

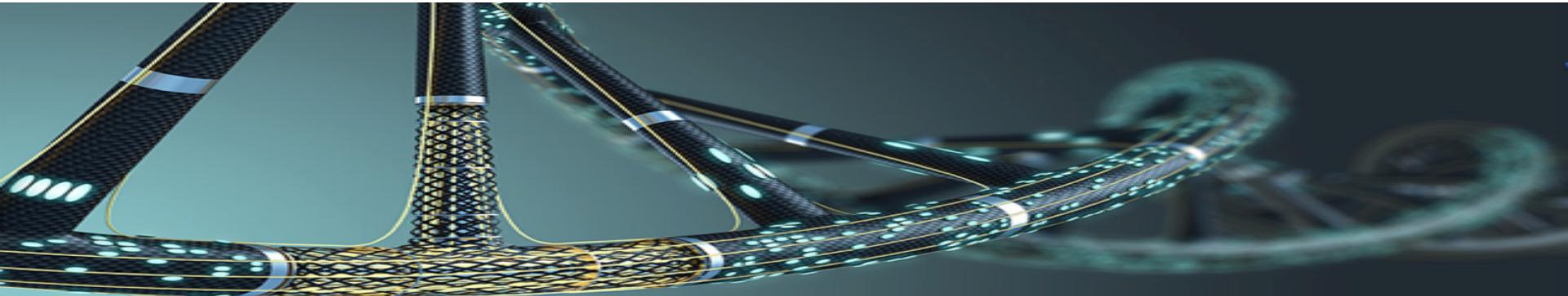


Майнер по биоинформатике

Семестр 2

Лекция 12

Мария Попцова



Неандерталец



Человек

The original Neanderthal skeleton from the Neander Valley (1856)



Display, LVR-LandesMuseum Bonn

Initial Neandertal mitochondrial genomes

Cell. 2008 August 8; 134(3): 416–426. doi:10.1016/j.cell.2008.06.021.

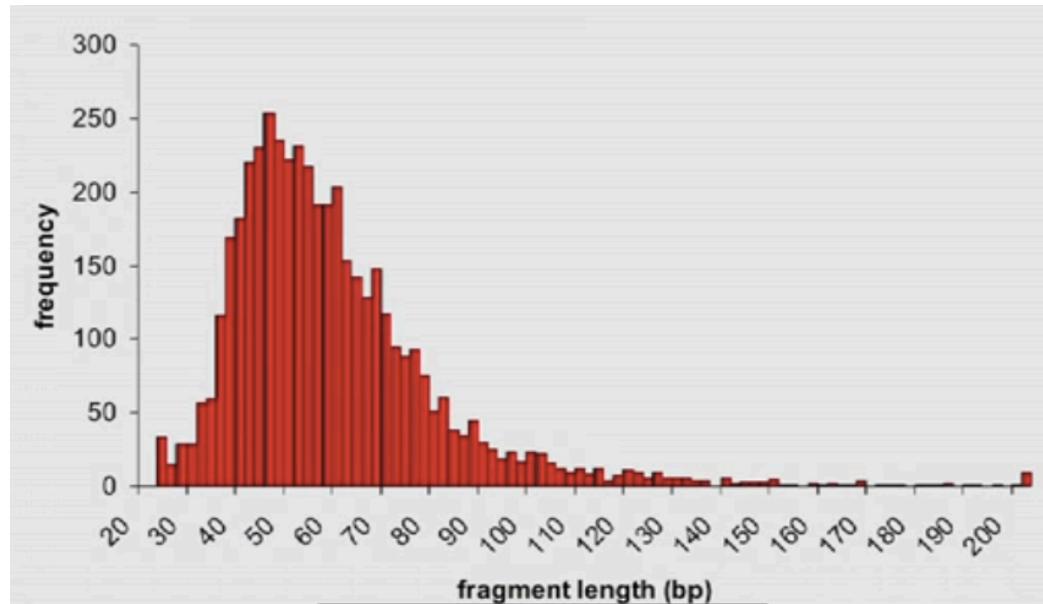
A complete Neandertal mitochondrial genome sequence determined by high-throughput sequencing

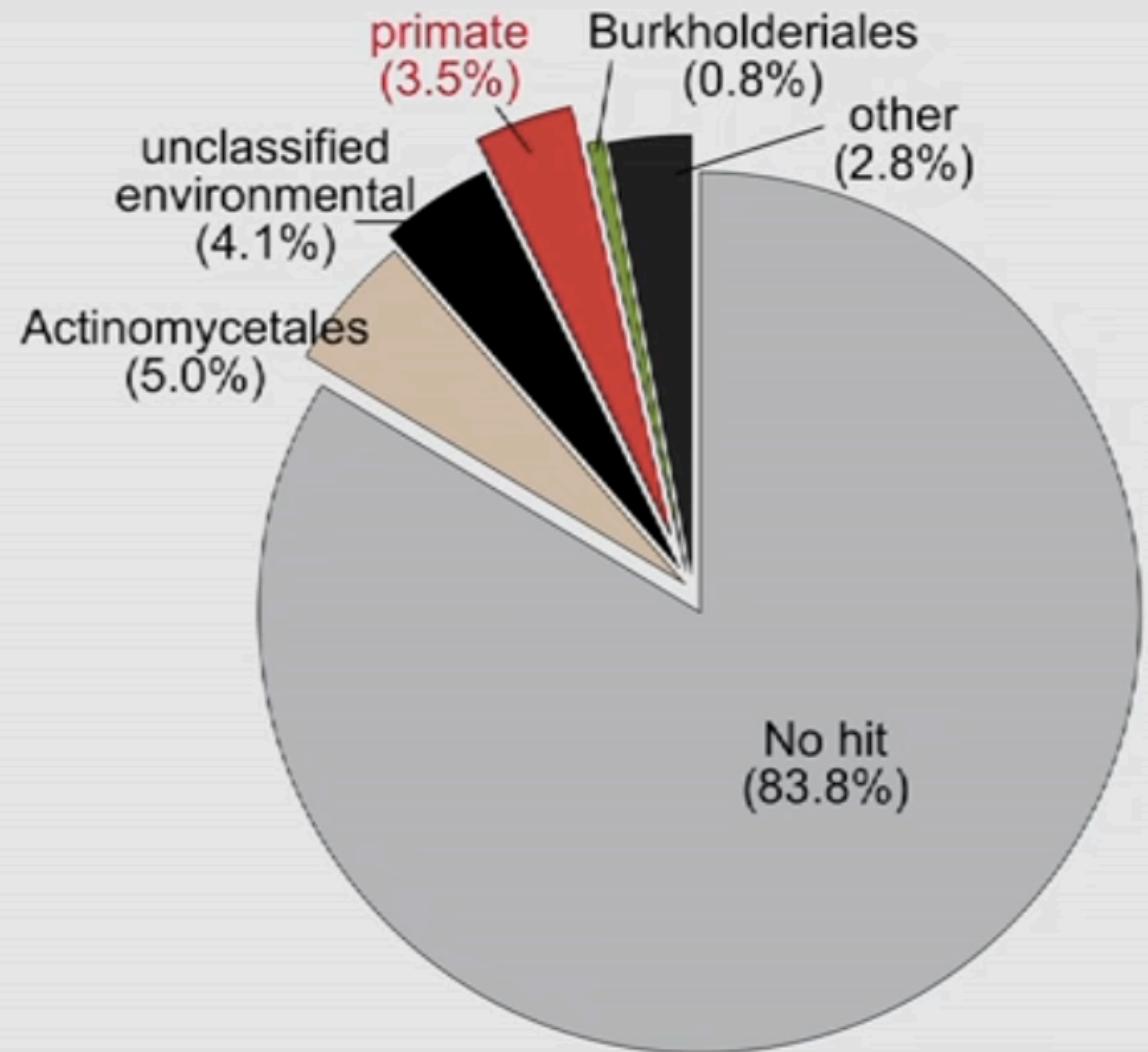
Richard E. Green¹, Anna-Sapfo Malaspinas², Johannes Krause¹, Adrian W. Briggs¹, Philip L. F. Johnson³, Caroline Uhler⁴, Matthias Meyer¹, Jeffrey M. Good¹, Tomislav Maricic¹, Udo Stenzel¹, Kay Prüfer¹, Michael Siebauer¹, Hernán A. Burbano¹, Michael Ronan⁵, Jonathan M. Rothberg⁶, Michael Egholm⁵, Pavao Rudan⁷, Dejana Brajković⁸, Željko Kućan⁷, Ivan Gušić⁷, Mårten Wikström⁹, Liisa Laakkonen¹⁰, Janet Kelso¹, Montgomery Slatkin², and Svante Pääbo¹

