Session 1: Increasing Ancestral Diversity in Emerging Precision Medicine for Neurological and Psychiatric Disorders

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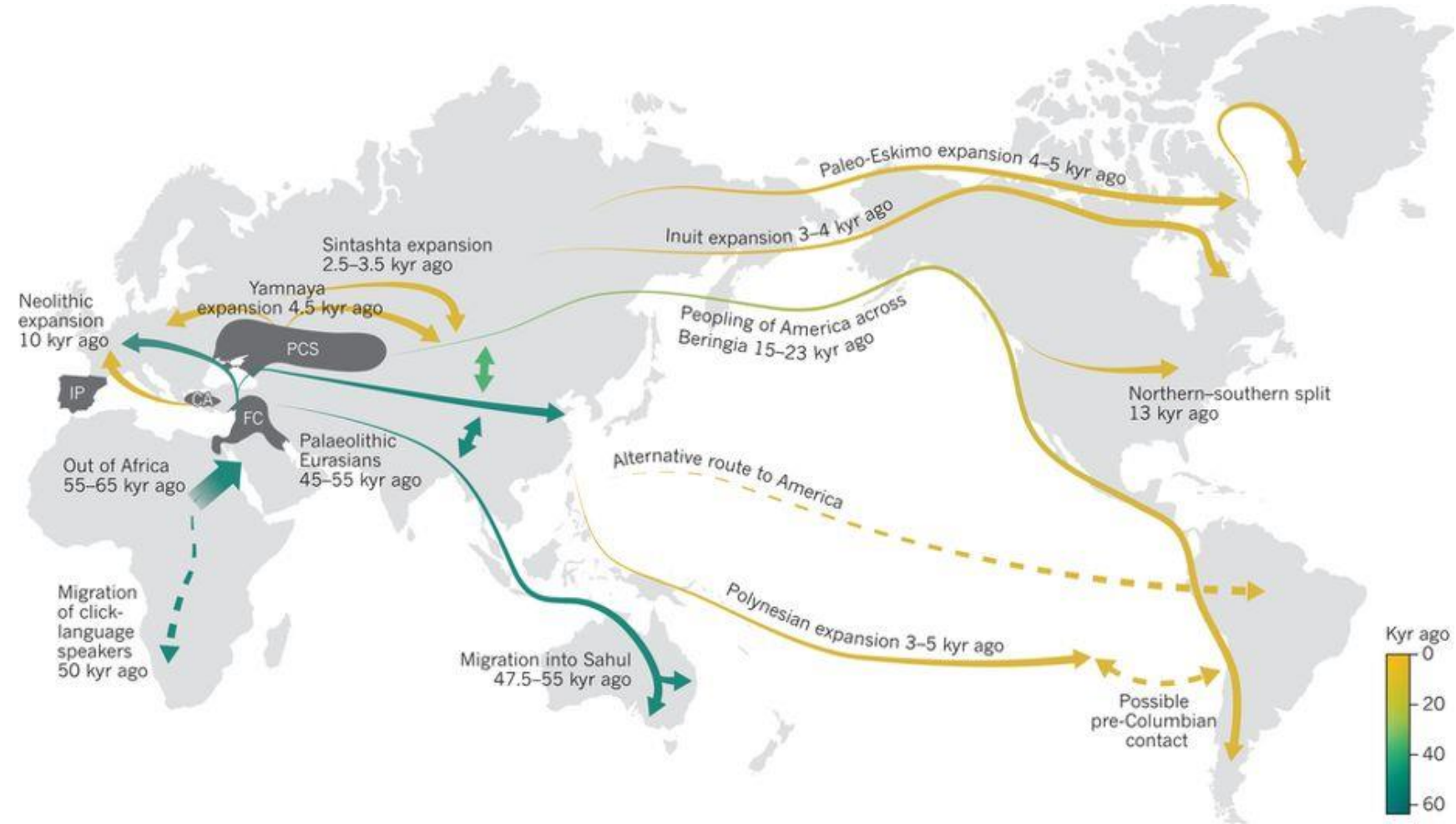
Penn Center for Global Genomics & Health Equity
Inclusion • Innovation • Impact

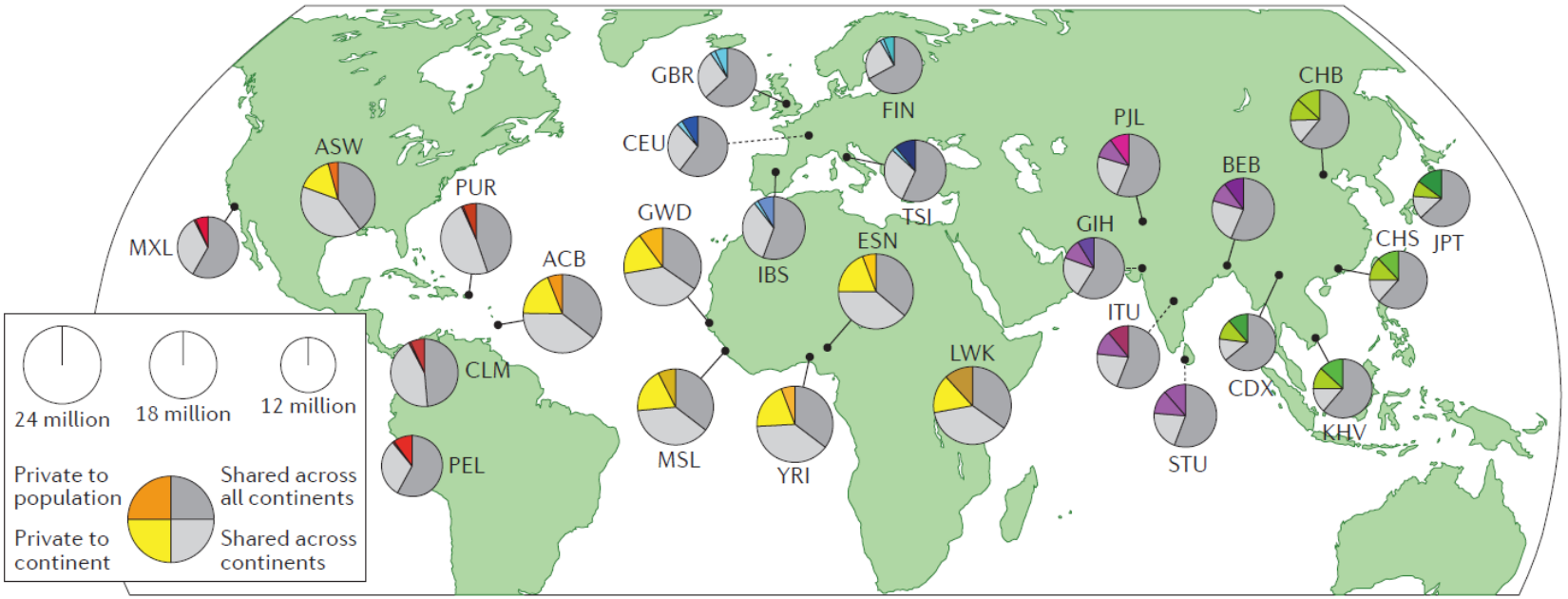
Penn Arts & Sciences

Major Migration Routes



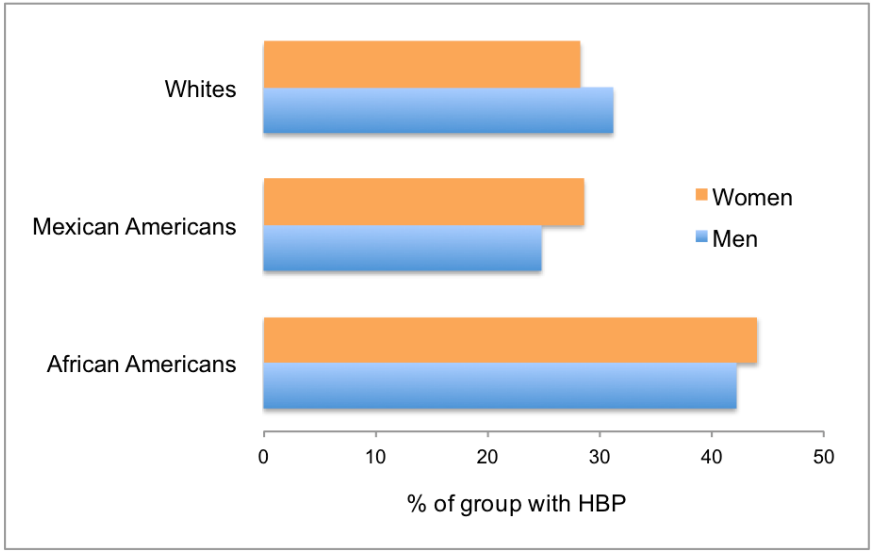
Nielsen et al. 2017

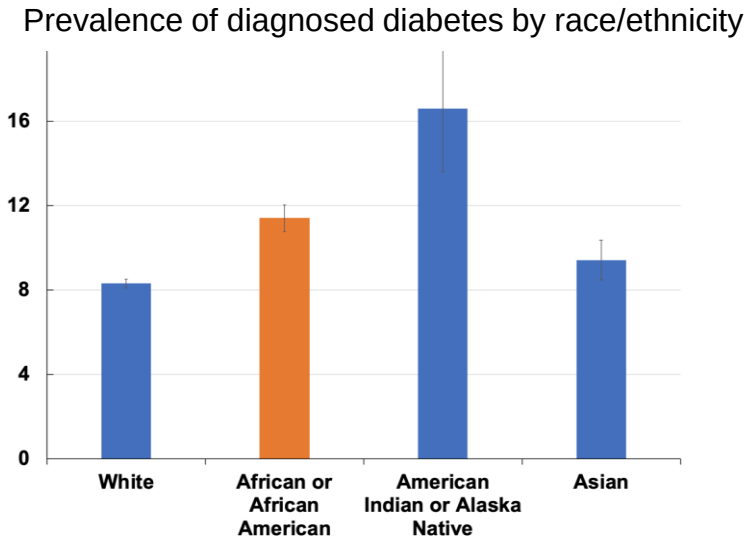
Distribution of “private” genetic variation



