Admixture between Archaic and Modern Humans

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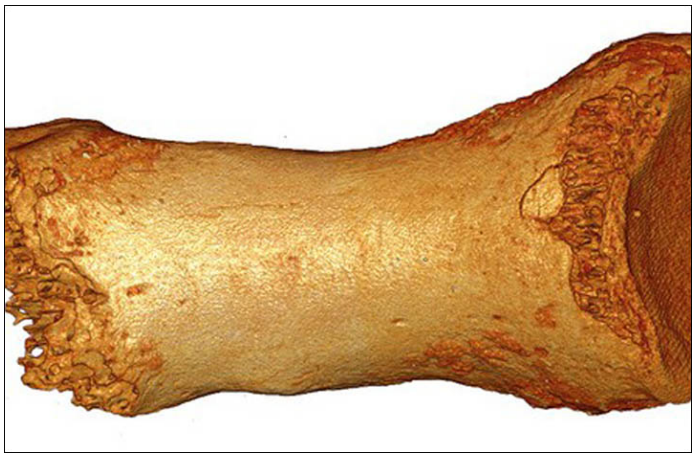
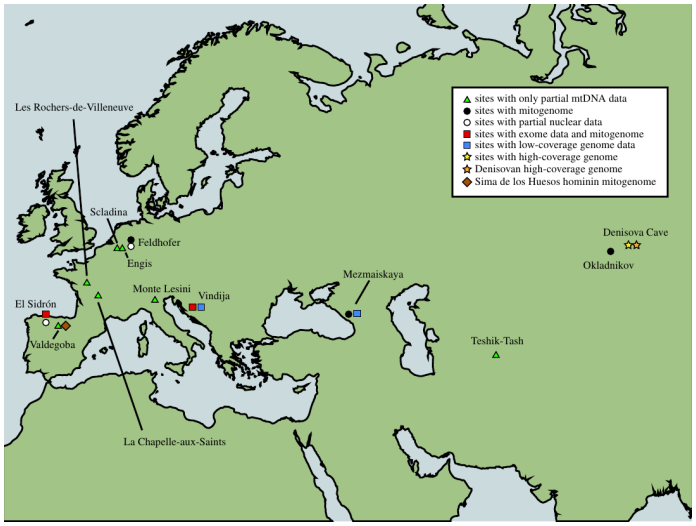
Fossils From Vindija Cave, Croatia (38–44 kya)

Hominin tooth from Denisova Cave, Altai Mtns, southern Siberia (41 kya)

Hominin finger from Denisova Cave



Sites yielding Archaic hominin DNA



Outline

- Estimating admixture from shared derived alleles
- Deep separation plus extensive LD.
- Selection against archaic DNA
- Excess Neanderthal in Asia
- Consequences of small population size
- Multiple Denisovan populations

Nucleotide site patterns

	Nucleotide Site Pattern		
	ea	*en*	*an*
Eur	1	1	0
Afr	1	0	1
Nea	0	1	1
Chmp	0	0	0
#	303,340	103,612	95,347

Ancestral allele (0) is shared with chimp.

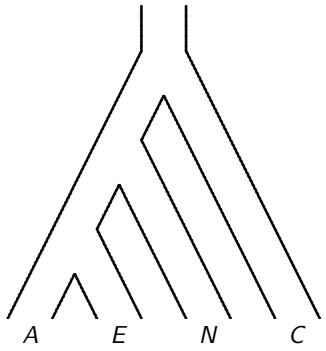
Derived allele (1) shared by two human populations.

Pattern *ea*: most common; reflects history of population splits.

Patterns *en* & *an*: how do they arise?

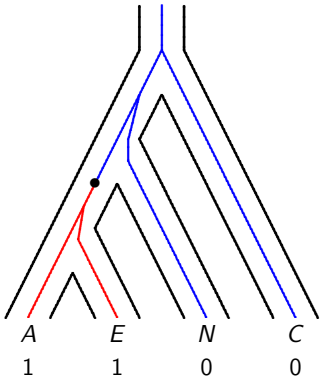
Why does *en* exceed *an*?

