
LIMITS OF LONG-TERM SELECTION AGAINST NEANDERTAL INTROGRESSION



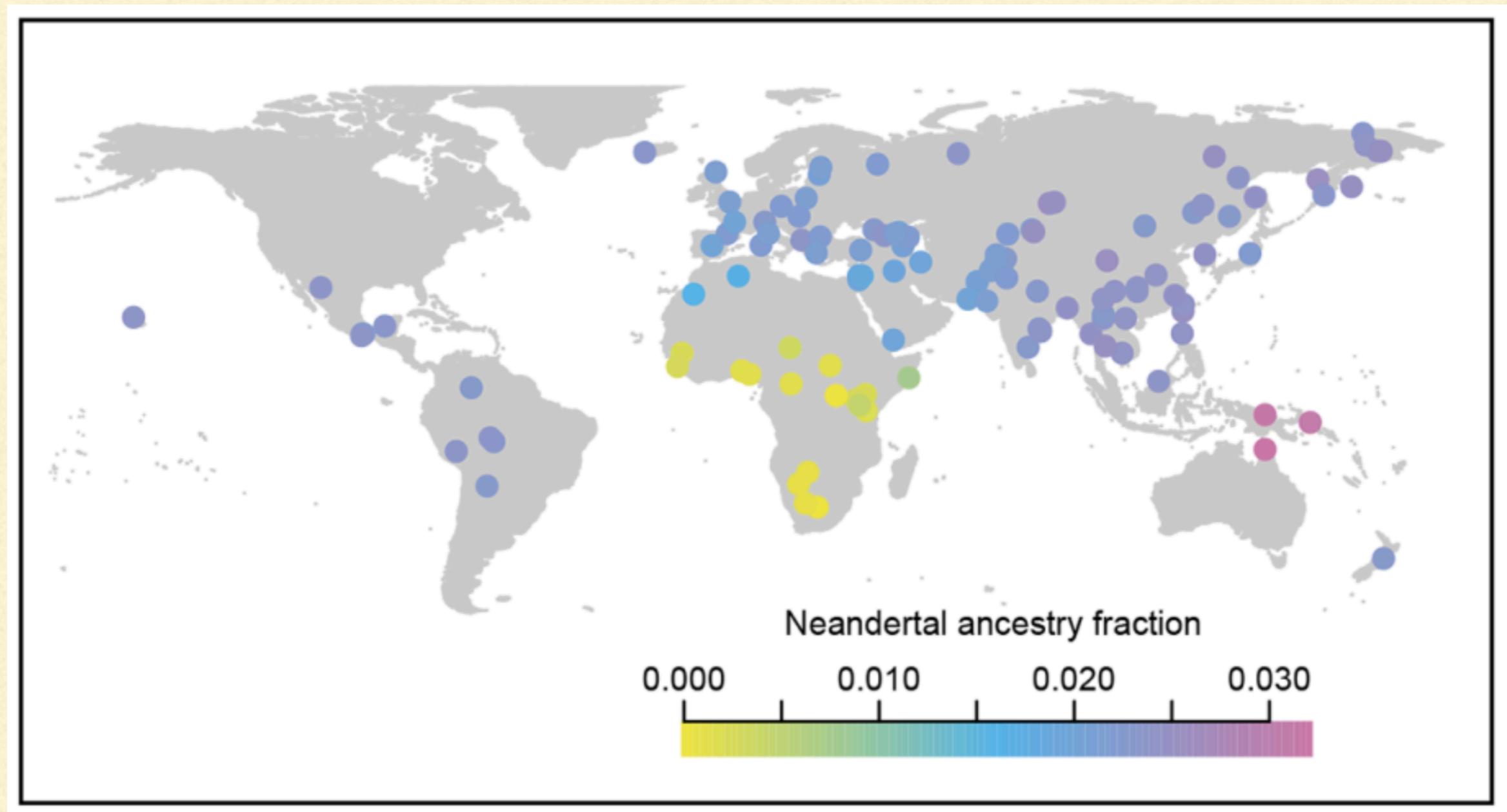
MAX-PLANCK-GESELLSCHAFT

Martin Petr

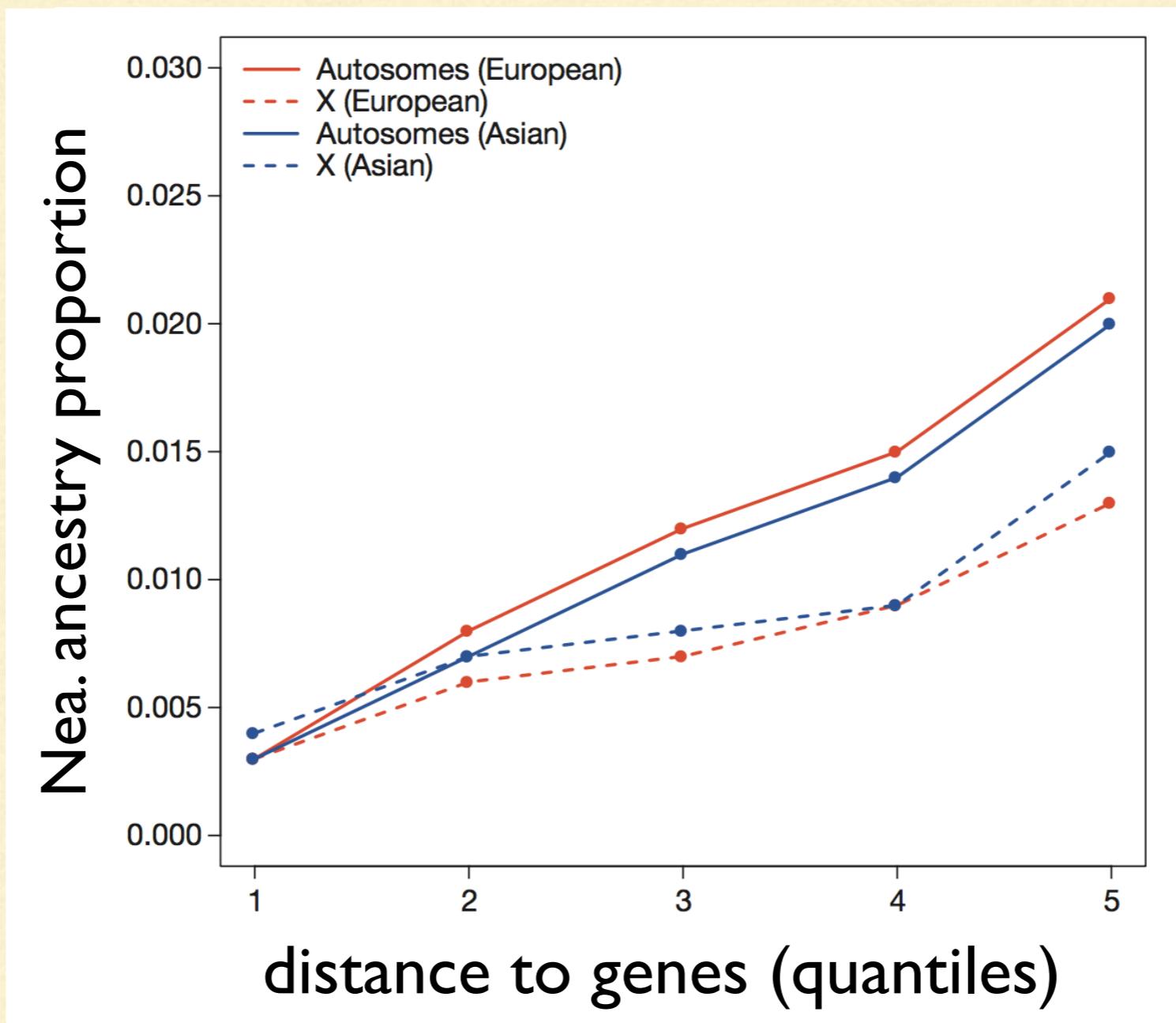
Minerva Research Group for Bioinformatics

Max Planck Institute for Evolutionary Anthropology

NEANDERTAL INTROGRESSION

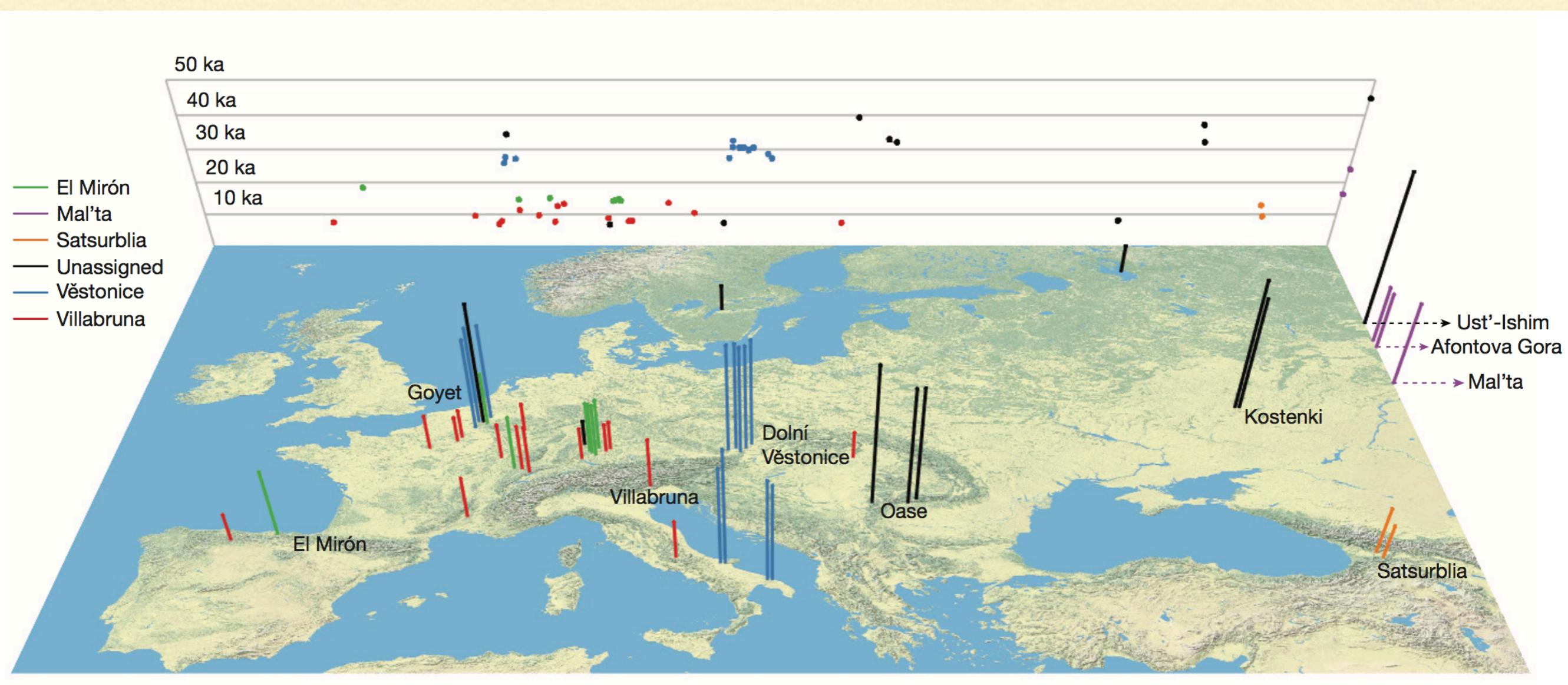


NEANDERTAL DNA UNDER NEGATIVE SELECTION

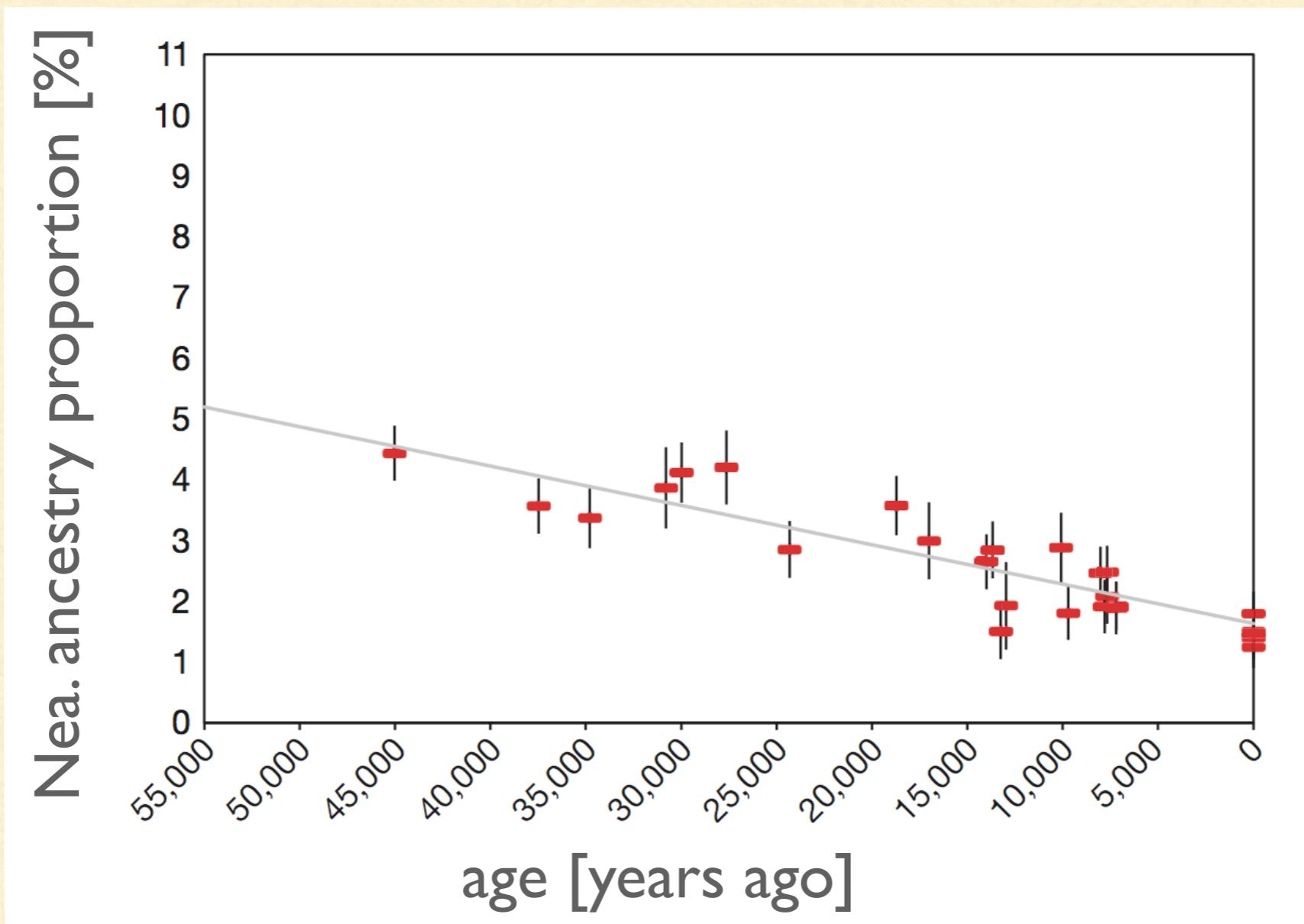


THE GENETIC HISTORY OF ICE AGE EUROPE

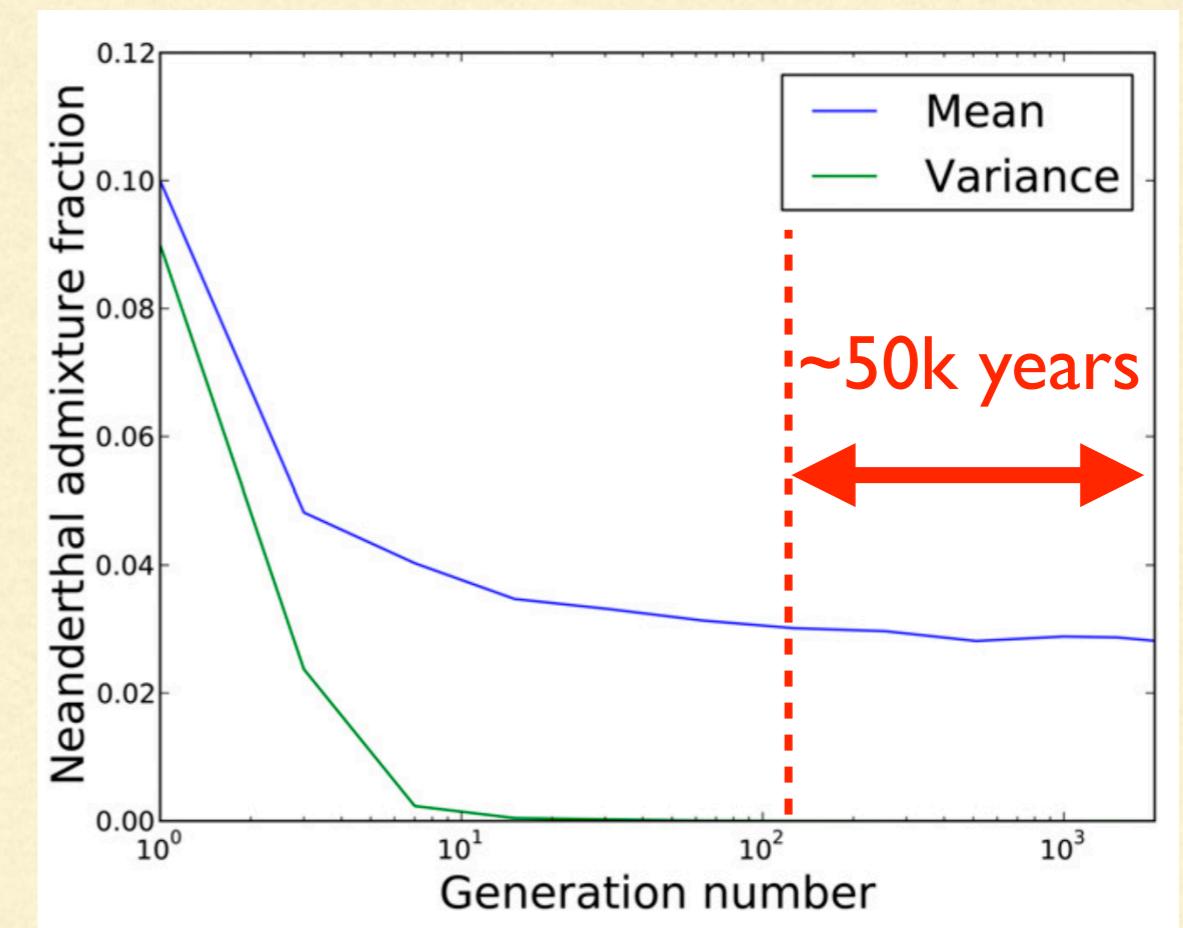
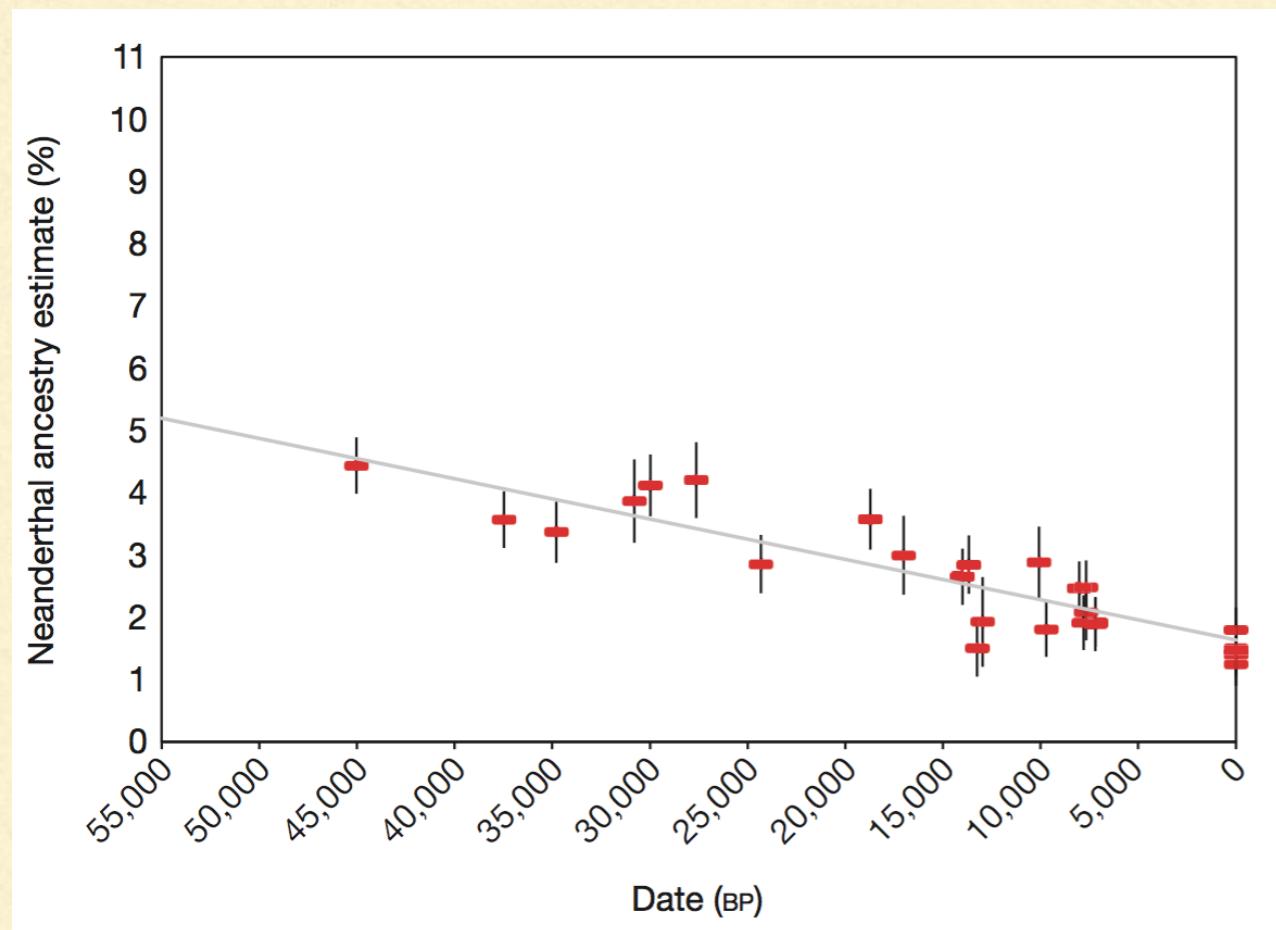
SNP capture: 51 West Eurasians, ~45,000–7,000 years old