Hindorff et al, *Nature Review Genetics*, 2017

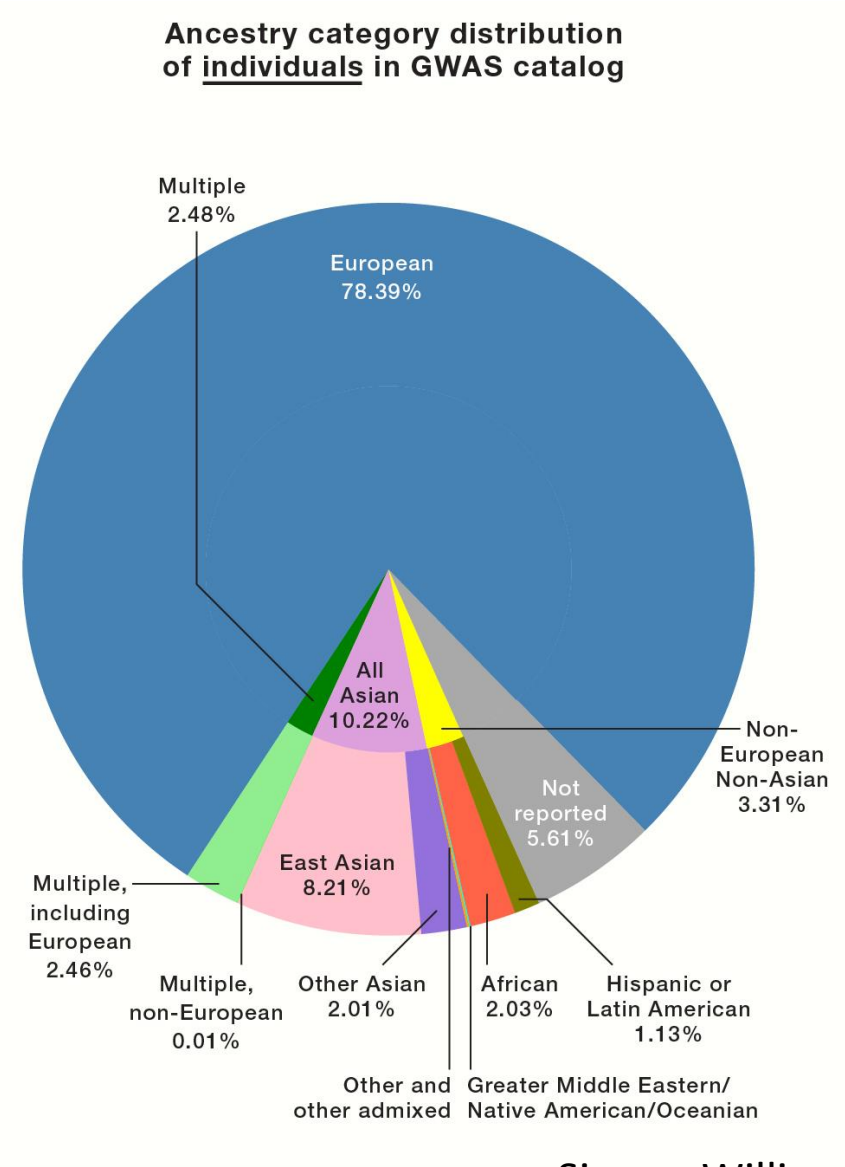
Health Disparities for Hypertension and Diabetes





Center for Disease Control

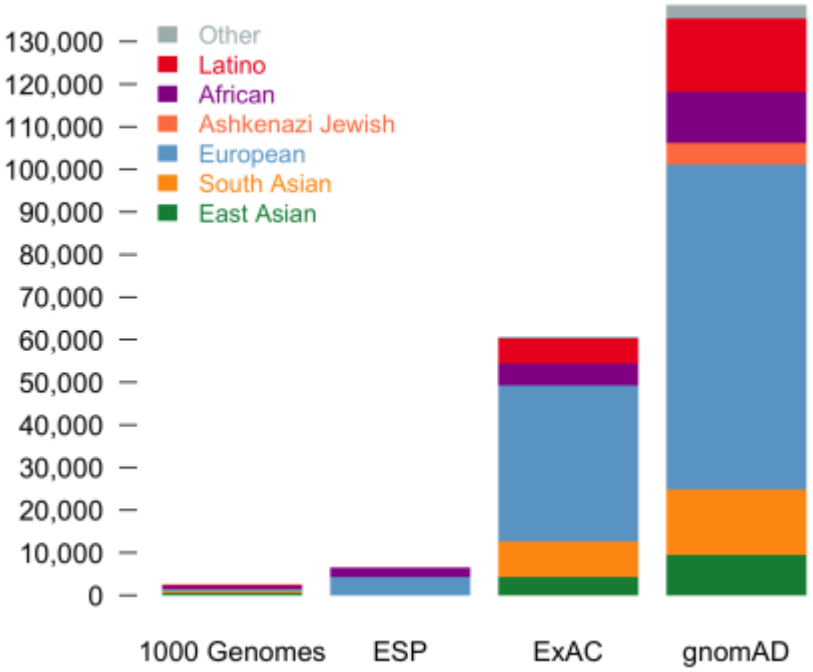
European Bias in Genome Wide Association Studies



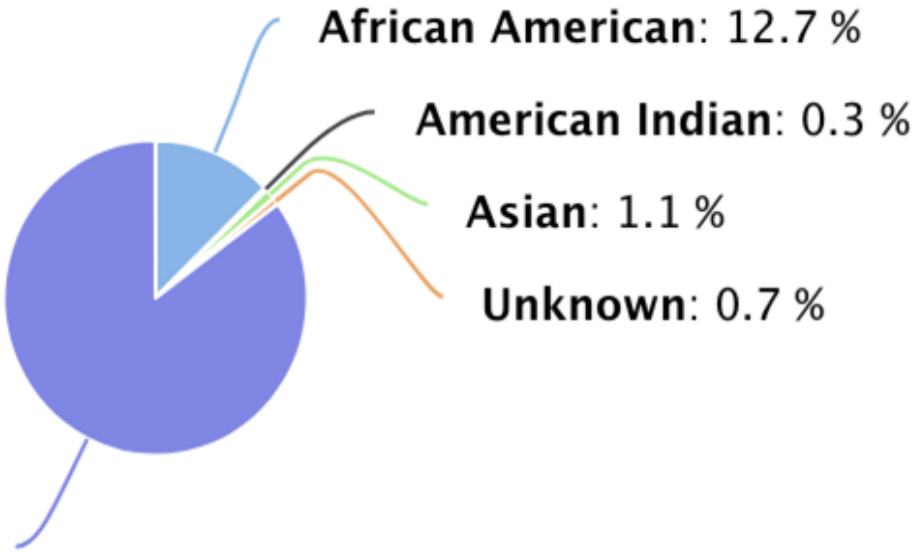
Sirugo, Williams, and Tishkoff, Cell, 2019

