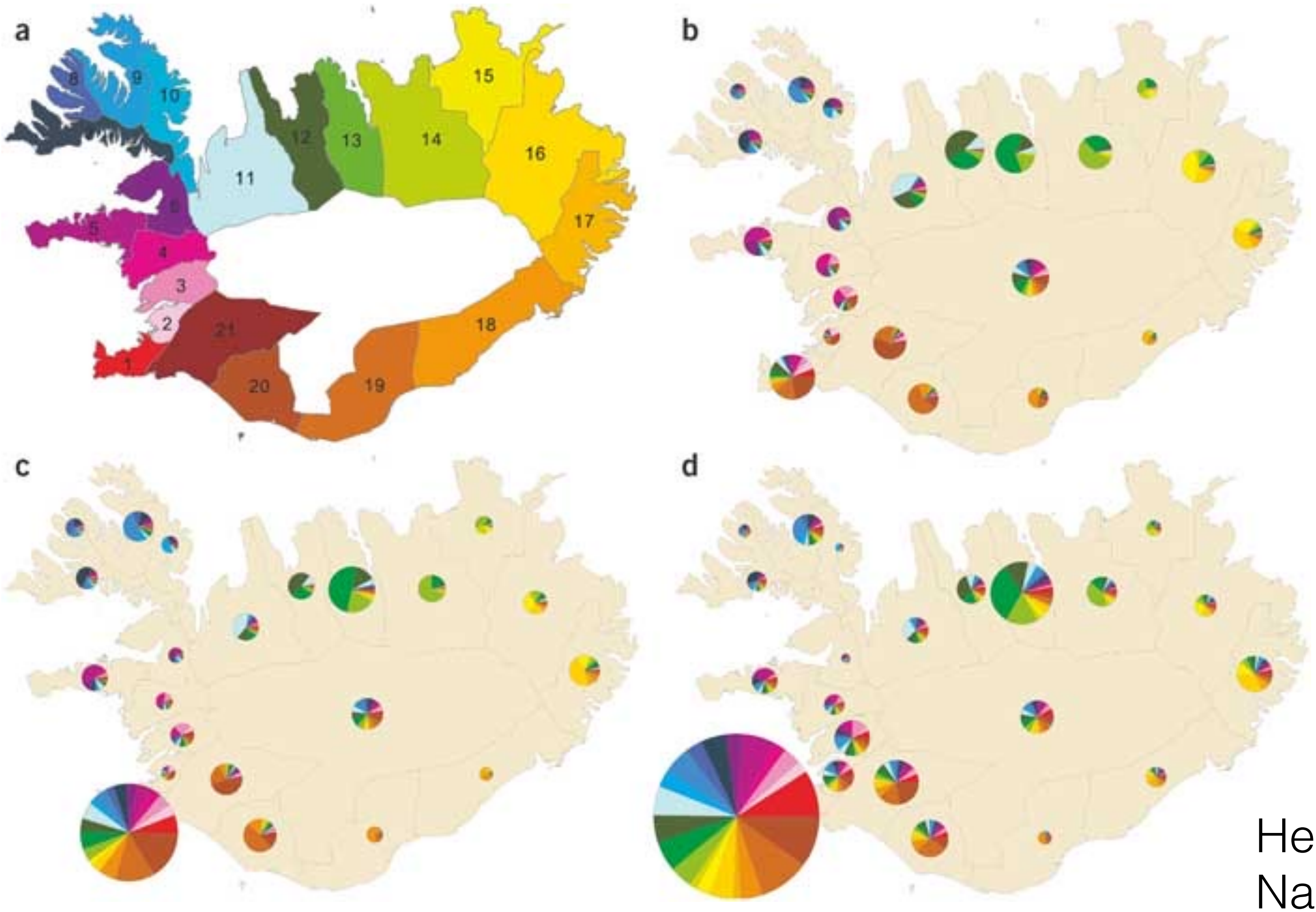
Cryptic Relatedness and fine-scale population structure

Learning objectives

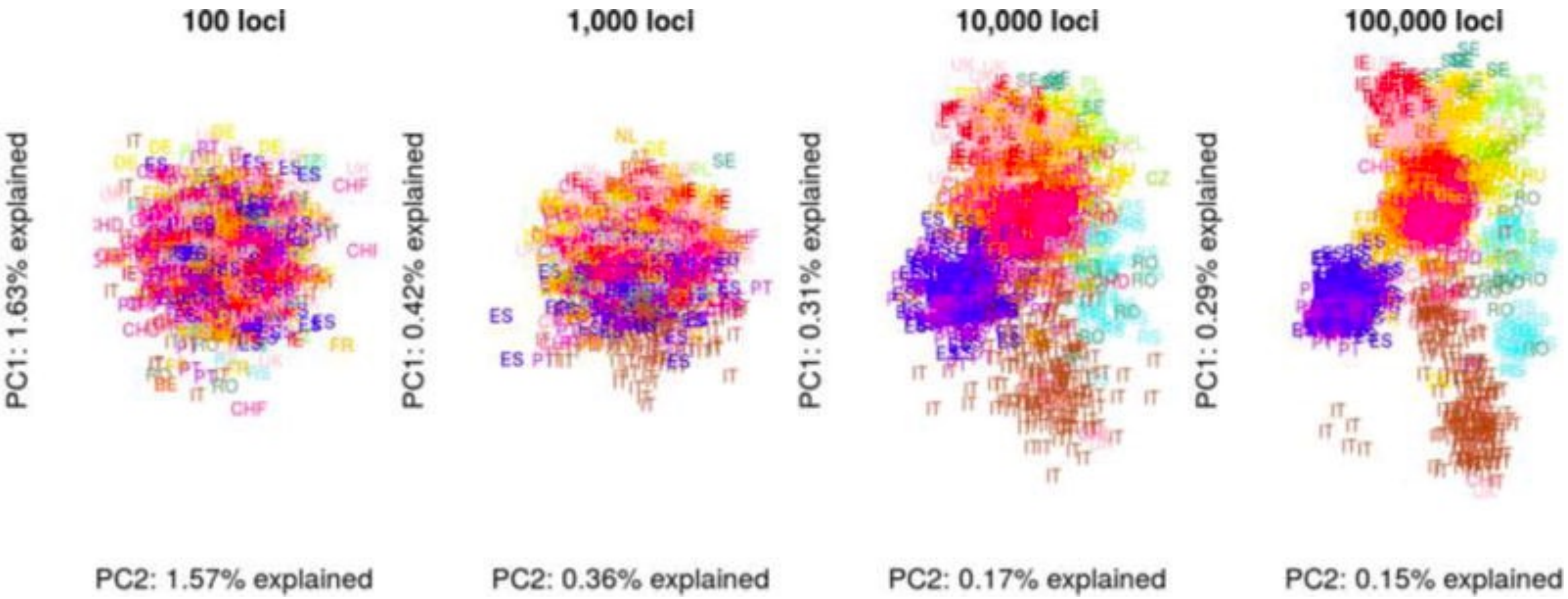
- Define fine-scale population structure and cryptic relatedness
- How is it identified
  - Identity-by-descent
  - Rare variation
  - Estimated Effective Migration Surfaces
- Why it can be important for association analyses, especially of rare variants.

Cryptic Population Structure



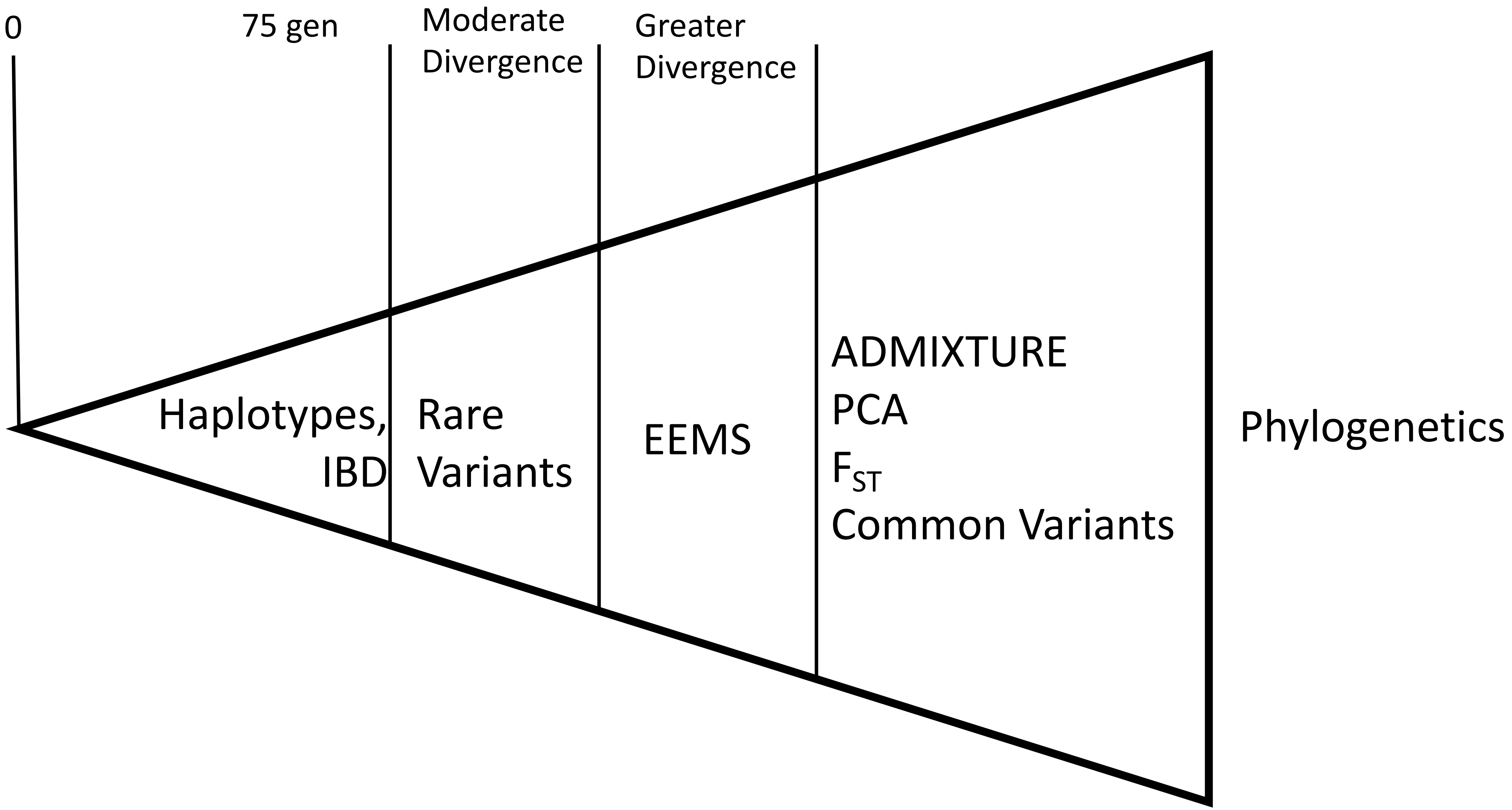
Helgason et al. (2004)
Nature Genet.

“A large number of loci is required to reveal fine-scale population structure using PCA”



Novembre & Peter (2017) Curr Opin Genet Dev.

Demographic Inference Time Frames



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75 gen

Moderate Divergence

Greater Divergence

Haplotypes, IBD

Rare Variants

EEMS

ADMIXTURE

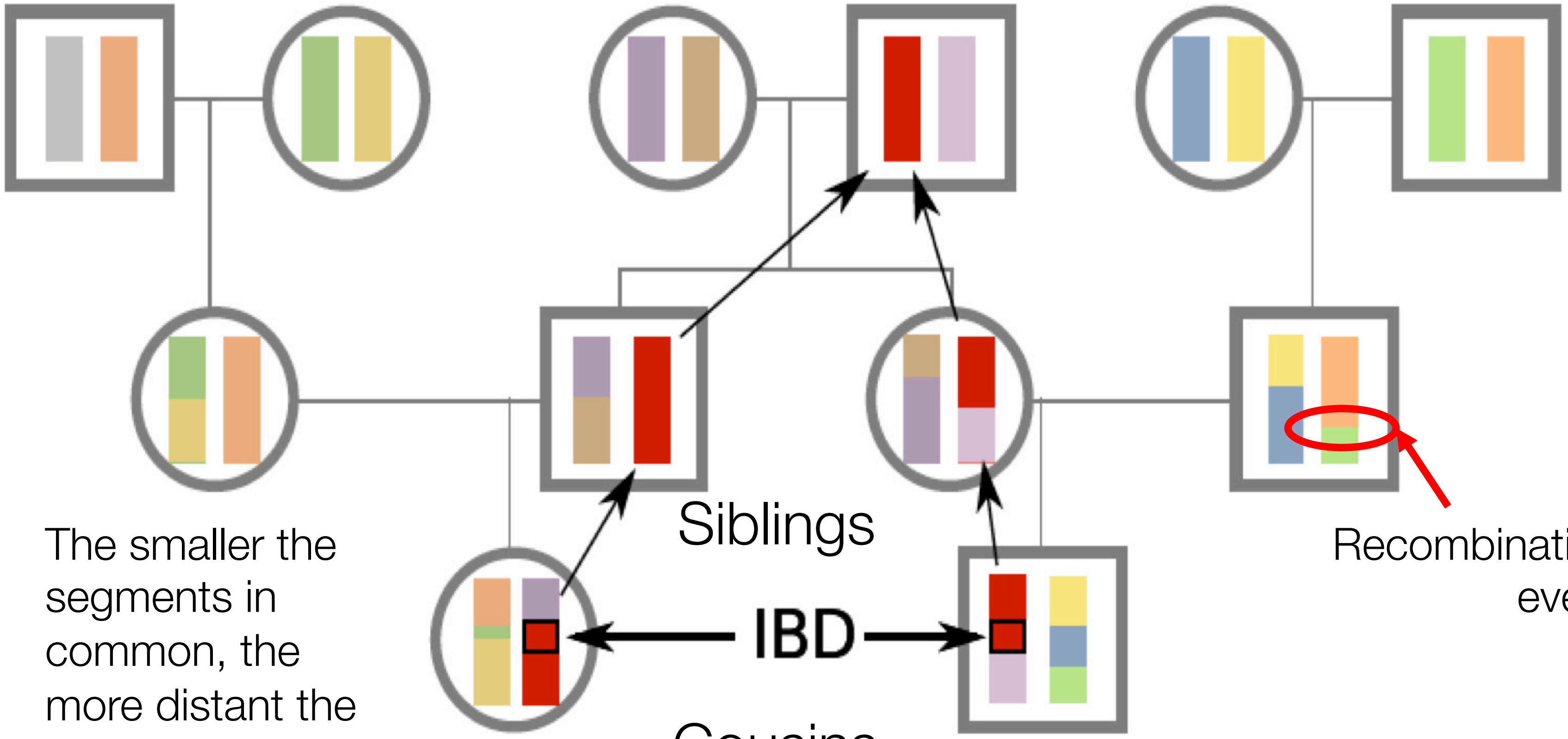
PCA

F_{ST}

Common Variants

Phylogenetics

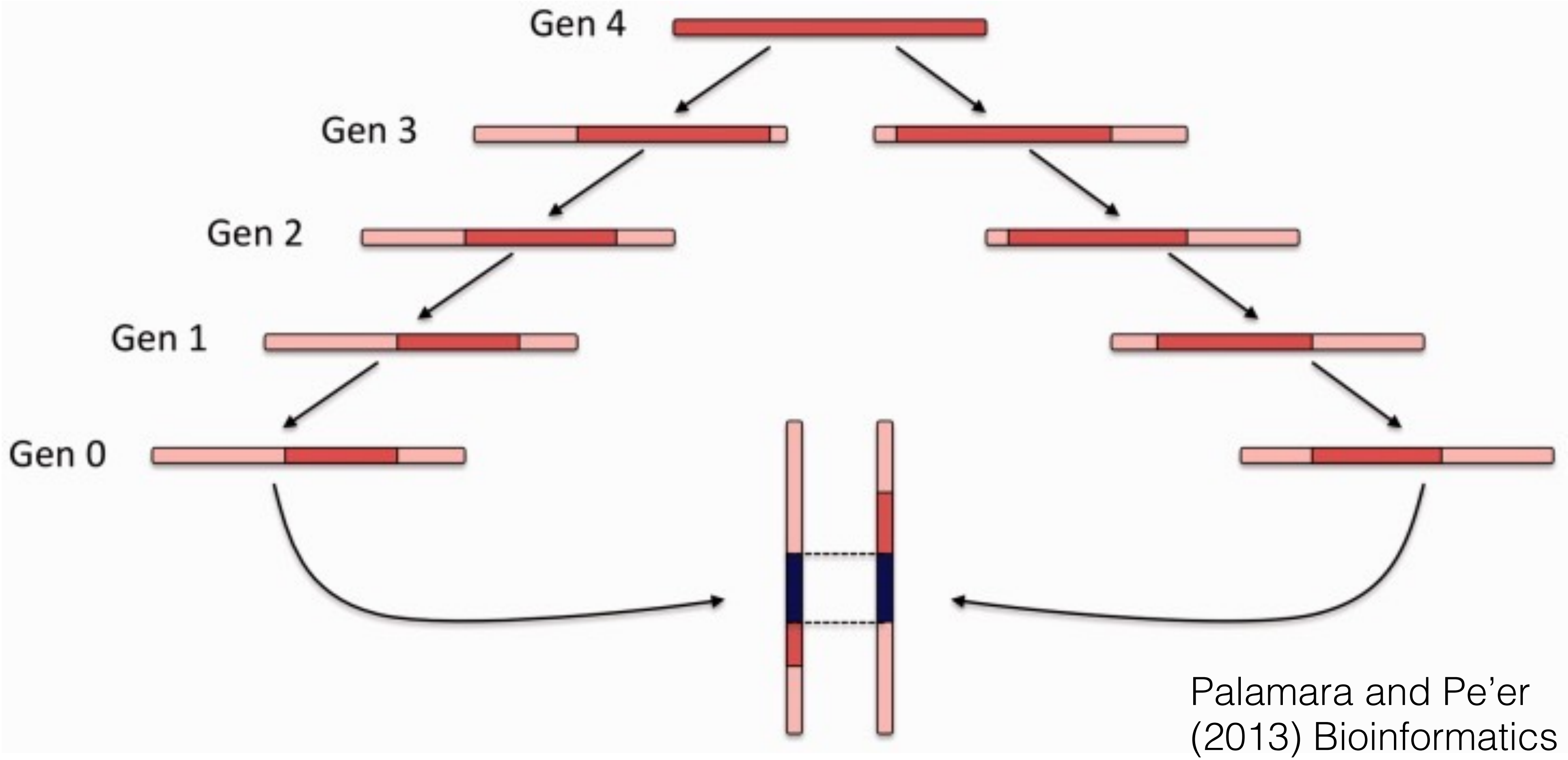
Identity by Decent (IBD): A method to find both distant and recent relationships



The smaller the segments in common, the more distant the relationship.

Recombination event

IBD length is correlated with historical relationships.

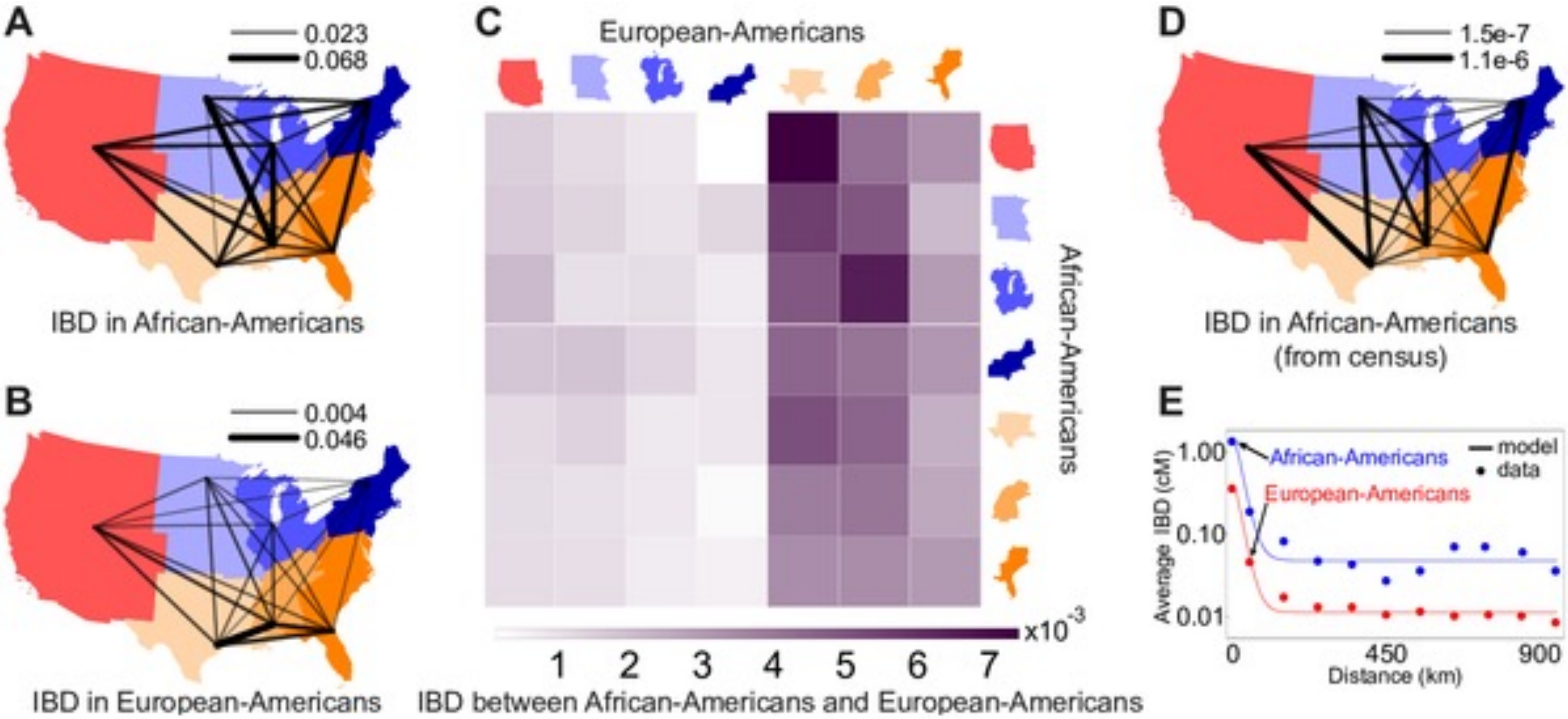


Palamara and Pe’er (2013) Bioinformatics

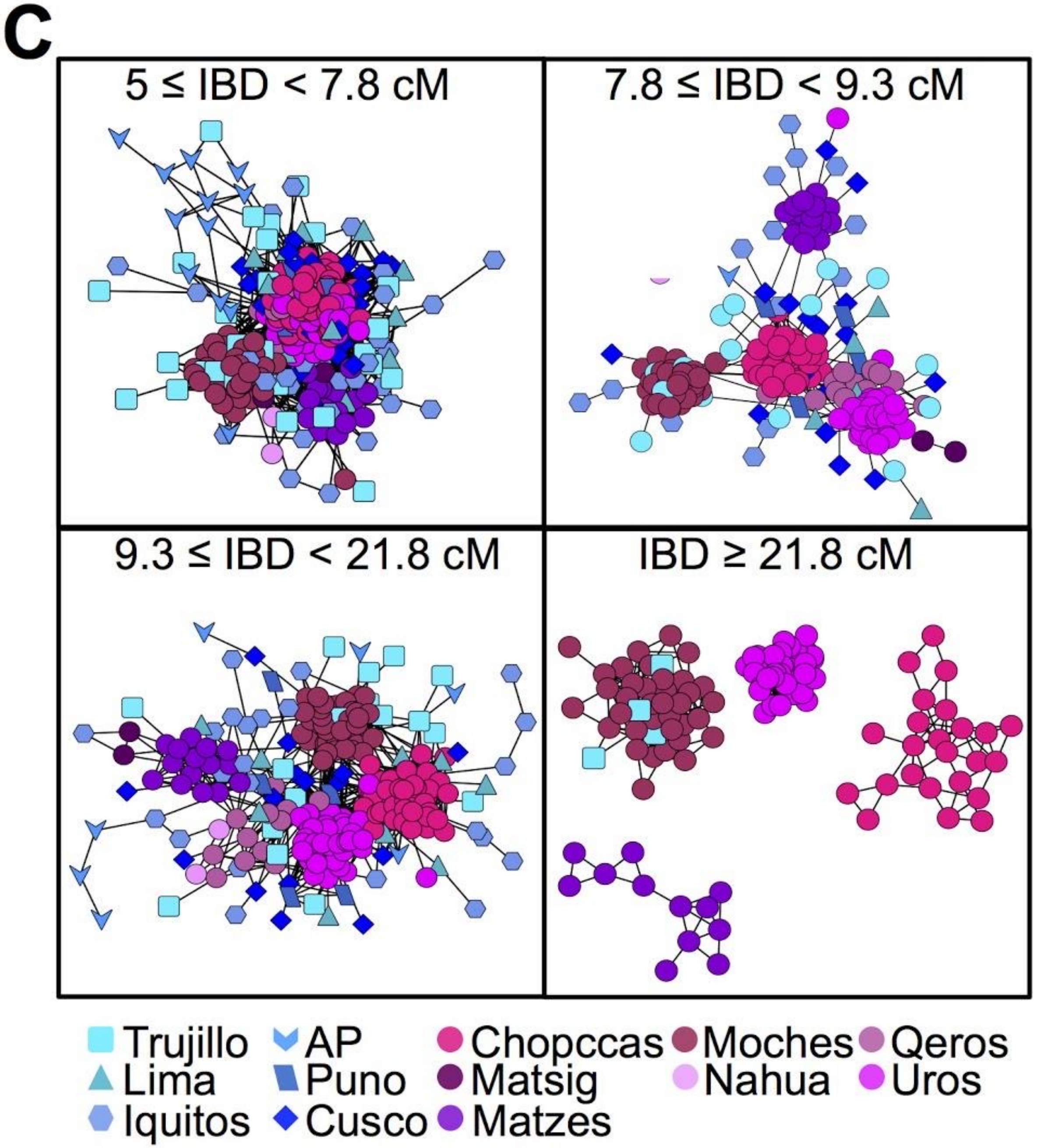
$$E[g|l] \cong \frac{3}{2 * l}$$

Baharian et al. (2016) PLoS Genet.