NEANDERTAL ANCESTRY DECLINE



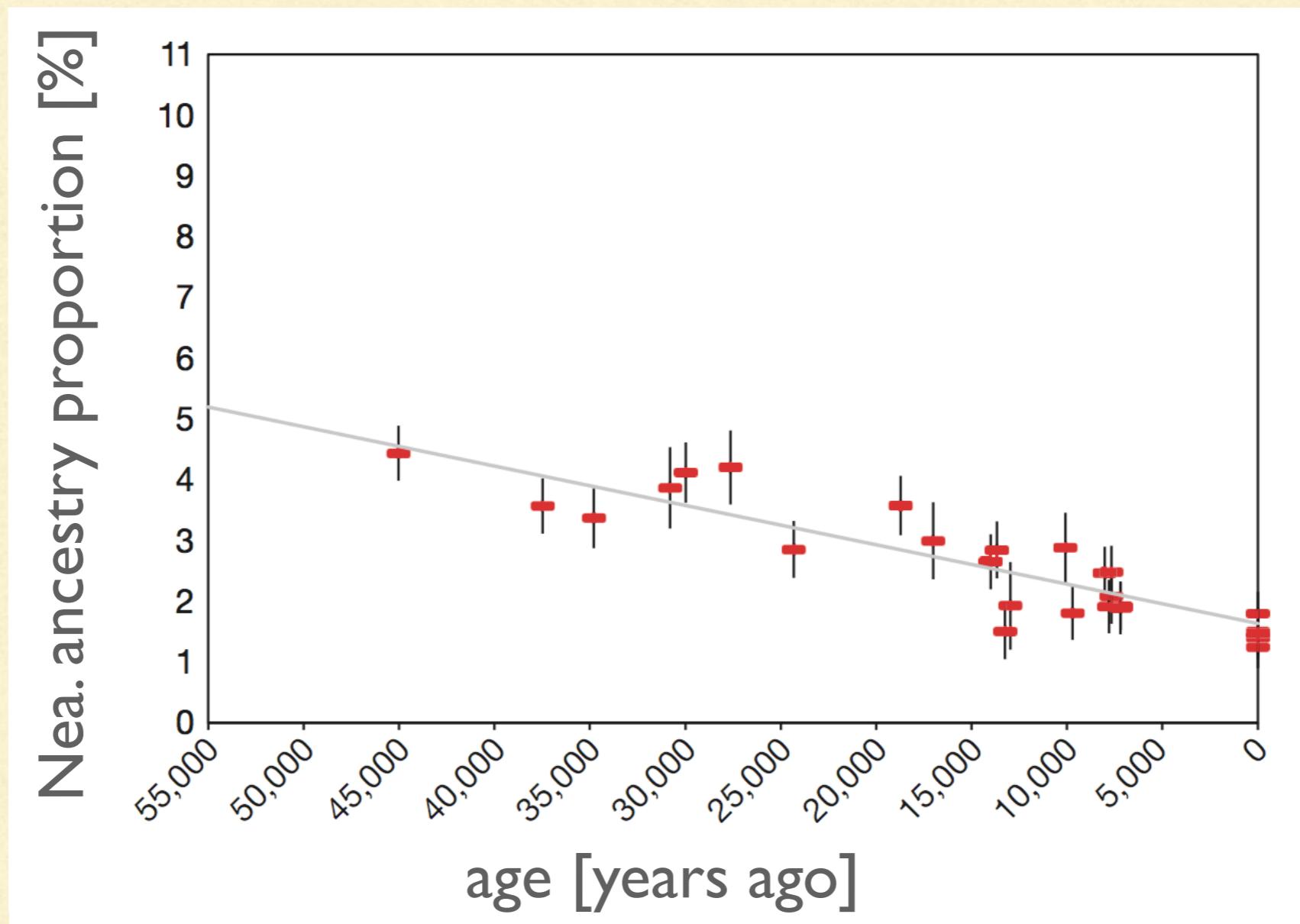
DATA CONTRADICTS THEORY ?



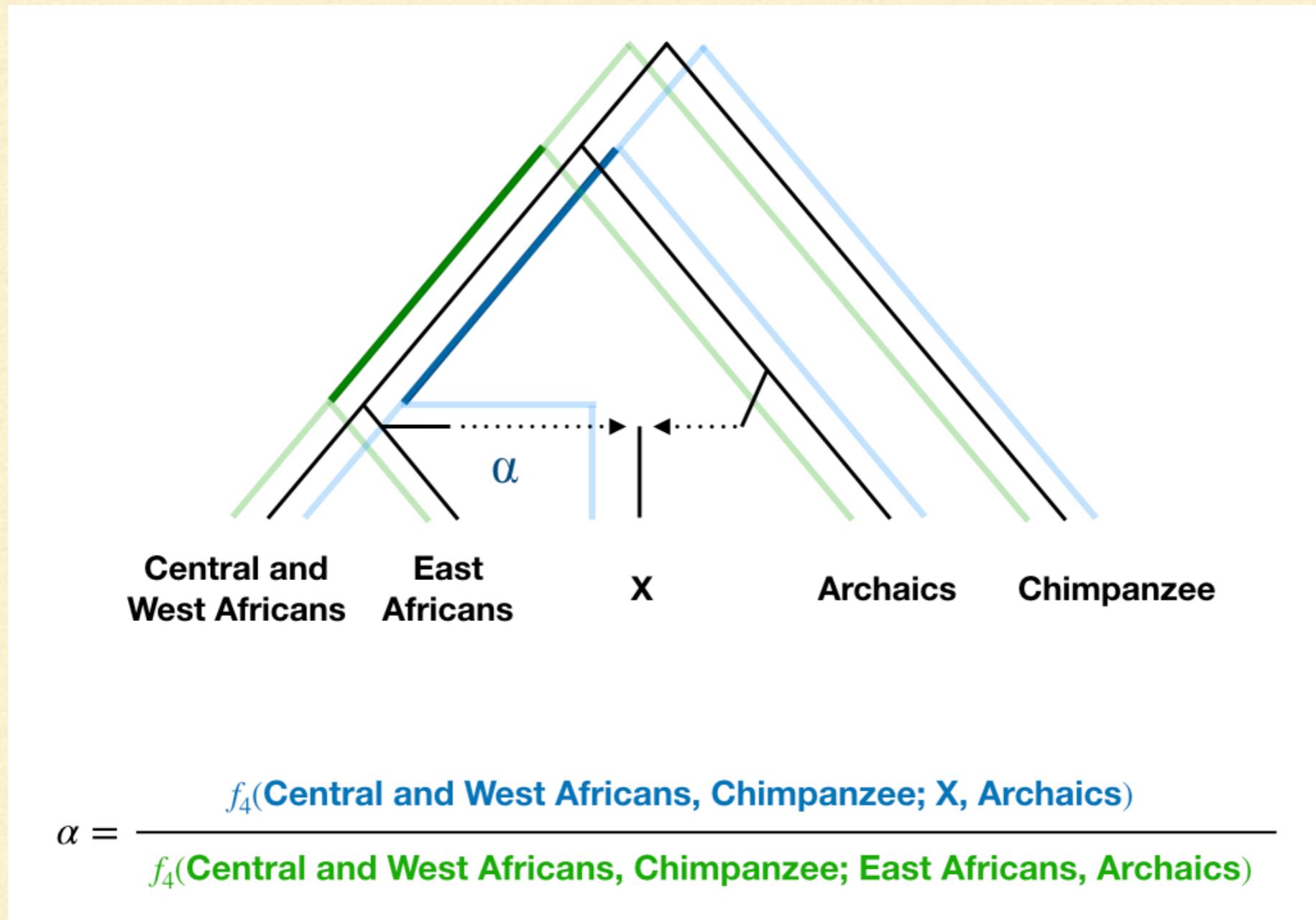
Fu et al. *Nature*. 2016.

Harris and Nielsen. *Genetics*. 2016.

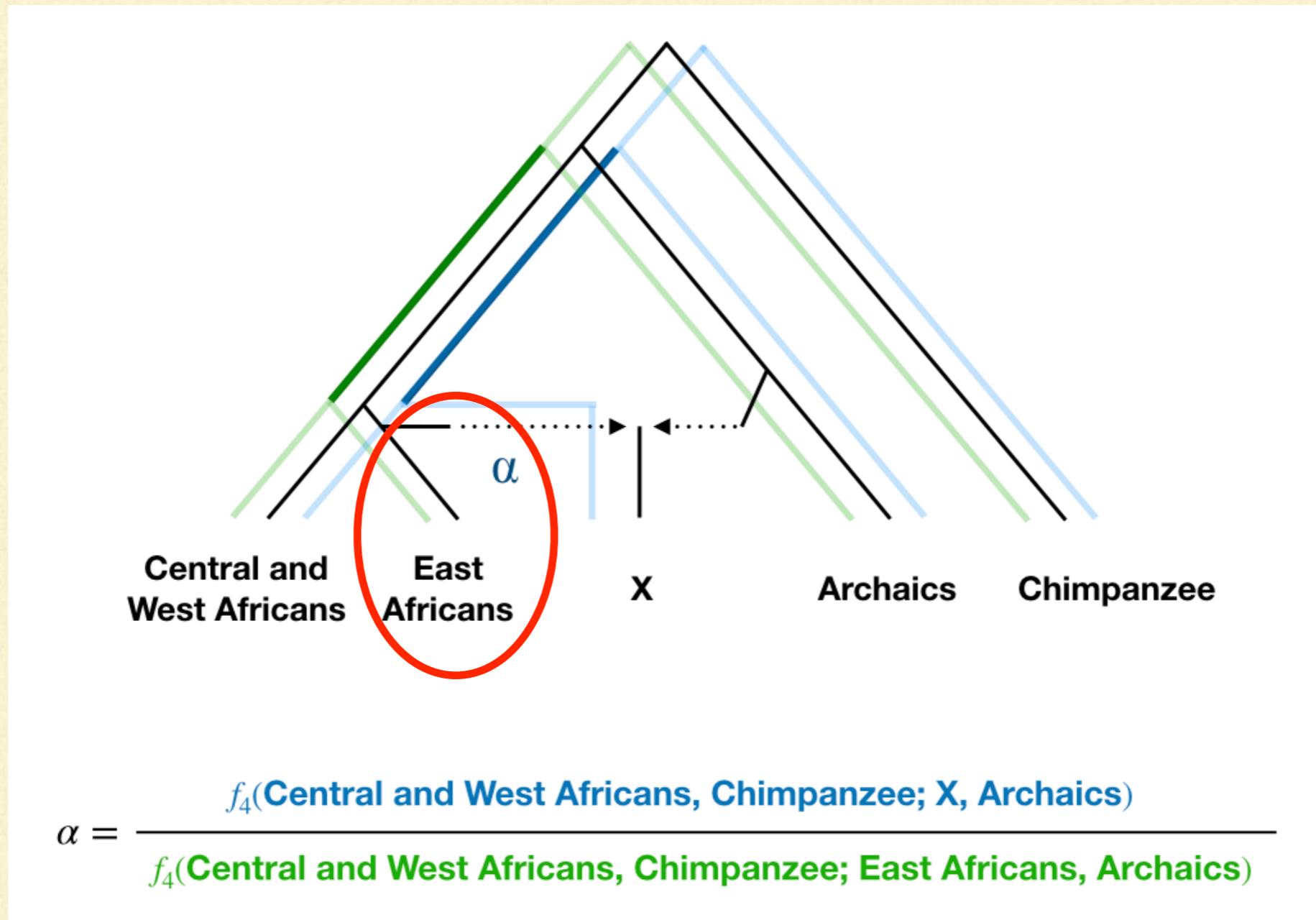
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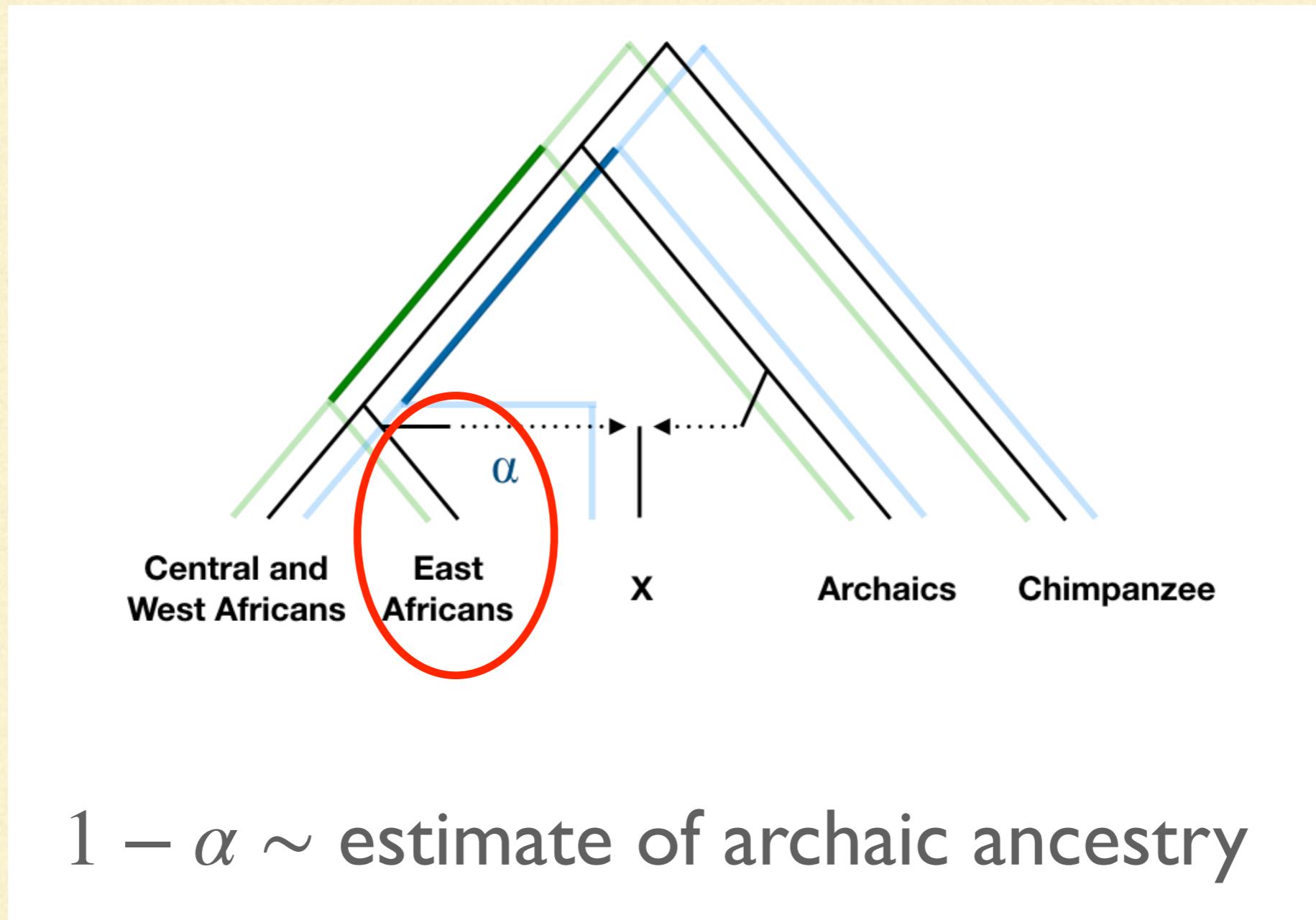
'INDIRECT' F_4 -RATIO NEANDERTAL ANCESTRY ESTIMATE