Lack of ethnic diversity in public genomic databases

gnomAD



GTEx



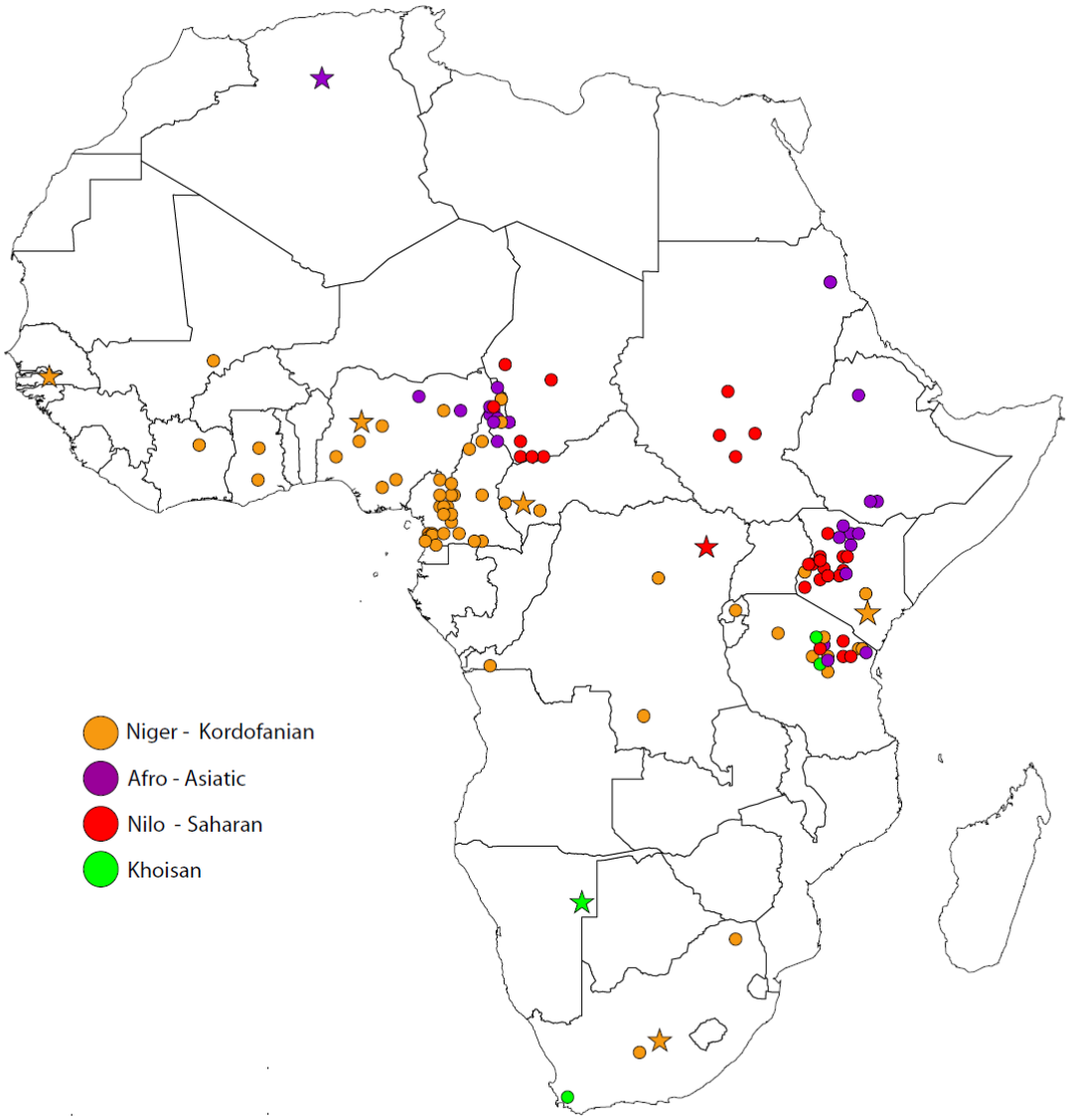
https://www.gtexportal.org/home/tissueSummaryPage

Problems resulting from lack of ethnic diversity in human genomics research

- Impedes our ability to fully understand the genetic factors influencing human disease and exacerbates health inequalities.
- Our ability to translate genetic research into clinical practice or public health policy may be incomplete, or worse, mistaken.
- May result in inaccurate assessment of pathogenic variants in clinical genomic studies.
- Attempts to use estimates of genetic risk (e.g. polygenic risk scores) from European-based studies in non-Europeans may result in inaccurate assessment of risk and lack of appropriate interventions.

