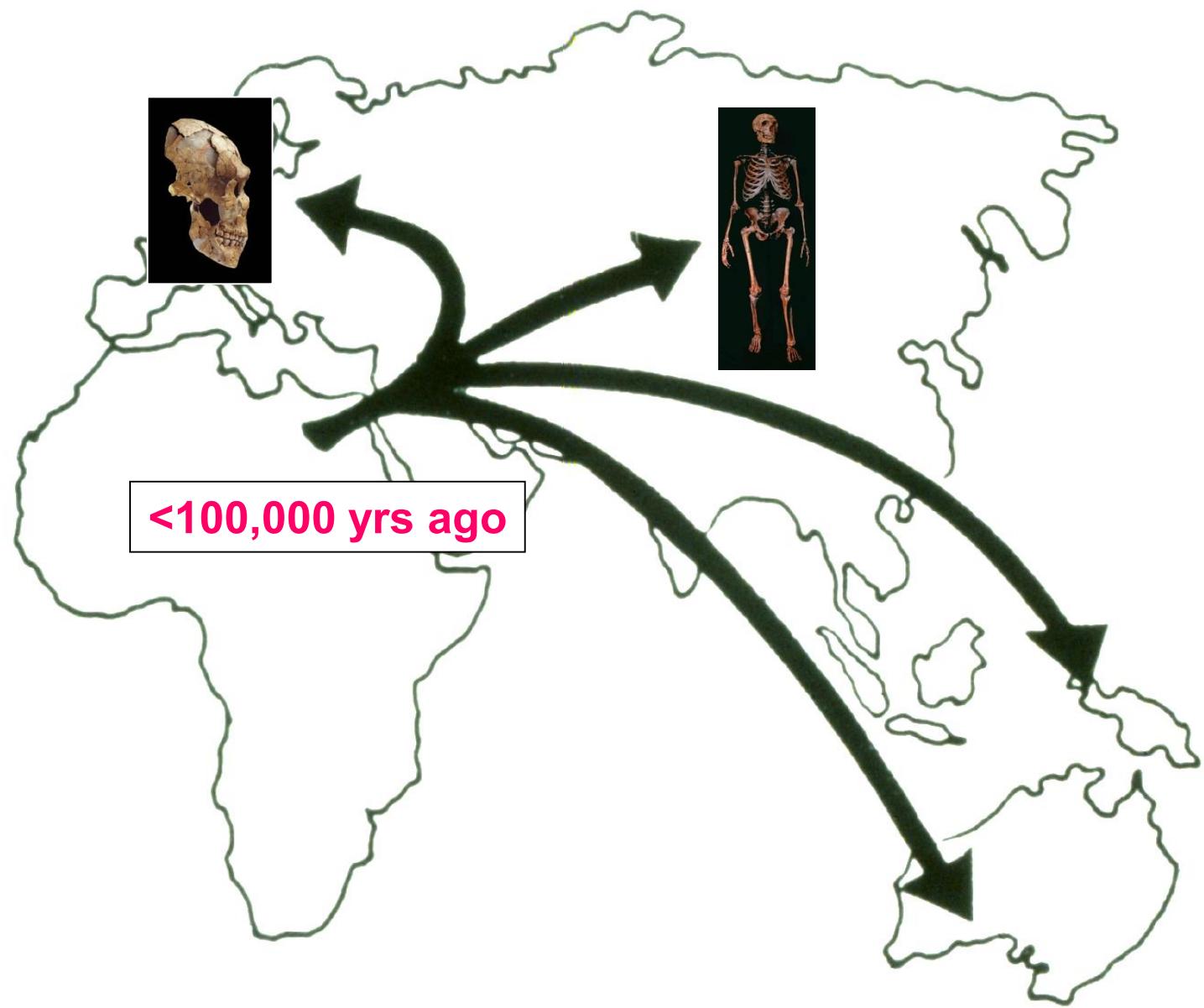


# **The Neandertal Genome and The Evolution of Modern Humans**

**Svante Pääbo**

**Max Planck Institute for Evolutionary Anthropology,  
Leipzig, Germany**

**Okinawa Institute of Science and Technology,  
Onna-son, Japan**



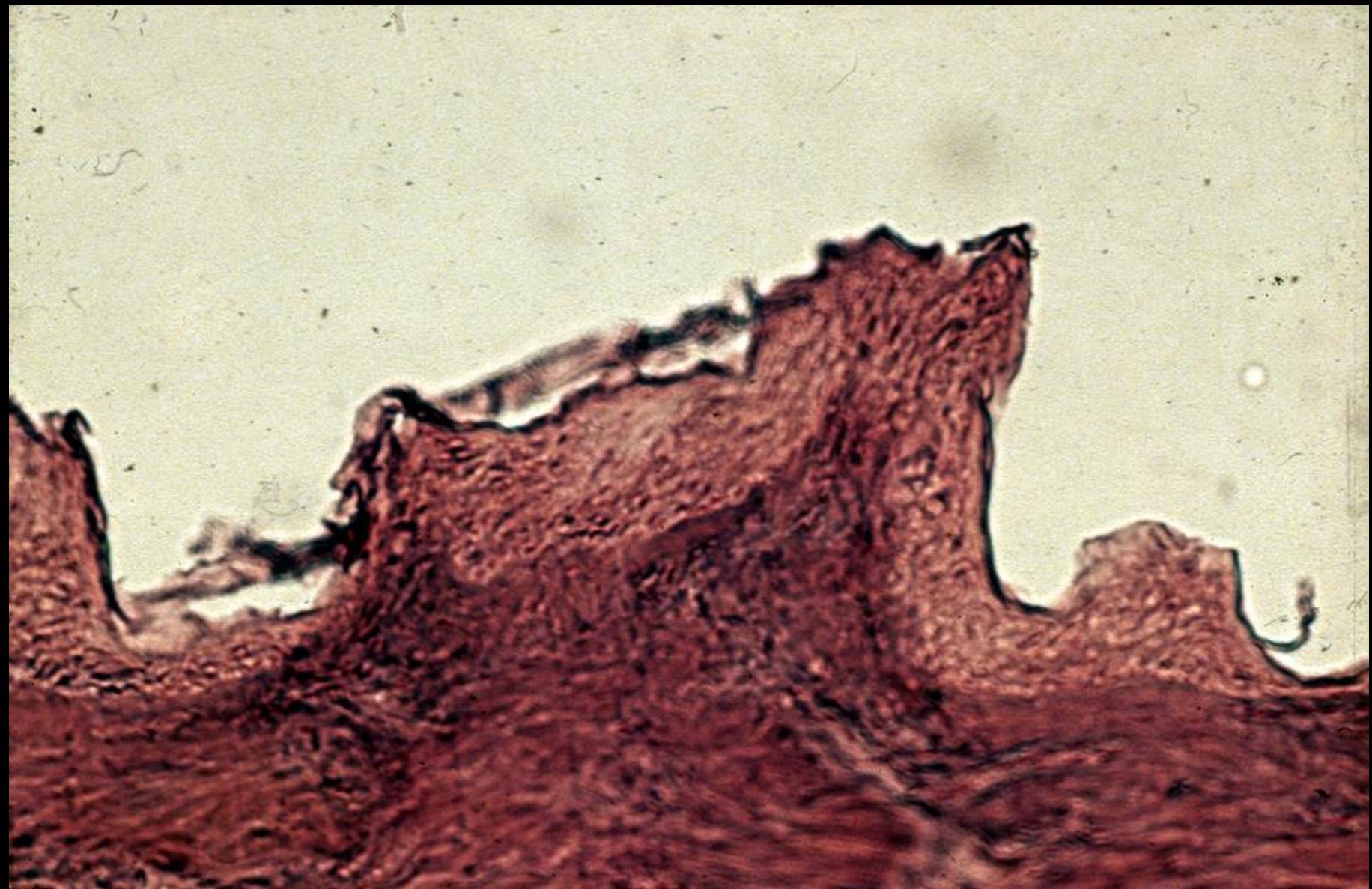
# The Neandertals “define” modern humans

## How are we related to Neandertals?

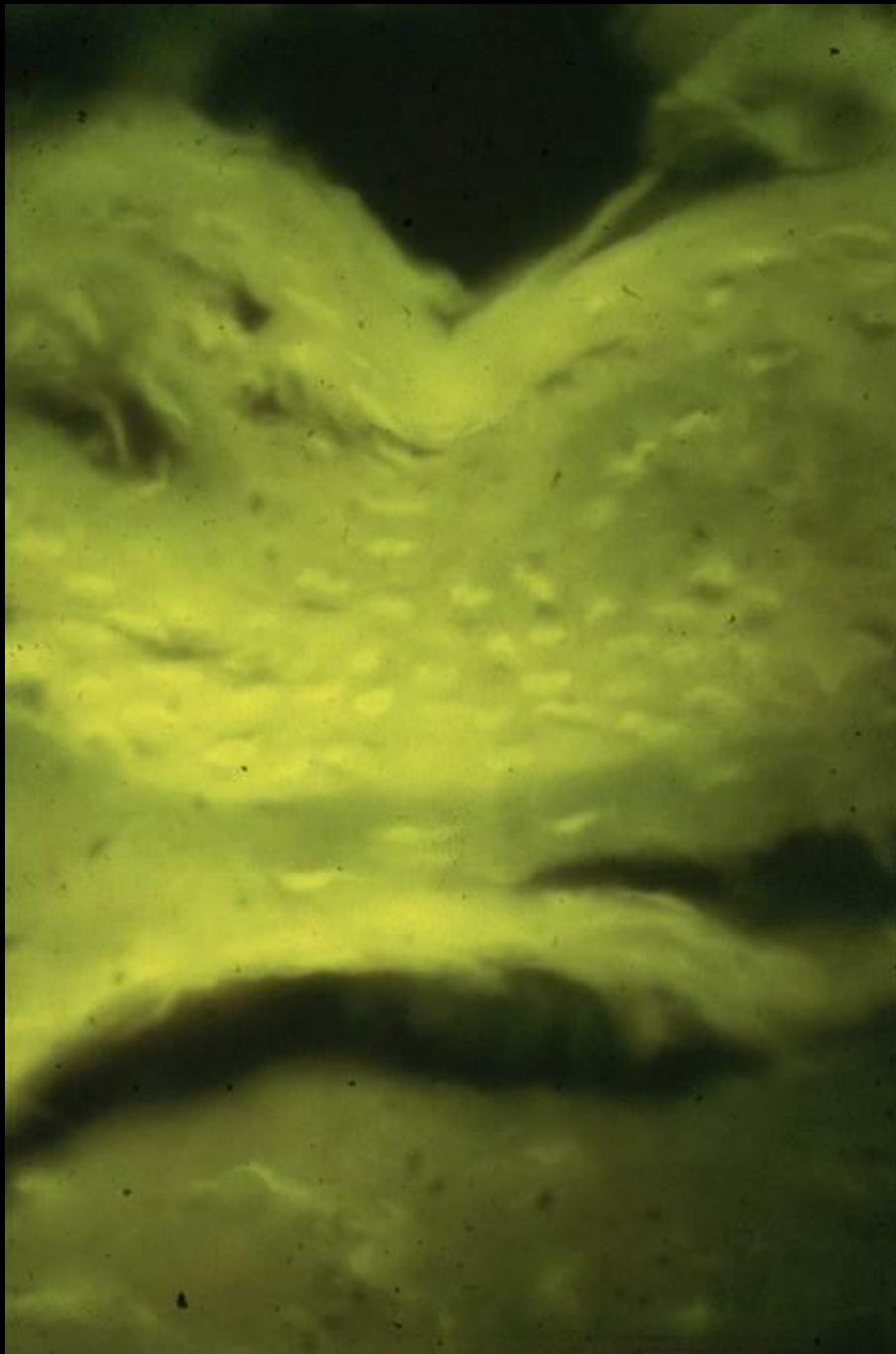




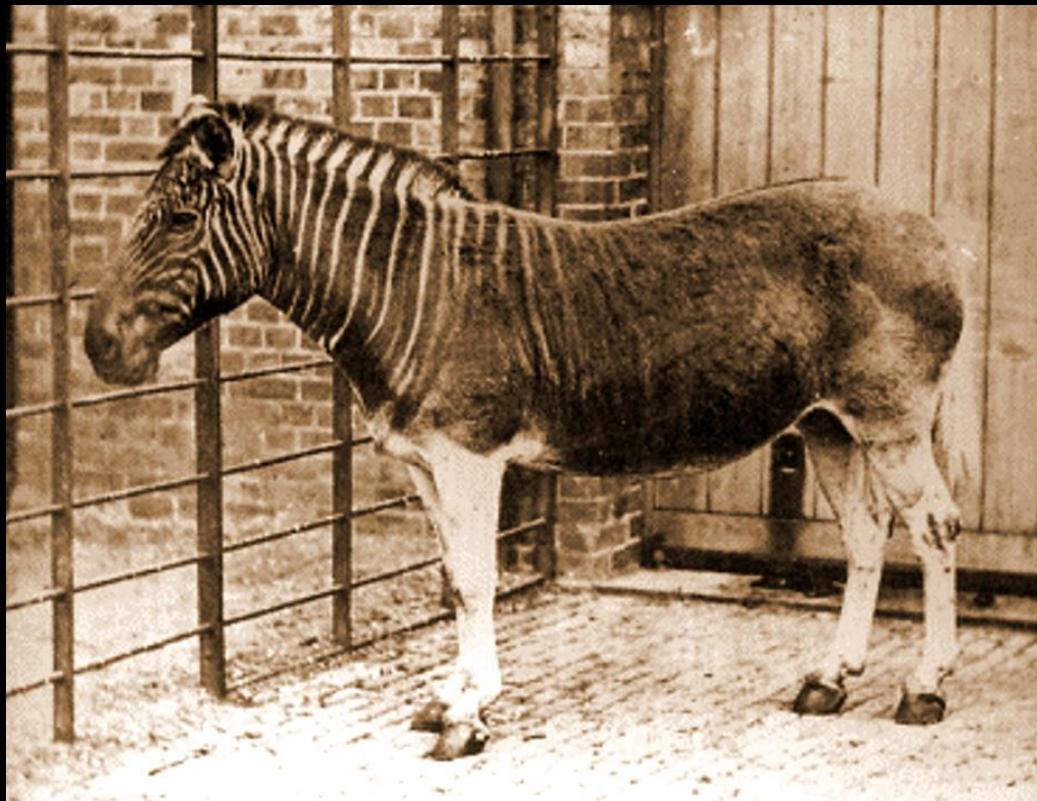
Pääbo, Das Altertum, 1984



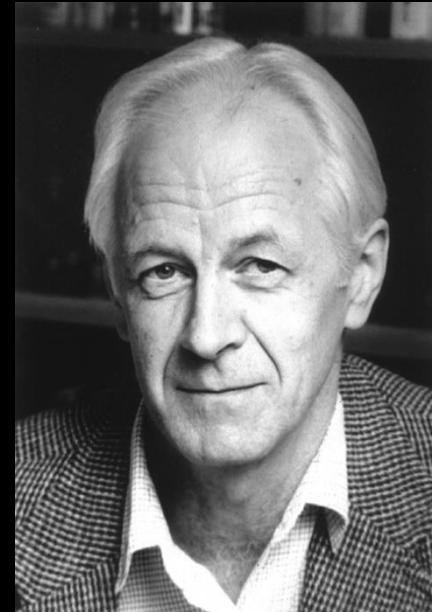
Pääbo, Das Altertum, 1984



Pääbo, Das Altertum, 1984



Higuchi *et al.* Nature 1984.



Allan C. Wilson

ural genes originating from than the results of the activation of the recipient strains. (The explanation for the three compounds through natural discussed in ref. 21.) The derrhodin A, since, of the (which led to 61) all contain a complete 304, pIJ2308, pIJ2312 and act mutants of *S. coelicolor* have recently been shown hydroxylation involved in and H.G.F., unpublished). Between the actinorhodin and indicated also by compare pIJ2308, but not by the

## Molecular cloning of Ancient Egyptian mummy DNA

Svante Pääbo

Department of Cell Research, The Wallenberg Laboratory, University of Uppsala, Box 562, S-75122 Uppsala, Sweden and Institute of Egyptology, Gustavianum, University of Uppsala, S-75120 Uppsala, Sweden

**Artificial mummification was practised in Egypt from ~2600 BC until the fourth century AD. Because of the dry Egyptian climate, however, there are also many natural mummies preserved from earlier as well as later times. To elucidate whether this unique source of ancient human remains can be used for molecular genetic**

for DNA content. One and to contain DNA that vector. I report here that

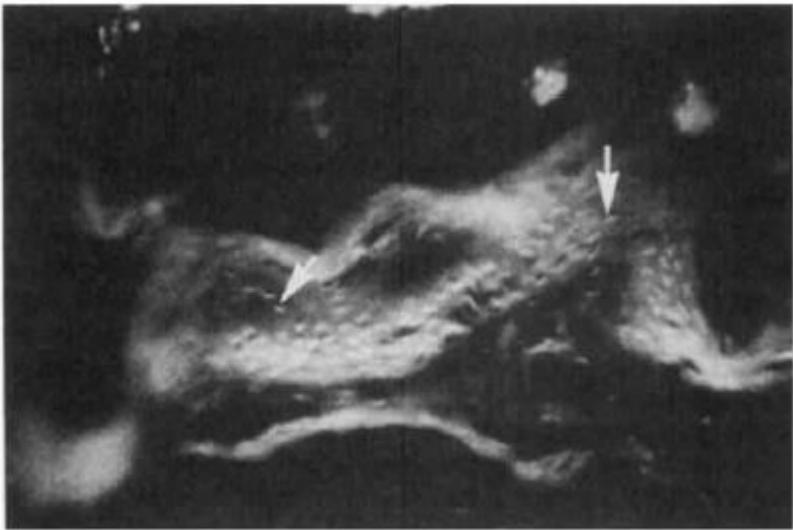


Fig. 1 Tissue section of skin from the left lower leg of the Berlin mummy used for molecular DNA cloning. Ethidium bromide staining allows the visualization of nucleic acids in the cell nuclei (arrows).

and repeat, the strongly hybridizing clone pMUM2:9 was isolated<sup>7</sup>. One of the *Alu* repeats as well as 500 bp of flanking DNA were sequenced according to the Maxam and Gilbert procedure<sup>22</sup> after labelling of the *Sph*I and *Nde*I restriction sites indicated.

## LETTERS TO NATURE

645

CTTCAACCTTTAGGCTTTTCUTATGTCUTCTGTAGTATGGATCTTGCGGCGCTTCATCATTATATCATCTATAGAATTAACAAAGTTCGCCGTTTCATCTCTGTT  
TTCGCAGCTGGAAGTCGGGAGCTGGTAARGGAGTCAGCAGGTGAATGCCATTCACAACTATCTTCACCAGCTGGCTCAGCTACTCTGTTTCATCTCTGTT  
CTTCACAATAATCAAAATAAAATTGTAGCTAACGCTTGTAAATCTGAAACATGGGATGTCAATTGTTTTACATATITCTATGAAATGTTACATTTTTTTTT  
ATTAACGGAATCTTTTAGTTAAATTGAGAAATTAATTCATTCTTCATAATTCTAACGCAATTCATCTCTTCACCTCACCTAAATTAACGAACT  
MMGAAAGTGGGCCAGACATGGTCCATDCCCTAATCCCAGTGGGGAGGGCCAGGCAAGTATTGGCCTGGAGTTGGAGACAGGCTGGCAACATAGC  
consensus: ---TG-G-G-----CA-----TG-T----CC---CTCA---CA-----C---G-T  
CG-----T-----C-----GC-----CT-----AA-C-----G-G-----CA-----A-T-G-----AC-C-----GGT  
GAGGCGATGATGCCACCAAGCTGCGAGGCCACAGAGAGAGCTGTCTCTCAAAGGAAGAGGAAGAAGAGAAGAGAAGAGGAGG  
GA-----G-----T-----C-----CA-----  
ACGAGAAGGCCAGCAAAAACAAACAAAGAAGAACGGAGAGGAAACACAGATTAATTCTGG

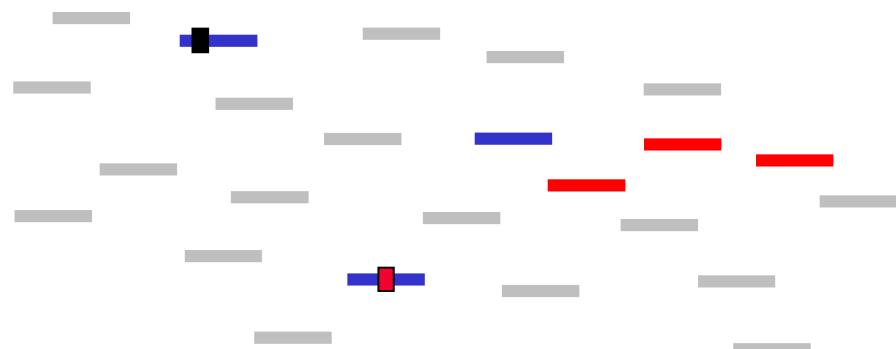
kaline phosphatase-treated pUC8 plasmid<sup>6</sup>. Then, 700 of the white clones were transferred into the isolated<sup>7</sup> 550-bp *Bgl*II/*Sph*I fragment from a HLA-DR pseudogene<sup>21</sup>, which contains an *Alu* repeat. The strongly hybridizing clone pMUM2:9 was isolated and restriction-mapped. Two *Alu* repeats were identified by Southern hybridization<sup>9</sup>. One of the *Alu* repeats as well as 500 bp of flanking DNA were sequenced according to the Maxam and Gilbert procedure<sup>22</sup> after labelling of the *Sph*I and *Nde*I restriction sites indicated.

## Fresh DNA



~1 $\mu$ g DNA  
per gram tissue

## Ancient DNA



~0.0000001-0.0001 $\mu$ g DNA  
per gram tissue

## Microbial DNA

# Contamination prevention



## Alu sequences:

	10	20	30	40	50	60	70	80
Consensus	GGCCGGGCGCGGTGGCTCACGCCGTAA	TCATCCCAGC	ACTTTGGGAGGCCGAGGC	GAGGCGGATCAC	--GAGGTCAGGAGATC			
11:2			T..	.....	A...A	.....		
12:2	.ATCA.	TAAC.C..	AAAAG..T..					
12:4					T....T	.....		
12:5	.A...A.....	A.....		T....A..A.....	CT....			

## D loop:

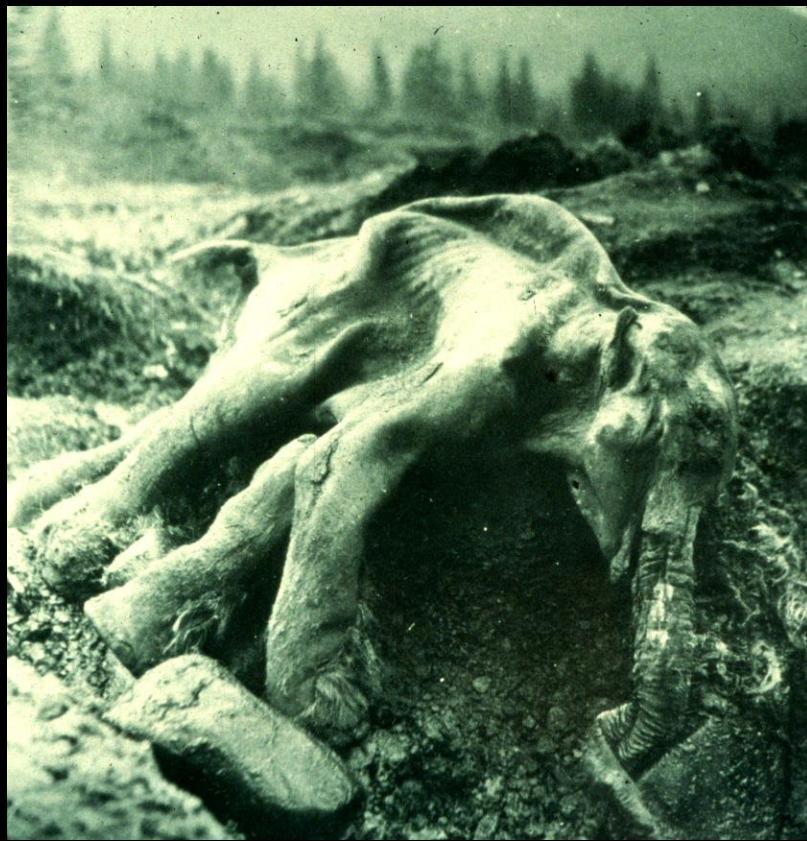
Reference 16210-ACAGCAATCAACCCTCAACTATCACACATCAACTGCAACTCCAAA-16254  
Nekht-ankh .....T.....C....