Pairwise genetic relatedness across

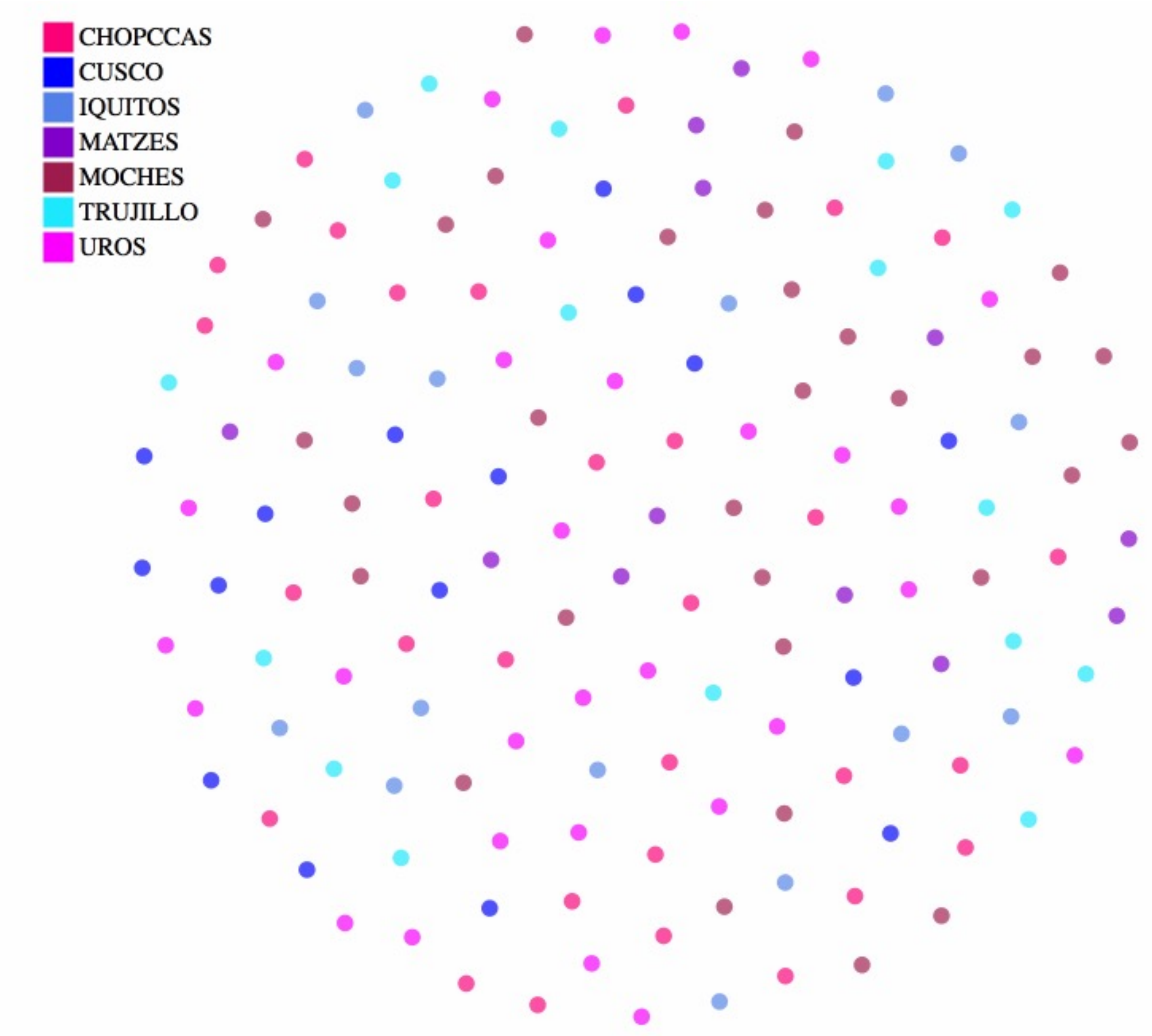


Baharian et al. (2016) PLoS Genet.



Identity-by-descent as a means to look at fine-scale structure over time

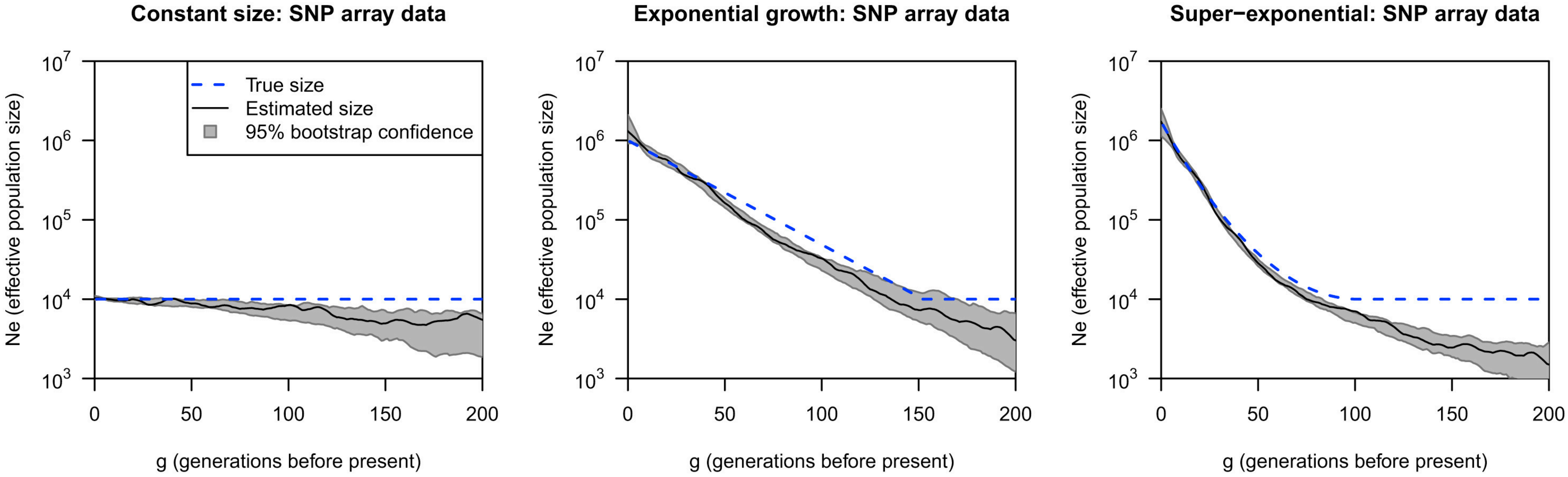
Harris et al. (2018) PNAS



Identity-by-descent as a means to look at fine-scale structure over time

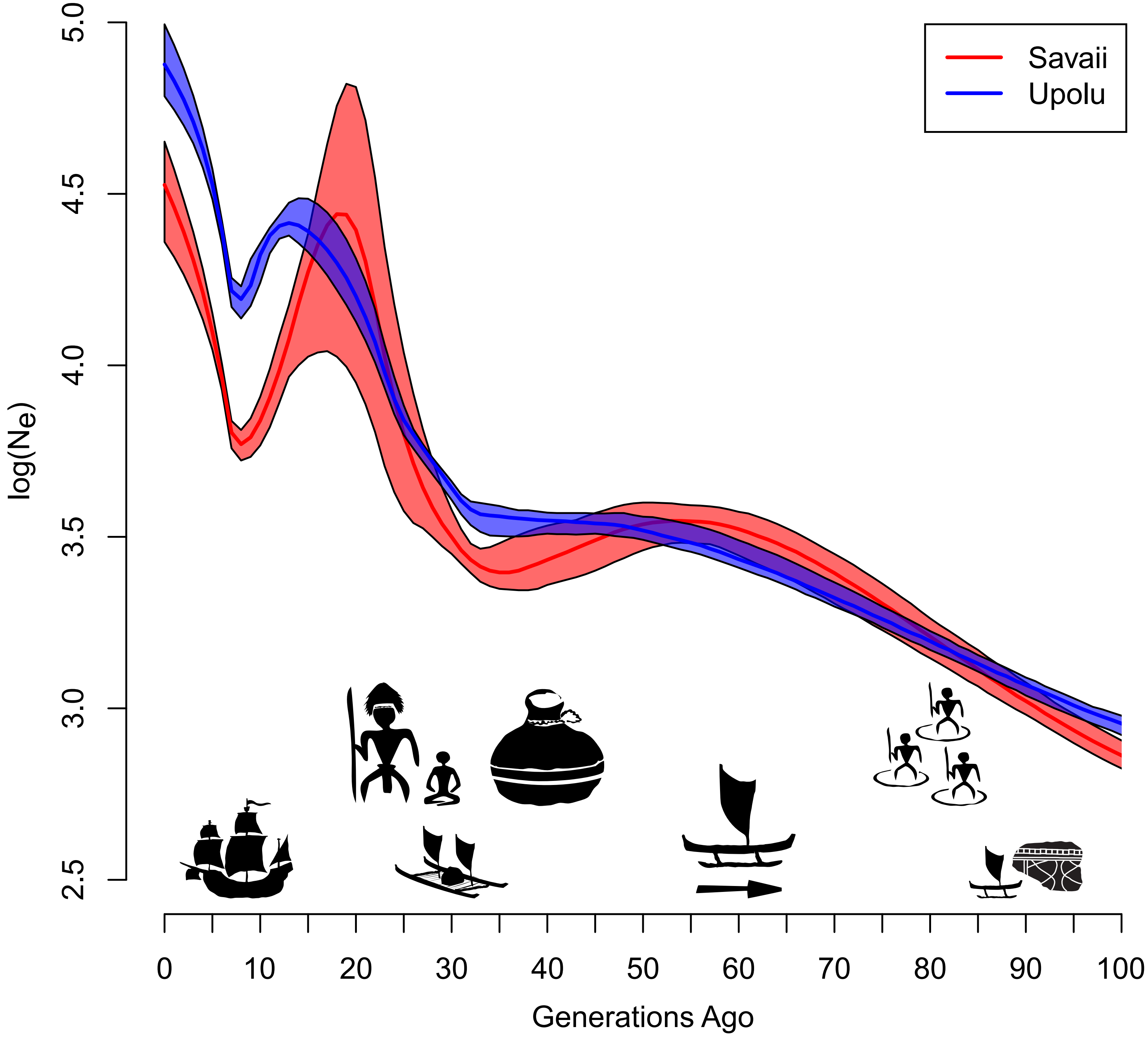
Harris et al. (2018) PNAS

IBD can estimate effective population size over time.



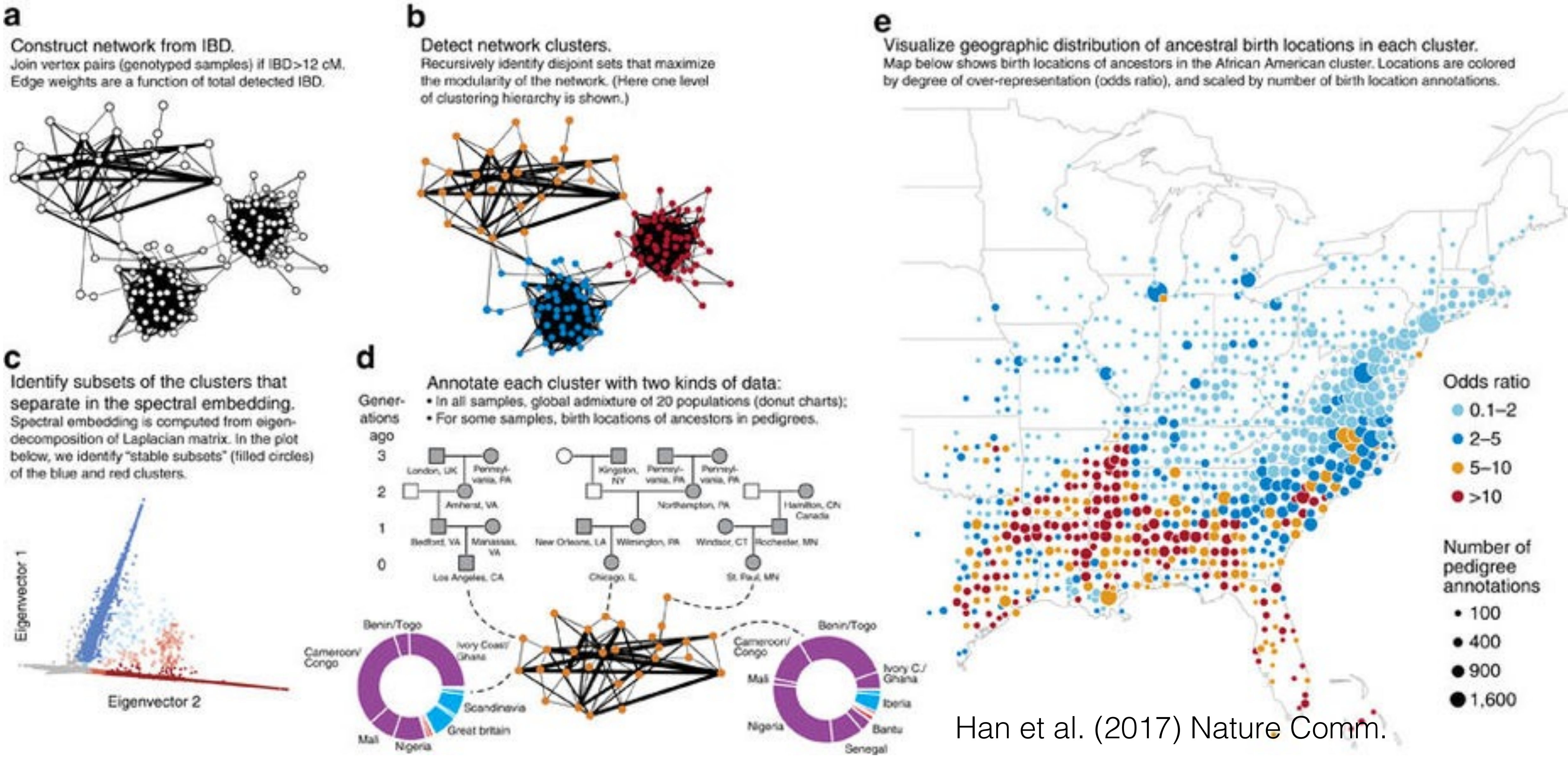
Browning &Browning (2016) Am. J. Human Genetics

IBDNe in Samoa!



Harris et al. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3329885)

IBD on a large scale



a

Construct network from IBD.
Join vertex pairs (genotyped samples) if IBD>12 cM.
Edge weights are a function of total detected IBD.

b

Detect network clusters.
Recursively identify disjoint sets that maximize the modularity of the network. (Here one level of clustering hierarchy is shown.)

c

Identify subsets of the clusters that separate in the spectral embedding.
Spectral embedding is computed from eigen-decomposition of Laplacian matrix. In the plot below, we identify "stable subsets" (filled circles) of the blue and red clusters.

d

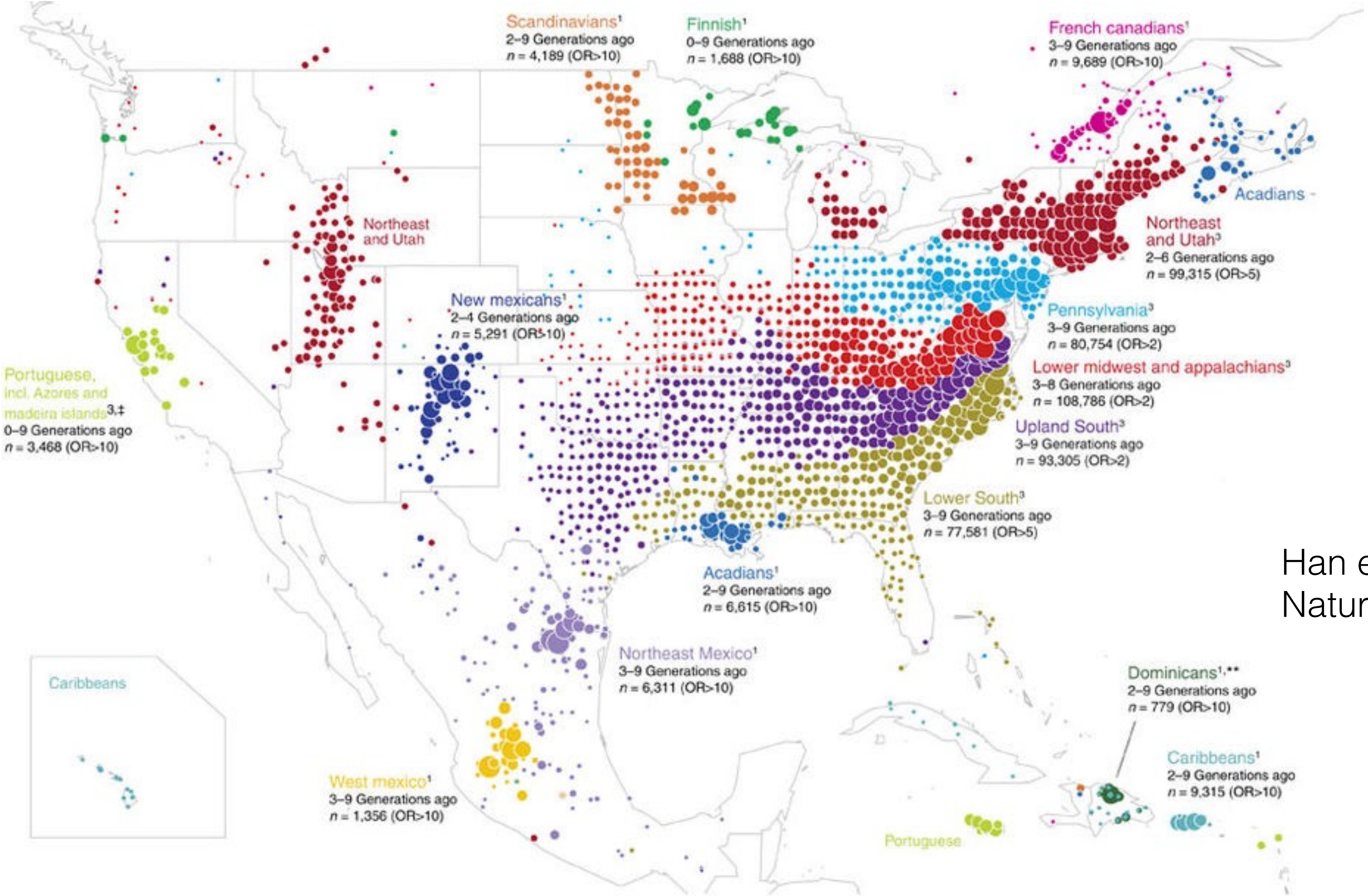
Annotate each cluster with two kinds of data:
- In all samples, global admixture of 20 populations (donut charts);
- For some samples, birth locations of ancestors in pedigrees.

e

Visualize geographic distribution of ancestral birth locations in each cluster.
Map below shows birth locations of ancestors in the African American cluster. Locations are colored by degree of over-representation (odds ratio), and scaled by number of birth location annotations.

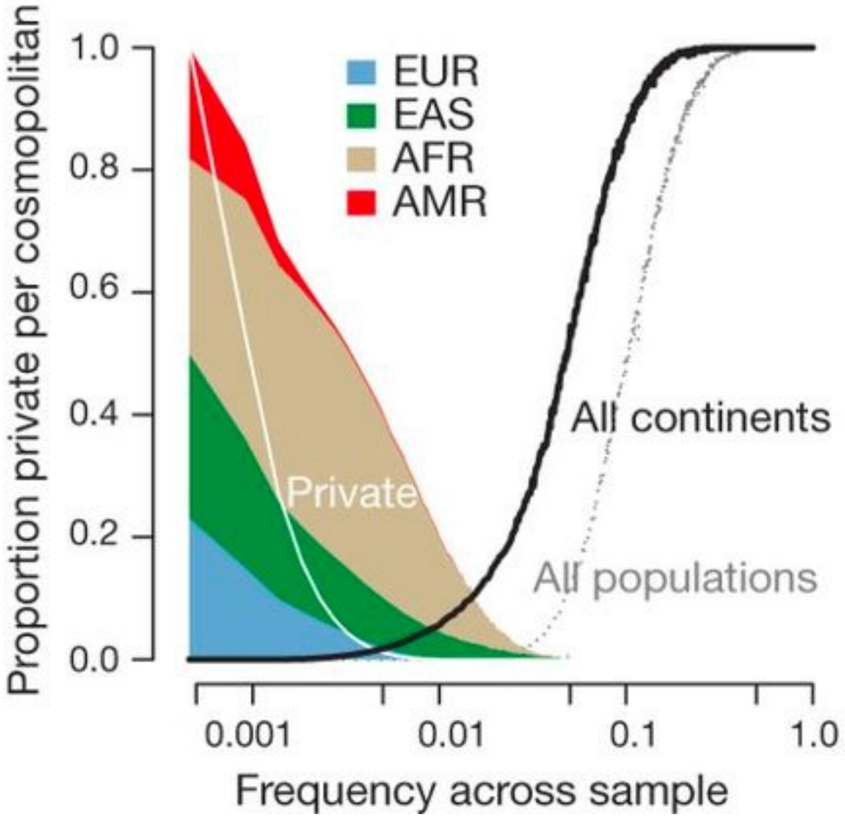
Han et al. (2017) Nature Comm.

IBD on a large scale



Han et al. (2017) Nature Comm.

Do rare variants help identify recent population structure?



