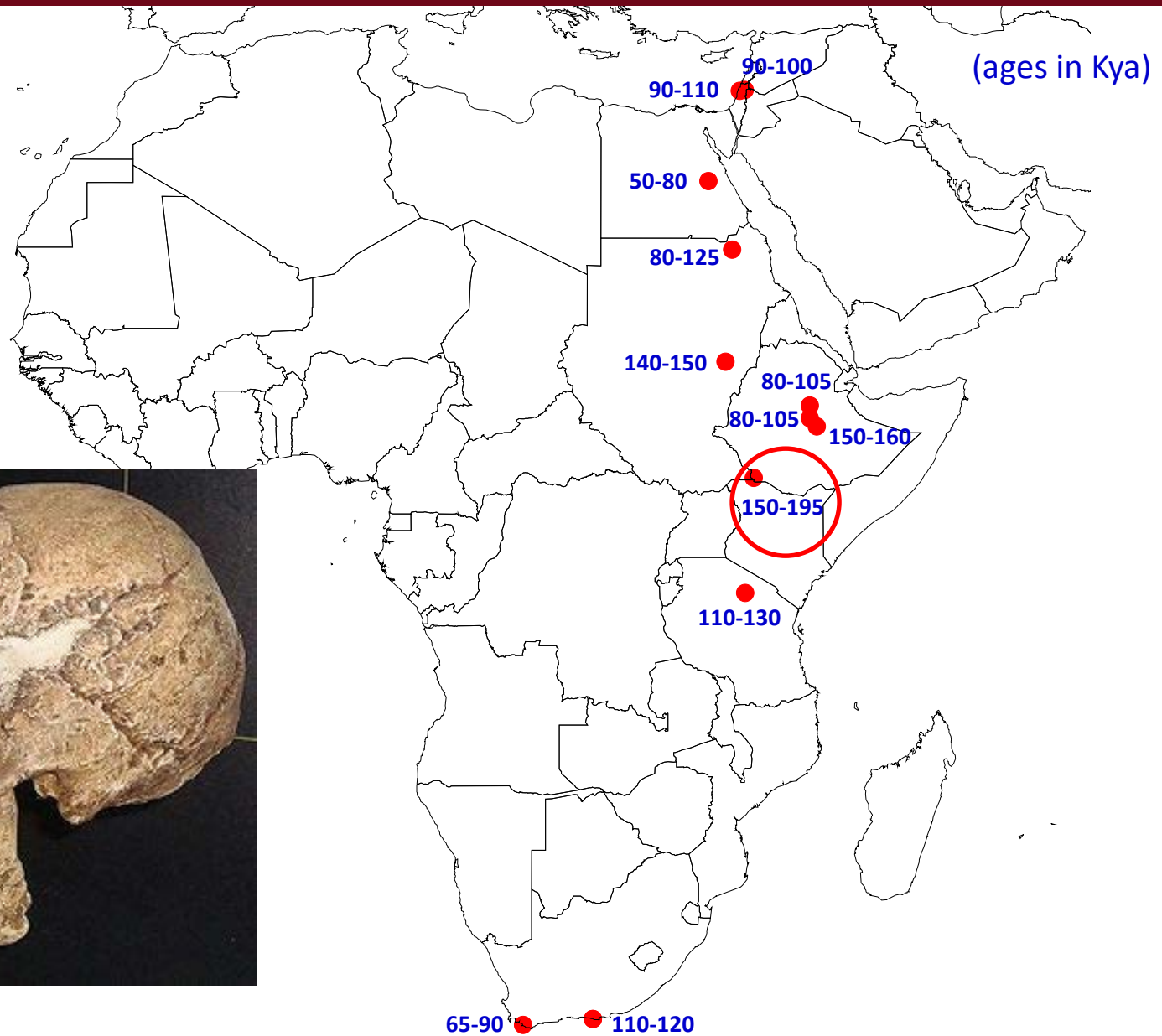
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University of Pennsylvania

# Evolutionary Forces Influencing Genetic Variation

- Mutation
- Genetic Drift
- Migration
- Selection

# Modern Human Fossil Record



# Major Migration Routes



Human Molecular Genetics, 3/e (©Garland Science 2004)

# How much do we differ?

- Identical twins



0

- Unrelated humans



1/1,000

- Human vs. chimp



1/100

- Human vs. mouse



1/30

- Human vs. broccoli



2/3

- 3 billion DNA bases → 3 million differences between each pair of individuals

(slide courtesy of Lynn Jorde)

**<0.1% divergence**



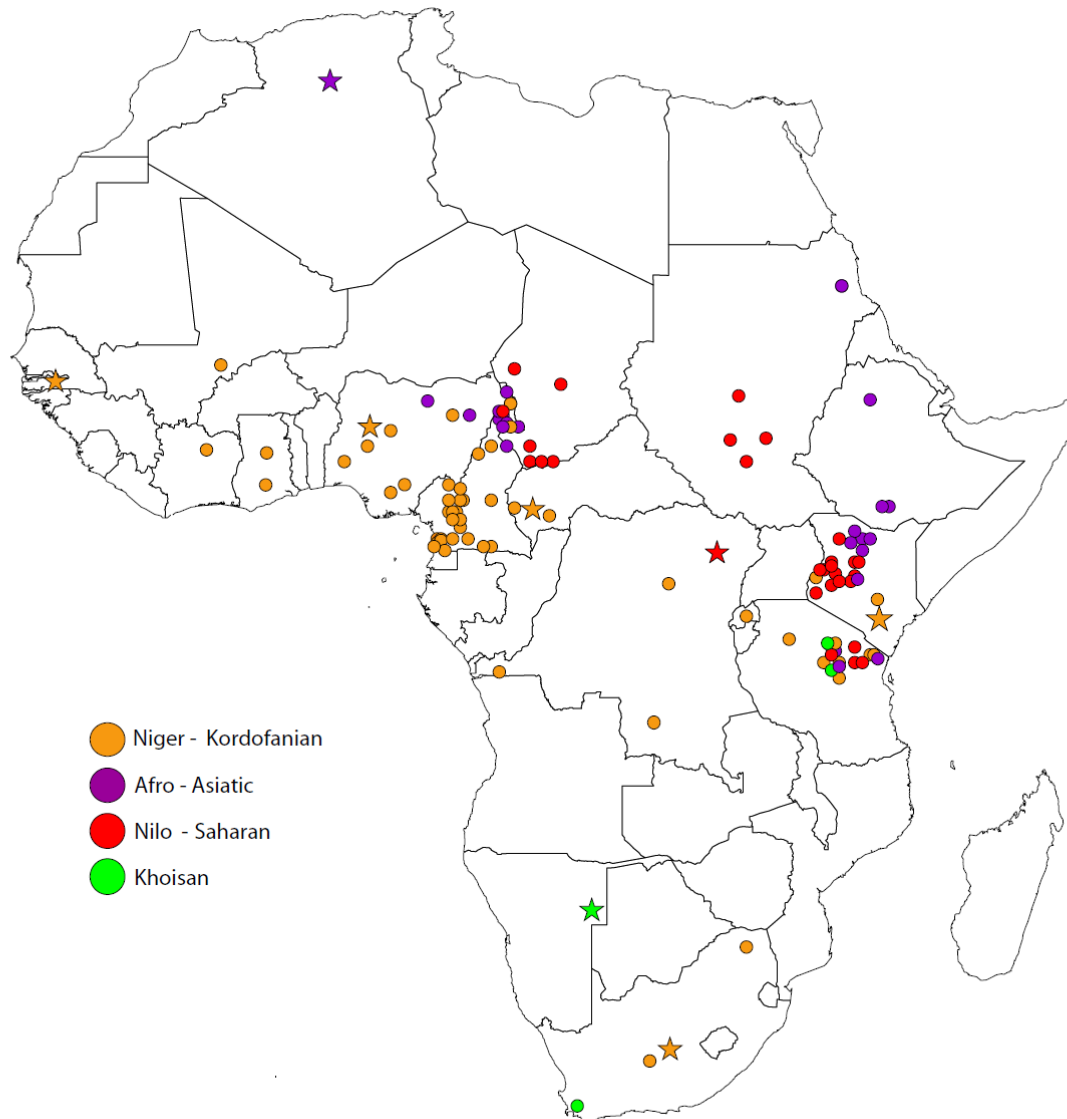
<http://dariaburke.wordpress.com/2011/03/21/ethic-diversity-at-estee-lauder/>