Population tree



A, Africa; *E*, Europe; *N*, Neanderthal; *C*, chimpanzee

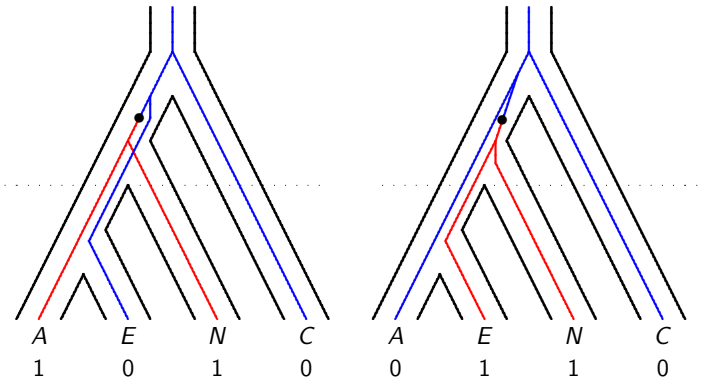
Embedded gene genealogy with mutation



- Genealogy of 4 genes shown in color.
- Bullet (•) marks mutation from allele 0 to allele 1.
- Descendants of mutant have allele 1; others have 0.
- Gene genealogy matches phylogeny
- Mutant allele shared by closest relatives, *A* and *E*.

Incomplete lineage sorting

Pattern *an* Pattern *en*



These two should be equally common

Nucleotide site patterns again

	Nucleotide Site Pattern		
	ea	*en*	*an*
European	1	1	0
African	1	0	1
Neanderthal	0	1	1
Chimpanzee	0	0	0
# sites	303,340	103,612	95,347

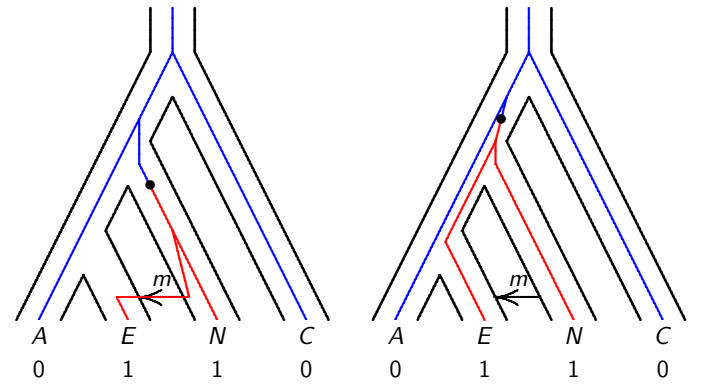
Common pattern (*ea*) reflects history of population splits.

Absent admixture, the other two should be equally common

Why does *en* exceed *an*?

Neanderthal admixture inflates *en* site pattern.

Admixed locus Not admixed



Key: *A*, Africa; *E*, Europe; *N*, Neanderthal; *C*, chimpanzee.

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 Neanderthal from Caucasus (Mezmaiskaya). (Prüfer et al 2014)

Eurasians share some derived alleles with archaics

Neanderthal matches French 4.6% more often than Yoruban (African).

Denisova matches French 1.8% more often than Yoruban (African).

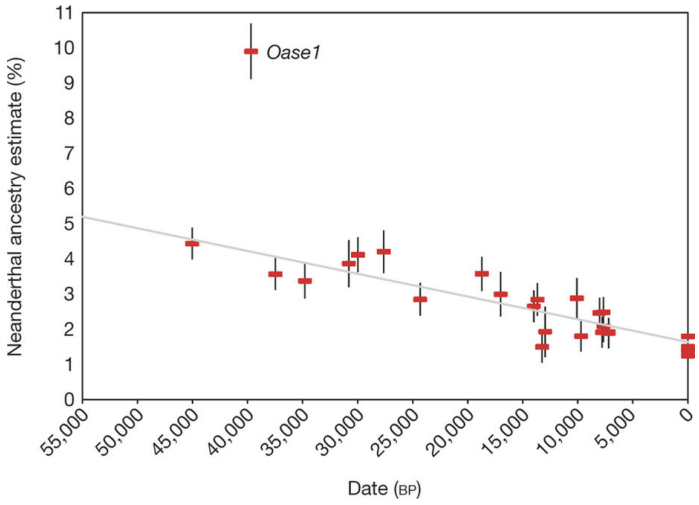
Archaic component of Eurasian genome more Neanderthal than Denisovan.

Green et al 2010; Reich et al. 2010.

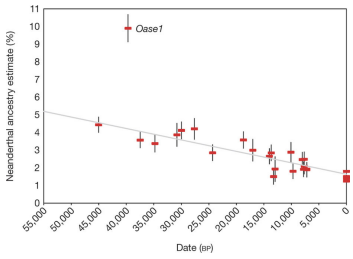
So do Asians and Papuans

Asians and Papuans carry as many Neanderthal alleles as Europeans do: 1.5–2.1%.

