Selection on Archaic Genes

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Outline

- Adaptive introgression of archaic alleles.
- Purifying selection against archaic alleles.

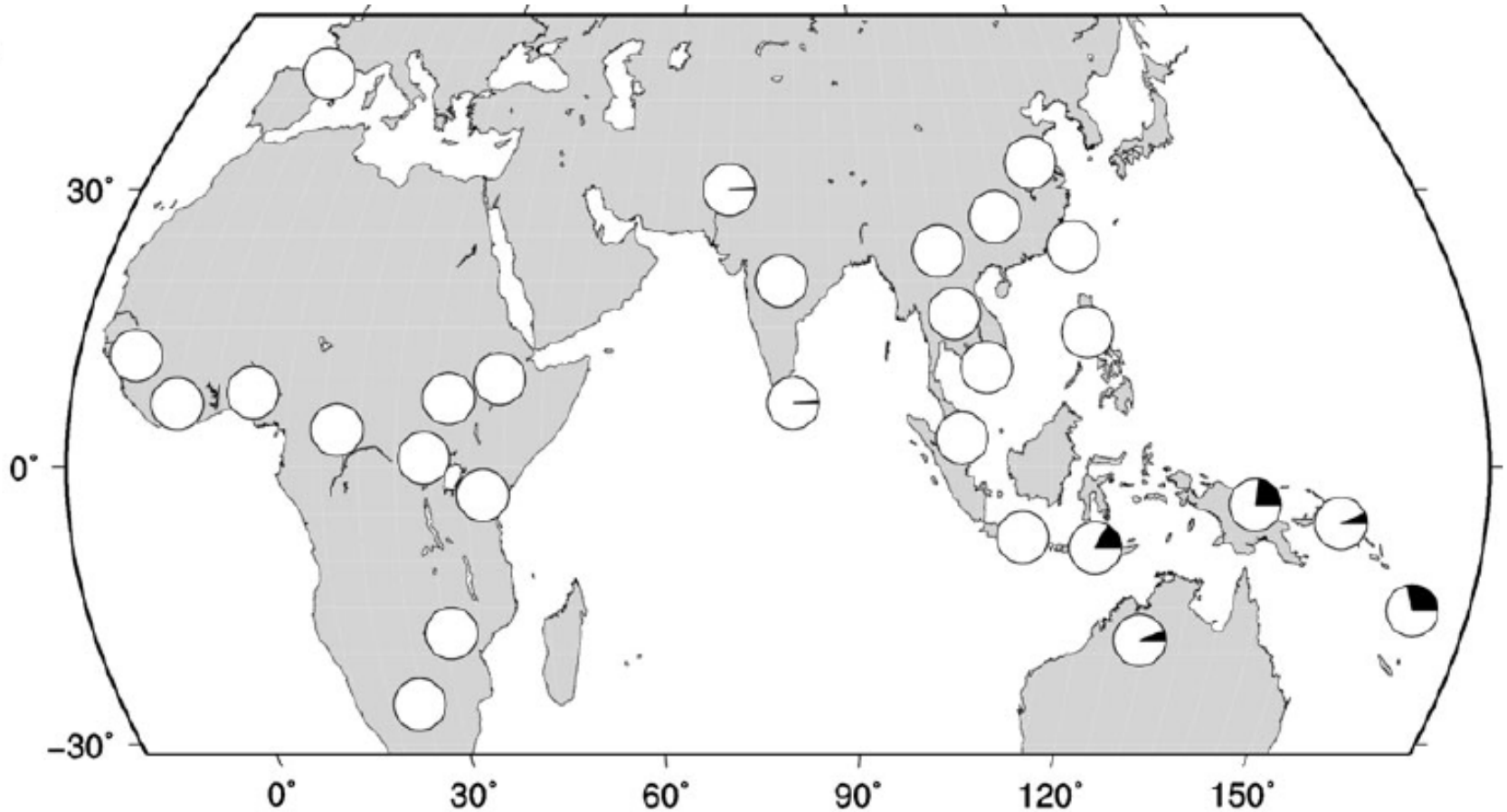
Using LD to discover admixed chromosome segments

1. Recent introgression $\rightarrow$ modern genomes should contain long segments archaic chromosome.
2. These segments should differ a lot, because of the long separation time.

