

## Archaic Genes in Modern Humans

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### Outline

- ▶ History of thought about archaic admixture
- ▶ Inferring admixture from derived allele patterns and aDNA.
- ▶ Inferring admixture from LD in modern DNA.
- ▶ Multiple Denisovan populations

### Hypotheses of modern human origins

**Multiregional** Modern humans evolved in a worldwide population united by gene flow (Wolpoff 1989).

**Replacement** “A single origin, outward migration of separate stirps, like the sons of Noah, and an empty world to occupy, with no significant threat of adulteration by other gene pools or even evaporating gene puddles” (Howells 1976).

**Admixture** Expansion from a single origin, involving “encounters between populations of modern man and of other forms, with consequent gene flow” (Howells 1976; also: Brauer 1984, Smith et al 1989, Trunkhaus 2005).

### Geneticists on admixture

Consensus among geneticists during 1990s: little or no admixture between moderns and archaics.

Eswaran et al 2002, 2005: argued for admixture

Hawks et al 2006: Small amounts of admixture can have a big effect, because advantageous alleles are most likely to introgress.

Green et al 2010: sequenced Neanderthal genome; showed that 1.3–2.7% of European genes came from Neanderthals. [current estimate 1.5–2.1%]

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### Nucleotide site patterns

	Nucleotide Site Pattern		
	xy	yn	xn
Afr (X)	1	0	1
Eur (Y)	1	1	0
Nea (N)	0	1	1
Chi	0	0	0
#	303,340	103,612	95,347

Ancestral allele (0) is shared with chimp.

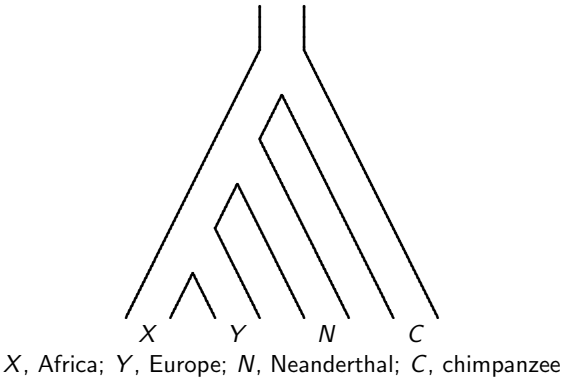
Mutant allele (1) shared by two human populations.

Pattern xy: most common; reflects history of population splits.

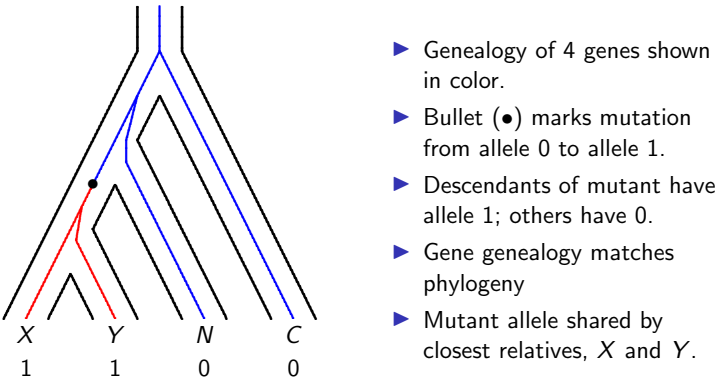
Patterns yn & xn: how do they arise?

Why does yn exceed xn?