Apparent gradual decline in Neanderthal admixture



Apparent gradual decline in Neanderthal admixture

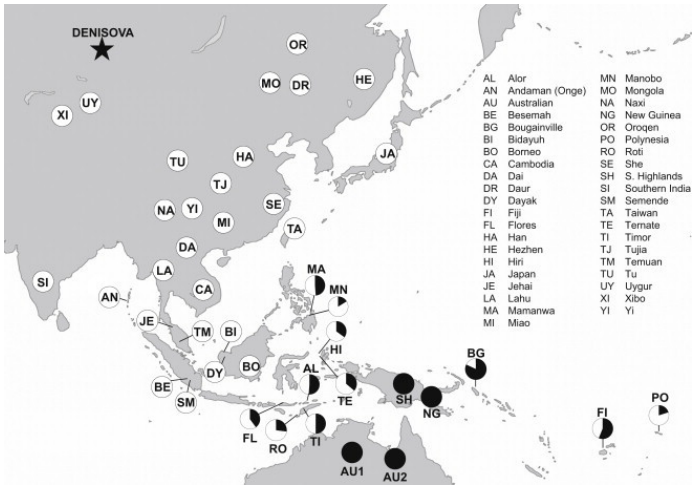


This turned out to be an artifact.

The estimators of admixture were biased.

Magnitude of bias differed in samples of different age.

Denisovan DNA most common in Australia, NG, and Oceania



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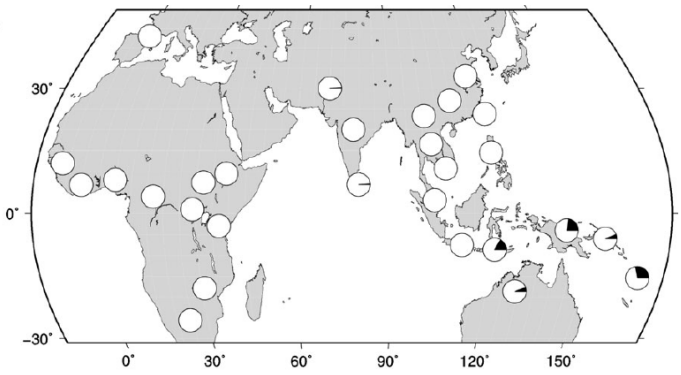
Another approach: look for deep separation plus extensive LD

- Examine variation in modern human DNA.
- Look for long segments of chromosome with many nucleotide differences.
- Many nucleotide differences ⇒ deep separation.
- Long segment ⇔ extensive LD
- Extensive LD ⇒ short residence in modern population.

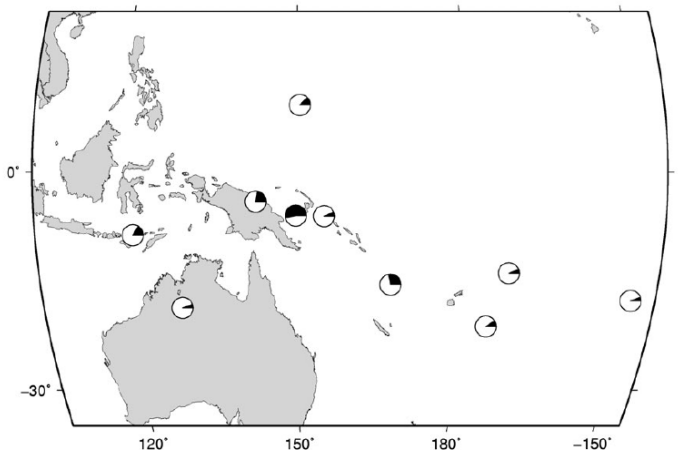
OAS1 innate immunity locus

- 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 ⇒ separation time ∼3.4 my.
- Long (90 kb) LD block ⇒ they've been together only ∼25 ky
- Melanesian allele matches that in Denisovan hominin skeleton.

⇒ archaic admixture into Melanesia

Introgressed segments in Eurasian genomes

Blue, Europe; red, Asia.

Inserts are dense in some regions, scarce in others.

Vernot and Akey (2014)