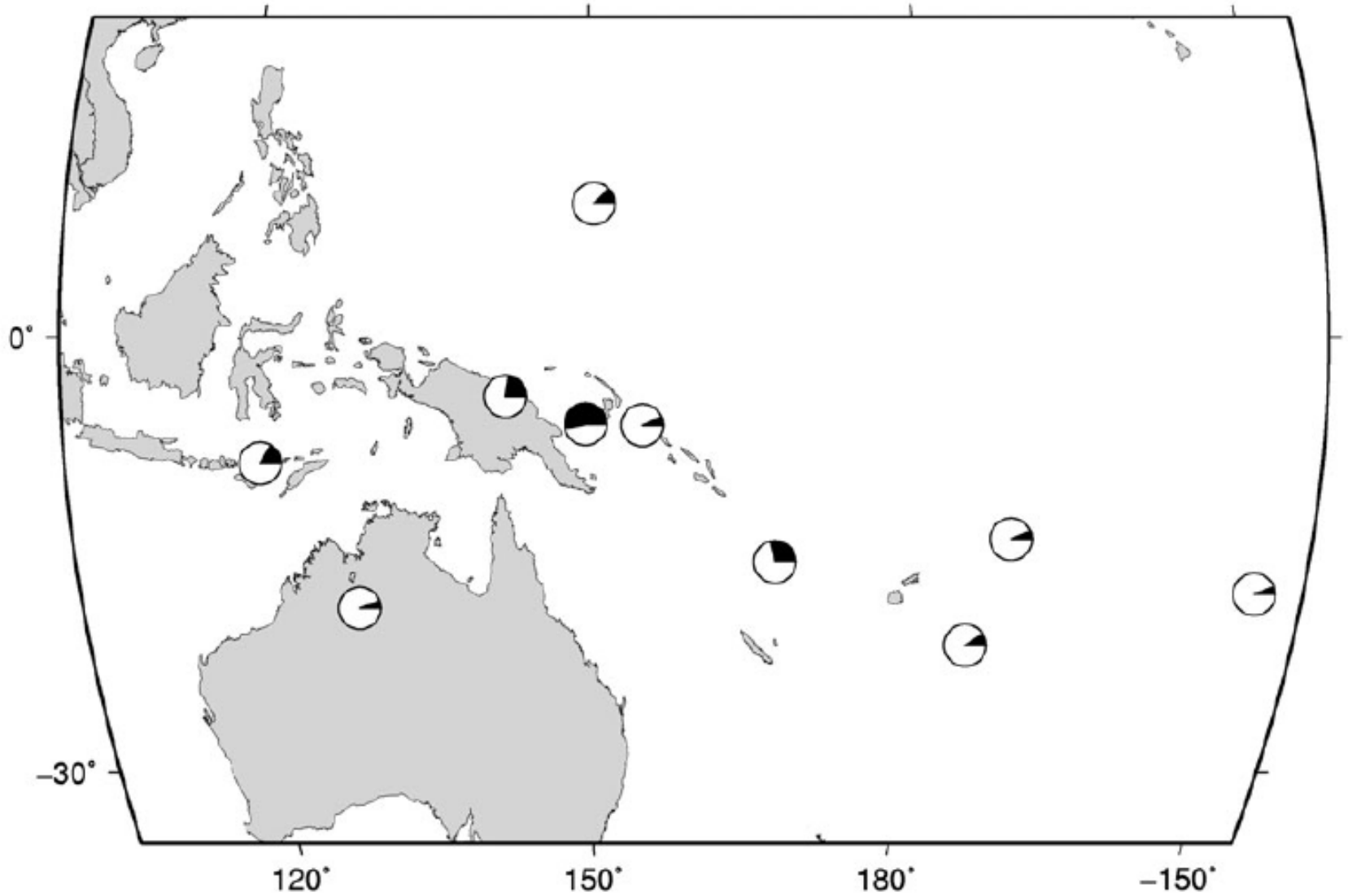
OAS1 innate immunity locus

- two forms of gene in Melanesia:
- one shared with rest of world
- one only in Melanesia

Worldwide frequency of Melanesian OAS1 allele



Melanesian OAS1 allele w/i Melanesia



Melanesian OAS1 allele is old yet young

- The 2 alleles differ at many nucleotide sites $\Rightarrow$ separation time $\sim$3.4 my.
- Long (90 kb) LD block $\Rightarrow$ they've been together only $\sim$25 ky
- Melanesian allele matches that in Denisovan hominin skeleton.

$\Rightarrow$ archaic admixture into Melanesia

HLA loci

The loci of the HLA system underlie adaptive immunity in humans.

Abi-Rached et al (2011) estimate that $> 50\%$ of Eurasian HLA alleles came from archaics.