1000 Genomes Project (2012) Nature

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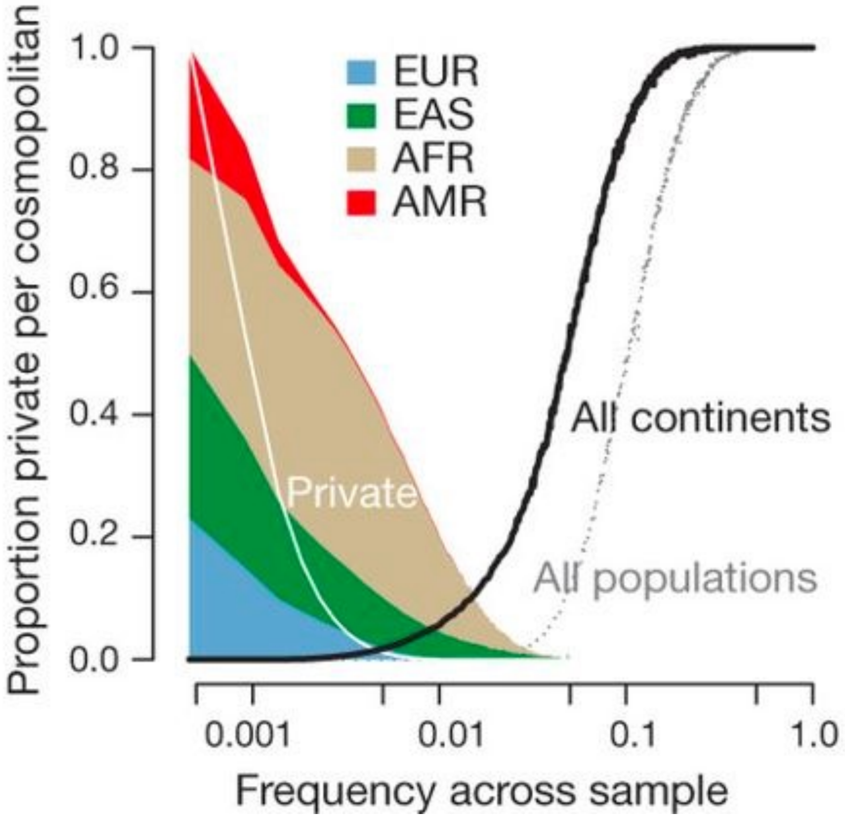
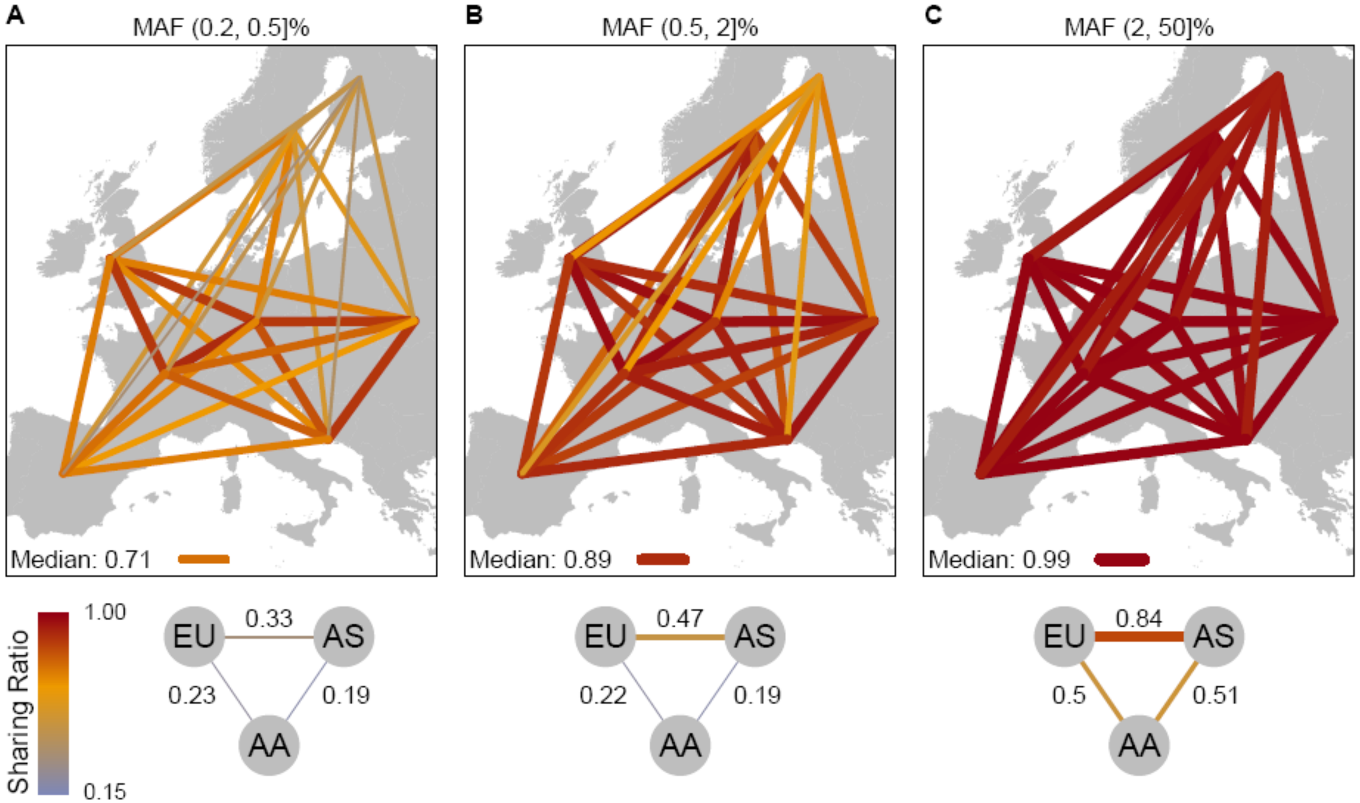
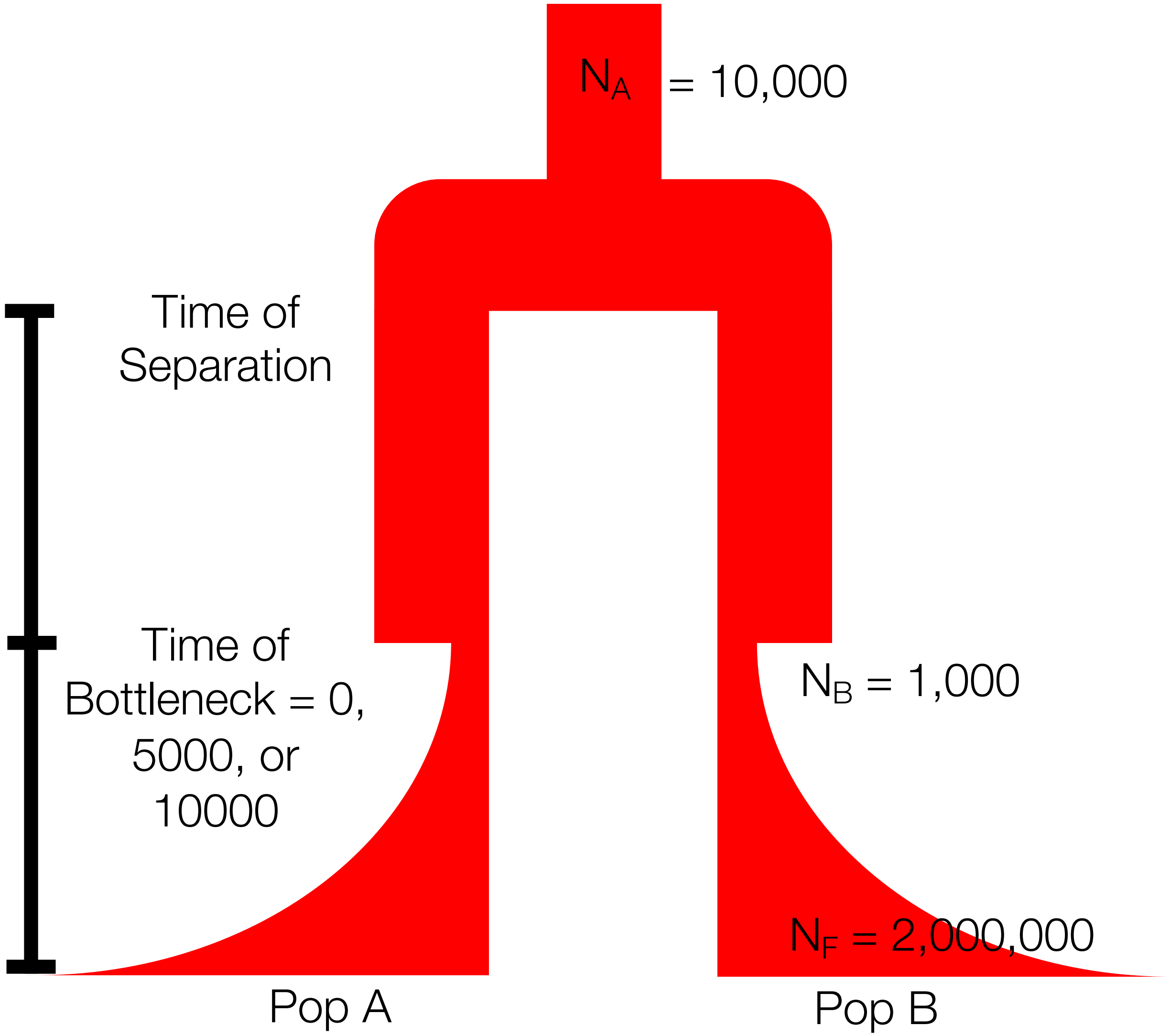


1000 Genomes Project (2012) Nature



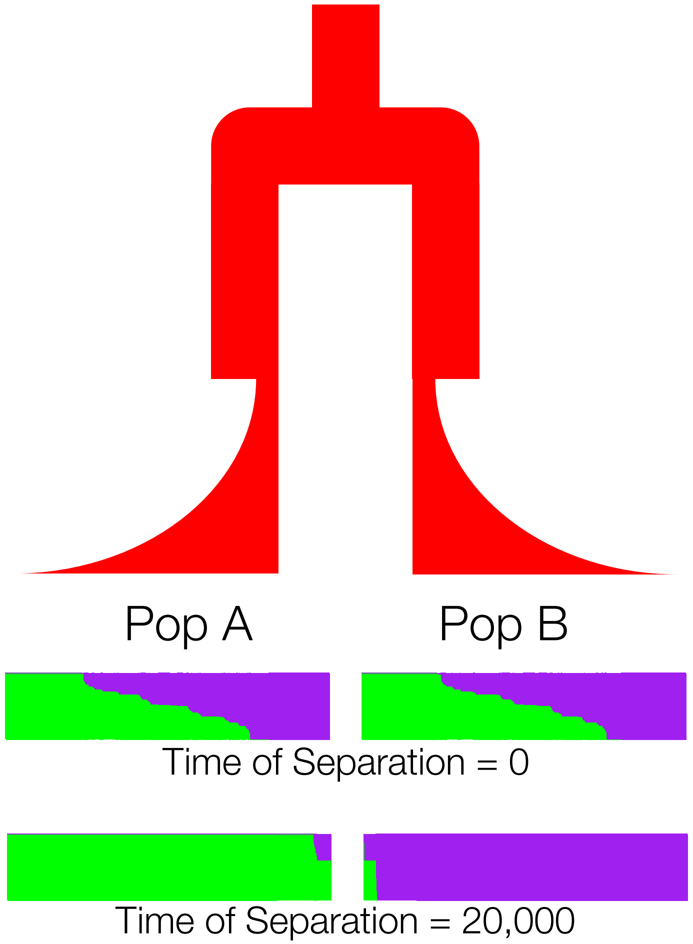
Novembre et al. (2012) Science

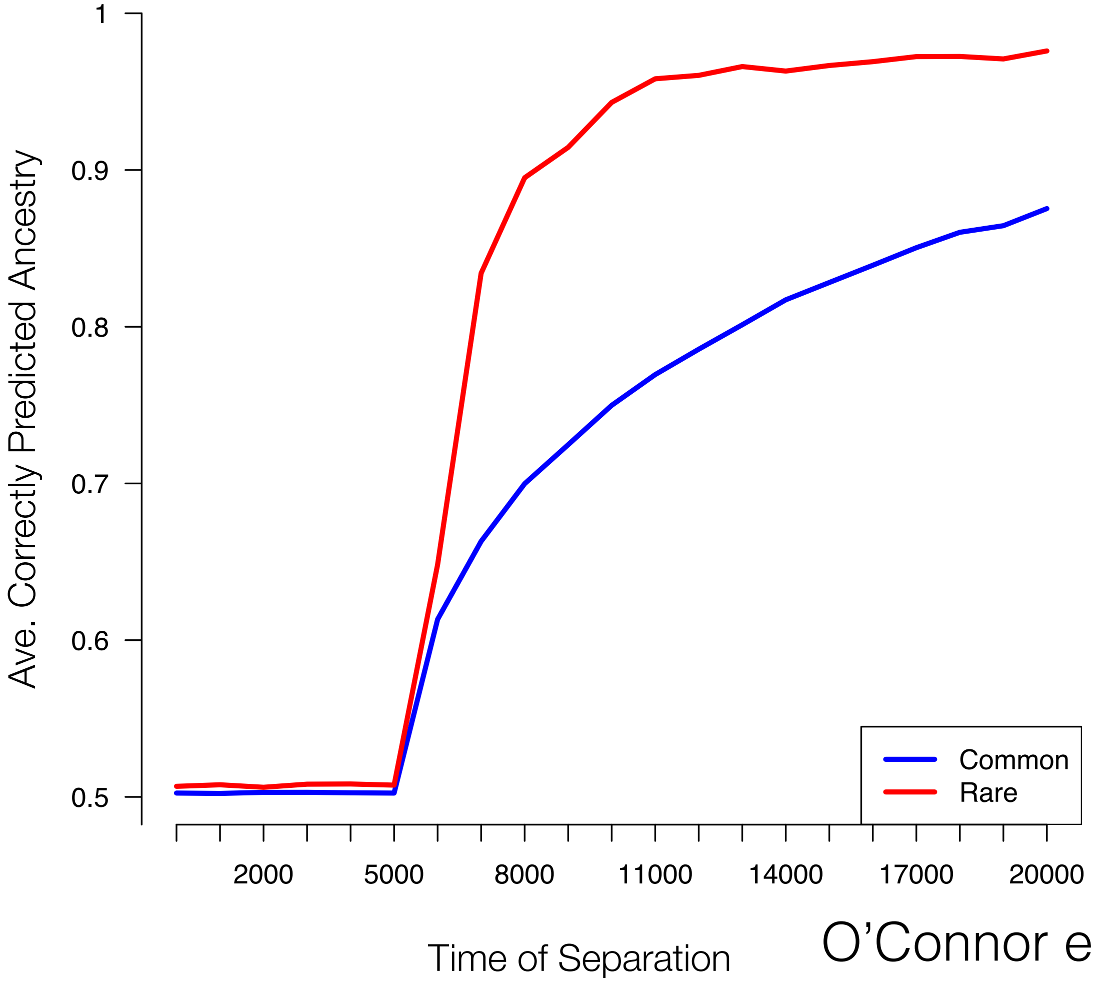
Rare VS Common: Population Structure Simulations



O'Connor et al. (2014)
Mol. Biol. Evol.

Rare VS Common:
Assignment of Ancestry Proportions





O’Connor et al. (2014)
Mol. Biol. Evol.

Rare VS Common: Which has Greater Information? And When?

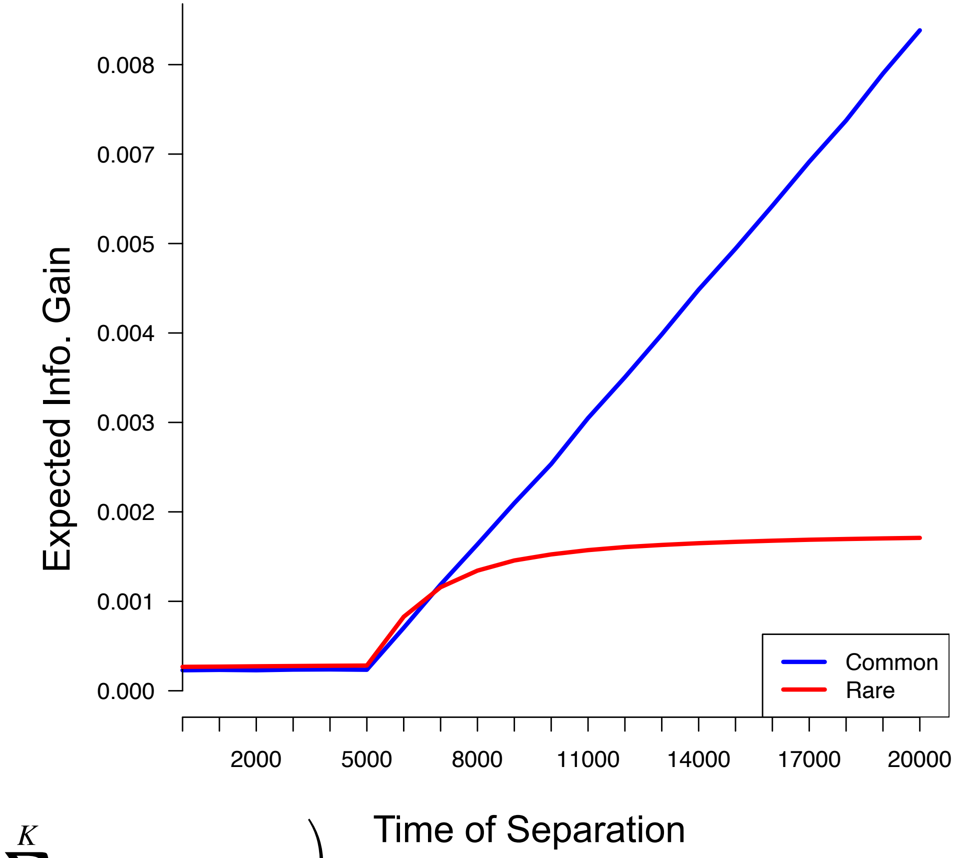
Information Gain: how well a variant can distinguish between populations. (Rosenberg et al. 2003)

$$I_n(Q;J) = \sum_{j=1}^{N}\left(-p_j \ln p_j + \sum_{i=1}^{K} q_i p_{ij} \ln p_{ij}\right)$$

Expected Information Gain

- Calculate for a specific site count
- Correct for missing data
- Weighted average to calculate across a range of frequency (rare or common)

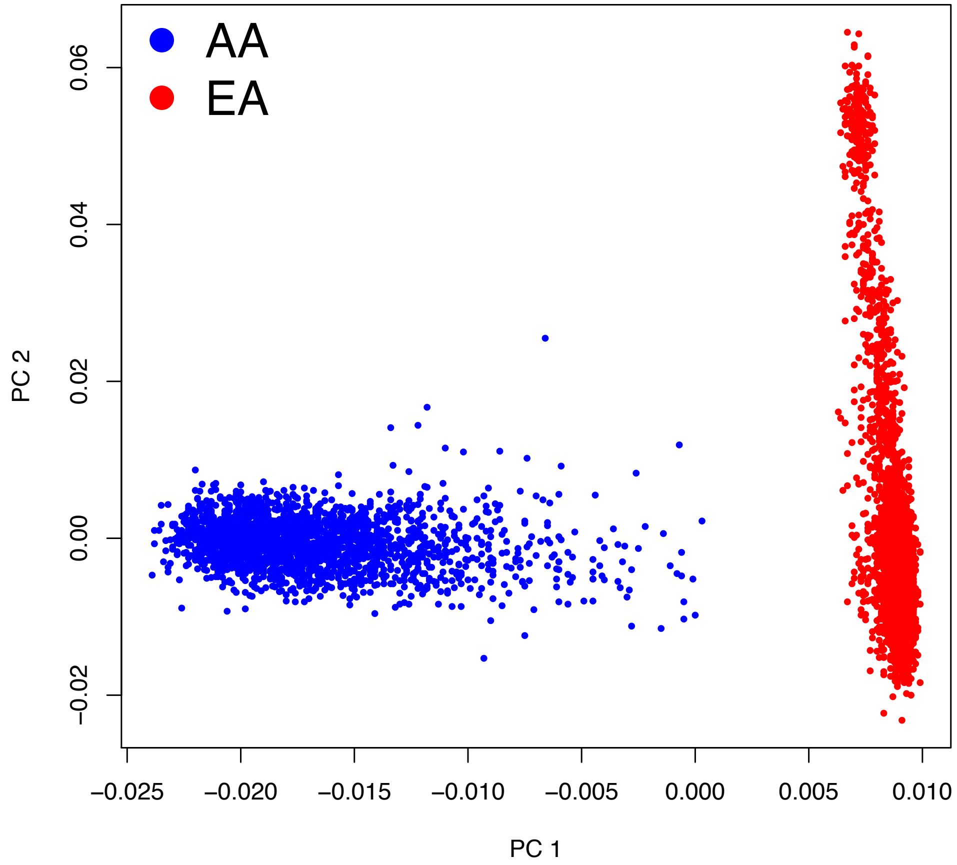
$$E(I_n \mid C,M) = \sum_{m\in M}\sum_{l=0}^{C} r_{lm} \times \sum_{j=1}^{N}\left(-p_{jlm} \ln p_{jlm} + \sum_{i=1}^{K} q_i p_{ijlm} \ln p_{ijlm}\right)$$



O'Connor et al. (2014) Mol. Biol. Evol.

Rare Variants Identify Cryptic Populations

Common (MAF > 10%)



O’Connor et al. (2014)
Mol. Biol. Evol.

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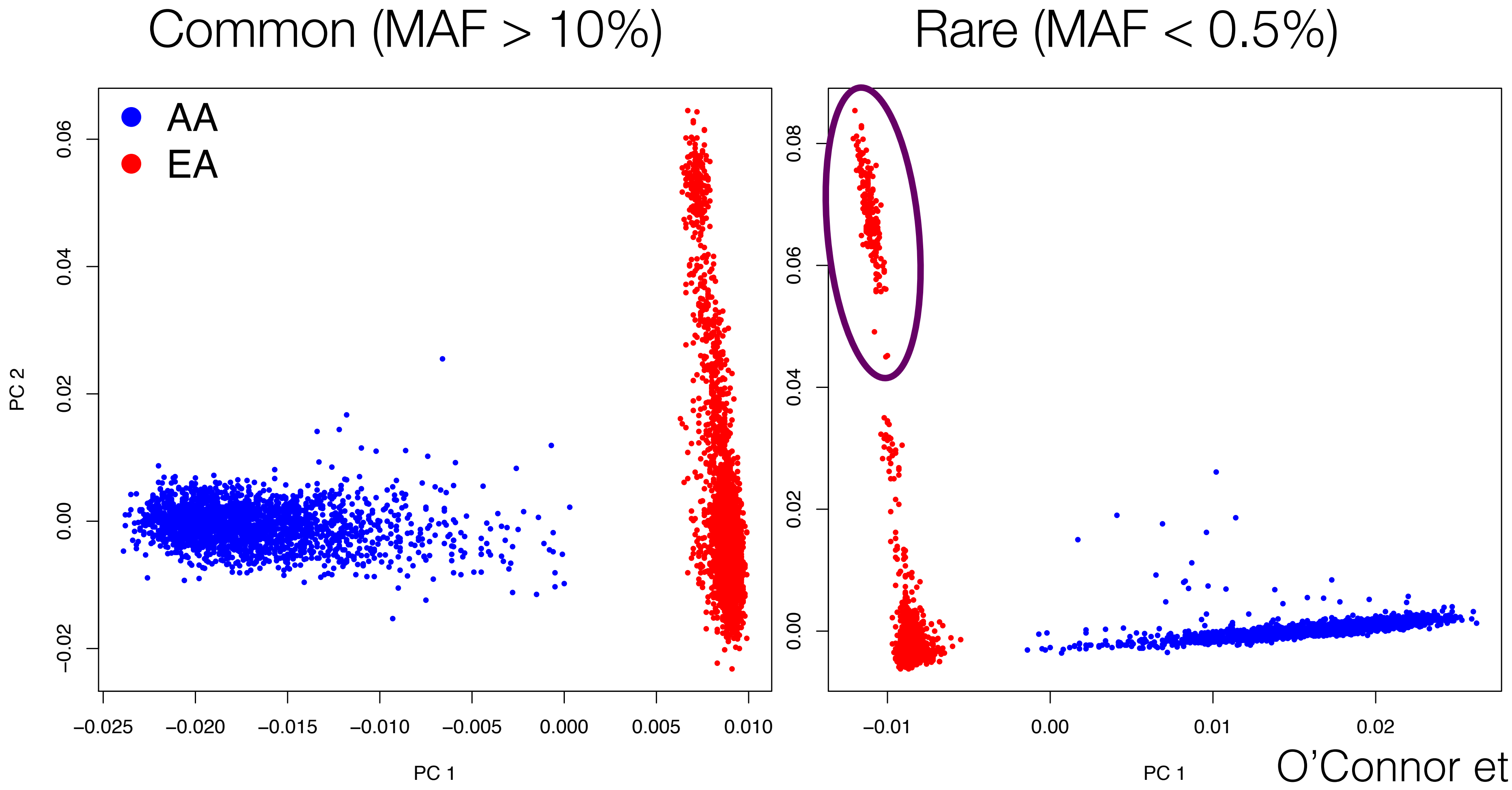
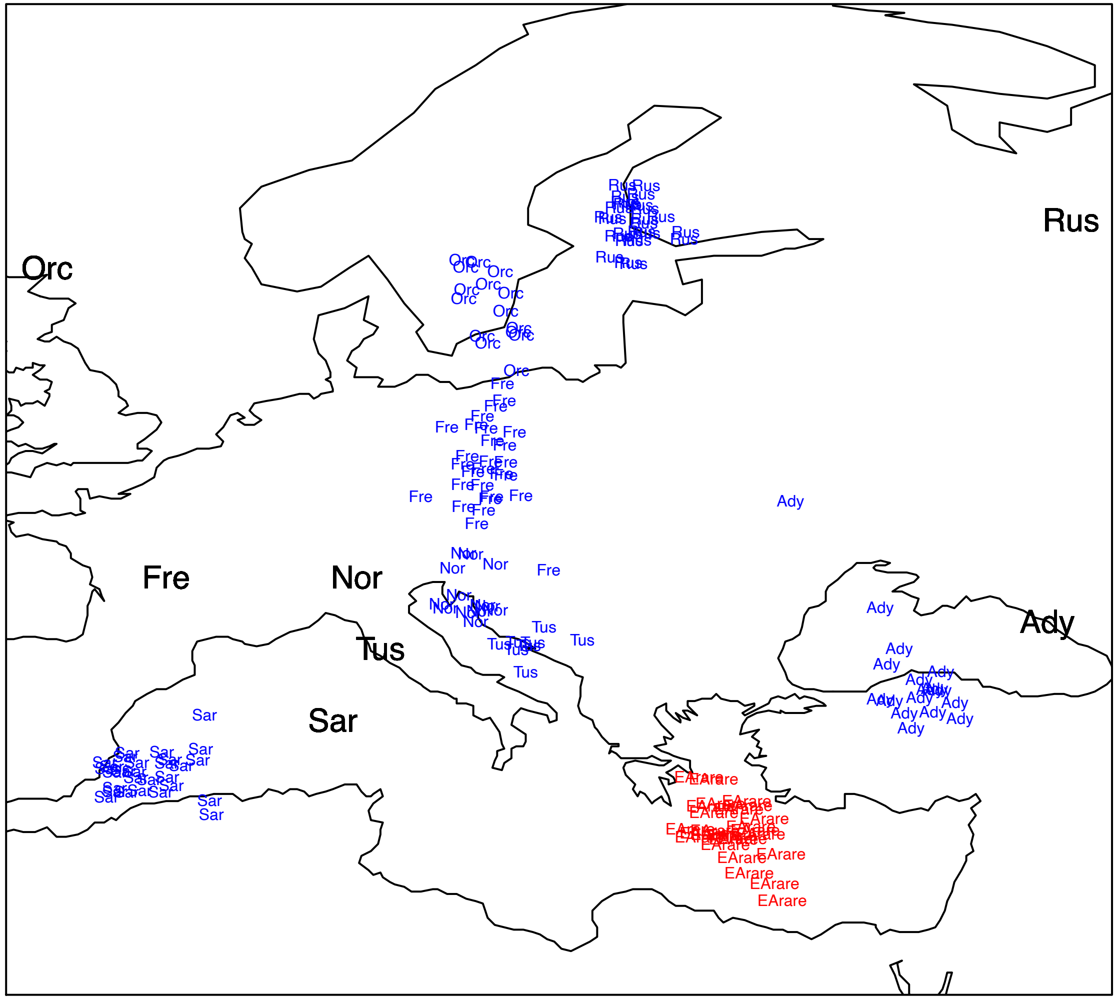