# Genetic Diversity Within and Between Humans

- There is also considerable structural variation across human genomes (insertions/deletions, gene duplications, and inversions)
- More genetic variation within (~85%) relative to between populations (~15%)

# The Genetic Structure and History of Africans and African Americans

Tishkoff et al. *Science* May 22;324(5930):1035-44. 2009



1165 Microsatellite and In/Del Polymorphisms

Genotyped in >2,500 Africans from 121 ethnic populations

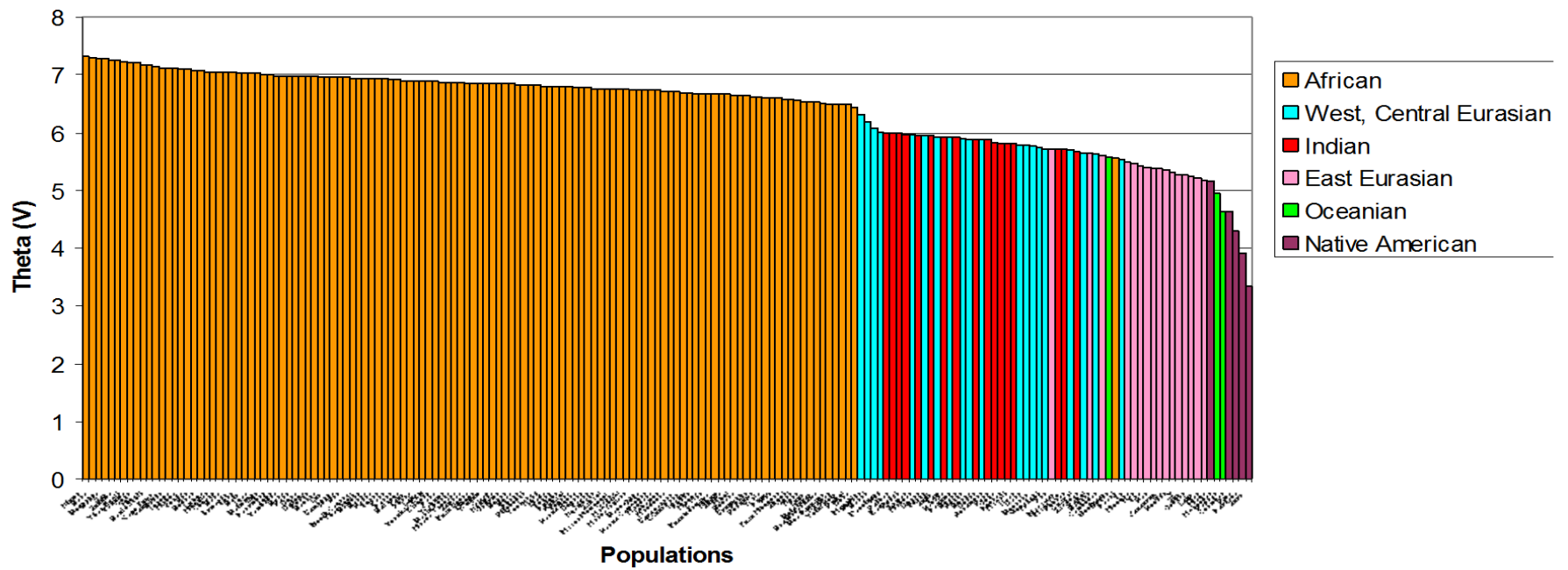
98 African Americans from four regions in the US

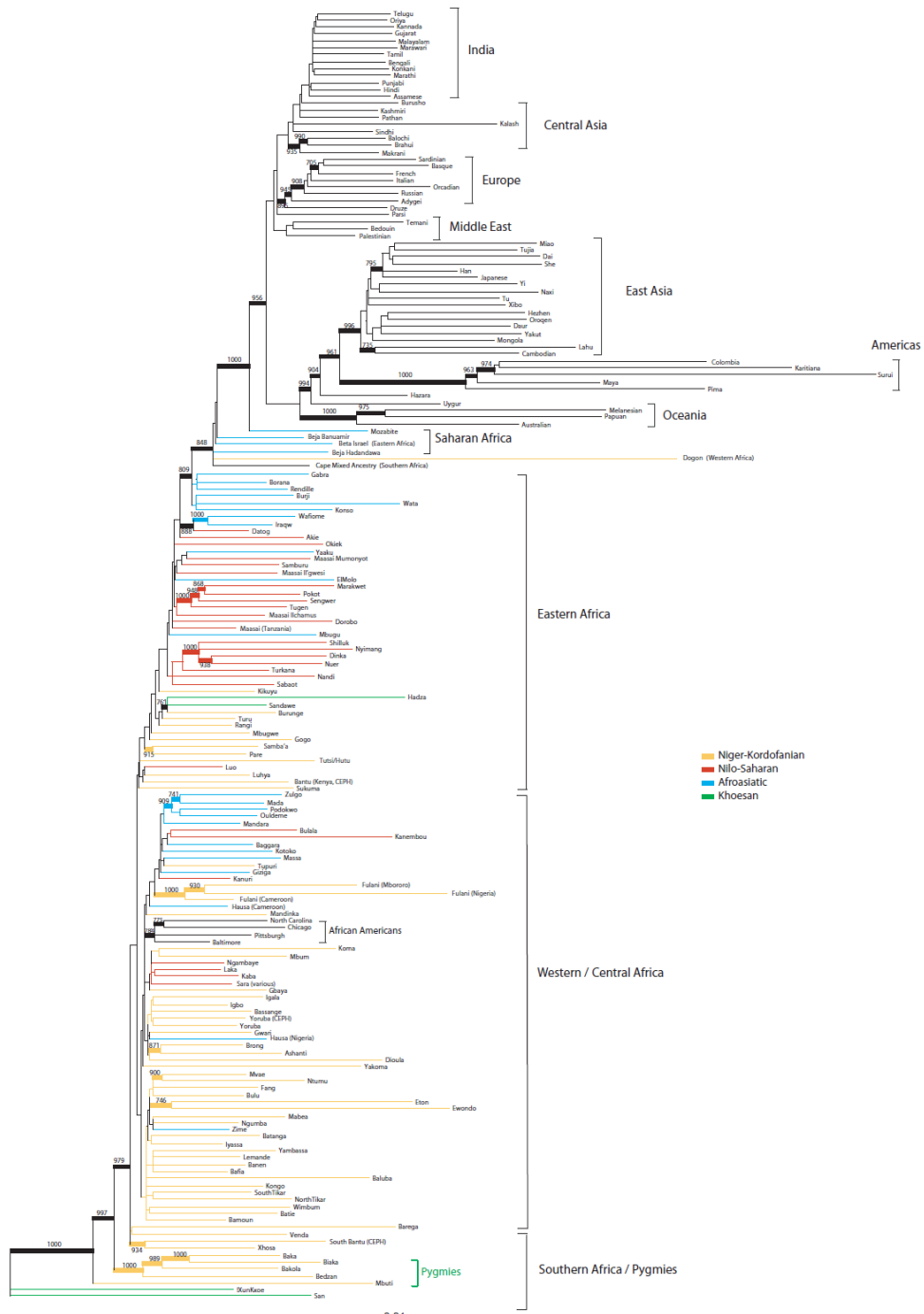
>1,500 comparative non-African individuals