Vindija Cave, Croatia

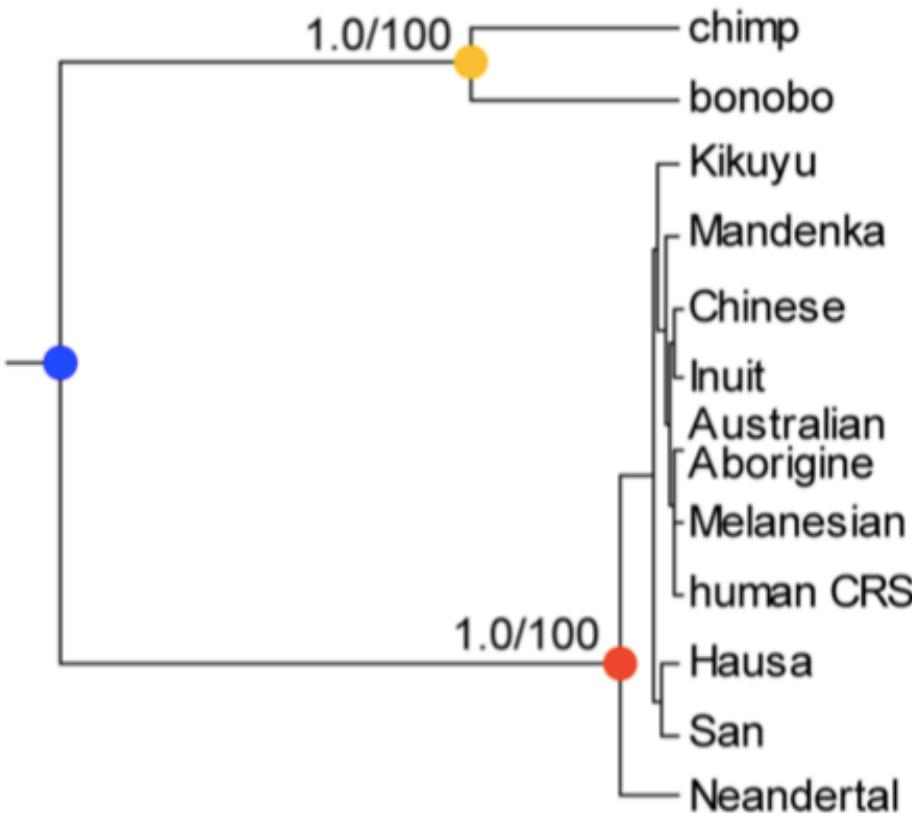


Vi 33.16; AMS date: 38, 310 +/- 2,130 BP





Neandertal is our brother



Abstract

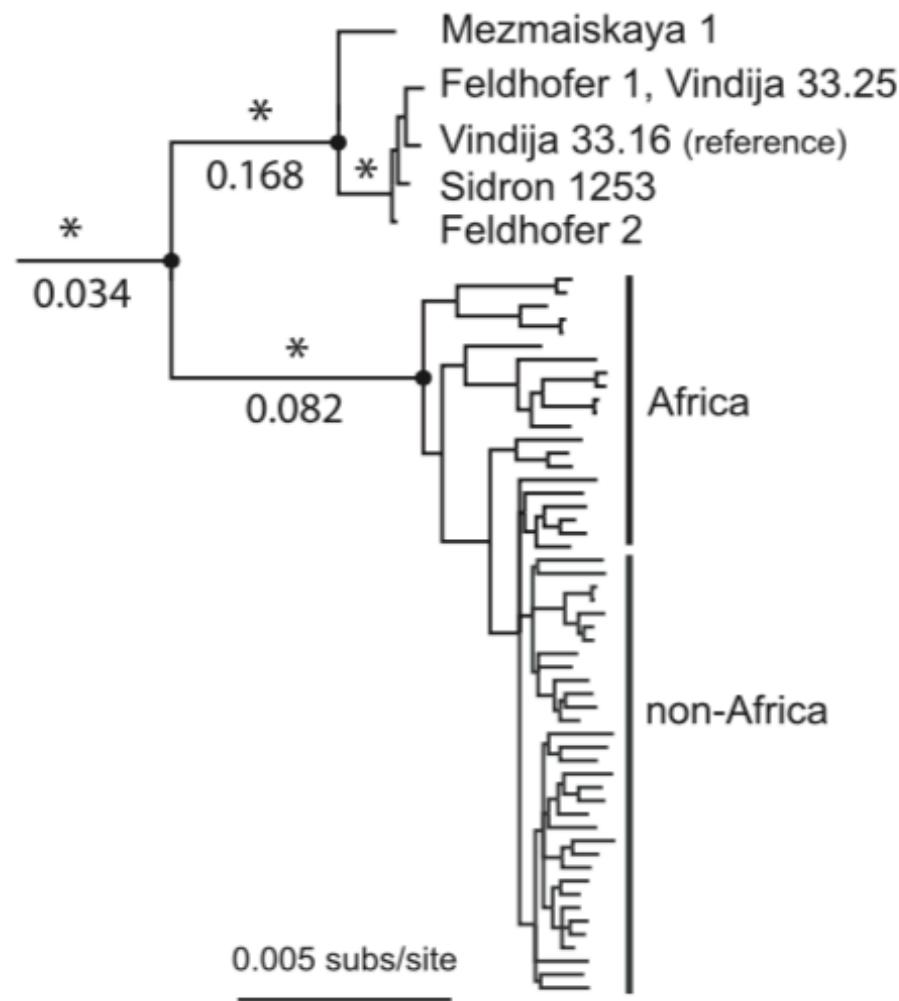
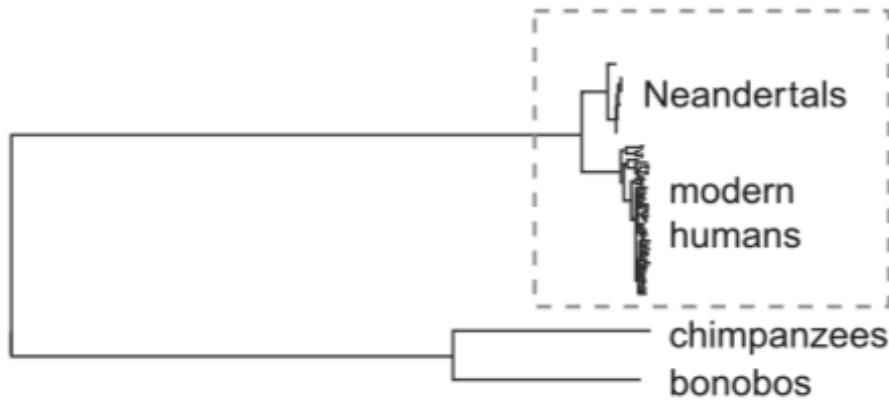
A complete mitochondrial (mt) genome sequence was reconstructed from a 38,000-year-old Neandertal individual using 8,341 mtDNA sequences identified among 4.8 Gb of DNA generated **from ~0.3 grams of bone**. Analysis of the assembled sequence unequivocally establishes that the Neandertal mtDNA falls outside the variation of extant human mtDNAs and allows an estimate of the divergence date between the two mtDNA lineages of $660,000 \pm 140,000$ years. **Of the 13 proteins encoded in the mtDNA, subunit 2 of cytochrome c oxidase of the mitochondrial electron transport chain has experienced the largest number of amino acid substitutions in human ancestors since the separation from Neandertals.** There is evidence that purifying selection in the Neandertal mtDNA was reduced compared to other primate lineages suggesting that the effective population size of Neandertals was small.

Targeted Retrieval and Analysis of Five Neandertal mtDNA Genomes

Adrian W. Briggs,^{1*} Jeffrey M. Good,¹ Richard E. Green,¹ Johannes Krause,¹ Tomislav Maricic,¹ Udo Stenzel,¹ Carles Lalueza-Fox,² Pavao Rudan,³ Dejana Brajković,⁴ Željko Kućan,³ Ivan Gušić,³ Ralf Schmitz,^{5,6} Vladimir B. Doronichev,⁷ Liubov V. Golovanova,⁷ Marco de la Rasilla,⁸ Javier Fortea,⁸ Antonio Rosas,⁹ Svante Pääbo¹

Science 2009

Analysis of Neandertal DNA holds great potential for investigating the population history of this group of hominins, but progress has been limited due to the rarity of samples and damaged state of the DNA. We present a method of targeted ancient DNA sequence retrieval that greatly reduces sample destruction and sequencing demands and use this method to reconstruct the complete mitochondrial DNA (mtDNA) genomes of five Neandertals from across their geographic range. We find that mtDNA genetic diversity in Neandertals that lived 38,000 to 70,000 years ago was approximately one-third of that in contemporary modern humans. Together with analyses of mtDNA protein evolution, these data suggest that the long-term effective population size of Neandertals was smaller than that of modern humans and extant great apes.



Neandertal Genome Project



[Svante Pääbo](#), director of the Department of Genetics at the Max Planck Institute for Evolutionary Anthropology and head of its Neanderthal genome project.

A Draft Sequence of the Neandertal Genome Science 2010

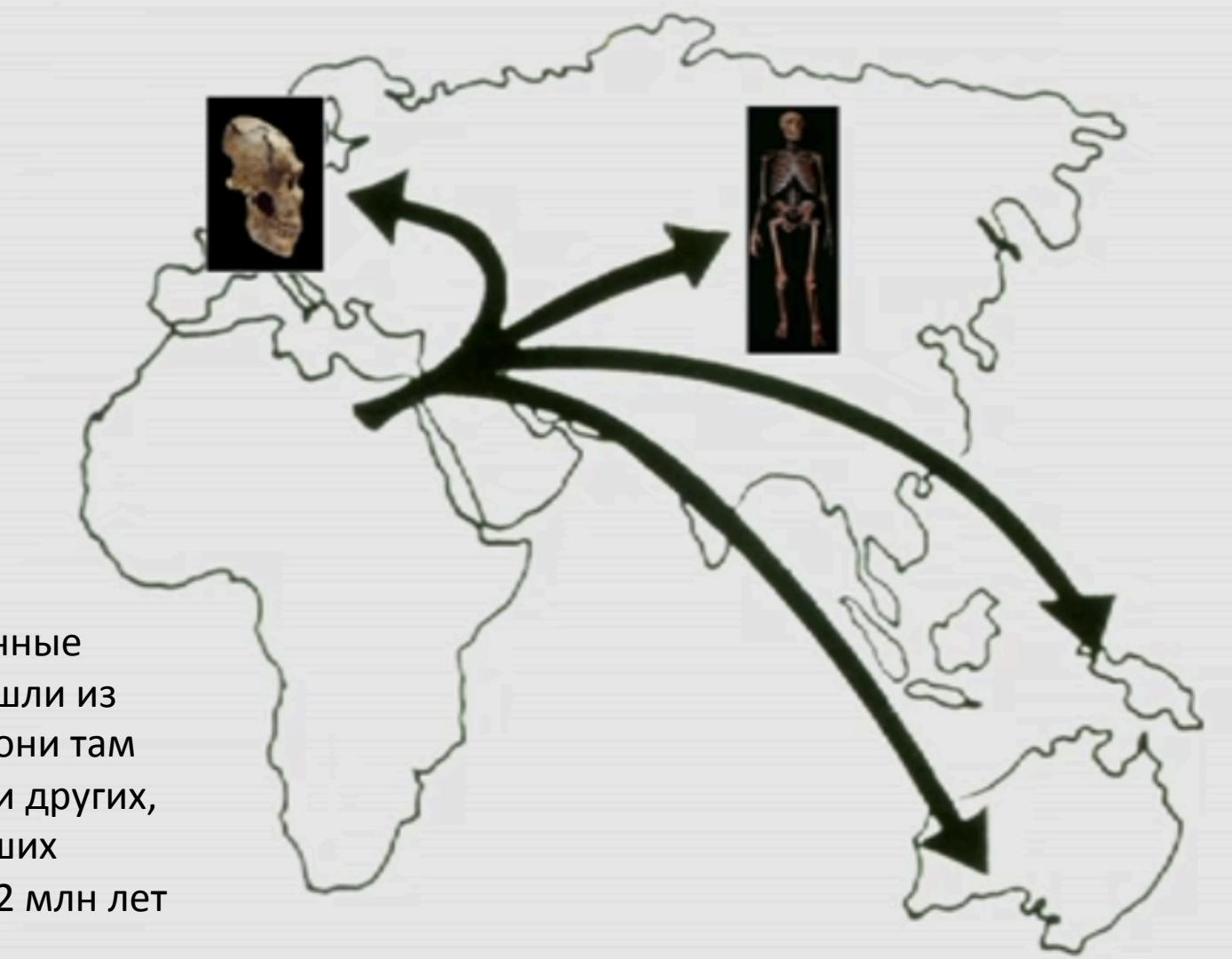
Richard E. Green,^{1*}†‡ Johannes Krause,^{1†§} Adrian W. Briggs,^{1†§} Tomislav Maricic,^{1†§}
Udo Stenzel,^{1†§} Martin Kircher,^{1†§} Nick Patterson,^{2†§} Heng Li,^{2†} Weiwei Zhai,^{3†||}
Markus Hsi-Yang Fritz,^{4†} Nancy F. Hansen,^{5†} Eric Y. Durand,^{3†} Anna-Sapfo Malaspinas,^{3†}
Jeffrey D. Jensen,^{6†} Tomas Marques-Bonet,^{7,13†} Can Alkan,^{7†} Kay Prüfer,^{1†} Matthias Meyer,^{1†}
Hernán A. Burbano,^{1†} Jeffrey M. Good,^{1,8†} Rigo Schultz,¹ Ayinuer Aximu-Petri,¹ Anne Butthof,¹
Barbara Höber,¹ Barbara Höffner,¹ Madlen Siegemund,¹ Antje Weihmann,¹ Chad Nusbaum,²
Eric S. Lander,² Carsten Russ,² Nathaniel Novod,² Jason Affourtit,⁹ Michael Egholm,⁹
Christine Verna,²¹ Pavao Rudan,¹⁰ Dejana Brajkovic,¹¹ Željko Kucan,¹⁰ Ivan Gušić,¹⁰
Vladimir B. Doronichev,¹² Liubov V. Golovanova,¹² Carles Lalueza-Fox,¹³ Marco de la Rasilla,¹⁴
Javier Fortea,^{14¶} Antonio Rosas,¹⁵ Ralf W. Schmitz,^{16,17} Philip L. F. Johnson,^{18†} Evan E. Eichler,^{7†}
Daniel Falush,^{19†} Ewan Birney,^{4†} James C. Mullikin,^{5†} Montgomery Slatkin,^{3†} Rasmus Nielsen,^{3†}
Janet Kelso,^{1†} Michael Lachmann,^{1†} David Reich,^{2,20*}† Svante Pääbo^{1*†}