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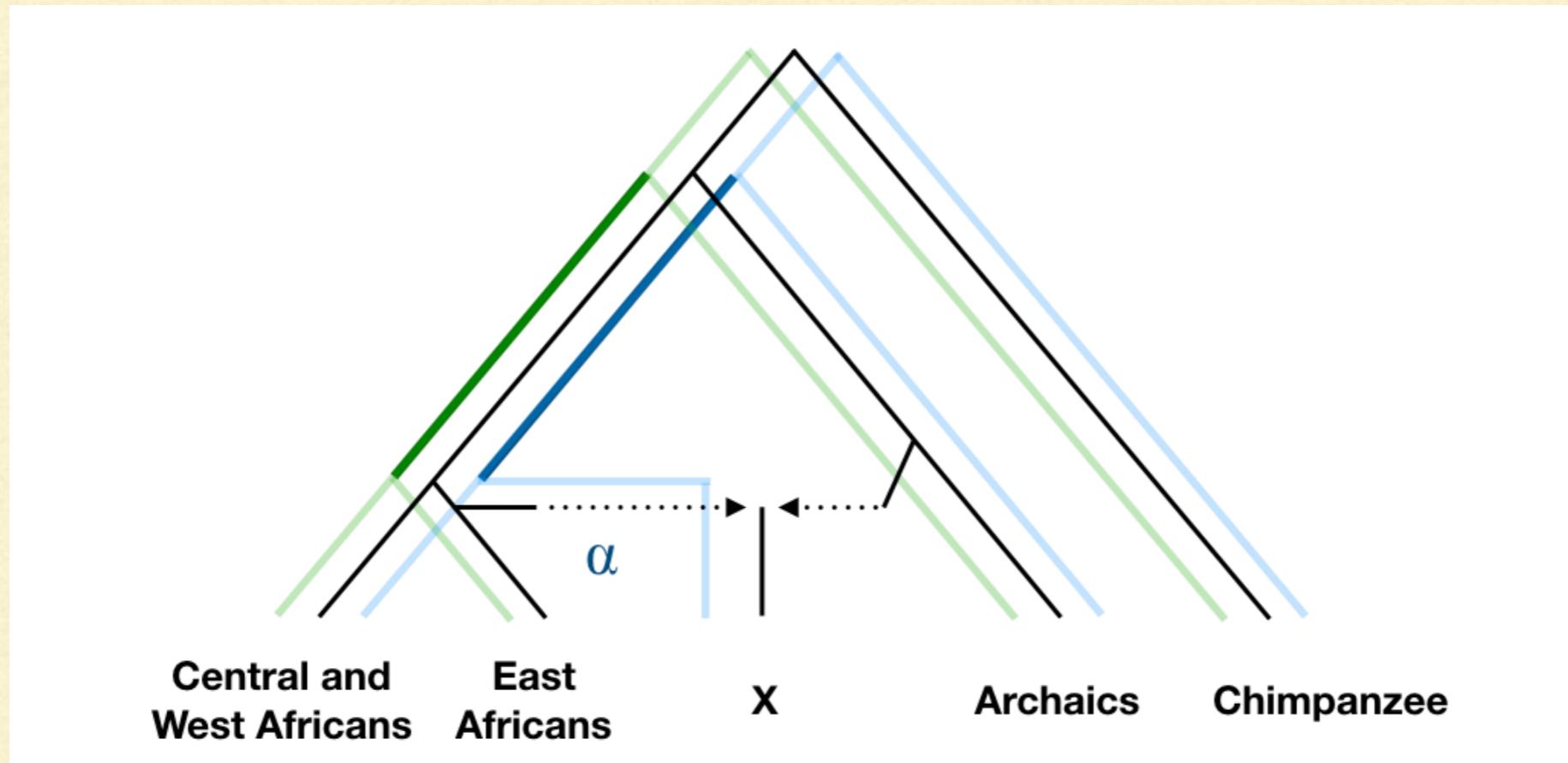


'INDIRECT' F_4 -RATIO NEANDERTAL ANCESTRY ESTIMATE



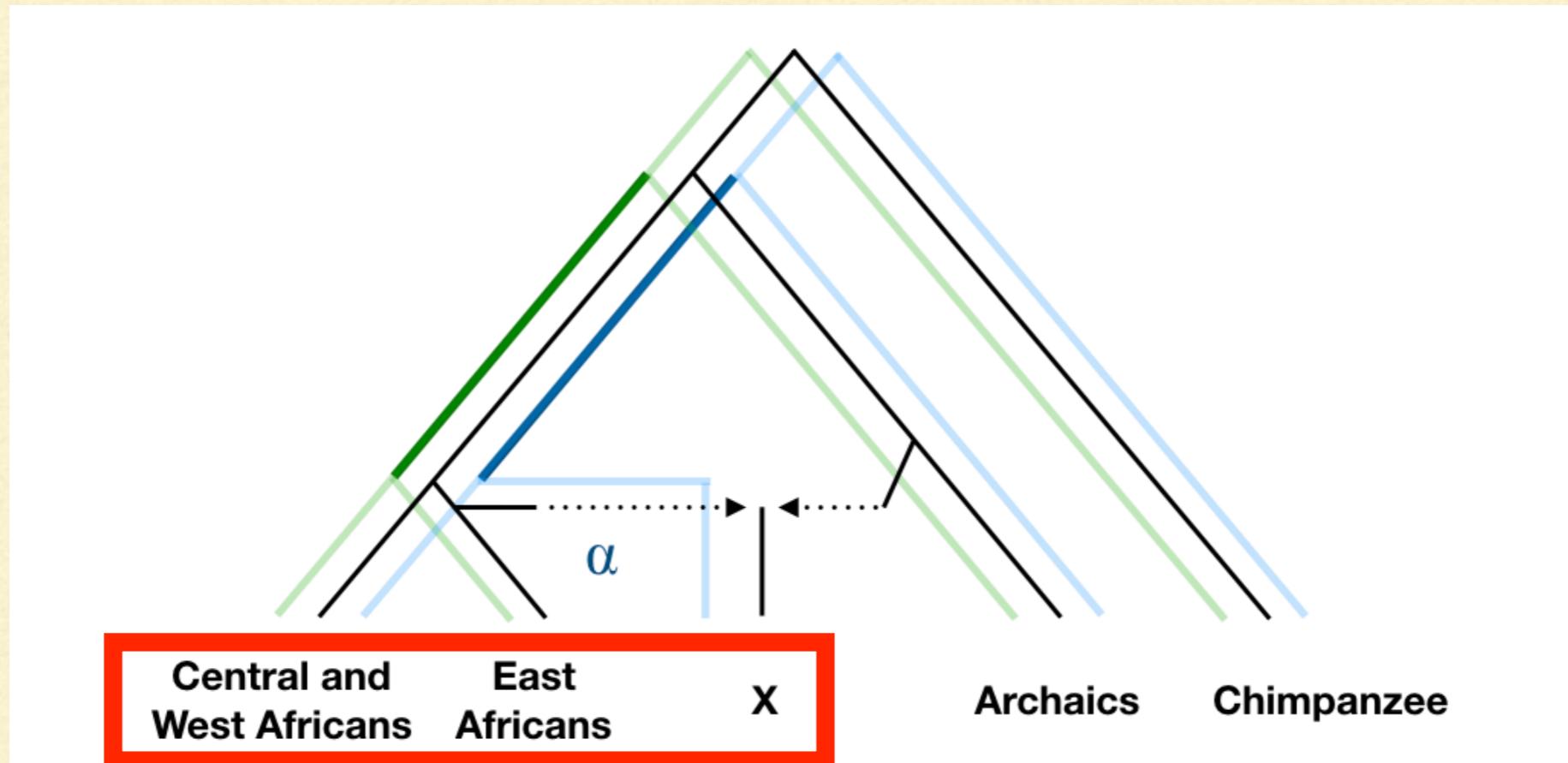
INDIRECT F_4 -RATIO

ASSUMPTIONS OF THE STATISTIC



INDIRECT F_4 -RATIO

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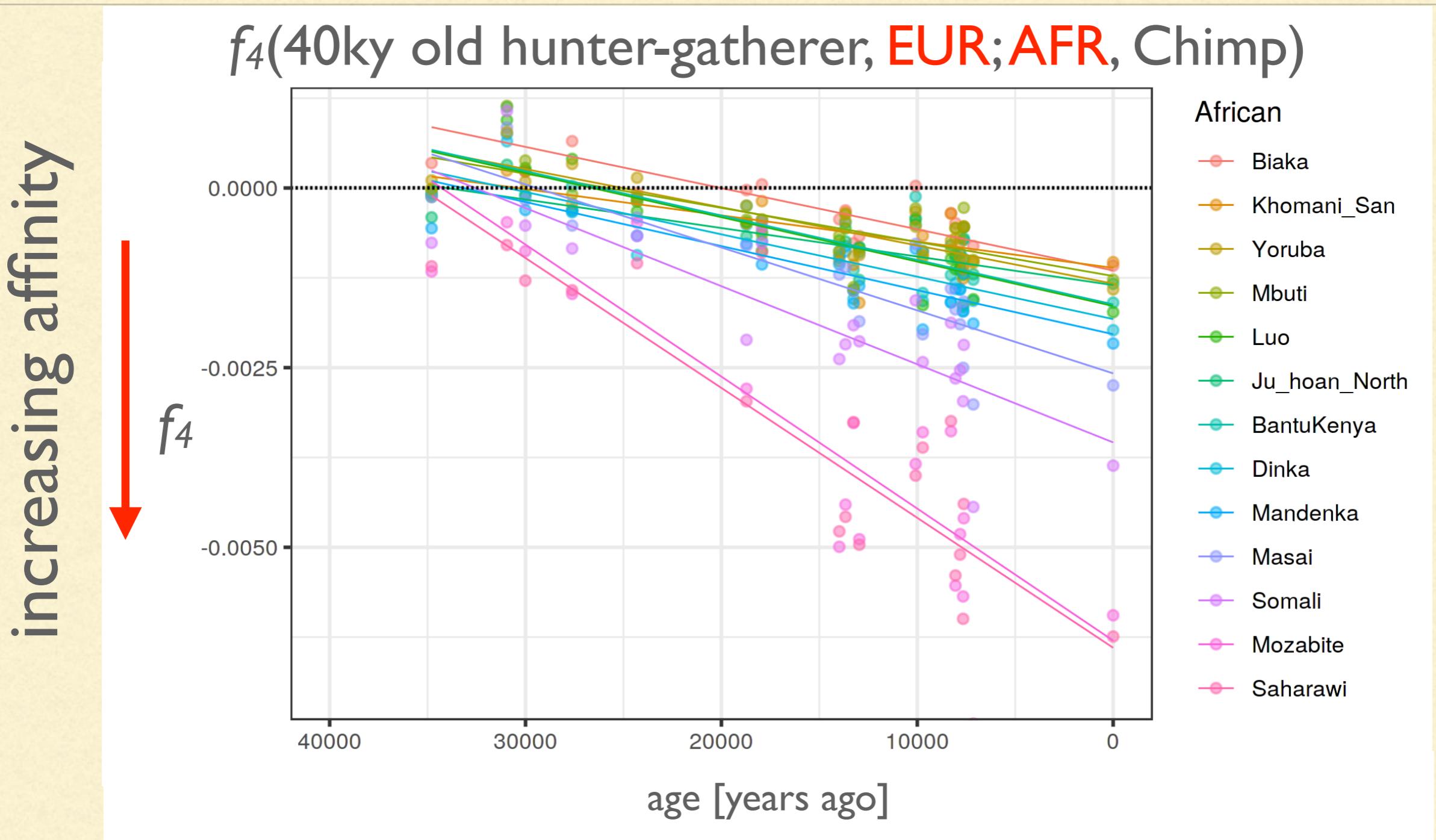


Assumes **constant relationship between Africans and Eurasians (X)** over time.

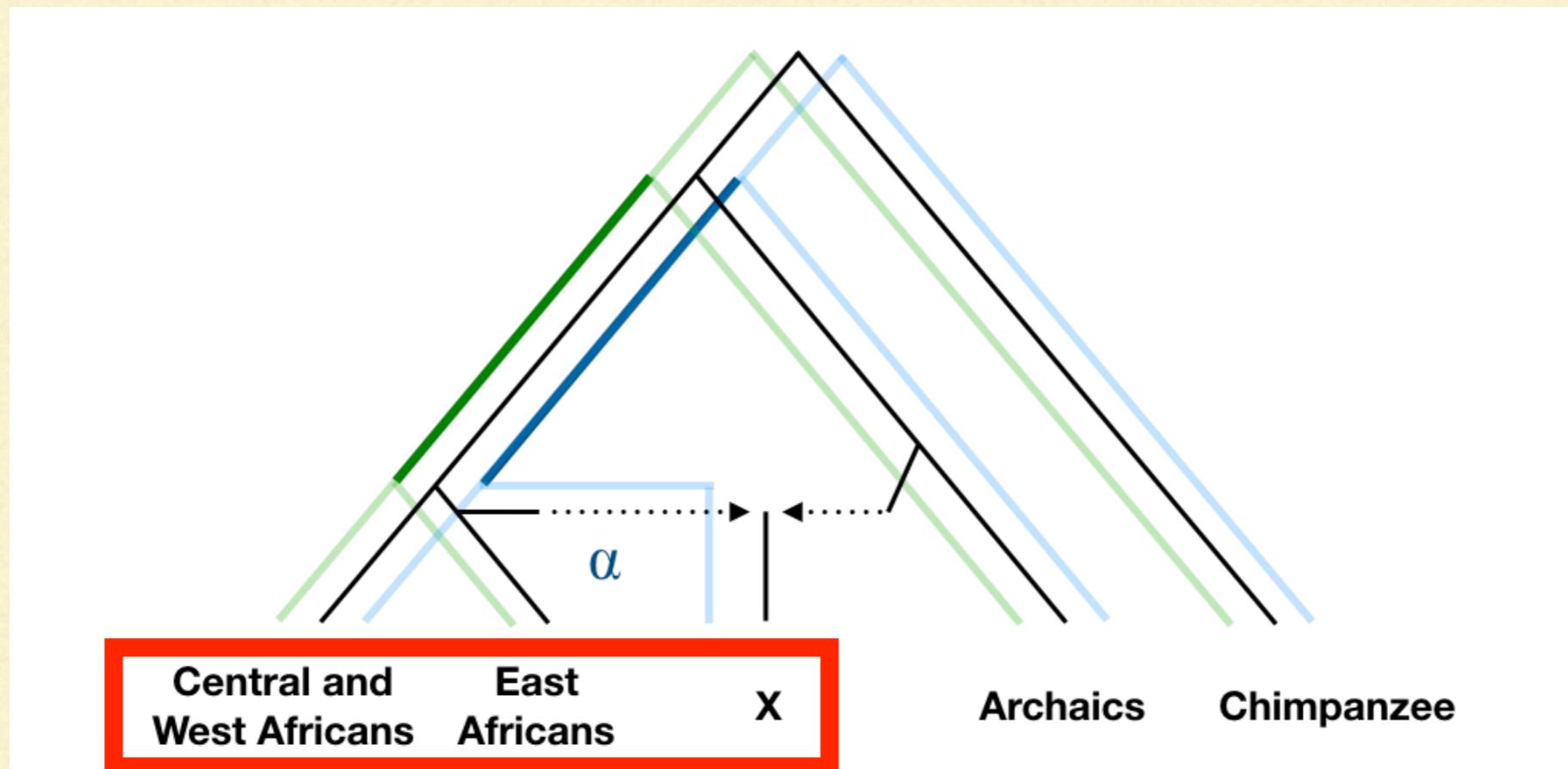
EUR-AFR ALLELE SHARING INCREASES OVER TIME

$f_4(40\text{ky old hunter-gatherer, EUR; AFR, Chimp})$

EUR-AFR ALLELE SHARING INCREASES OVER TIME



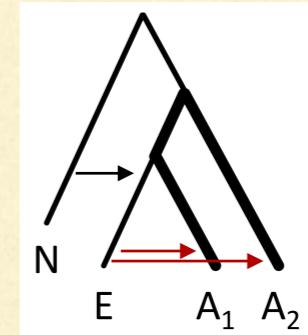
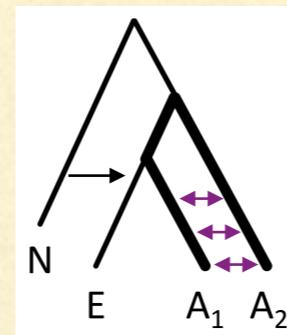
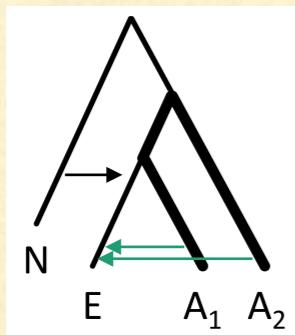
INDIRECT F_4 -RATIO



Assumptions do not hold!

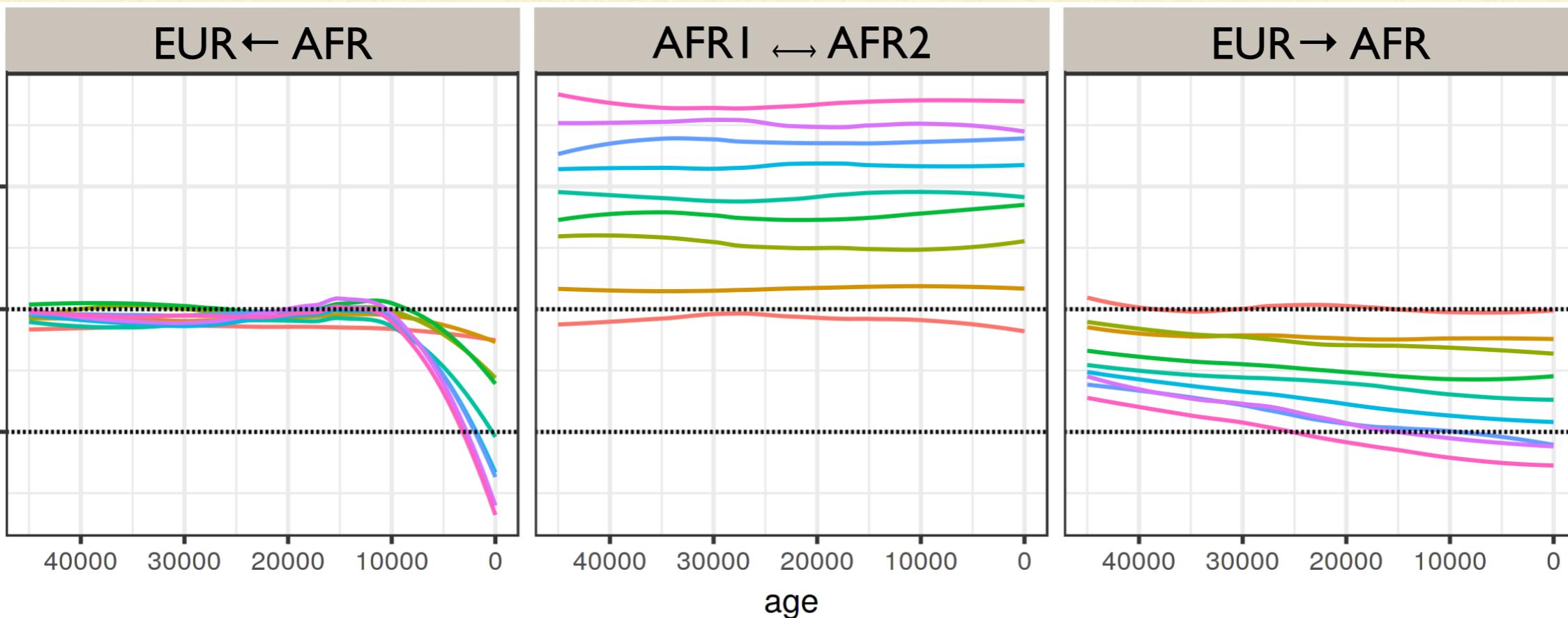
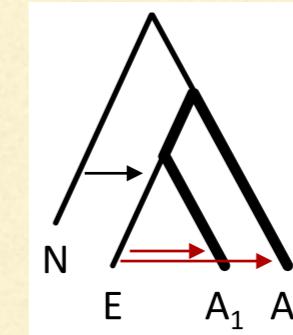
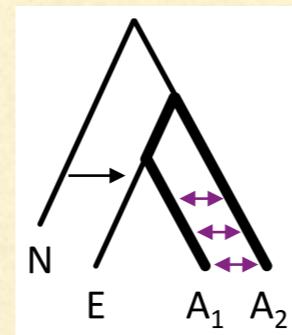
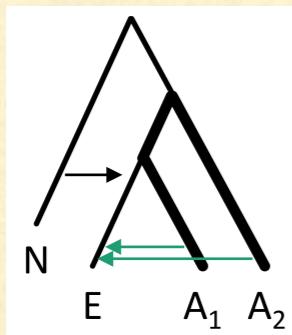
INDIRECT F_4 -RATIO

SIMULATING THE EFFECT OF MODERN HUMAN GENE FLOW



INDIRECT F_4 -RATIO

SIMULATING THE EFFECT OF MODERN HUMAN GENE FLOW



[true Neandertal proportion 3%, EUR-AFR gene flow at 10 kya]