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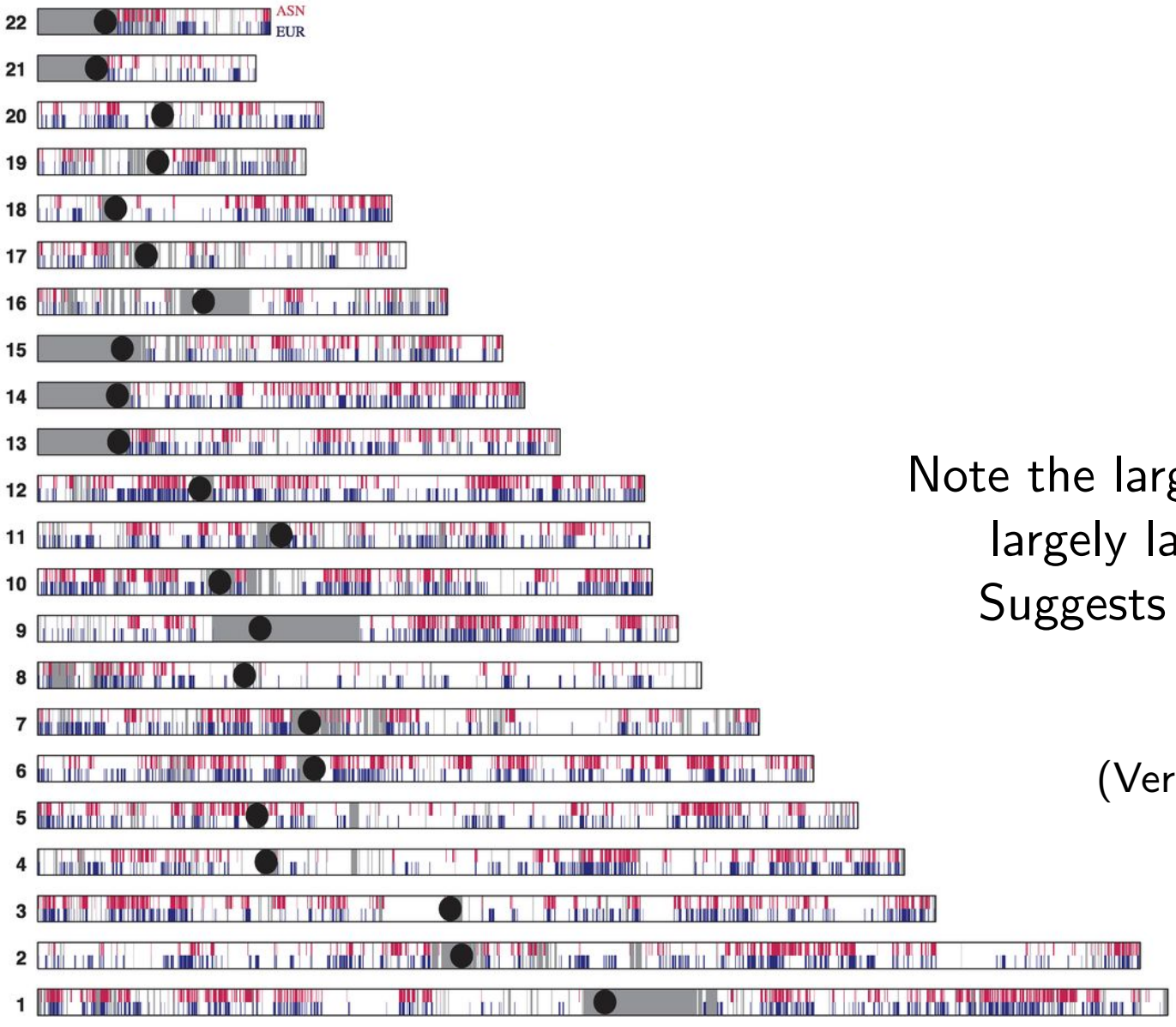
Method of Vernot and Akey (2014)

1. S^* statistic (Plagnol & Wall 2006) uses modern LD to find candidate introgressed segments.
2. Accept candidate if matches Neanderthal sequence better than chance.
3. Studied 379 Europeans and 286 East Asians.
4. Found 15 Gb introgressed sequence spanning 20% of Neanderthal genome.

Neandertal segments in modern genomes



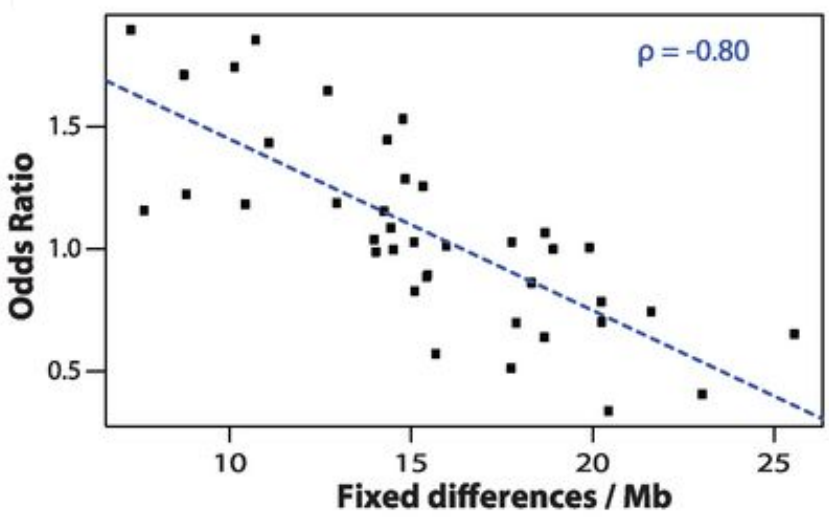
red: Asians

blue Europeans

Note the large "deserts" that largely lack archaic DNA. Suggests selection against archaic alleles.

(Vernot and Akey 2014)