A

Vi33-16 Vi33-25 Vi33-26

**B**

Fig. 1. Samples and sites from which DNA was retrieved. **(A)** The three bones from Vindija from which Neandertal DNA was sequenced. **(B)** Map showing the four archaeological sites from which bones were used and their approximate dates (years B.P.).

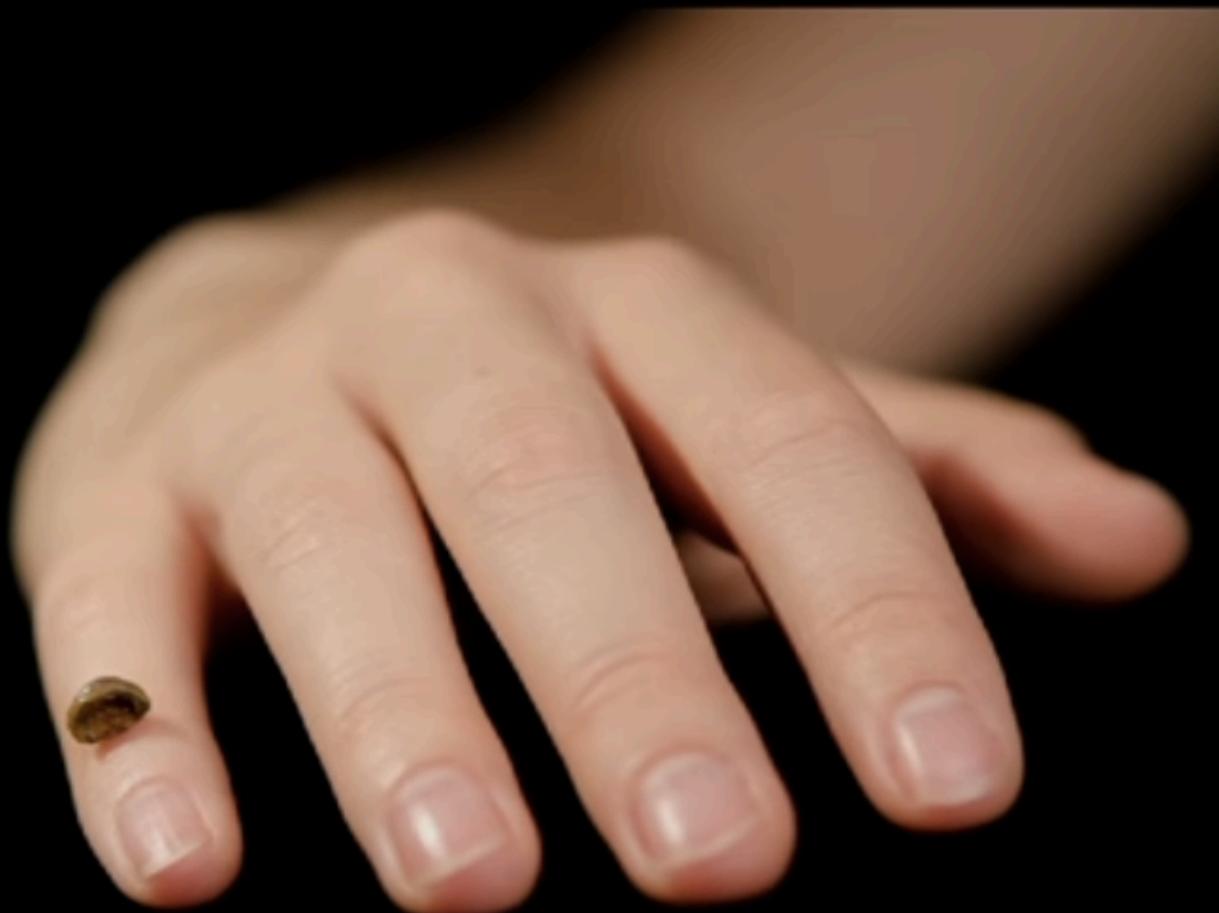


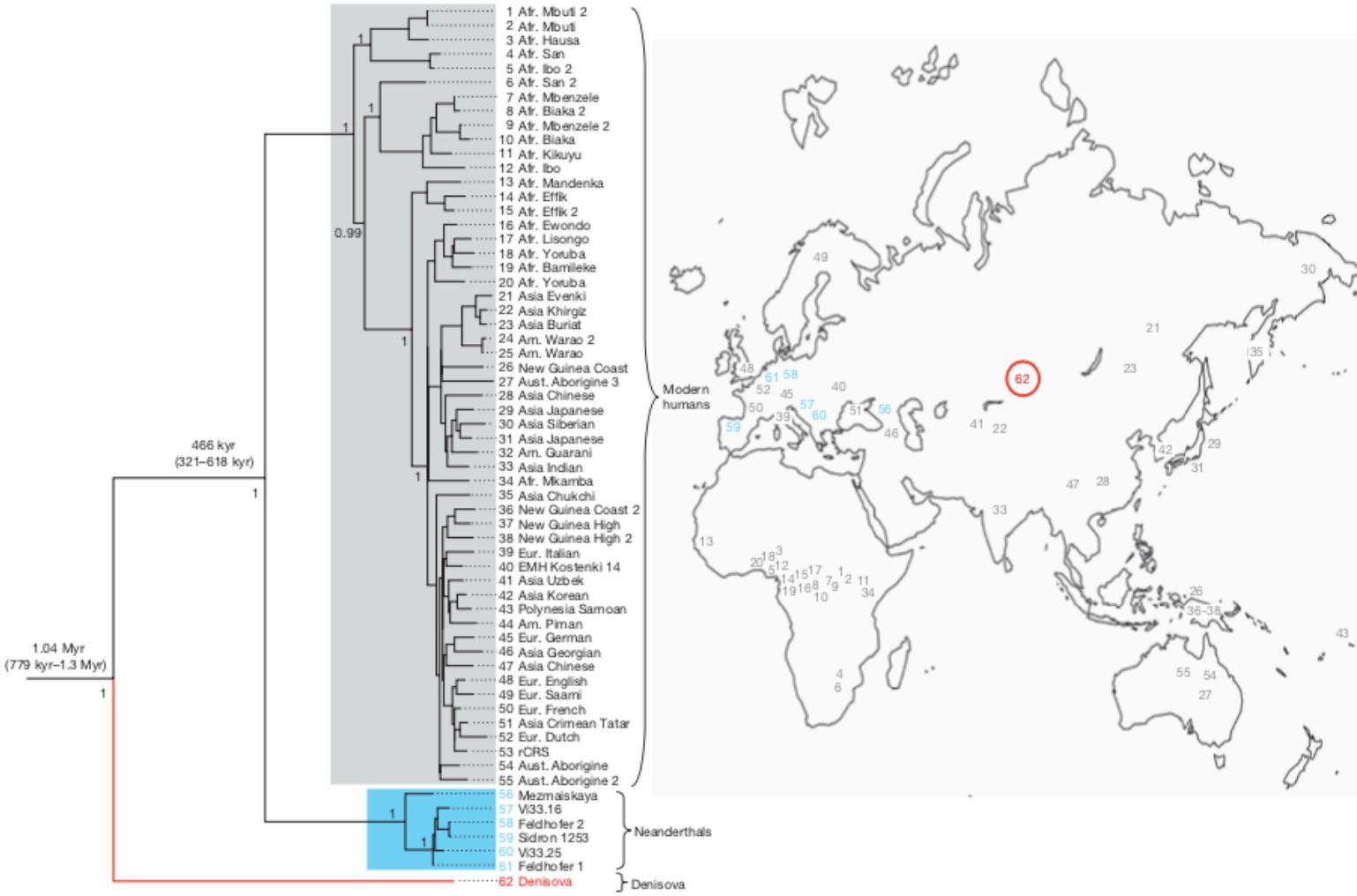
Когда
современные
люди вышли из
Африки, они там
встретили других,
уже живших
порядка 2 млн лет