TWO NEANDERTAL GENOMES

The complete genome sequence of a Neanderthal from the Altai Mountains

Kay Prüfer¹, Fernando Racimo², Nick Patterson³, Flora Jay², Sriram Sankararaman^{3,4}, Susanna Sawyer¹, Anja Heinze¹, Gabriel Renaud¹, Peter H. Sudmant⁵, Cesare de Filippo¹, Heng Li³, Swapan Mallick^{3,4}, Michael Dannemann¹, Qiaomei Fu^{1,6}, Martin Kircher^{1,5}, Martin Kuhlwilm¹, Michael Lachmann¹, Matthias Meyer¹, Matthias Ongyerth¹, Michael Siebauer¹, Christoph Theunert¹, Arti Tandon^{3,4}, Priya Moorjani⁴, Joseph Pickrell⁴, James C. Mullikin⁷, Samuel H. Vohr⁸, Richard E. Green⁸, Ines Hellmann^{9†}, Philip L. F. Johnson¹⁰, Hélène Blanche¹¹, Howard Cann¹¹, Jacob O. Kitzman⁵, Jay Shendure⁵, Evan E. Eichler^{5,12}, Ed S. Lein¹³, Trygve E. Bakken¹³, Liubov V. Golovanova¹⁴, Vladimir B. Doronichev¹⁴, Michael V. Shunkov¹⁵, Anatoli P. Derevianko¹⁵, Bence Viola¹⁶, Montgomery Slatkin², David Reich^{3,4,17}, Janet Kelso¹ & Svante Pääbo¹

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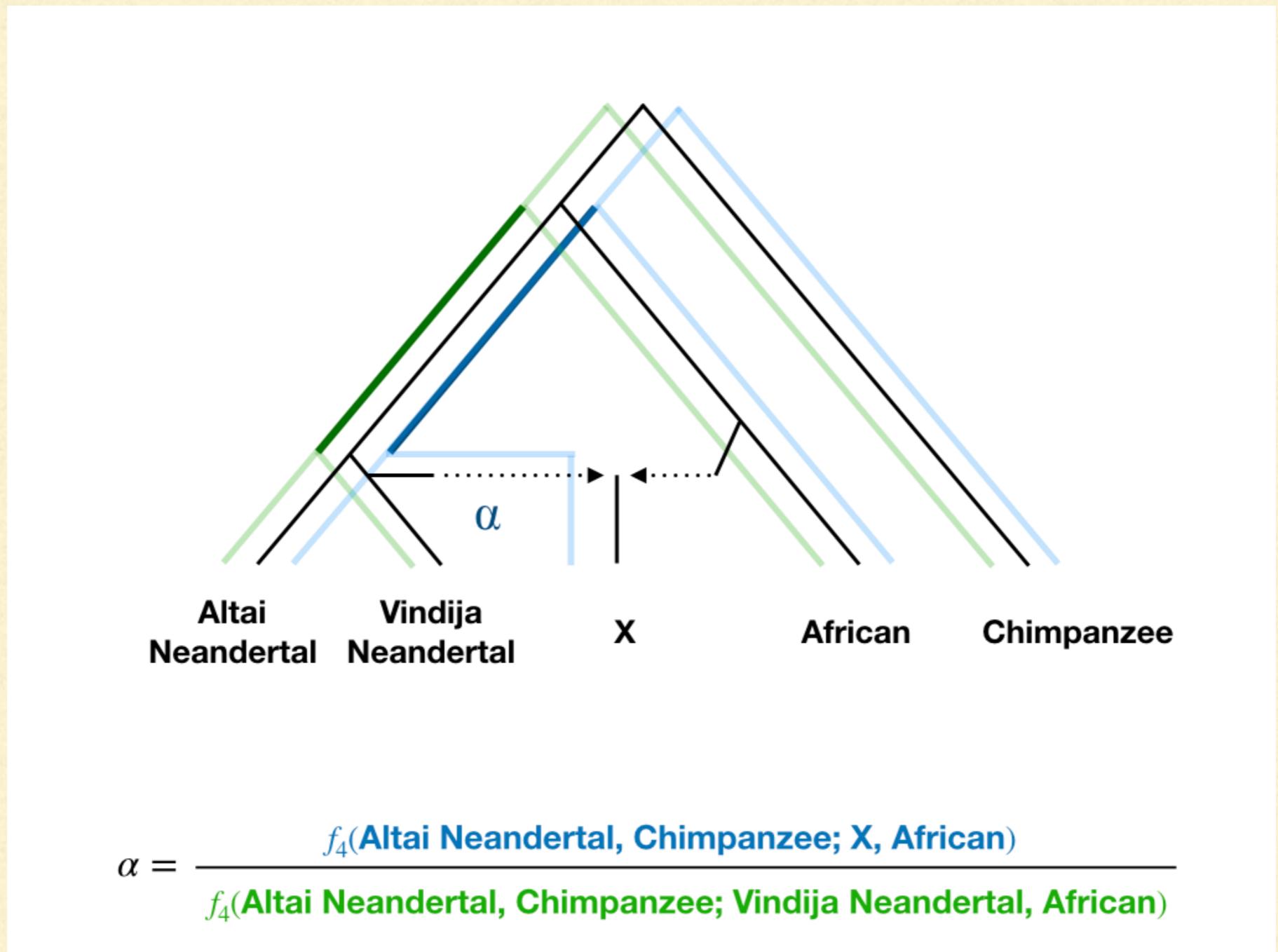
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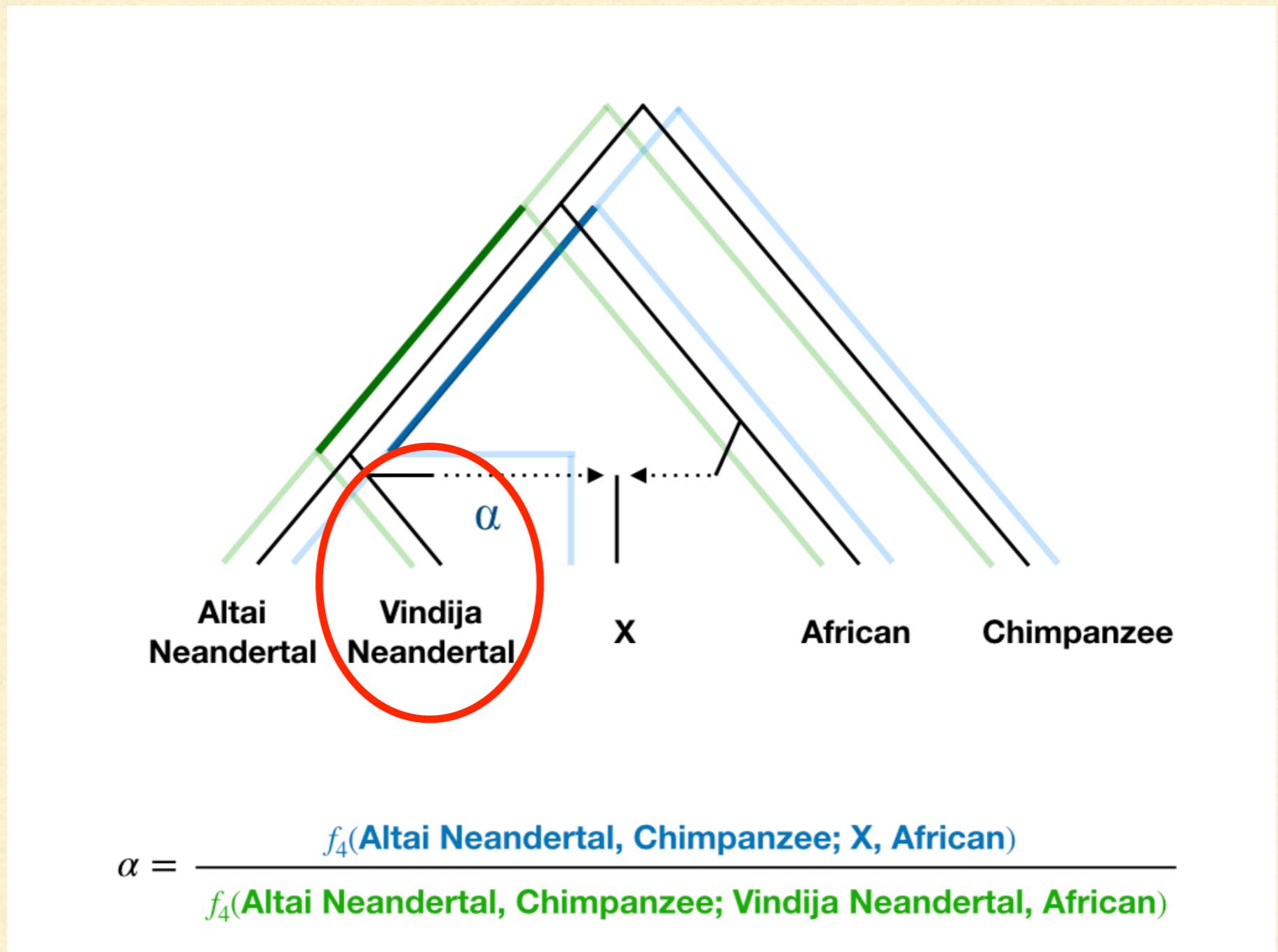
A high-coverage Neandertal genome from Vindija Cave in Croatia

Kay Prüfer,^{1*} Cesare de Filippo,^{1†} Steffi Grote,^{1†} Fabrizio Mafessoni,^{1†} Petra Korlević,¹ Mateja Hajdinjak,¹ Benjamin Vernot,¹ Laurits Skov,² Pinghsun Hsieh,³ Stéphane Peyrégne,¹ David Reher,¹ Charlotte Hopfe,¹ Sarah Nagel,¹ Tomislav Maricic,¹ Qiaomei Fu,⁴ Christoph Theunert,^{1,8} Rebekah Rogers,⁸ Pontus Skoglund,⁵ Manjusha Chintalapati,¹ Michael Dannemann,¹ Bradley J. Nelson,³ Felix M. Key,¹ Pavao Rudan,⁶ Željko Kućan,⁶ Ivan Gušić,⁶ Liubov V. Golovanova,⁷ Vladimir B. Doronichev,⁷ Nick Patterson,⁵ David Reich,^{5,9,10} Evan E. Eichler,^{3,11} Montgomery Slatkin,⁸ Mikkel H. Schierup,² Aida Andrés,¹ Janet Kelso,¹ Matthias Meyer,¹ Svante Pääbo^{1*}

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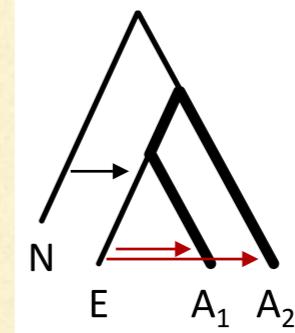
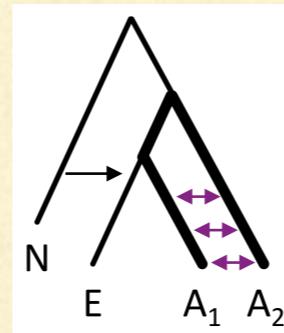
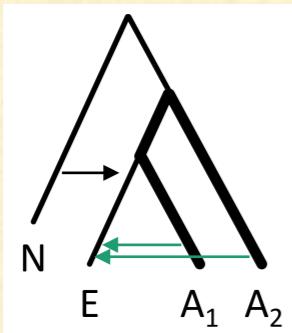


'DIRECT' F_4 -RATIO NEANDERTAL ANCESTRY ESTIMATE



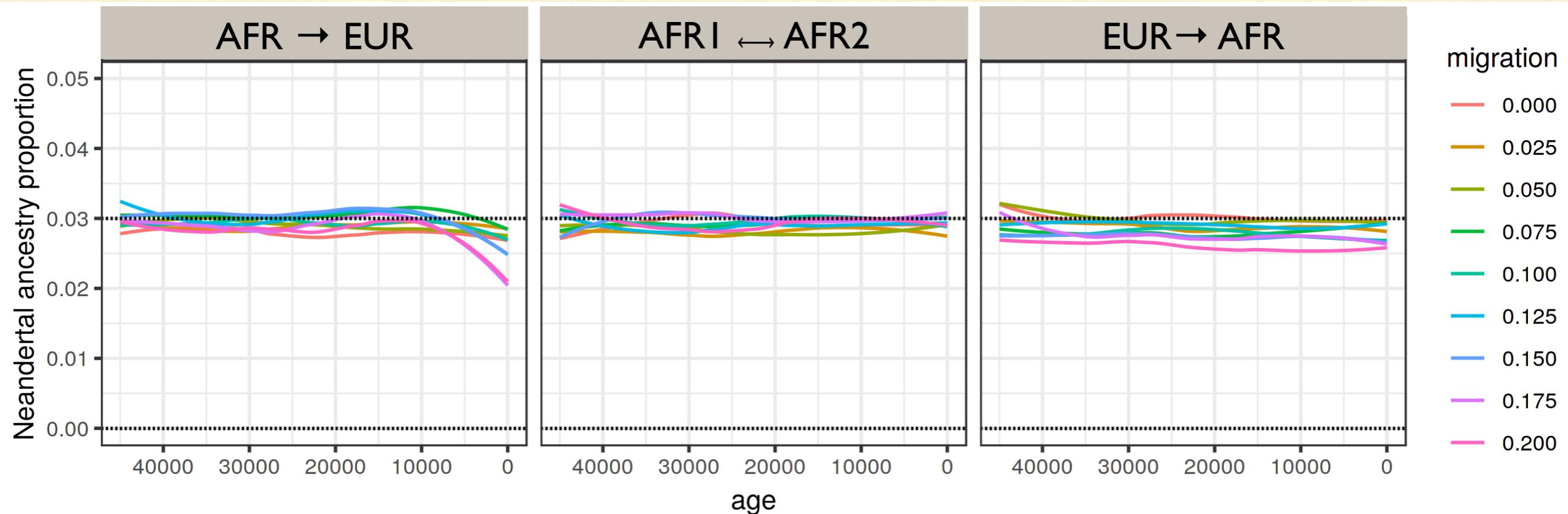
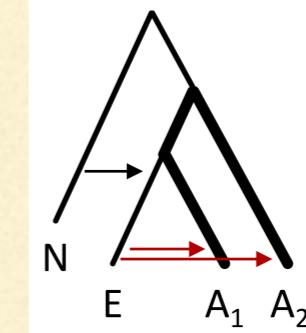
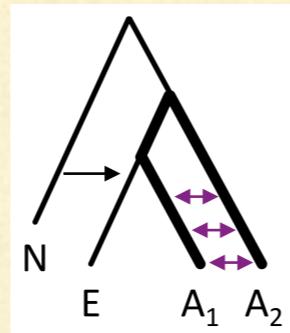
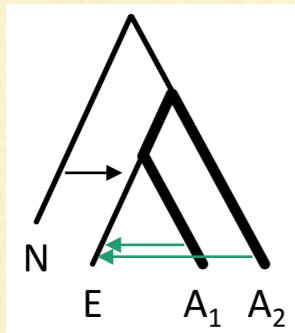
DIRECT F_4 -RATIO

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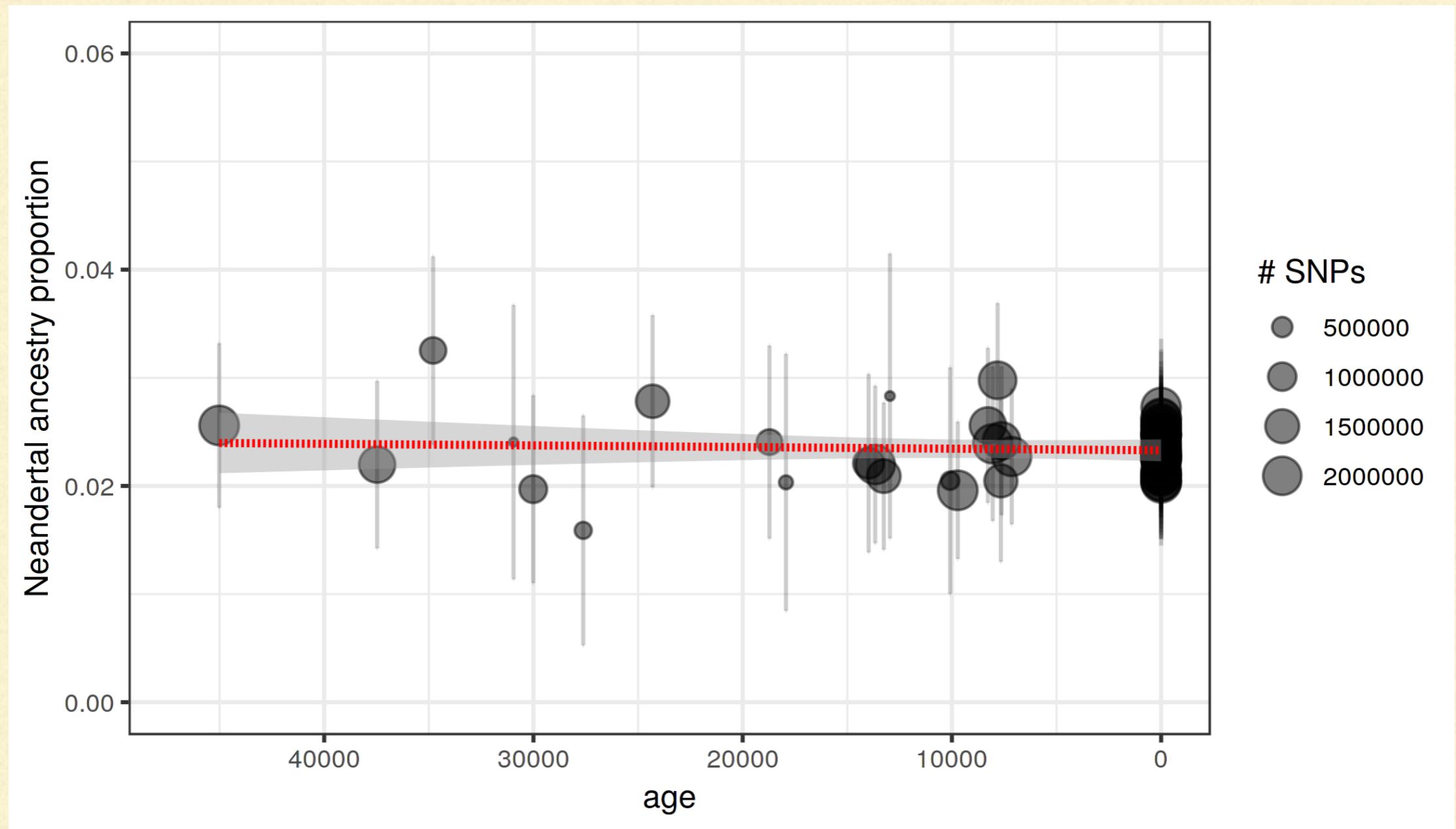
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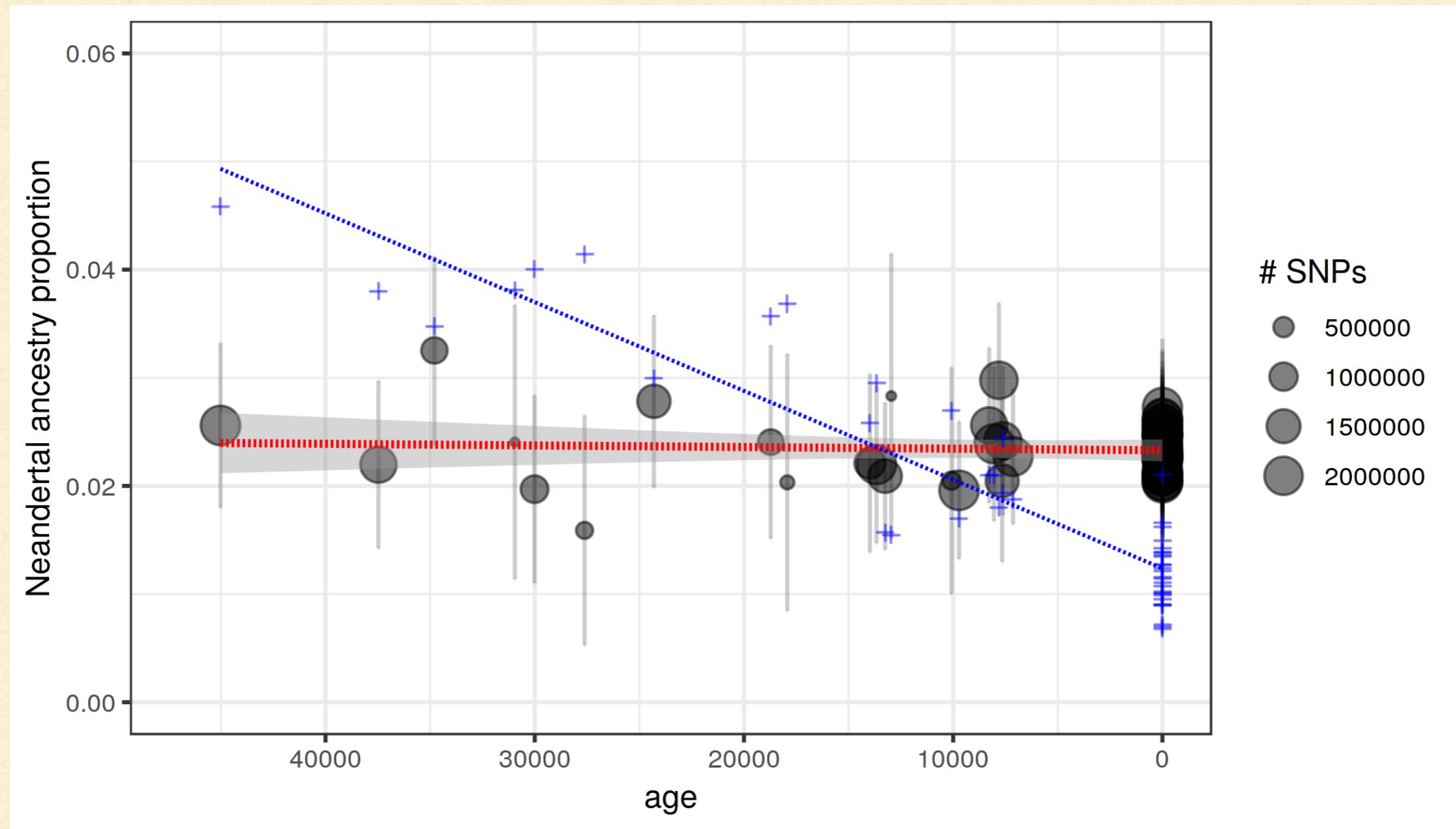