## Region V:

Reference 8216-CTAGAATTAAATTCCCTAAAAATCTTGAAATAGGGCCGTATTTACCTATAGCACCCCCCTCTACCCCCCTTAGAGCCA-8296  
Nekht-ankh .....A.....



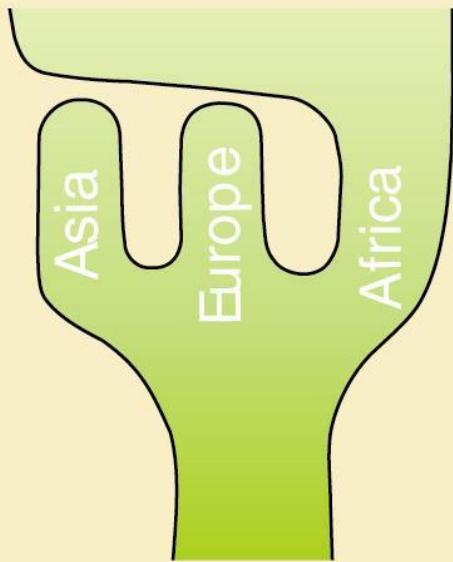
By P. Snowball, in "On the track of Ice Age mammals", 1985.



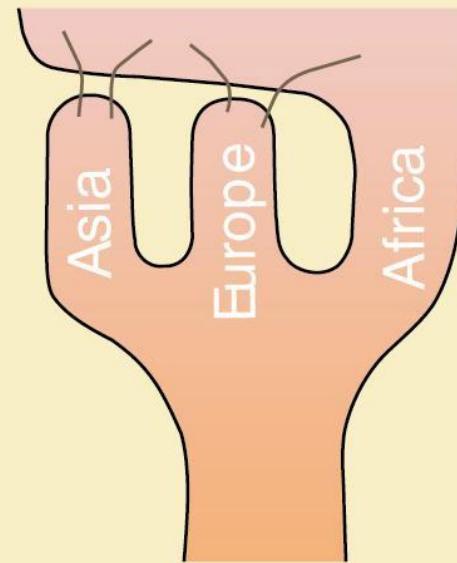
[https://commons.m.wikimedia.org/wiki/File:Mamut\\_enano-Beringia\\_rusa-NOAA.jpg](https://commons.m.wikimedia.org/wiki/File:Mamut_enano-Beringia_rusa-NOAA.jpg)



## Replacement



## Assimilation



**Total Replacement**

**Total Continuity**

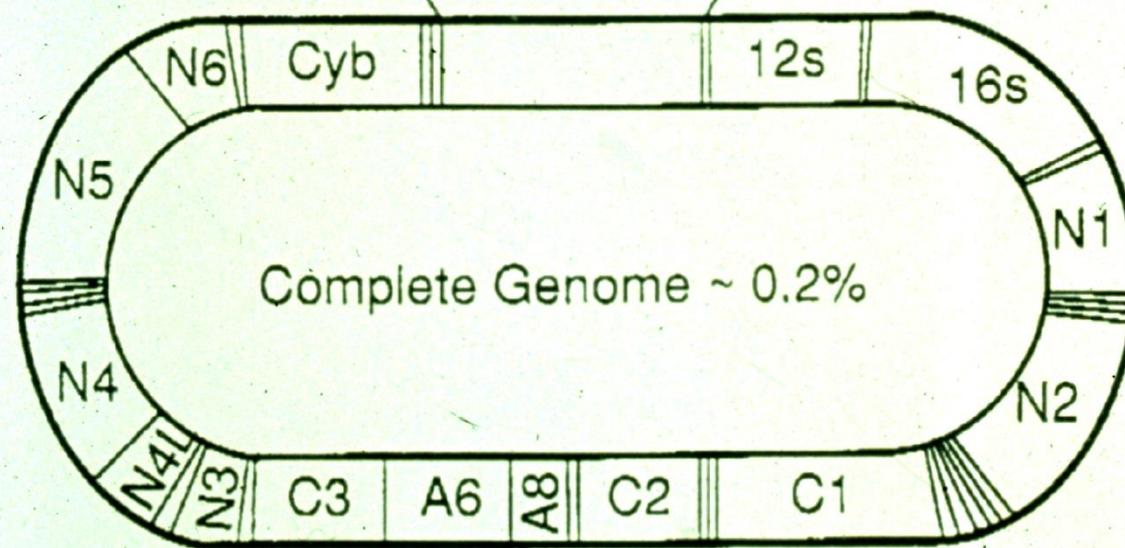
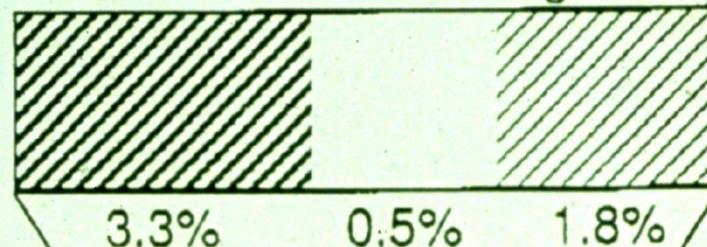


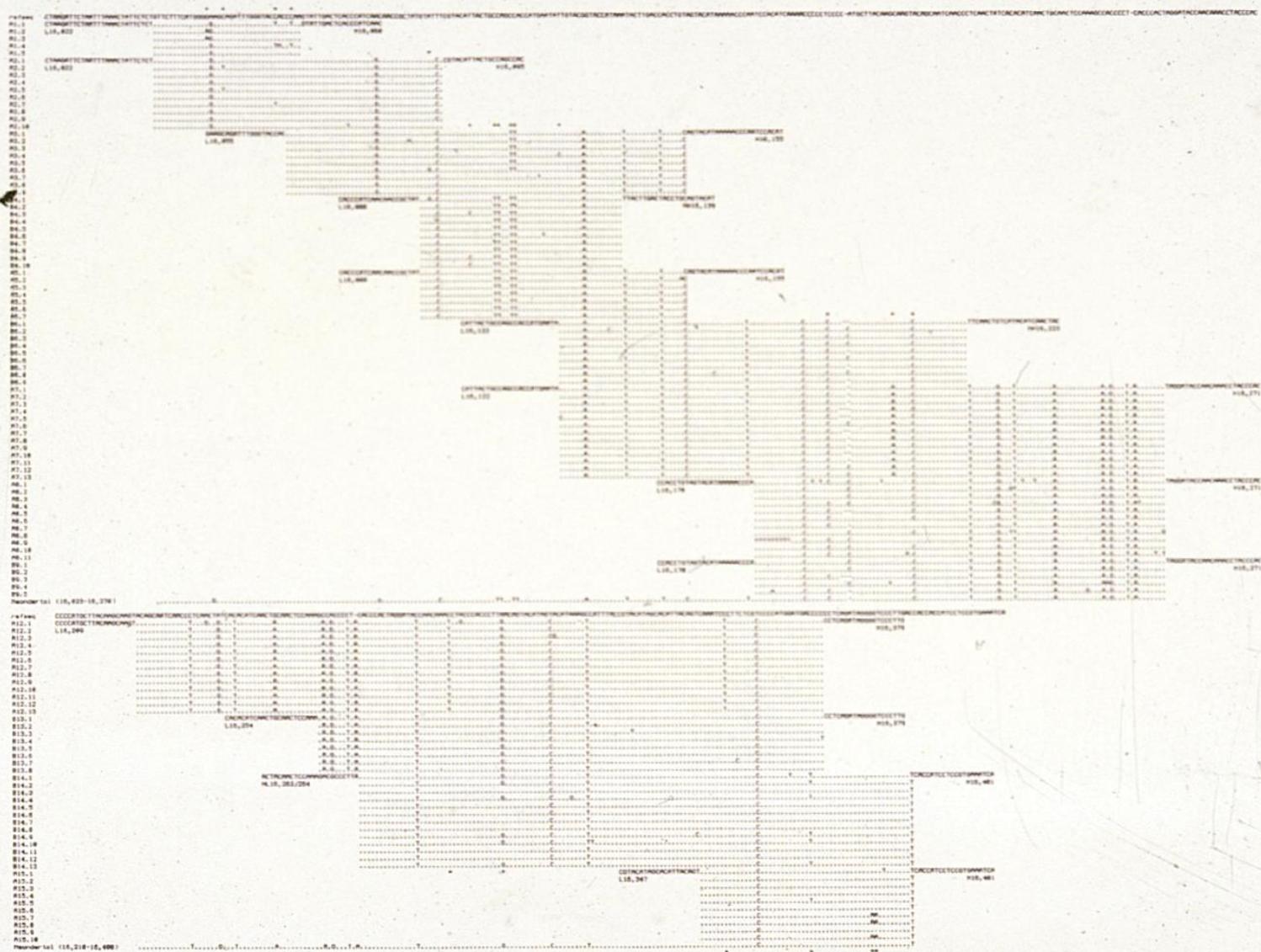


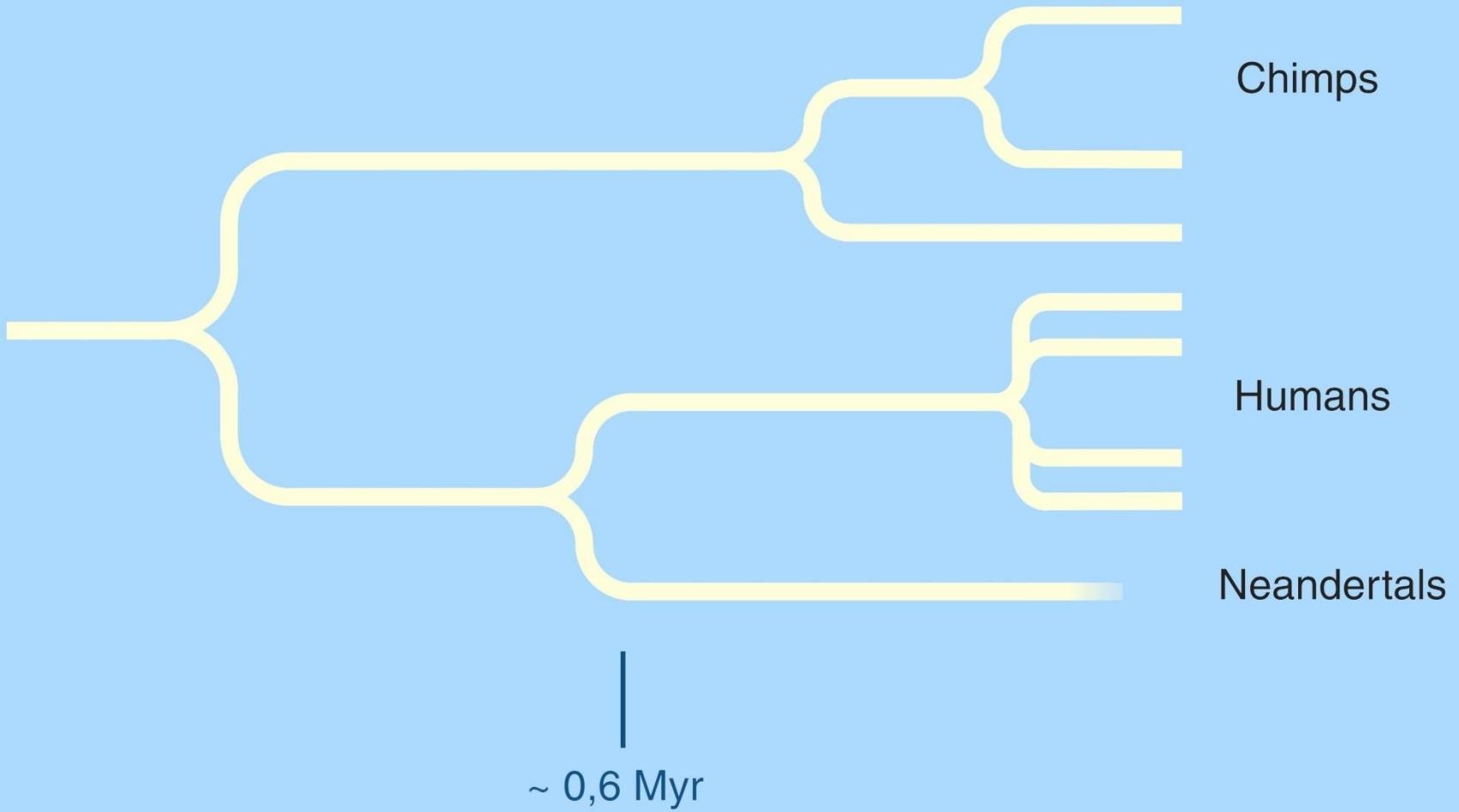


% Divergence per 100,000 years

C o n t r o l R e g i o n







**Total Replacement**

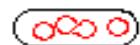
**Total Continuity**

0%

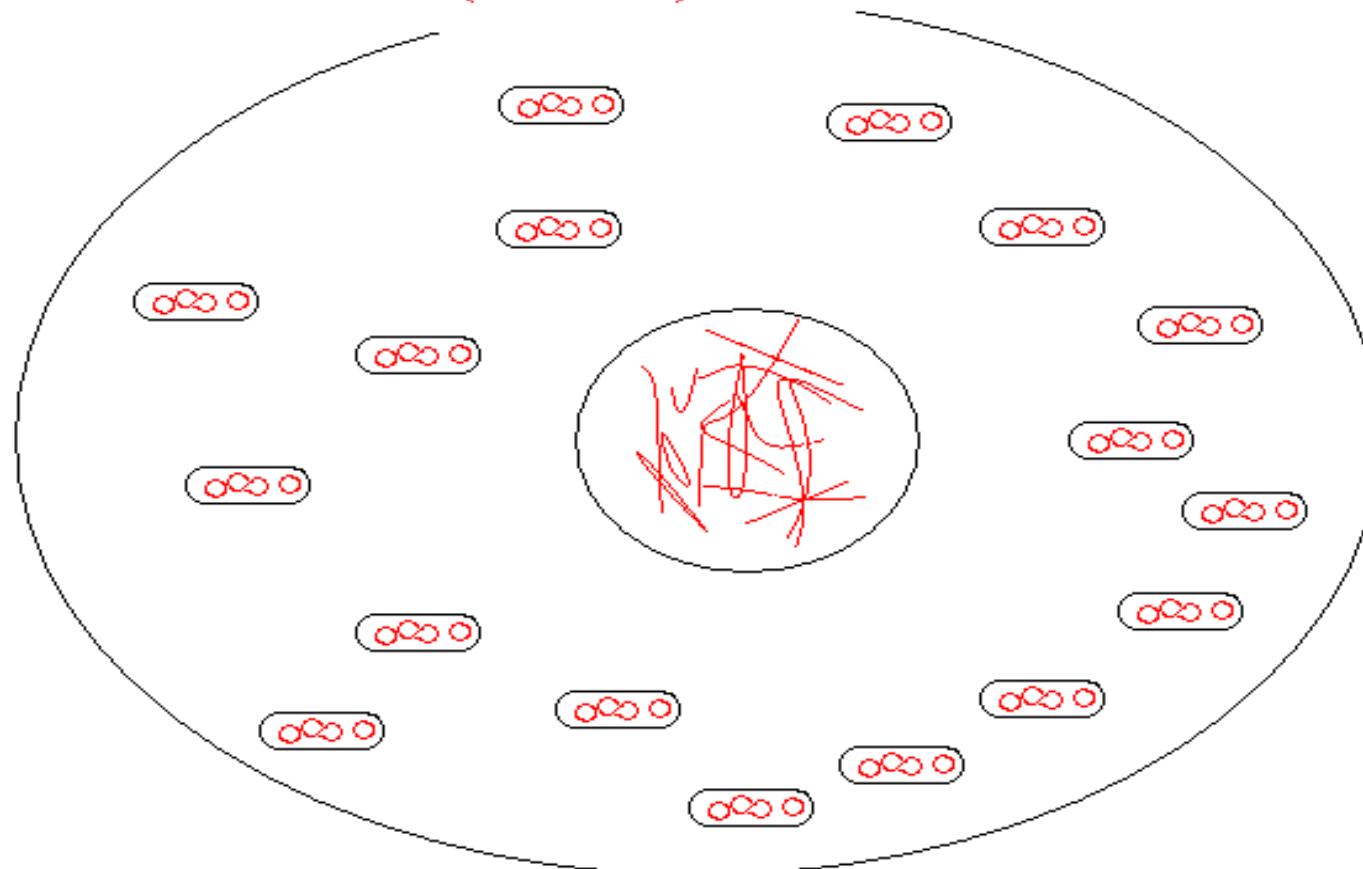
100%



**mtDNA**



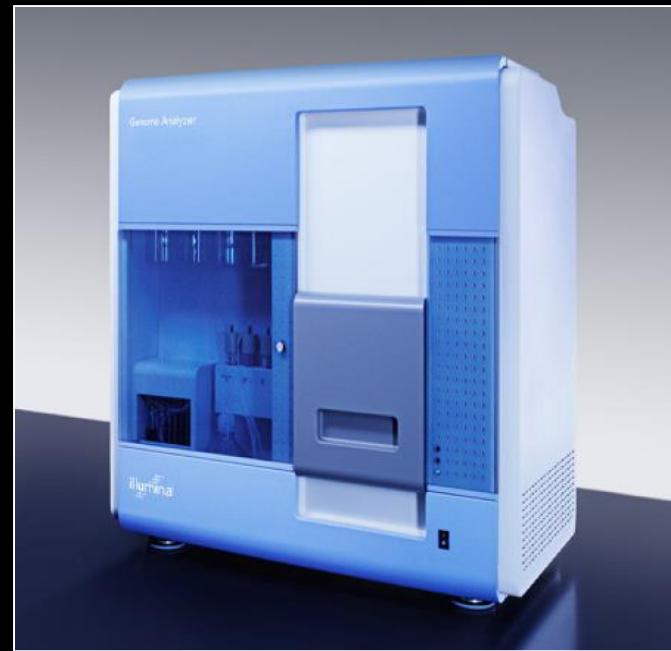
## mtDNA (>1000)



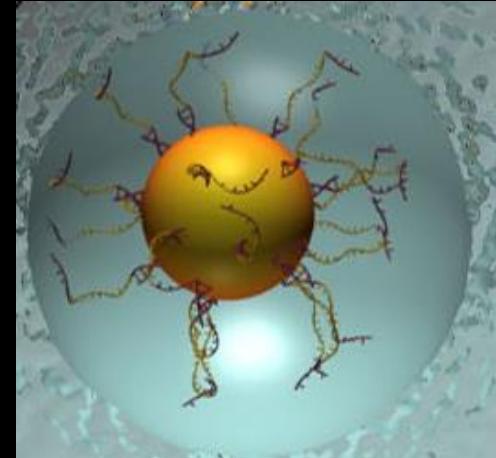
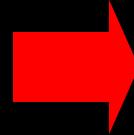
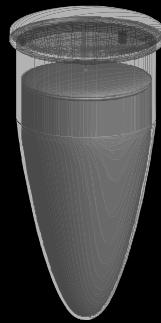
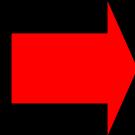
# High Throughput DNA Sequencing



~500 million bp; ~500 bp reads

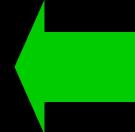
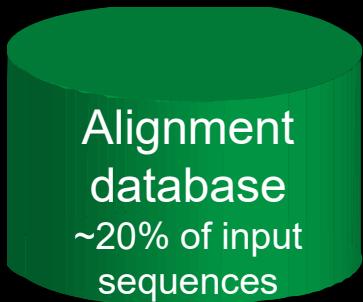
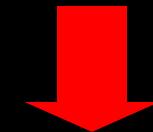


~95 billion bp; ~150 bp reads

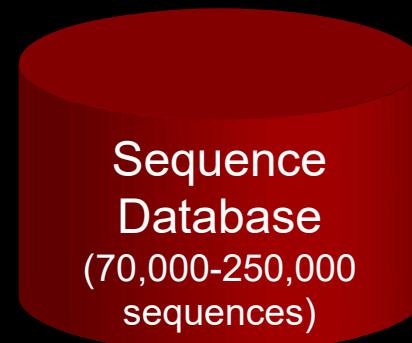
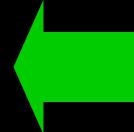