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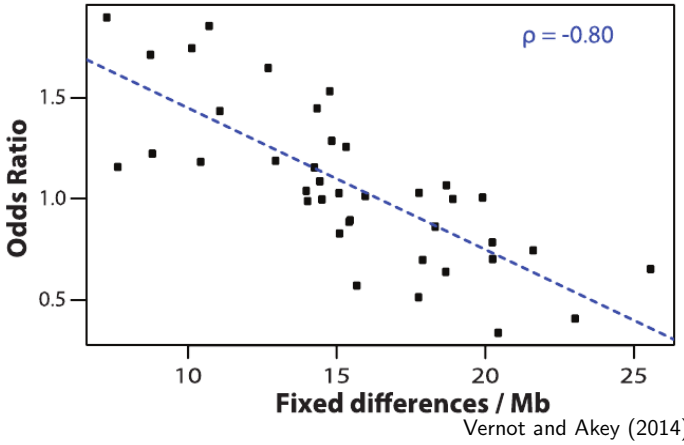
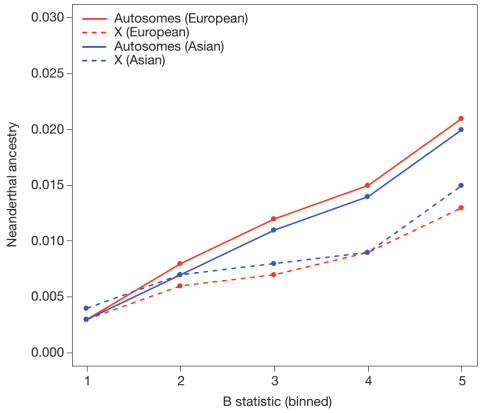
Selection against hybrids



Vernot and Akey (2014)

Introgressed segments rare where modern-Neandertal difference large.



Neanderthal inserts rare where selection is strong

Sankararaman et al (2014)

Decreasing selection →

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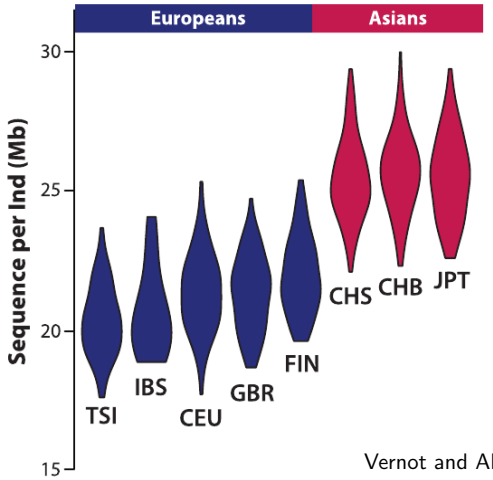
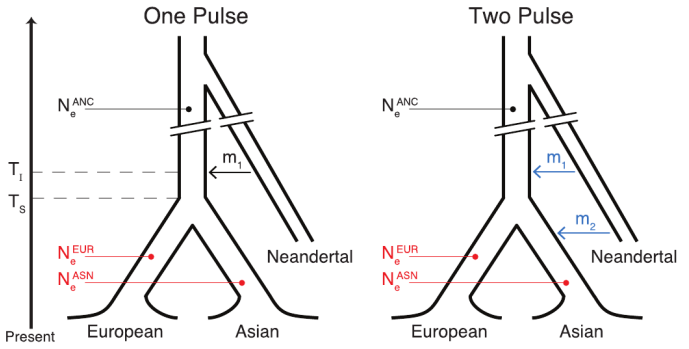
Asians have more Neandertal than Europeans

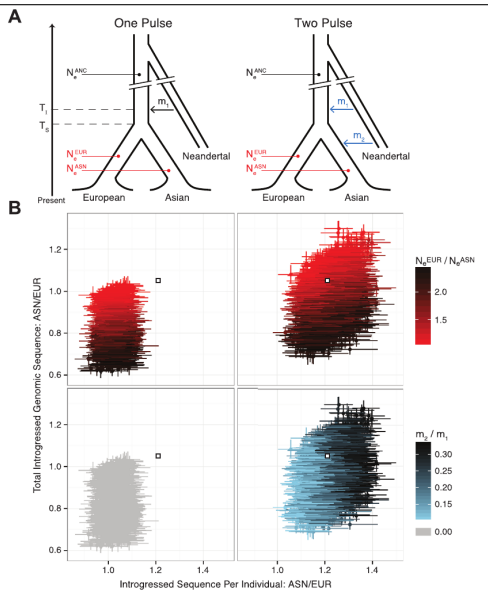


Vernot and Akey (2014)

Did Asians receive a 2nd dose on Neanderthal DNA?



Vernot and Akey (2014)



2-pulse model fits; 1-pulse model doesn't

Vernot and Akey (2014)

Why do Asians have more Neanderthal DNA than Europeans?

Hypotheses

1. 2nd pulse of Neanderthal admixture into Asia
2. European dilution. 2nd pulse of non-Neanderthal admixture into Europe.
3. Purifying selection. Selection against Neanderthal alleles more effective in Europe, because of larger population size.

Two recent papers have tested hypothesis 3.

Has selection removed Neanderthal DNA in Europe

- Selection removes variation.
- Other things equal, variation should be low where selection has been strong.
- Hypothesis: such regions should contain fewer Neanderthal inserts in Europe than in Asia.