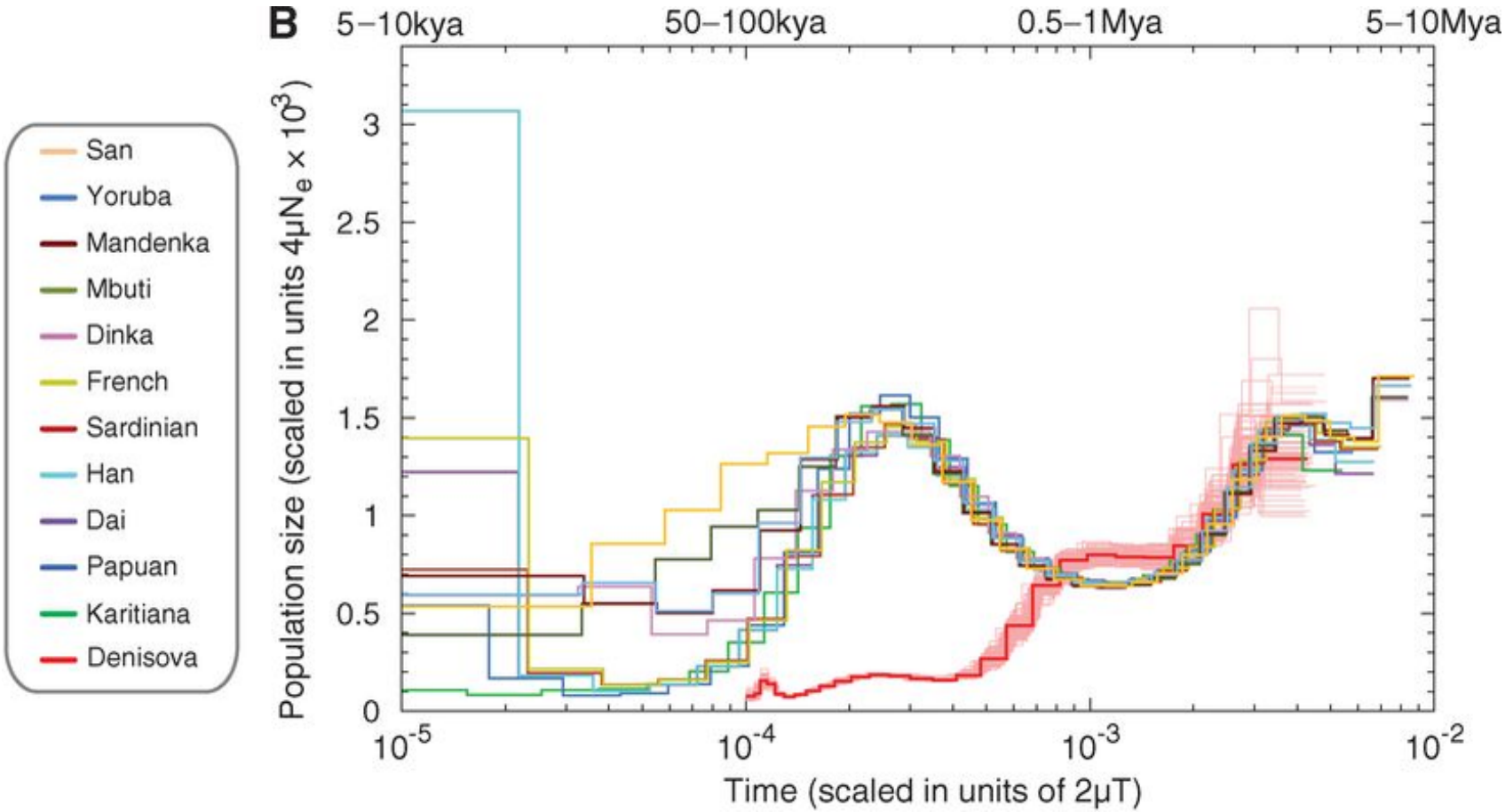
Barrier to gene flow between Neanderthals and moderns



Introgressed segments rare in genomic regions where moderns differ greatly from Neanderthals.