DNA extract

Direct  
sequencing



NCBI  
GenBank  
Target genomes





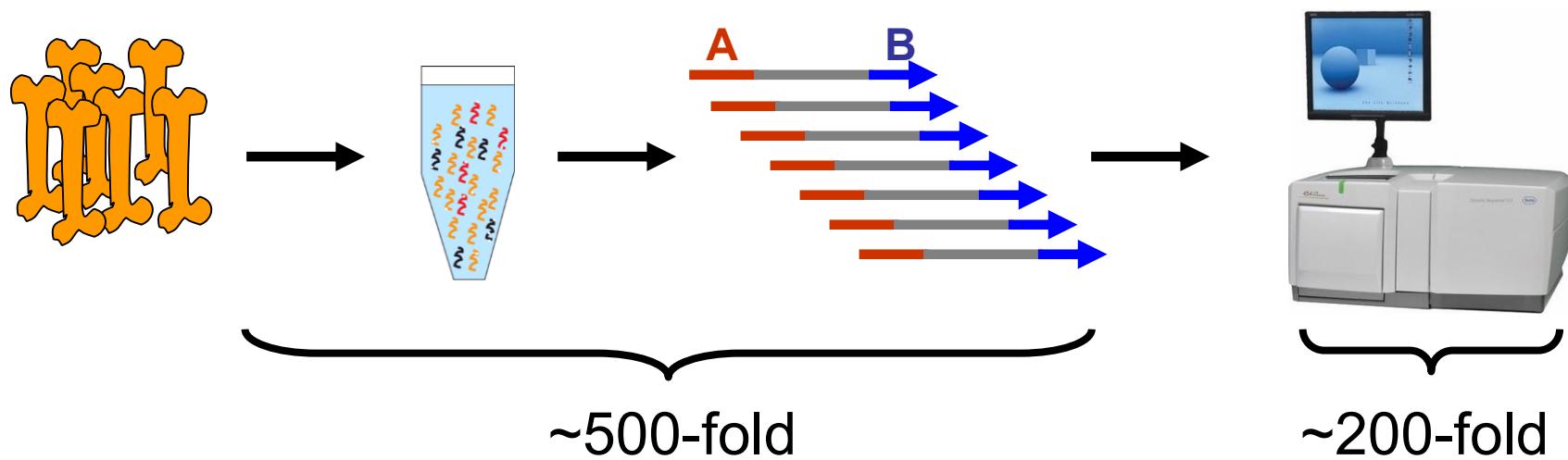
Vindija Cave, Croatia

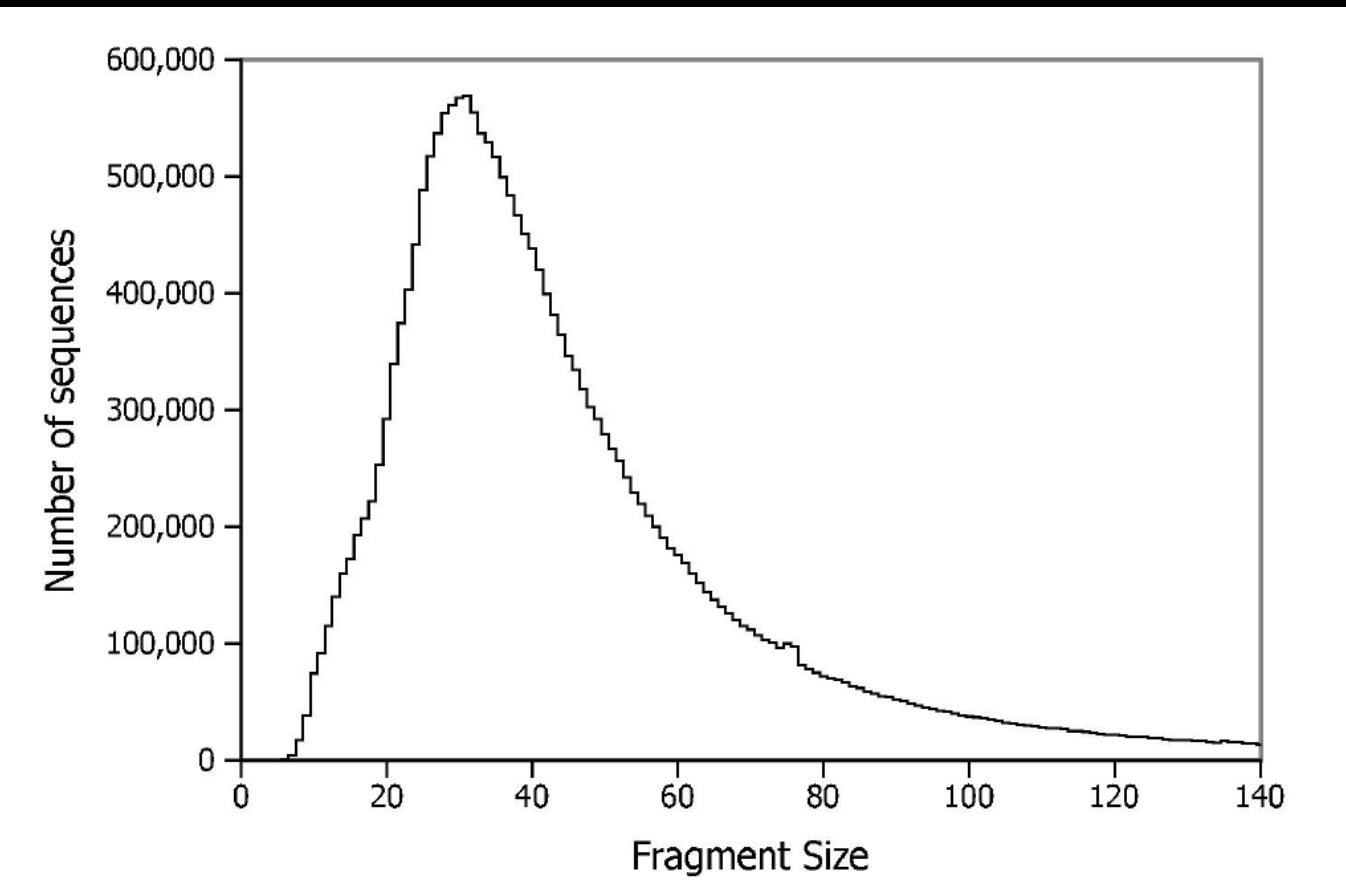
# Vindija Cave, Croatia



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

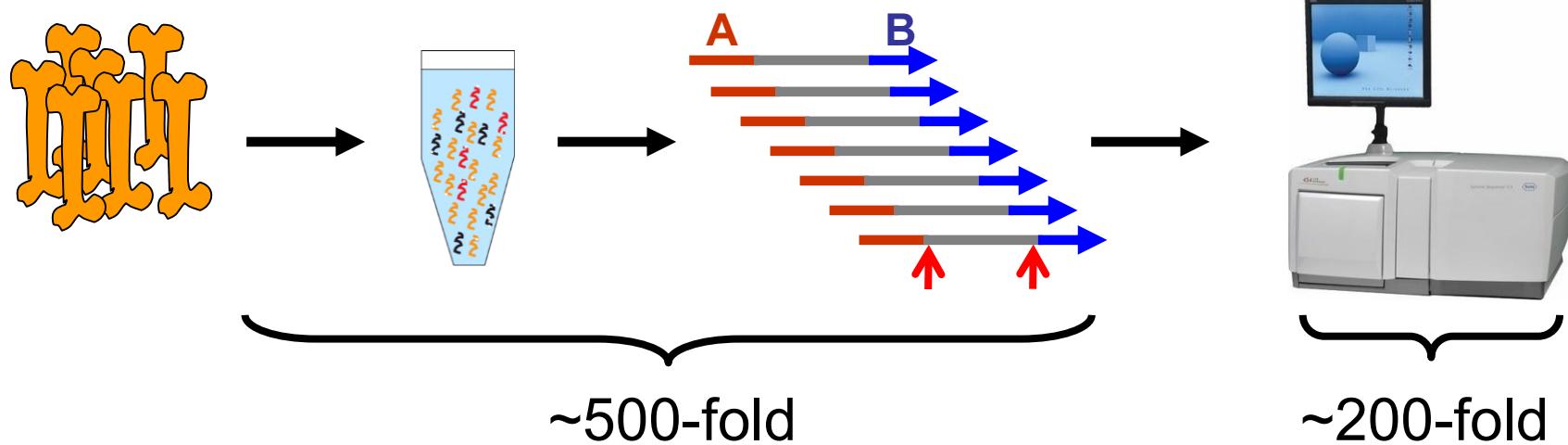
2005-2010



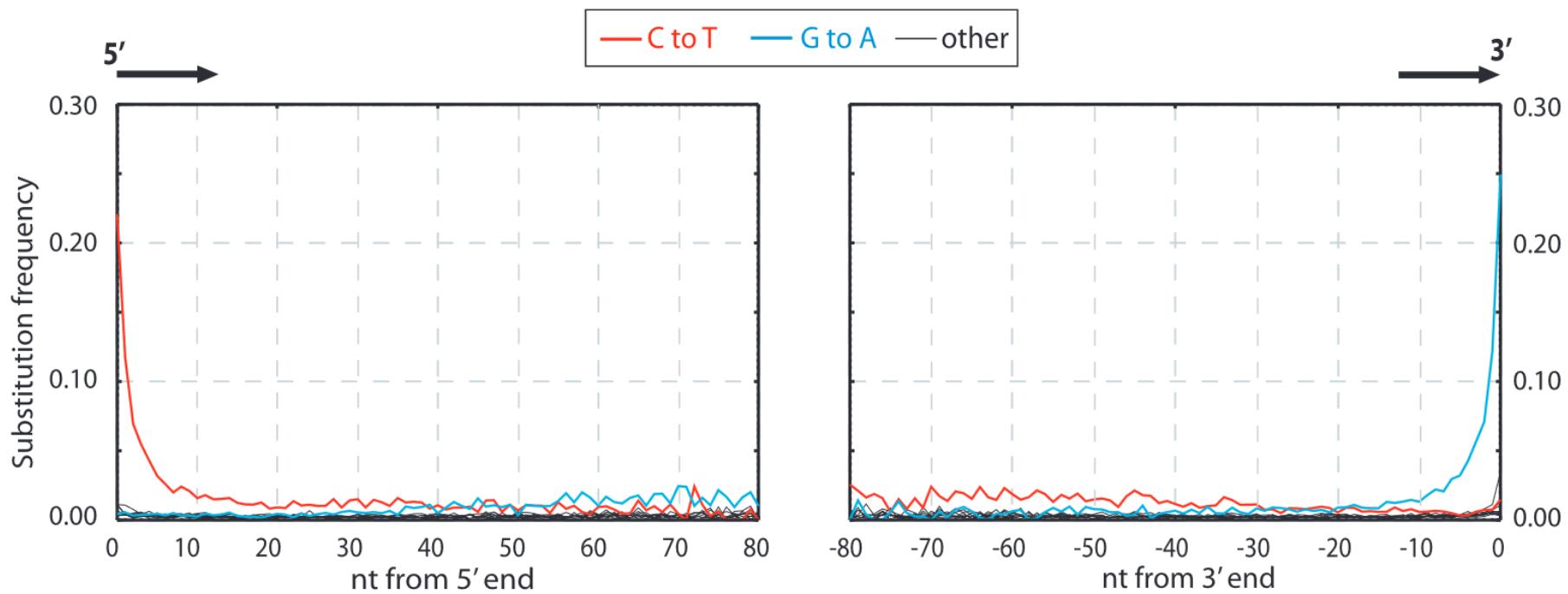


Meyer *et al.*, Nature, 2014.

2005-2010



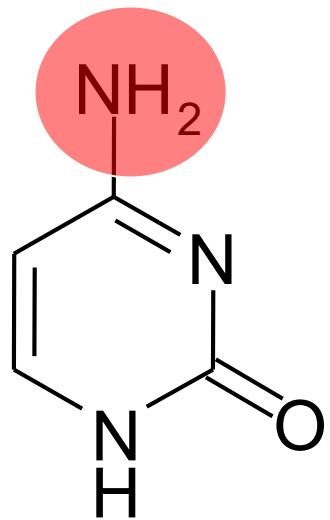
# Patterns of DNA damage



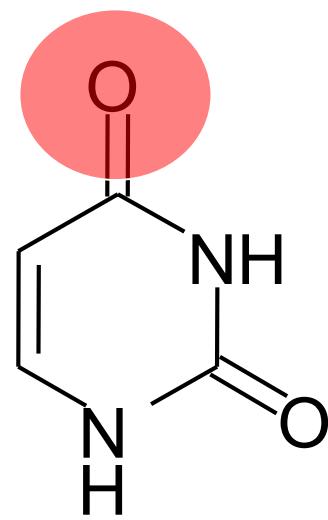
Briggs *et al.*, PNAS, 2007.



Adrian Briggs



Cytosine



Uracil

C

Deamination



U



T



Johannes Krause



Vi33-25

Vi33-26

Vi33-16



Tomislav Maričić

**454 FLX/Titanium**



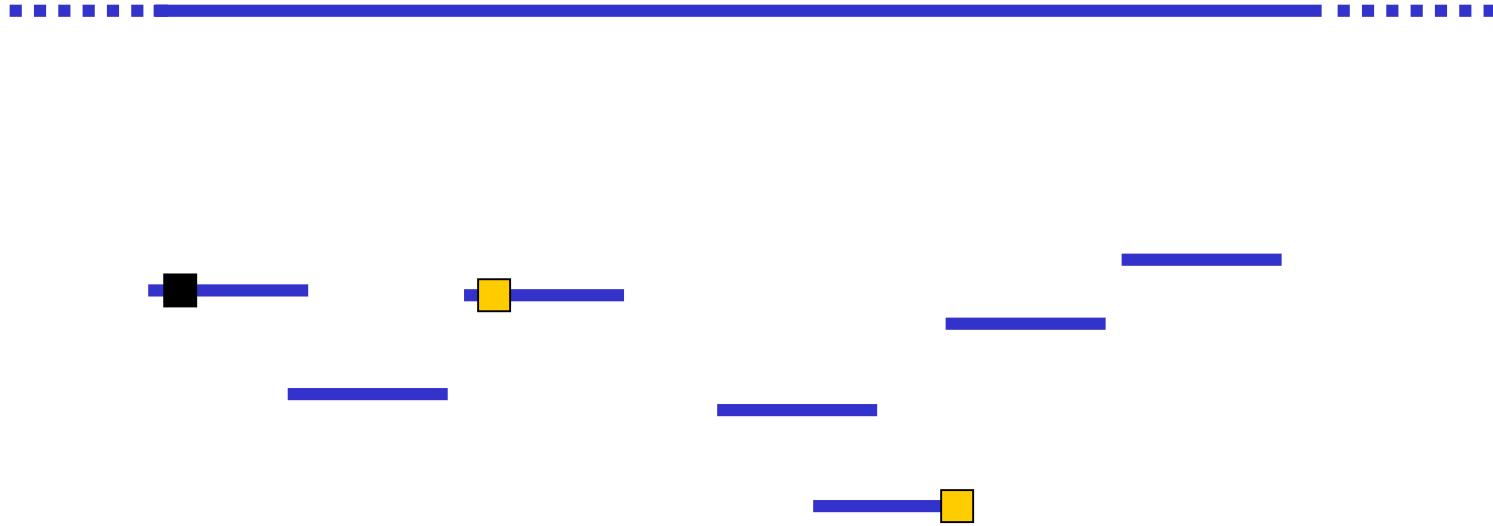
**200,848,155  
fragments**

**Illumina/Solexa GA<sub>II</sub>**



**1,135,450,518  
fragments**

# Human genome



**Neandertal genome  
(One-fold coverage)**



Janet Kelso

[Genome Browser](#)[ENCODE](#)[Blat](#)[Table Browser](#)[Gene Sorter](#)[In Silico PCR](#)[Genome Graphs](#)[Galaxy](#)[VisiGene](#)[Proteoms](#)[Browser](#)[Utilities](#)[Downloads](#)[Release Log](#)[Custom Tracks](#)[Microbial Genomes](#)[Mirrors](#)[Archives](#)[Training](#)[Credits](#)[Publications](#)[Cite Us](#)[Licenses](#)[Jobs](#)[Staff](#)[Contact Us](#)

## Neandertal Genome Analysis Consortium Tracks at UCSC

Neandertals are the closest extant relatives of humans. They lived from several hundred thousand years ago until their disappearance approximately 30,000 years ago. The Neandertal genome sequence (published by Green et al. in *Science*, May 2010) consists of short sequence fragments, usually about 10 base pairs long, mapped largely from three Neandertal bones, each about 40,000 years old, from the Vindija Cave in Croatia: VD314, VD315, and VD316. The full sequencing was carried out on the Illumina GAII platform. Neandertal DNA was identified from among the background of microbial sequences in the bones by similarity to the human genome.

This portal provides access to the sequence data and alignment to the reference human genome (NCBI Build 36 [hg18](#)) as well as the reference chimpanzee genome (CGSC 2.1 [panTro2](#)) and several associated analyses (see [Downloads](#) and [References](#)).

All data were originally mapped to NCBI Build 36 [hg18](#) and are still available there. However, for the convenience of our users, we have remapped the data to the more recent human assembly (GCF007 [hg19](#)).

The following annotations are available on the human hg18 genome assembly:

- [Neandertal Alleles in Human Clump Coding](#)
- [Selective Sweep Scan \(See Neandertal\)](#)
- [Selective Sweep Scan \(1.1% Neandertal\)](#)
- [SNPs Used for Selective Sweep Scan \(1.1%\)](#)
- [Candidate Regions for Gene Flow from Neandertals](#)
- [Neandertal Genome Coverage](#)
- [Neandertal Sequence Read: Short Neandertal](#)
- [Alignment of Sequence Read from "Modern"](#)
- [Neandertal Mitochondrial Sequence: Short](#)



Entrance of the Vindija Cave, Croatia  
Copyright: Jelena Knezevic, The Chinese Center for Rock Art Research. All rights reserved.

# ~55%

## of Neandertal genome

(<http://genome.ucsc.edu/Neandertal/>)

(2010)

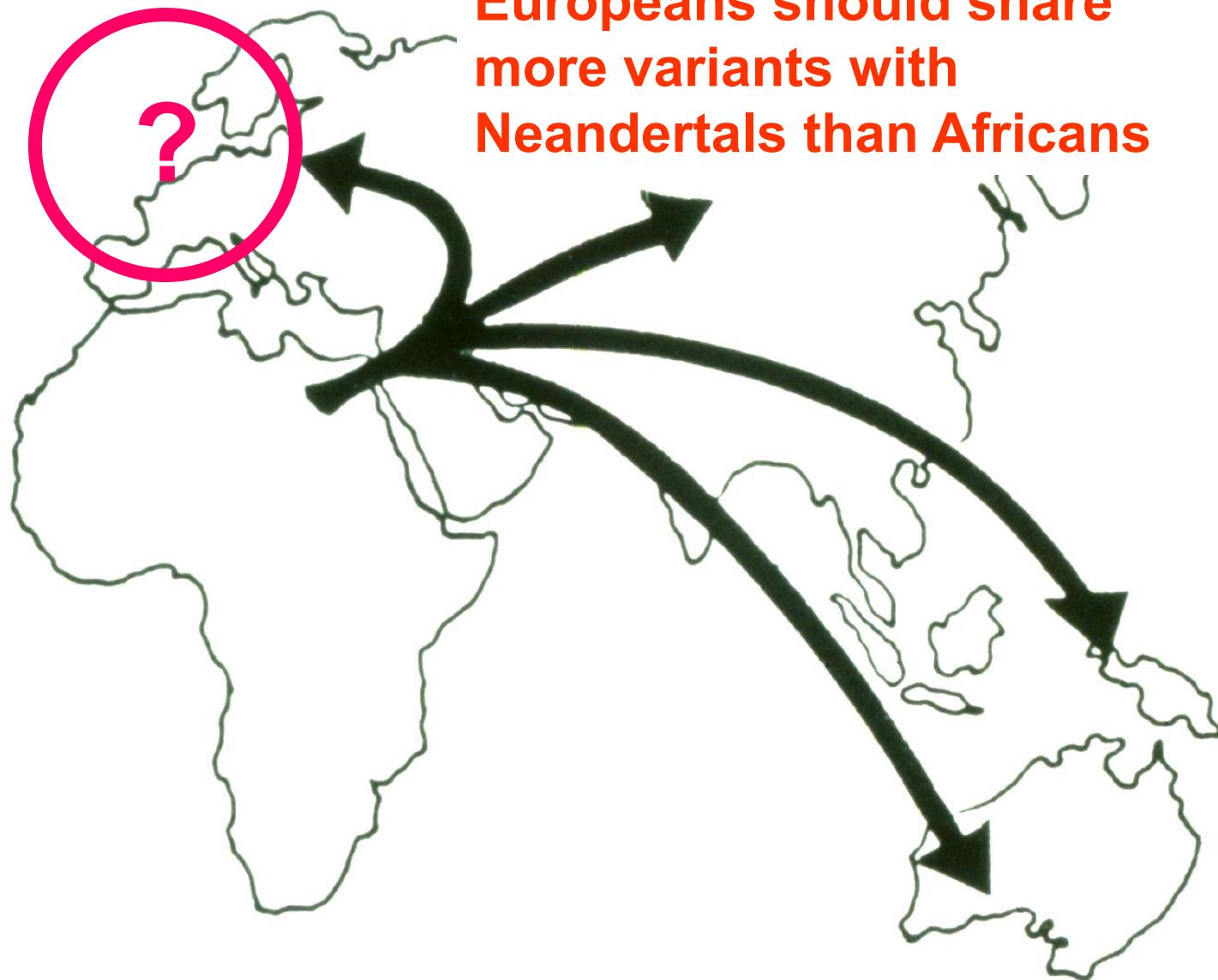


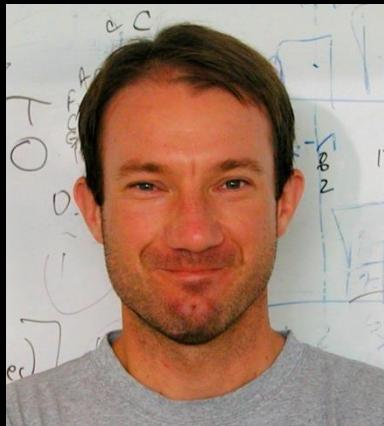
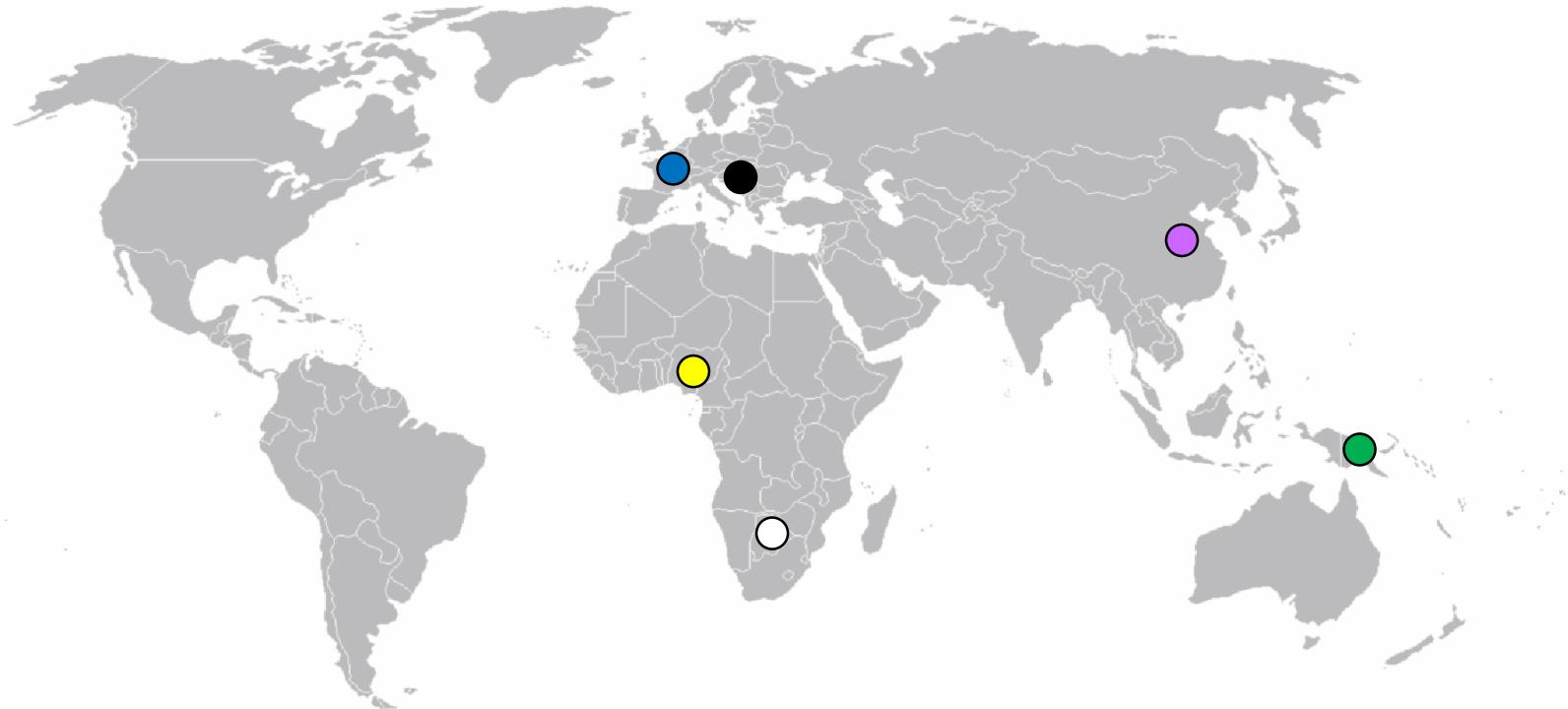
likely to be ancestral  
to genome

positive selection in early humans

provides evidence for gene flow from Neandertals to modern humans

**Expectation:**  
**Europeans should share**  
**more variants with**  
**Neandertals than Africans**





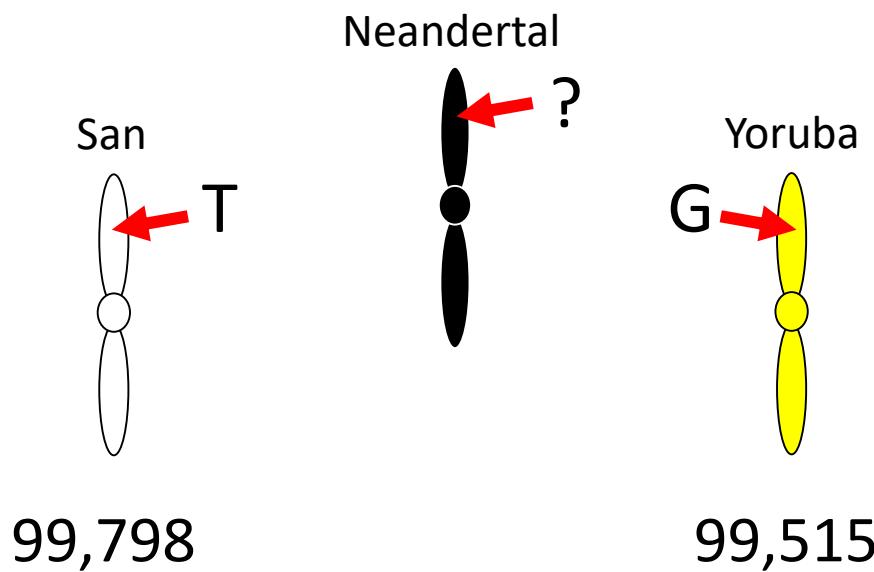
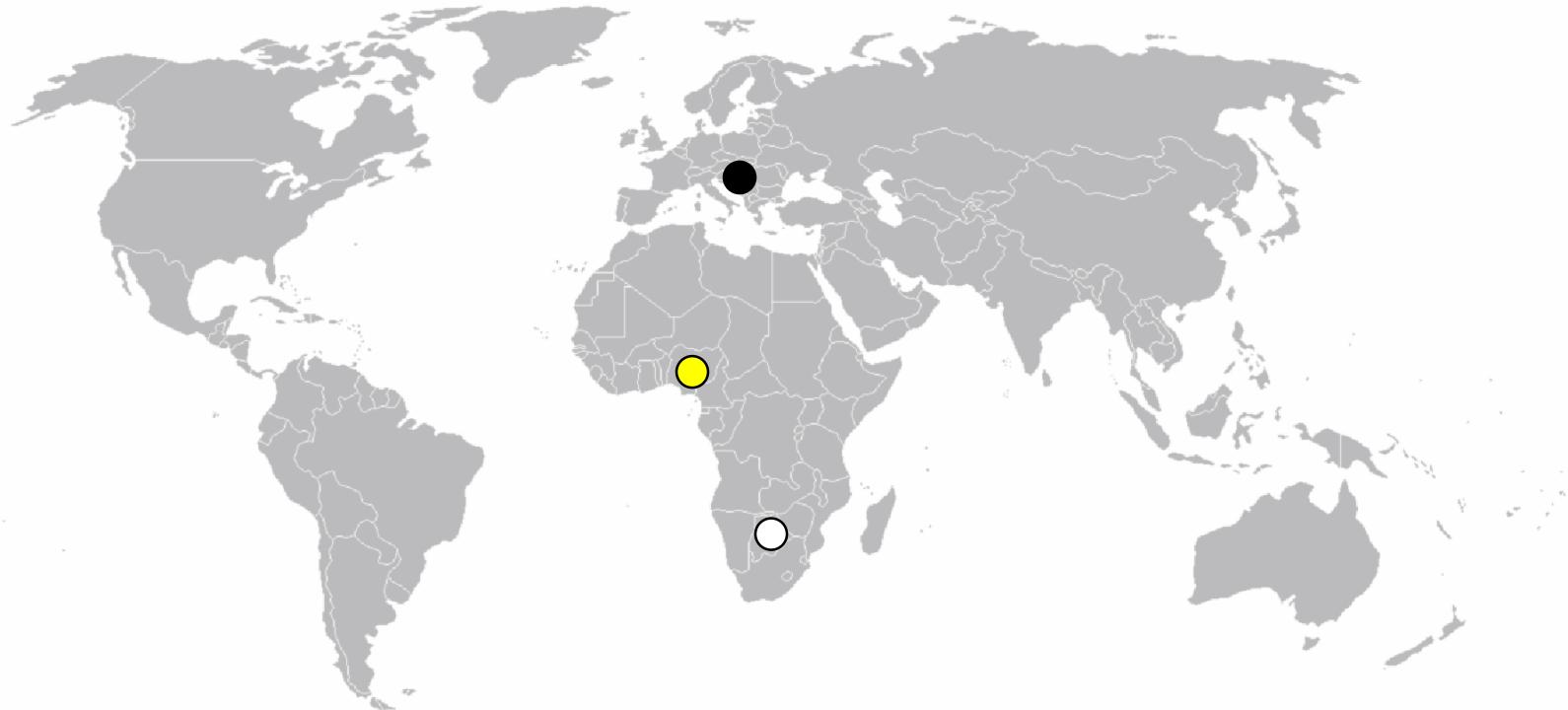
**Ed Green**