Vernot and Akey (2015)

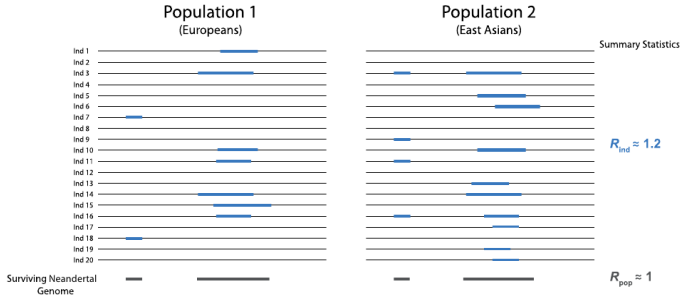
Measuring these effects

B measures the strength of purifying selection. $B = 0$ means strong selection; $B = 1$ means no selection.

$R_{ind} > 1$ means the average Asian has more Neanderthal DNA than the average European.

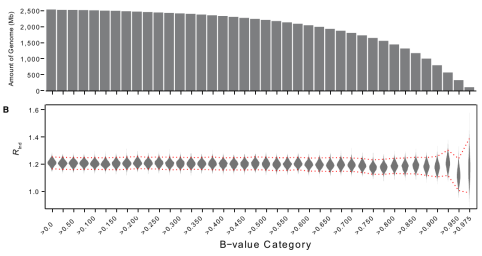
$R_{pop} > 1$ means the Asian population includes more of the Neanderthal genome than the European one.

Illustration of R_{ind} and R_{pop} (not real data)



$R_{ind} = 1.2 \Rightarrow$ Average Asian has 20% more Neanderthal DNA than average European.
$R_{pop} = 1 \Rightarrow$ Asia and Europe include same fraction of Neanderthal genome.

Selection doesn't explain Asian excess

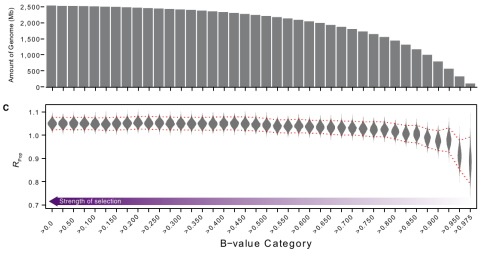


Decreasing selection →

Selective constraint decreases from left to right.

No effect on R_{ind}

Selection not responsible for Asian excess.
(Vernot et al 2015)



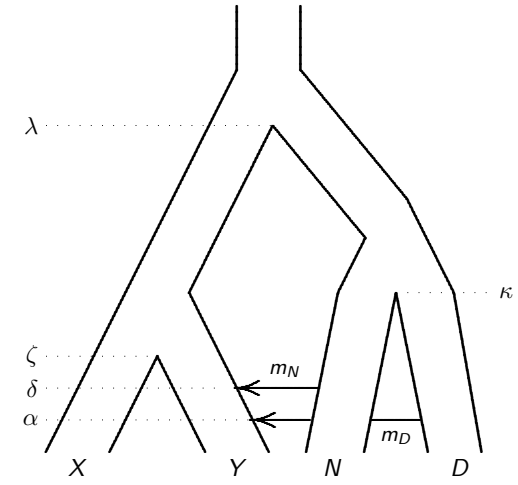
Decreasing selection →

Selective constraint decreases from left to right.

R_{pop} declines where selection is weak.

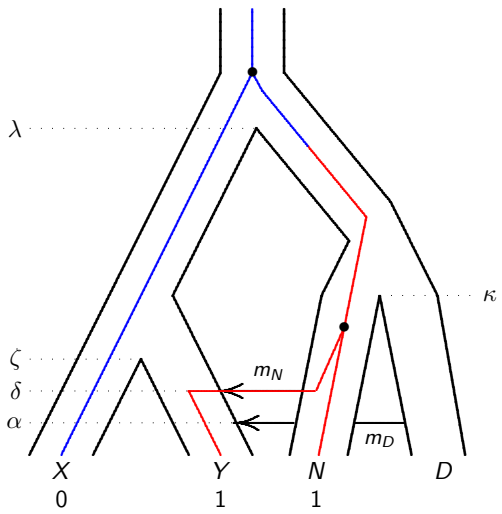
Vernot and Akey attribute this to greater drift in Asia. (But why does this affect only neutral loci?)