The Genetic Structure and History of Africans and African Americans

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

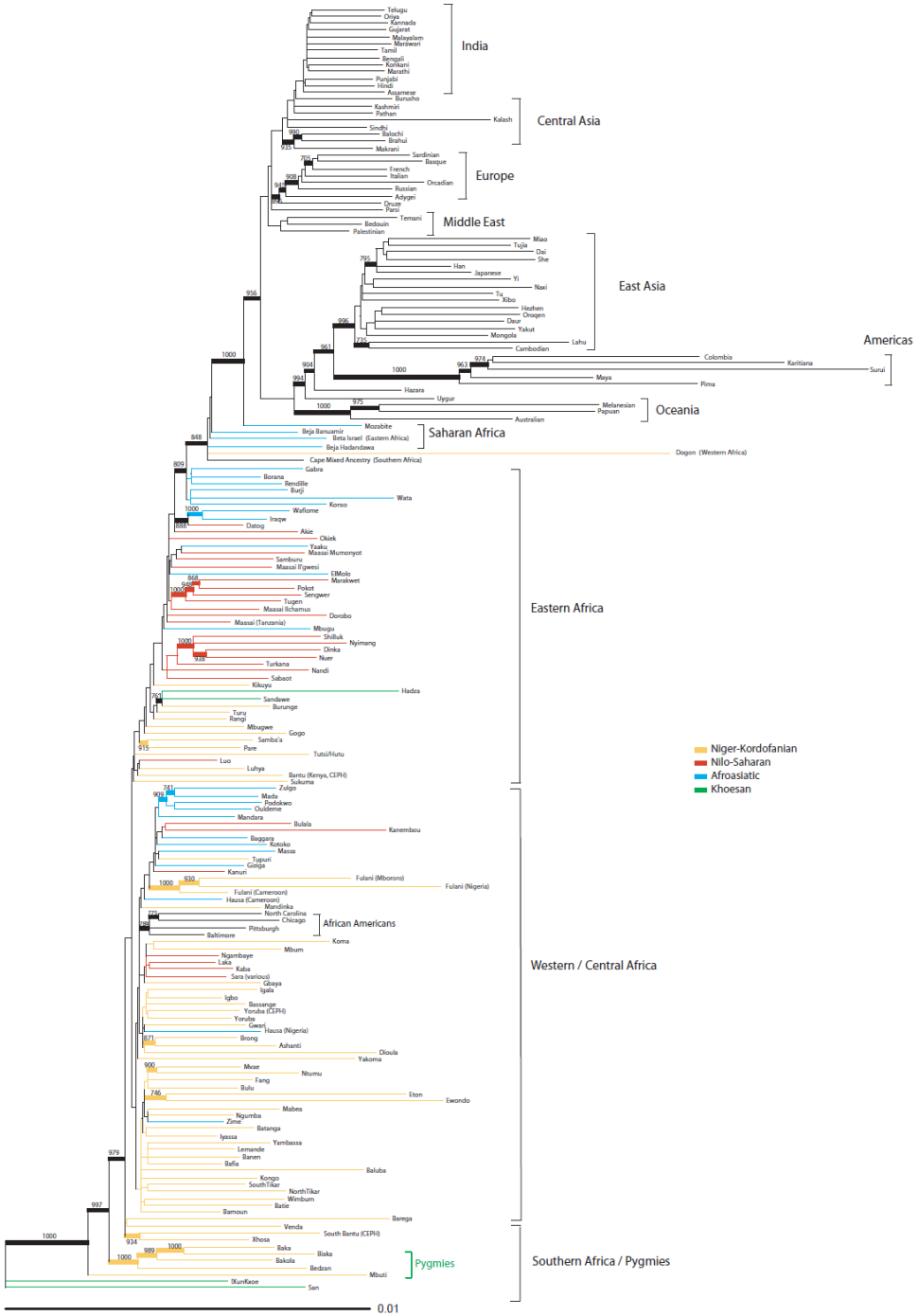


1165 Microsatellite and In/Del Polymorphisms

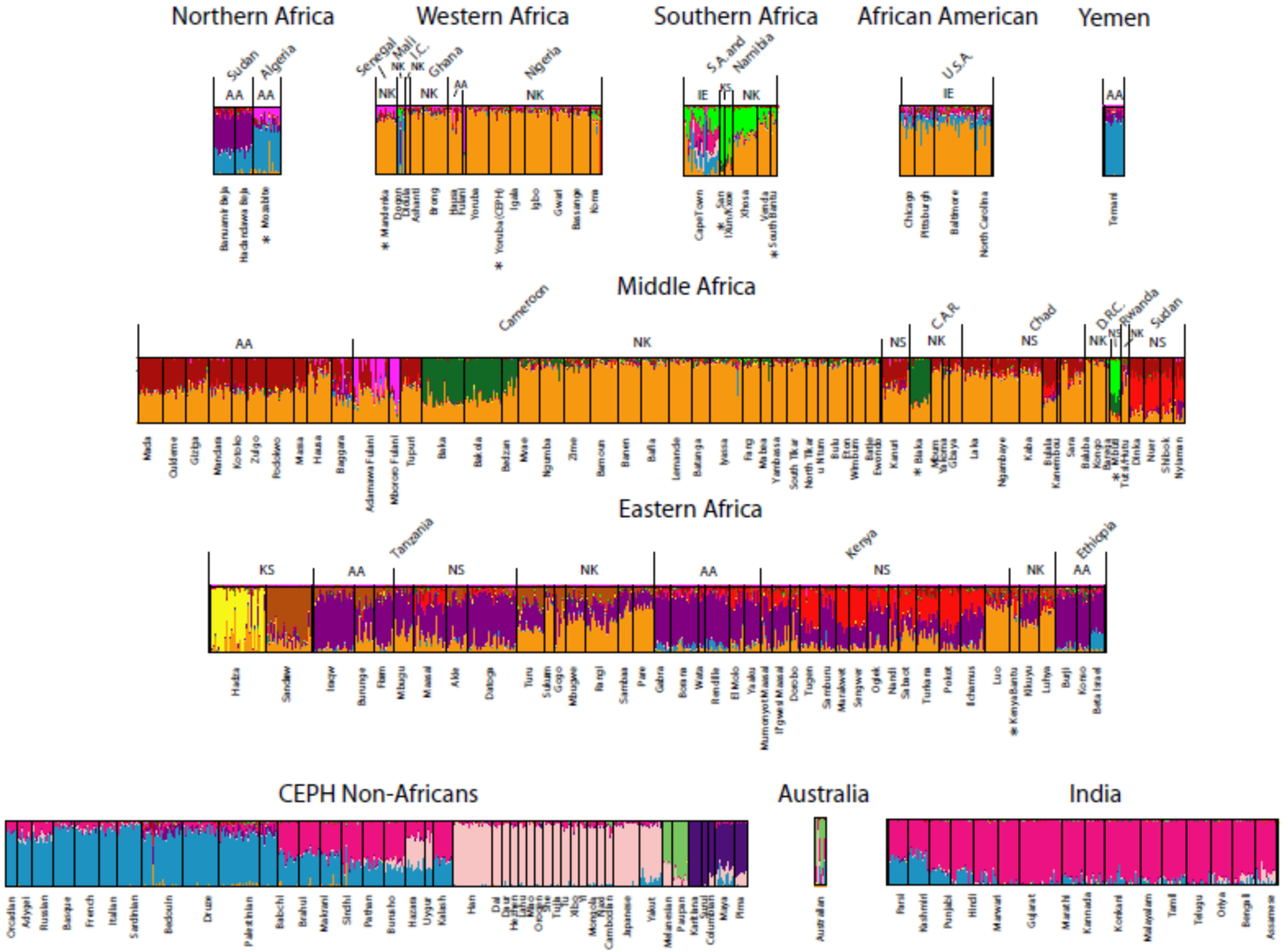
Genotyped in >2,500 Africans from 121 ethnic populations

98 African Americans from four regions in the US

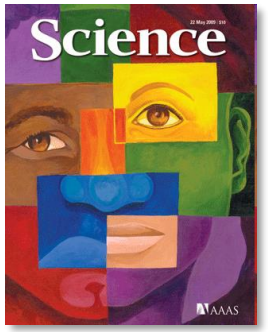
>1,500 comparative non-African individuals


India
Telugu
Oriya
Kannada
Gujarat
Malayalam
Marawari
Tamil
Bengali
Konkani
Marathi
Punjabi
Hindi
Asamese
Burusho
Central Asia
Kashmiri
Pathan
Kalash
Sindhi
Balochi
Brahui
Makrani
Europe
Sardinian
Basque
French
Italian
Orcadian
Russian
Adygei
Druze
Parsi
Middle East
Temani
Bedouin
Palestinian
East Asia
Miao
Tujia
Dai
She
Han
Japanese
Yi
Naxi
Tu
Xibo
Hezhen
Oroqen
Daur
Yakut
Mongola
Lahu
Cambodian
Americas
Colombia
Karitiana
Surui
Maya
Pima
Oceania
Melanesian
Papuan
Australian
Saharan Africa
Mozabite
Beja Banuamir
Beta Israel (Eastern Africa)
Beja Hadandowa
Cape Mixed Ancestry (Southern Africa)
Dogon (Western Africa)
Eastern Africa
Gabra
Borana
Rendille
Burji
Wata
Konso
Wafiome
Iraqw
Datog
Akie
Okiek
Yaaku
Maasai Mumonyot
Samburu
Maasai Ilgwesi
Elmolo
Marakwet
Pokot
Sengwer
Tugen
Maasai Ilchamus
Dorobo
Maasai (Tanzania)
Mbugu
Shilluk
Nyimang
Dinka
Nuer
Turkana
Nandi
Sabaot
Kikuyu
Hadza
Sandawe
Burunge
Turu
Rangi
Mbugwe
Gogo
Samba'a
Pare
Tutsi/Hutu
Luo
Luhya
Bantu (Kenya, CEPH)
Sukuma
Zulgo
Mada
Podokwo
Ouldeme
Mandara
Bulala
Kanembou
Baggara
Kotoko
Massa
Tupuri
Gisiga
Kanuri
Fulani (Mbororo)
Fulani (Nigeria)
Fulani (Cameroon)
Hausa (Cameroon)
Mandinka
North Carolina
Chicago
Pittsburgh
Baltimore
African Americans
Koma
Mbum
Ngambaye
Laka
Kaba
Sara (various)
Gbaya
Ipala
Igbo
Bassange
Yoruba (CEPH)
Yoruba
Gwari
Hausa (Nigeria)
Brong
Ashanti
Dioula
Yakoma
Mvae
Ntumu
Fang
Bulu
Eton
Ewondo
Mabea
Ngumba
Zime
Batanga
Iyassa
Yambassa
Lemande
Banen
Bafia
Baluba
Kongo
SouthTikar
NorthTikar
Wimbum
Batie
Bamoun
Barega
Venda
South Bantu (CEPH)
Xhosa
Baka
Biaka
Bakola
Bedzan
Mbuti
Pygmies
!KunKwe
San
Western / Central Africa
Southern Africa / Pygmies
Niger-Kordofanian
Nilo-Saharan
Afroasiatic
Khoesan
0.01

Global Patterns of Substructure and Ancestry

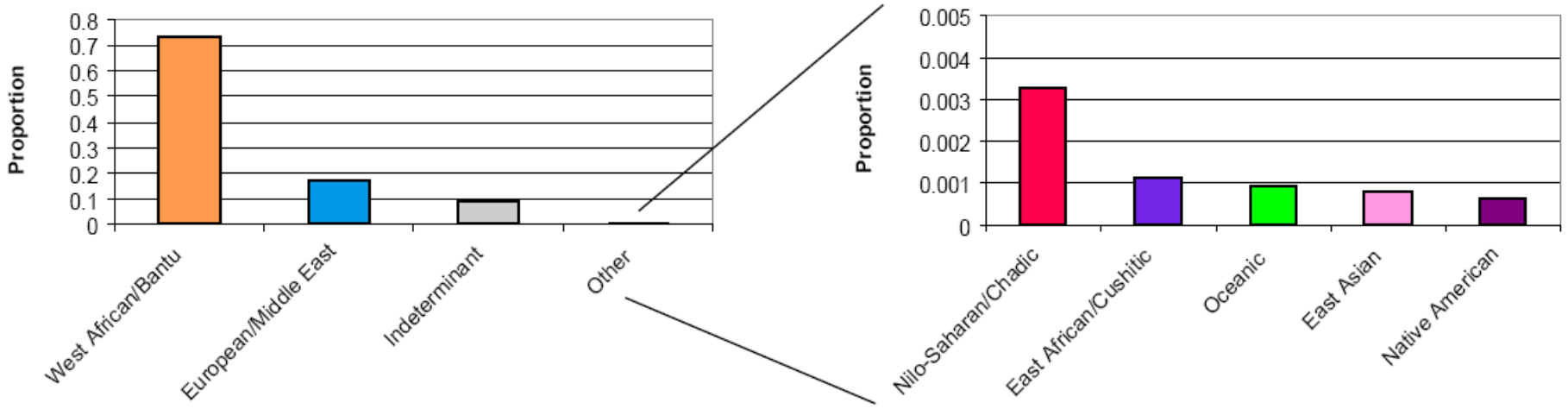


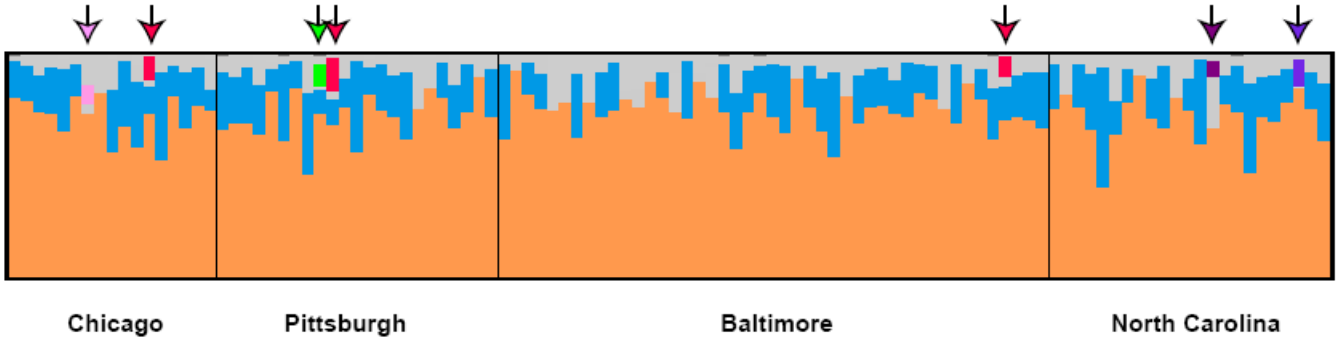
Genetic Variation and Structure in Africa