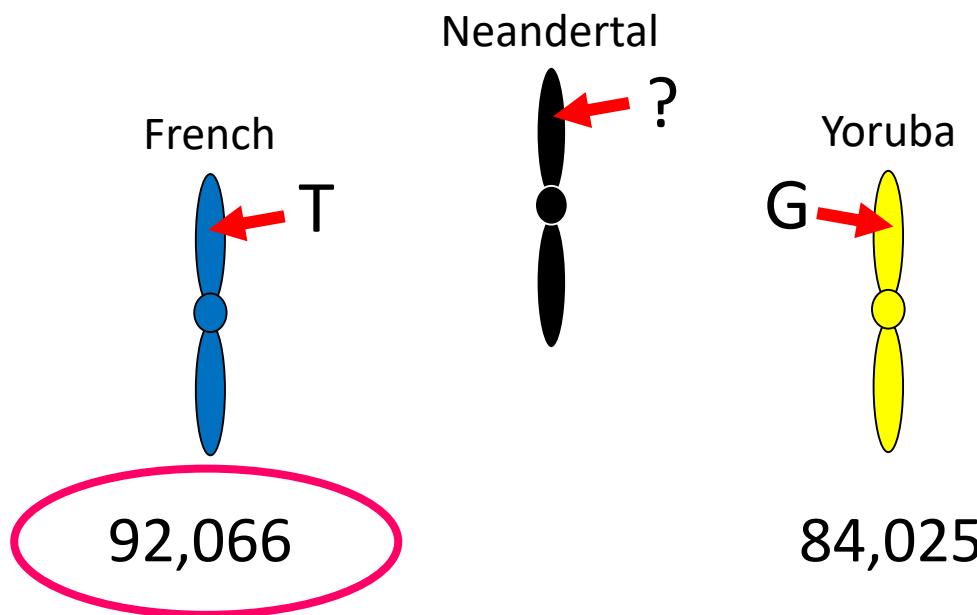
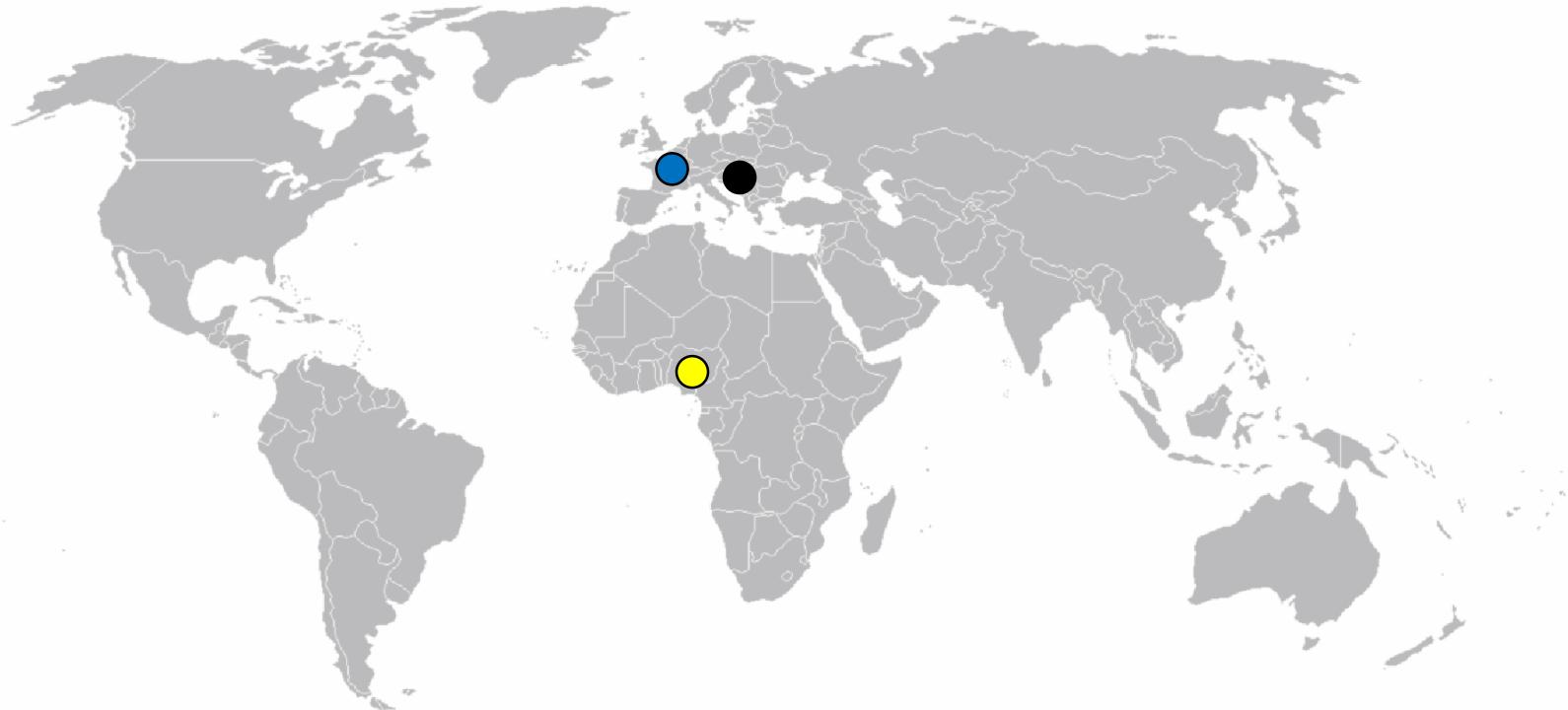


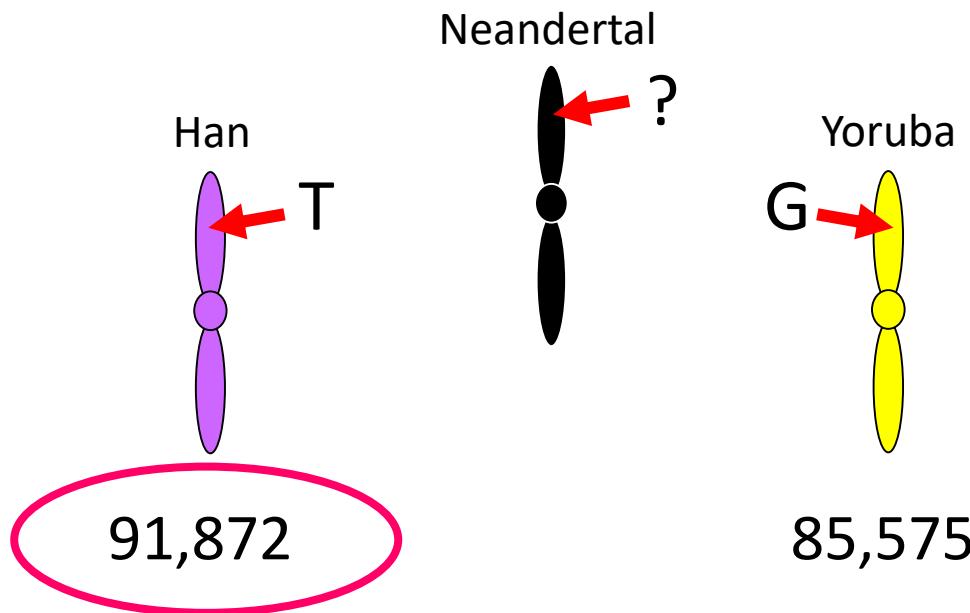
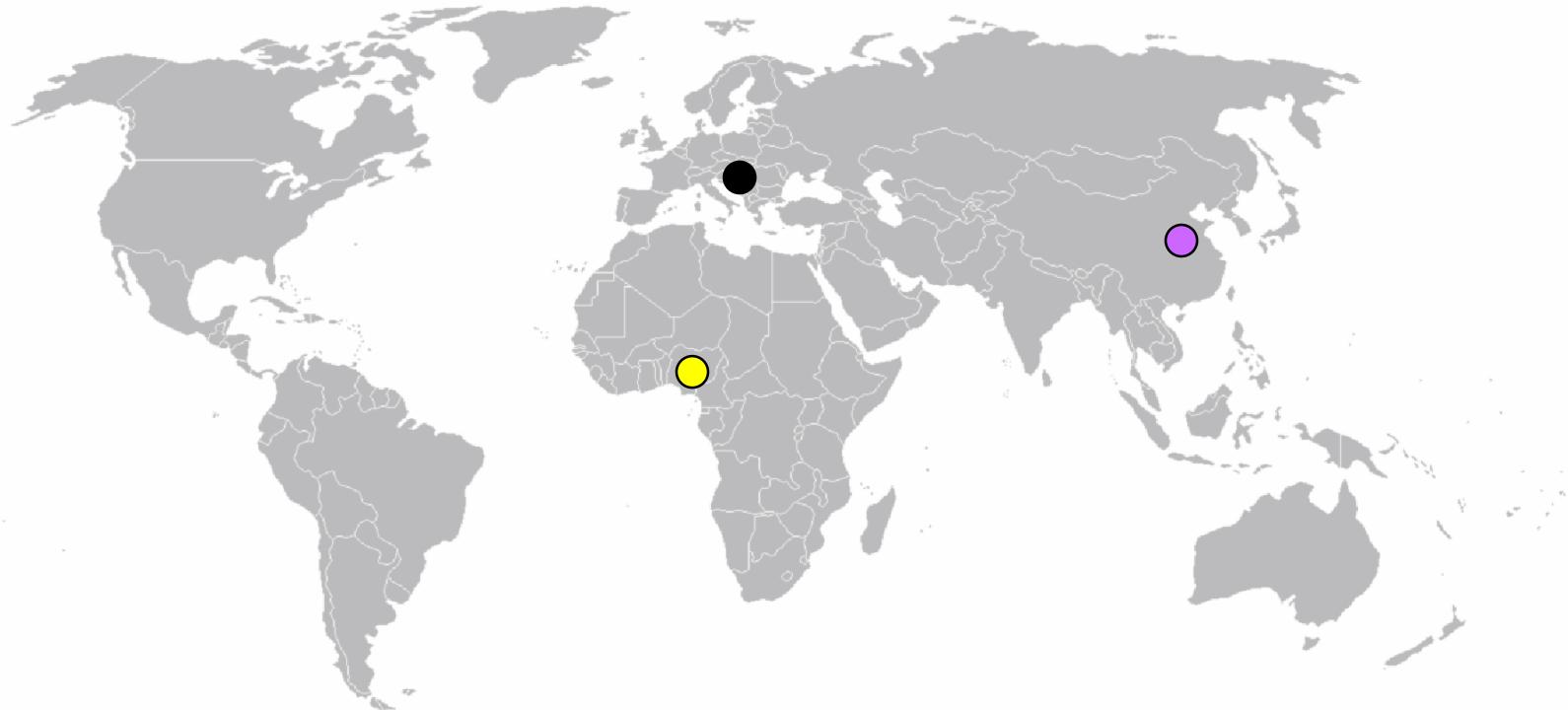
**David Reich**  
**Broad Institute**

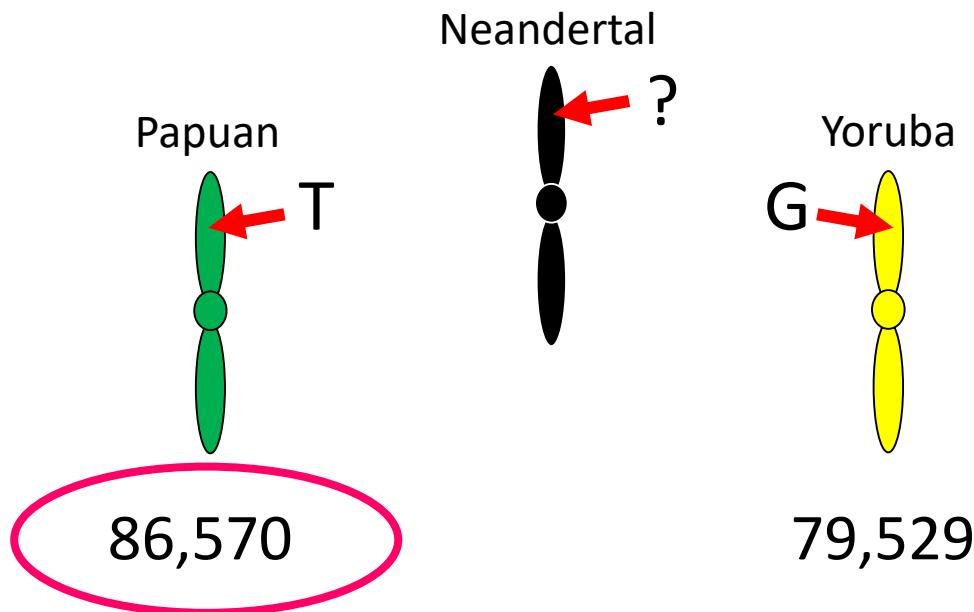
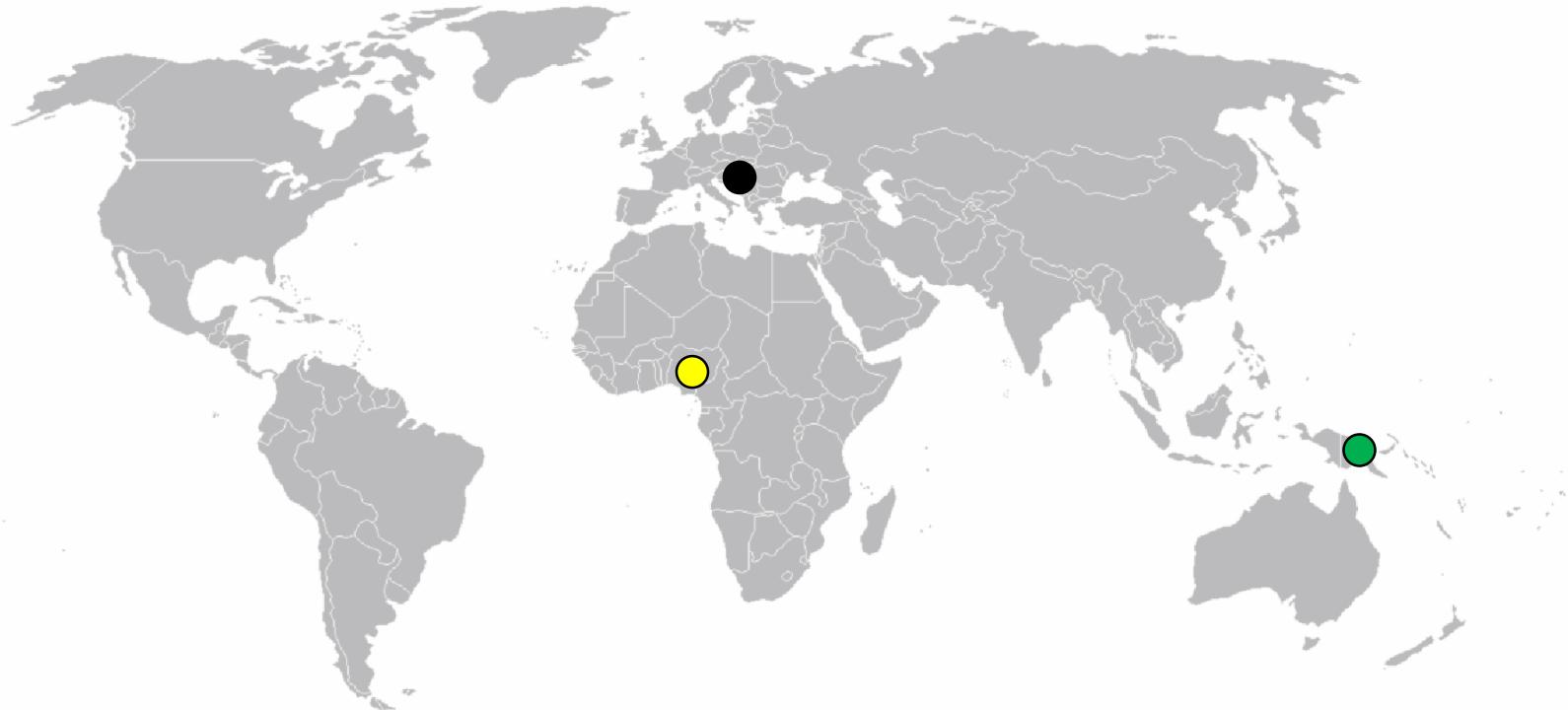


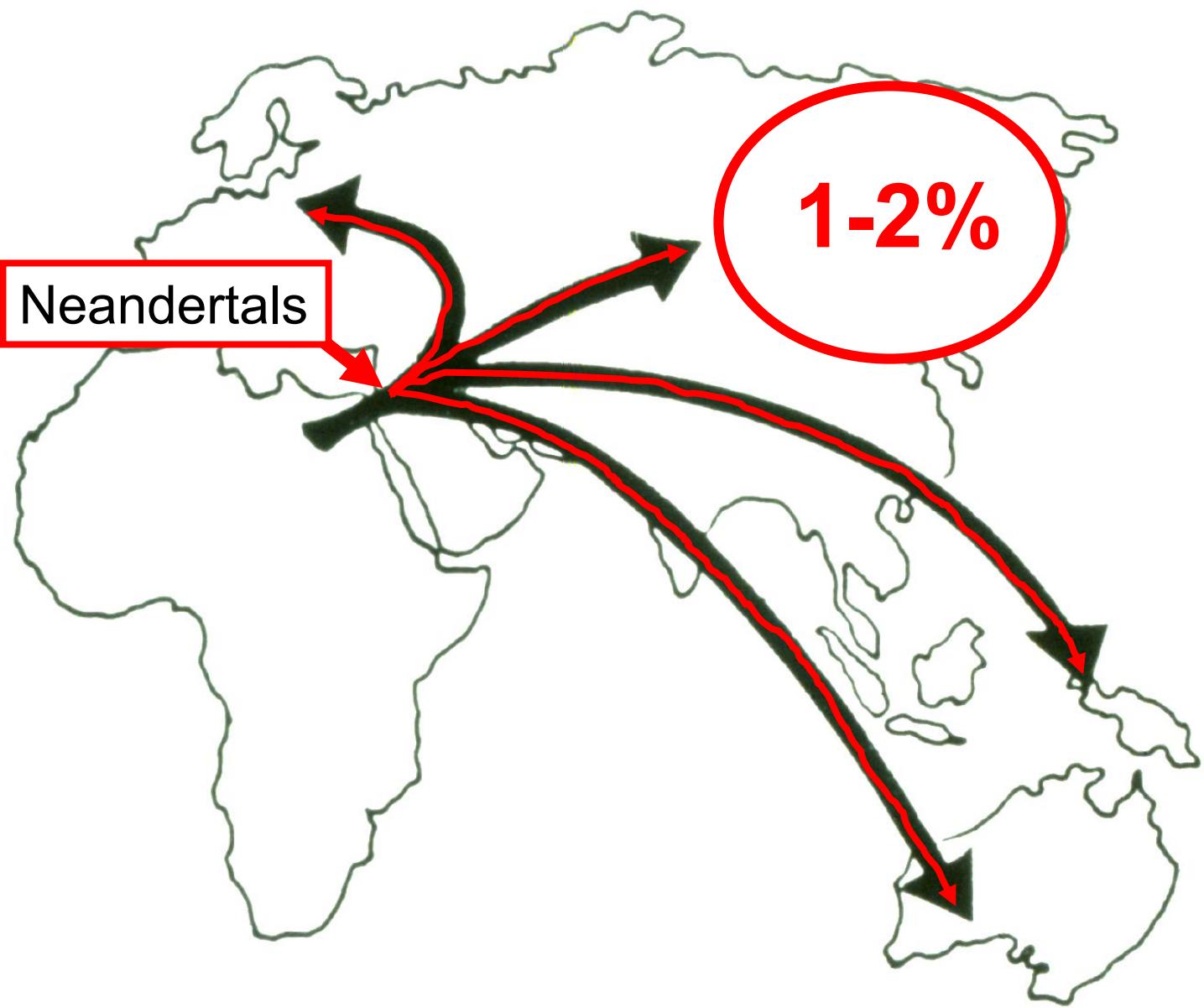
**Monty Slatkin**  
**UC Berkeley**



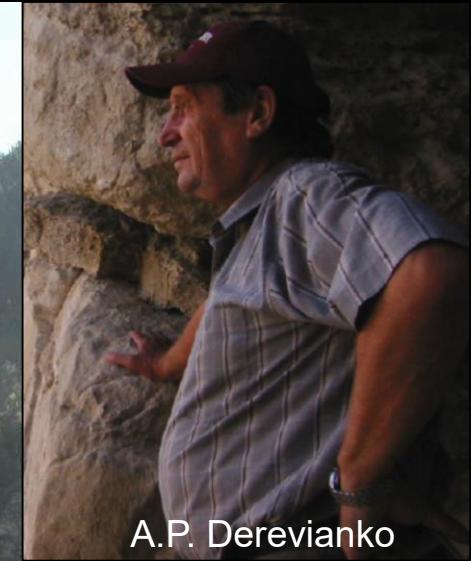








# Good Neandertal Genomes!



Denisova Cave, Altai Mountains, Russia

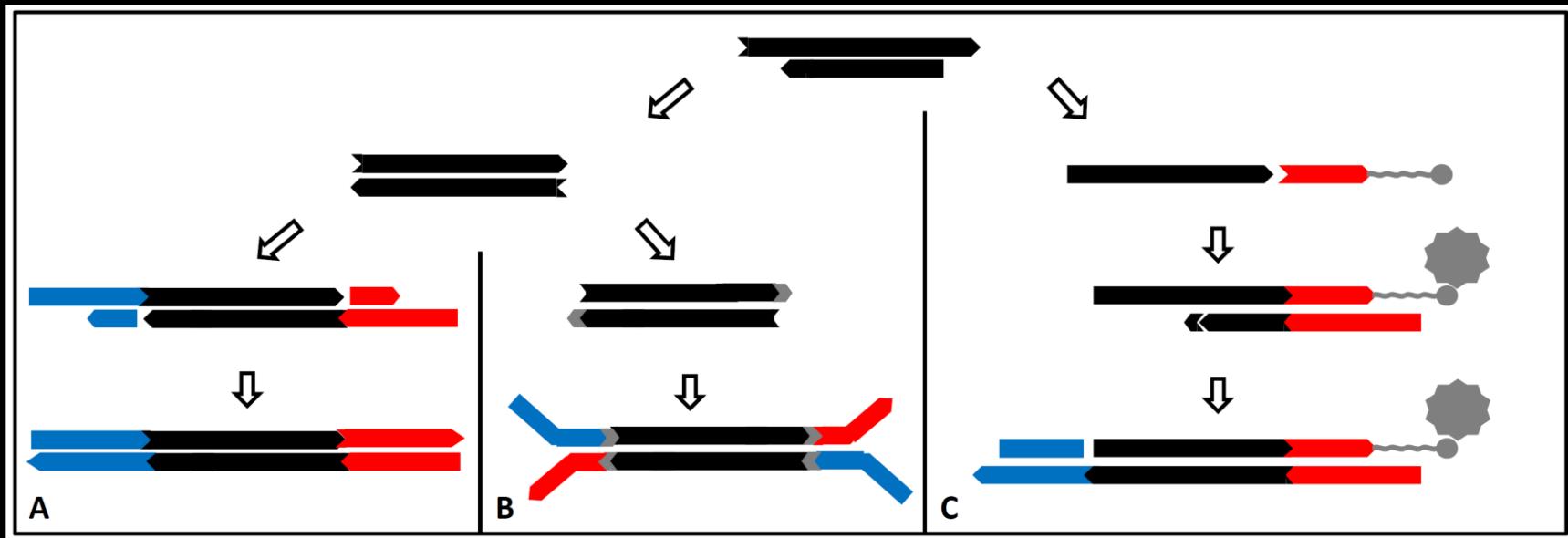


0                  1 cm

From M.B. Mednikova (2011)