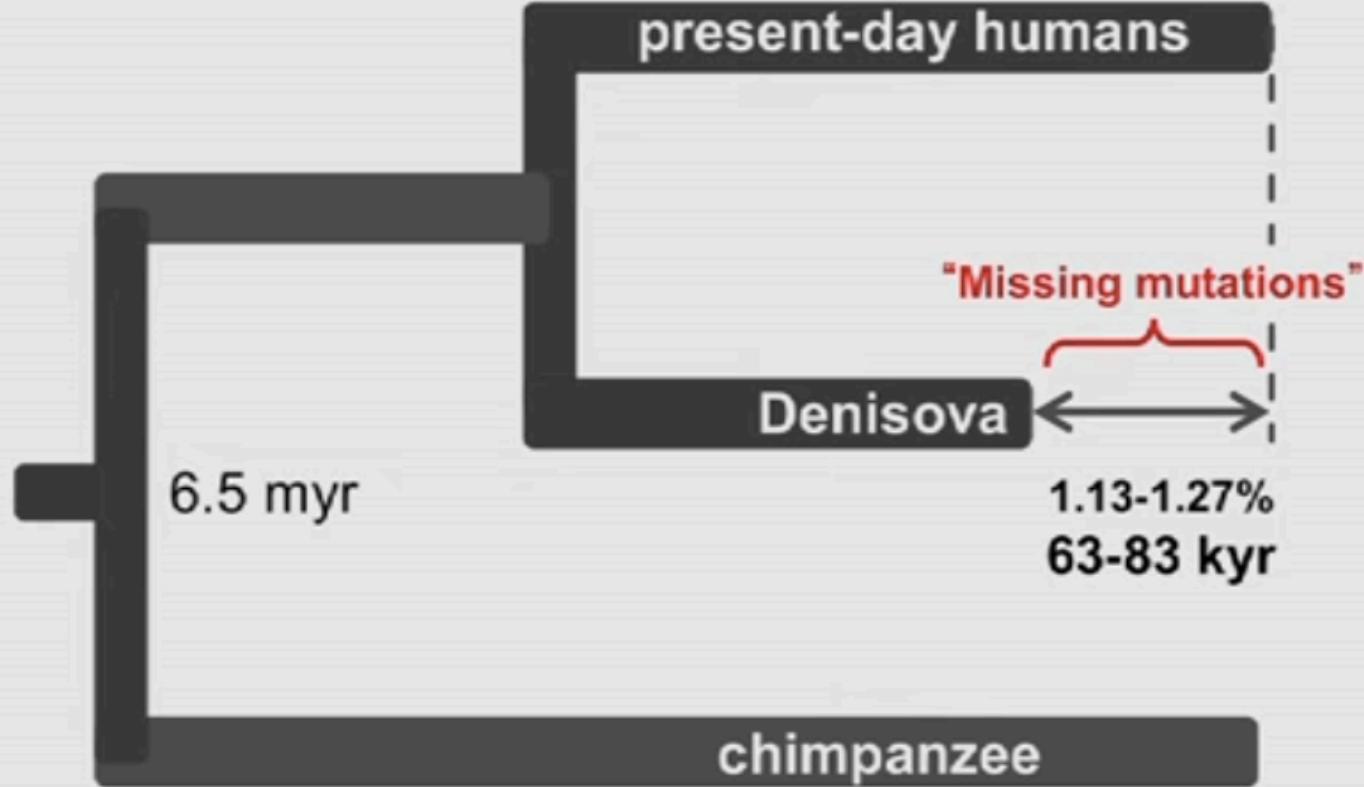
LETTERS

The complete mitochondrial DNA genome of an unknown hominin from southern Siberia

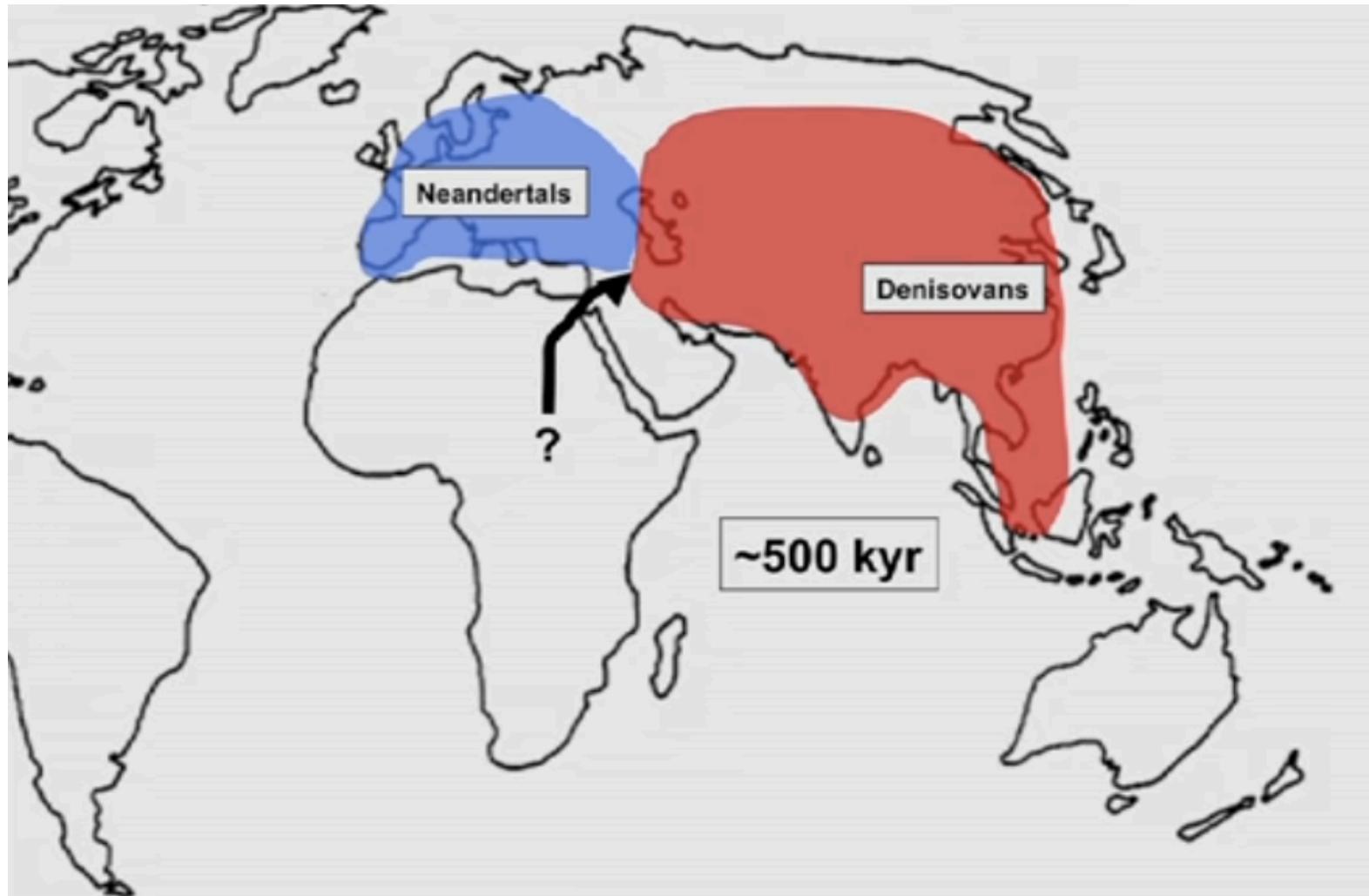
Johannes Krause¹, Qiaomei Fu¹, Jeffrey M. Good², Bence Viola^{1,3}, Michael V. Shunkov⁴, Anatoli P. Derevianko⁴ & Svante Pääbo¹