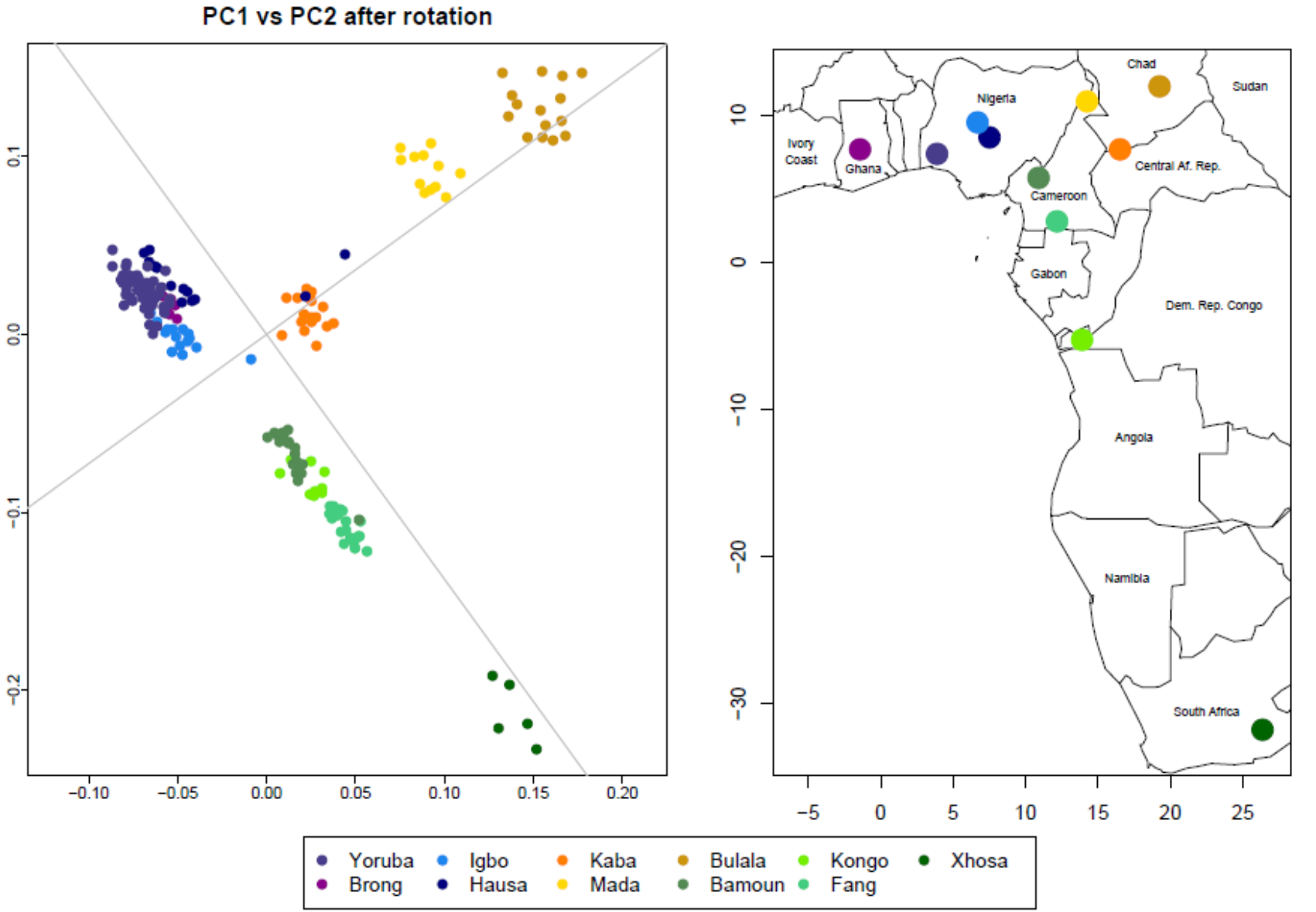
Tishkoff, *et al*
Science 2009

African American Ancestry





Genetic variation correlates with geography

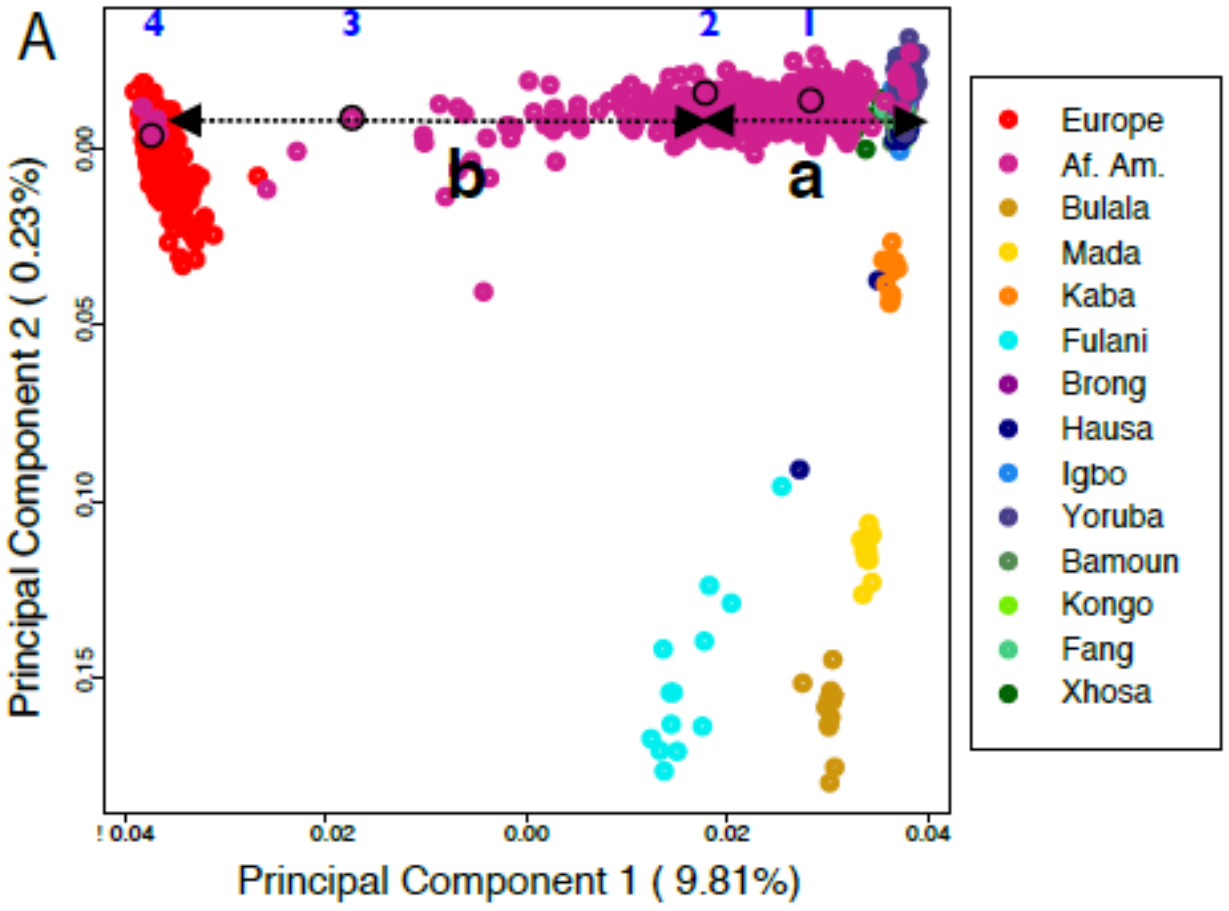


Bryc et al. PNAS, 2010

PCA-based admixture estimation

African Ancestry =

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

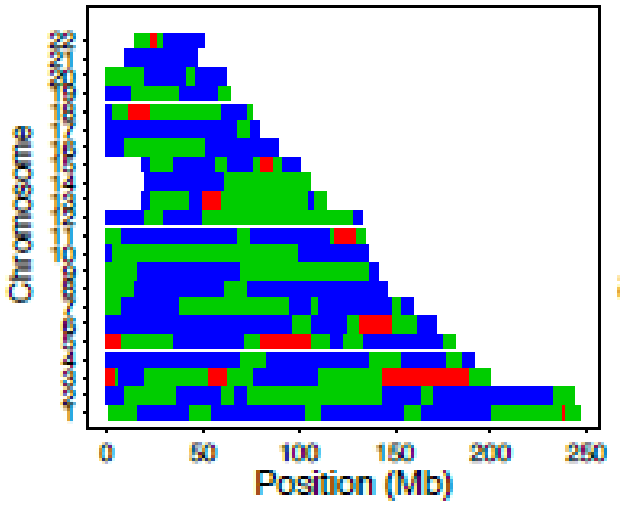


a and b are the chord distances from the European and African centroids

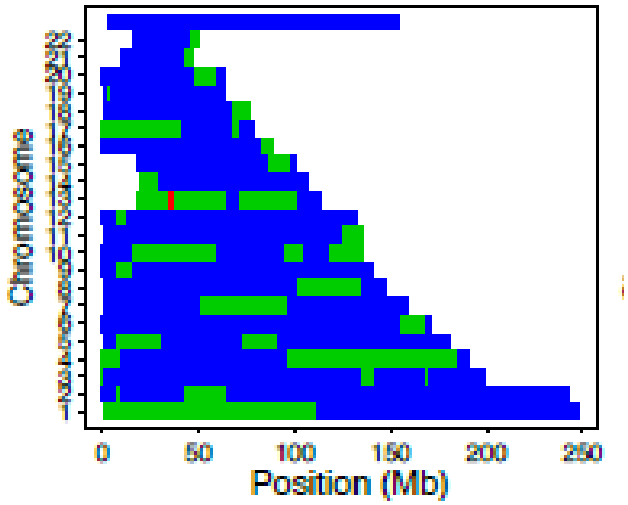
Local Genomic Ancestry in African Americans