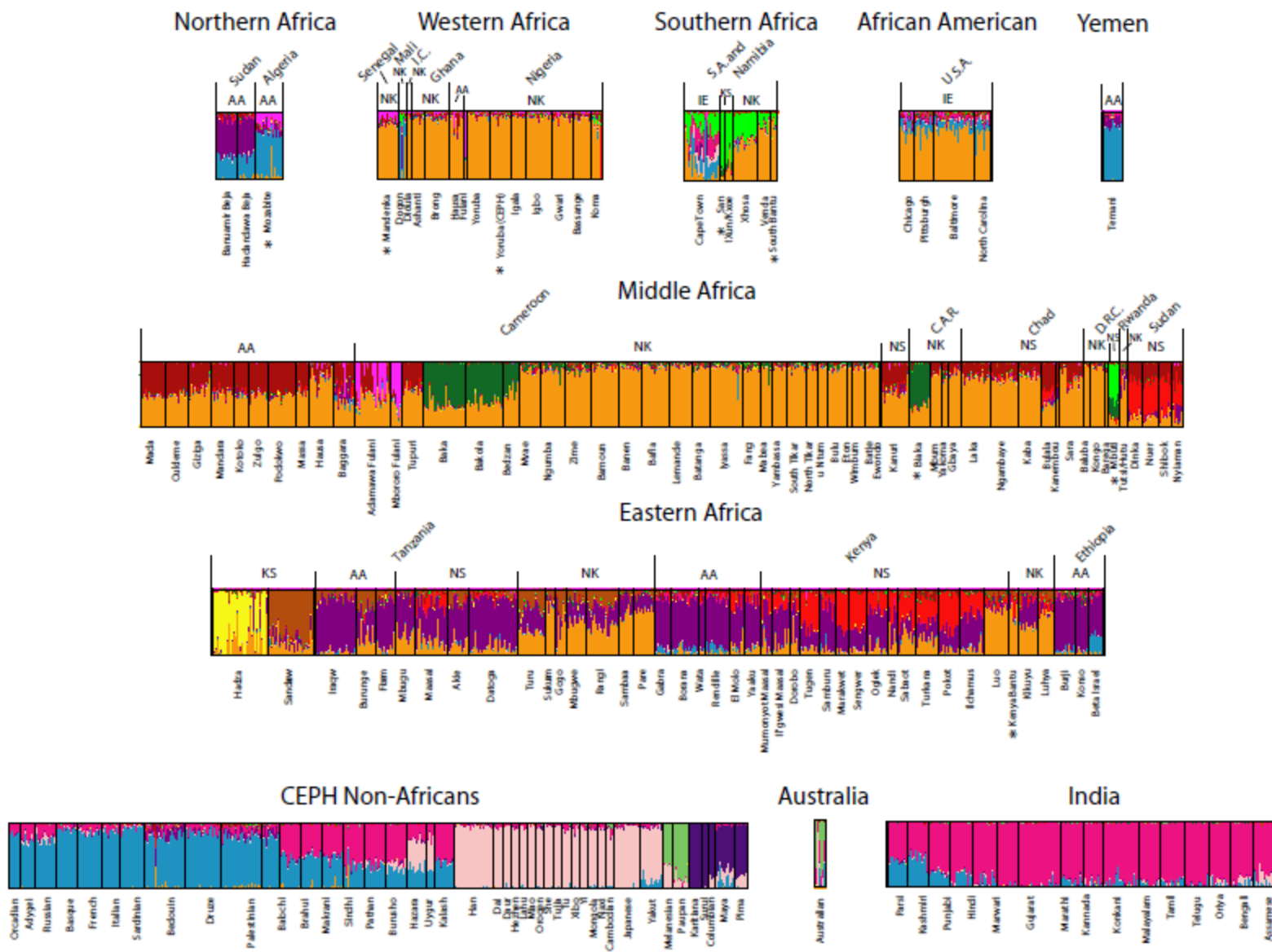


# Diversity Levels are Highest in Africa

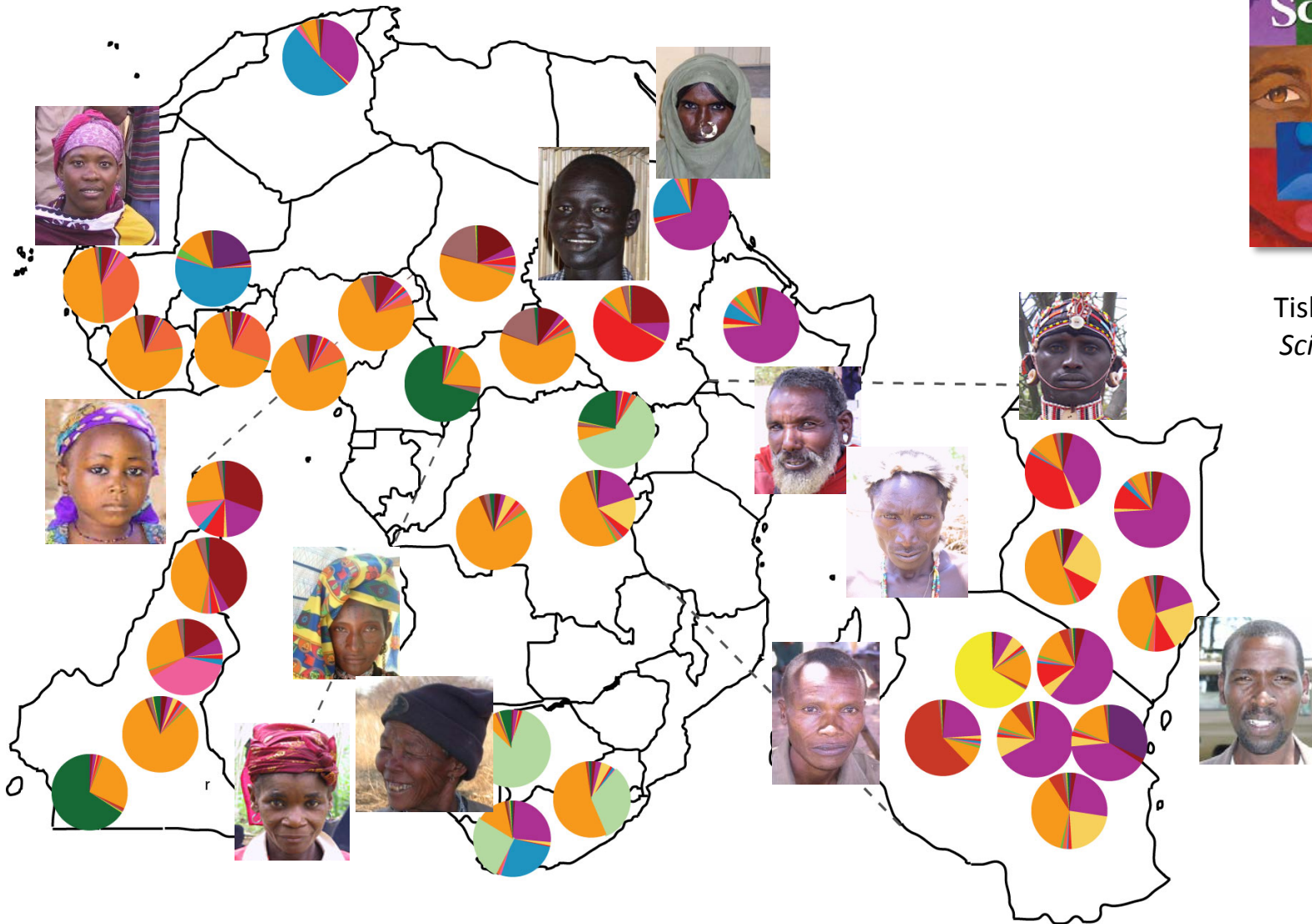




# Global Patterns of Substructure and Ancestry

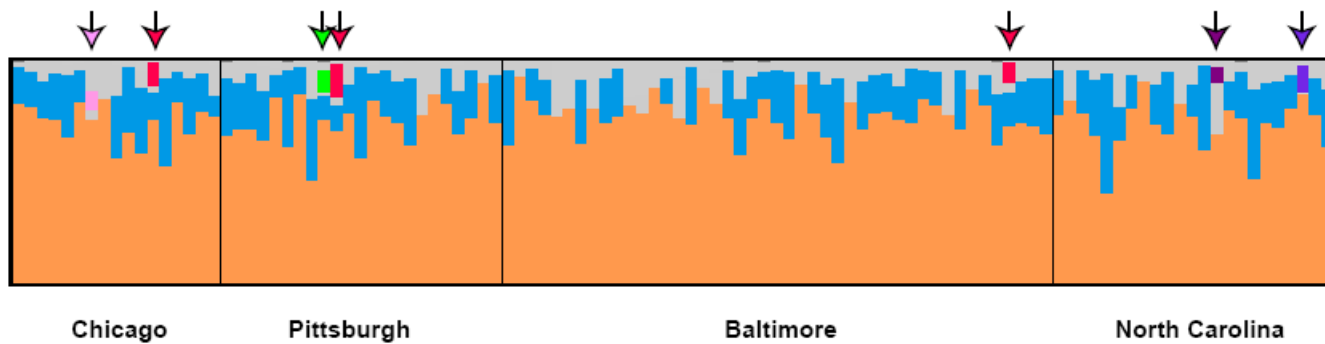
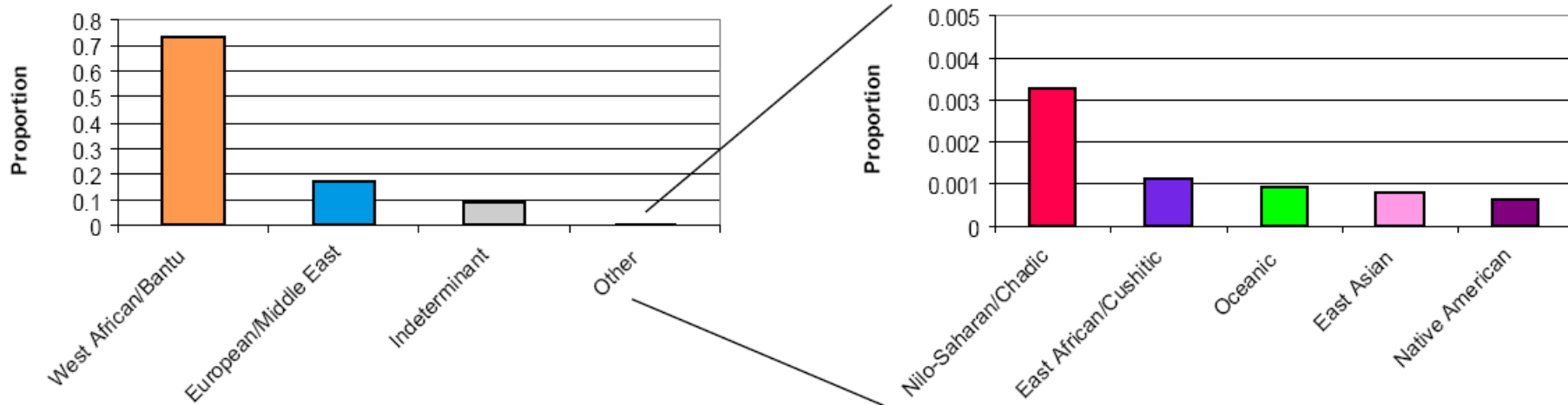