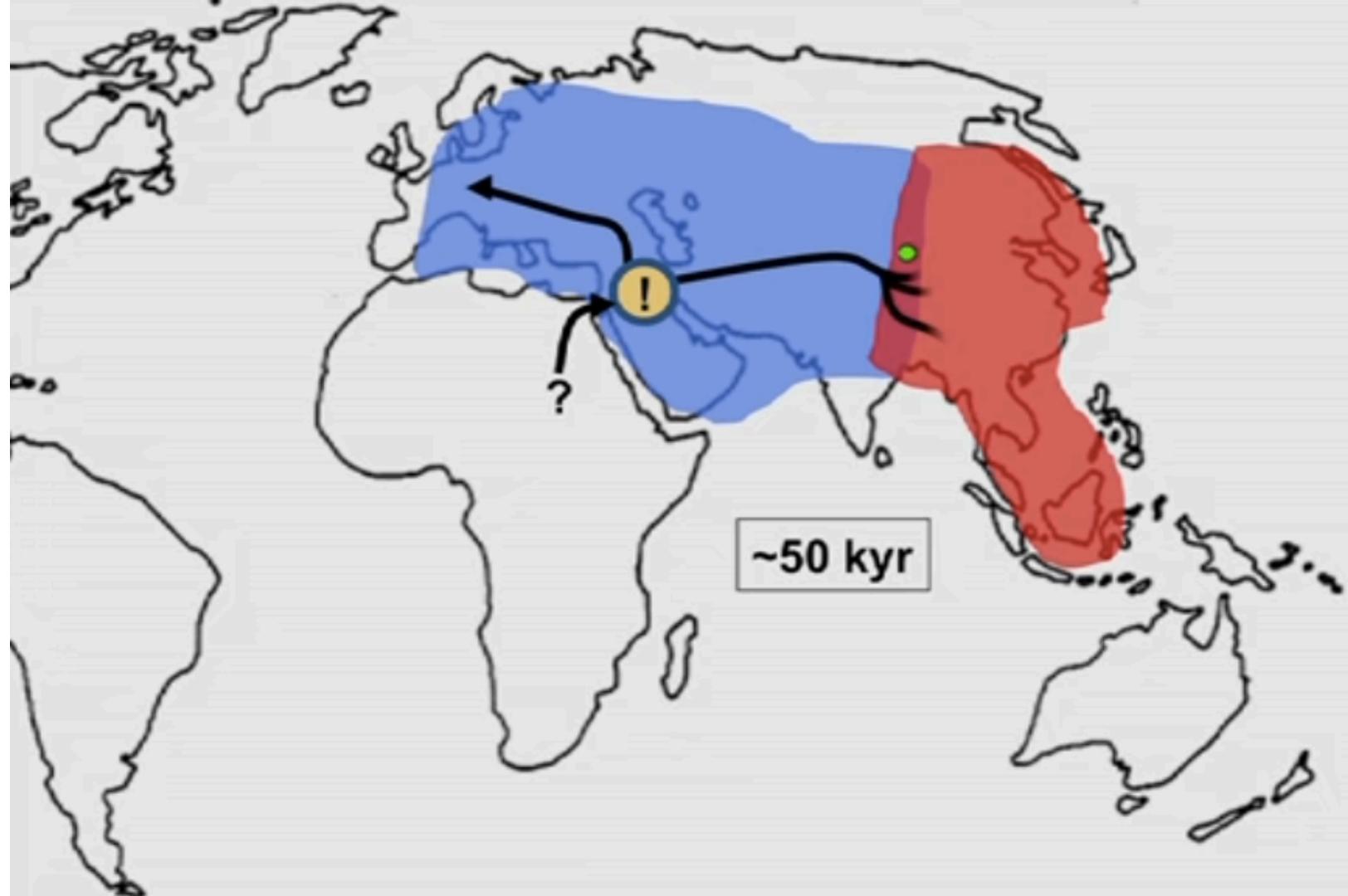


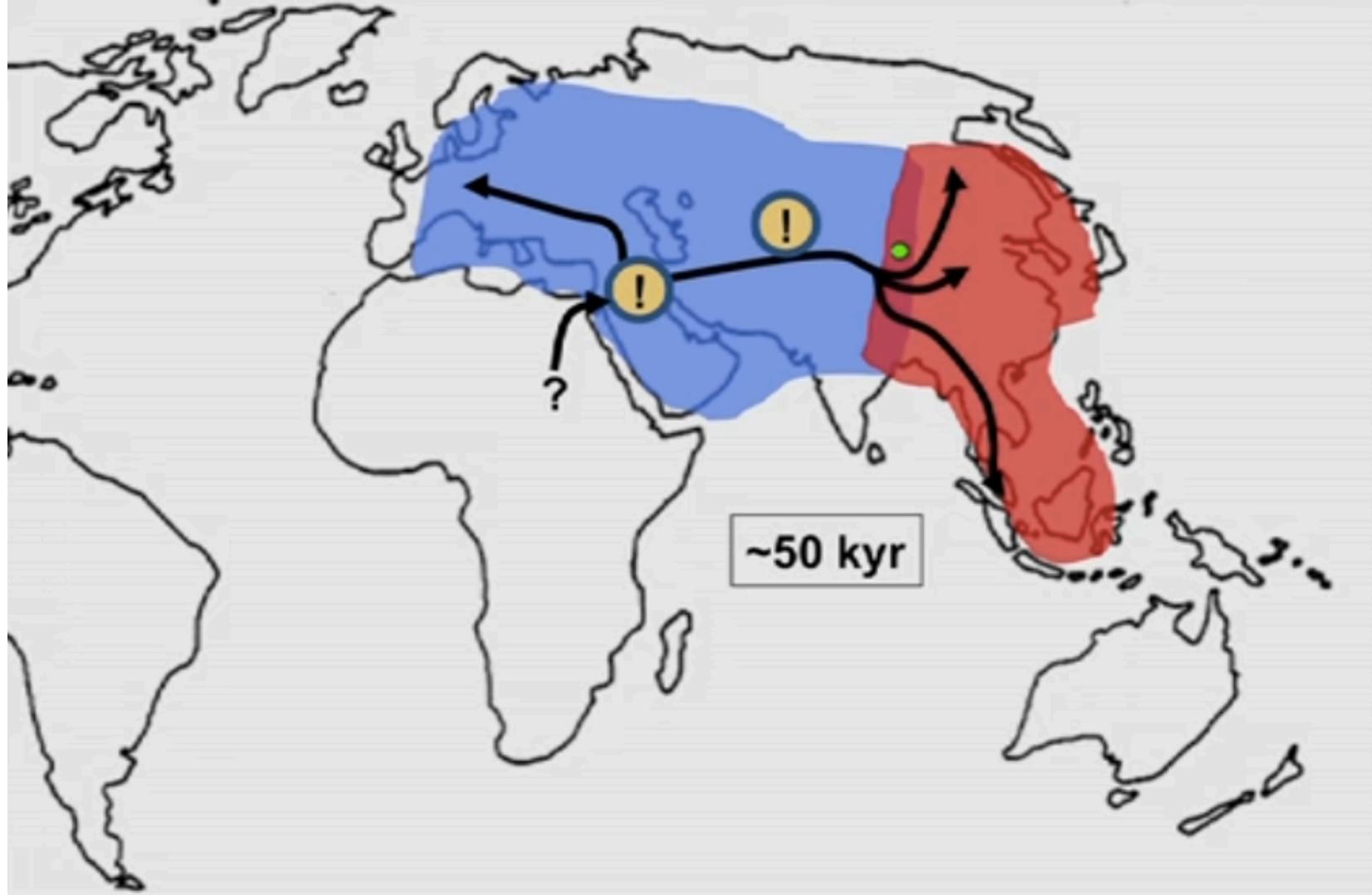




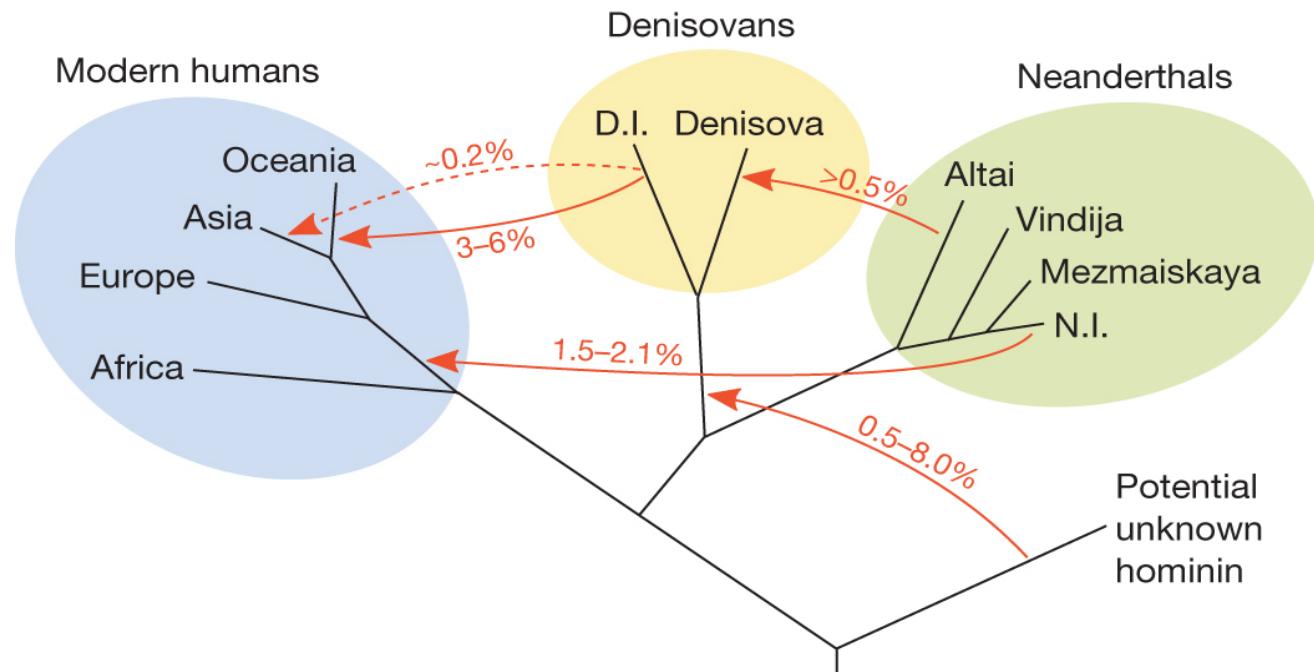


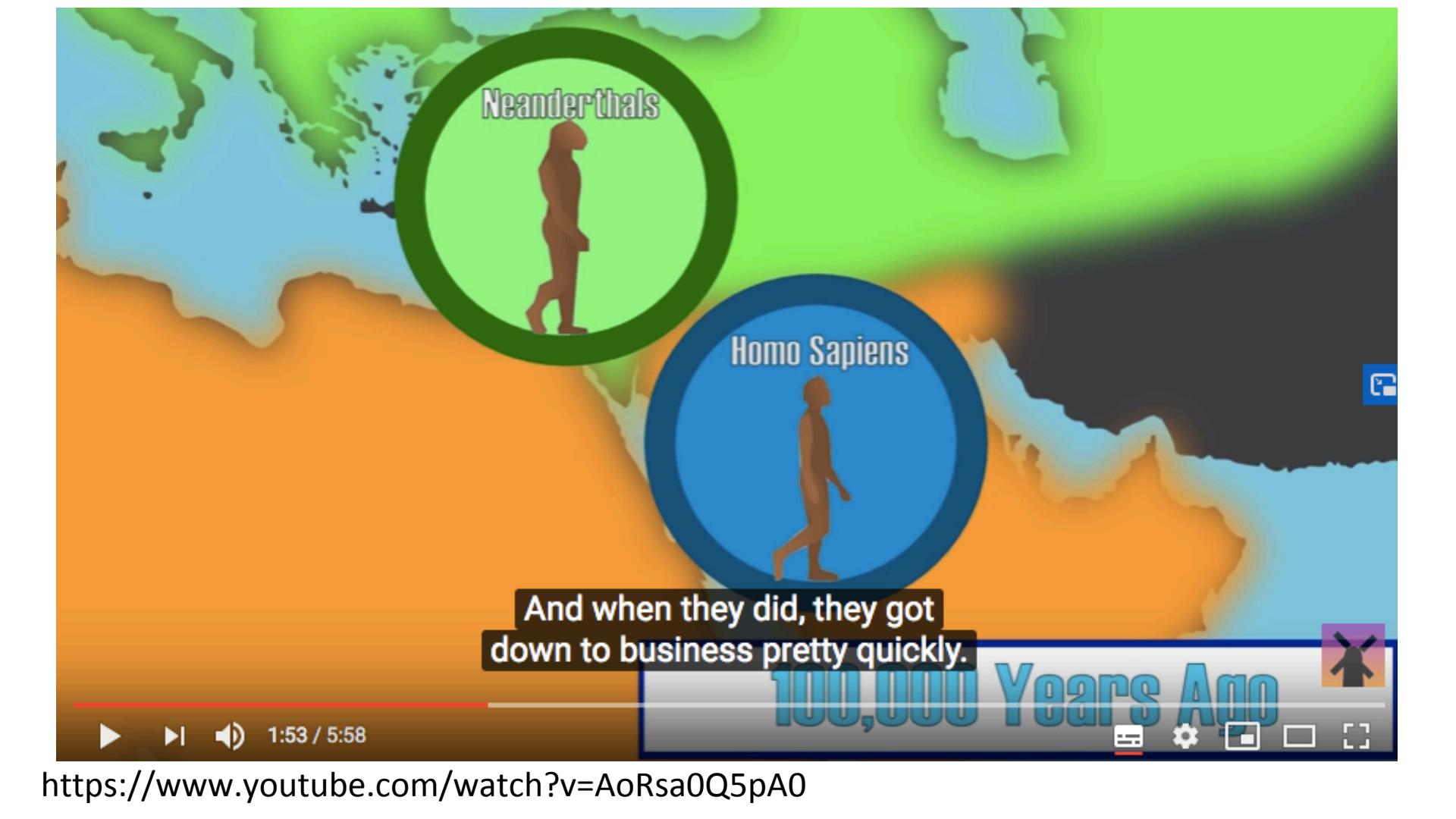






A possible model of gene flow events in the Late Pleistocene.





Neanderthals

Homo Sapiens

And when they did, they got
down to business pretty quickly.