Common (MAF > 10%)

Rare (MAF < 0.5%)

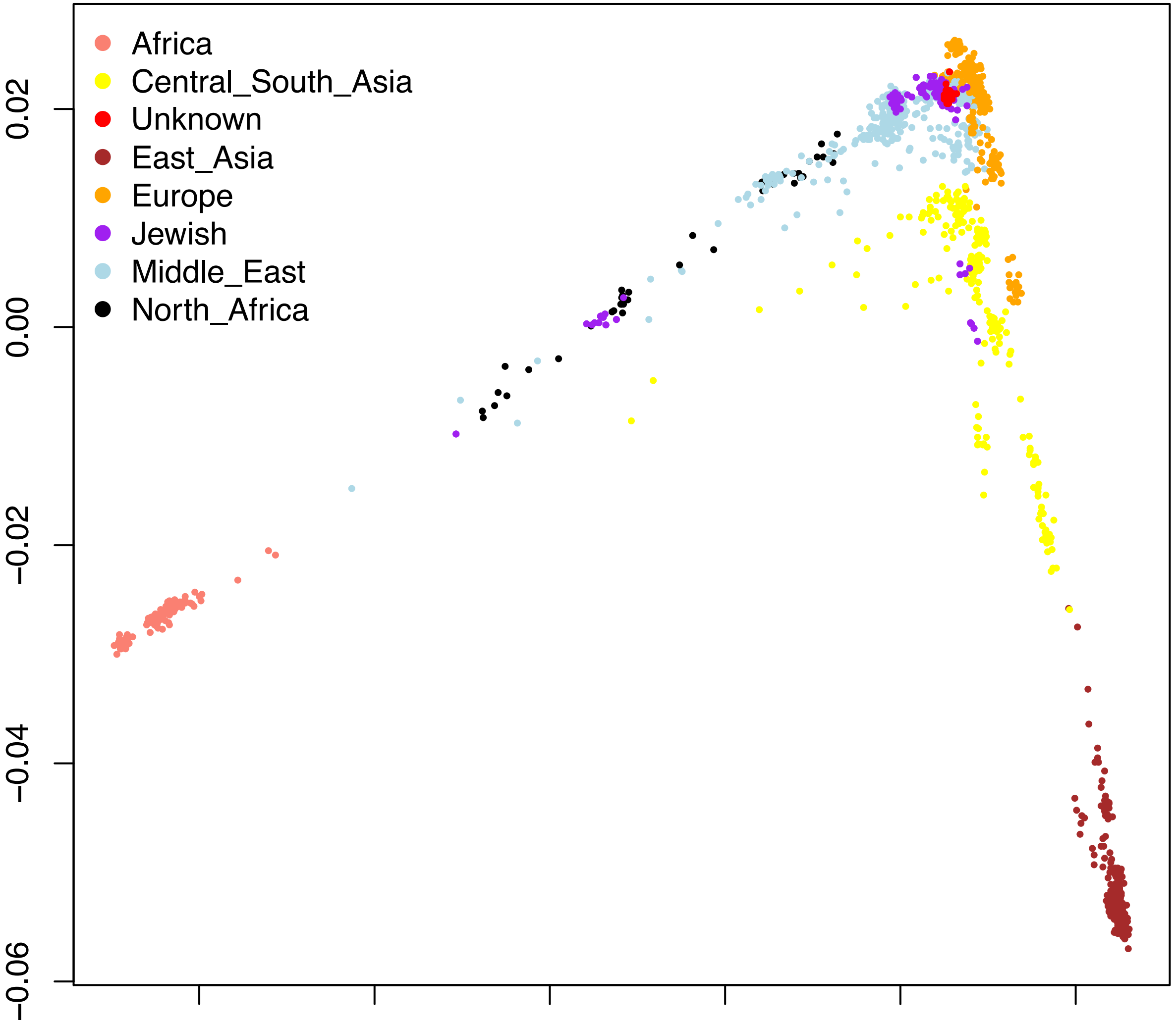
O’Connor et al. (2014)
Mol. Biol. Evol.

What is Their Geographic Ancestry?



O’Connor et al. (2014)
Mol. Biol. Evol.

PCA of Global Diversity Including Cryptic Population



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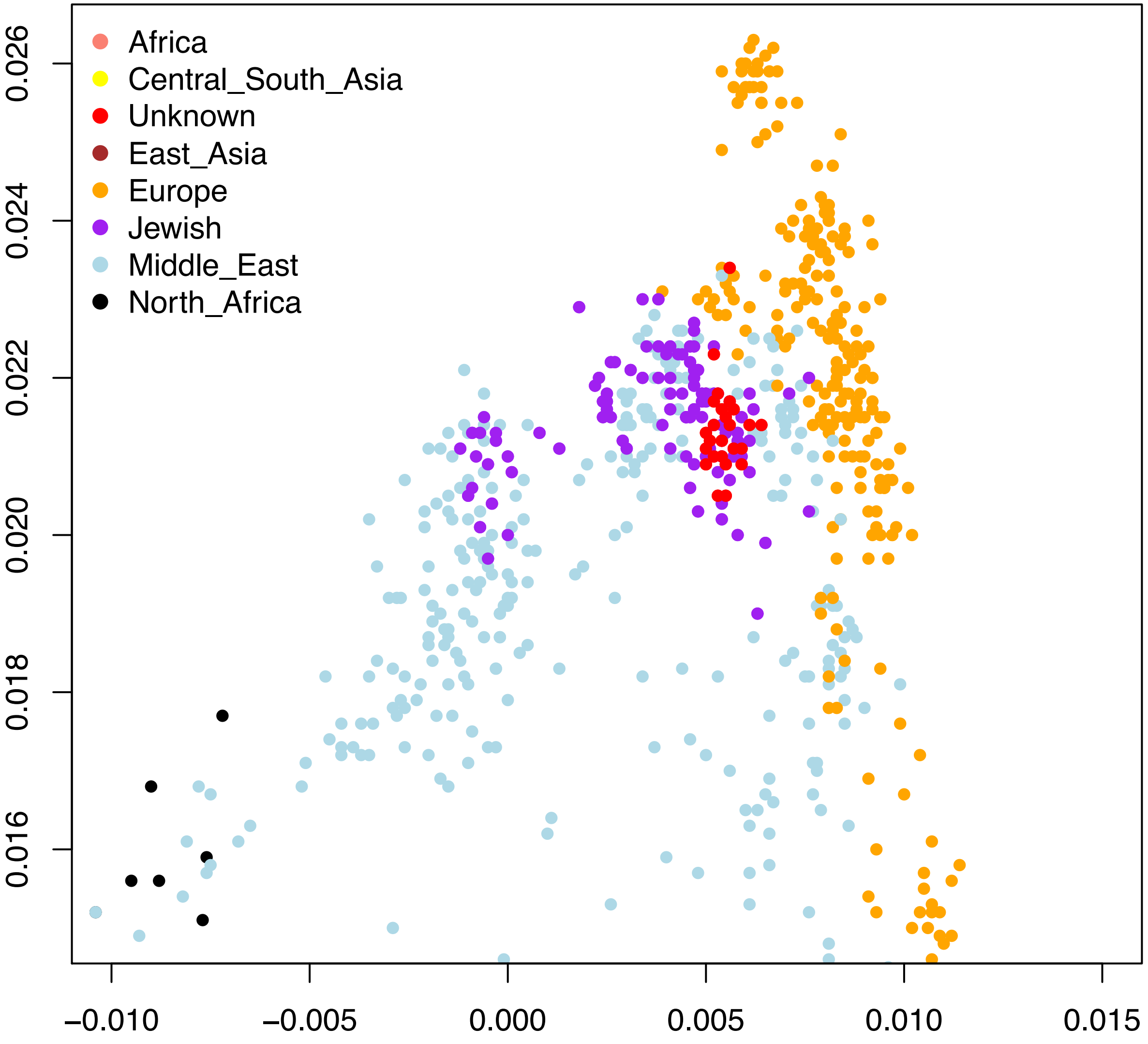
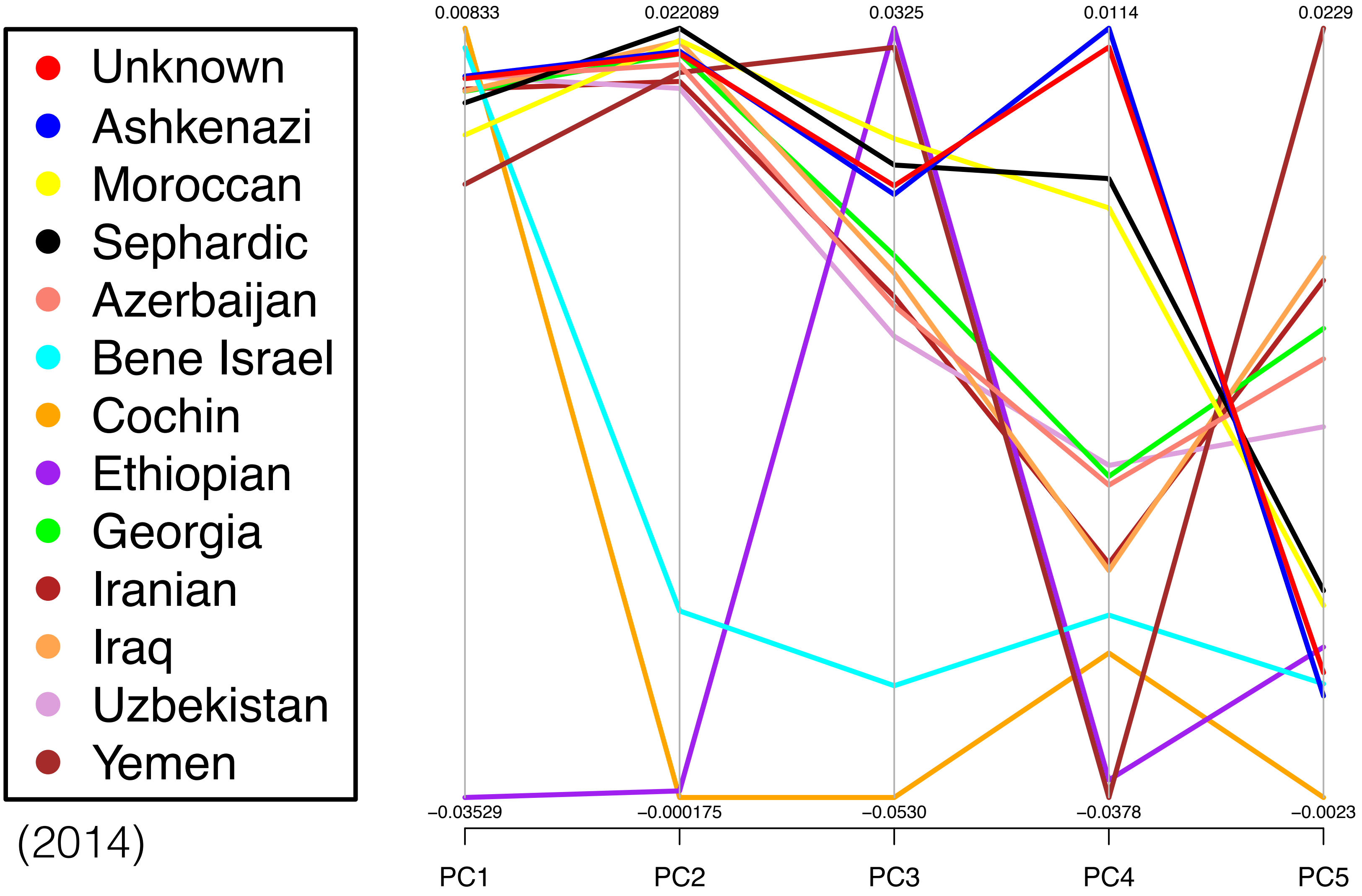


O’Connor et al. (2014)
Mol. Biol. Evol.

Population Average PCA with More Axes



O'Connor et al. (2014)
Mol. Biol. Evol.

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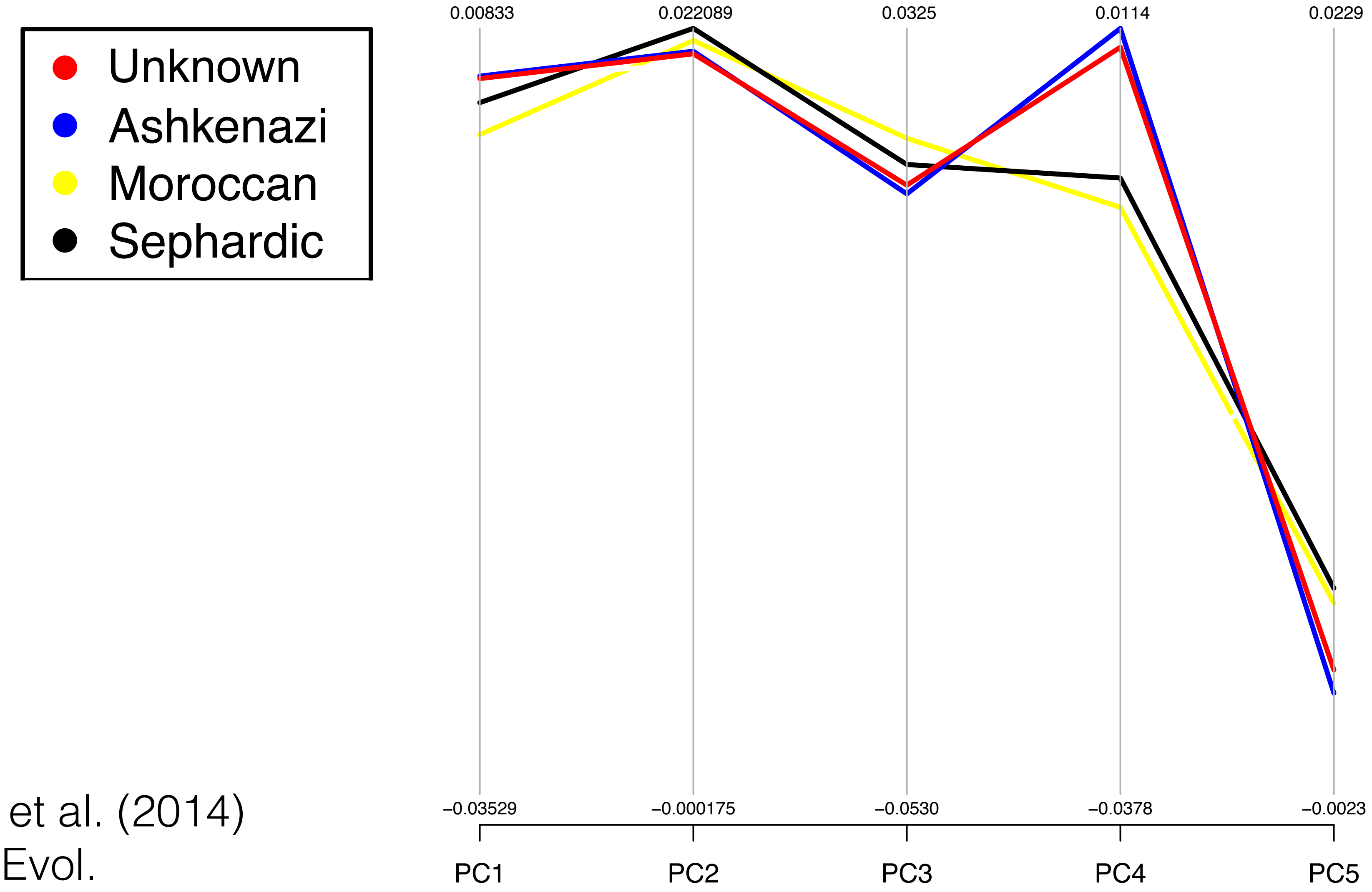
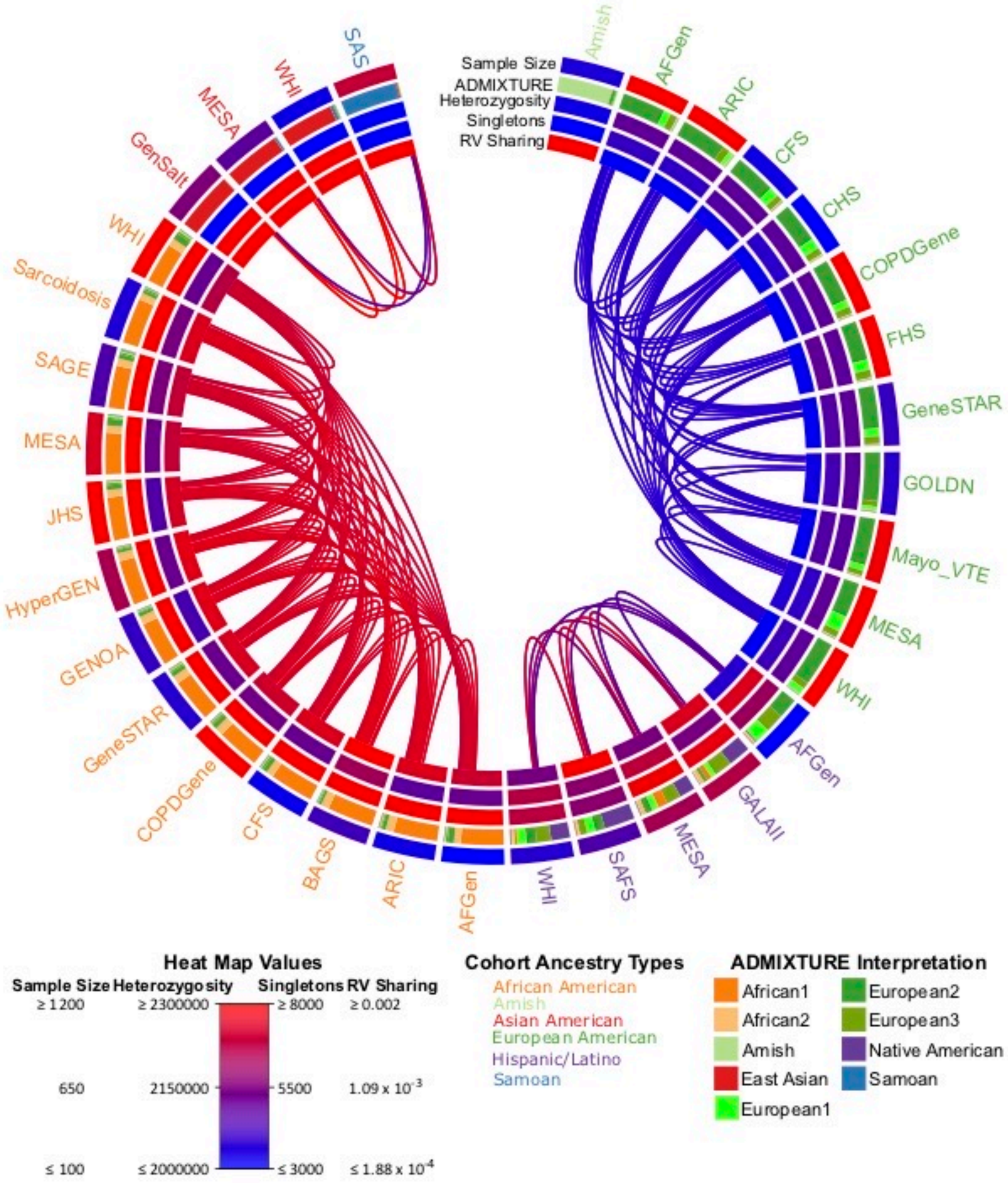


O'Connor et al. (2014)
Mol. Biol. Evol.

