



Human Genetics · Archaic Admixture · Sex Bias

Interbreeding Between Neanderthals and Modern Humans Was Strongly Sex Biased

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RESEARCH ARTICLES

HUMAN GENETICS

Interbreeding between Neanderthals and modern humans was strongly sex biased

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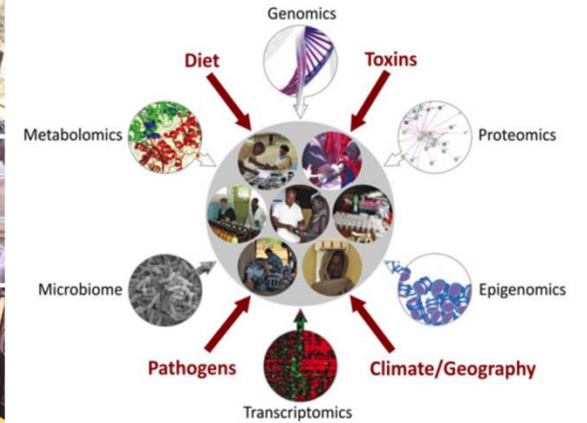


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Postdoctoral Fellow



Sarah Tishkoff, Ph.D.
Principal Investigator

Studying the Genetic Variation at the Genome Level in Global Populations

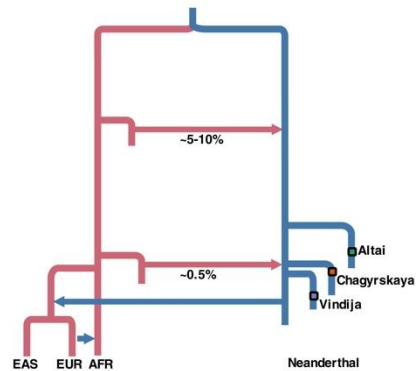


Research

- African Integrative Evolutionary Genomics
- African Genomic and Phenotypic Diversity Project
- The Genetic Basis of Resistance to Infectious Disease
- The Genetic Basis of Adaptation in Humans

The "Neanderthal Desert" Problem: Why Is the X Chromosome Special?

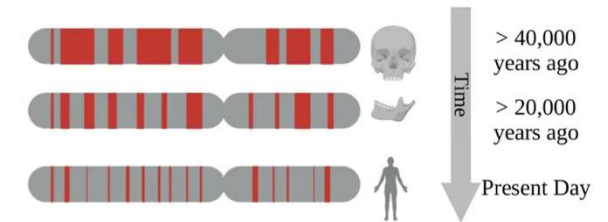
Key Timeline



(Liming Li et al. 2024, Science)

- ~250 ka** Neanderthal ← Early AMH (anatomically modern humans)
- 45–49 ka** Main Neanderthal → AMH admixture event
- Today** X depleted; deserts visible in earliest Eurasian AMHs

Catalog of Neanderthal segments in the genome



(Leonardo N. M. Iasi et al. 2024, Science)

⚠ The Core Anomaly

Neanderthal ancestry is **not uniformly distributed** across the modern human genome. Certain regions — termed "**Neanderthal deserts**" — are conspicuously devoid of archaic alleles. Critically, the **entire X chromosome** behaves as one massive desert.