# Genetic Variation and Structure in Africa

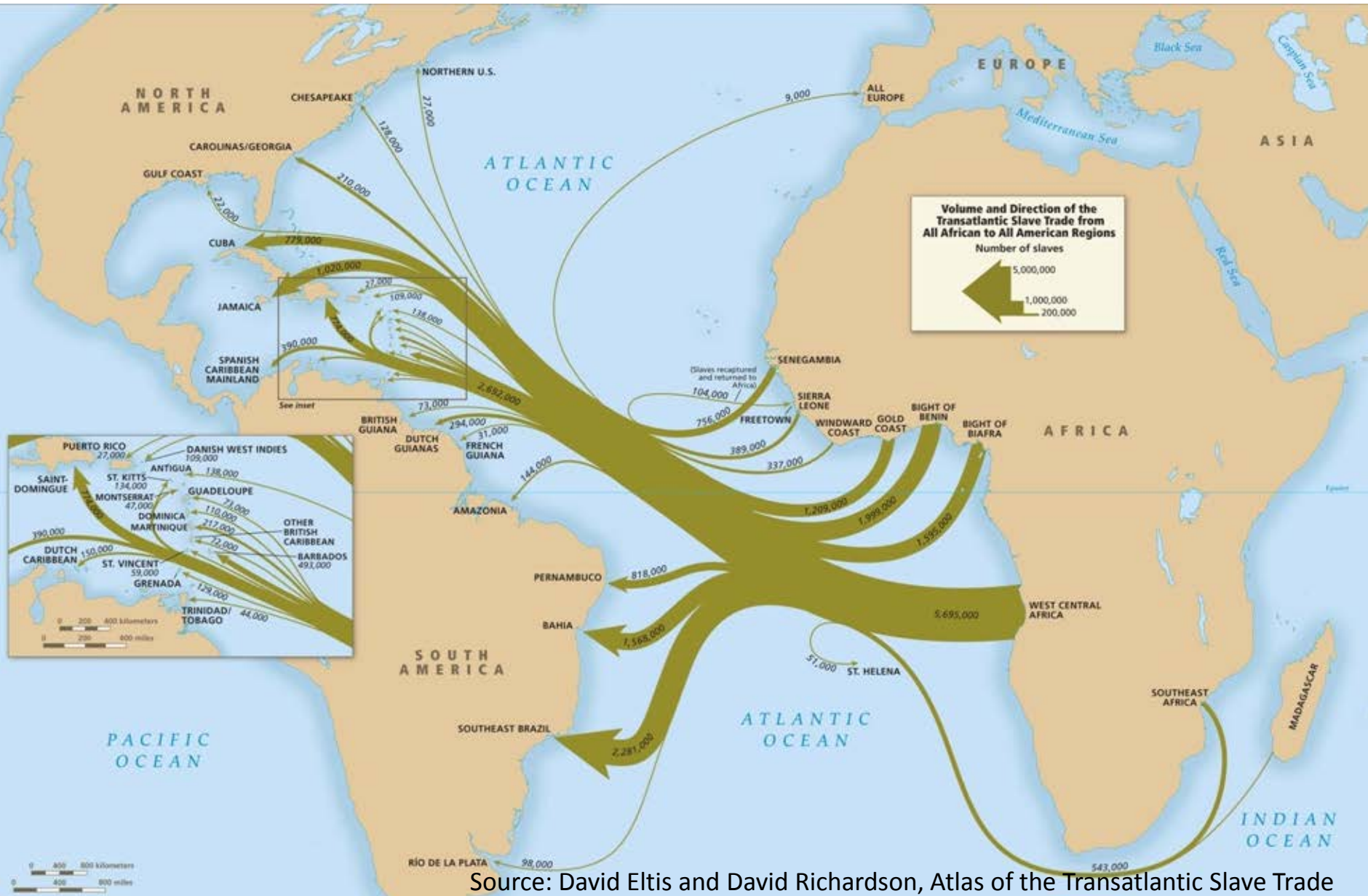


Tishkoff, *et al*  
*Science* 2009

# African American Ancestry

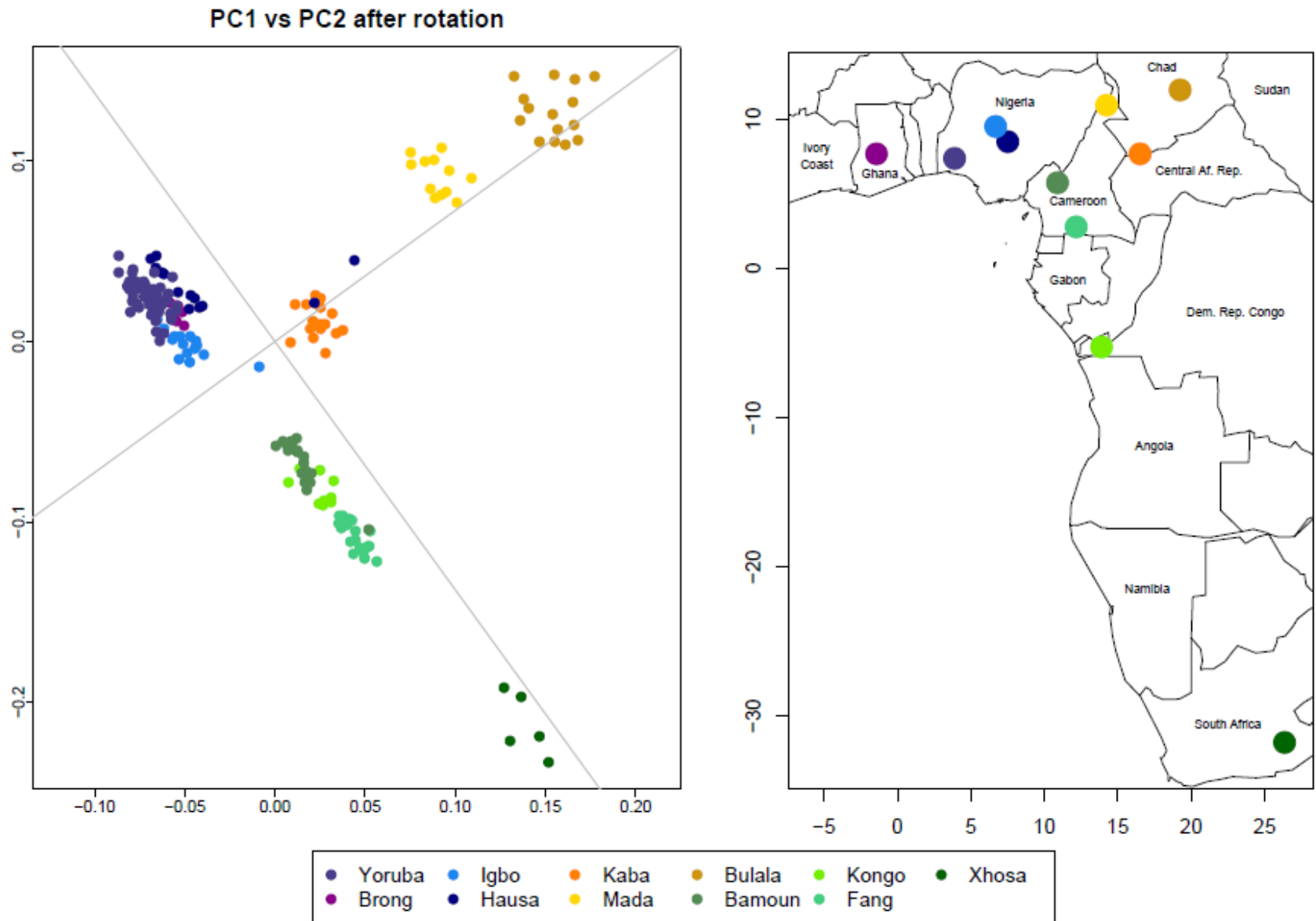


# Volume and Direction of the Transatlantic Slave Trade from Africa to the Americas



Source: David Eltis and David Richardson, Atlas of the Transatlantic Slave Trade