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

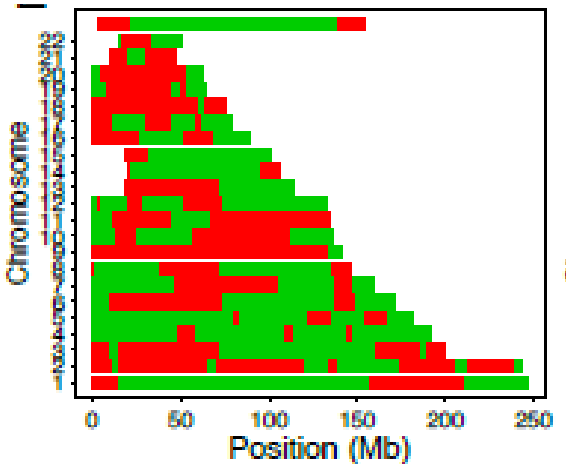
Representative African American



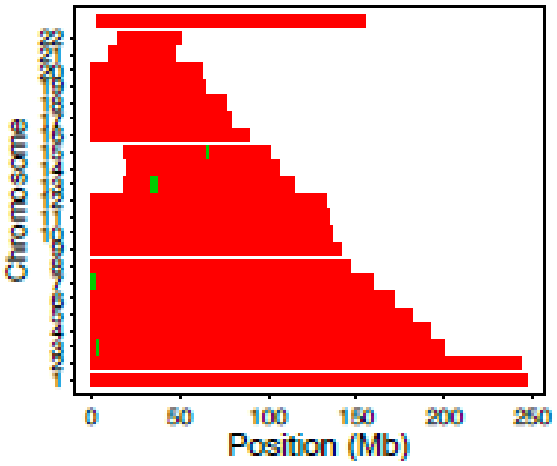
Recent admixture



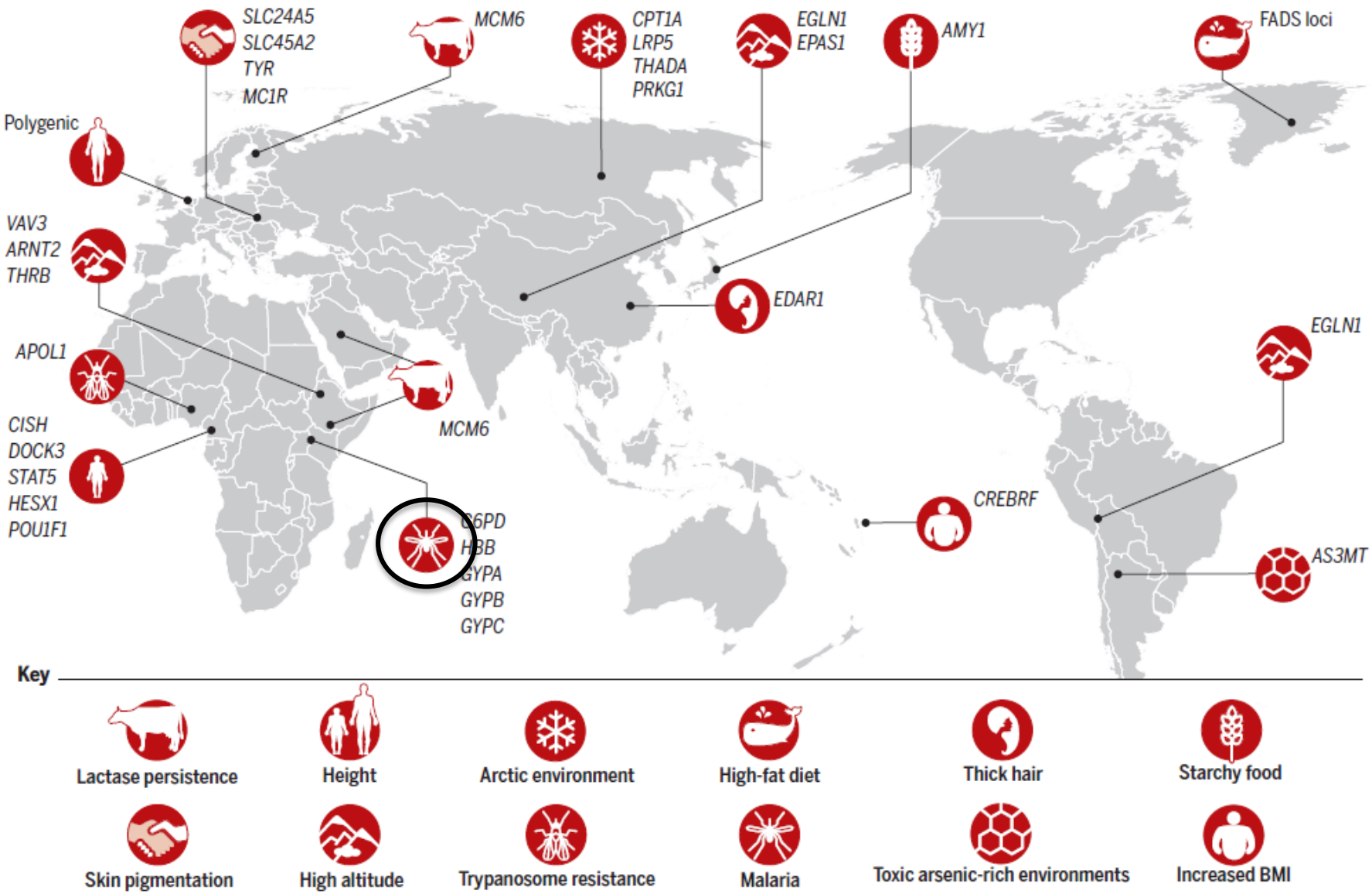
Recent European ancestry



High degree of European ancestry



Genetic adaptations to diverse environments

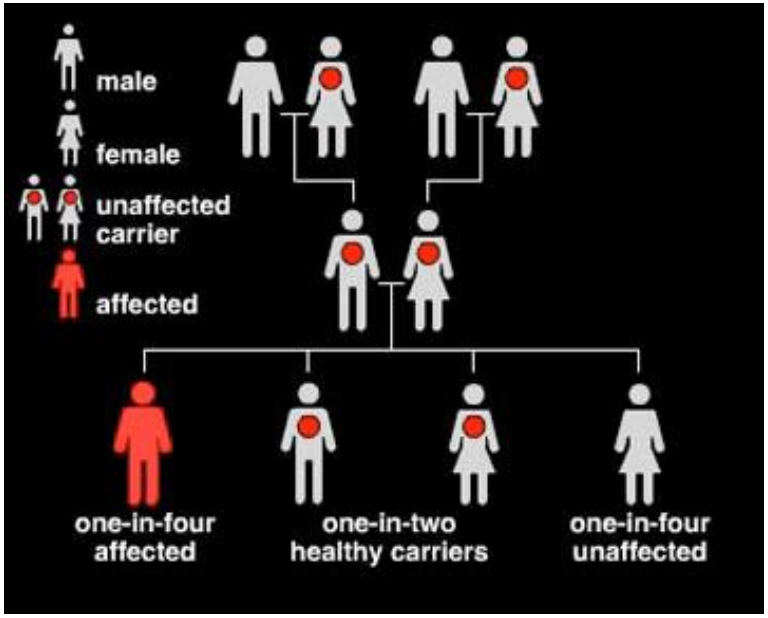


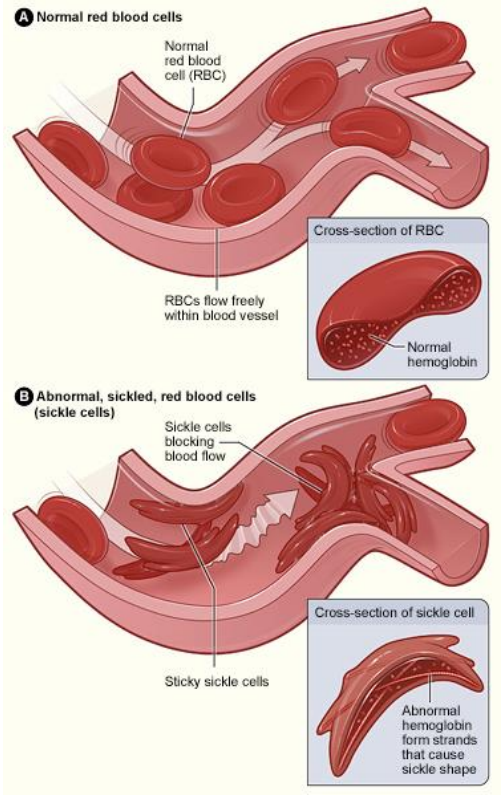
Fan et al *Science* 2016