Competing Hypotheses

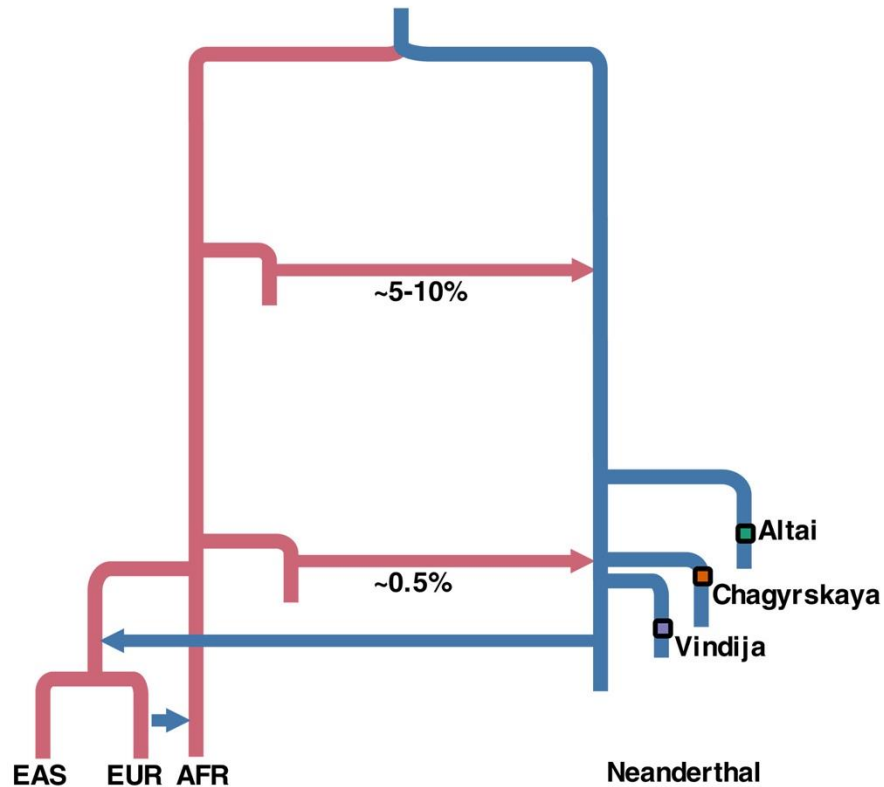
H1: Natural Selection

Neanderthal alleles were **selectively purged** from X chromosomes post-admixture via hybrid incompatibilities ("faster X") or mutational load.

H2: Sex-Biased Admixture

Interbreeding was directionally biased: ♂ **Neanderthal** × ♀ **AMH**. Fewer Neanderthal X chromosomes entered AMH pool from the start.

Methods & Analytical Design



(Liming Li et al. 2024, Science)

Three Neanderthal Specimens

Altai Neanderthal ★ - Female

122 ka · Primary

oldest high-quality genome; simplest admixture history.

Chagyrskaya - Female

80 ka · Replication

Vindija - Female

52 ka · Replication

AMH Reference Panel

73 Sub-Saharan – Female (3 populations)

< 0.1% Nean

! Natural selection's effect is assumed to be consistent across all interbreeding events.

Testing Selection-Based Explanations

H1a: Faster-X / Genomic Incompatibility

→ Predicts: Neanderthal X has **LESS** AMH ancestry than autosomes

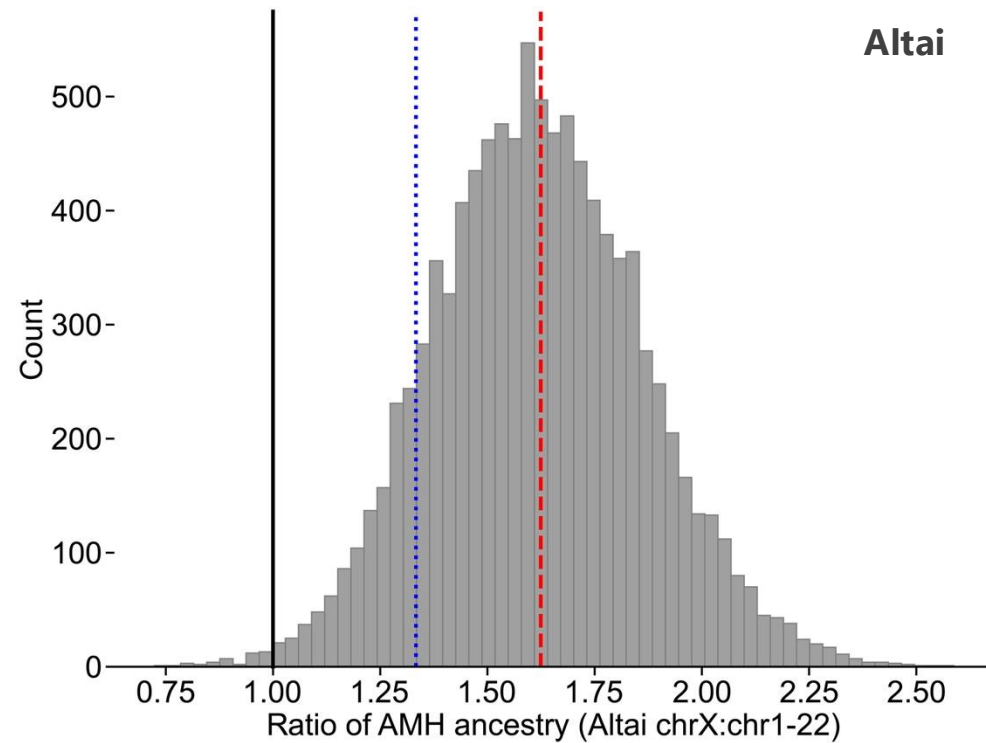
H1b: AMH X chromosome advantage or mutational load