[true Neandertal proportion 3%, EUR-AFR gene flow at 10 kya]

DIRECT F_4 -RATIO — REAL DATA

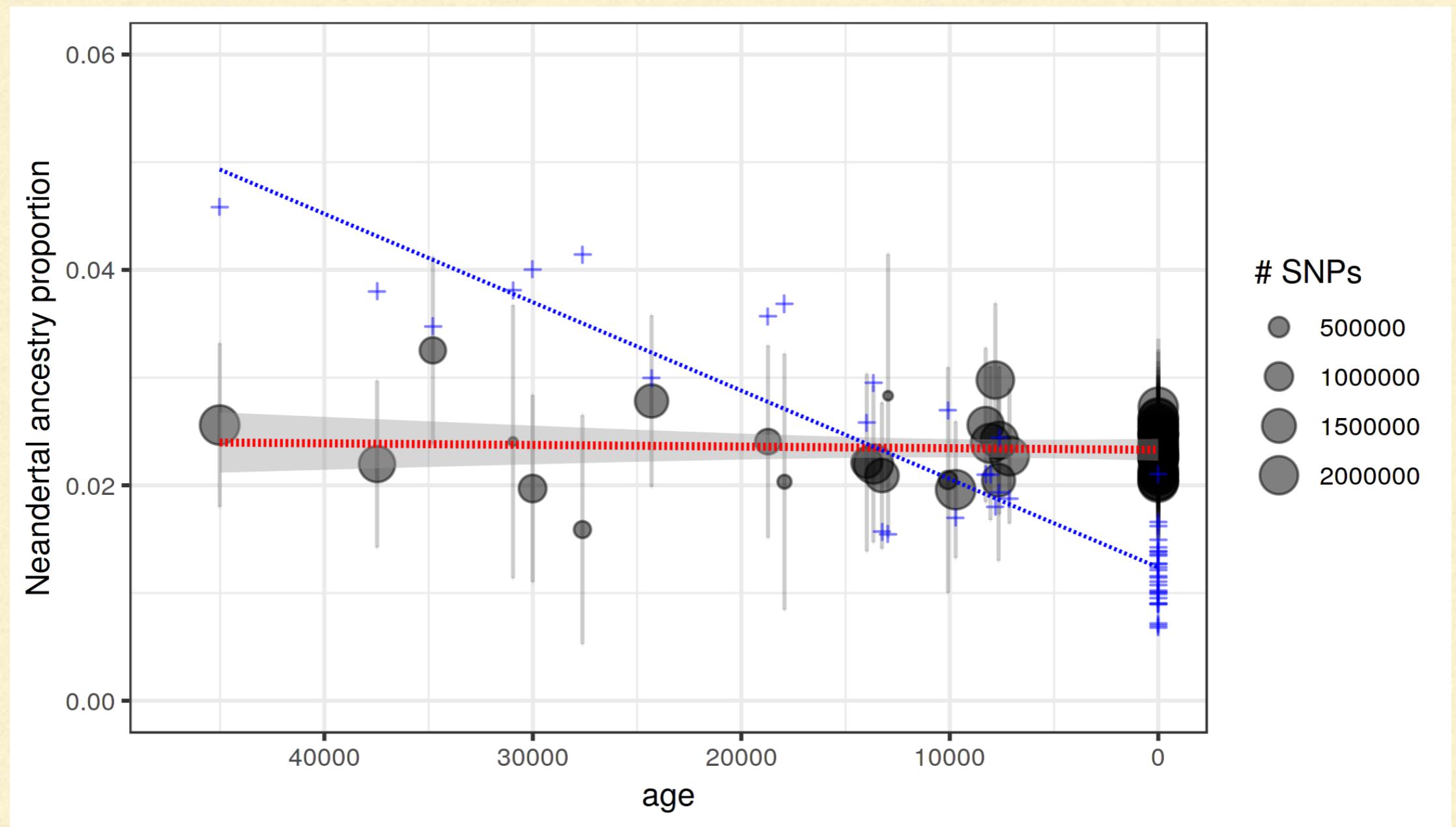


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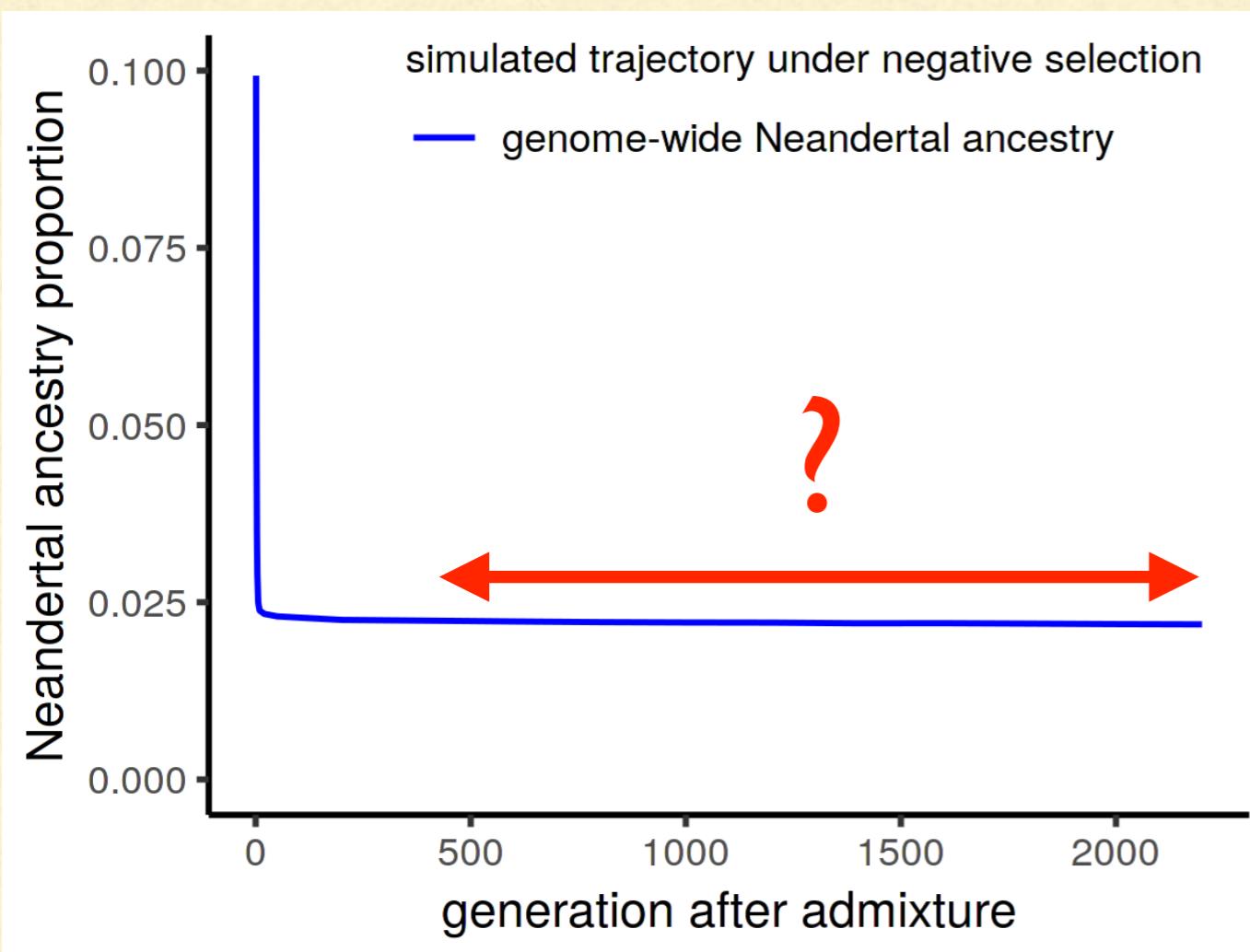
NO SIGNIFICANT DECLINE

—WHAT ABOUT NEGATIVE SELECTION?



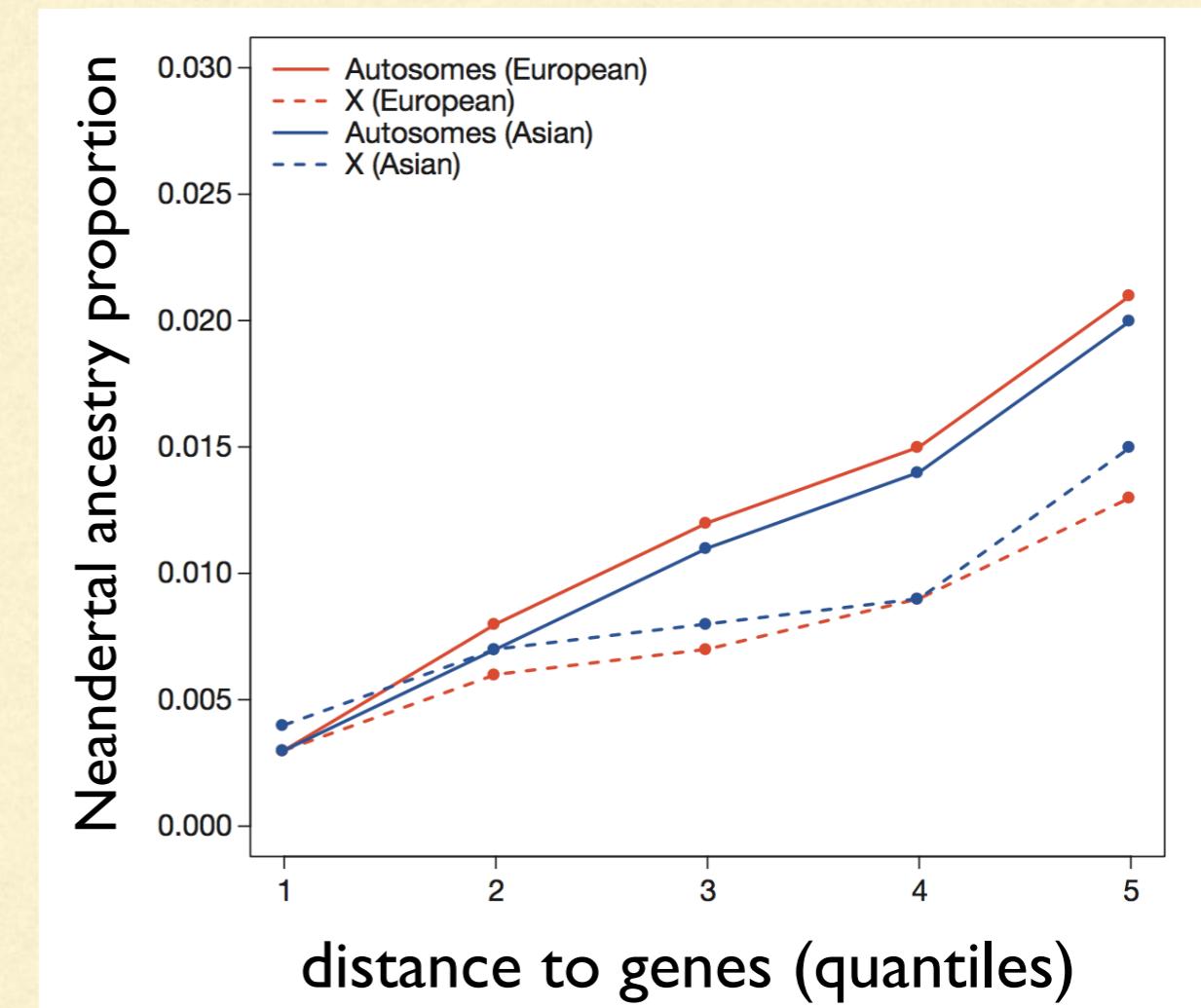
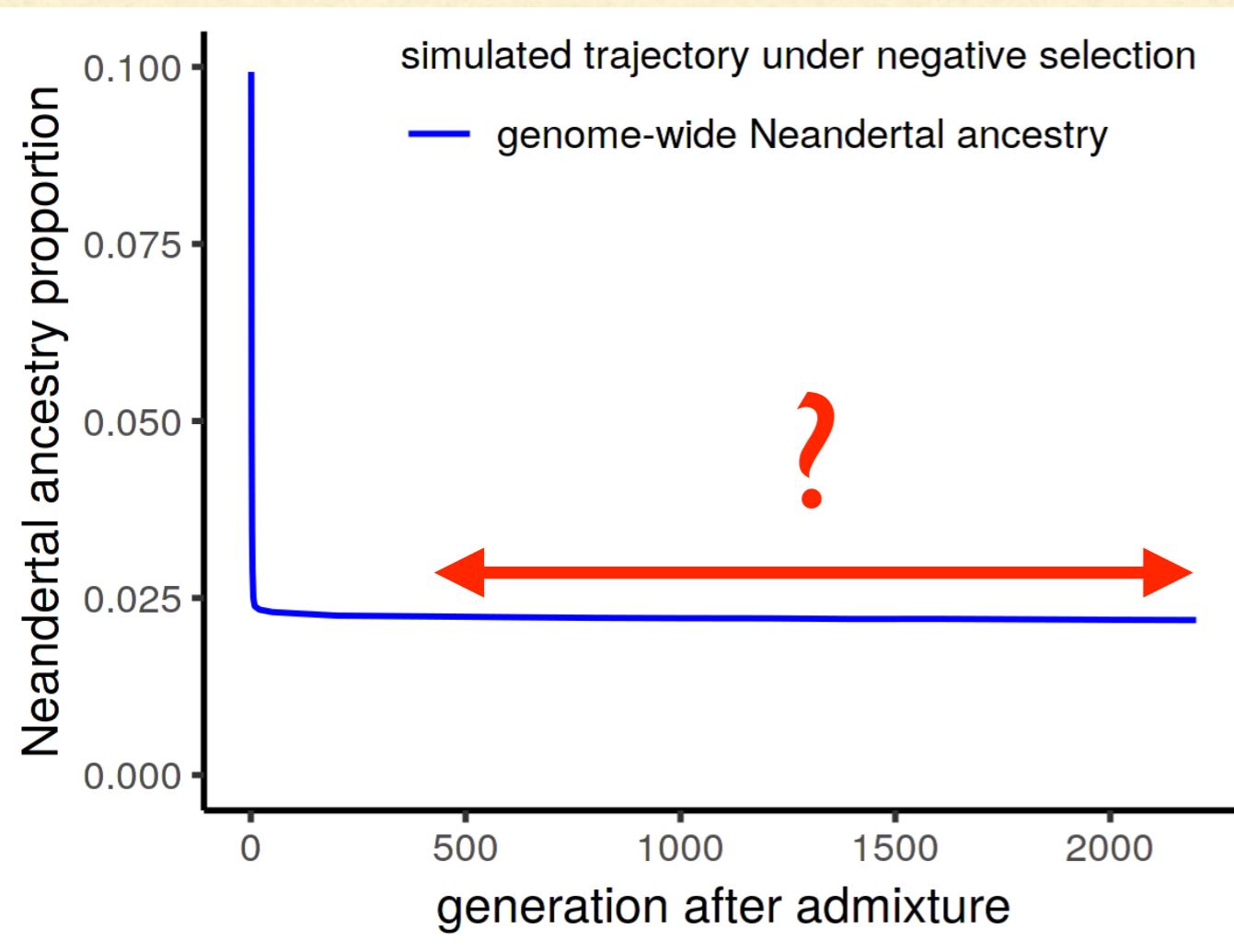
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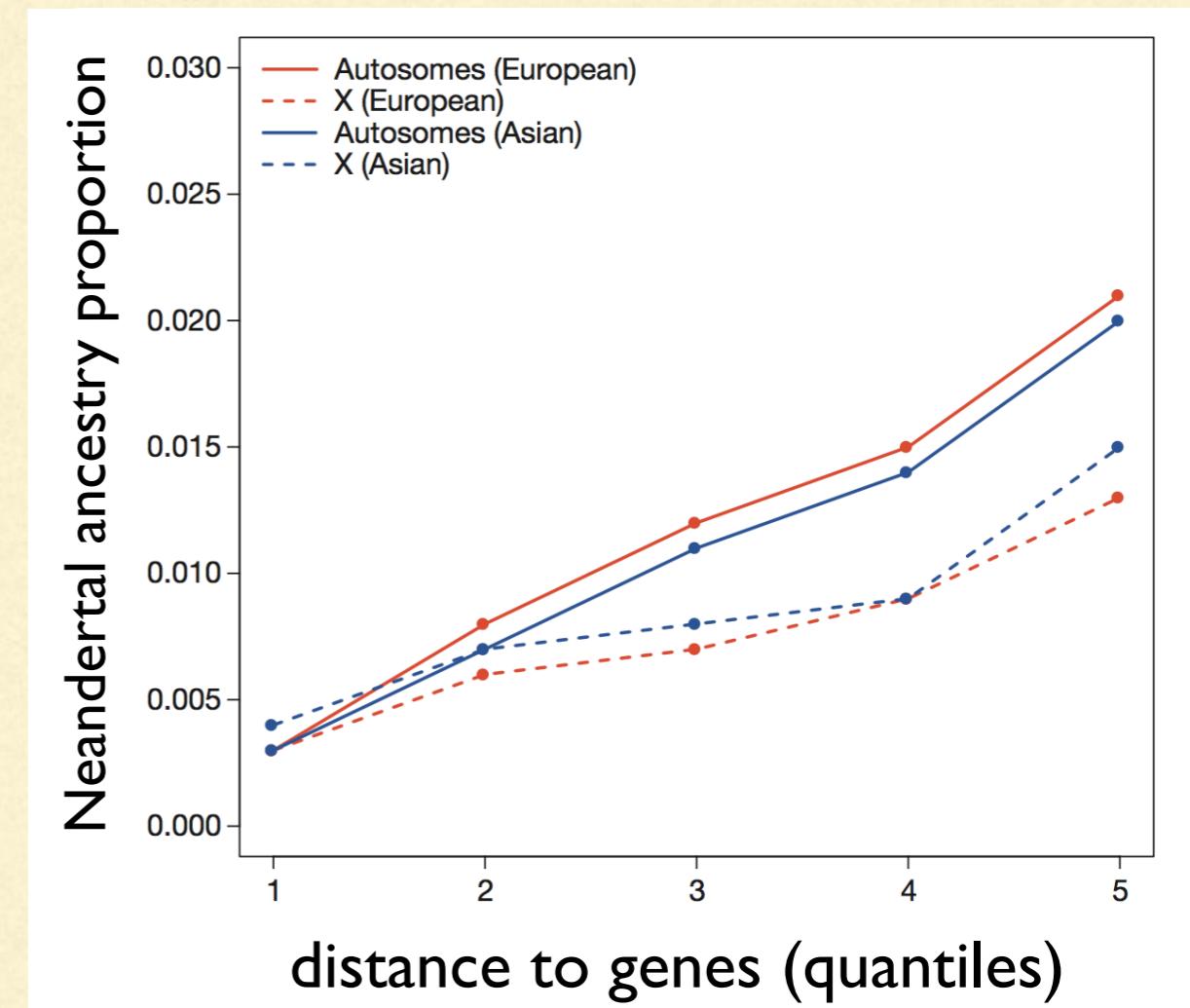
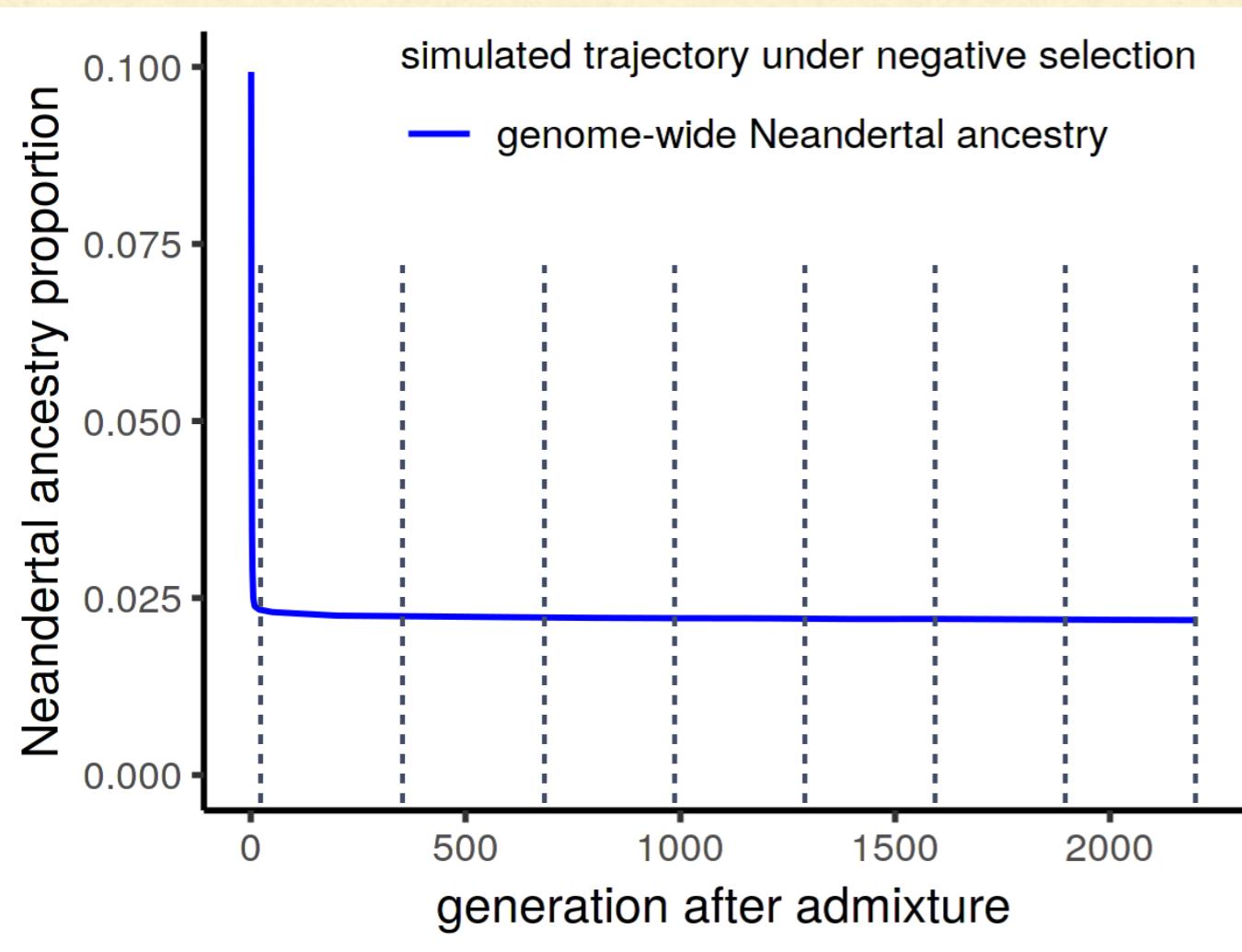
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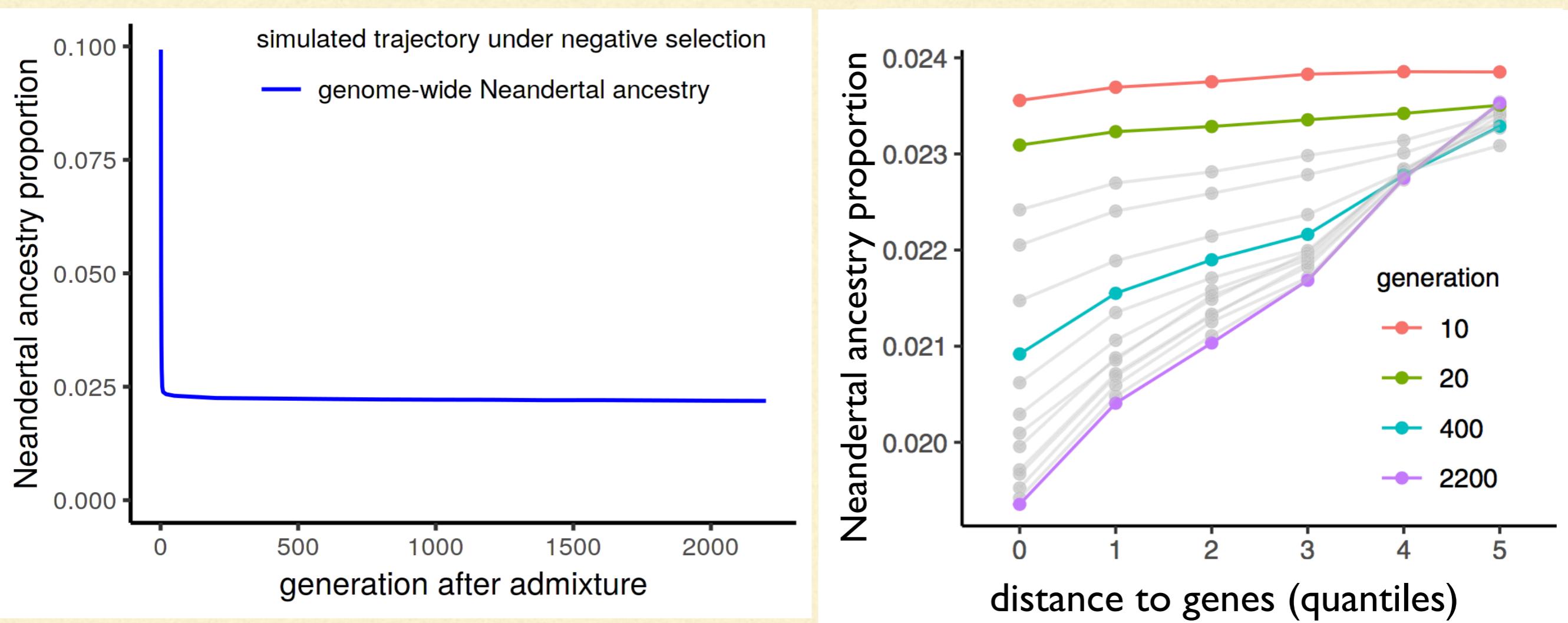
DYNAMICS OF NEGATIVE SELECTION