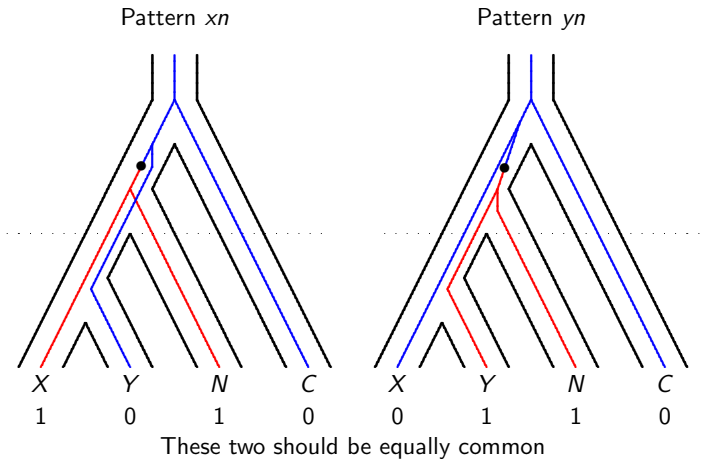
Population tree



Embedded gene genealogy with mutation



Incomplete lineage sorting



Nucleotide site patterns again

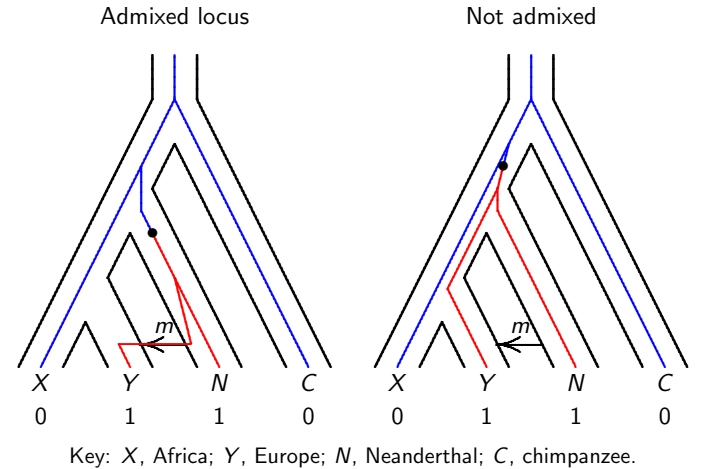
	Nucleotide Site Pattern		
	<i>xy</i>	<i>yn</i>	<i>xn</i>
African (X)	1	0	1
European (Y)	1	1	0
Neanderthal (N)	0	1	1
Chimpanzee	0	0	0
# sites	303,340	103,612	95,347

Common pattern (*xy*) reflects history of population splits.

Absent admixture, the other two should be equally common

Why does *yn* exceed *xn*?

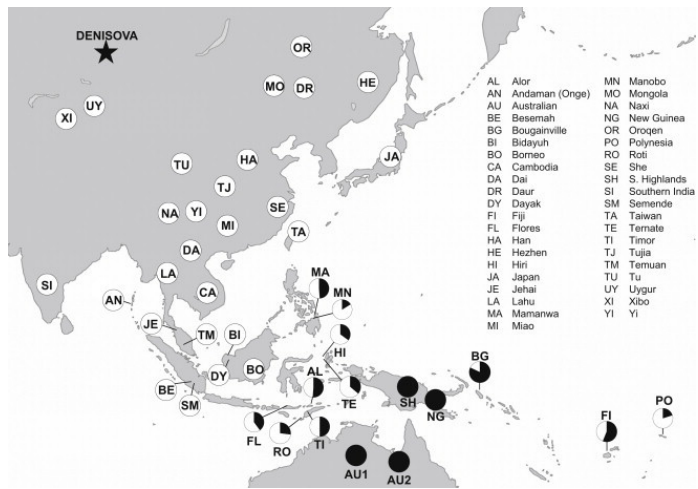
Neanderthal admixture inflates *yn* site pattern



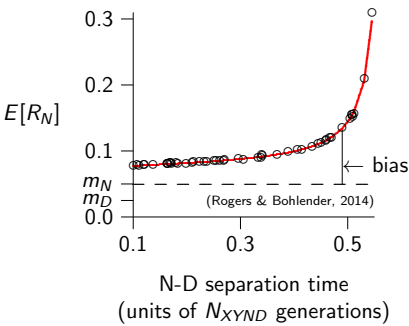
Estimate from Neandertal DNA

- ▶ DNA of modern Eurasians is 1.5–2.1% Neandertal (Prüfer et al 2014).
- ▶ Same is true for modern people of east Asia and Papua New Guinea, but not Africa. (Green et al (2010))
- ▶ Admixture must have occurred *after* moderns left Africa but *before* they expanded throughout the world.
- ▶ Eurasian introgressed segments most similar to Neandertal from Caucasus. (Prüfer et al 2014)

Denisovan DNA most common in Australia, NG, and Oceania



Some estimators have large biases



Bias is pronounced in populations that received gene flow from Denisovans as well as Neanderthals.

Worse in East Asia than in Europe.

Worse still in Melanesia.

All of the estimates reviewed above are suspect.

Legofit

Our own estimator, Legofit, is an estimator that avoids this bias. I'll discuss it in a separate lecture.