→ Predicts: AMH introgression **preferentially retained at functionally important loci** (exons, TFBS, enhancers)

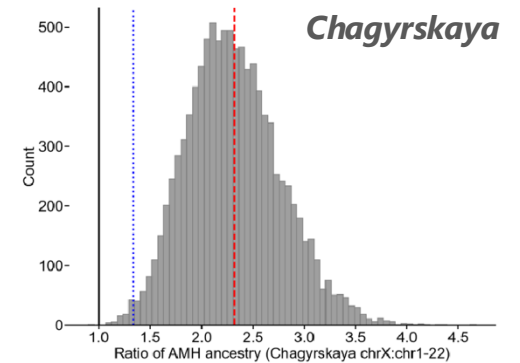
Neanderthal X Carries **More AMH Ancestry Than Autosomes**

By resampling AMH introgressions from 300 10-Mb autosomal windows and 16 X chromosome (chrX) windows, they made 10,000 pseudoreplicas of introgressed Neanderthal genomes.

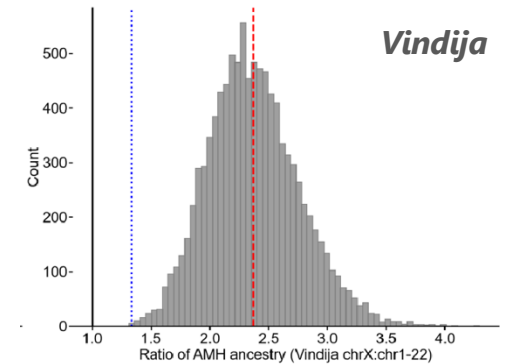
- ❑ The red dashed line indicates the ratio observed in the Neanderthal genome. Selection against gene flow on the X chromosome would predict a value < 1 (solid black line).



Altai



Chagyrskaya



Vindija

Fig. Ratio of proportion of AMH introgressions in Altai X chromosomes to AMH introgression in Neanderthal autosomes.

Neanderthal X preferentially **retains AMH alleles in nonfunctional regions**

Genome	X chromosome introgressed regions ^a	Annotation	Relative composition ^b	Resampling P value ^c
Altai	338	Exons	0.83	0.27
		Transcription factor binding sites	0.81	0.1
		Enhancers	0.74	0.007
		Combined	0.59	$<1 \times 10^{-5}$

Table 2. Analysis of functional annotations within X chromosome introgressed regions.

The X chromosome introgressed regions of the Altai Neanderthal are depleted of functionally annotated elements.

$R_i > 1$ indicates enrichment of annotation i in introgressed regions

$R_i < 1$ indicates depletion of this functional annotation i

$R_i \approx 1$ indicates no substantial difference from background.

Neanderthal X preferentially **retain AMH alleles in nonfunctional regions**

Genome	X introgressed regions ^a	Annotation	Relative composition ^b	Resampling p-value ^c
Vindija	354	Exons	0.87	0.07
		Transcription factor binding sites	0.98	0.34
		Enhancers	0.84	0.1
		Combined	0.56	<1e-5
Chagyrskya	276	Exons	0.81	0.01
		Transcription factor binding sites	0.96	0.24
		Enhancers	0.83	0.01
		Combined	0.53	<1e-5

Rejecting Selection-Based Explanations

H1a: Faster-X / Genomic Incompatibility

→ Predicts: Neanderthal X has **LESS** AMH ancestry than autosomes

X REJECTED: Altai X contains **1.62×** MORE AMH ancestry — opposite direction.