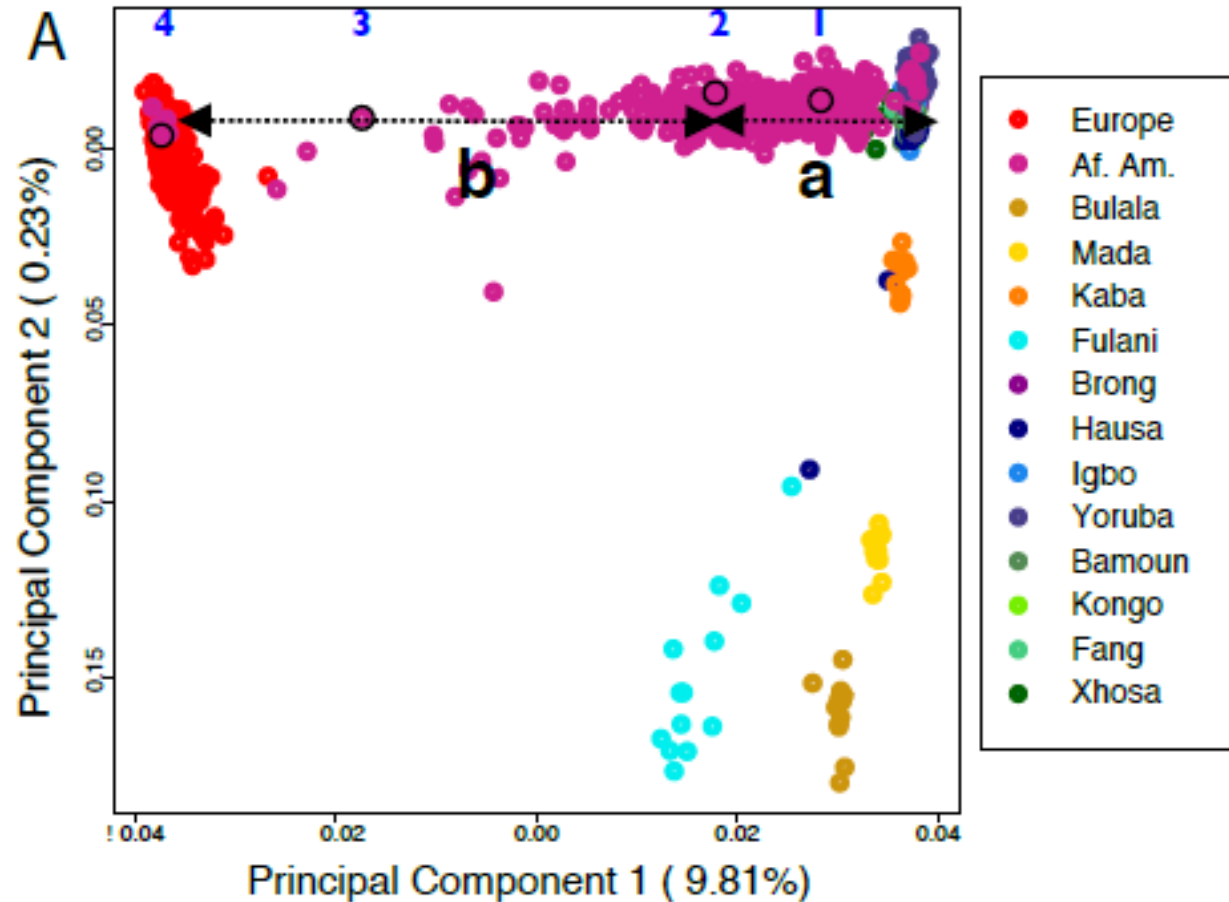
# Genetic variation correlates with geography



# PCA-based admixture estimation

African Ancestry =

$$\frac{b}{(a + b)}$$



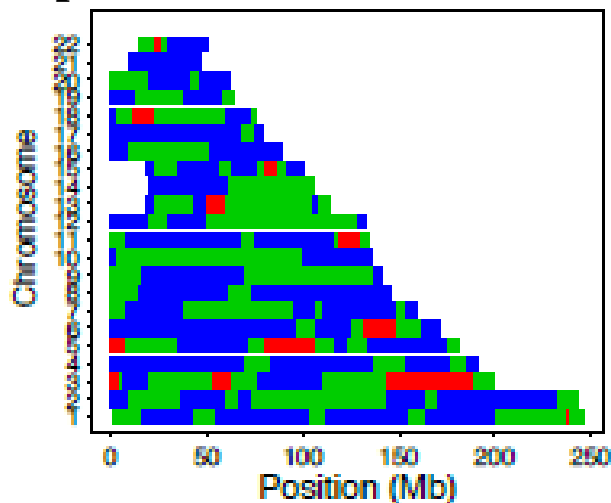
a and b are the chord distances from the European and African centroids



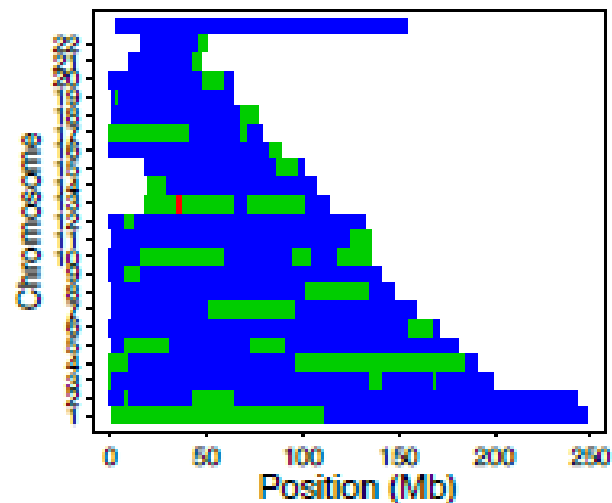
# Local Genomic Ancestry in African Americans