## Double-stranded methods

## Single-stranded method



Old

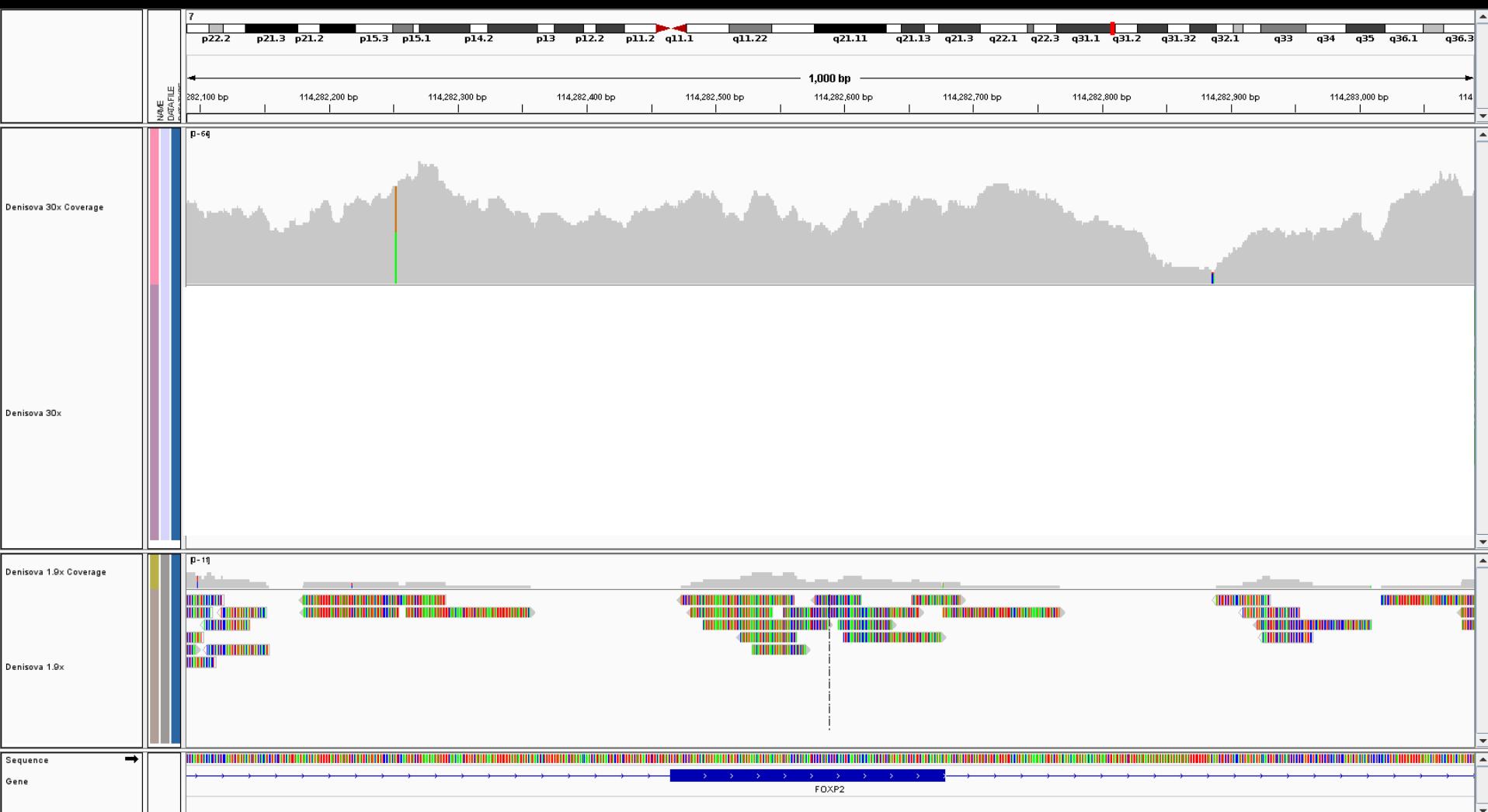
New



[www.agbt.org/speaker/matthias-meyer/](http://www.agbt.org/speaker/matthias-meyer/)

Matthias Meyer

Meyer et al., Science, 2012.



# High-quality Archaic Genomes

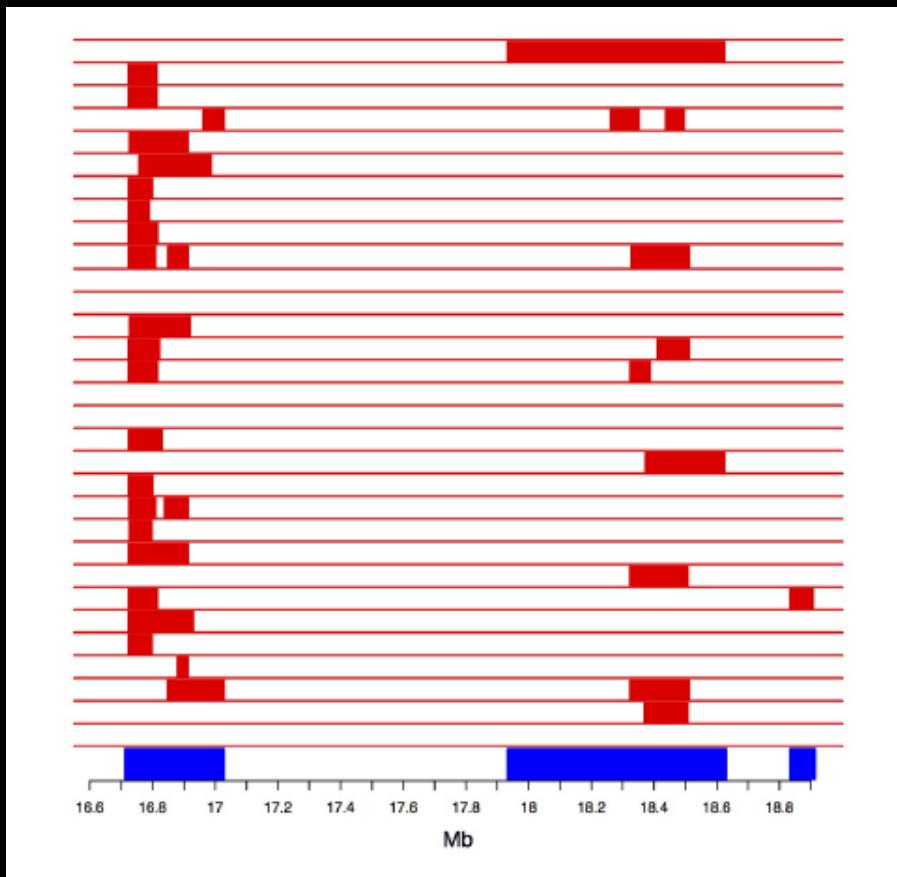
~50,000-120,000 years old



# Neandertal contributions

## Chr. 9

~1-2%  
per person



~40% (?)

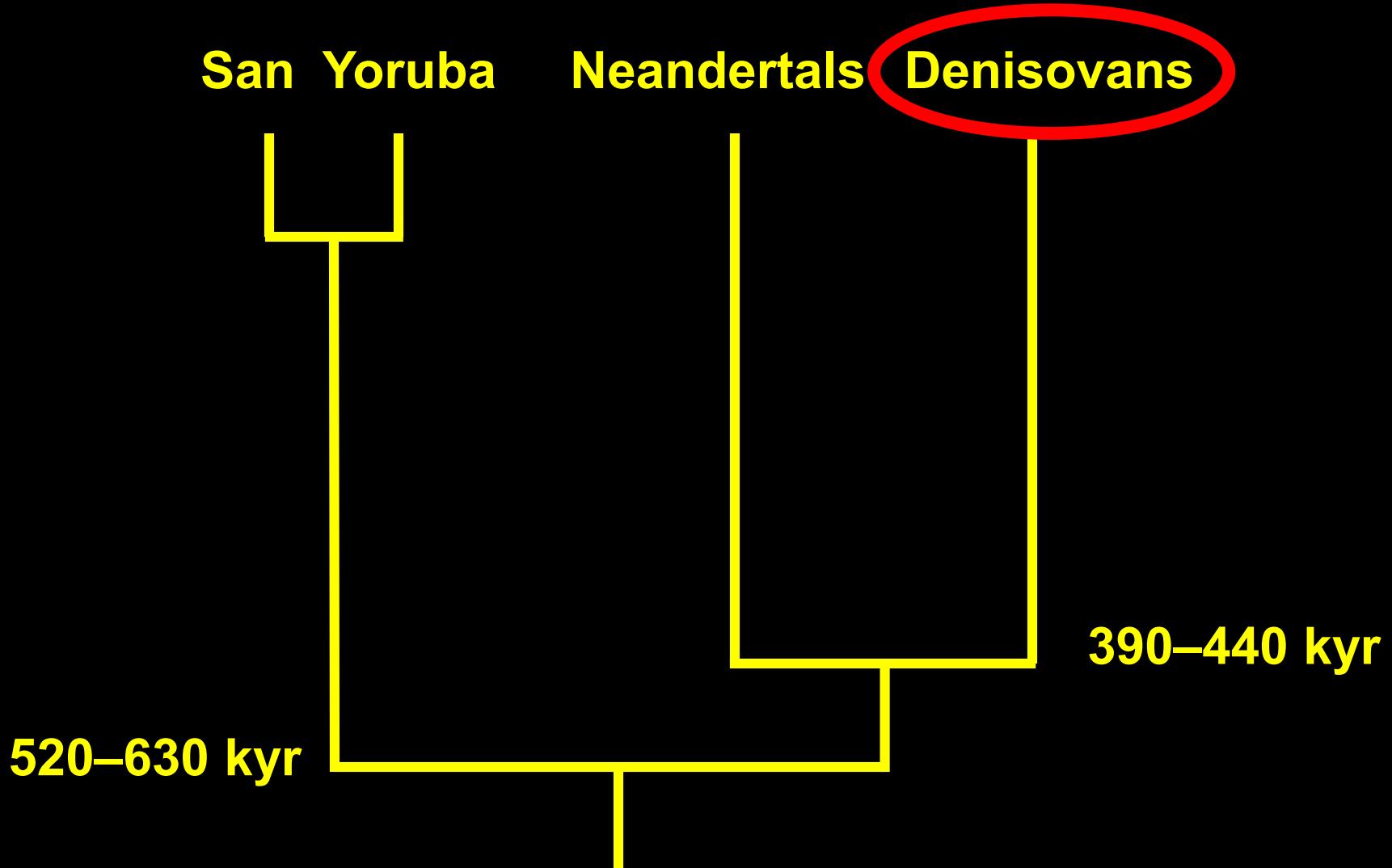
Sankaramanan *et al.*, Nature 2014.



Denisova Cave

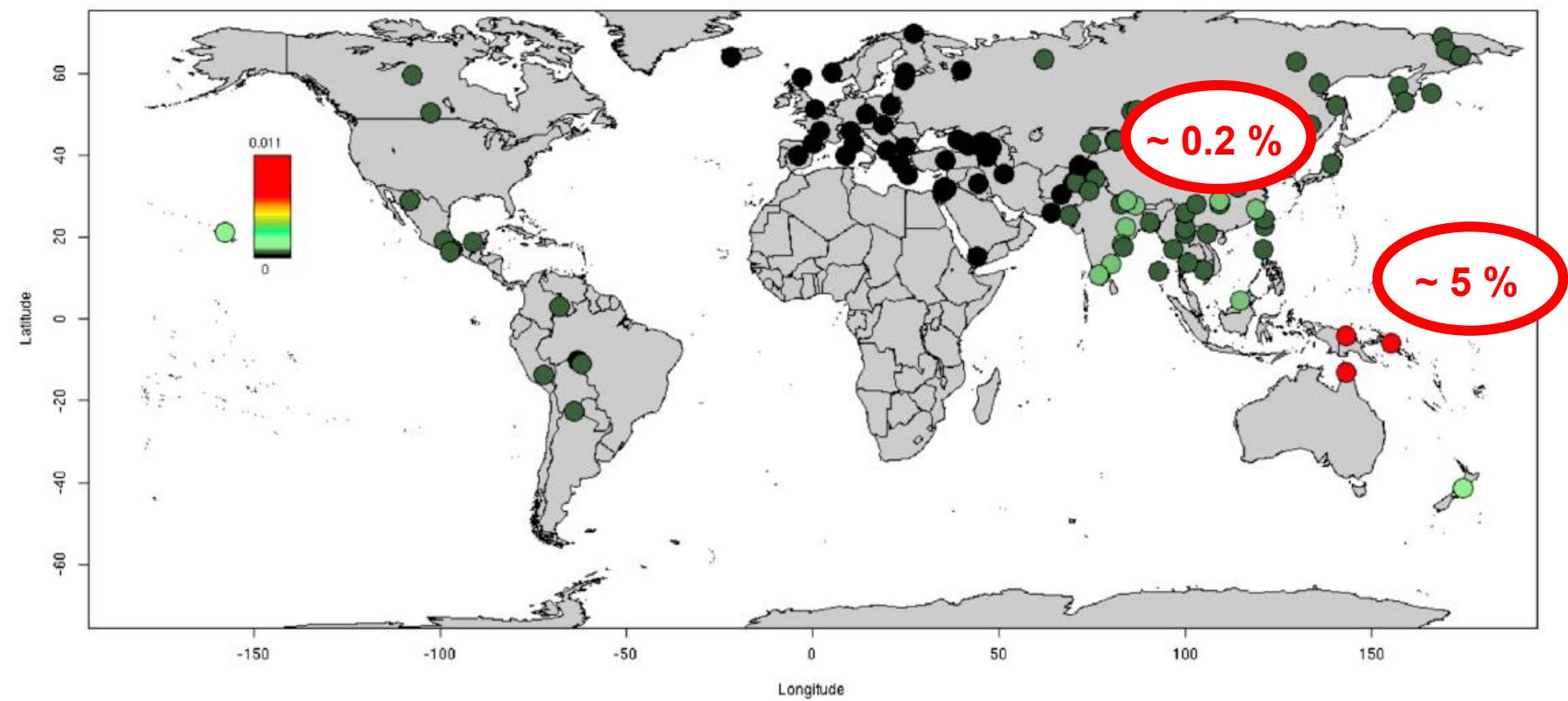


**30X genome**



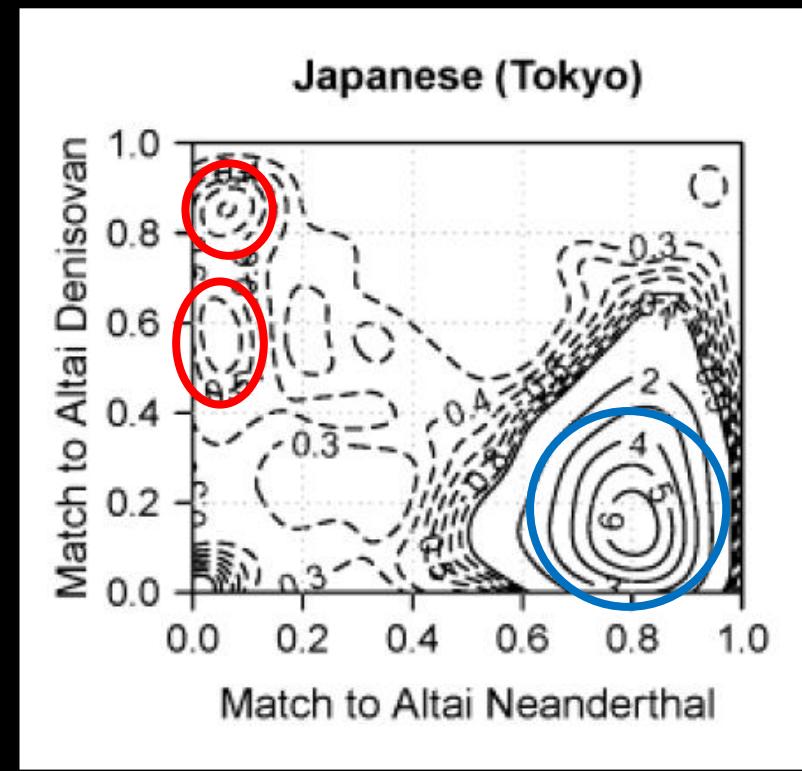
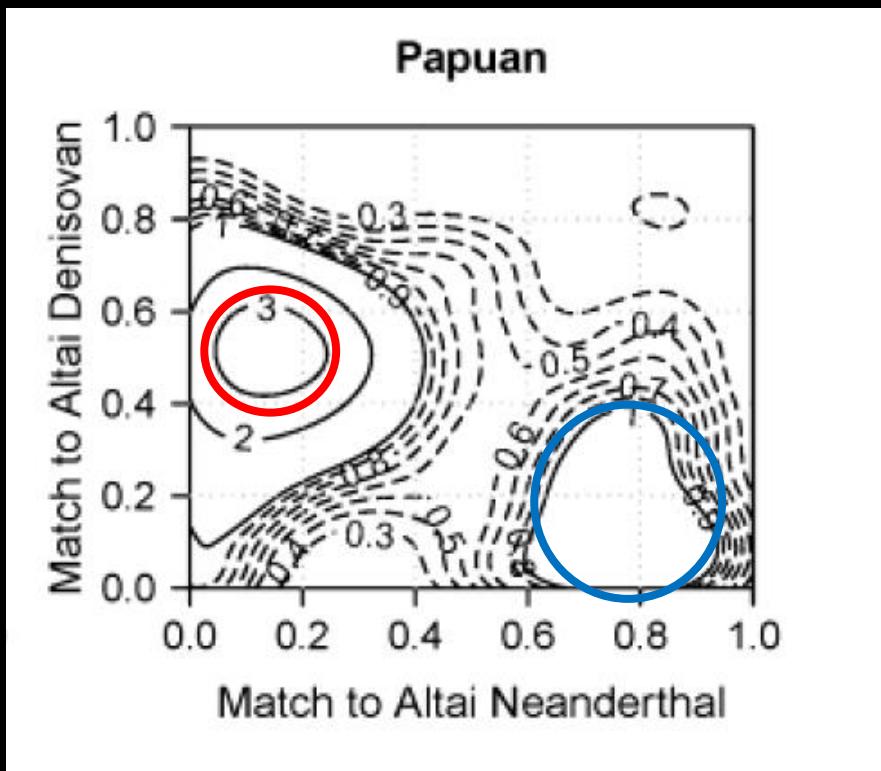
( $\mu=0.5 \times 10^{-9}/\text{bp/year}$ )

**“Denisovans”**

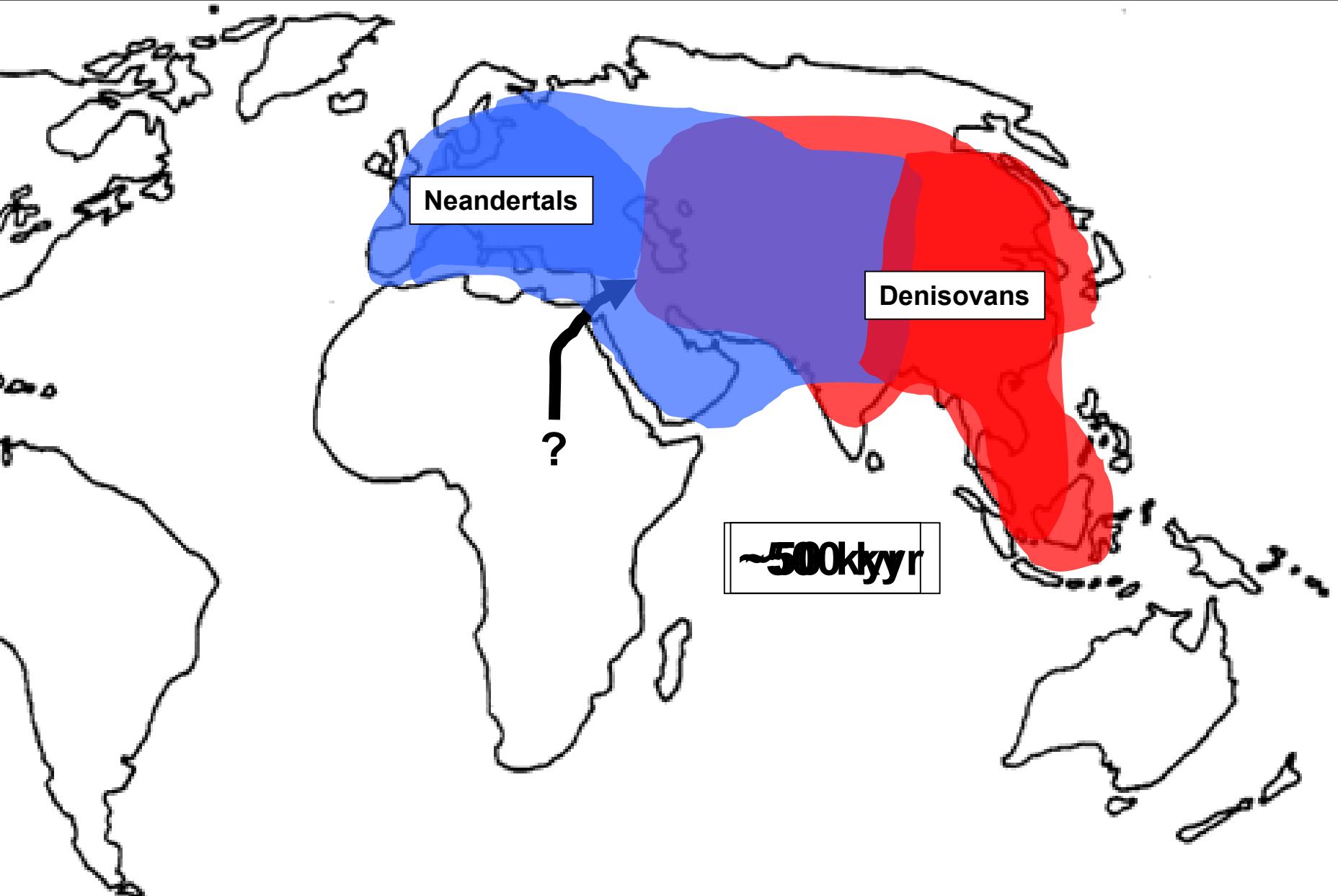


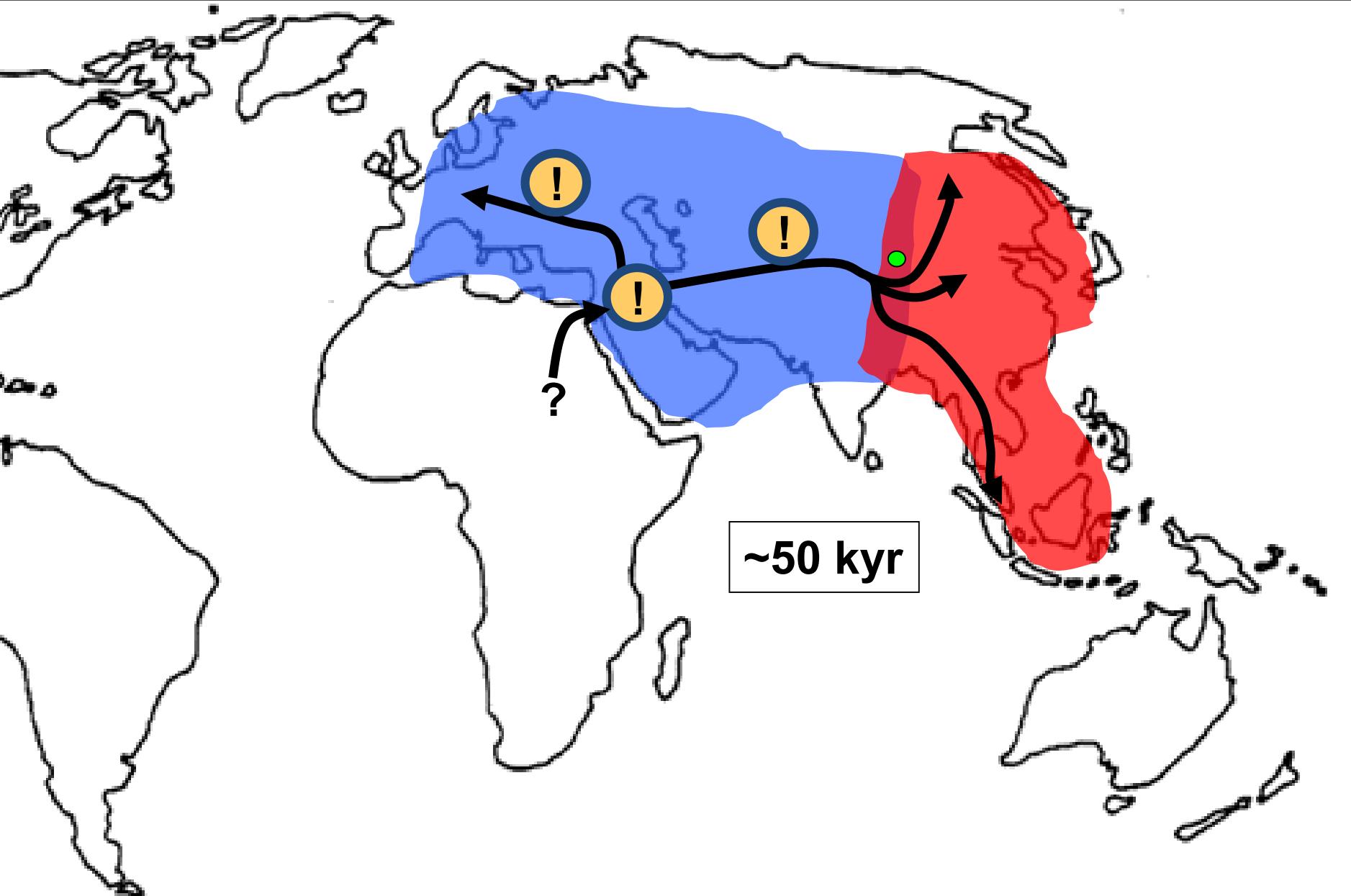
Sankaramanan *et al.*, Curr. Biol. 2016.