2nd source of admixture



X, Africa; Y, Europe; N, Neanderthal; D, Denisova

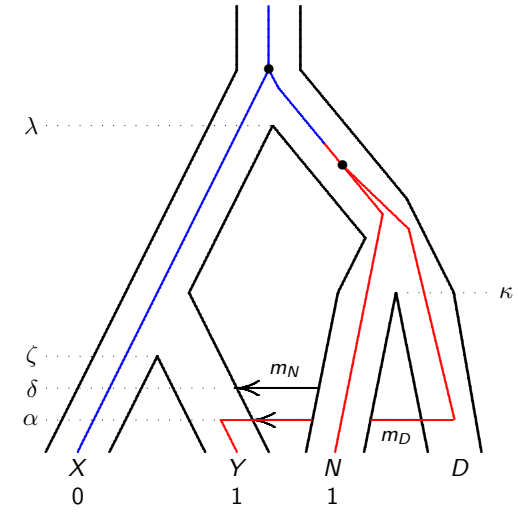
Primary archaic admixture

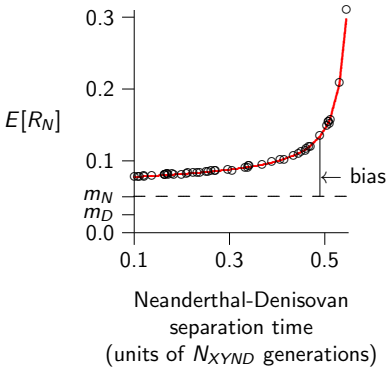


Red: derived

Blue: ancestral

Secondary (ghost) archaic admixture





Ghost admixture causes bias
Admixture: 5% Neanderthal & 2.5% Denisovan.

Red line and circles: Expected value of estimator of m_N.

Horizontal dashed line: true parameter value

The difference is *bias*.

Ghost admixture causes bias

If East Asians received genes from Denisovans as well as Neanderthals, our estimates of Neanderthal admixture would be inflated.

May explain Asian excess of Neanderthal admixture.

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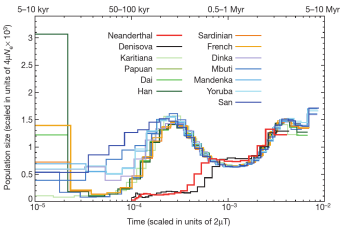
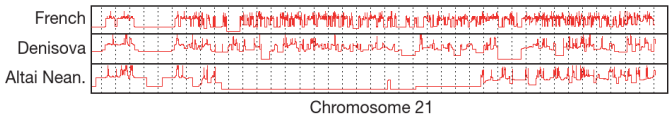
Consequences of small population size



Prüfer et al (2014)

- Low heterozygosity
- Drift strong, so deleterious mutations accumulate.
- Extinction?

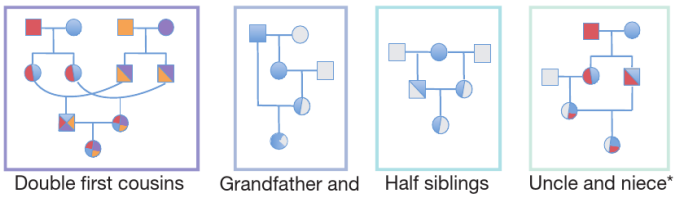
Estimated times to most recent common ancestor (TMRCA)



Long stretches of low TMRCA ⇒ recent close inbreeding.

(Prüfer et al 2014)

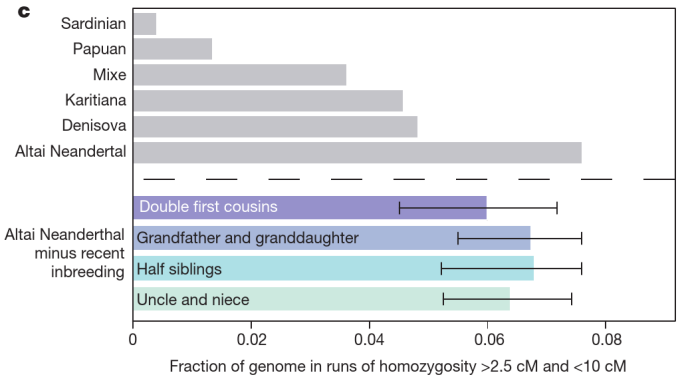
Altai Neanderthal was very closely inbred



All of these pedigrees are plausible.

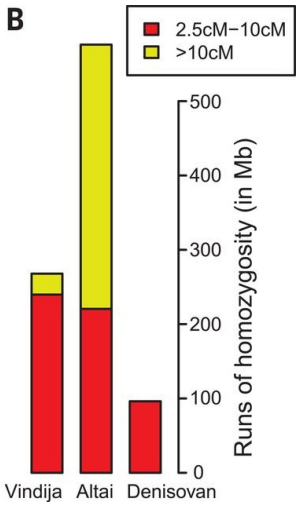
(Prüfer et al 2014)

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.