Trans-Omics for Precision Medicine (TOPMed) Cohorts

- N ≅ 55K
- Predominantly African, Latino, and European American
  - Samoa
  - Amish
- All are well characterized for heart, lung, blood, and sleep phenotypes

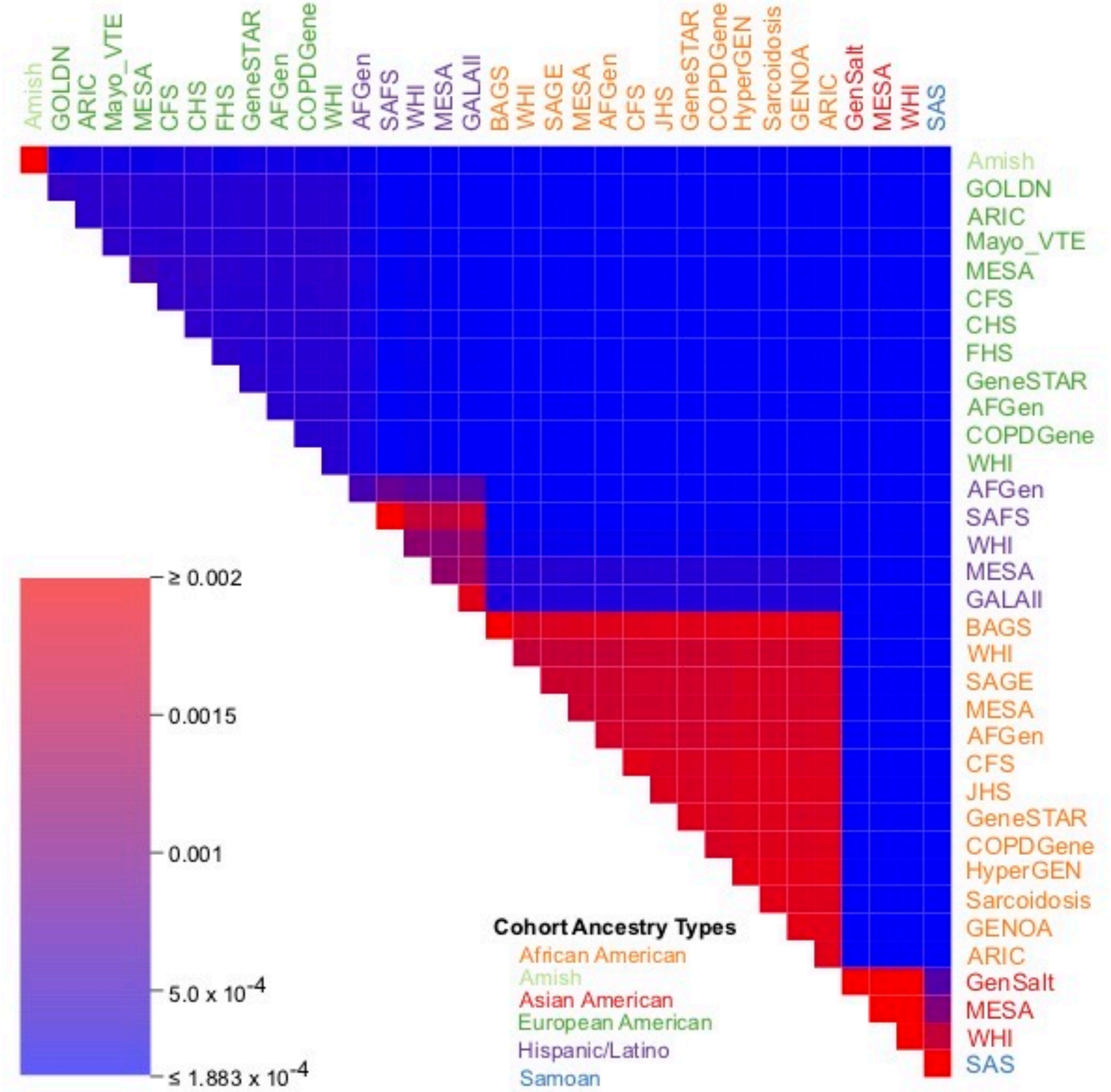


Taliun et al. (2019) Bioarxiv

Rare variant sharing across cohorts

- Allele Count 2 to 100
- Corrected for:
  - sample size
  - Genome-wide heterozygosity

Taliun et al. (2019) Bioarxiv



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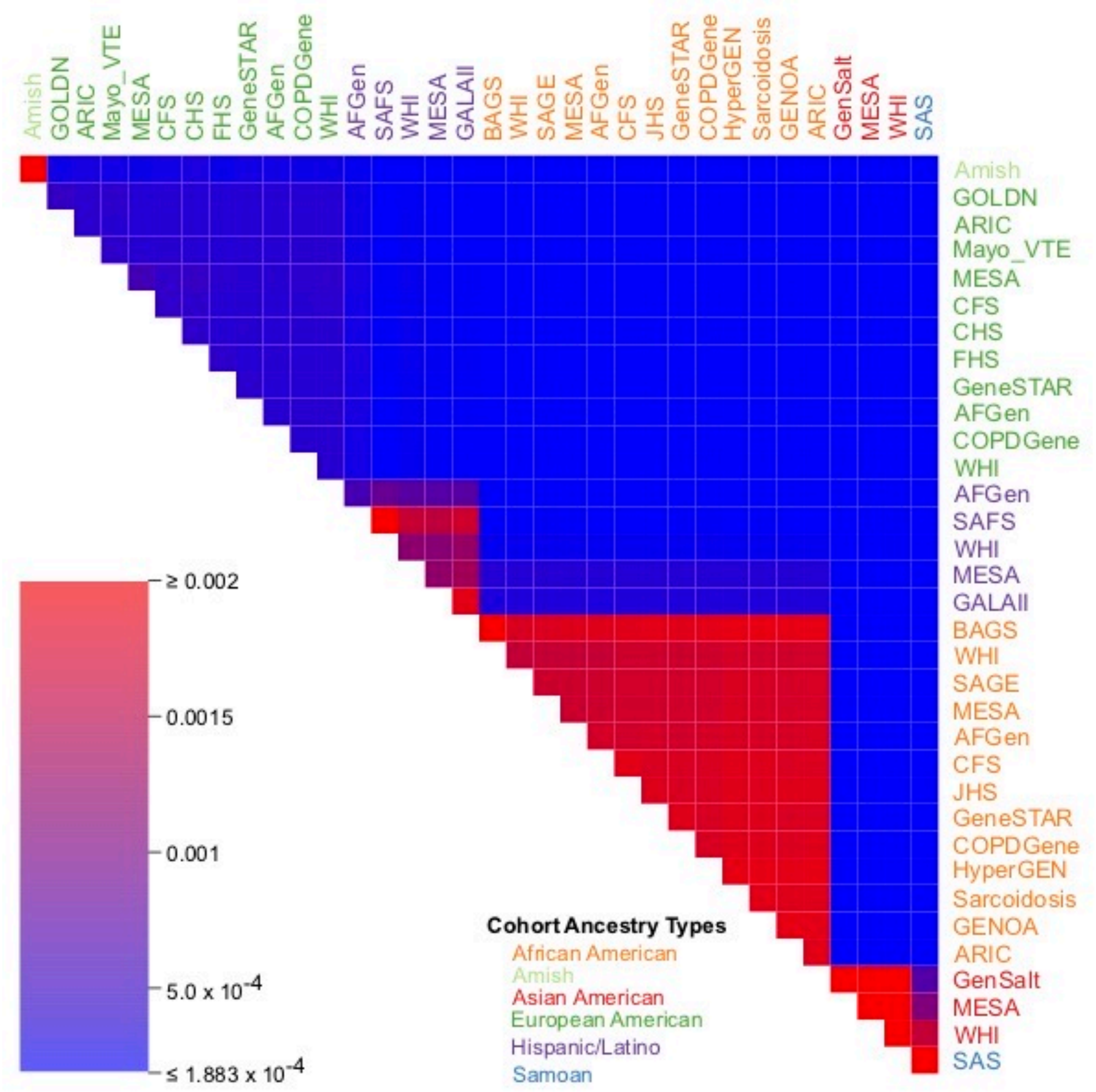

European

Rare variant sharing across cohorts

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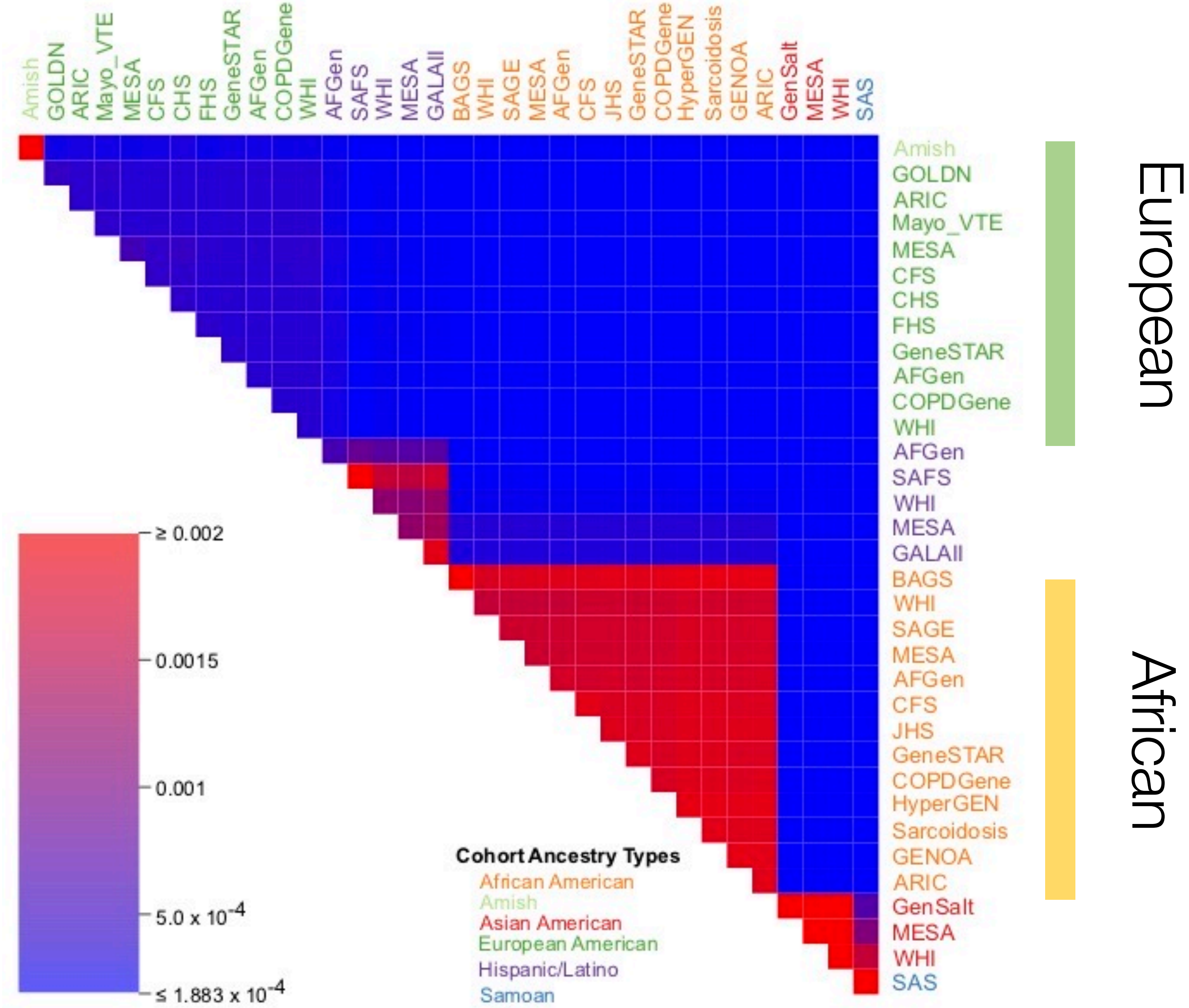
Taliun et al. (2019) Bioarxiv



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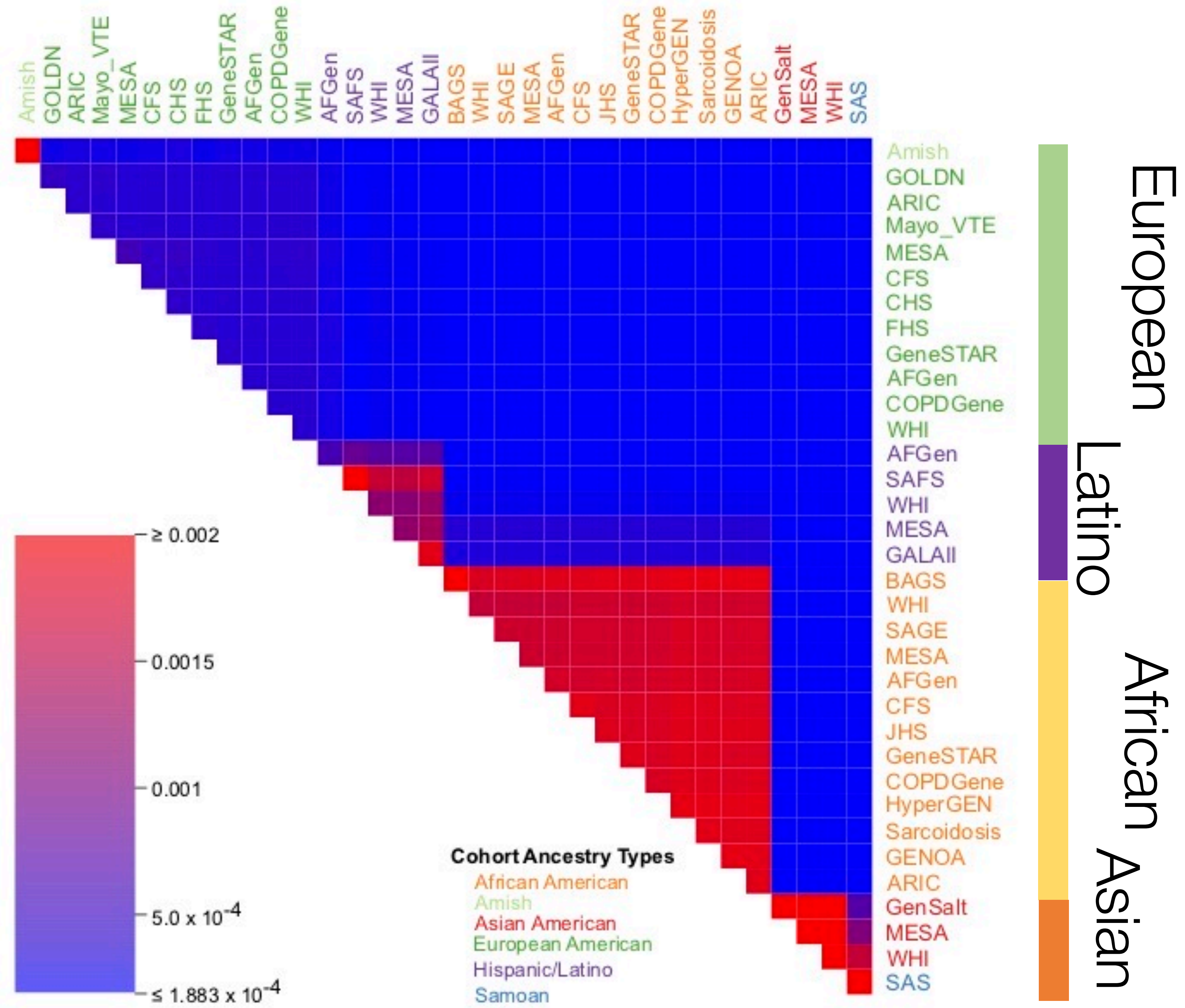
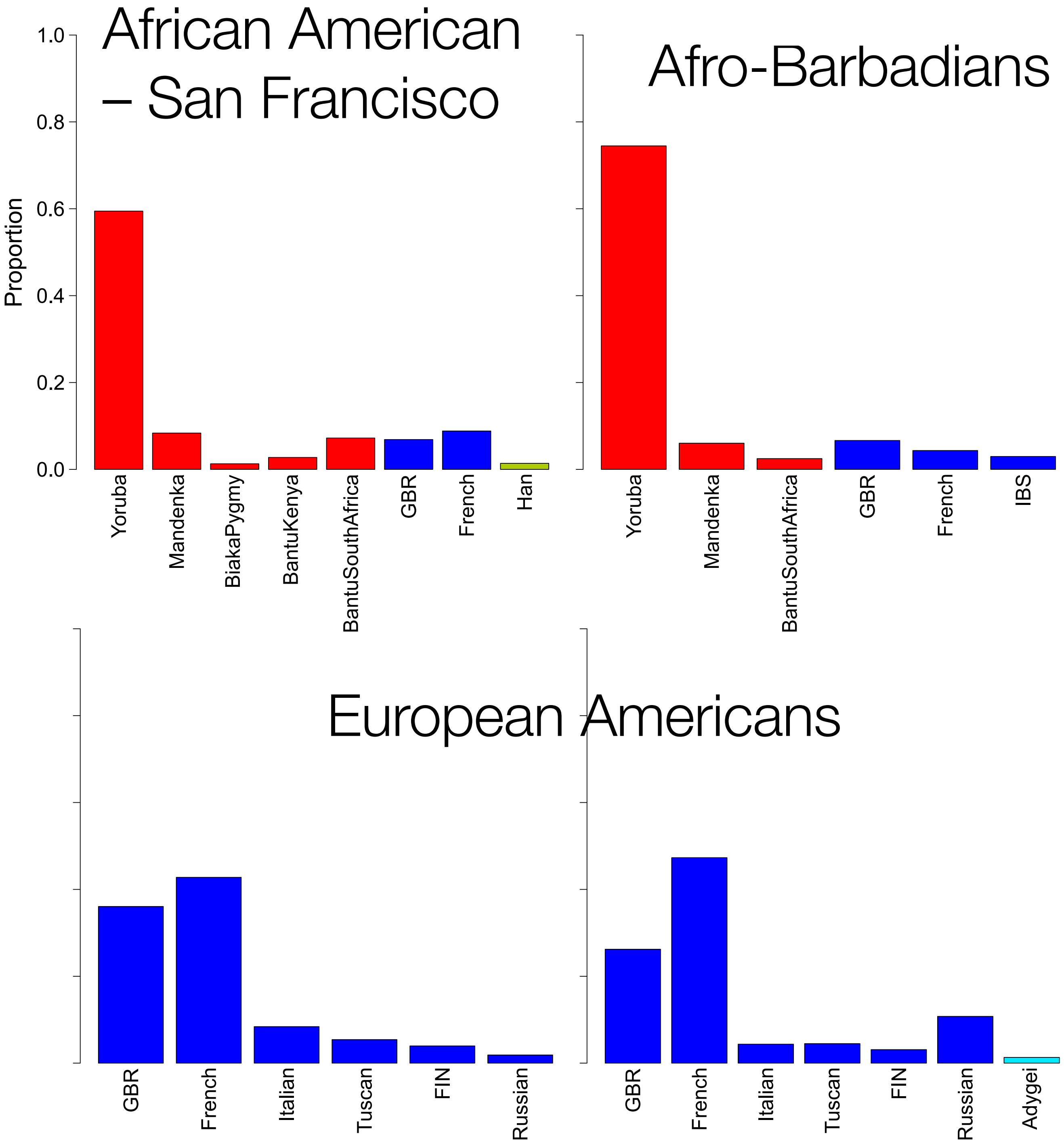


Taliun et al. (2019) Bioarxiv

fineStructure analysis of genome-wide ancestry

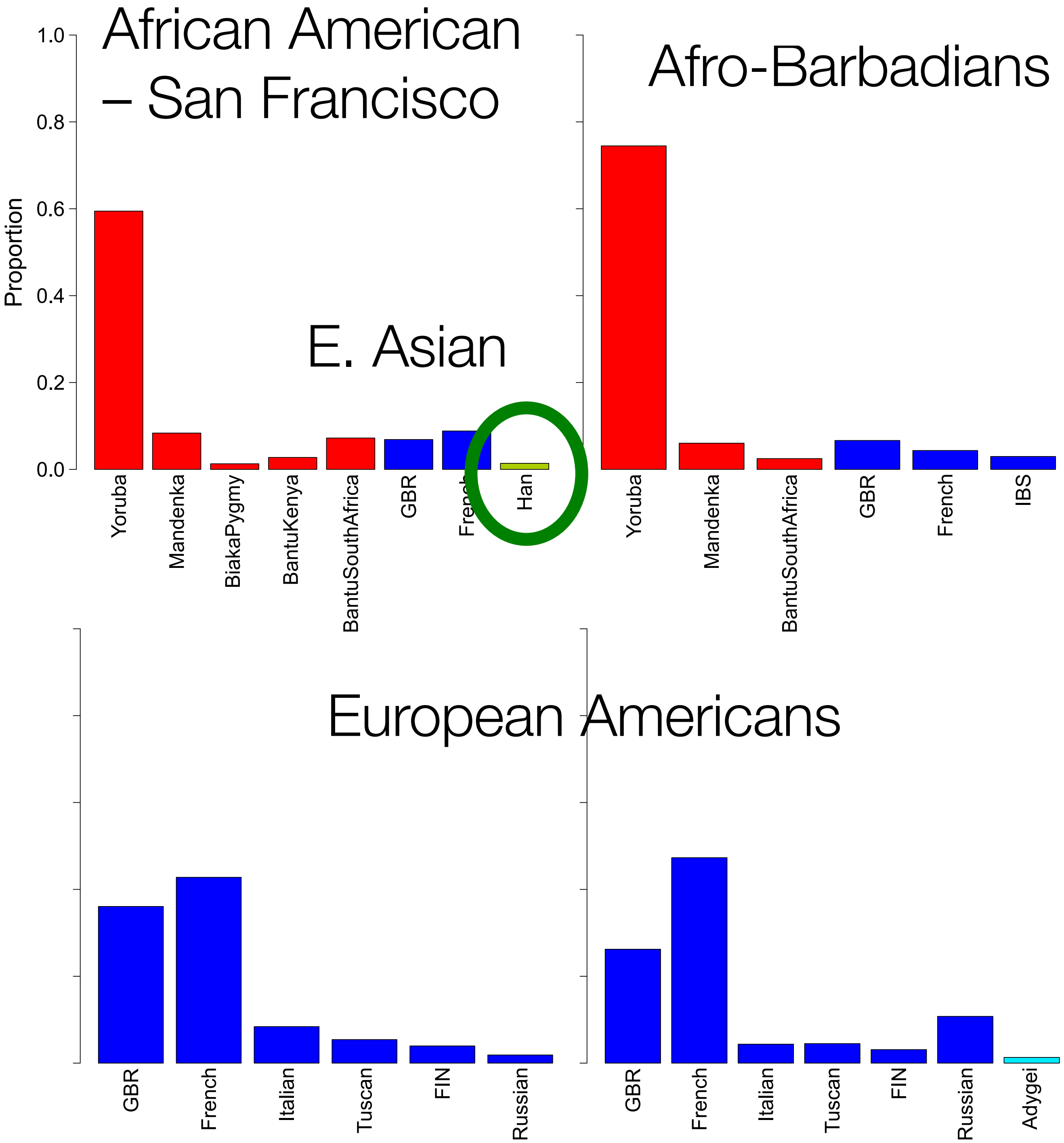

African American – San Francisco

Afro-Barbadians

European Americans

🟥 African
🟦 Caucasia
🟩 East Asian
🟦 European

fineStructure analysis of genome-wide ancestry



- 🟥 African
- 🟦 Caucasia
- 🟩 East Asian
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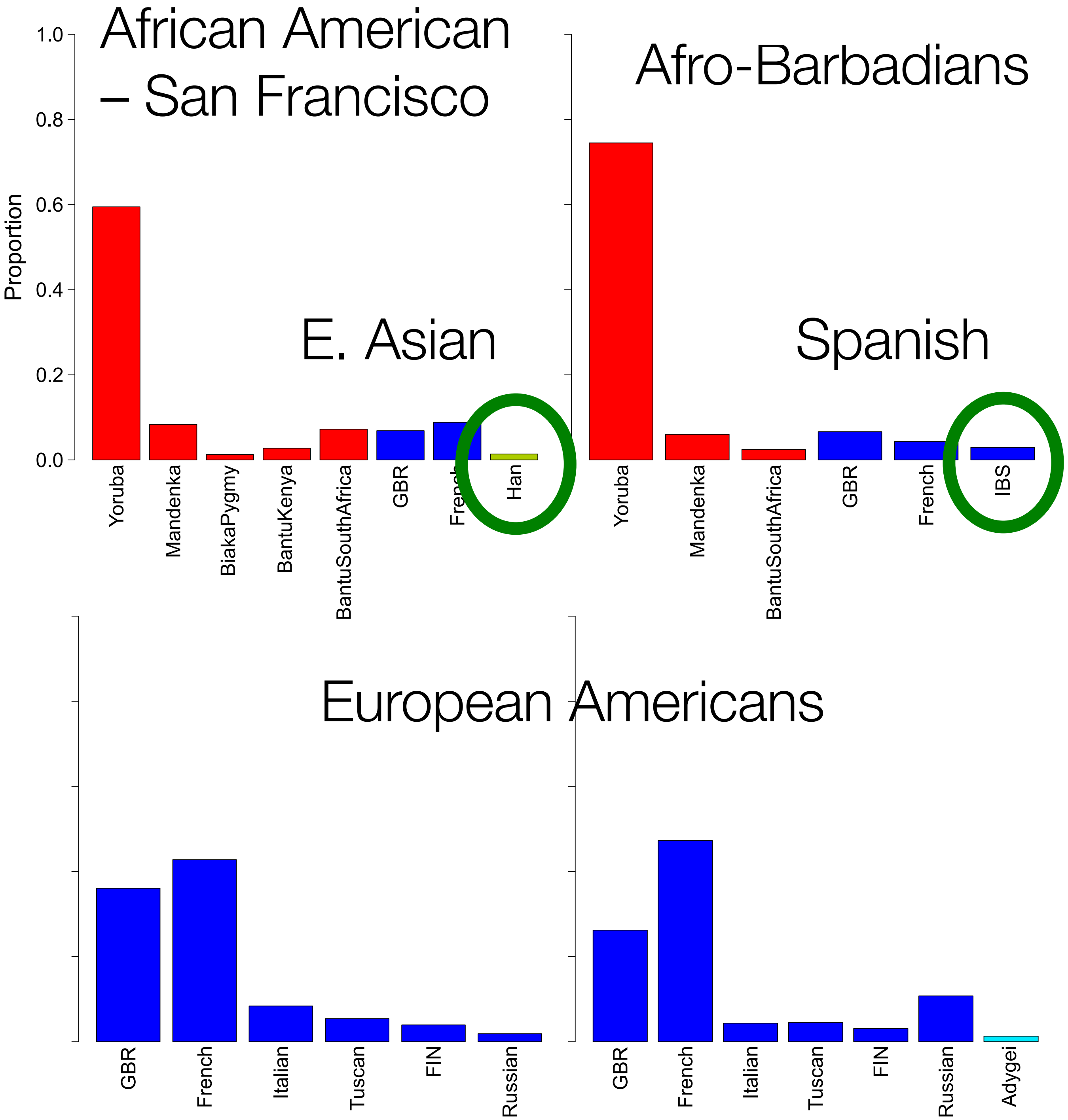