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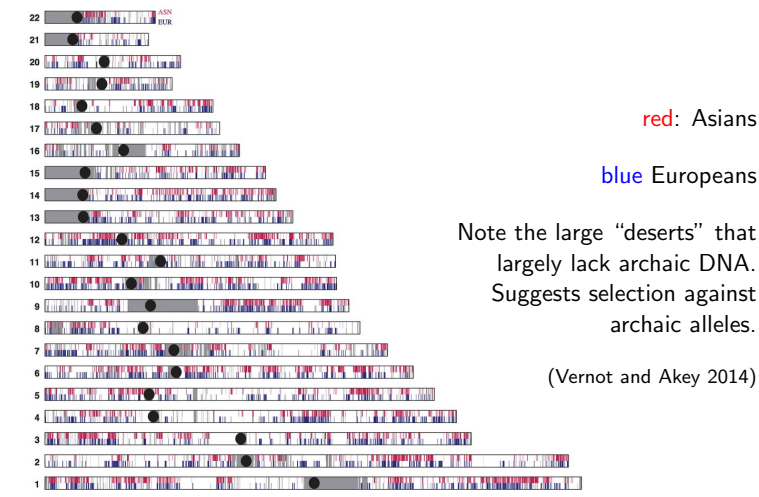
Using LD to discover admixed chromosome segments

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

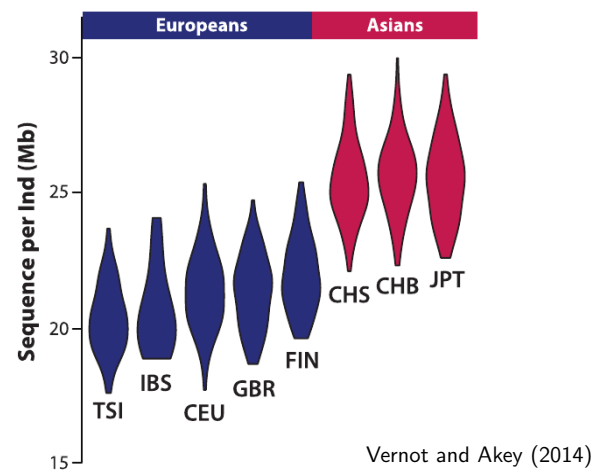
Method of Vernot and Akey (2014)

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.

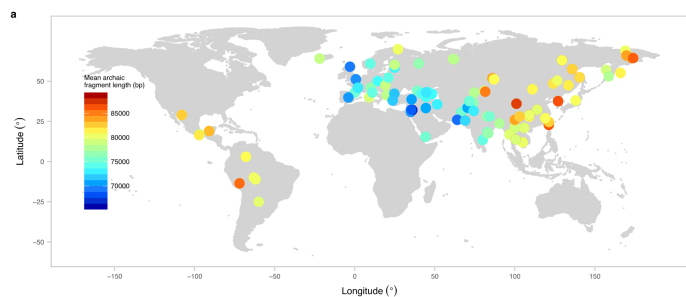
Neandertal segments in modern genomes



Asians seem to have more Neandertal than Europeans—why?



Asian excess may be misleading



Neanderthal fragments are longer in East Asia. Long fragments are easier to recognize. May explain East Asian excess. (Macia et al (2021))

Why are Neanderthal fragments short in Europe?

Perhaps admixture was older in Europe? Macia et al (2021) say no: the genomic regions covered by Neanderthal fragments are the same Europe and Asia. Implies a single episode of admixture.

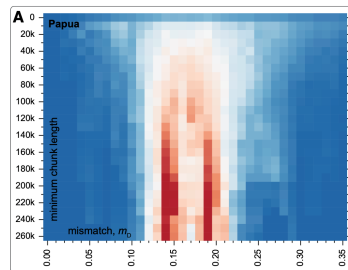
More derived alleles in Europe than Asia ⇒ Shorter generation time in Europe ⇒ More recombination in Europe.

So apparent excess of Neanderthal DNA in Asia may be an artifact caused by longer generation time there.

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Papuans got DNA from 2 Denisovan pops



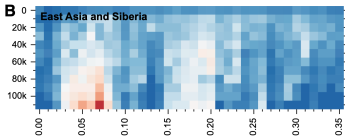
Vertical axis: length of introgressed segment

Horizontal: diff btw segment and Denisovan genome as fraction of Denisovan-modern diff.

Two Denisovan populations: one 0.15 and one at 0.2.

Jacobs et al (2019)

E Asians got DNA from 1 Denisovan pop



Vertical axis: length of introgressed segment

Horizontal: diff btw segment and Denisovan genome as fraction of Denisovan-modern diff.

One Denisovan population at 0.07.

Summary

- ▶ Neanderthal: all non-African populations have about same level (1.5–2.1%) of admixture. Suggests that admixture happened in one region.
- ▶ Denisovan: highest levels found in populations far from Africa. Suggests that admixture accumulated gradually.
- ▶ We can recognize chromosomal segments derived from Neanderthals or Denisovans, because they differ from modern haplotypes but resemble archaic haplotypes.
- ▶ Large regions of Eurasian genomes have little or no archaic introgression.
- ▶ East Asians have more archaic DNA than Europeans do.
- ▶ Papuans got DNA from 2 Denisovan pops.
- ▶ E Asians got DNA from a 3rd.