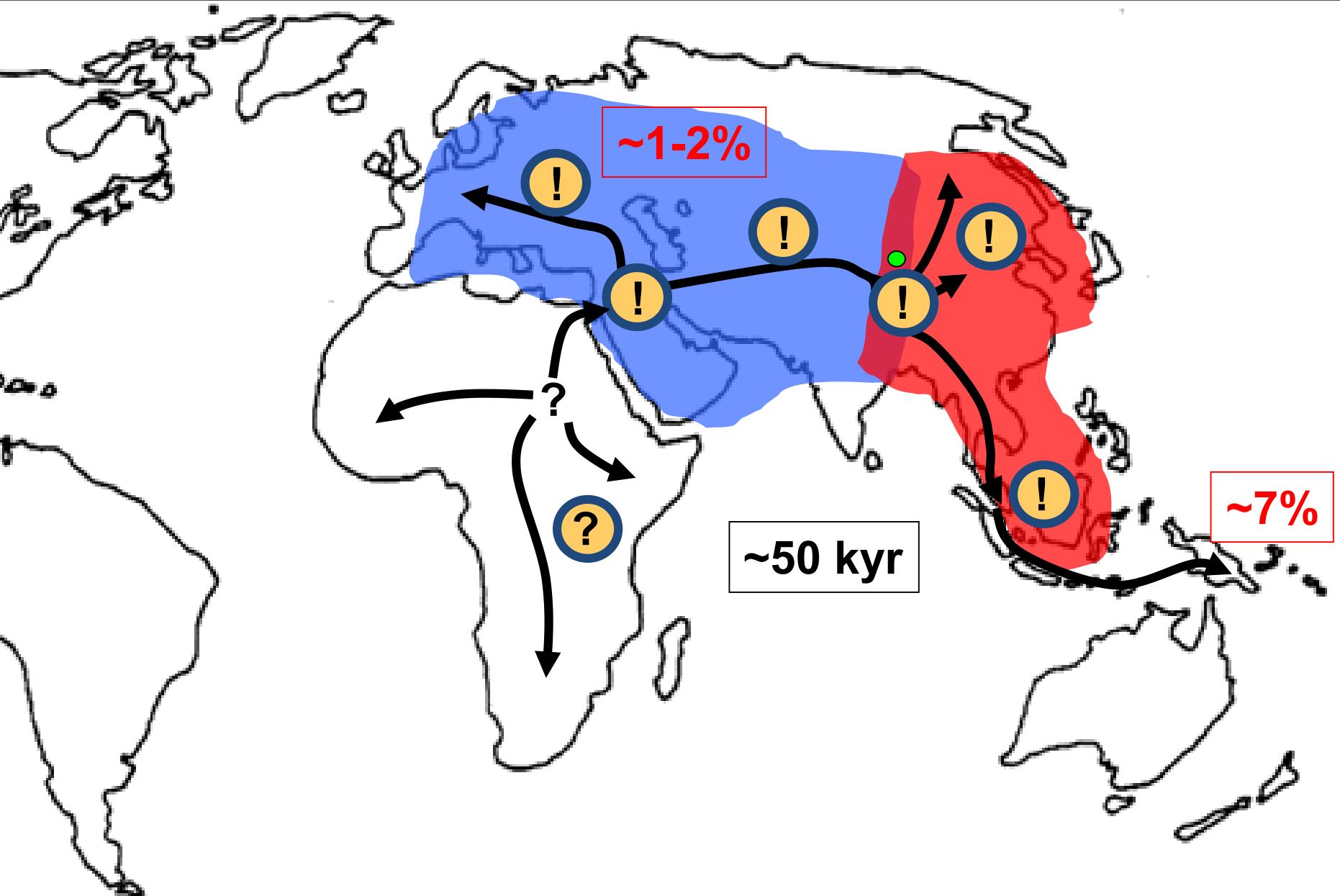
# Two Denisovan populations contributed to East Asians!



Browning et al., Cell 2018.









Hajdinjak et al., Nature, 2021.

# Oase Cave, Romania

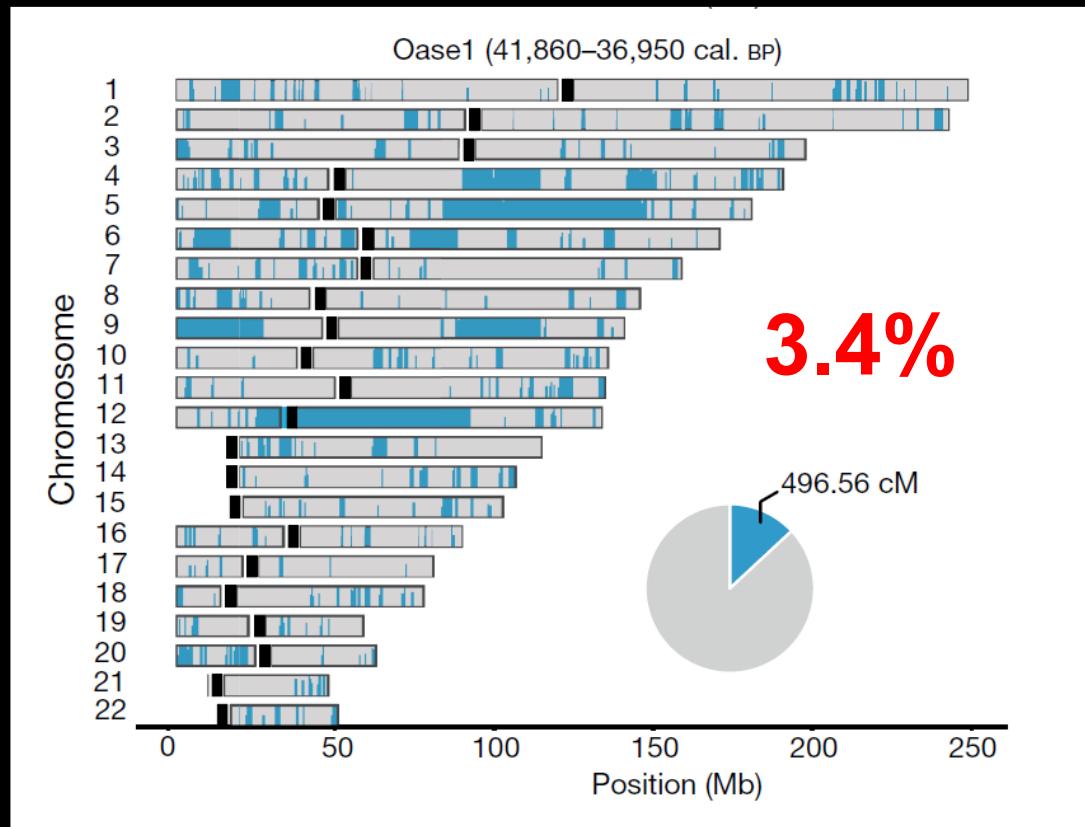


From Milota ř. et al., in: Trinkaus E., Constantin S. and Zilh o J. (Eds.), *Life and Death at the Pe era cu Oase*. Oxford University Press, New York, 2013.

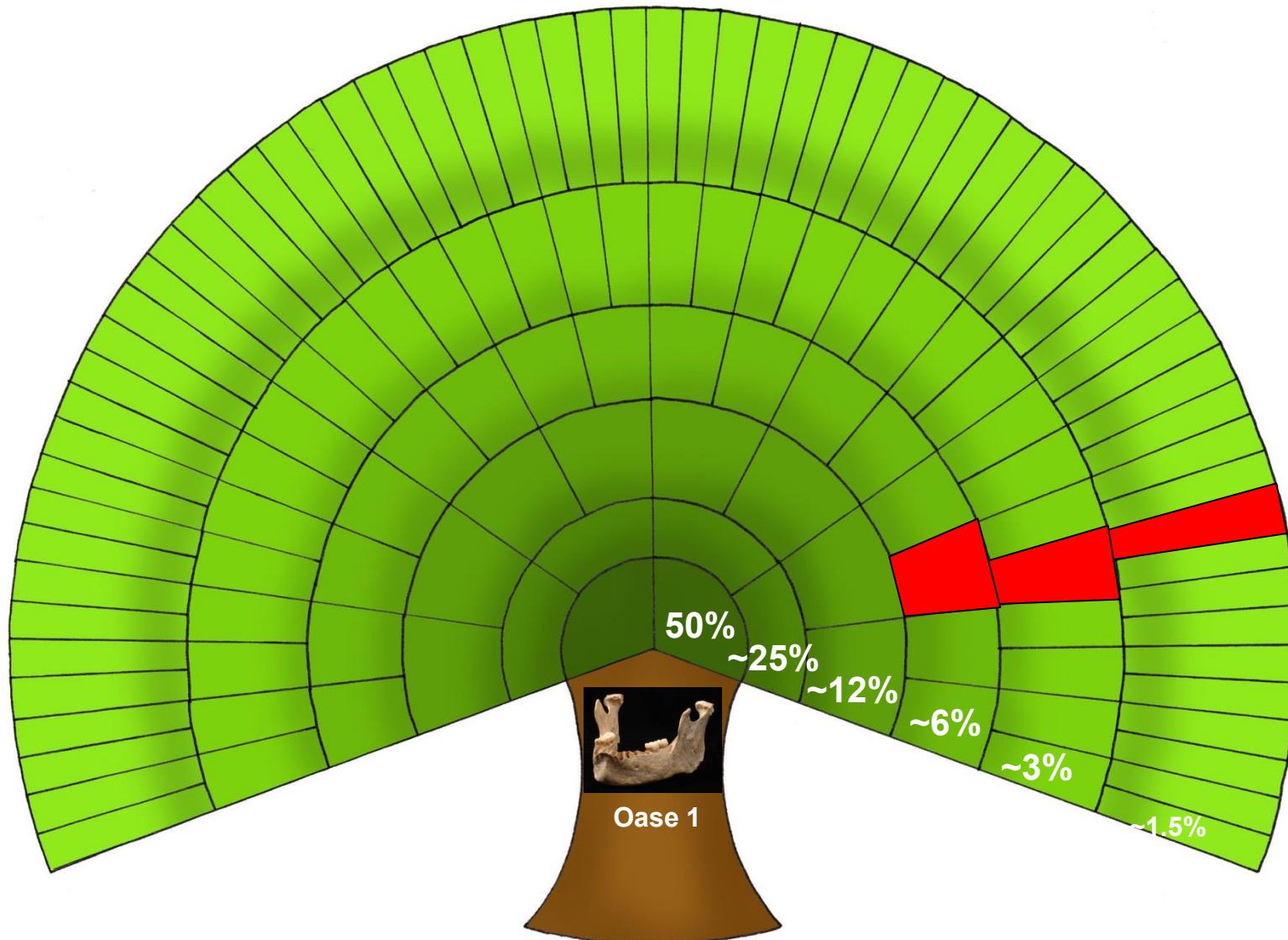
# Oase 1, Romania



~40,000 yrs



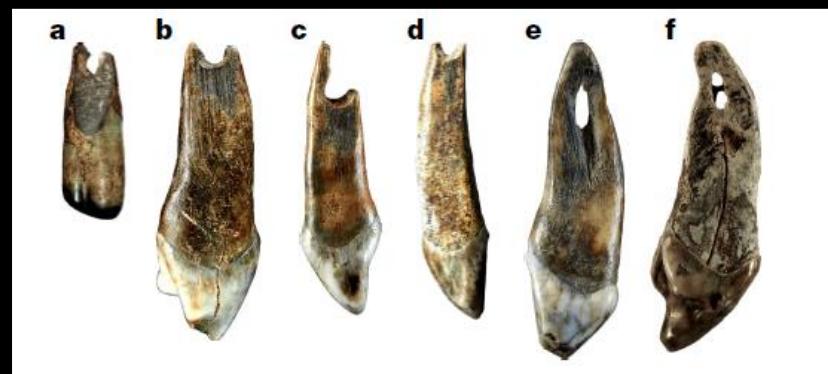
# My Family Tree





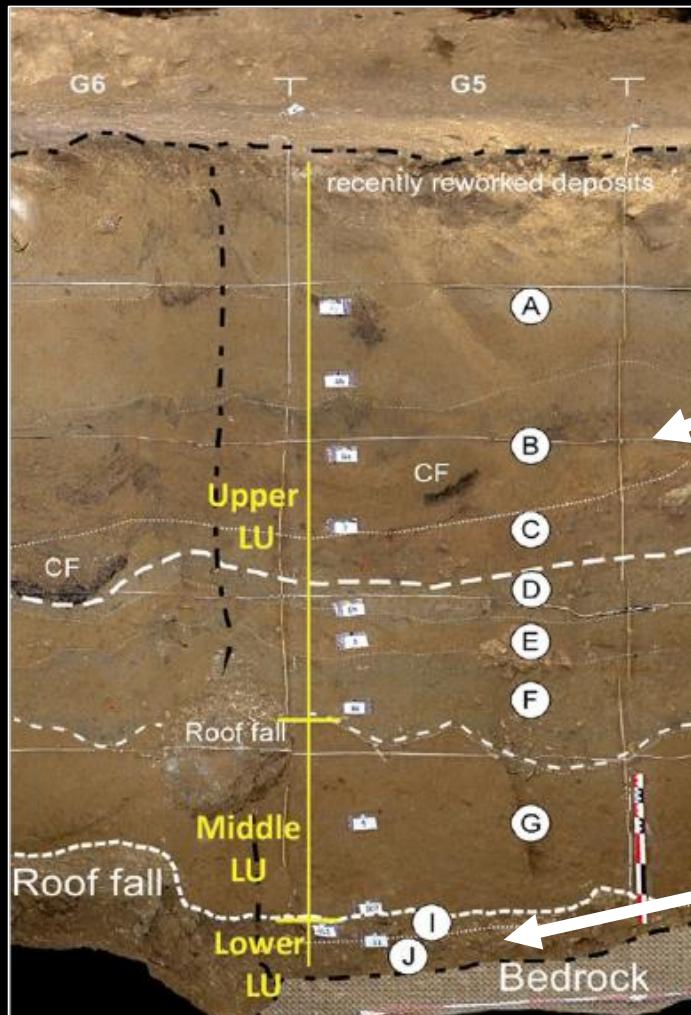
Hajdinjak et al., Nature, 2021.

# Batcho Kiro, Bulgaria



Hublin et al., Nature, 2020.

# Batcho Kiro



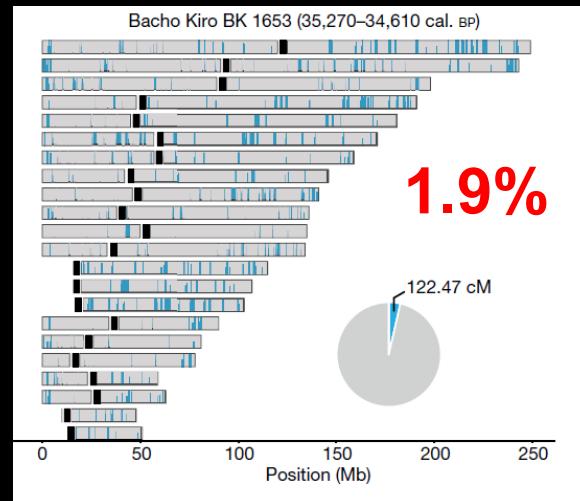
~35,000 BP



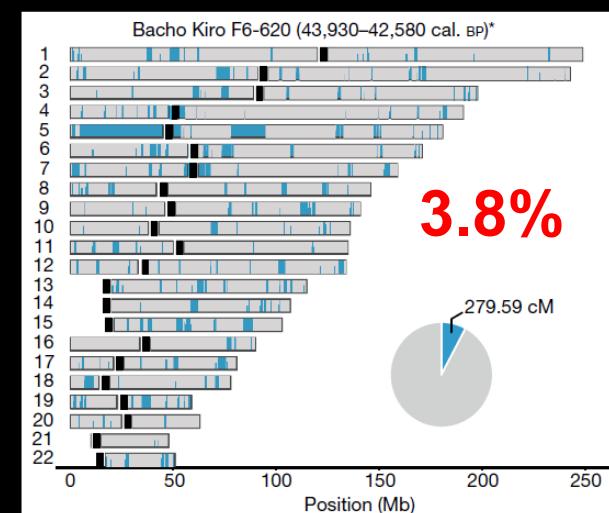
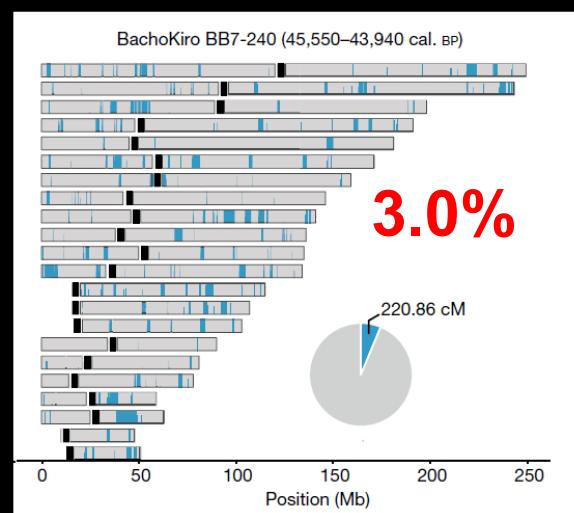
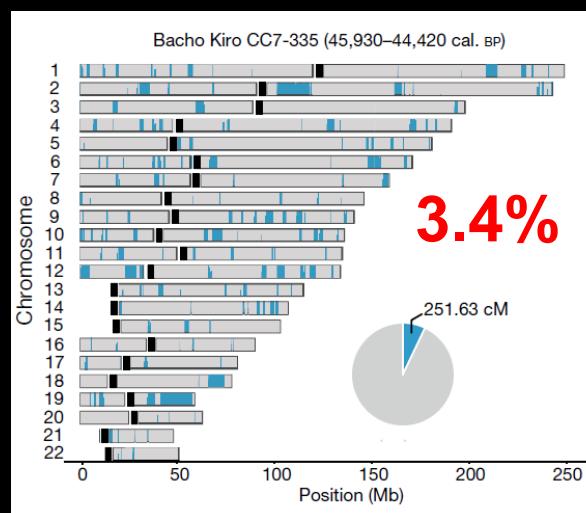
~45,000 BP

F6-620

**~35,000 BP**



**~45,000 BP**

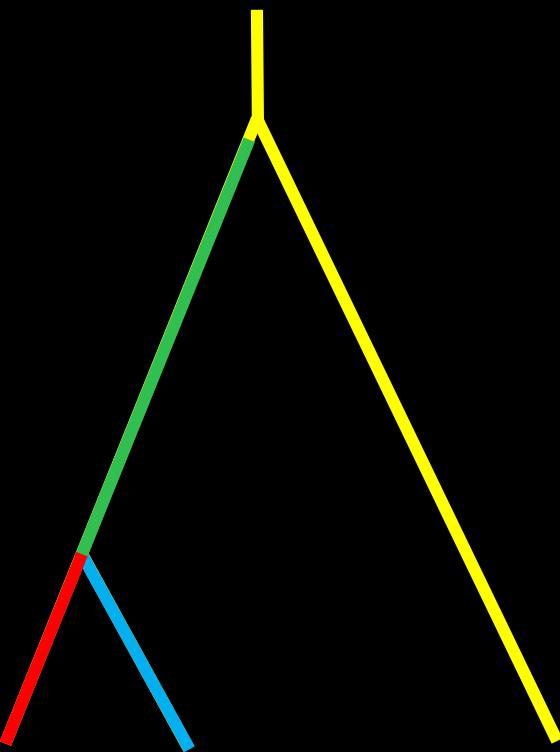


**~7 generations**

**~12 generations**

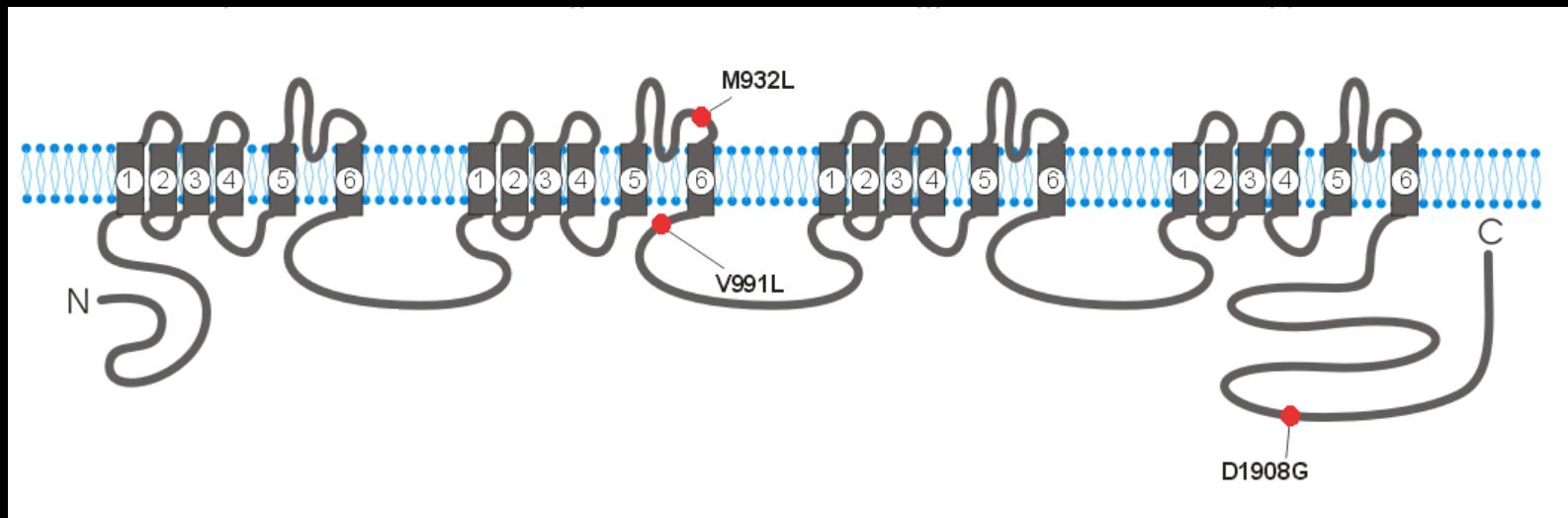
**~4 generations**

The first modern humans in Europe  
Neanderthals were probably (at least partially)  
assimilated into larger  
modern human populations