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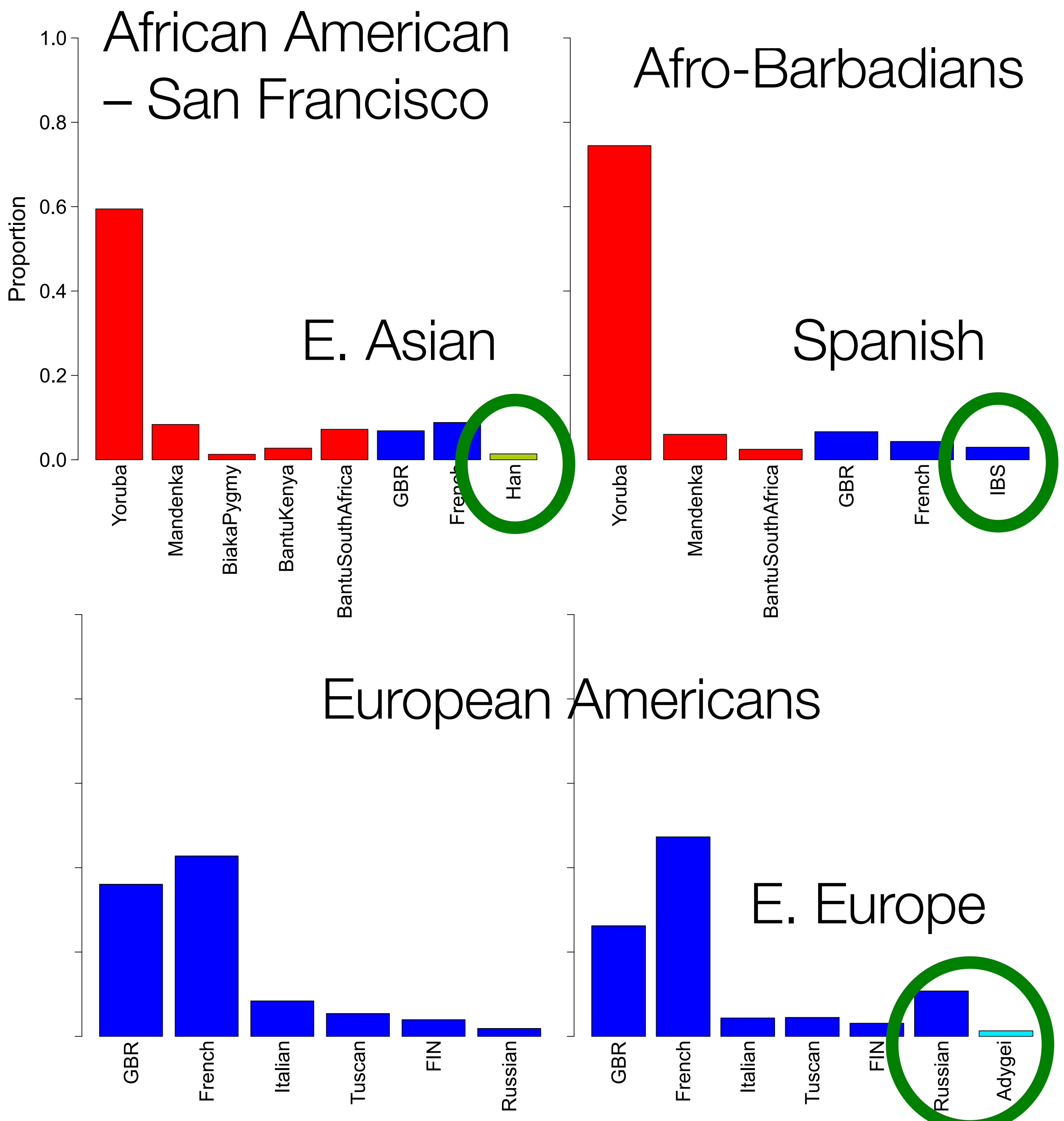
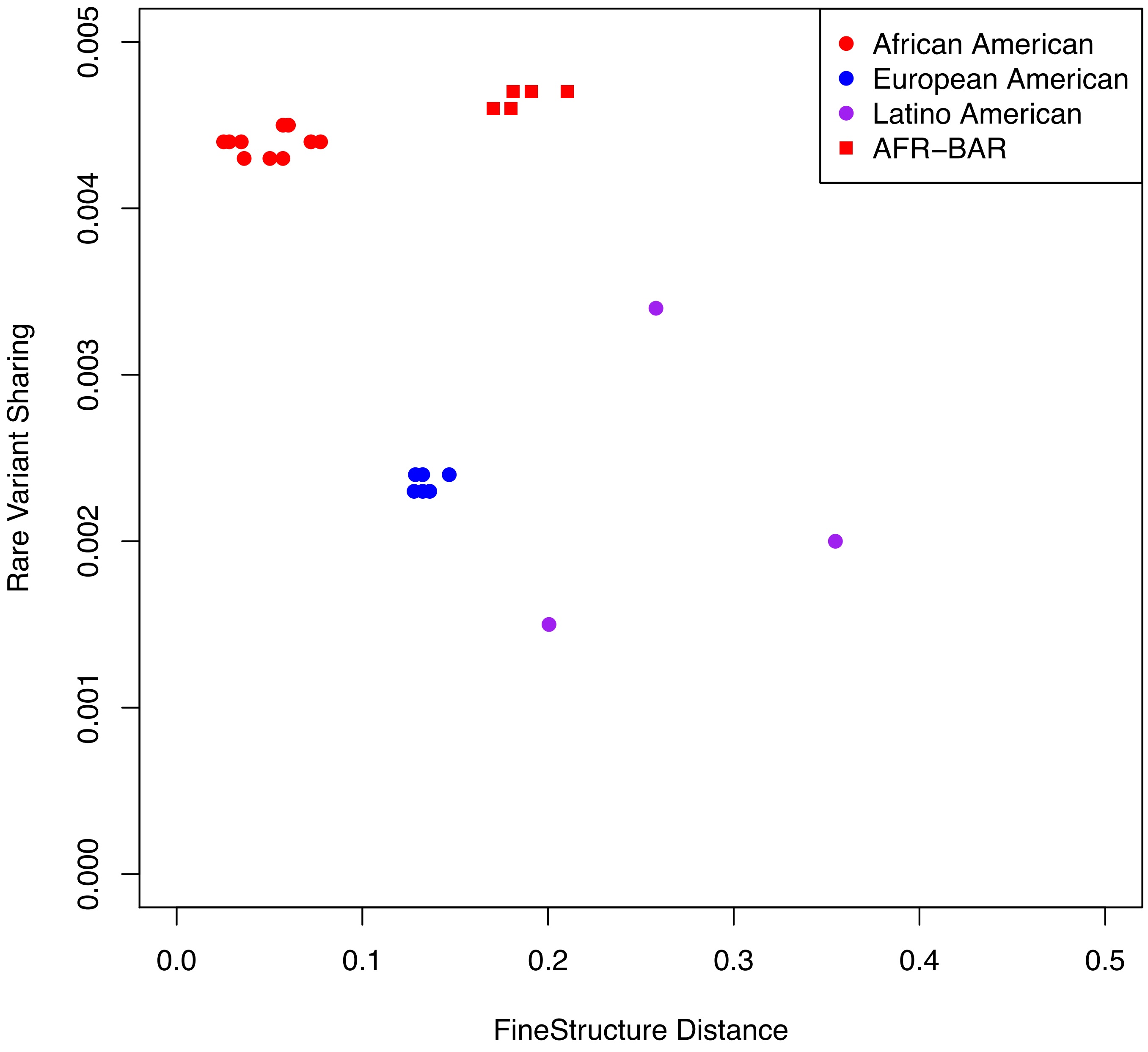


🟥 African
🟦 Caucasia
🟩 East Asian
🟦 European

African American’s have more homogeneous ancestral proportions

- Calculated Euclidian distance between fineSTRUCTURE proportions
- African American cohorts have the shortest distance and the greatest rare variant sharing



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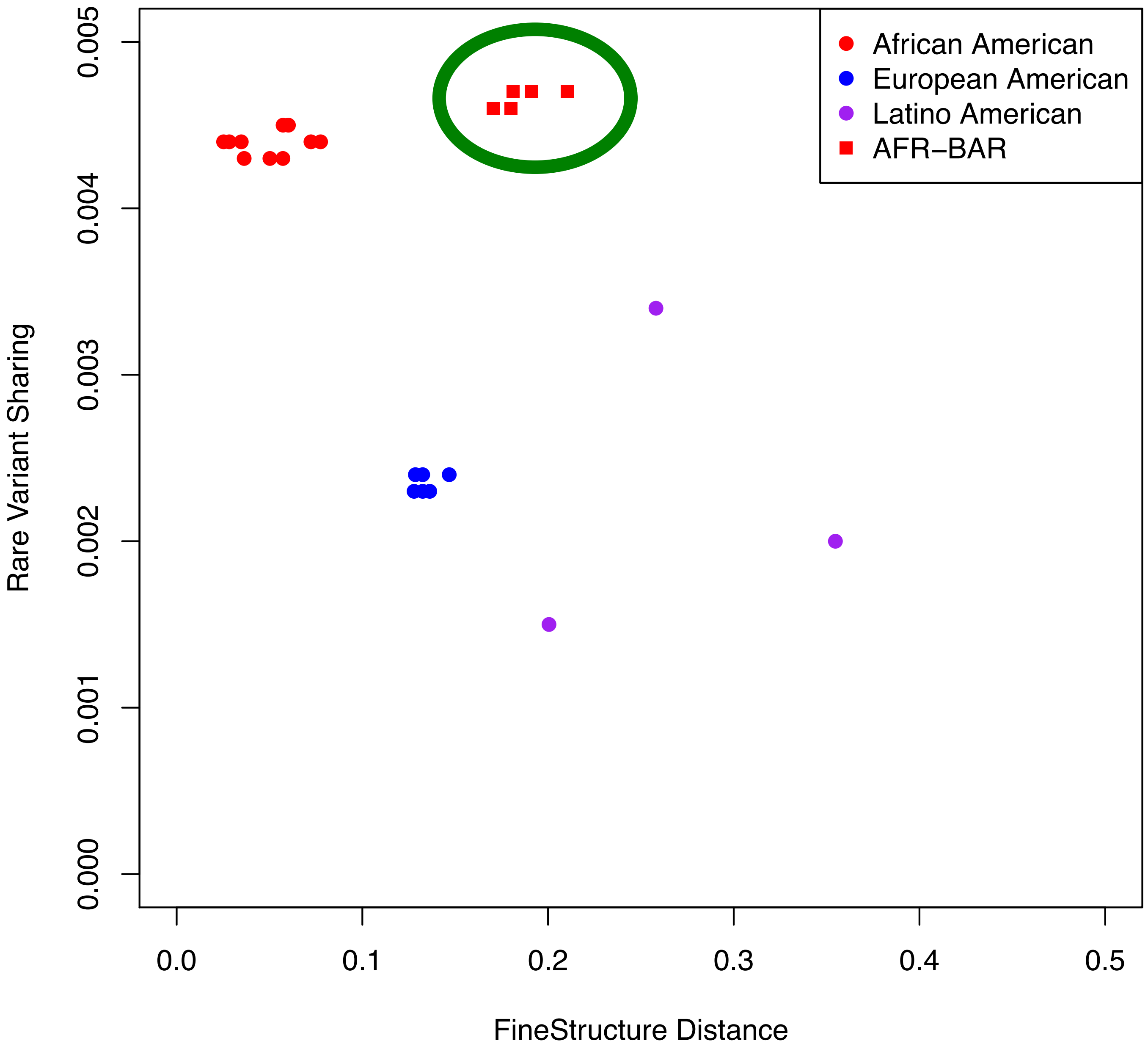
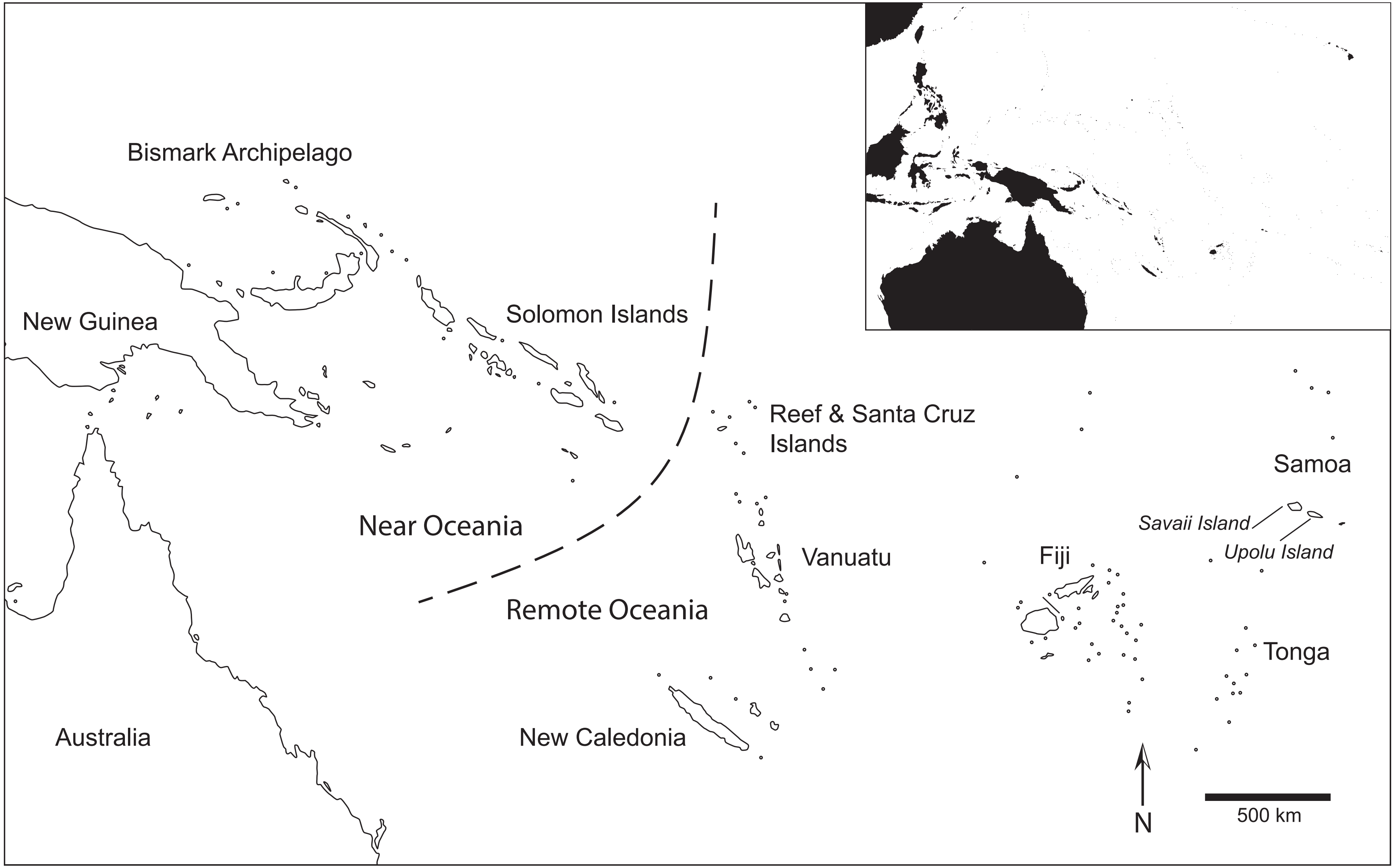


Quick background on Samoa



Harris et al. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3329885)

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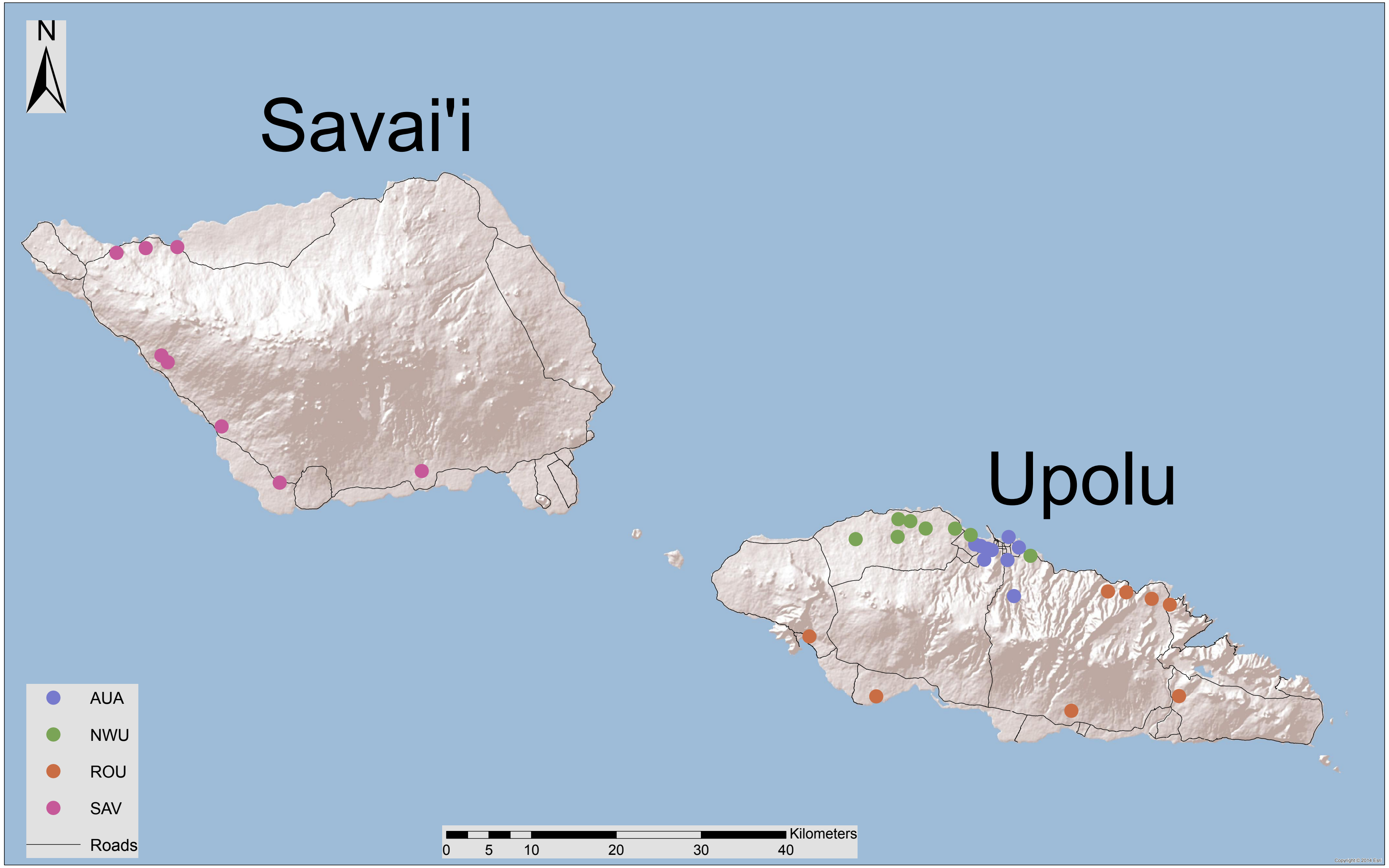
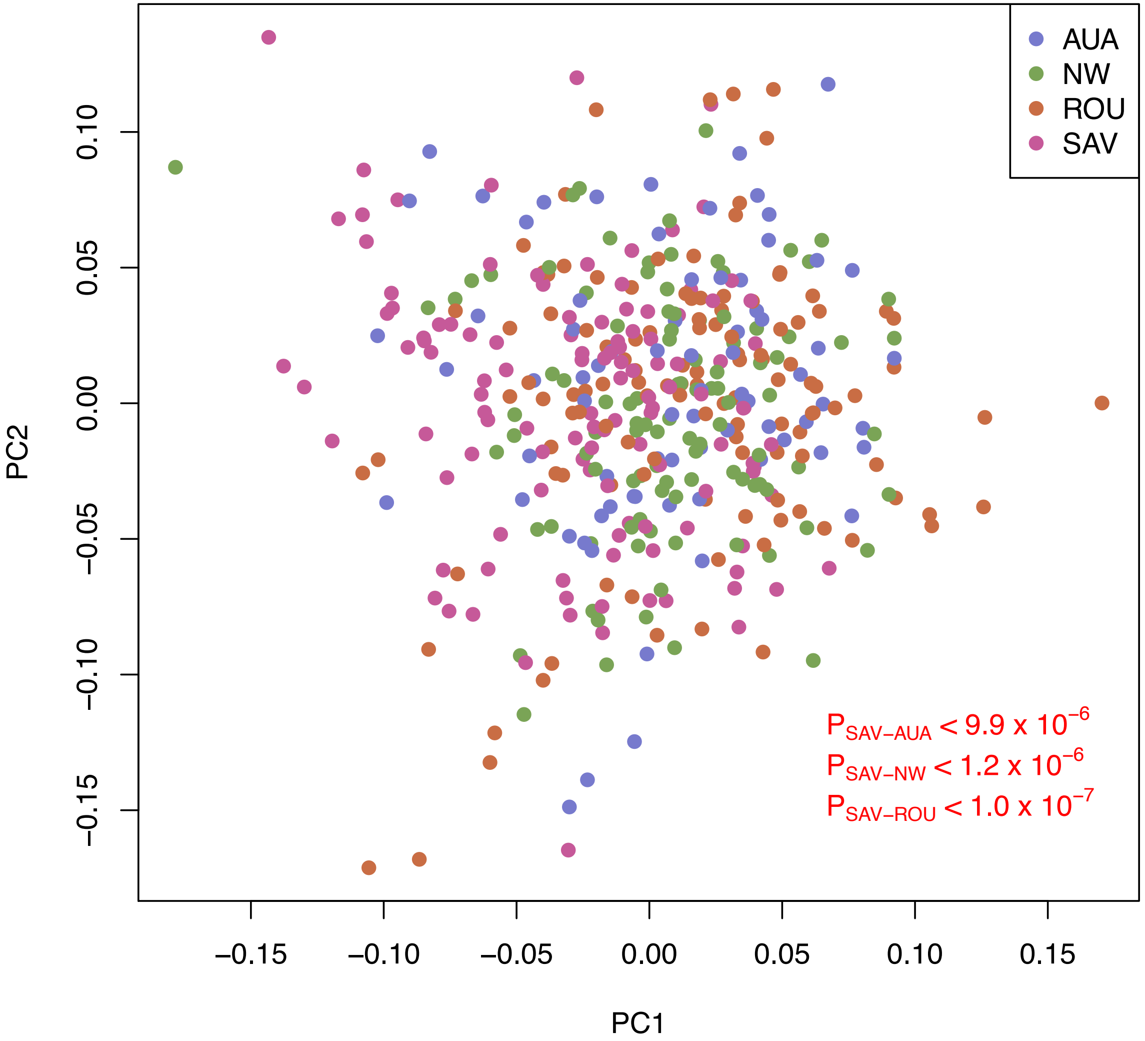


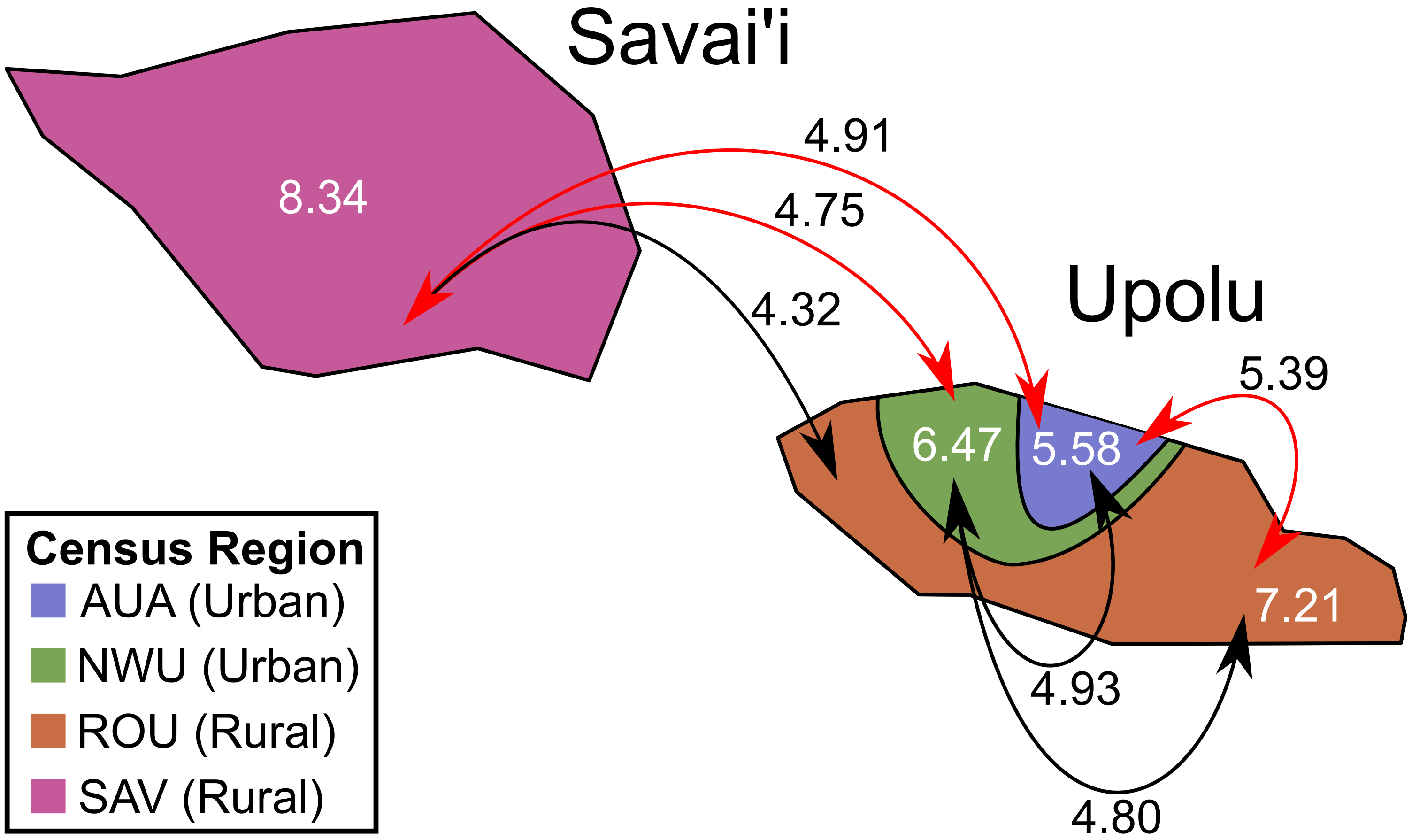
Harris et al. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3329885)

PCA with all variants can't distinguish the two islands well.