- African ancestry
- Shared African and European ancestry
- European ancestry

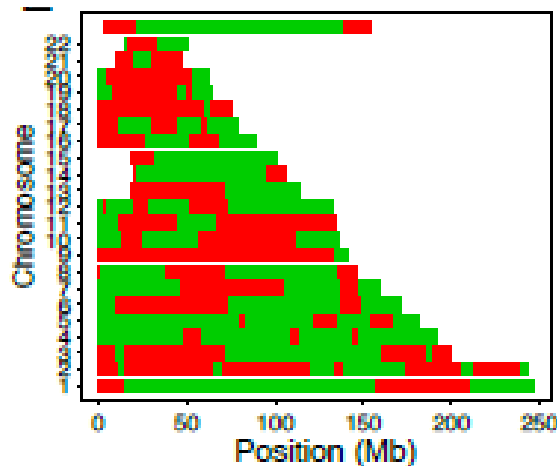
Representative African American



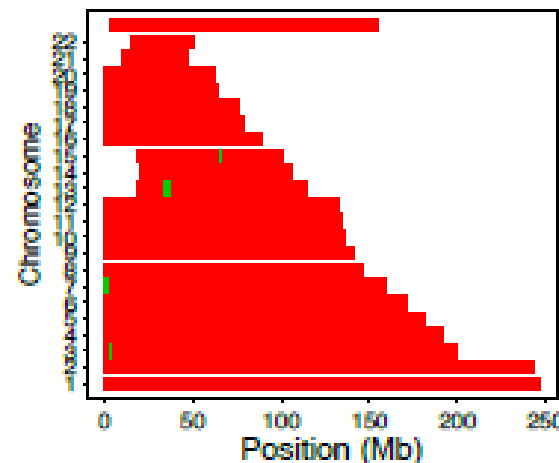
Recent admixture



Recent European ancestry

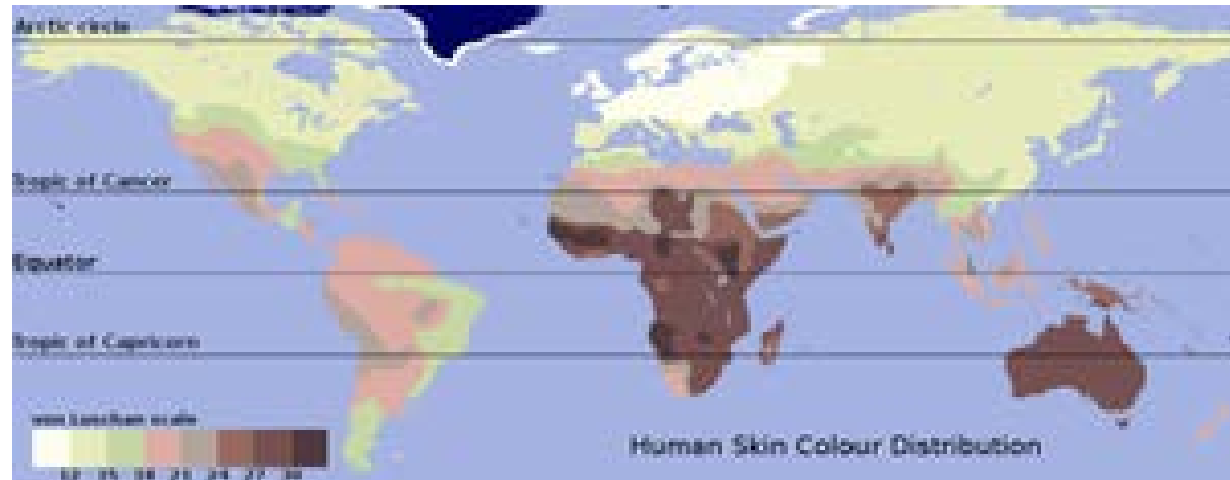


High degree of European ancestry

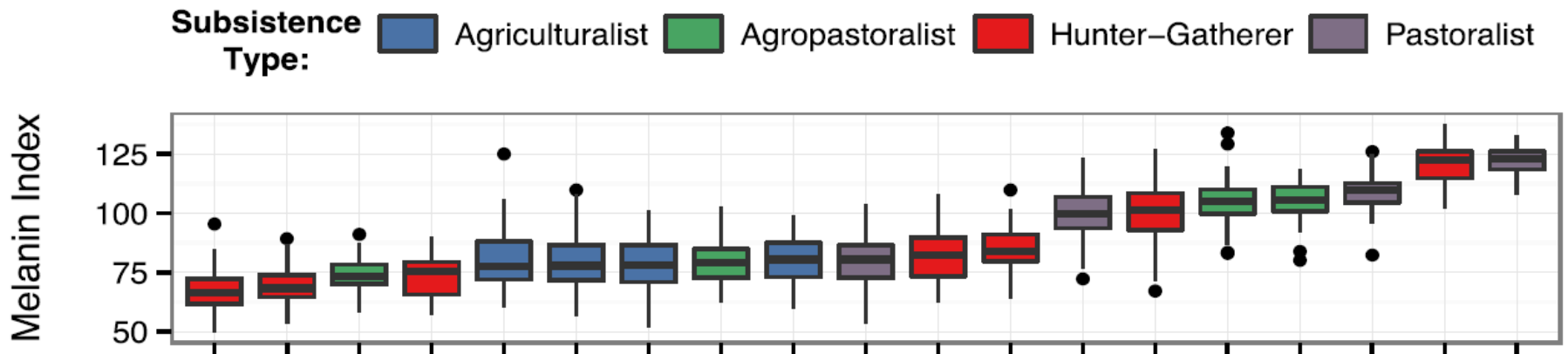


# Variation in Skin Pigmentation

- Under selection
  - Vitamin D
  - Folate
  - Melanoma



# Variation in Skin Pigmentation



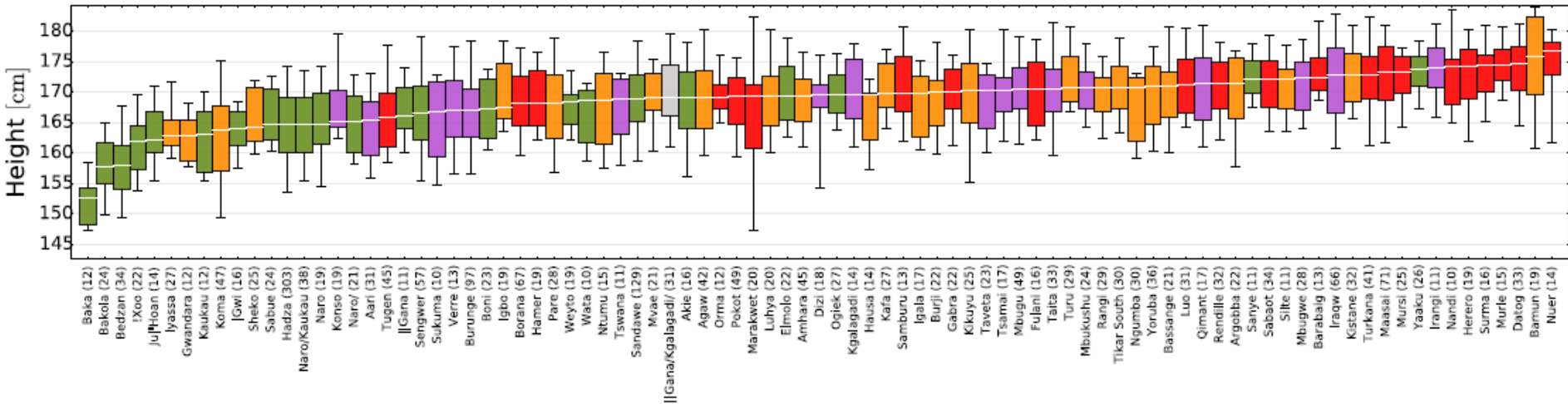
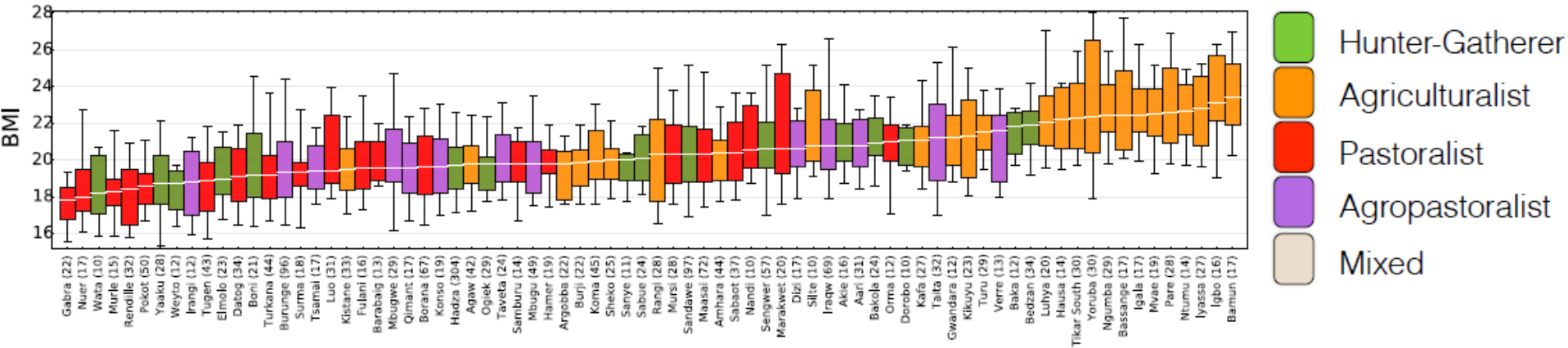
San