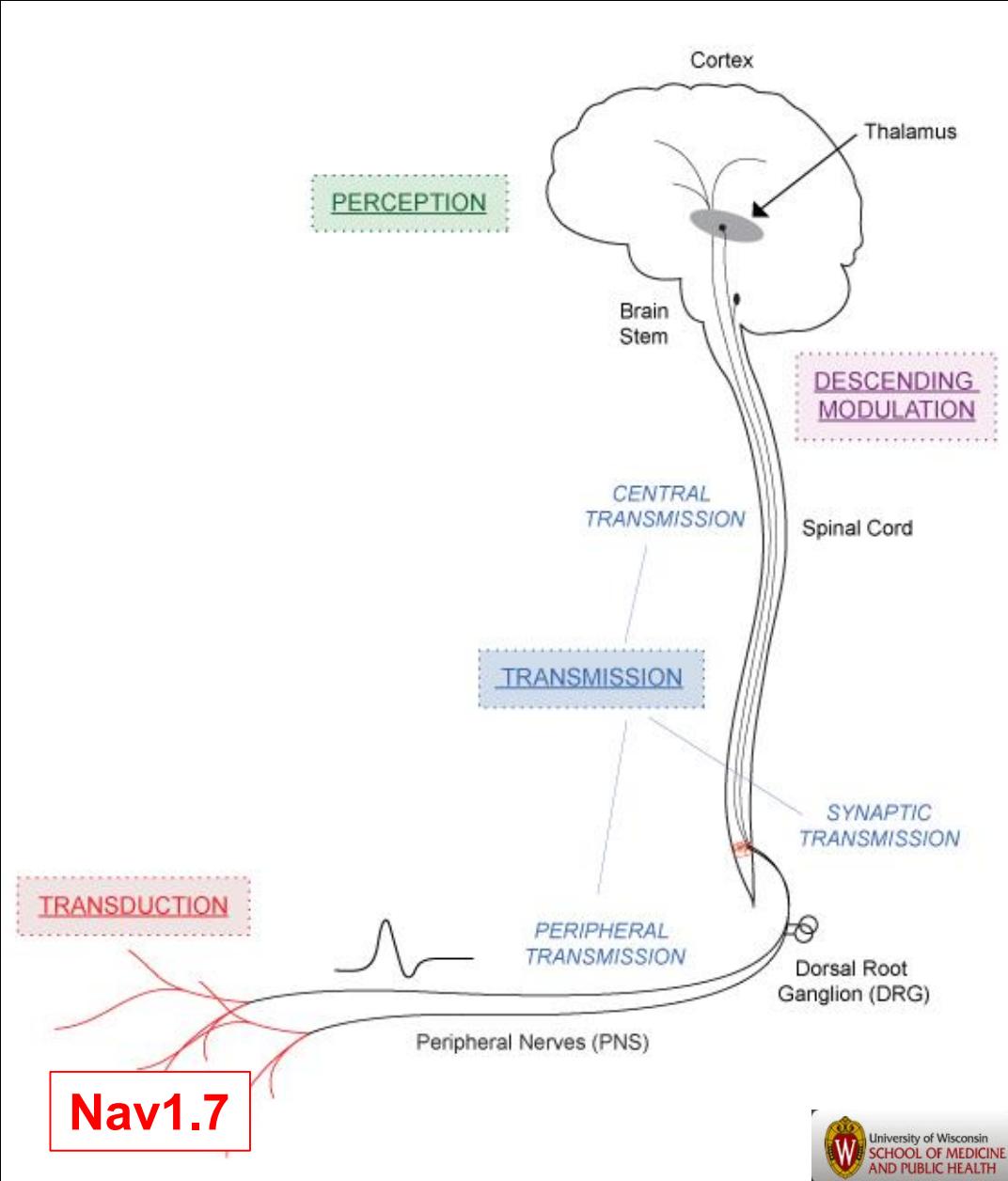


# Nav1.7

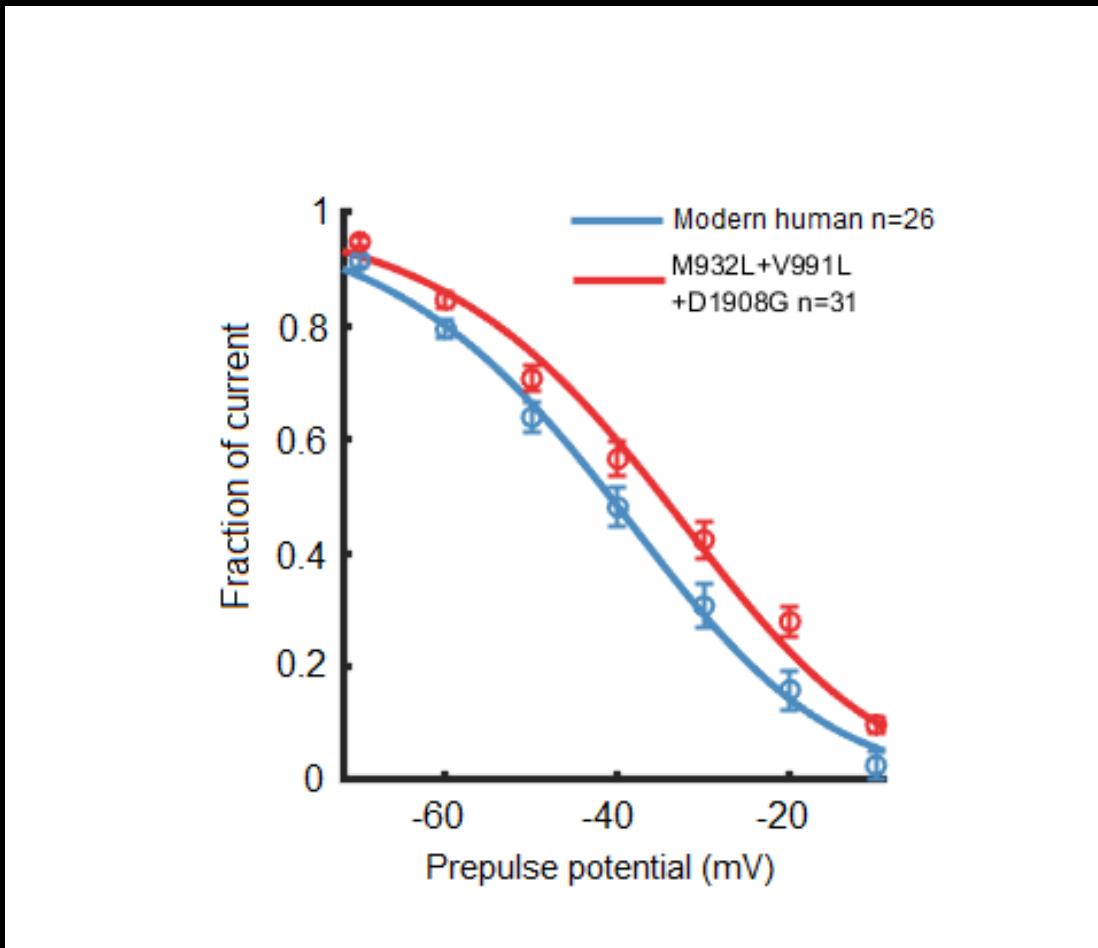
(*SCN9A*)



Hugo Zeberg, KI  
MPI-EVA

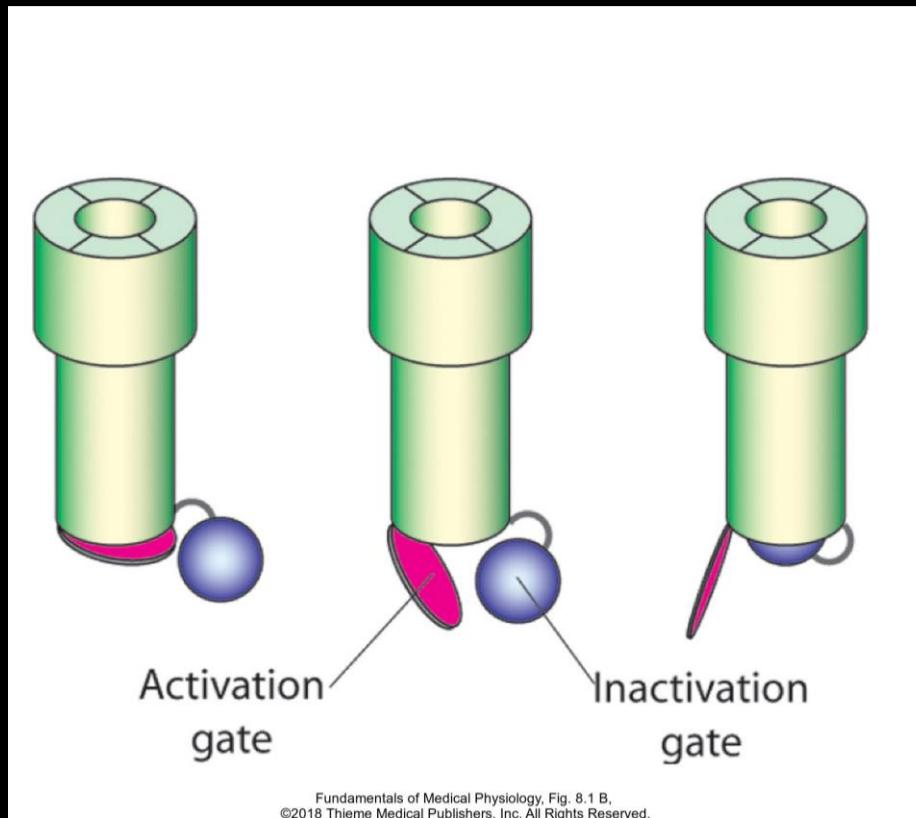


## Decreased inactivation (when co-expressed with Nav $\beta$ 3)

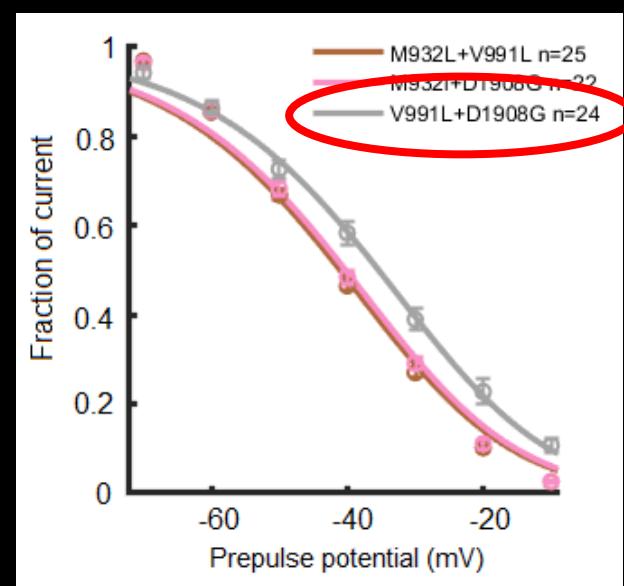
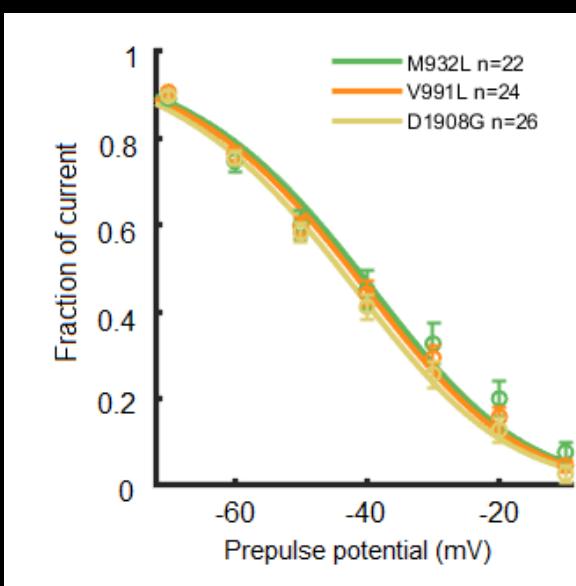
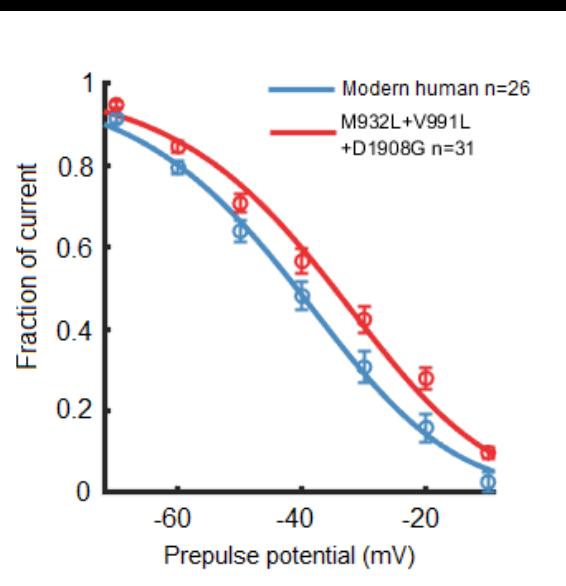


Zeberg et al., Curr. Biol. 2020.

## Decreased inactivation



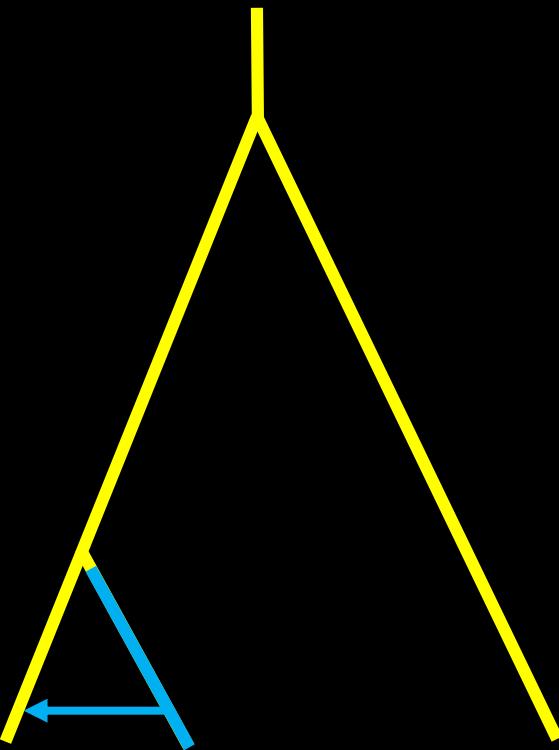
# Decreased inactivation (when co-expressed with Nav $\beta$ 3)



Zeberg et al., Curr. Biol. 2020.

# UK BioBank

362,944 individuals, 1,337 (0.4%) carry the Neandertal allele



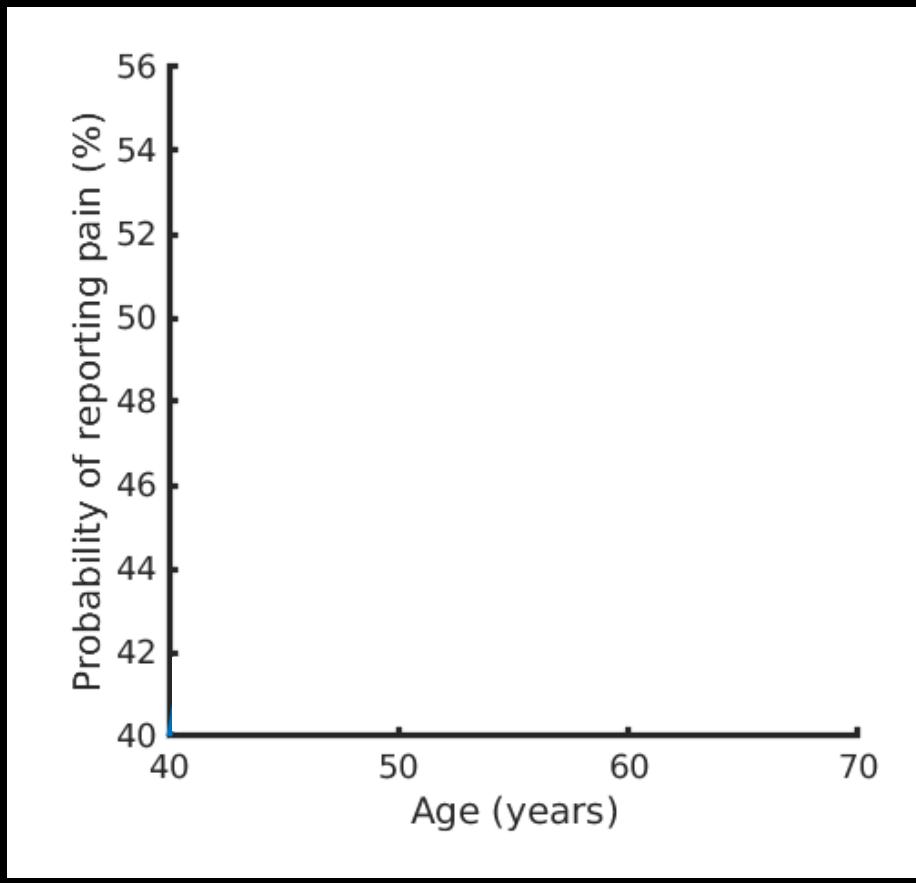
# UK BioBank

362,944 individuals, 1,337 (0.4%) carry the Neandertal allele

## Specific pain phenotypes

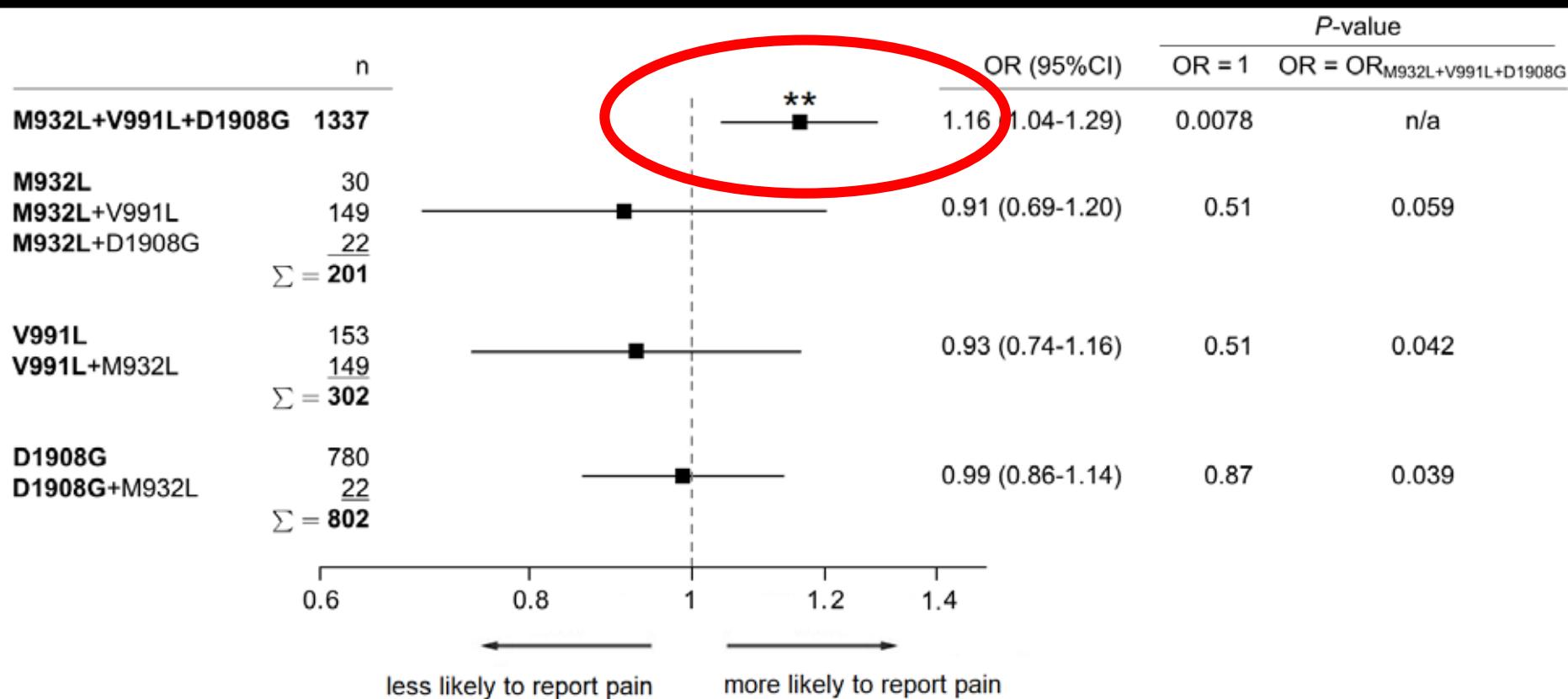
---

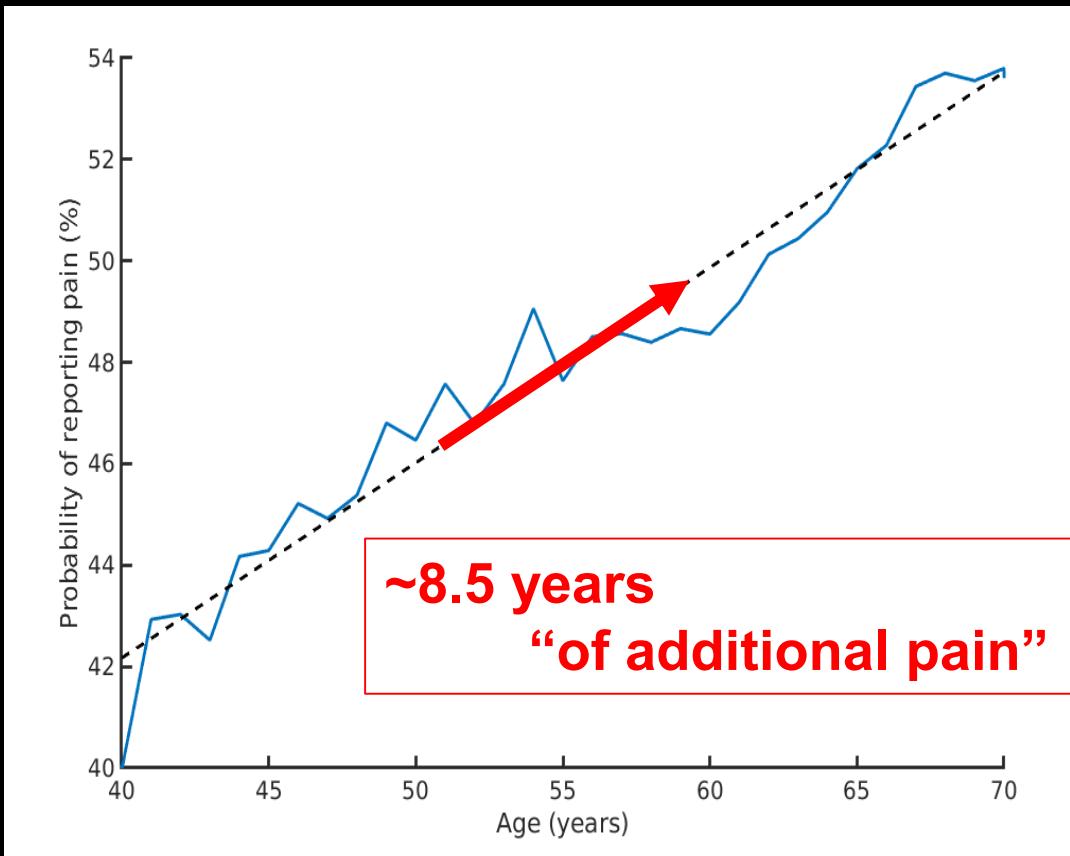
- Chest pain due to walking ceases when standing still
- Knee pain for 3 months
- Facial pains for 3 months
- Neck/shoulder pain for 3 months
- General pain for 3 months
- Chest pain or discomfort
- Back pain for 3 months
- Chest pain or discomfort when walking uphill or hurrying
- Chest pain or discomfort walking normally
- Leg pain when walking normally
- Leg pain on walking
- Stomach/abdominal pain for 3 months
- Leg pain when standing still or sitting
- Hip pain for 3 months
- Chest pain felt outside physical activity
- Leg pain when walking uphill or hurrying
- Leg pain in calf/calves
- Leg pain when walking ever disappears while walking
- Chest pain felt during physical activity