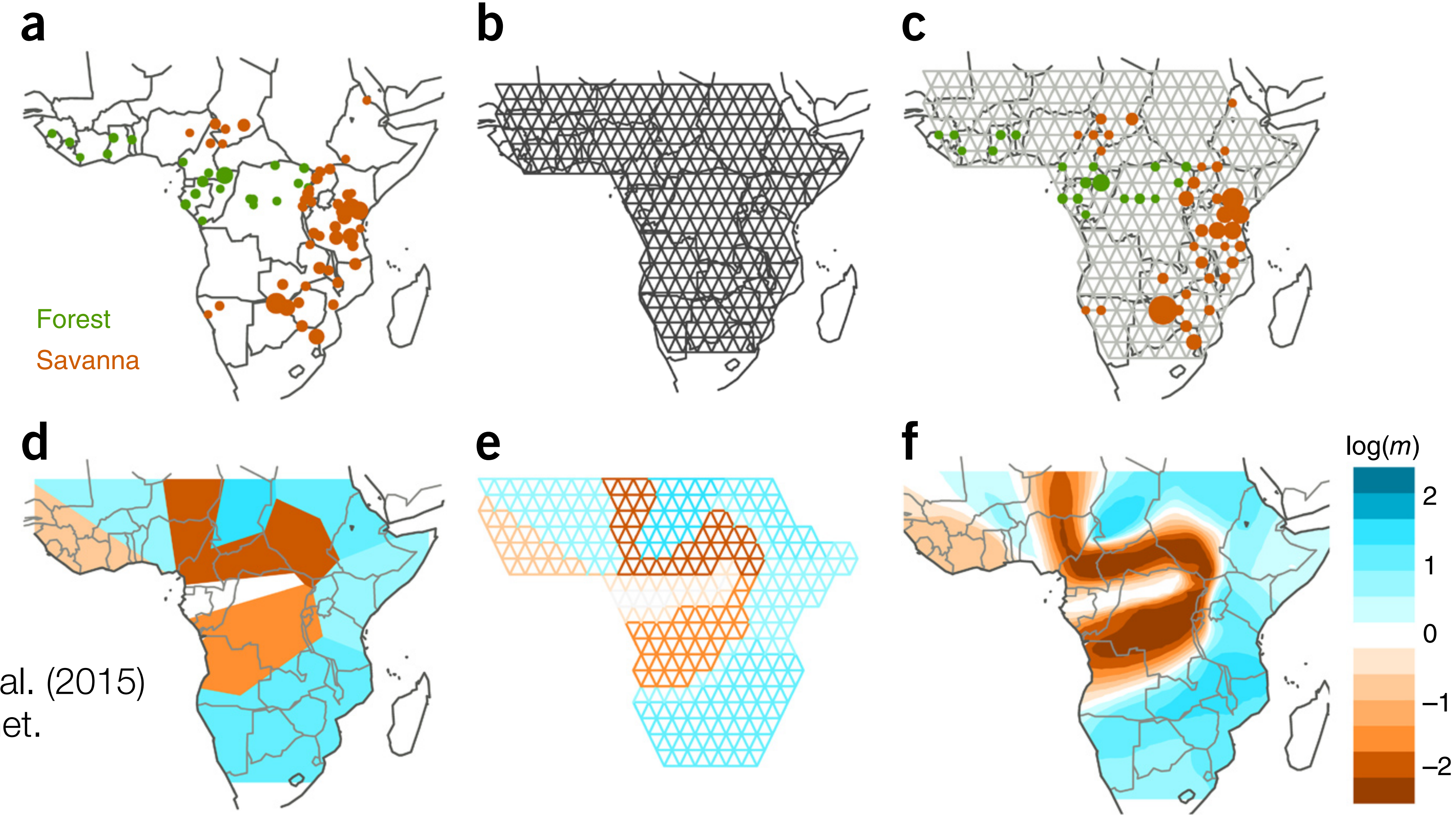
Harris et al. (2020)
PNAS

Rare variant Sharing in Samoa



Harris et al. (2020)
PNAS

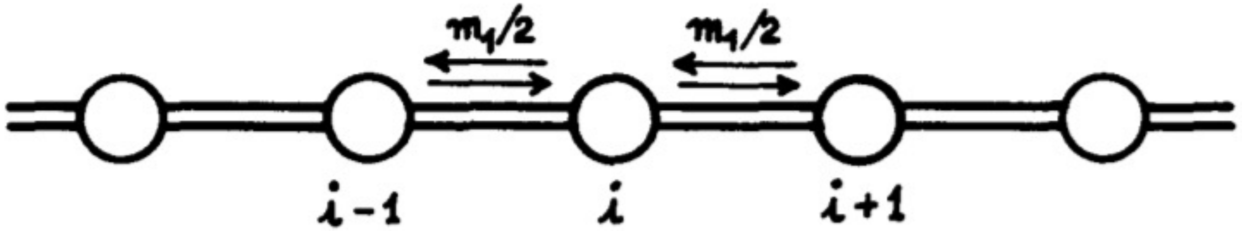
Estimated Effective Migration Surfaces (EEMS)



Petkova et al. (2015) Nature Genet.

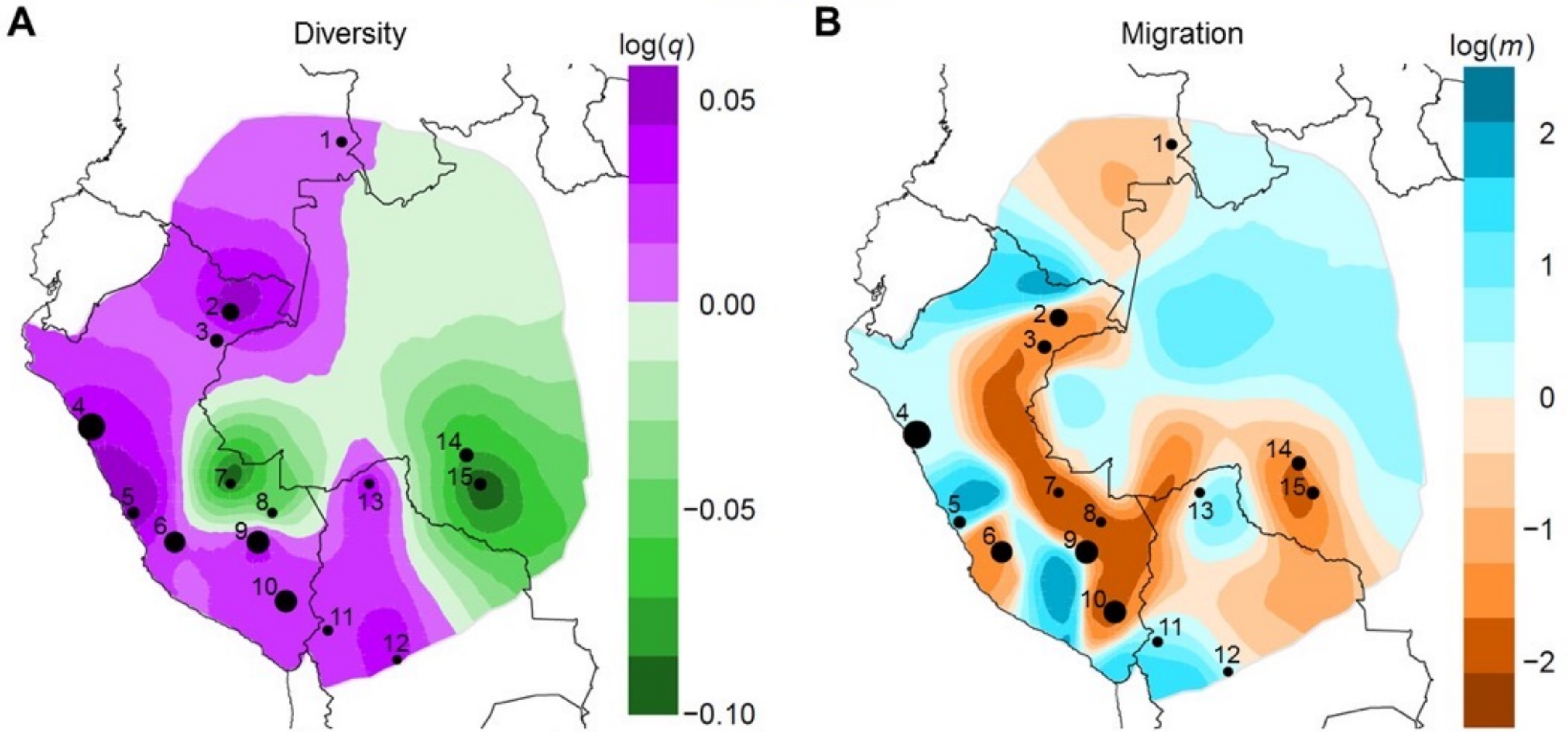
Assumptions: Stepping Stone Model

- Migration can only occur between adjacent demes
- Migration rate between each deme is assumed to be equal



Kimura and Weiss (1964)

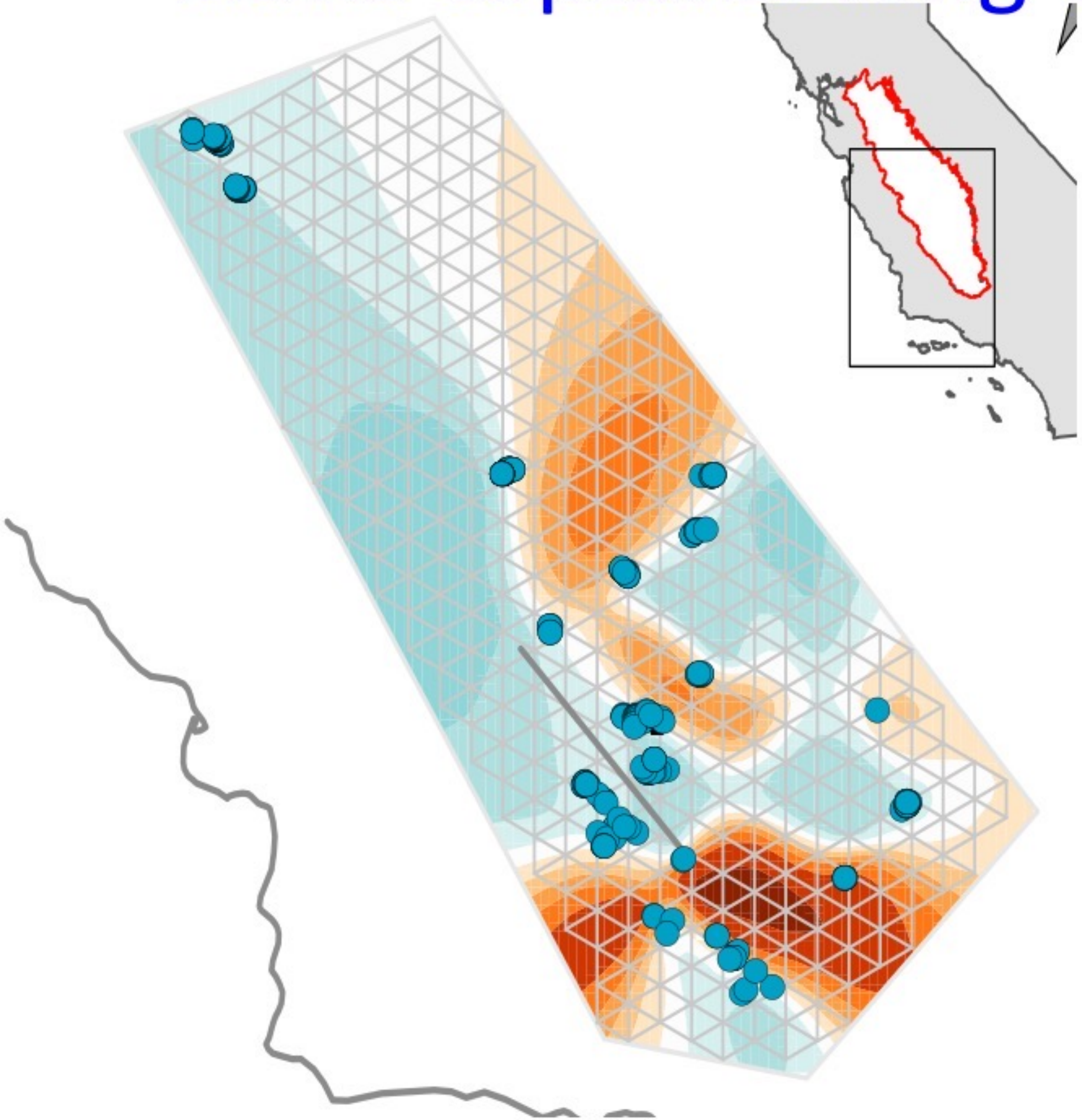
EEMS: Migration and diversity within Peru

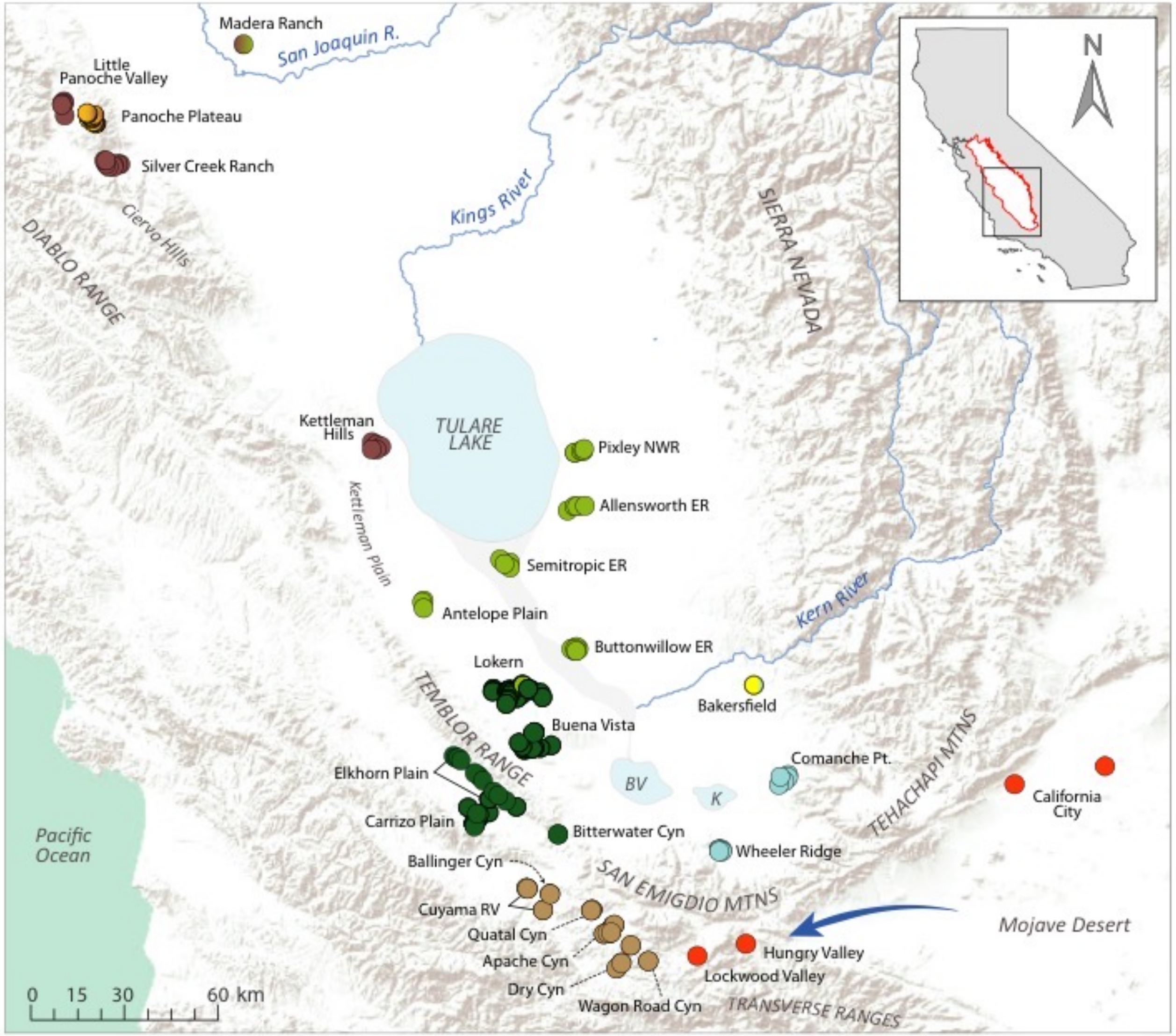


Deme	Populations	Deme	Populations	Deme	Populations	Deme	Populations
1	Piapoco	5	Lima	9	Cusco, Qeros, Quechua	15	Surui
2	Iquitos	6	Chopccas	10	Puno, Uros		
3	Matzes	7	Nahua	11,12,13	Bolivian		
4	Moches, Trujillo	8	Matsiguenka	14	Karitiana		

Harris et al. (2018) PNAS

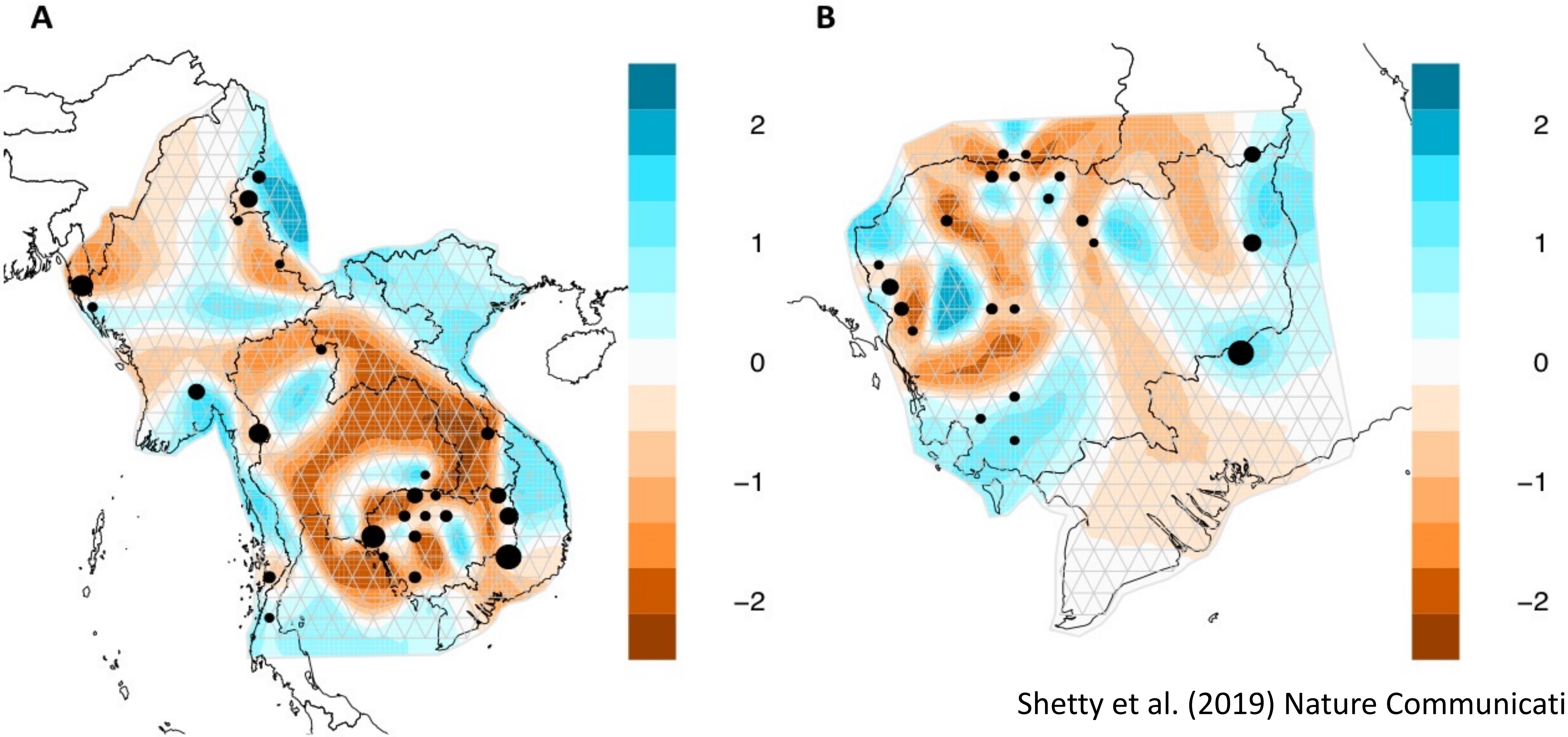
EEMS captures long-term migration patterns





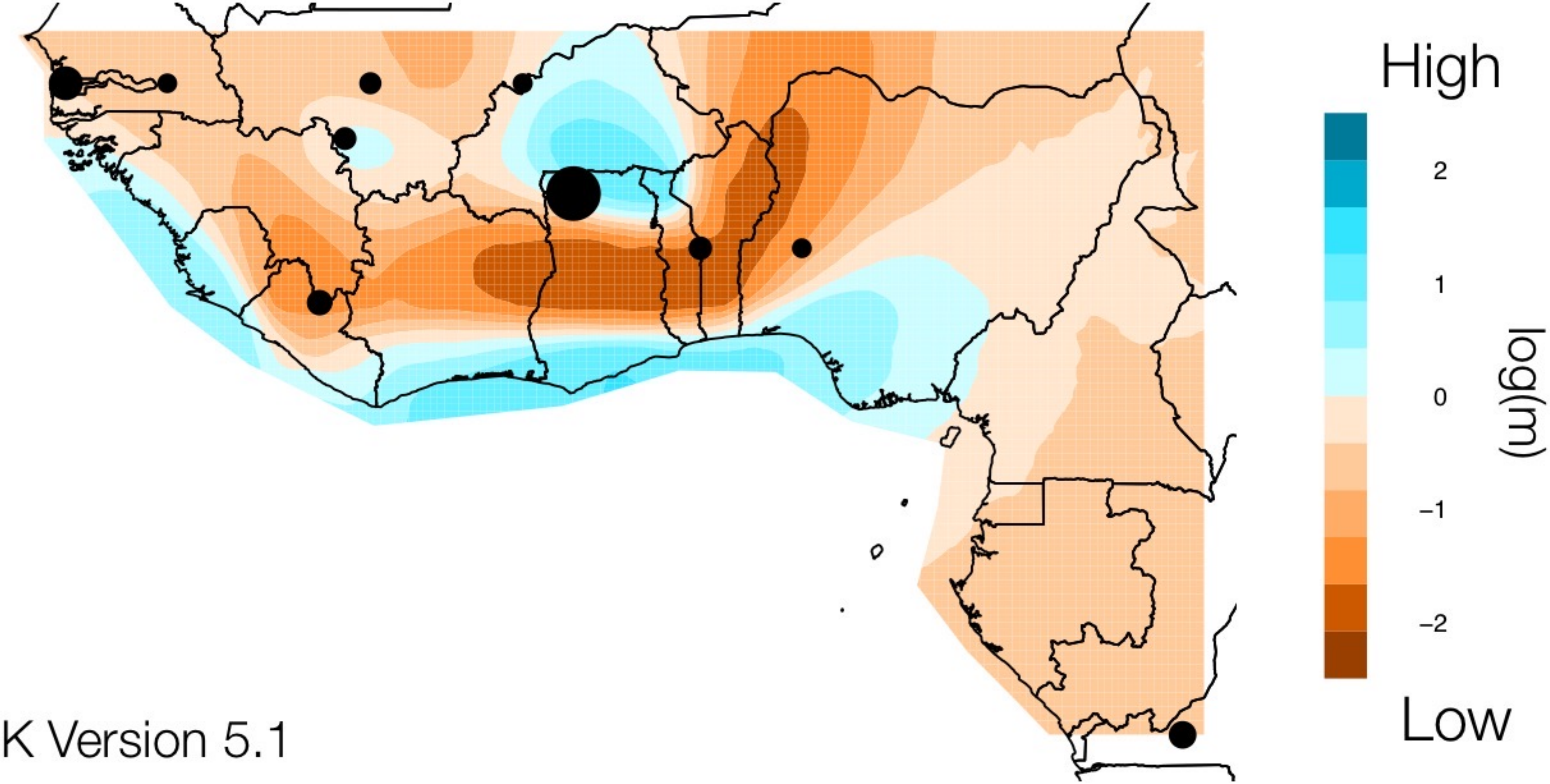
Richmond et al. (2015) Molecular Ecology