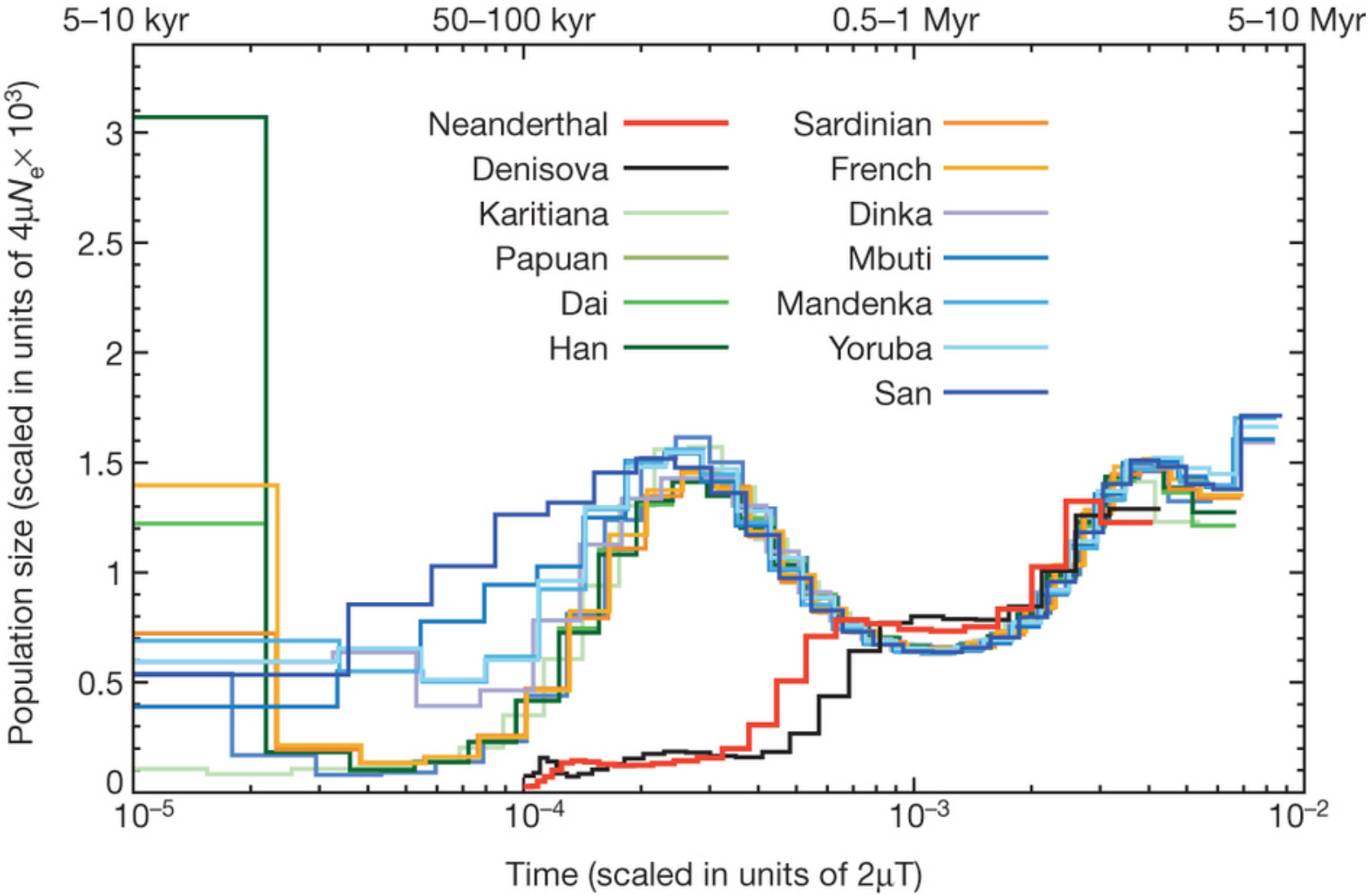
Suggests partial reproductive isolation.

History of population size from single diploid genomes: the pairwise sequentially Markovian coalescent (PSMC)



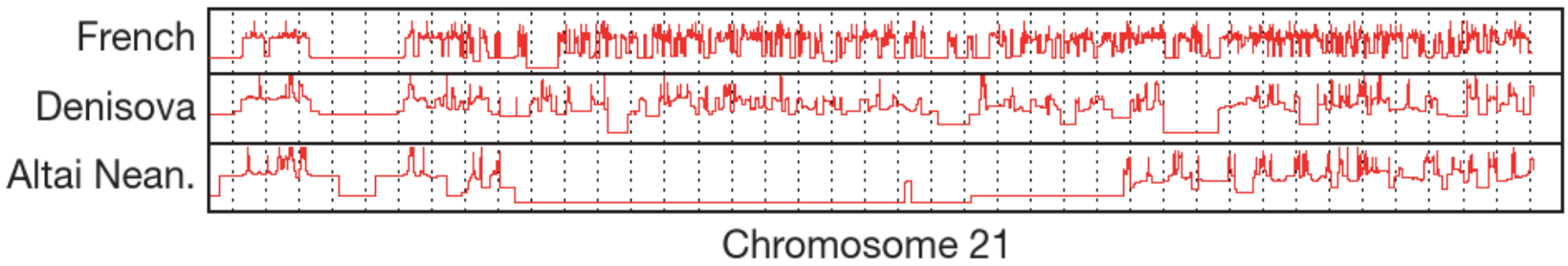
(Meyer et al 2012)

PSMC with Neanderthal as well as Denisova



(Prüfer et al 2014)

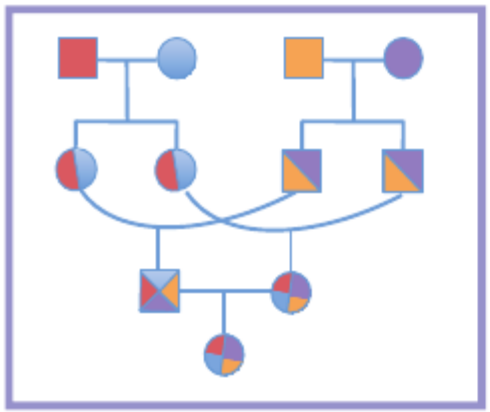
Estimated times to most recent common ancestor (TMRCA)



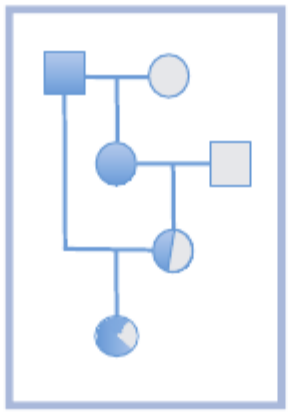
Long stretches of low TMRCA $\Rightarrow$ recent close inbreeding.