100,000 Years Ago

▶ ▶ 🔍 1:53 / 5:58



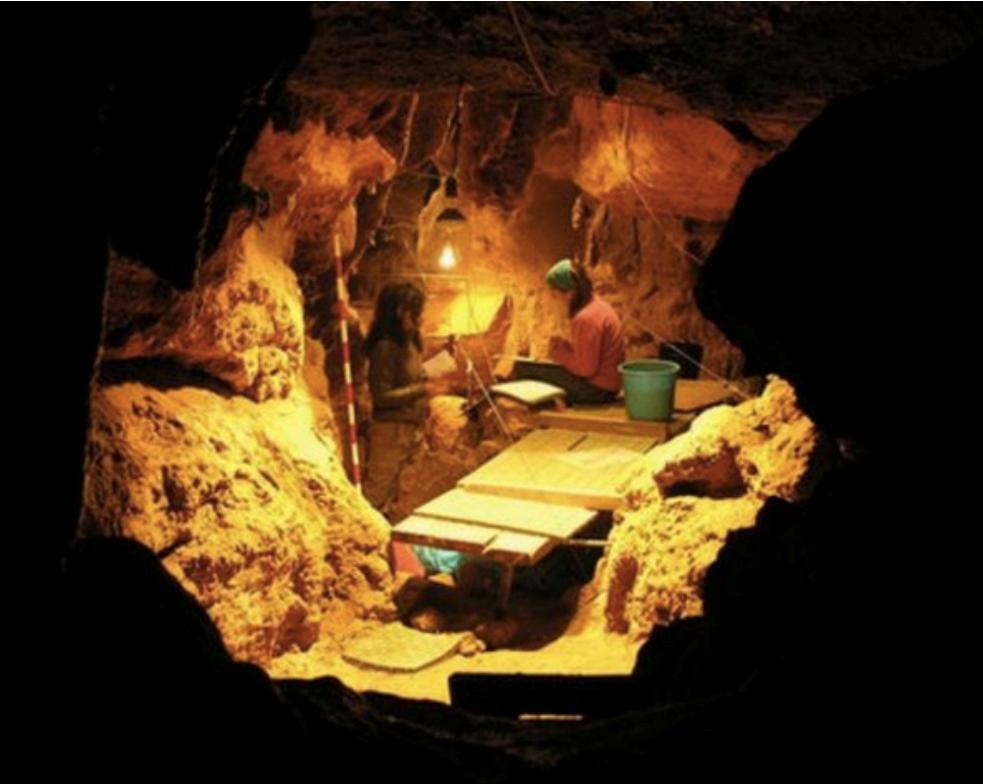
Genetic evidence for patrilocal mating behavior among Neandertal groups

Carles Lalueza-Fox^{a,1}, Antonio Rosas^{b,1}, Almudena Estalrich^b, Elena Gigli^a, Paula F. Campos^c, Antonio García-Tabernero^b, Samuel García-Vargas^b, Federico Sánchez-Quinto^a, Oscar Ramírez^a, Sergi Civit^d, Markus Bastir^b, Rosa Huguet^e, David Santamaría^f, M. Thomas P. Gilbert^c, Eske Willerslev^c, and Marco de la Rasilla^f

^aInstitute of Evolutionary Biology, Consejo Superior de Investigaciones Científicas-Universitat Pompeu Fabra, 08003 Barcelona, Spain; ^bPaleoanthropology Group, Department of Paleobiology, Museo Nacional de Ciencias Naturales, Consejo Superior de Investigaciones Científicas, 28006 Madrid, Spain; ^cCentre for GeoGenetics, Natural History Museum of Denmark, University of Copenhagen, Øster Voldgade 5-7, 1350 Copenhagen, Denmark; Department of Statistics, Faculty of Biology, University of Barcelona, 08028 Barcelona, Spain; ^dInstitut Català de Paleoecología Humana i Evolució Social, Unitat Asociada al Consejo Superior de Investigaciones Científicas, Universitat Rovira i Virgili, 43002 Tarragona, Spain; and ^fÁrea de Prehistoria, Departamento de Historia, Universidad de Oviedo, 33011 Oviedo, Spain

Edited by C. Owen Lovejoy, Kent State University, Kent, OH, and approved November 12, 2010 (received for review August 3, 2010)

Archaeologists in Spain have unearthed the remains of a possible family of 12 Neanderthals who were killed 49,000 years ago.



The genetic data suggested that while the three adult males in the group shared the same maternal lineage, the three adult females had different maternal origins.

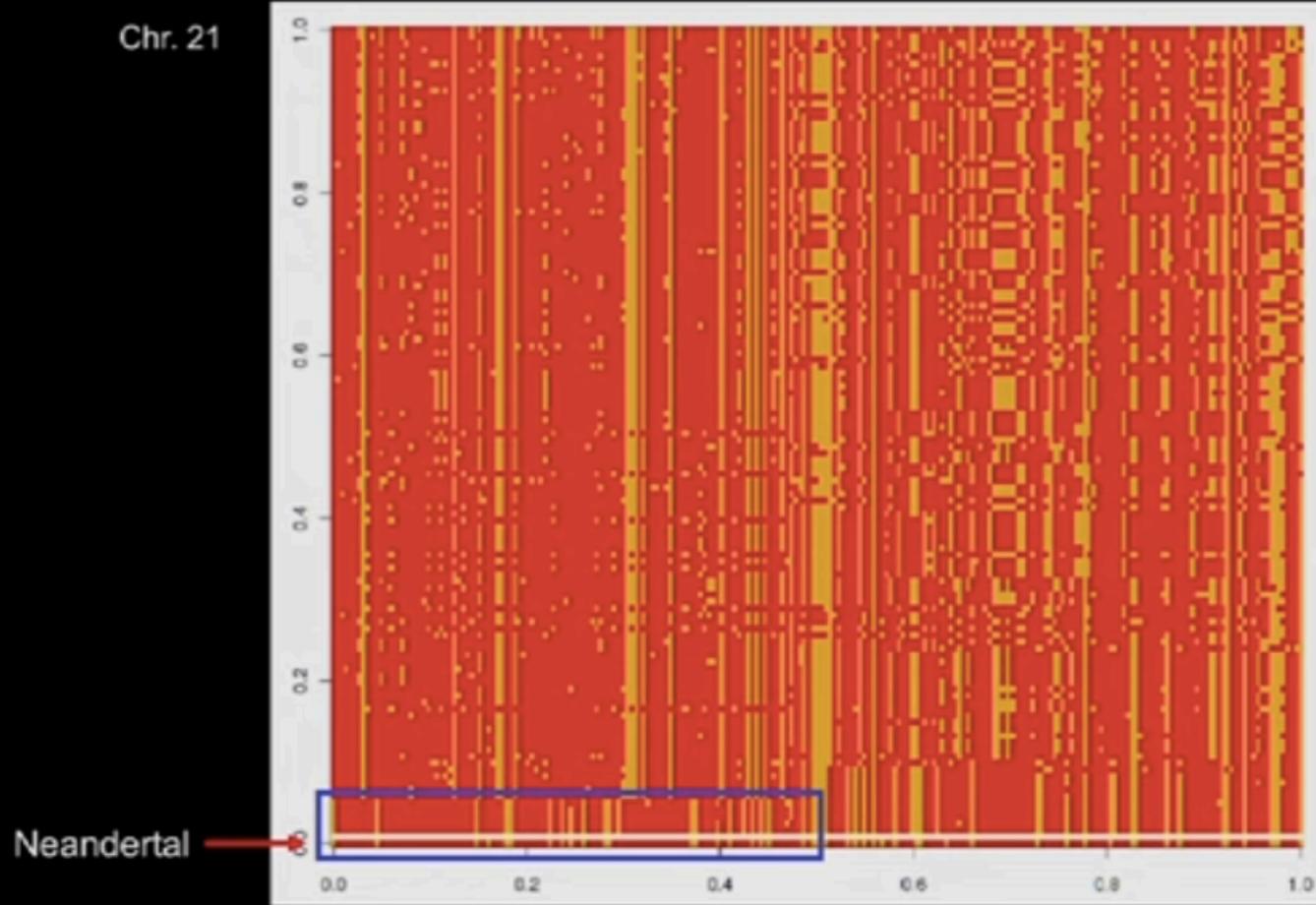
Table 1. Age and sex structure mitochondrial DNA lineage attribution of the 12 Neandertal individuals present at the El Sidrón site

Individual	Sample	Age	Morphological sex	Genetic sex	Mitochondrial lineage
Adult 1	Tooth	Young adult	Male	Male	A
Adult 2	Tooth	Young adult	Male	Male	A
Adult 3	Mandible	Adult	Female	?	B
Adult 4	Tooth	Young adult	Female	?	C
Adult 5	Tooth	Adult	Female	?	A
Adult 6	Tooth	Adult	Male	Male	A
Adolescent 1	Tooth	12–15 y	Male	Male	C
Adolescent 2	Tooth	12–15 y	Male?	?	A
Adolescent 3	Tooth	12–15 y	Male	?	A
Juvenile 1	Femur	5–6 y	?	?	C
Juvenile 2	Tooth	8–9 y	?	?	A
Infant	Phalanx	2–3 y	?	?	C

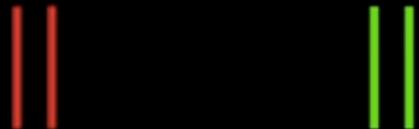
Lineage A has the 200A-204T-16124A haplotype, lineage B the 200G-204C-16124G haplotype, and lineage C the 200G-204T-16124G haplotype (Vi33.16 reference sequence). In addition, all lineages differ from the Vi33.16 Neandertal by an A to C transversion at position 16177. Vi33.16 has the following haplotype at El Sidrón polymorphic positions: 200G,-204T-16124A.

1000G Europeans

Chr. 21



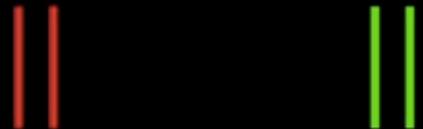
Neandertal Modern human



1 generation later



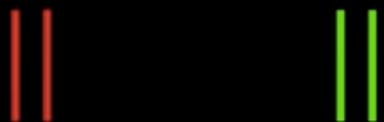
Neandertal Modern human



2 generations later



Neandertal Modern human



Many generations later



The Date of Interbreeding between Neandertals and Modern Humans

Sriram Sankararaman^{1,2*}, Nick Patterson², Heng Li², Svante Pääbo^{3*}, David Reich^{1,2*}

1 Department of Genetics, Harvard Medical School, Boston, Massachusetts, United States of America, **2** Broad Institute of MIT and Harvard, Cambridge, Massachusetts, United States of America, **3** Department of Evolutionary Genetics, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

We estimate this date by measuring the extent of linkage disequilibrium (LD) in the genomes of present-day Europeans and find that the last gene flow from Neandertals into Europeans likely occurred 37,000–86,000 years before the present (BP), and most likely 47,000–65,000 years ago.

2-3% of neandertal genomes?