EEMS in Malaria Parasites of South East Asia



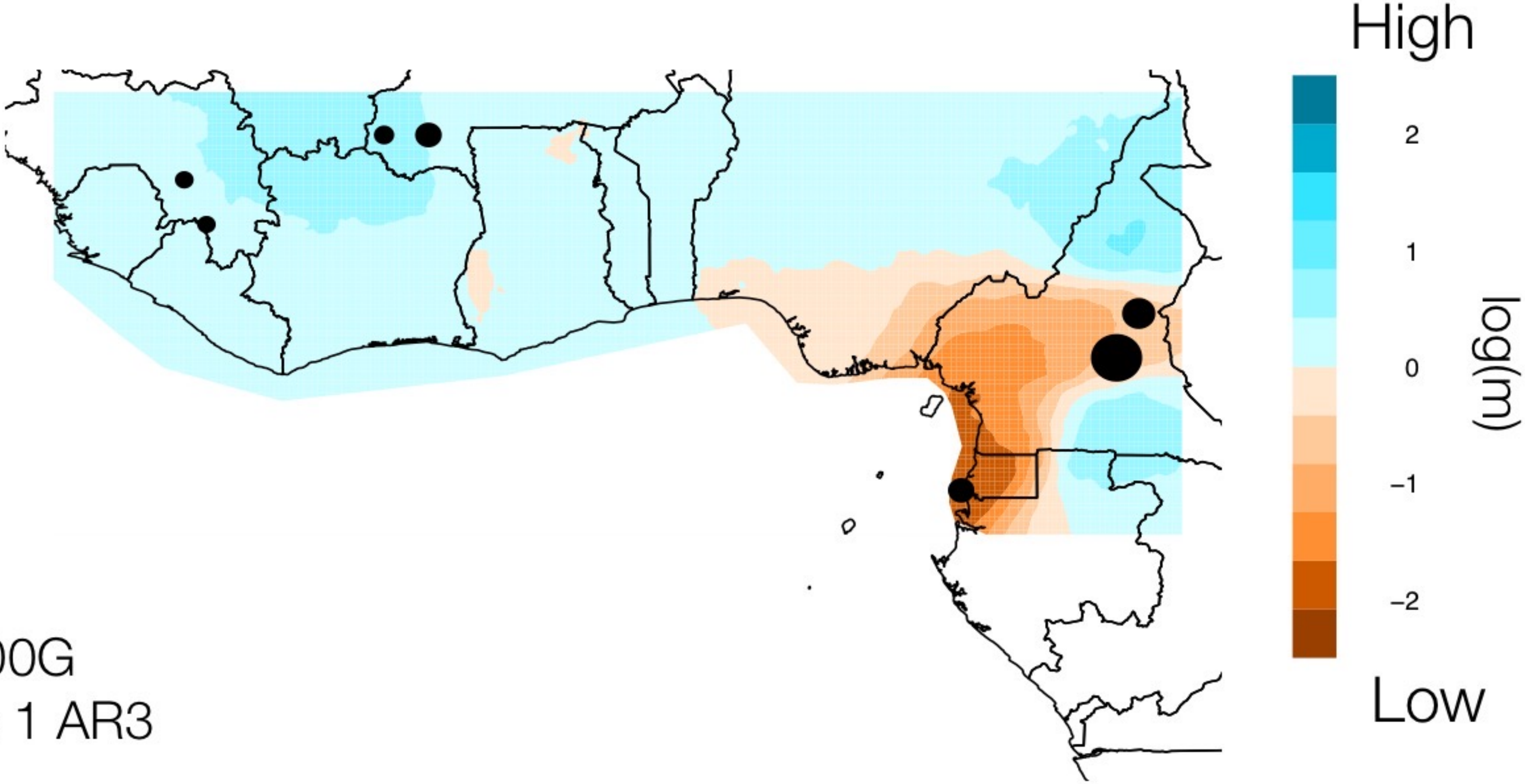
Shetty et al. (2019) Nature Communications

Application to Malaria Parasites in W. Africa



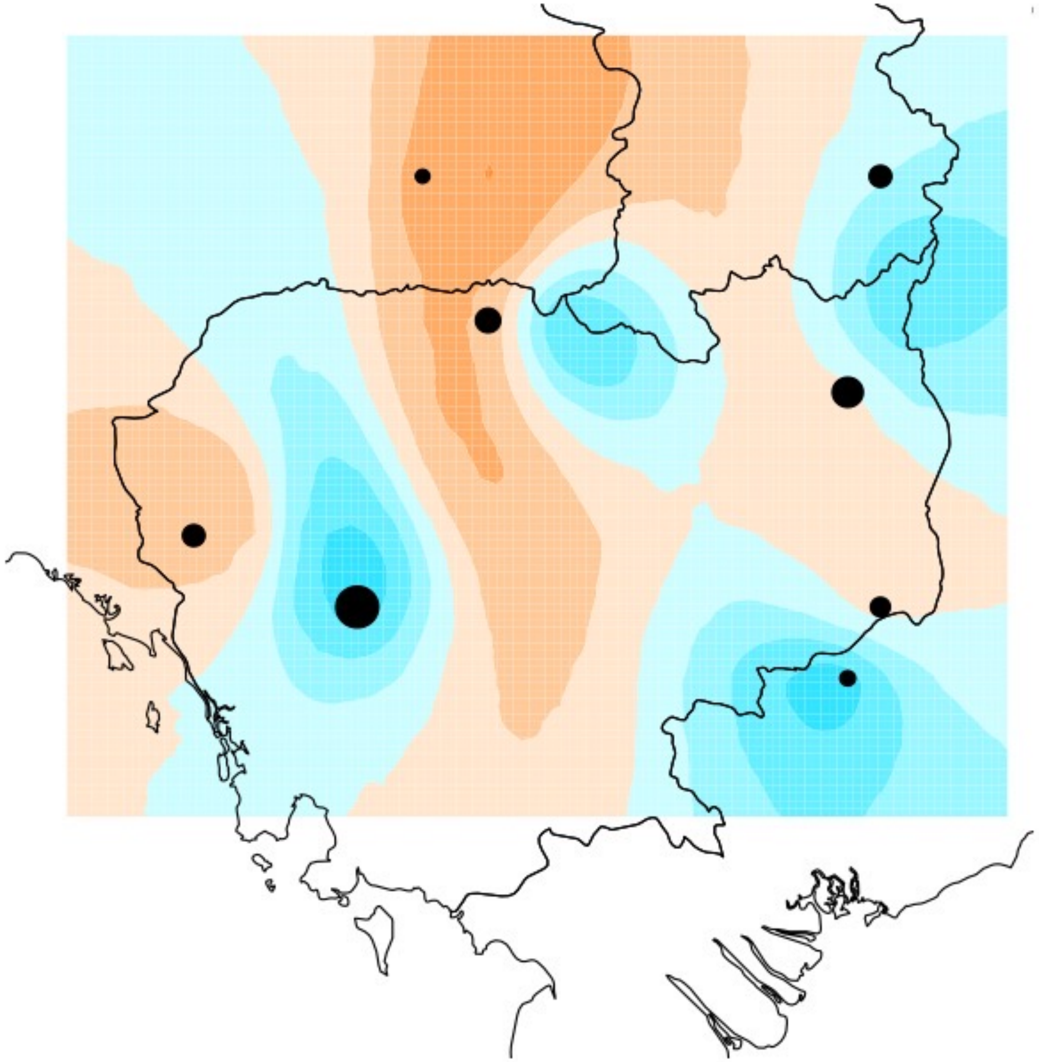
Pf3K Version 5.1

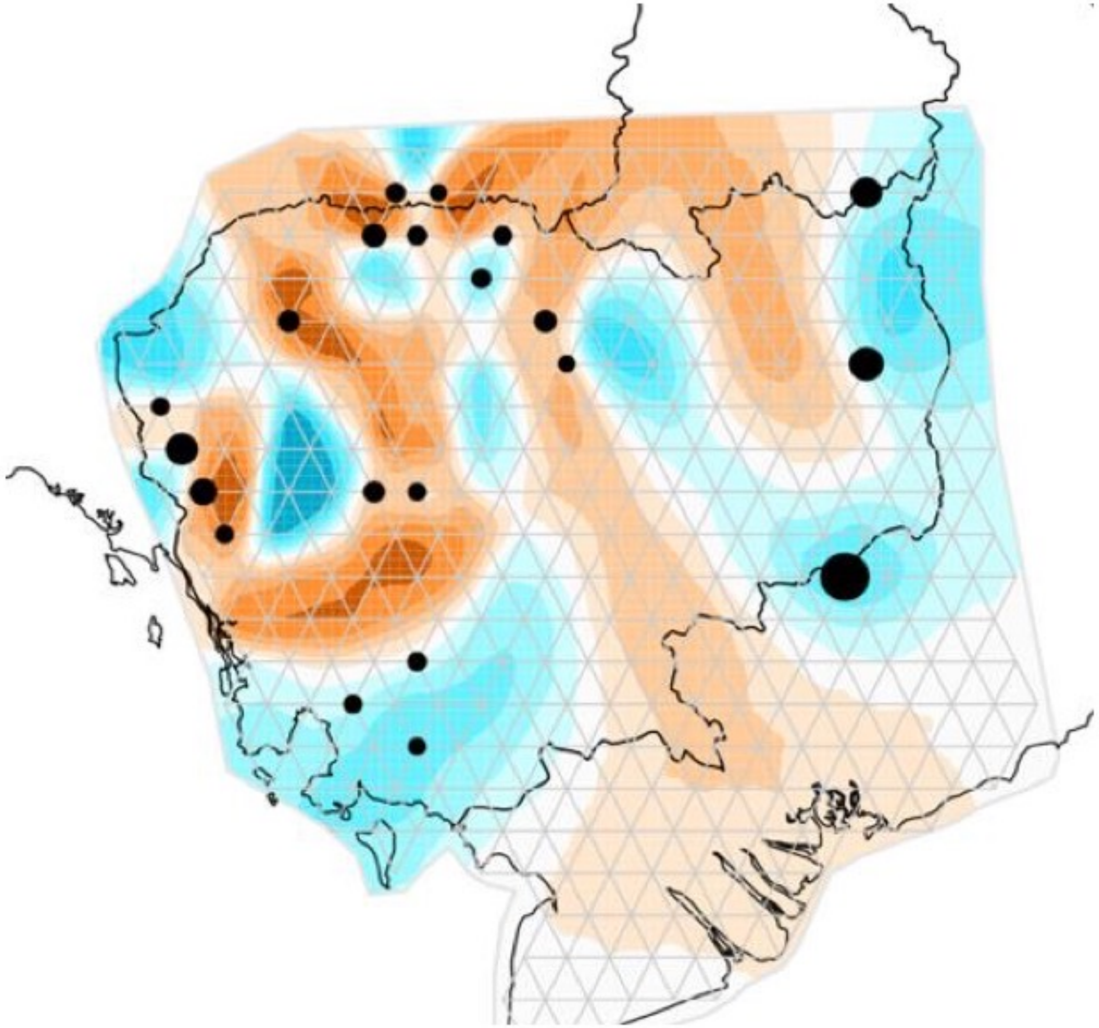
Application to Mosquito in W. Africa



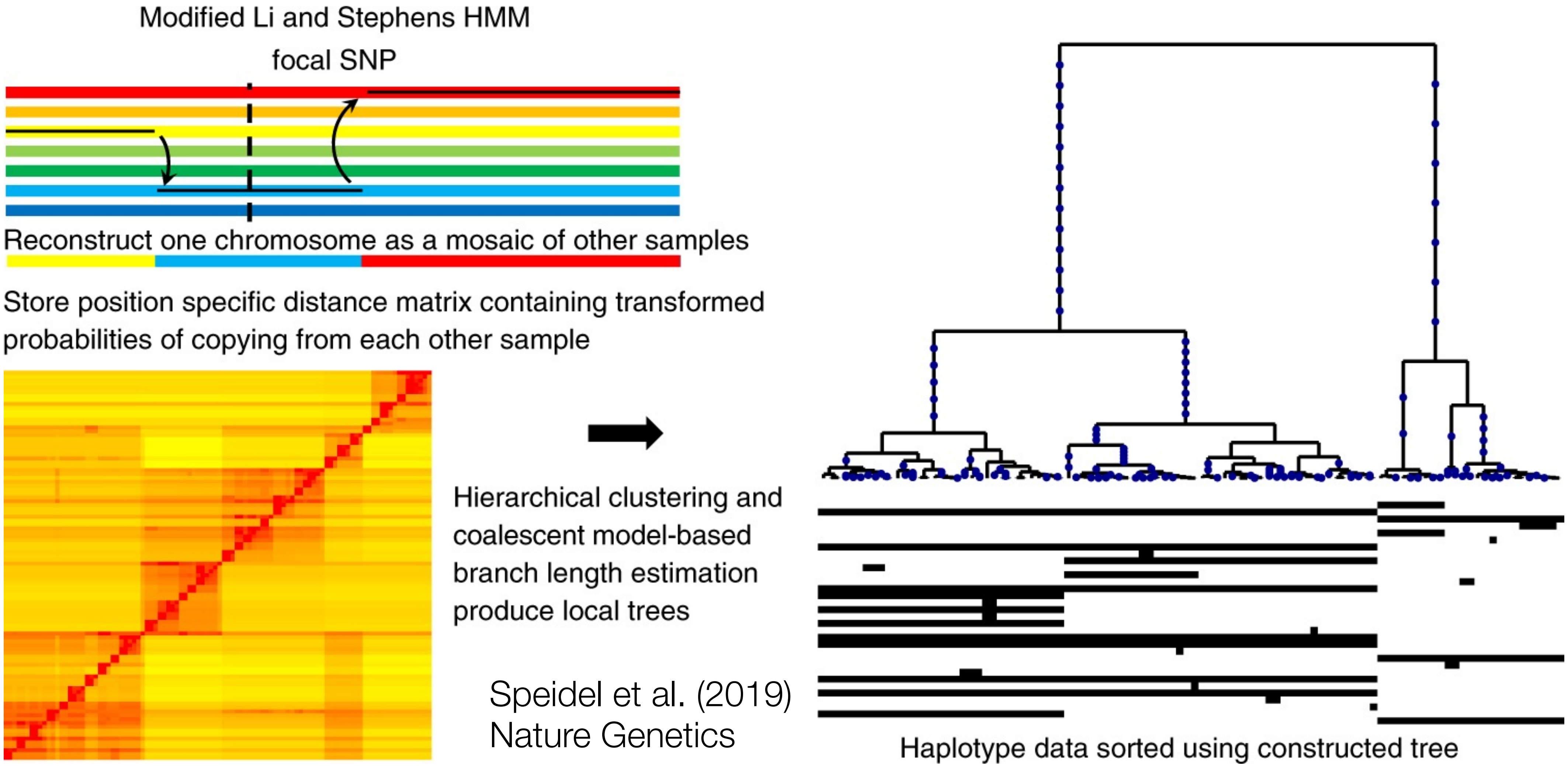
Ag1000G
Phase 1 AR3

Robustness of Sampling on EEMS





RELATE: a means of finding genealogical local genomic relationships



Modified Li and Stephens HMM

focal SNP

Reconstruct one chromosome as a mosaic of other samples

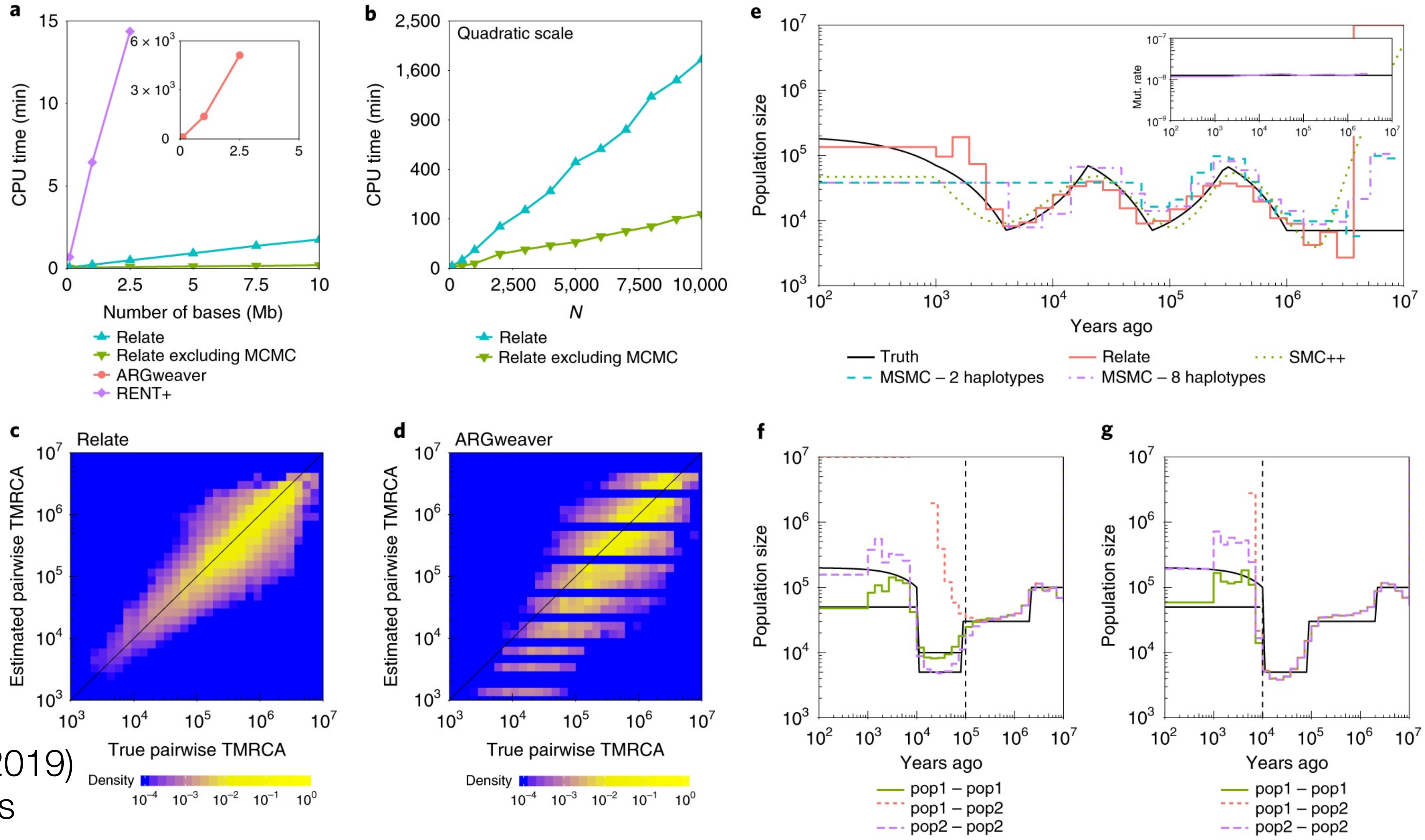
Store position specific distance matrix containing transformed probabilities of copying from each other sample

Hierarchical clustering and coalescent model-based branch length estimation produce local trees

Haplotype data sorted using constructed tree

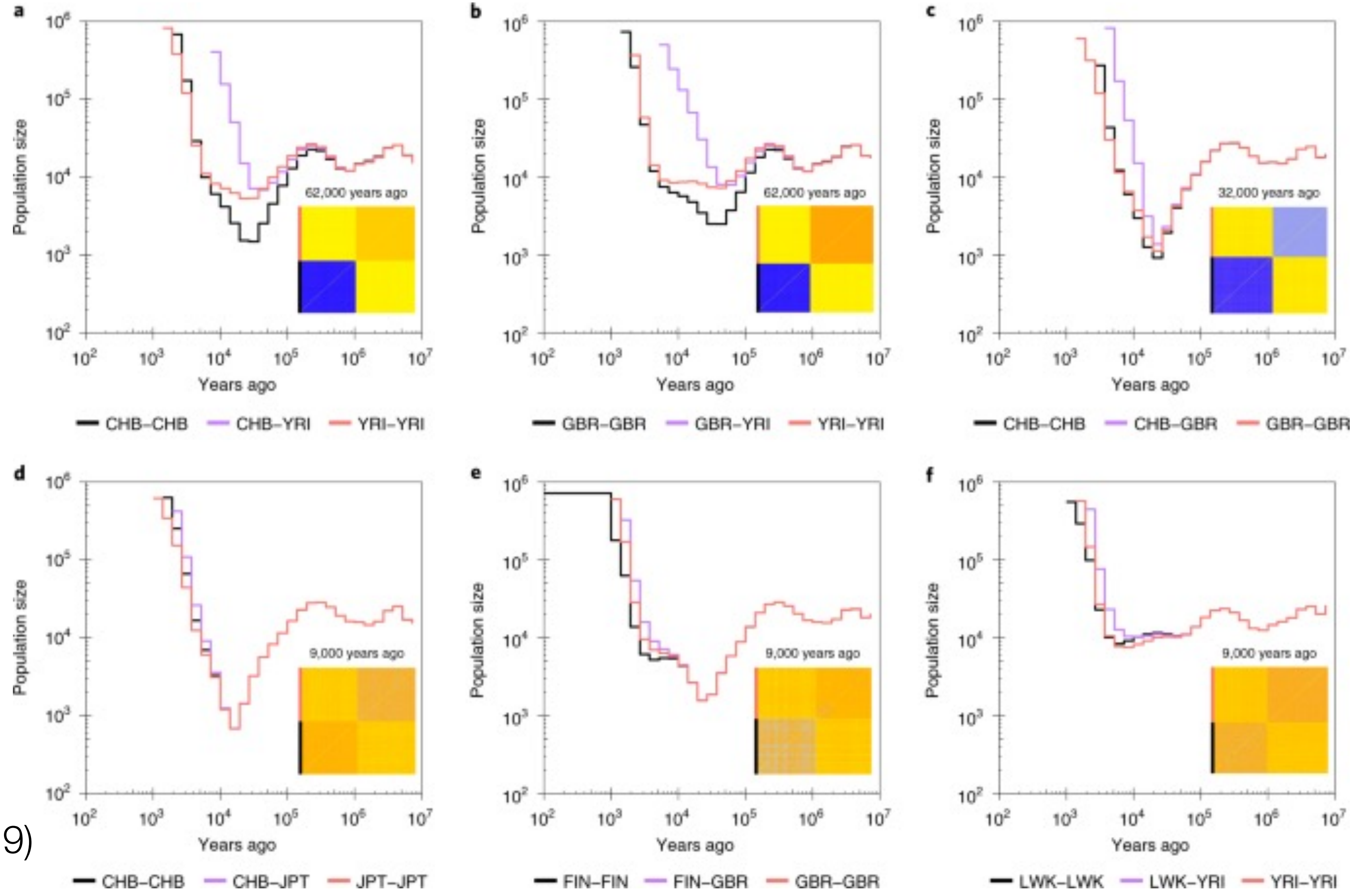
Speidel et al. (2019)
Nature Genetics

RELATE of course was tested with simulation!



Speidel et al. (2019)
Nature Genetics

RELATE tested on 1000 Genomes Data



Speidel et al. (2019)
Nature Genetics

Concluding summary

- Fine-scale population structure is subdivisions of individuals on an ever increasingly granular scale
- Identity-by-descent and rare variant sharing are a powerful methods of identifying recent relationships and can be scaled by time.
- Cryptic population structure arises with extended relationships within a cohort, unknown to the investigators.
- EEMS can visualize migration patterns on a fine-scale illustrating cryptic structure not observed with other methods

Questions?