(Prüfer et al 2014)

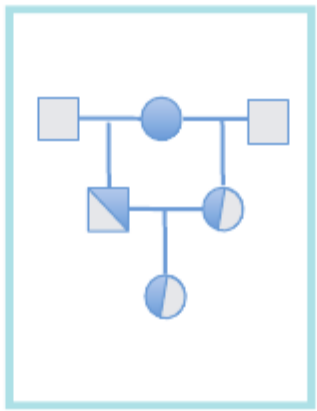
Altai Neanderthal was very closely inbred



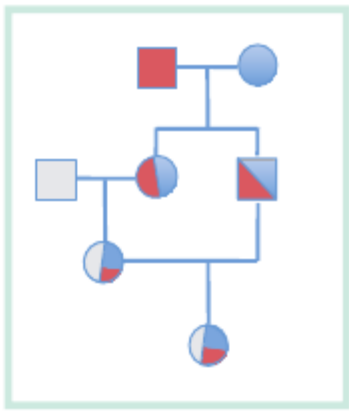
Double first cousins



Grandfather and granddaughter*



Half siblings

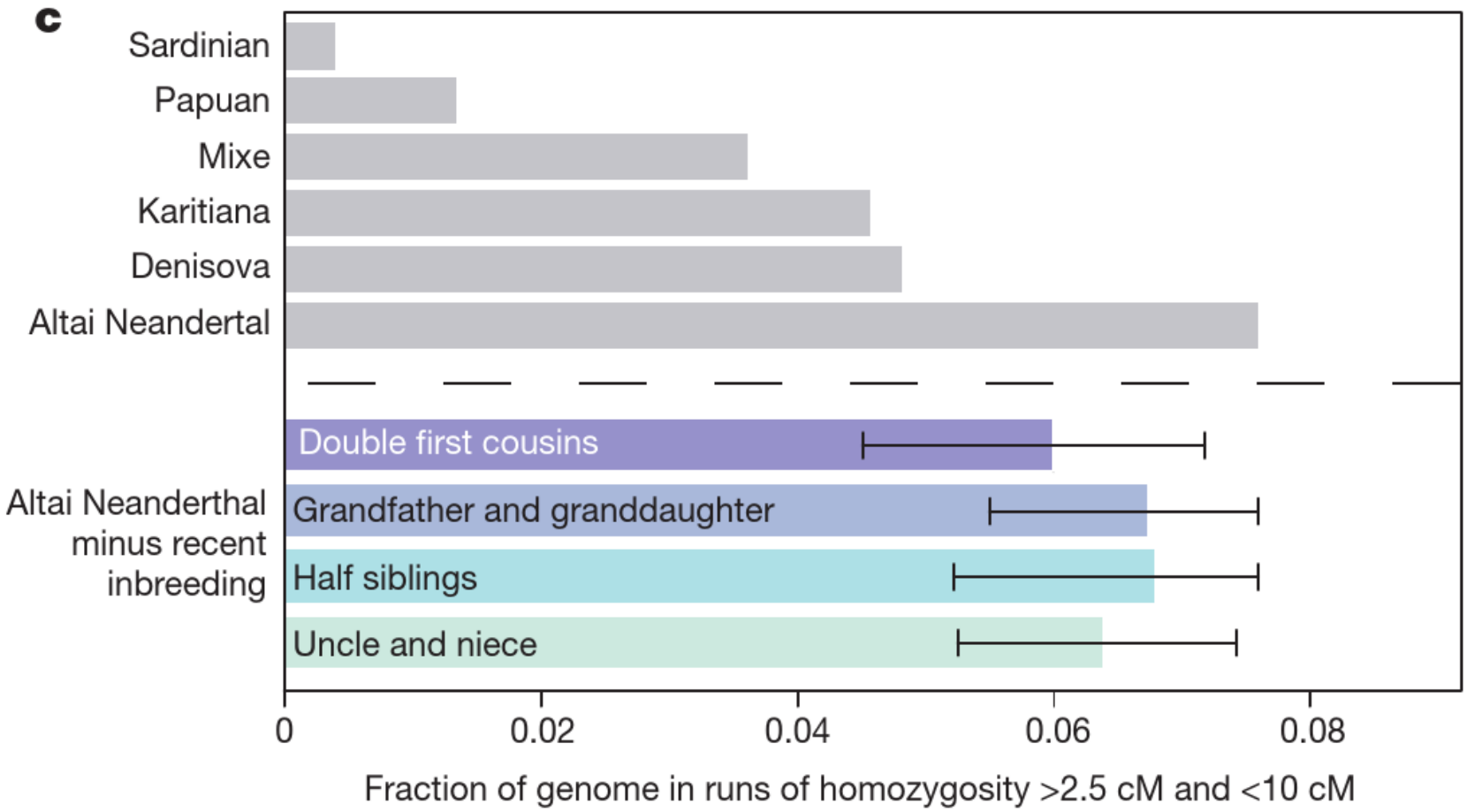


Uncle and niece*

All of these pedigrees are plausible.

(Prüfer et al 2014)

Long history of small population size



Even after removing the effects of inbreeding during the last few generations, the Altai Neandertal is still highly inbred.

Coding sequence variation in archaics

Castellano et al (2014) study 17,367 protein-coding genes in several Neanderthals, the Denisovan, and several moderns.