H1b: Neanderthal Mutational Load

→ Predicts: AMH introgression **preferentially retained at functionally important loci** (exons, TFBS, enhancers)

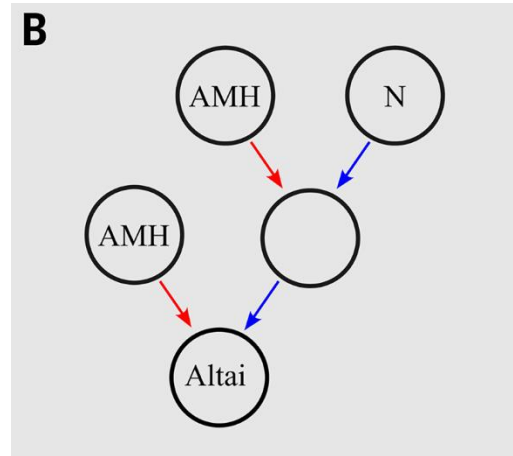
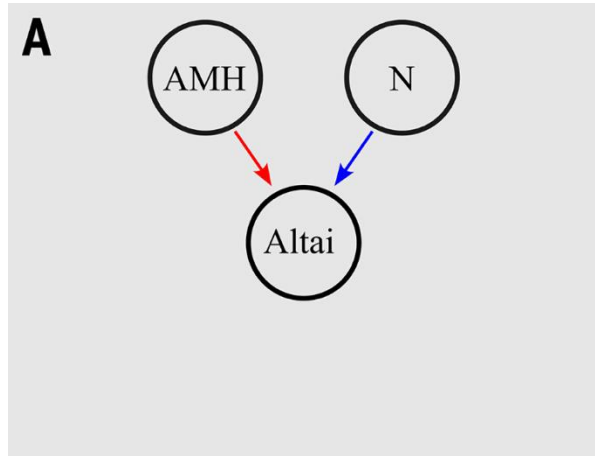
X REJECTED: Relative composition(Combined) = 0.59 with $p < 10^{-5}$ in Altai X

Supporting Sex-Biased Admixture

H2: Sex-Biased Admixture: *Neanderthal X Carries More AMH Ancestry Than Autosomes*

✓ Convergent results across three independent Neanderthal lineages rule out specimen-specific artifacts.

Sex-biased Demographic Processes / Ancestry-Specific Mate Preference



$$\frac{X'}{A'} = \frac{4}{3} \cdot \frac{1 + \frac{\varphi}{3}}{1 + \frac{\varphi}{2}}$$

The gray shading behind panels (A) and (B) indicates that the models were unable to explain observed Neanderthal X:autosome AMH introgression ratios over 4:3 (1.33).