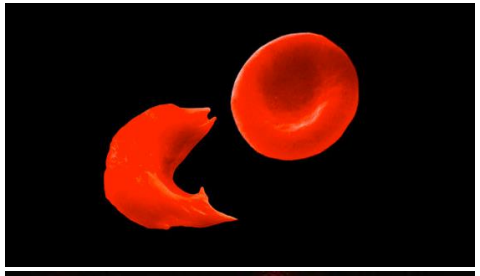
Genetic Basis of Sickle Cell Disease

Anthony Allison

Homozygosity is fatal without medical intervention. Heterozygotes may be anemic, but symptoms are variable and often slight.







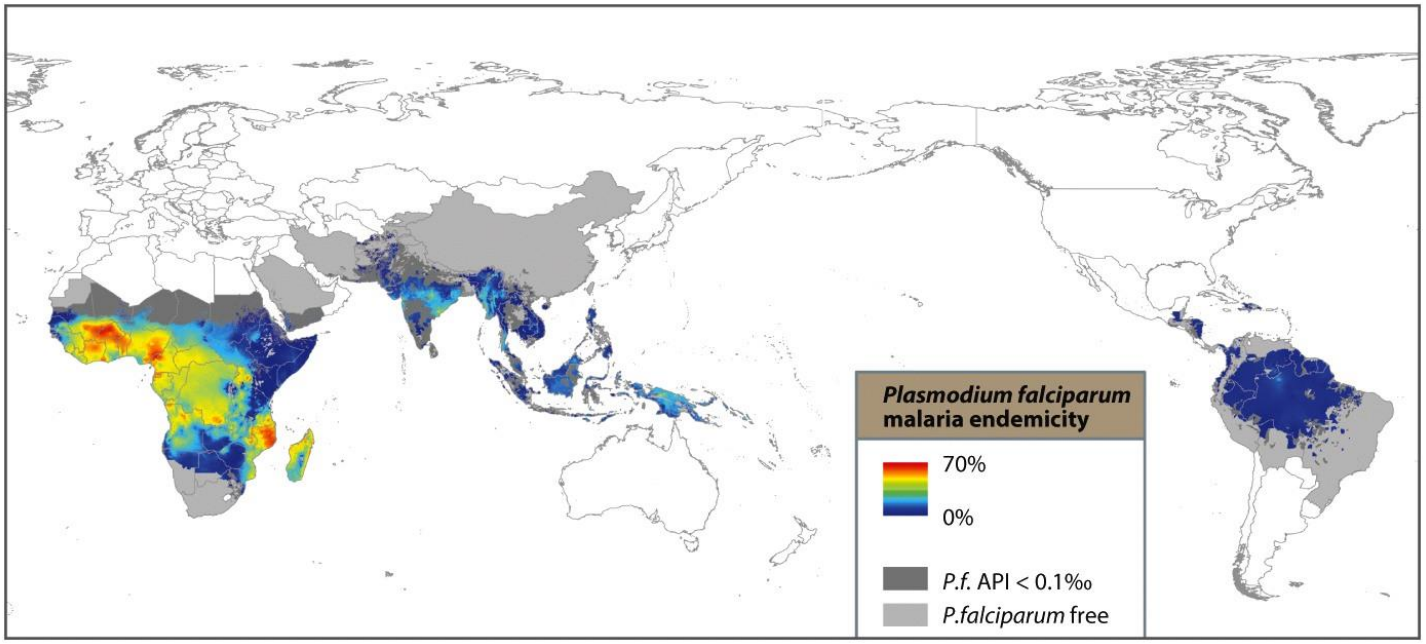


Figure 16.6a Human Evolutionary Genetics, 2nd ed. (© Garland Science 2014)

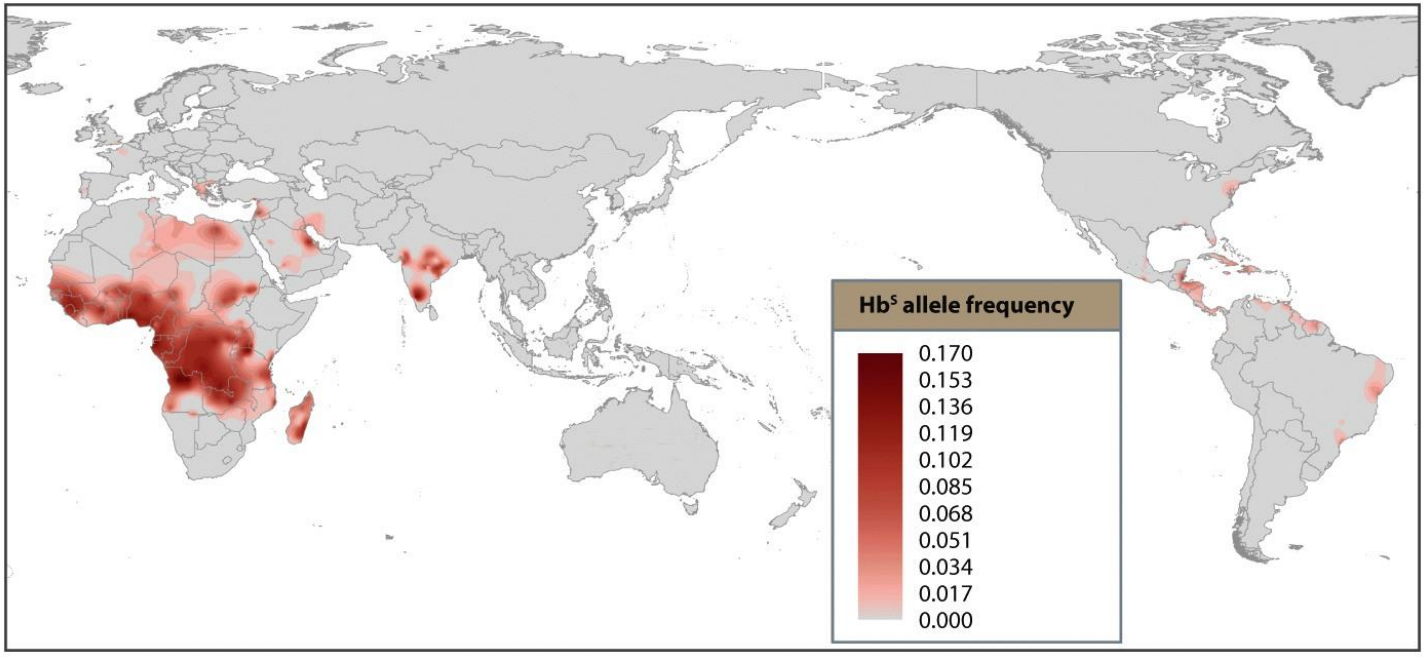
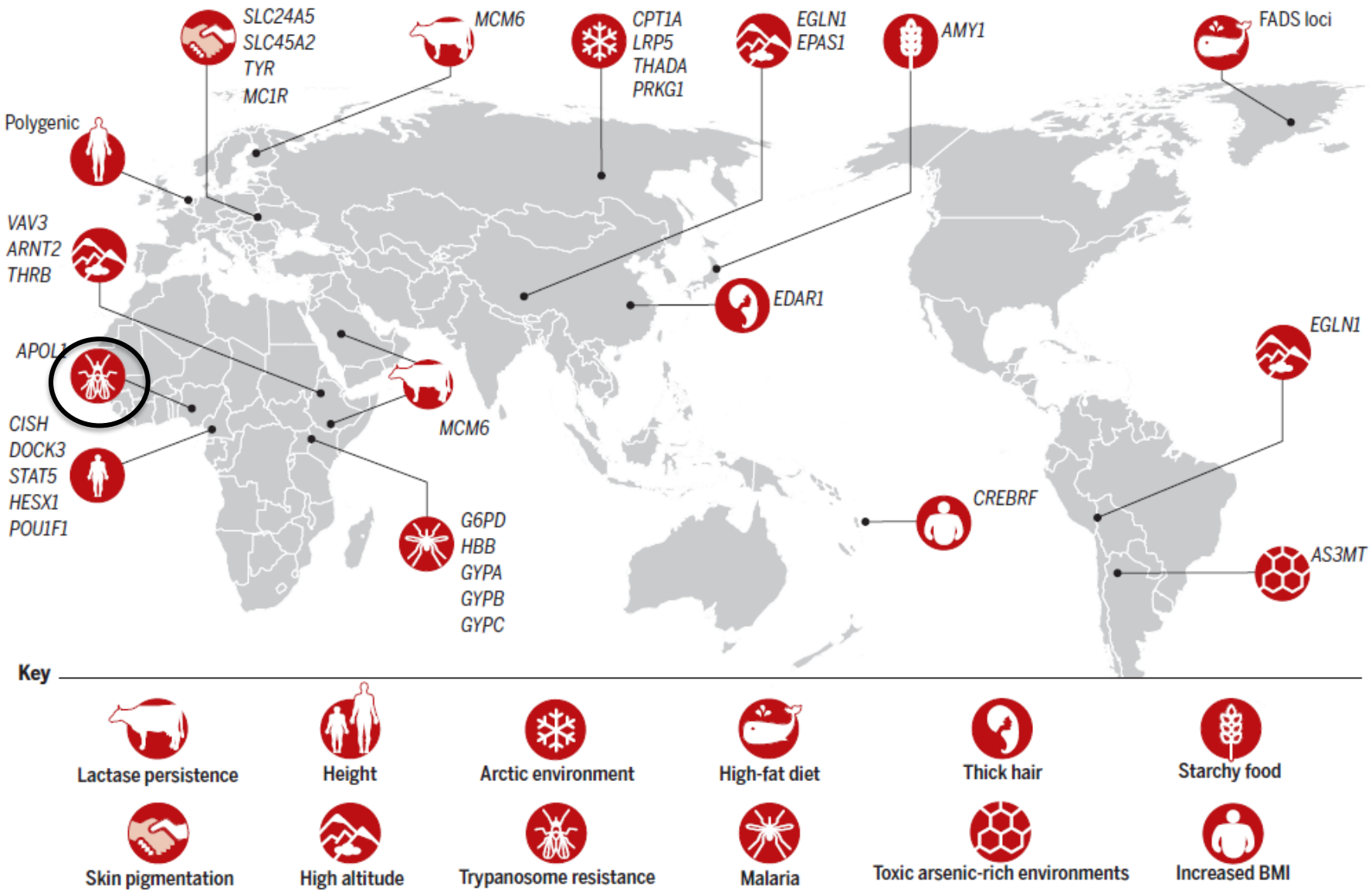