Neanderthals had low heterozygosity

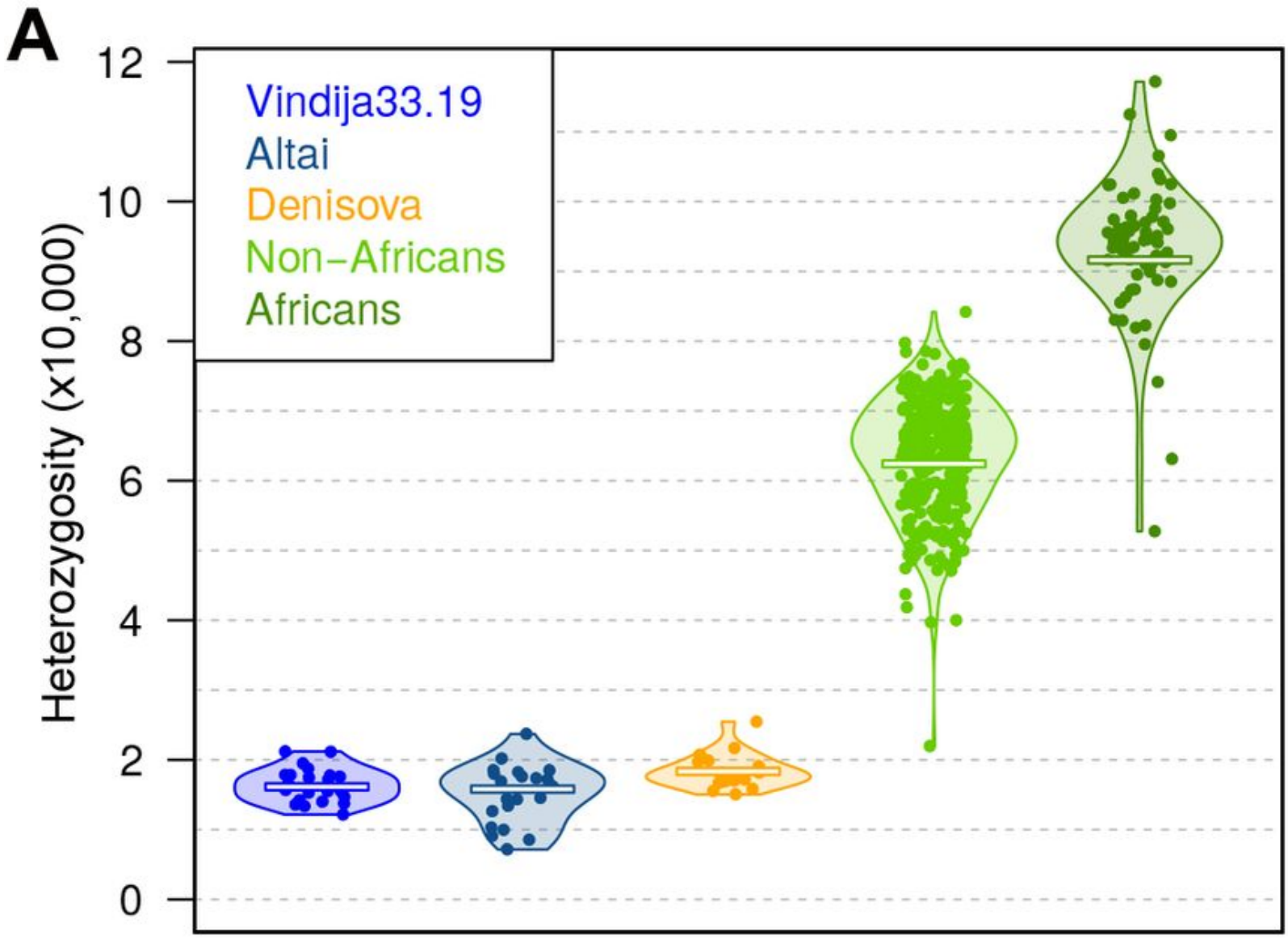
Species	Population	Heterozygosity $\times 1000$
Neanderthal	El Sidrón	0.143
	Vindija	0.127
	Altai	0.113
Modern	African	0.507
	European	0.387
	Asian	0.358

Low heterozygosity $\Rightarrow$ small population.