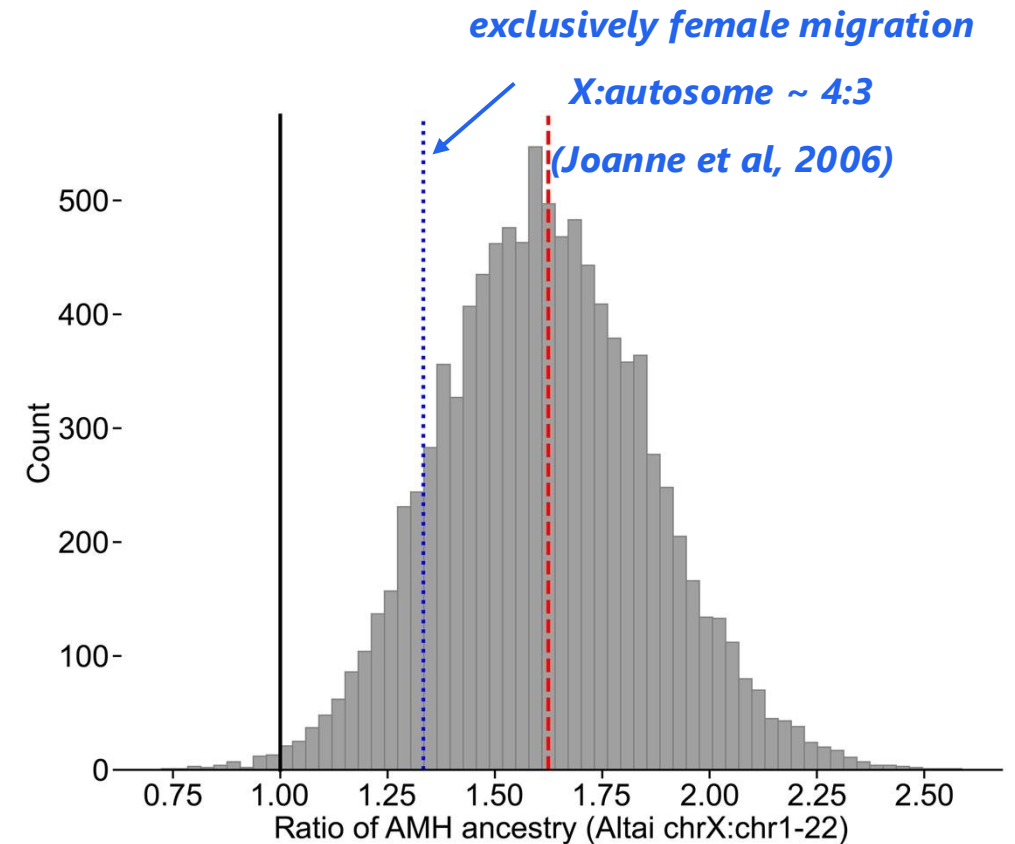
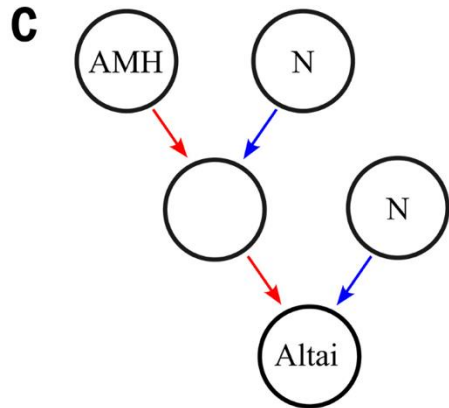


Fig. Evaluation of mechanisms of sex-biased admixture

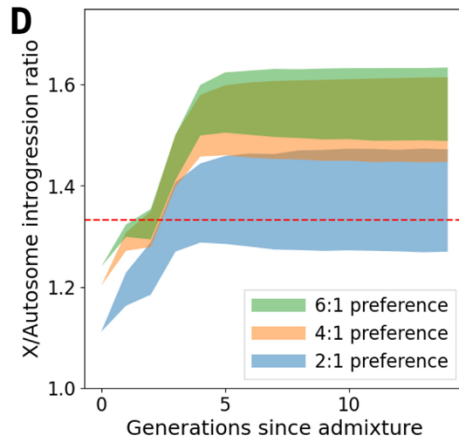
Sex-biased Demographic Processes / Ancestry-Specific Mate Preference



Primary Event: Female AMH → Neanderthal population 1

Secondary Event: Admixed females (from population 1) → Neanderthal population 2 with equation becomes (max ~ 1.77):

$$\frac{4}{3} \leq \frac{X}{A} = \frac{4(\delta)}{3(\gamma)} \leq \left(\frac{4}{3}\right)^2$$



Generation zero: 5×10^5 males and 5×10^5 females is comprised of 97% Neanderthals and 3% AMH

Subsequent generations include a bias favoring pairs of male Neanderthals with hybrid females over female Neanderthals with hybrid males.

The middle 95% from 2500 numerical simulations of generation-by-generation Neanderthal X:autosome AMH introgression ratios

Summary & Implications & Vulnerabilities

1 The Pattern: entire X chromosome behaves as one massive 'Neanderthal desert'

2 Natural Experiment: The 250 ka Altai Admixture Event

3 Selection Hypotheses Rejected

4 Demographic Models Capped at $4:3 = 1.33$

5 Mate Preference: The Parsimonious Explanation

Implications

Speciation Theory

Human Evolution Framework

Modern Human Health

Vulnerabilities & Open Questions

- Limited $N=3$ Specimens & solutions
- Assumed consistency of selection may not hold
- Observed ratio $\sim E$ (Mate Preference) + F (demographics) + G (selection)

Thank you