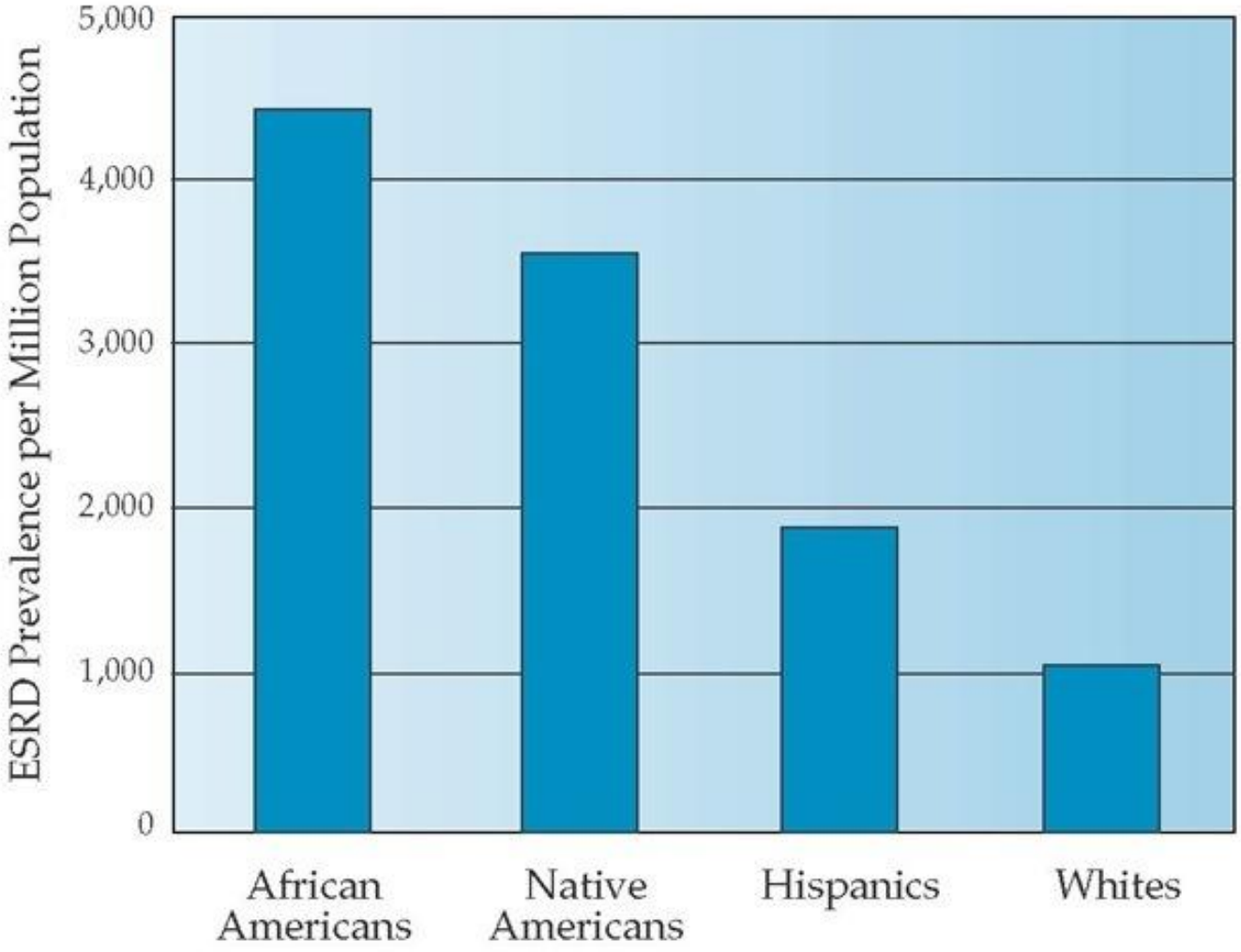
Figure 16.6b Human Evolutionary Genetics, 2nd ed. (© Garland Science 2014)

Genetic adaptations to diverse environments



Fan et al *Science* 2016

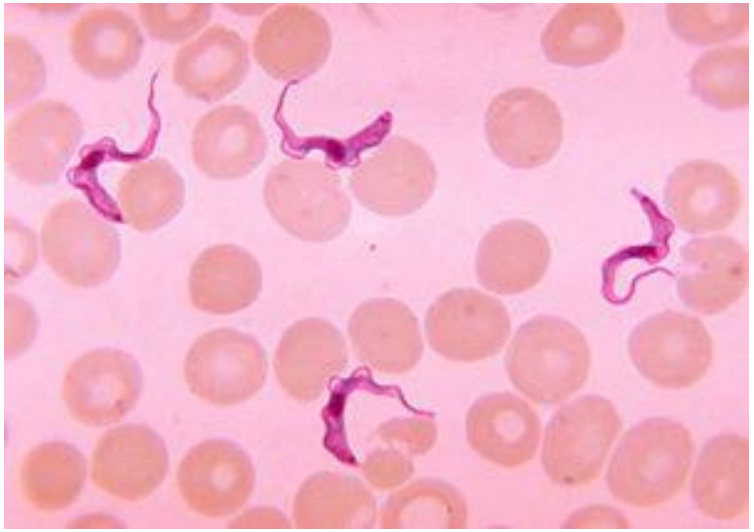
APOL1 is associated with risk for kidney disease



APOL1 variants associated with a 7 – 10 X increased risk of disease

http://what-when-how.com/acp-medicine/chronic-renal-failure-and-dialysis-part-1/

Human African Trypanosomiasis (HAT)



Caused by *Trypanosoma brucei*

Questions

- What are the biggest barriers for including diverse populations in human genomics research?
- What are some of the ethical concerns when including minority populations in human genomics research?
- How do we best build global capacity for human genomics research and ensure benefit sharing?
- Should we be using “race” or “ancestry” in biomedical research and in the clinic?
- How can we develop polygenic risk scores that are accurate for individuals of diverse ancestry?
- How can we distinguish the role of genetics and environment on disease risk?