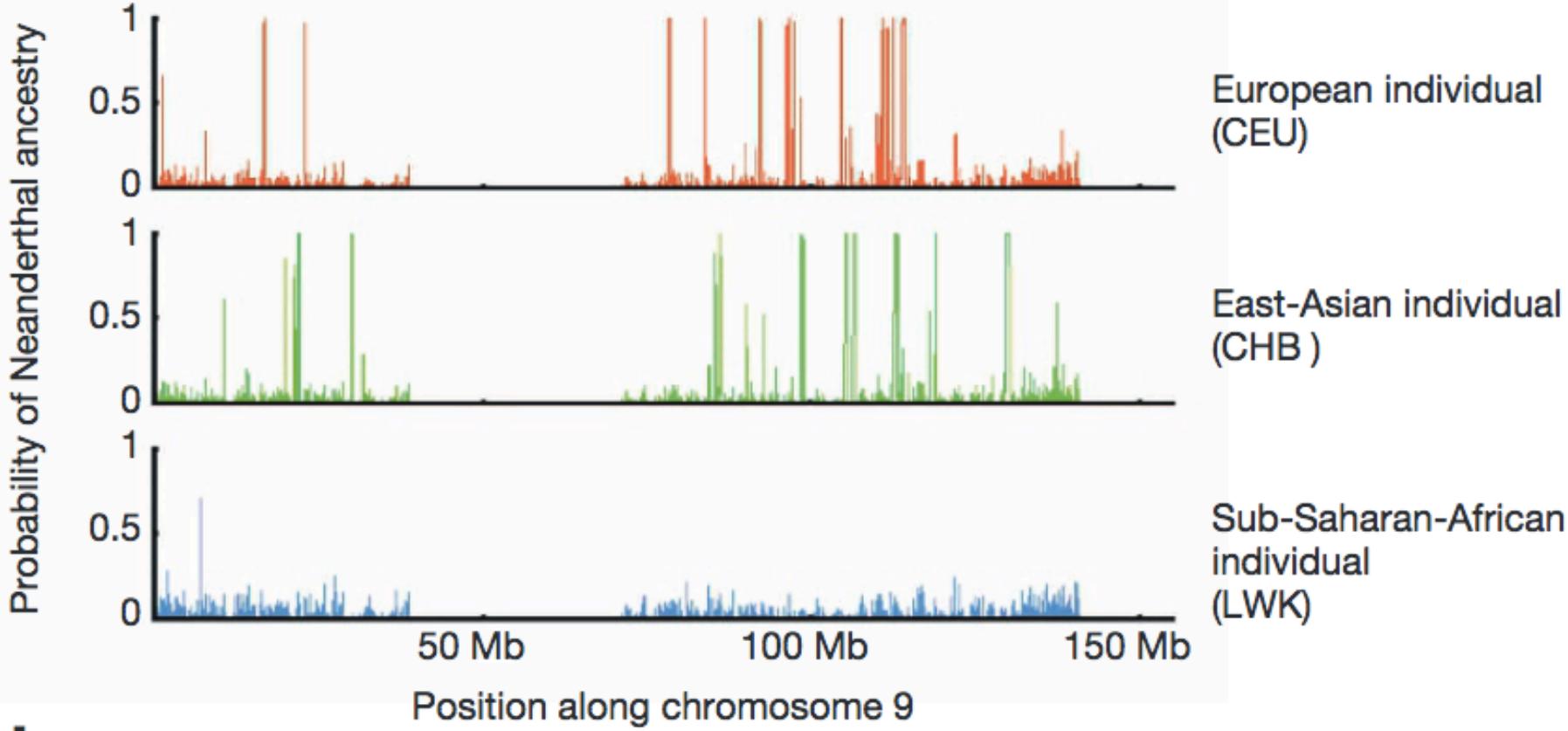


From Draft Genome Paper – more than 60 genes

ID	Pos	AA	GS	Description/function
RPTN	785	*/R	—	Multifunctional epidermal matrix protein
GREB1	1164	R/C	180	Response gene in estrogen receptor–regulated pathway
OR1K1	267	R/C	180	Olfactory receptor, family 1, subfamily K, member 1
SPAG17	431	Y/D	160	Involved in structural integrity of sperm central apparatus axoneme
NLRX1	330	Y/D	160	Modulator of innate immune response
NSUN3	78	S/F	155	Protein with potential SAM-dependent methyl-transferase activity
RGS16	197	D/A	126	Retinally abundant regulator of G-protein signaling
BOD1L	2684	G/R	125	Biorientation of chromosomes in cell division 1-like
CF170	505	S/C	112	<i>Uncharacterized protein: C6orf170</i>
STEA1	336	C/S	112	Metalloreductase, six transmembrane epithelial antigen of prostate 1
F16A2	630	R/S	110	<i>Uncharacterized protein: family with sequence similarity 160, member A2</i>
LTK	569	R/S	110	Leukocyte receptor tyrosine kinase
BEND2	261	V/G	109	<i>Uncharacterized protein: BEN domain-containing protein 2</i>
052W1	51	P/L	98	Olfactory receptor, family 52, subfamily W, member 1
CAN15	427	L/P	98	Small optic lobes homolog, linked to visual system development
SCAP	140	I/T	89	Escort protein required for cholesterol as well as lipid homeostasis
TTF1	474	I/T	89	RNA polymerase I termination factor
OR5K4	175	H/D	81	Olfactory receptor, family 5, subfamily K, member 4
SCML1	202	T/M	81	Putative polycomb group (PcG) protein
TTL10	394	K/T	78	Probable tubulin polyglutamylase, forming polyglutamate side chains on tubulin
AFF3	516	S/P	74	Putative transcription activator, function in lymphoid development/oncogenesis
EYA2	131	S/P	74	Tyrosine phosphatase, dephosphorylating "Tyr-142" of histone H2AX
NOP14	493	T/R	71	Involved in nucleolar processing of pre-18S ribosomal RNA
PRDM10	1129	N/T	65	PR domain containing 10, may be involved in transcriptional regulation
BTLA	197	N/T	65	B and T lymphocyte attenuator
O2AT4	224	V/A	64	Olfactory receptor, family 2, subfamily AT, member 4
CAN15	356	V/A	64	Small optic lobes homolog, linked to visual system development

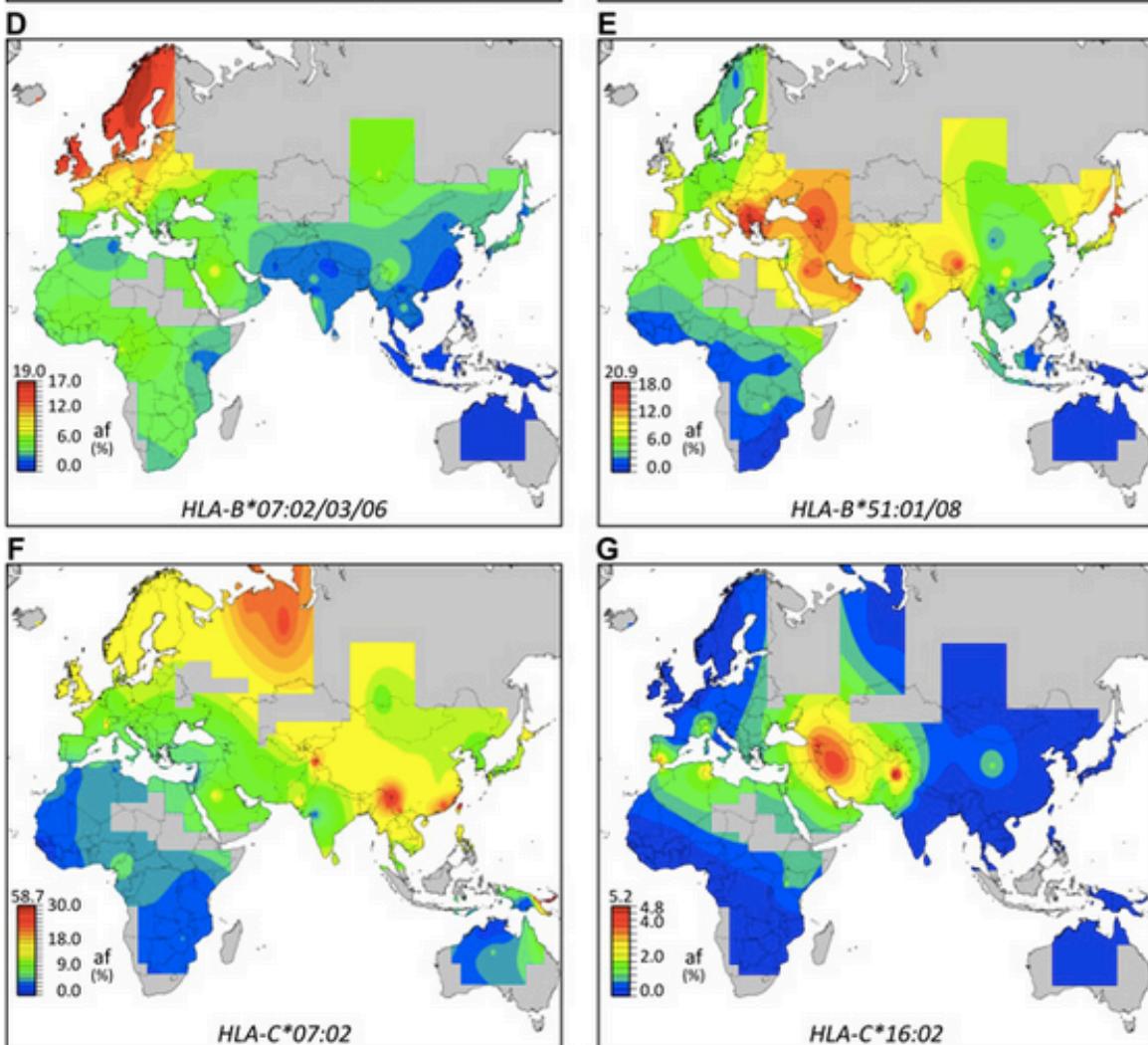
The genomic landscape of Neanderthal ancestry in present-day humans

Sriram Sankararaman^{1,2}, Swapan Mallick^{1,2}, Michael Dannemann³, Kay Prüfer³, Janet Kelso³, Svante Pääbo³, Nick Patterson^{1,2}
& David Reich^{1,2,4}

a**b**

Neandertal Antigen- presenting Genes

Neandertal *HLA-A*, *-B* and *-C* alleles are identical to modern *HLA class I* alleles.