— WHOLE-GENOME SIMULATIONS

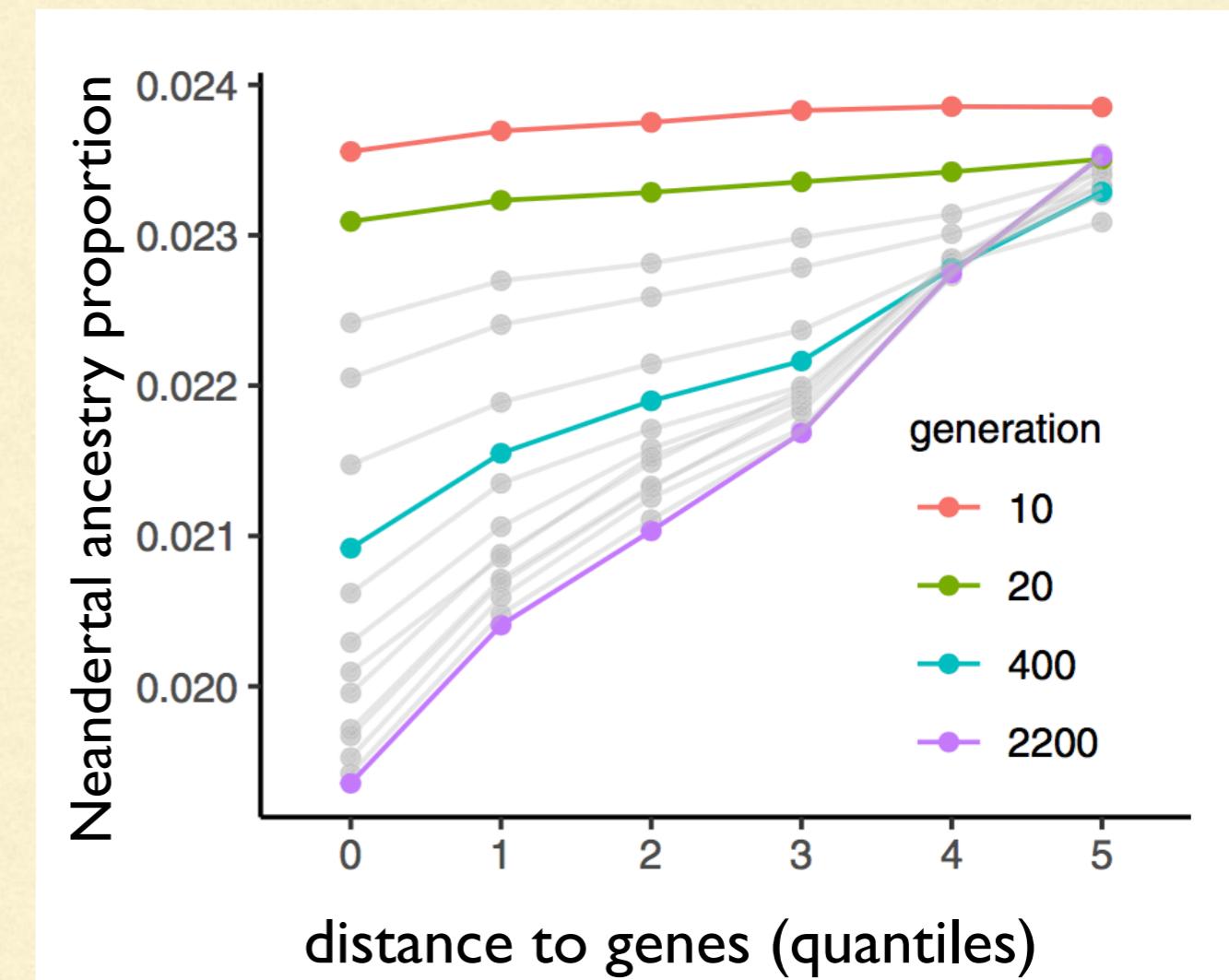
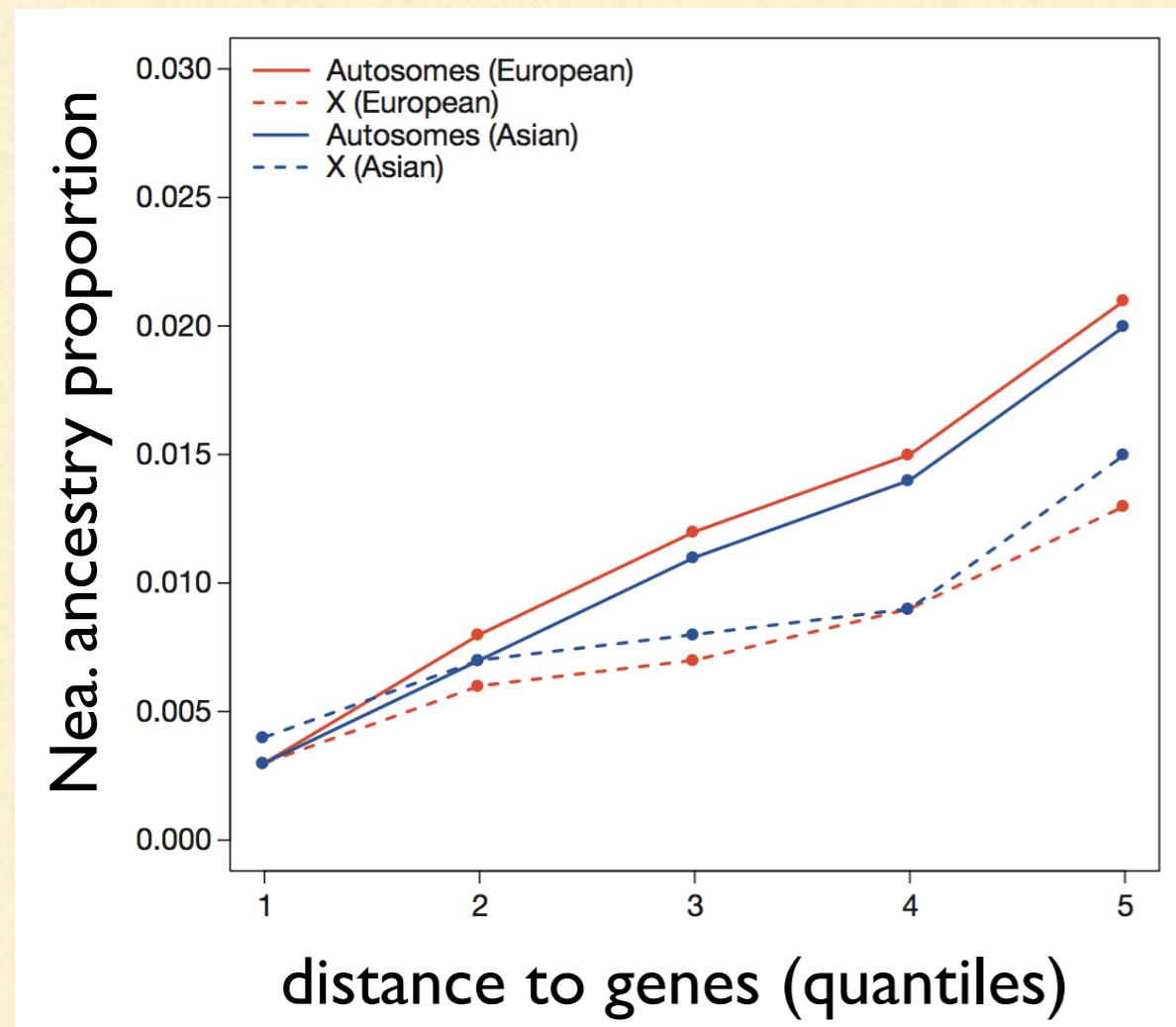


DYNAMICS OF NEGATIVE SELECTION

— WHOLE-GENOME SIMULATIONS



LONG-TERM NEGATIVE SELECTION STILL OCCURS



CONCLUSIONS

- Model assumptions matter:
 - "Hidden" gene flow can have surprising effects.
 - Crucial for time series analyses.
 - When in doubt, run simulations!

CONCLUSIONS

- Model assumptions matter:
 - "Hidden" gene flow can have surprising effects.
 - Crucial for time series analyses.
 - When in doubt, run simulations!
 - No significant decline in Neandertal ancestry.
 - Long-term negative selection on a local scale.
-

THANK YOU!



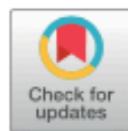
Janet Kelso



Ben Vernot



Svante Pääbo



Limits of long-term selection against Neandertal introgression

Martin Petr^a, Svante Pääbo^a, Janet Kelso^{a,1,2}, and Benjamin Vernot^{a,1,2}

^aDepartment of Evolutionary Genetics, Max Planck Institute for Evolutionary Anthropology, 04103 Leipzig, Germany

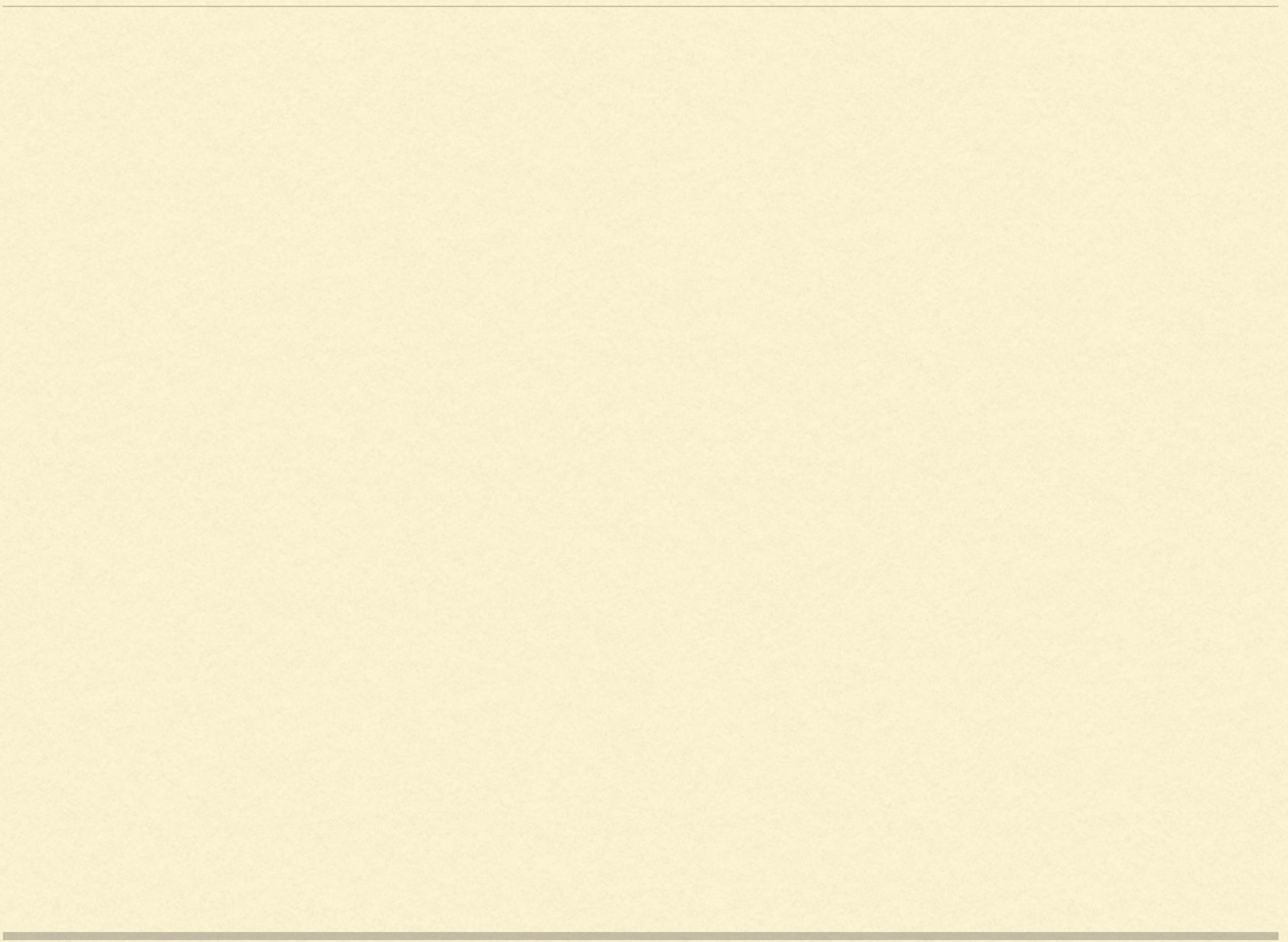
Edited by Sarah A. Tishkoff, University of Pennsylvania, Philadelphia, PA, and approved December 12, 2018 (received for review August 22, 2018)

Several studies have suggested that introgressed Neandertal DNA was subjected to negative selection in modern humans. A striking observation in support of this is an apparent monotonic decline in Neandertal ancestry observed in modern humans in Europe over the past 45,000 years. Here, we show that this decline is an artifact likely caused by gene flow between modern human populations, which is not taken into account by statistics previously used to estimate Neandertal ancestry. When we apply a statistic that avoids assumptions about modern human demography by taking advantage of two high-coverage Neandertal genomes, we find no evidence for a change in Neandertal ancestry in Europe over the past 45,000 years. We use whole-genome simulations of selection and introgression to investigate a wide range of model parameters and find that negative selection is not expected to cause a significant long-term decline in genome-wide Neandertal ancestry. Nevertheless, these models recapitulate previously observed signals of selection against Neandertal alleles, in particular the depletion of Neandertal ancestry in conserved genomic regions. Surprisingly, we find that this depletion is strongest in regulatory and conserved noncoding regions and in the most conserved portion of protein-coding sequences.

studies. Our analysis shows that the Neandertal ancestry proportion in Europeans has not decreased significantly over the last 45,000 y. Using simulations of selection and introgression, we show that a model of weak selection against deleterious Neandertal variation also does not predict significant changes in Neandertal ancestry during the time period covered by existing ancient modern human samples. In contrast, these simulations do predict a depletion of Neandertal ancestry around functional genomic regions. We then use our updated Neandertal ancestry estimates to examine the genomic distribution of introgressed Neandertal DNA and find that selection against introgression was strongest in regulatory and conserved noncoding regions compared with protein-coding sequence (CDS), suggesting that regulatory differences between Neandertals and modern humans may have been more extreme than protein-coding differences.