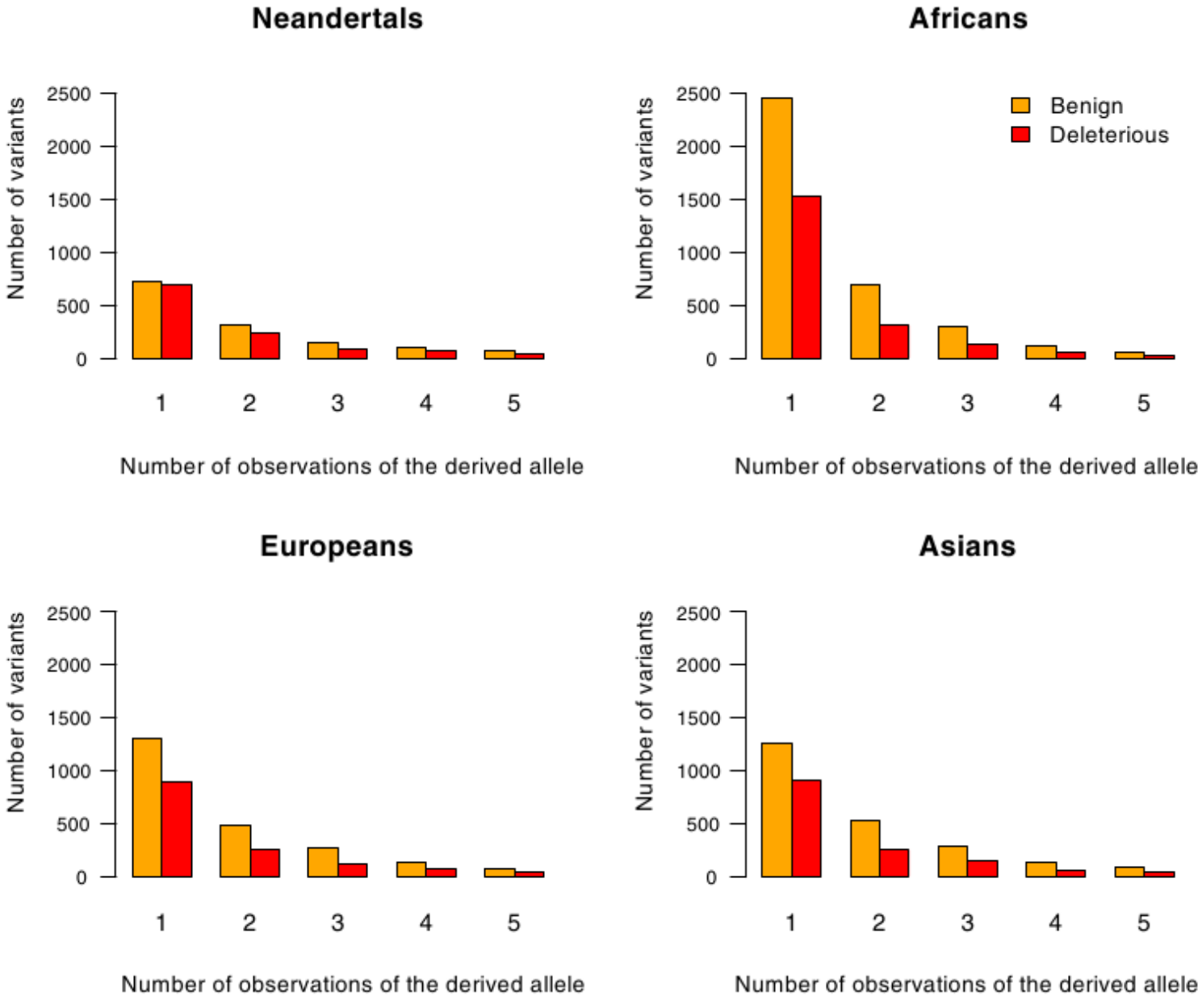
Long runs of homozygosity $\Rightarrow$ recent close inbreeding.

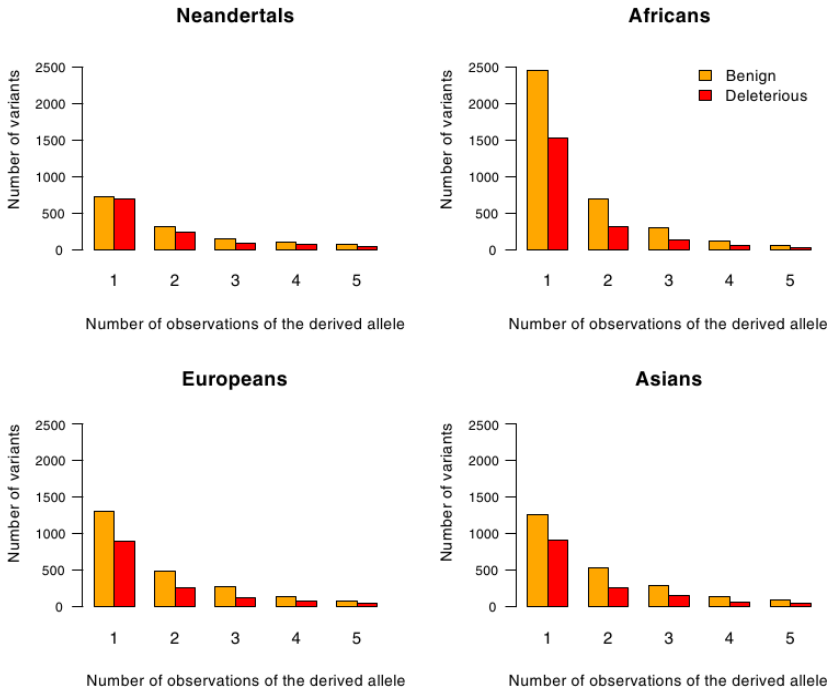
Castellano et al (2014)

Neanderthals had low heterozygosity



Selection less effective in Neanderthals





Selection less effective in Neanderthals

Many Neanderthal alleles have large effect on protein structure and are probably deleterious.

(Castellano et al 2014)

Summary

- Archaic alleles are over-represented at immune loci in modern humans.
- Modern humans needed help from archaics to fight Eurasian pathogens.
- But many archaic alleles seem to have been deleterious.
- This may be because the small sizes of archaic populations allowed deleterious alleles to drift to high frequencies.