Article | Open Access | Published: 01 April 2014

Neanderthal ancestry drives evolution of lipid catabolism in contemporary Europeans

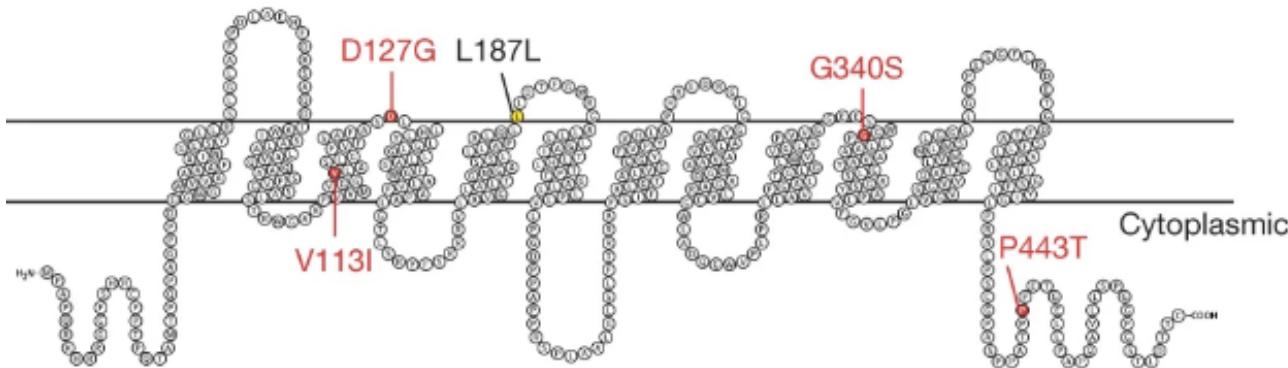
Ekaterina E. Khrameeva, Katarzyna Bozek, Liu He, Zheng Yan, Xi Jiang, Yuning Wei, Kun Tang, Mikhail S. Gelfand, Kay Prüfer, Janet Kelso, Svante Paabo, Patrick Giavalisco , Michael Lachmann  & Philipp Khaitovich 

Nature Communications **5**, Article number: 3584 (2014) | Cite this article

2380 Accesses | **35** Citations | **346** Altmetric | Metrics

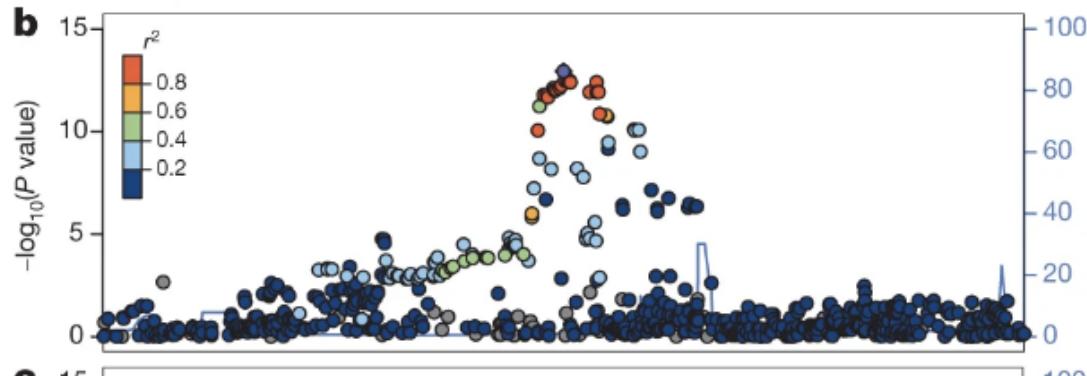
Рисковая аллель диабета 2 типа

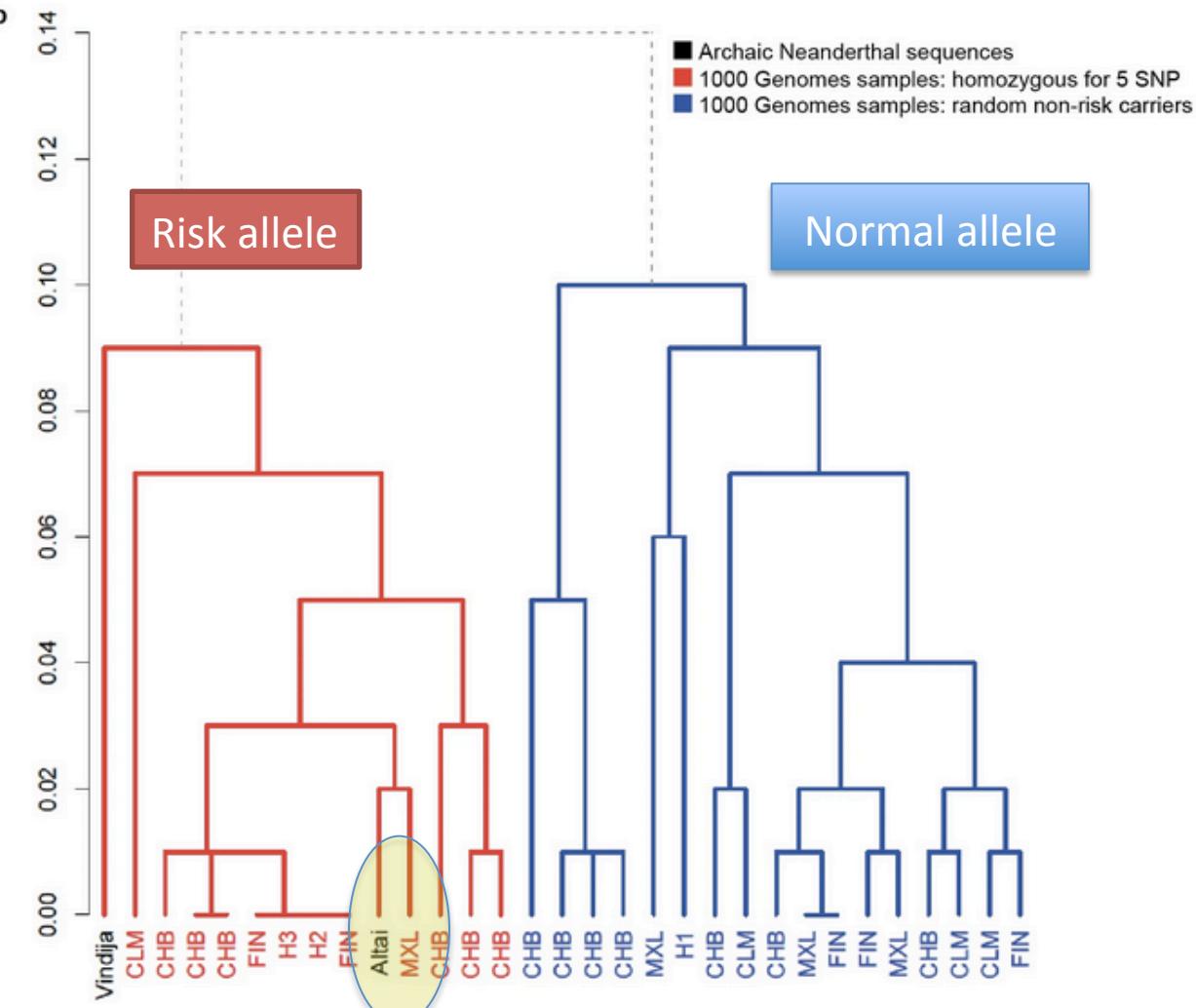
SLC16A11 predicted membrane topology



Chromosome 17p13 at *SLC16A11/13* locus

Plotted SNPs





Dendrogram generated from haplotypes across the 73-kb Neanderthal introgressed region.

Neanderthal with Mexican

Tibetans inherited high-altitude gene from ancient human

EPAS1

regulates the body's production of hemoglobin.



Breathing easy. This Tibetan inherited a beneficial high-altitude gene from archaic Denisovan people. BEIJING GENOMICS INSTITUTE

Letter | Published: 02 July 2014

Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA

Emilia Huerta-Sánchez, Xin Jin, [...] Rasmus Nielsen 

Nature **512**, 194–197(2014) | Cite this article

5897 Accesses | **373** Citations | **869** Altmetric | Metrics

 This article has been updated

Гены, отличающиеся от неандертальцев



Article | Open Access | Published: 11 June 2019

A catalog of single nucleotide changes distinguishing modern humans from archaic hominins

Martin Kuhlwilm & Cedric Boeckx 

Scientific Reports **9**, Article number: 8463 (2019) | Cite this article

4458 Accesses | **6** Citations | **76** Altmetric | Metrics

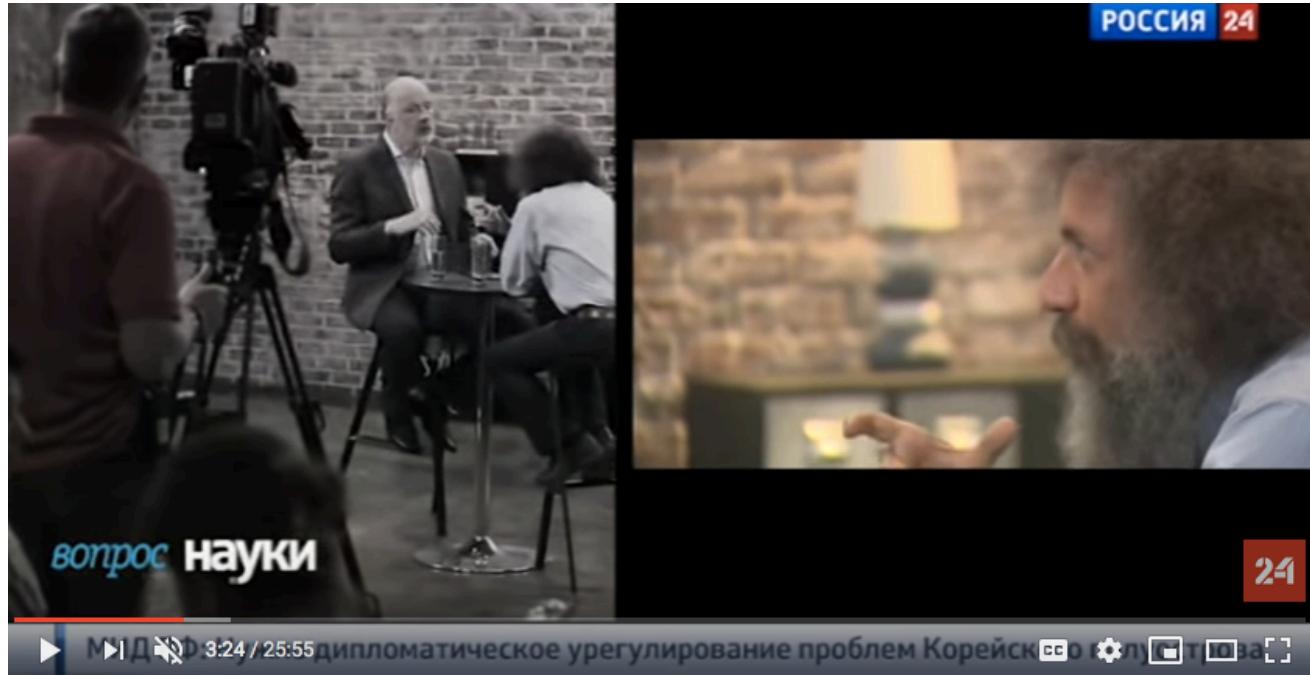
NEWS · 22 AUGUST 2018 · CORRECTION 23 AUGUST 2018

Mum's a Neanderthal, Dad's a Denisovan: First discovery of an ancient-human hybrid

Genetic analysis uncovers a direct descendant of two different groups of early humans.

Вопрос науки. Неандертальцы

Алексей Семихатов и Михаил Гельфанд



<https://www.youtube.com/watch?v=zbwymb6QGbk>