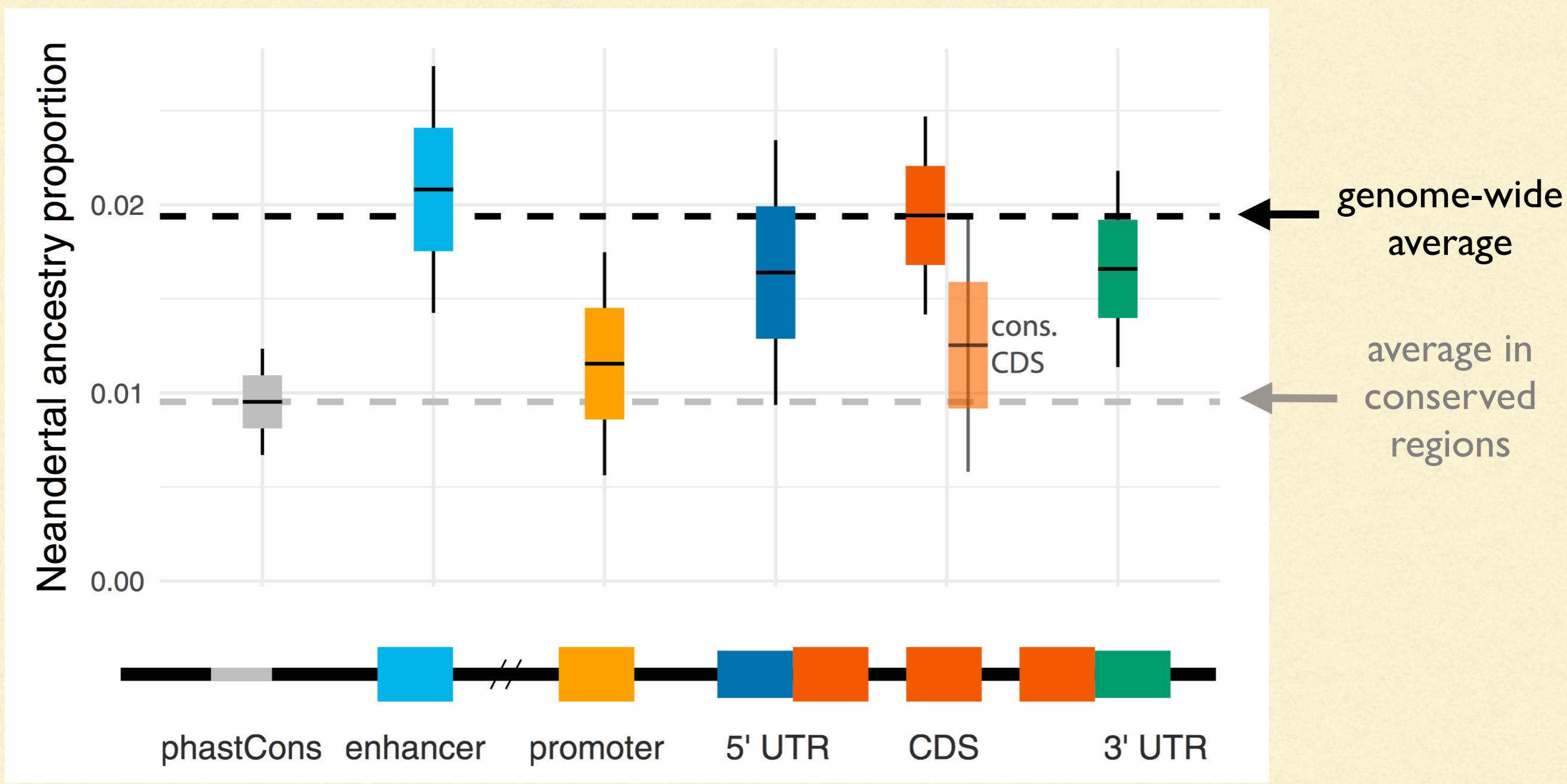
Results

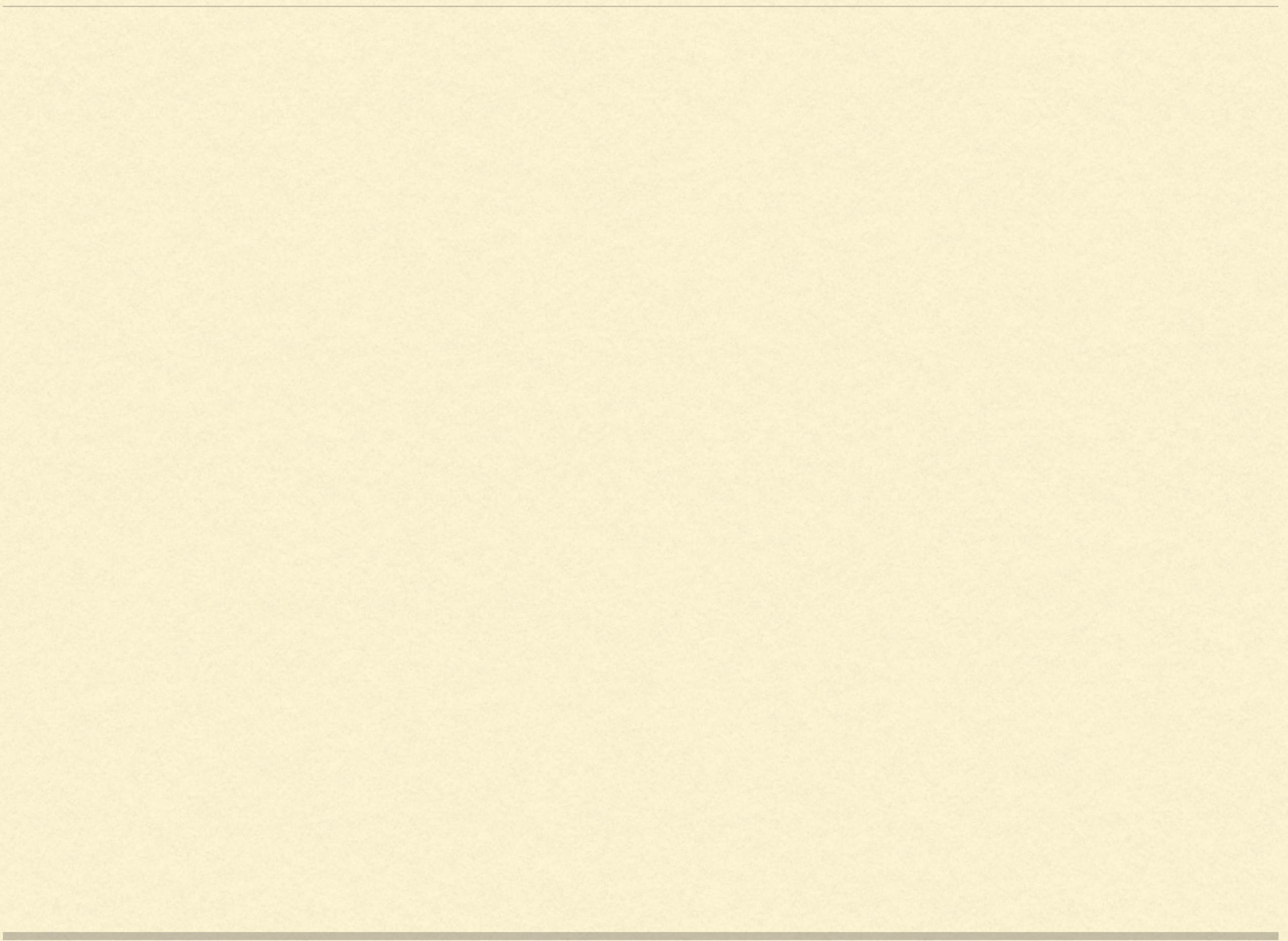
Previous Neandertal Ancestry Estimate. A number of methods have been developed to quantify Neandertal ancestry in modern human genomes (14). Among the most widely used is the f_4 -ratio statistic, which measures the fraction of drift shared with one of