Other archaics were less inbred



Altai Neanderthal had many runs of homozygosite longer than 10 cM.

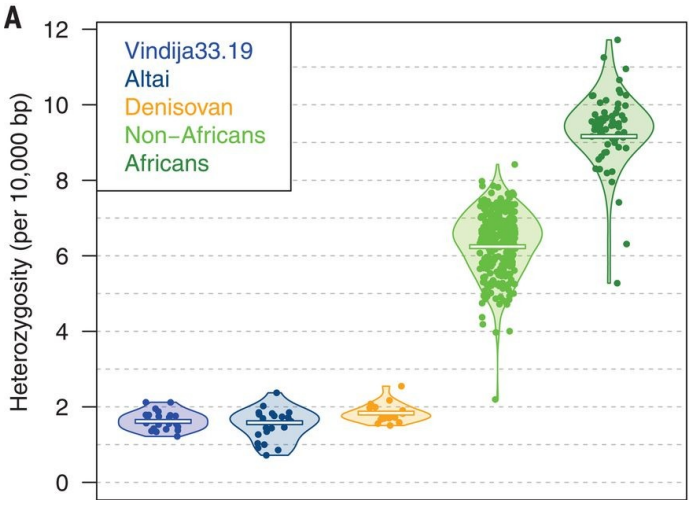
A centimorgan (cM) is about a million nucleotides.

Vindija Neanderthal had fewer such runs.

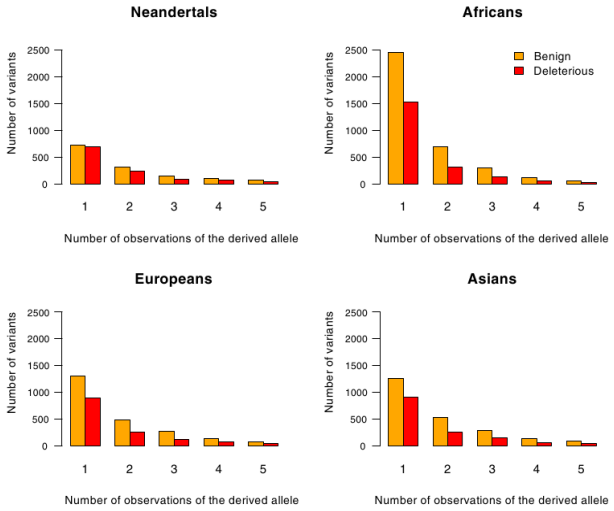
Denisovan had none.

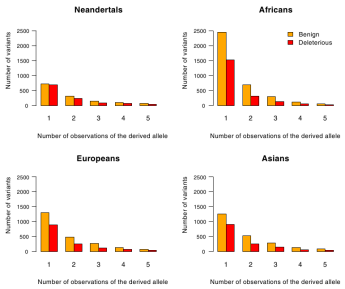
All had runs in range 2.5–10 cM.

Archaics had low heterozygosity



Selection less effective in Neanderthals

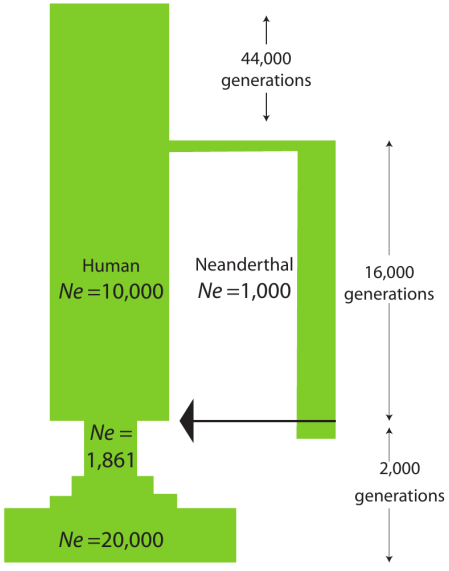




Selection less effective in Neanderthals

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

(Castellano et al 2014)



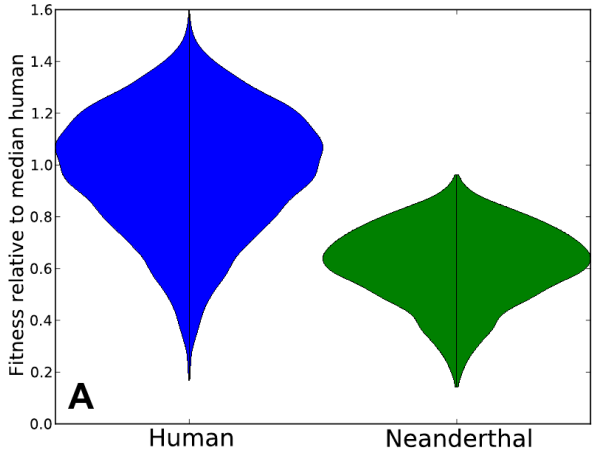
Small Neanderthal population size ⇒ deleterious mutations can drift to fixation.