N = 2200 for melanin

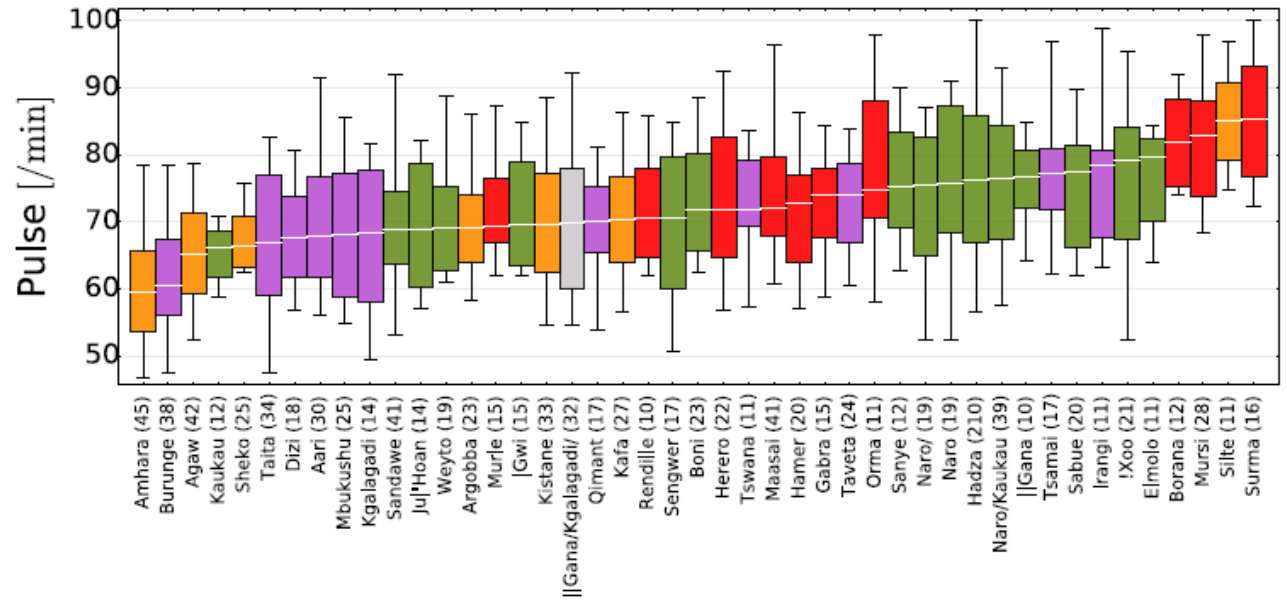
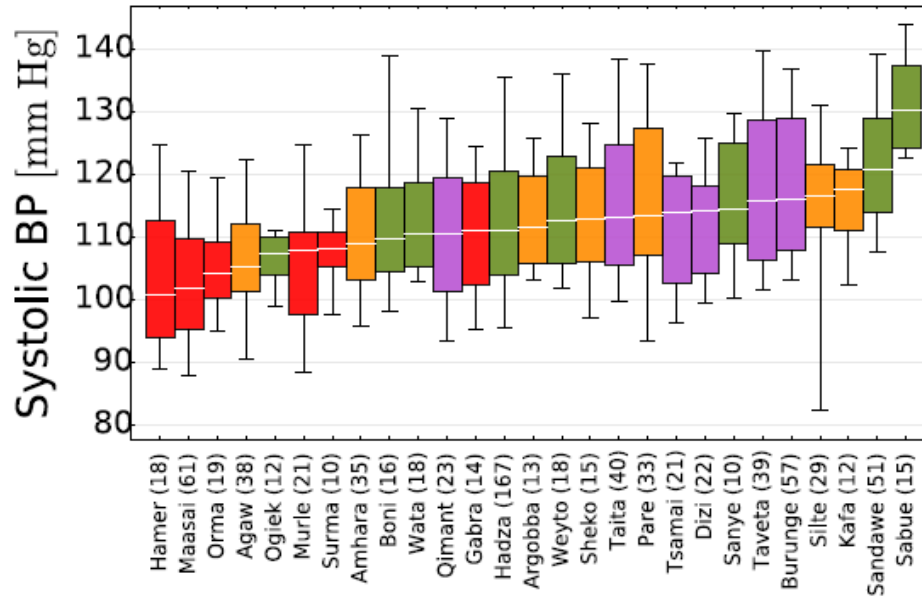