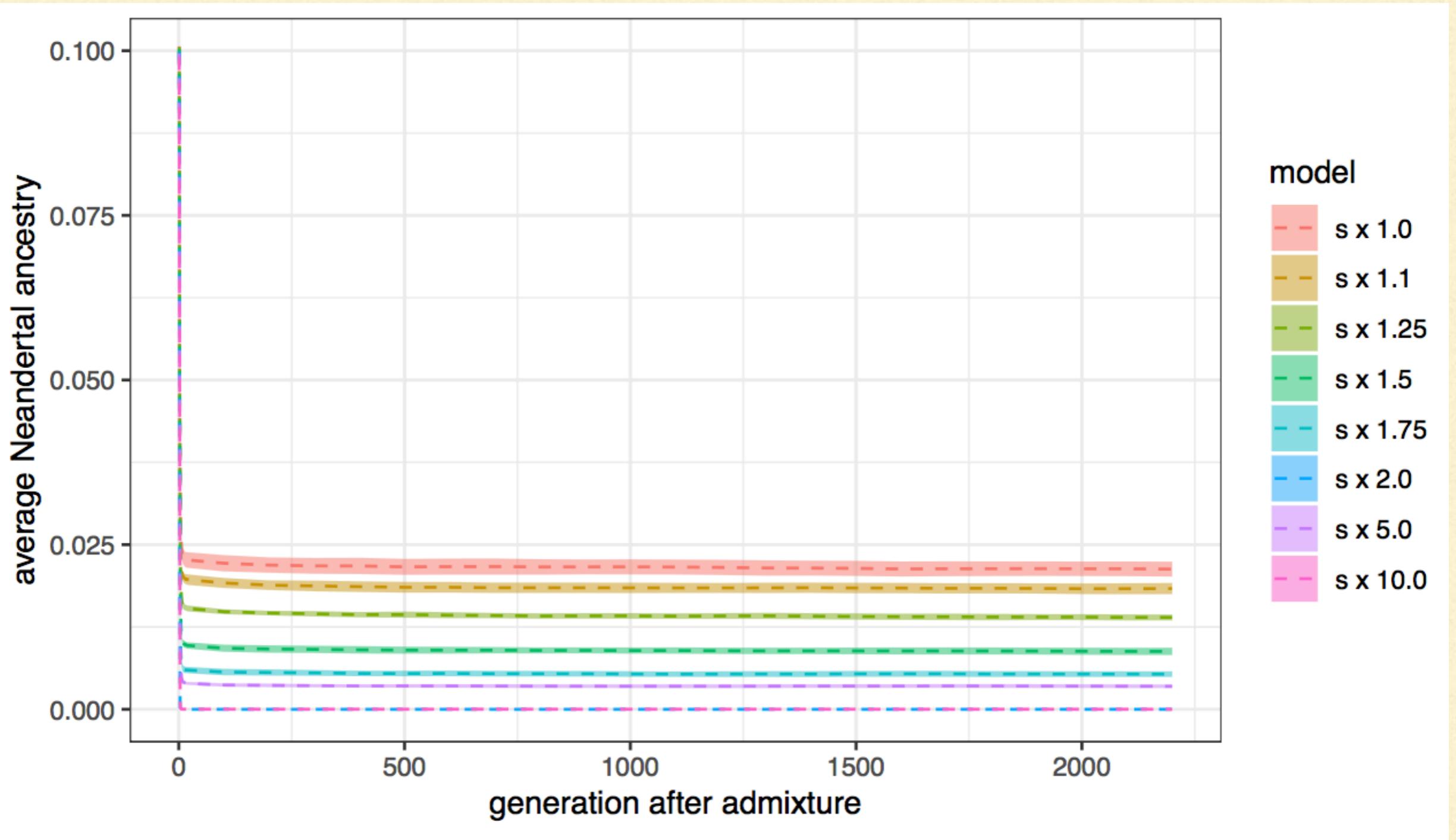


CODING VS REGULATORY REGIONS

—NEAND. ANCESTRY IN ~250 NON-AFRICANS



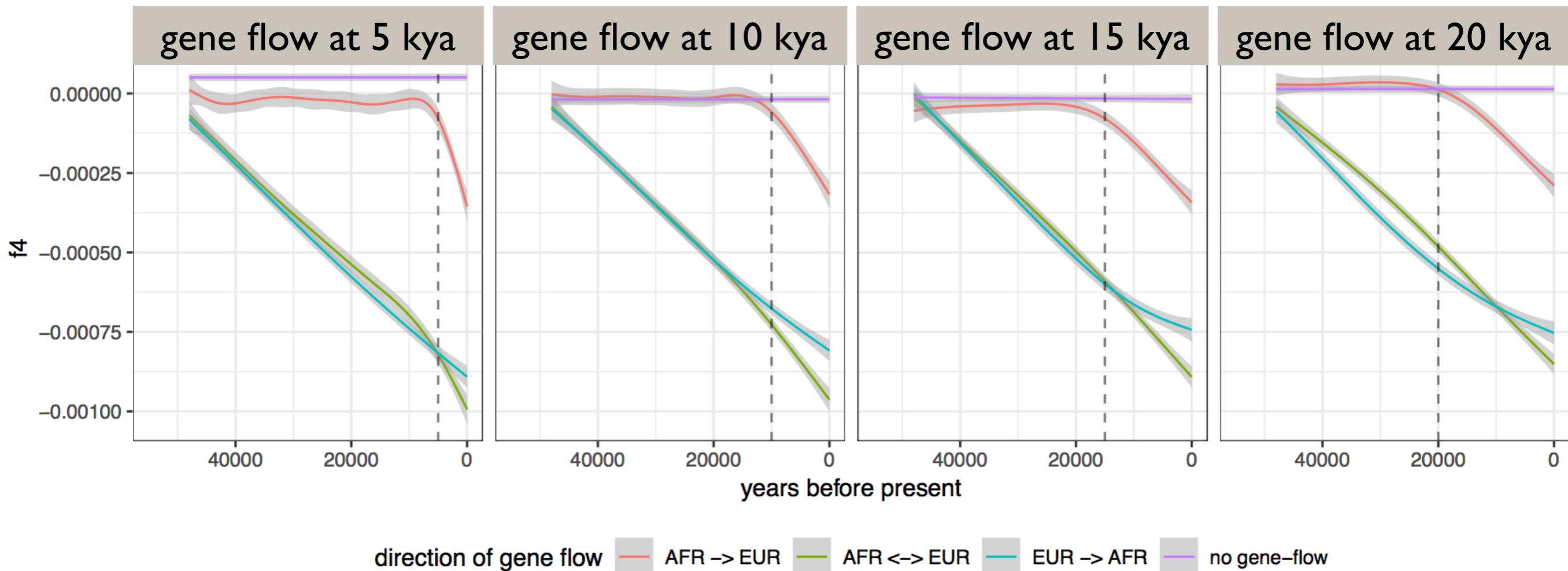




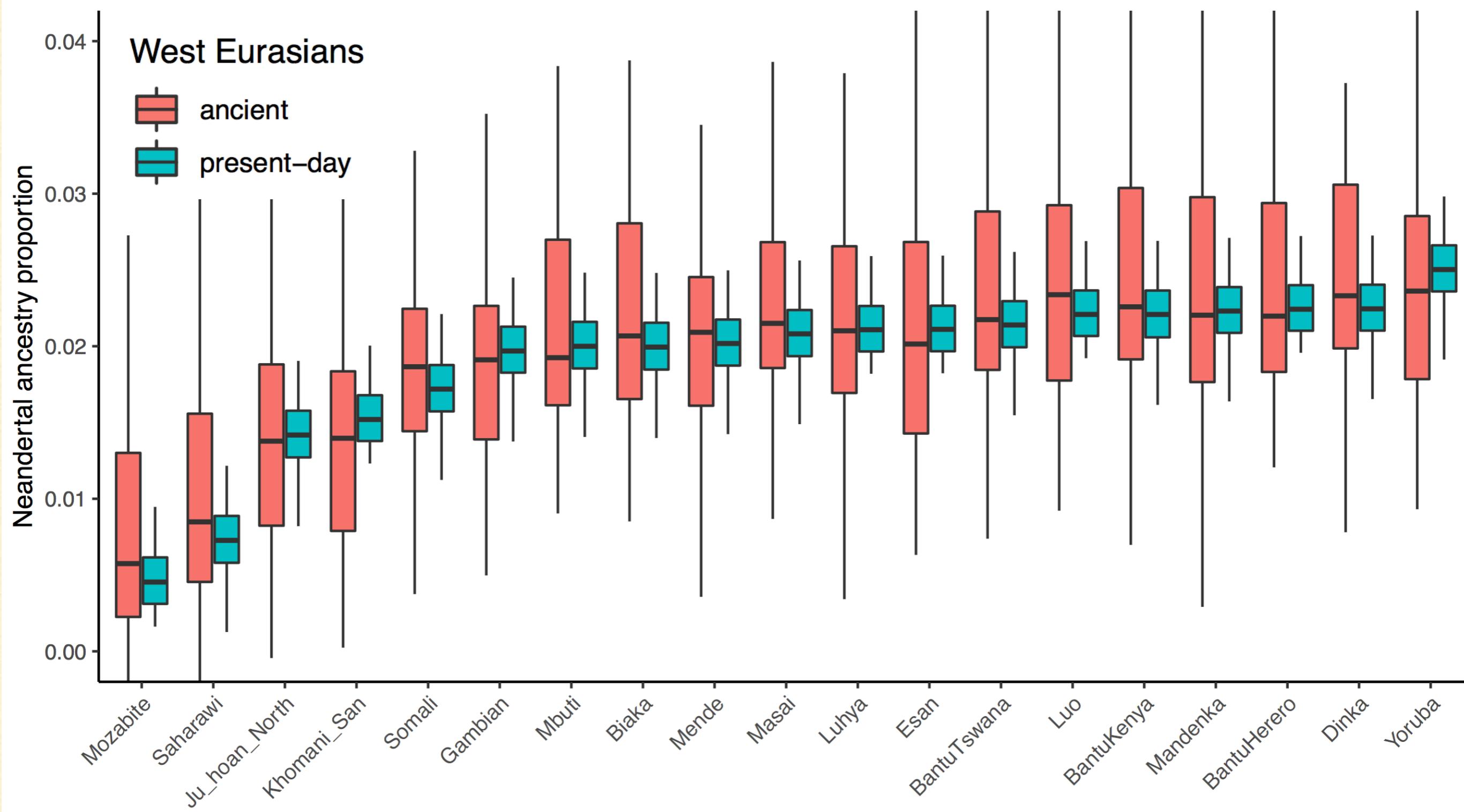
EUR VS AFR F_4

—SIMULATIONS

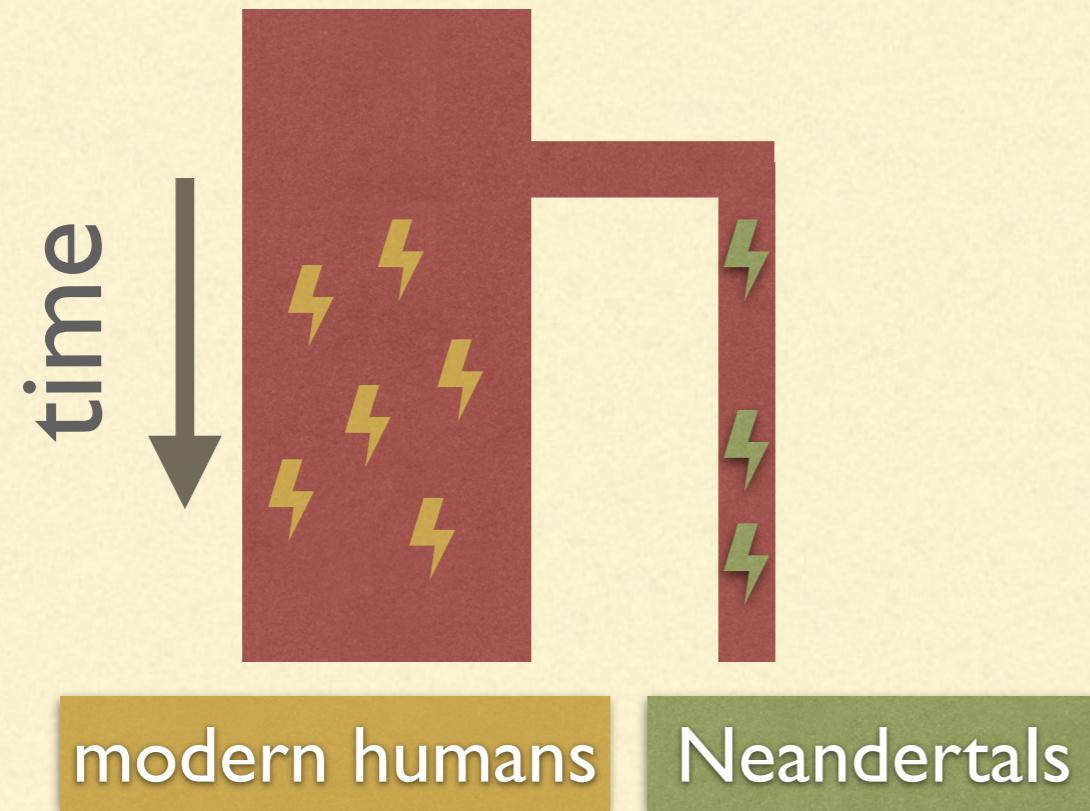
$f_4(\text{ancient hunter-gatherer}, \text{EUR } X; \text{AFR } Y, \text{Chimp})$



DIRECT F_4 -RATIO VS AFRICAN "REFERENCE"



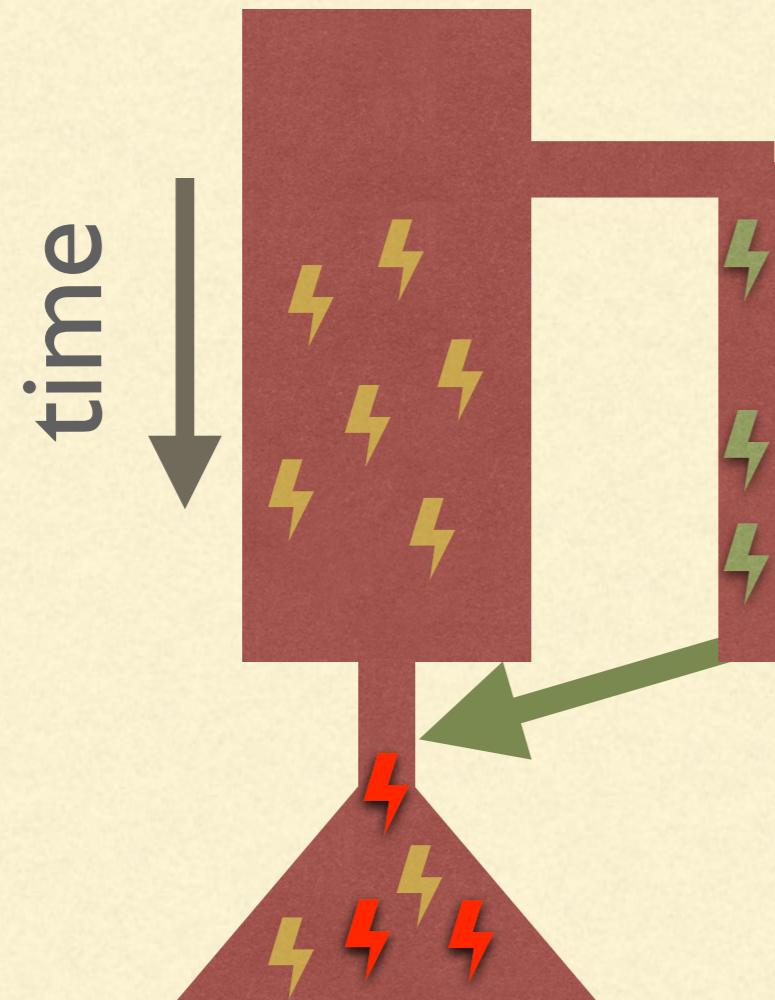
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⚡ ⚡ - deleterious mutations

Harris and Nielsen. *Genetics*. 2016.

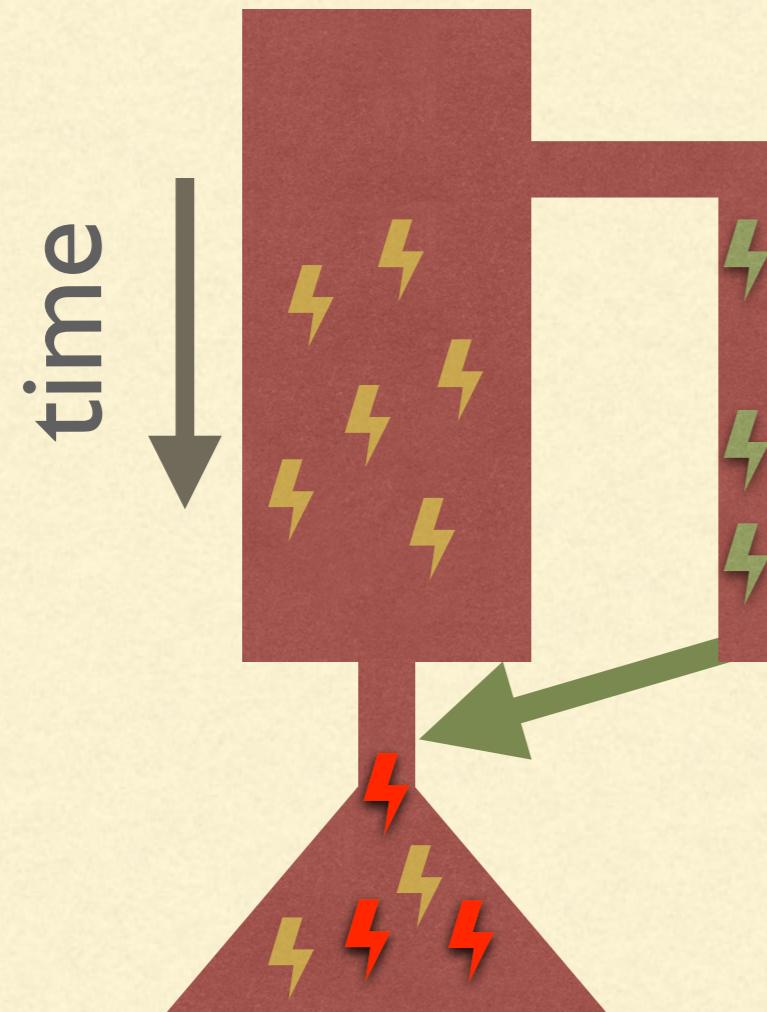
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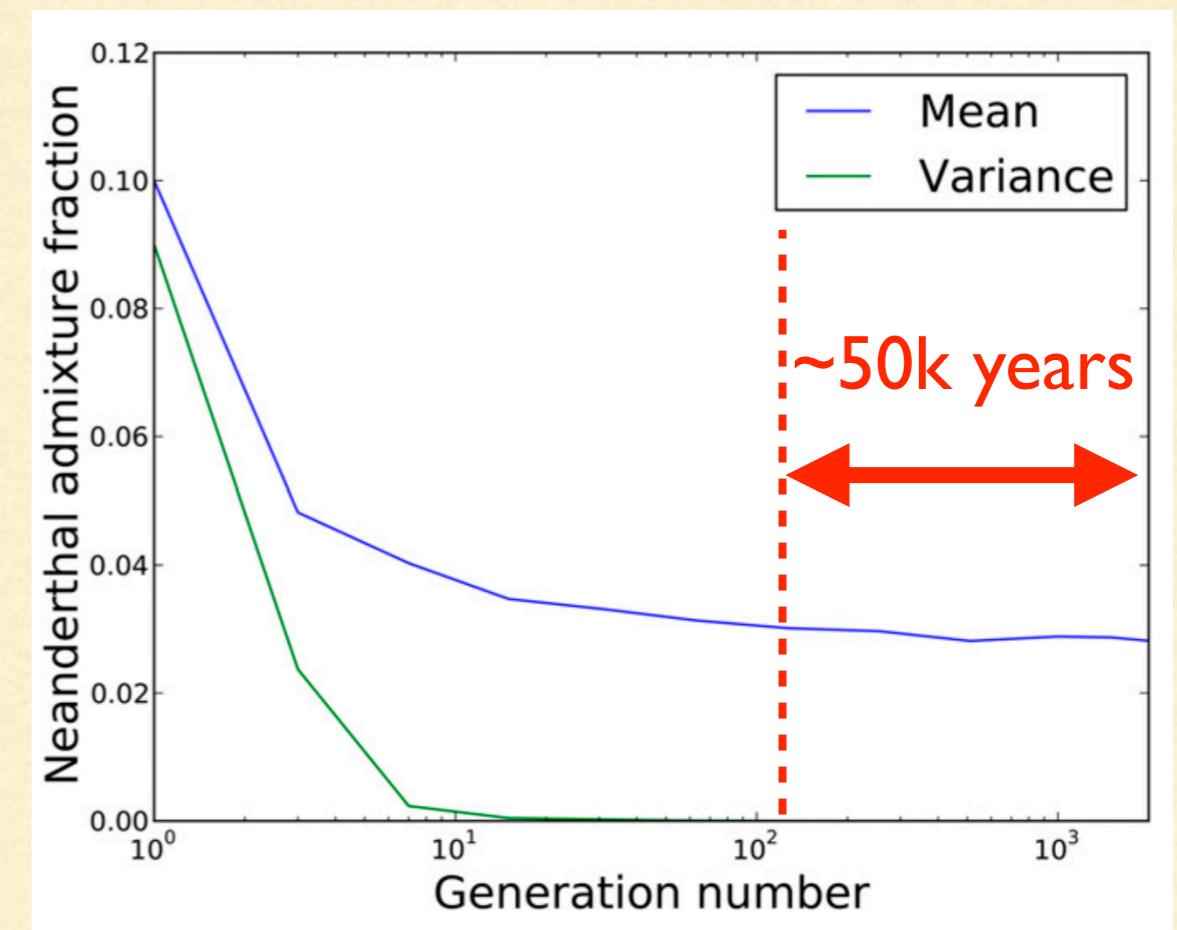
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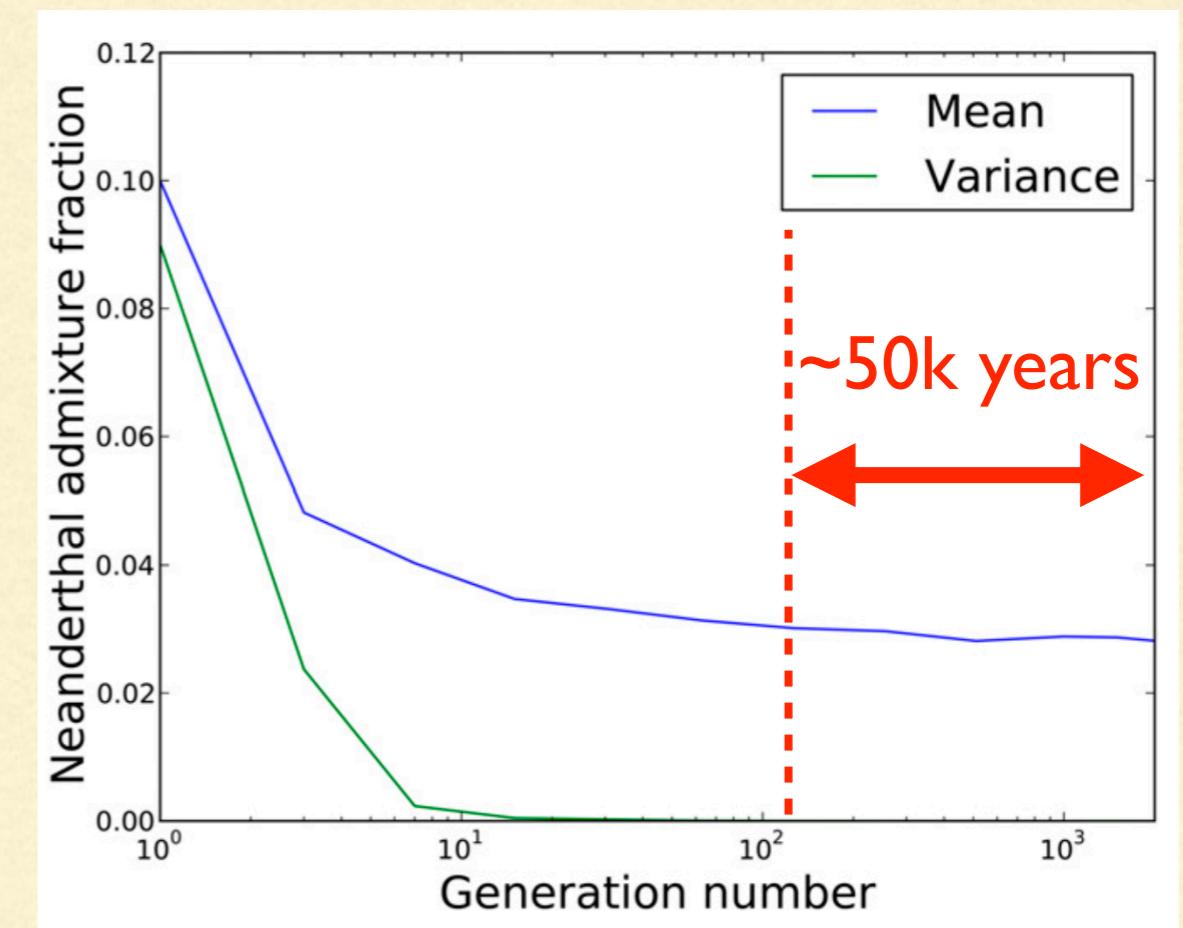
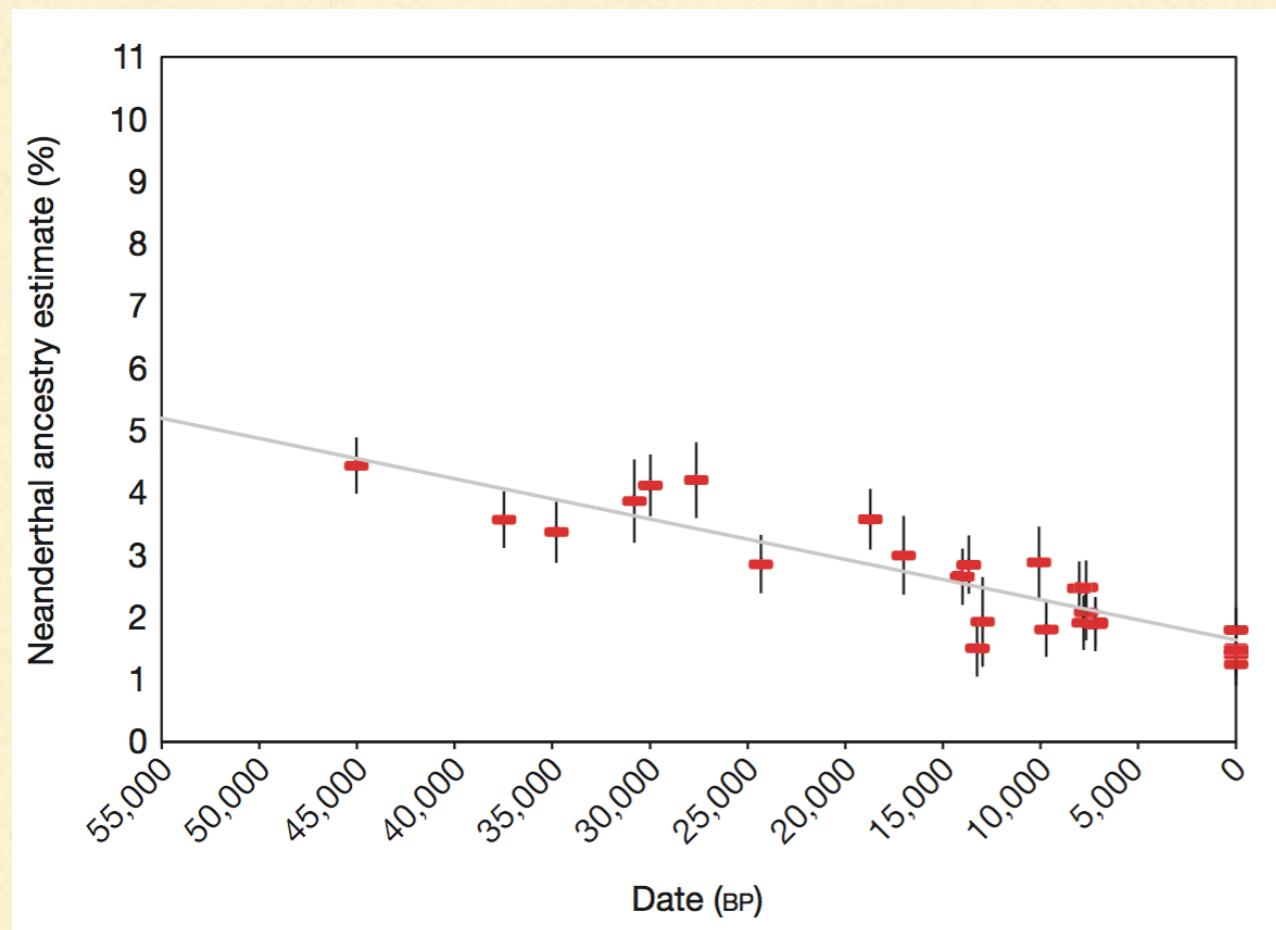


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