How large was effect?

Many slightly-deleterious mutations or a few large ones?

(Harris and Nielsen 2015)

Simulated fitnesses of Neanderthals and moderns



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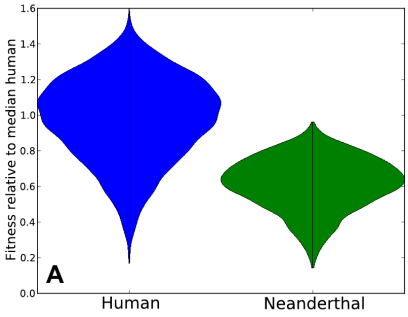
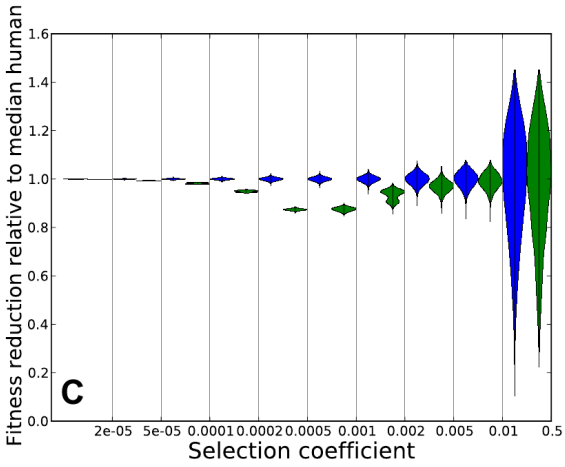


Suggests fitness of typical Neanderthal was ∼25% lower that of typical modern.

Was this caused by a few alleles with large effect or many with small effects?

Fitness reduction: many alleles with small effects



Most of the action is where $N_A s \approx 1$

Largest effect on fitness: $0.0001 < s < 0.001$

Or: $0.1 < N_A s < 1$, where N_A is size of archaic population.

Genetic disease dominated by alleles with small effect.

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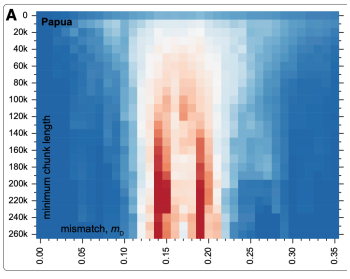
Papuans got DNA from 2 Denisovan pops



Jacobs et al (2019)

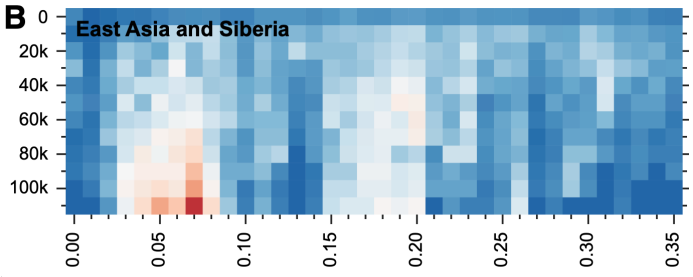
Vertical axis: length of introgressed segment

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

Color: number of fragments in this bin of length × dissimilarity

Two Denisovan populations: one 0.15 and one at 0.2.

E Asians got DNA from 1 Denisovan pop



Only one Denisovan population at 0.07.

Summary

- Two ways to detect archaic admixture:
  1. Admixture distorts the pattern by which archaic and modern populations share derived alleles.
  2. Deep separation plus extensive LD.
- Neanderthals $\rightarrow$ 1.5–2.1% of DNA in Eurasia; not Africa.
- Denisovan DNA most common in Melanesia and Oceania.
- Archaic DNA uneven along chromosome: rare where selection is strong or modern-archaic difference large.
- Neanderthal in Asia than Europe, probably because Asians received a 2nd pulse of admixture.
- Small archaic populations $\rightarrow$ many deleterious alleles.
- Fitness reduction probably reflects many weakly deleterious mutations.
- There were multiple Denisovan subpopulations, which made unequal contributions of moderns in different regions.