Mursi

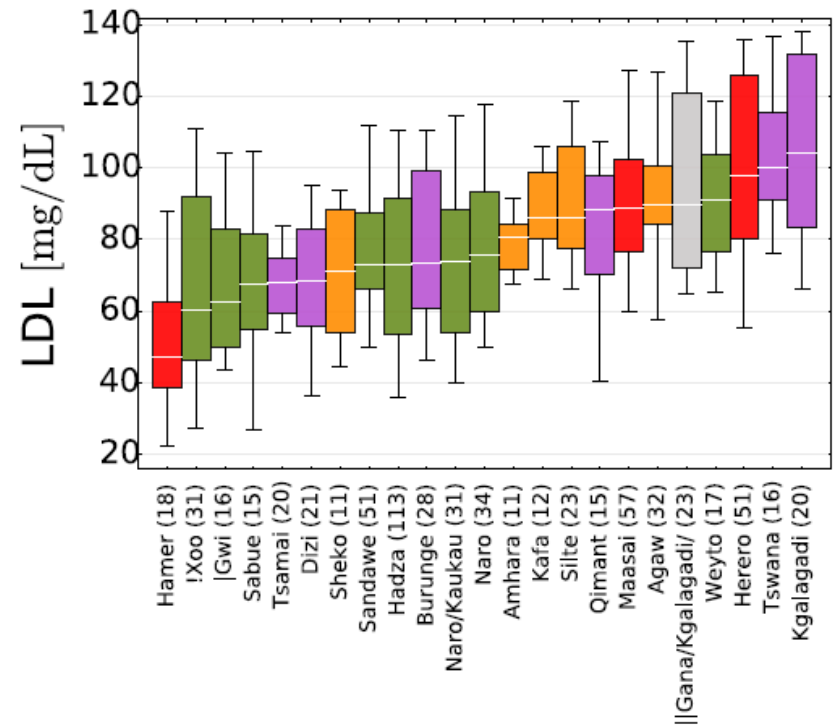
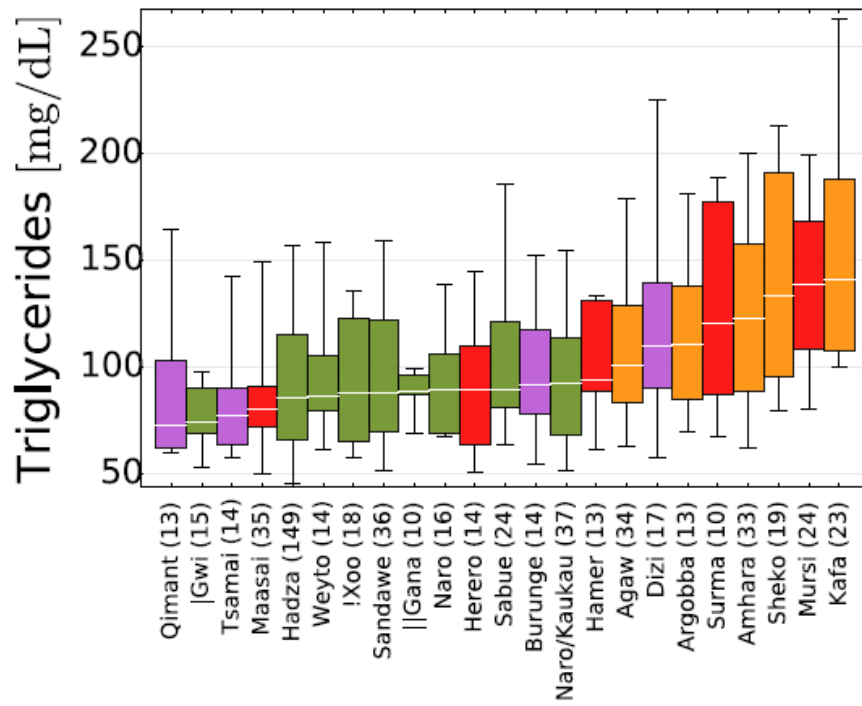
# Anthropometric trait variation in Africa



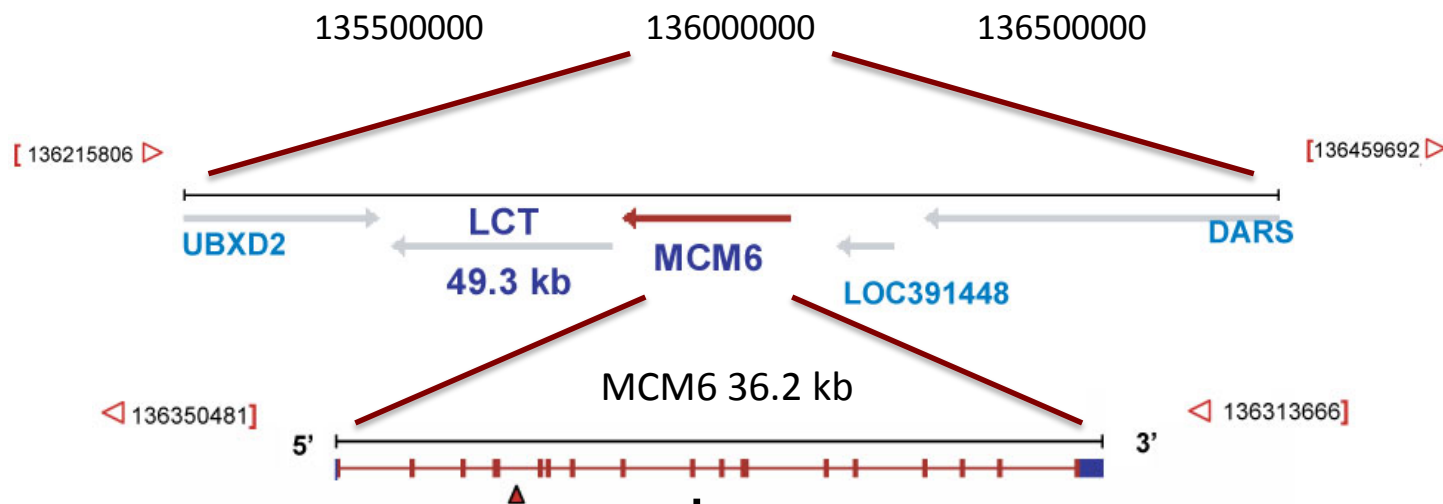
# Cardiovascular trait variation in Africa



# Lipid biomarker variation in Africa



# Identification of novel genetic variants associated with lactose tolerance and lactase gene expression in African pastoralist populations



...**C/G**TAAGTTACCA.....  
-14010 bp

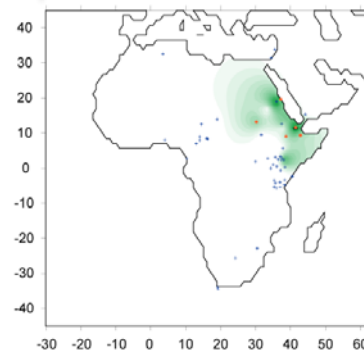
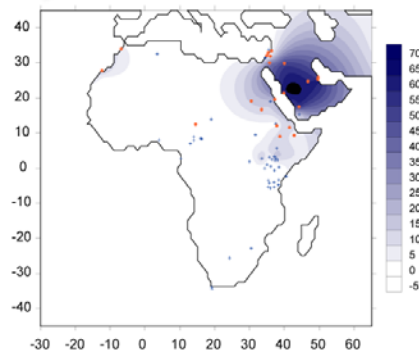
**C -14010**

...AAGATAA**T/G**GTAG**C/T****C/G**TG....  
-13915 bp -13910 bp -13907 bp

**G -13915**

**C -13907**

Intron 13



Tishkoff et al.,  
*Nature Genetics*,  
2007

Ranciaro et al.,  
*AJHG*, 2014

# Problems with Racial Classifications

**Historically, biological classification of races has been associated with:**

- **hierarchical ranking of races**
- **biological determinism**
- **Eugenics**
- **justification for genocide (e.g. the Nazi-led holocaust)**
- **colonialism, slavery, and other social inequities**



# Problems with Racial Classifications

- **Problem with using race as an identifier is the lack of a clear definition of race**
- **Historically, race has been classified based on both socio-cultural and biological characteristics**

**Race does not correlate with patterns of population structure inferred from genetic data**

# Implications for Medicine

- **Ethnic groups differ for risk to disease.**
- **People whose ancestors lived in distinct environments have been subject to different selection forces and have differing demographic histories.**
- **Some diseases may be influenced by geographically restricted susceptibility alleles.**
- **Information about **individual ancestry** could provide important medical information for diagnosis and treatment.**

# Implications for Medicine

- **However...**one must be wary of **racial profiling** and ignorance of the continuous nature of genetic variation and high levels of admixture in modern populations, which can result in misclassification and mis-diagnosis.
- Cannot make generalizations based on continental region of origin because there can be tremendous variation amongst populations within a region (i.e. Africa).
- Populations/ethnic groups differ in prevalence of disease due to both genetic and **environmental factors** and a key issue will be to disentangle these factors and to study their interaction.

# Implications for Medicine

- The goal should be **personalized medicine**—treating for the specific etiology in the individual patient.
- Information about “Race” could be important if trying to distinguish socio-cultural and environmental risk factors
- However, for many studies race will be an insufficient identifier and **detailed information about ethnicity, geographic origin, language, religion and/or culture will be important.**
- **“Ancestry” should supplant “race”** in discussions where the group identity of the patient is at issue.

# Thanks



## Tishkoff lab, University of Pennsylvania

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## Illumina 5 M GWAS study

Stephen Chanock/Meredith Yeager (NCI)



## African Collaborators

Sabah Omar / Muntaser Ibrahim / Thomas Nyambo / Godfrey Lema / Charles Wambebe/ Ogabara Doumbo / Mohamadu Thera/Gurja Belay/Dawit WoldeSabah Omar / Muntaser Ibrahim / Thomas Nyambo / Godfrey Lema / Charles Wambebe/ Ogabara Doumbo / Mohamadu Thera/Gurja Belay/Dawit Wolde



Population Studies Center at Penn