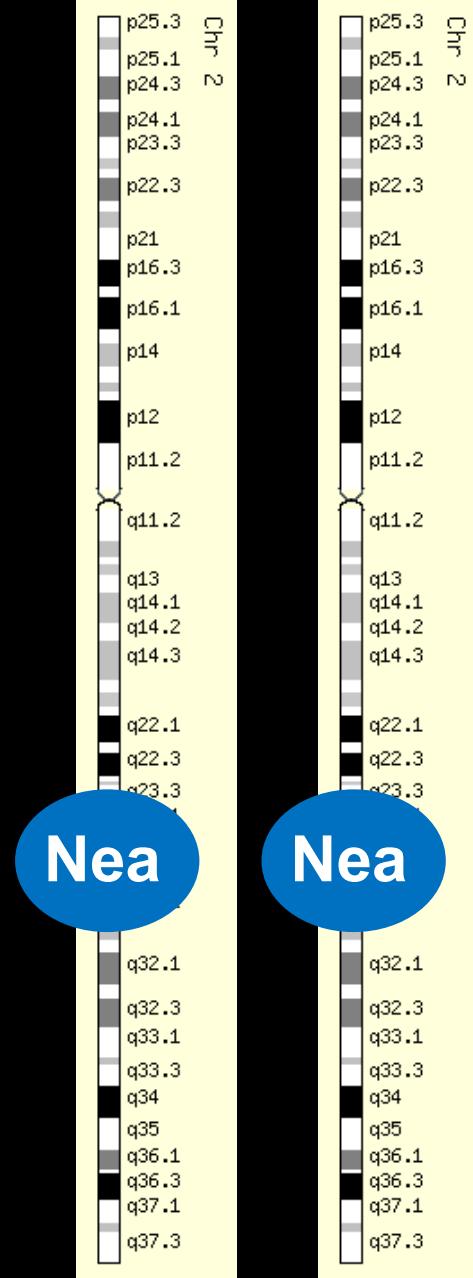
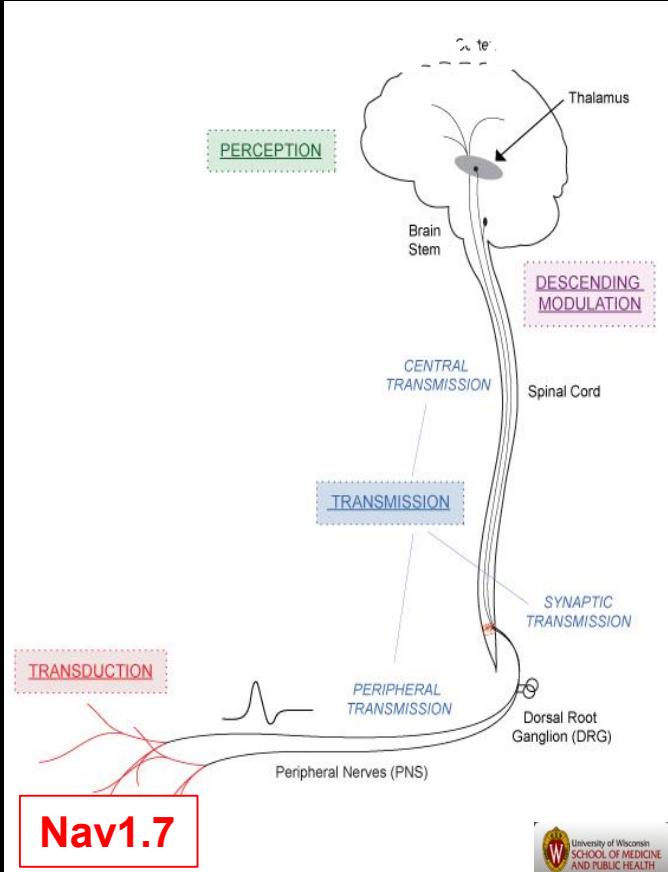
# UK BioBank

362,944 individuals, 1,337 (0.4%) carry the Neandertal allele





Zeberg *et al.*, Curr. Biol. 2020.

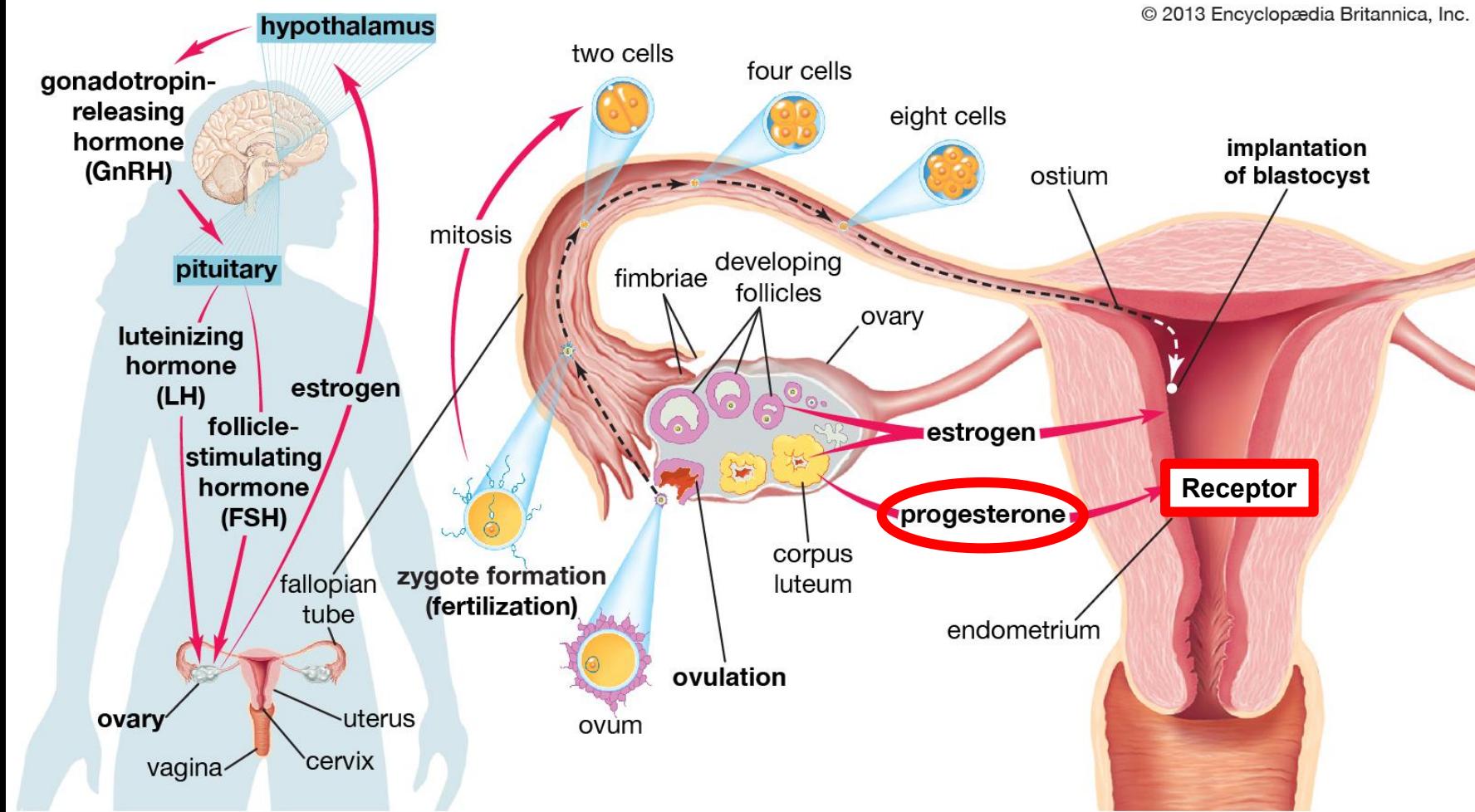


**Were they wimps?**

?

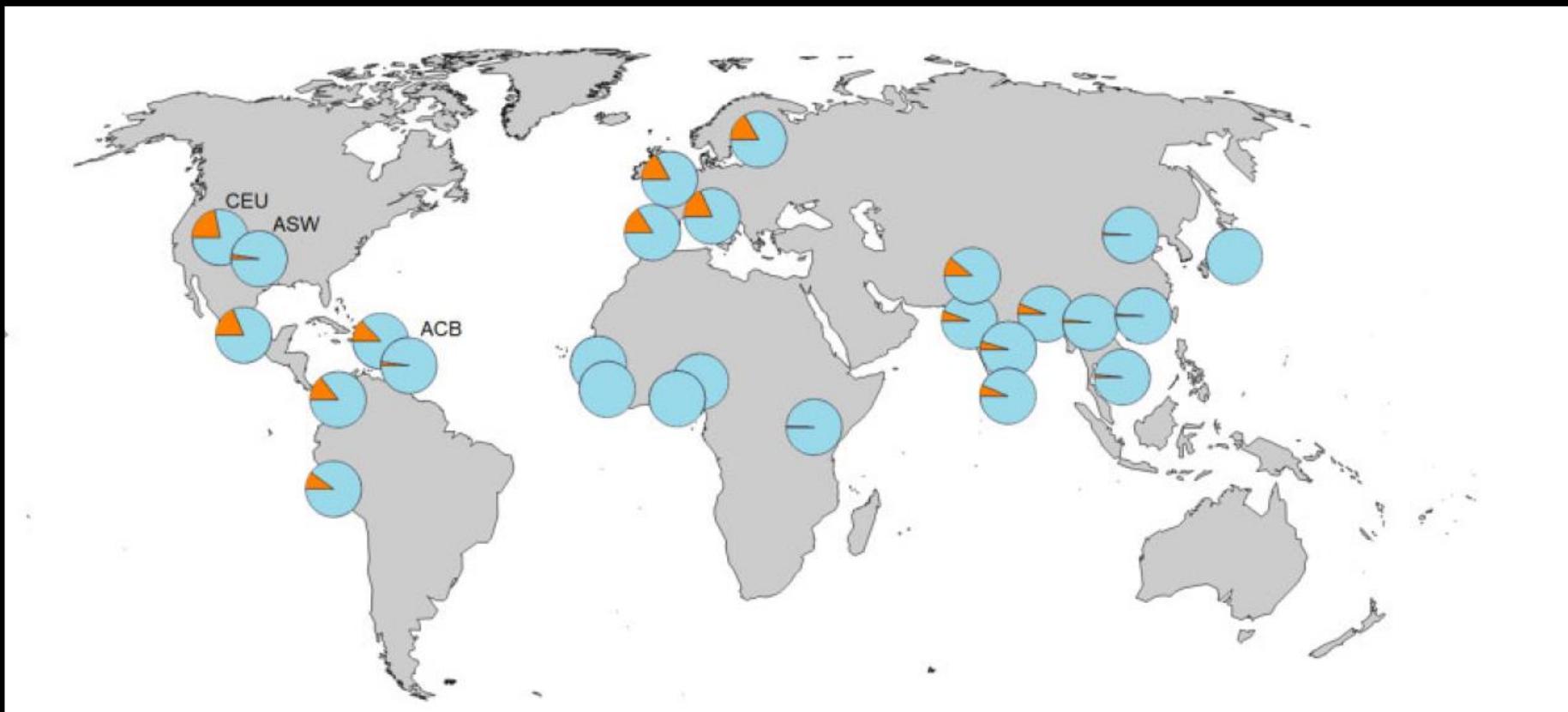
Nea

Nea



From: <https://www.britannica.com/science/ovulation>.

# A Neandertal variant associated with preterm births



Zeberg *et al.*, MBE 2020.

**Progesterone receptor**

Vindija Neanderthals,<sup>45</sup> it is likely that the risk allele of the missense PROGINs site had been fixed in Neanderthals. Therefore, fixation of the risk allele in this pregnancy-associated gene in Neanderthals likely posed a significant selective disadvantage.

Jingjing Li,<sup>1,2</sup> Xiumei Hong,<sup>3</sup> Sam Mesiano,<sup>5</sup> Louis J. Muglia,<sup>6</sup> Xiaobin Wang,<sup>3,4</sup> Michael Snyder,<sup>2</sup> David K. Stevenson,<sup>1,7,\*</sup> and Gary M. Shaw<sup>1,7,\*</sup>

The American Journal of Human Genetics 103, 45–57, July 5, 2018

# The Neandertal progesterone receptor in modern humans over time

15,000-14,500 BP



rs1042838

Zeberg *et al.*, MBE 2020.

# UK BioBank

Variant	Position	“Modern Allele”	Trait	Beta	p-value	MAF	HWE	imp. score	OR	beta*
rs1042838	100933412	C	Standing height	0.063378	1.084e-08	0.1654	0.362	genotyped	-	
rs1042838	100933412	C	Sitting height	0.028211	0.00017162	0.1654	0.362	genotyped	-	
rs1042838	100933412	C	K86 Other diseases of pancreas	0.0005389	0.00024481	0.1654	0.362	genotyped	1.22	
rs1042838	100933412	C	anxiety/panic attacks	0.0011388	0.00053558	0.1654	0.362	genotyped	1.09	
rs1042838	100933412	C	Mean corpuscular volume	0.032094	0.00075769	0.1654	0.362	genotyped	-	
rs1042838	100933412	C	O20 Haemorrhage in early pregnancy	0.00075152	0.0019825	0.1654	0.362	genotyped	1.2	
rs1042838	100933412	C	fracture	0.0011338	0.0023338	0.1654	0.362	genotyped	1.06	
rs1042838	100933412	C	Mean corpuscular haemoglobin	0.011735	0.0023662	0.1654	0.362	genotyped	-	
rs1042838	100933412	C	M17 Gonarthrosis [arthrosis of knee]	0.0017097	0.0036395	0.1654	0.362	genotyped	1.04	
rs1042838	100933412	C	Number of full sisters	-0.0088854	0.0036994	0.1654	0.362	genotyped	-	
rs1042838	100933412	C	Alcohol intake frequency.	-0.010763	0.0047155	0.1654	0.362	genotyped	-	
rs1042838	100933412	C	miscarriage	0.00060631	0.0093852	0.1654	0.362	genotyped	1.18	

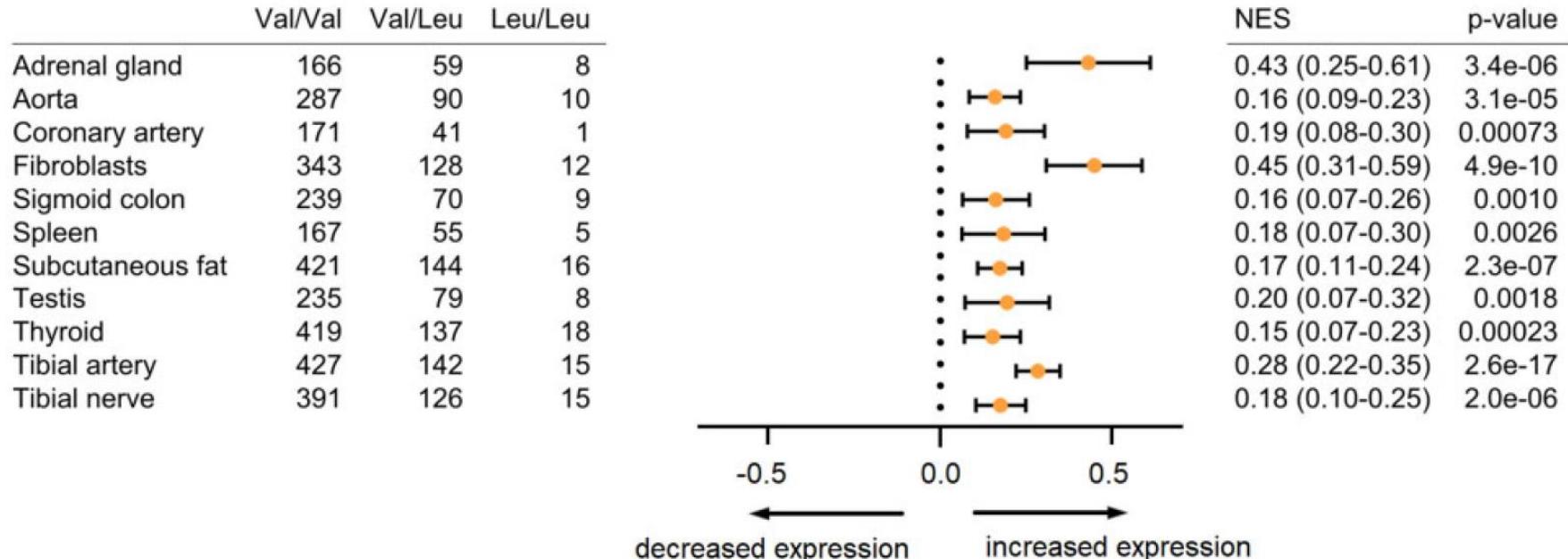
# The progesterone receptor

The Neandertal variant (A, V660L) is  
associated with preterm births

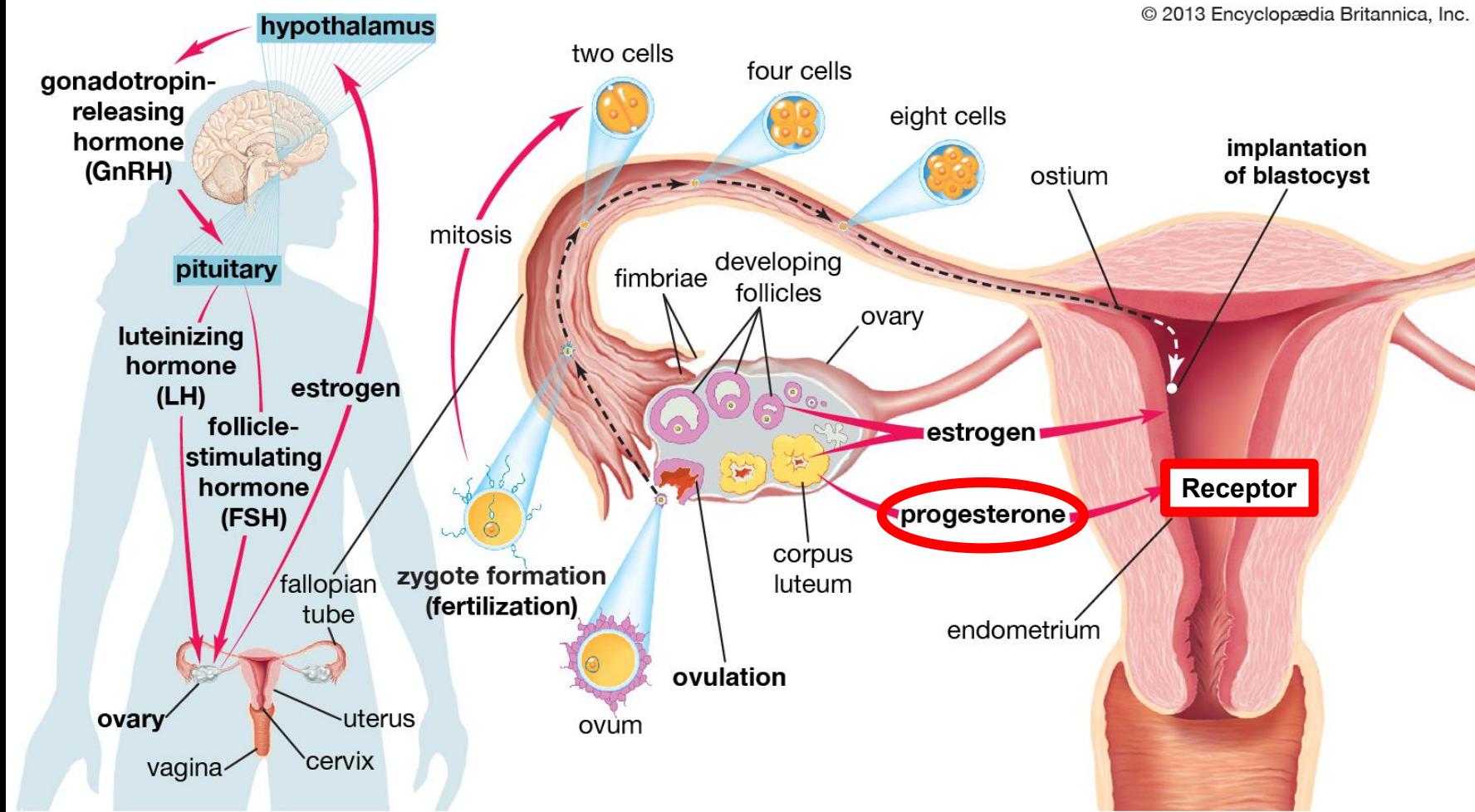
but

is also protective against miscarriage  
and results in more live births...

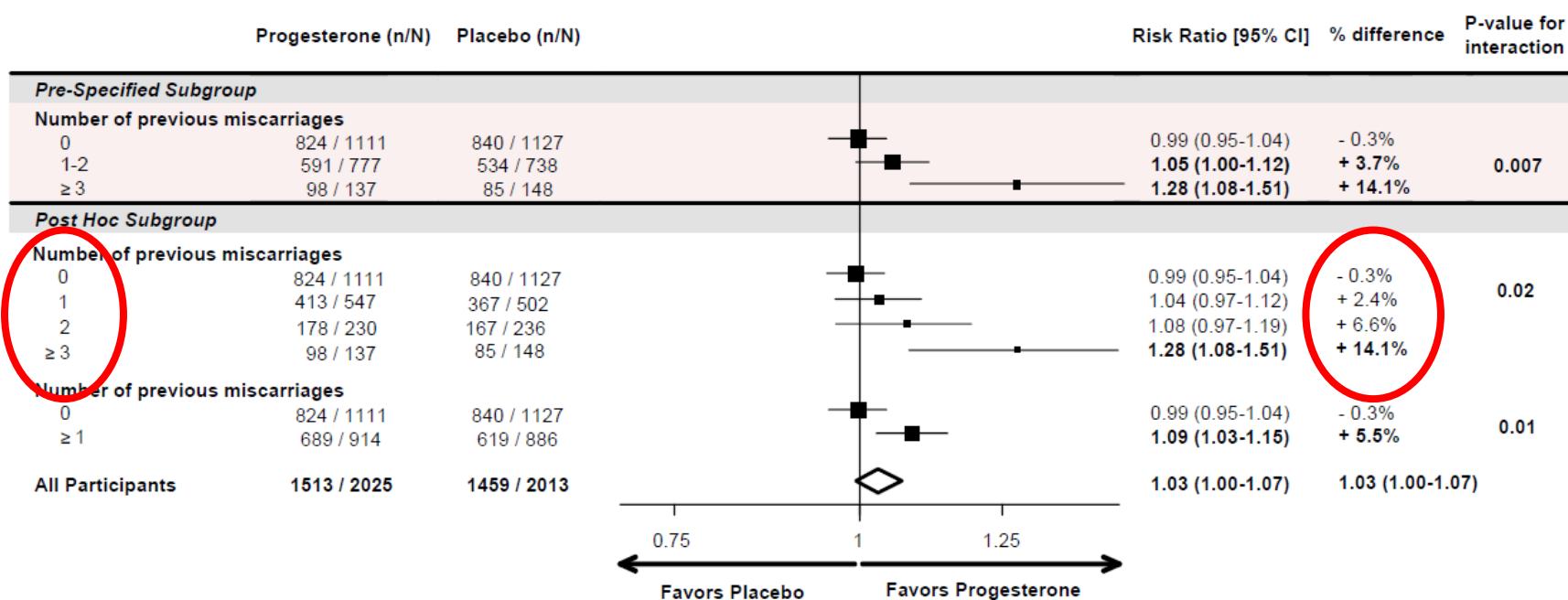
# Progesterone receptor expression



Zeberg et al., MBE 2020.

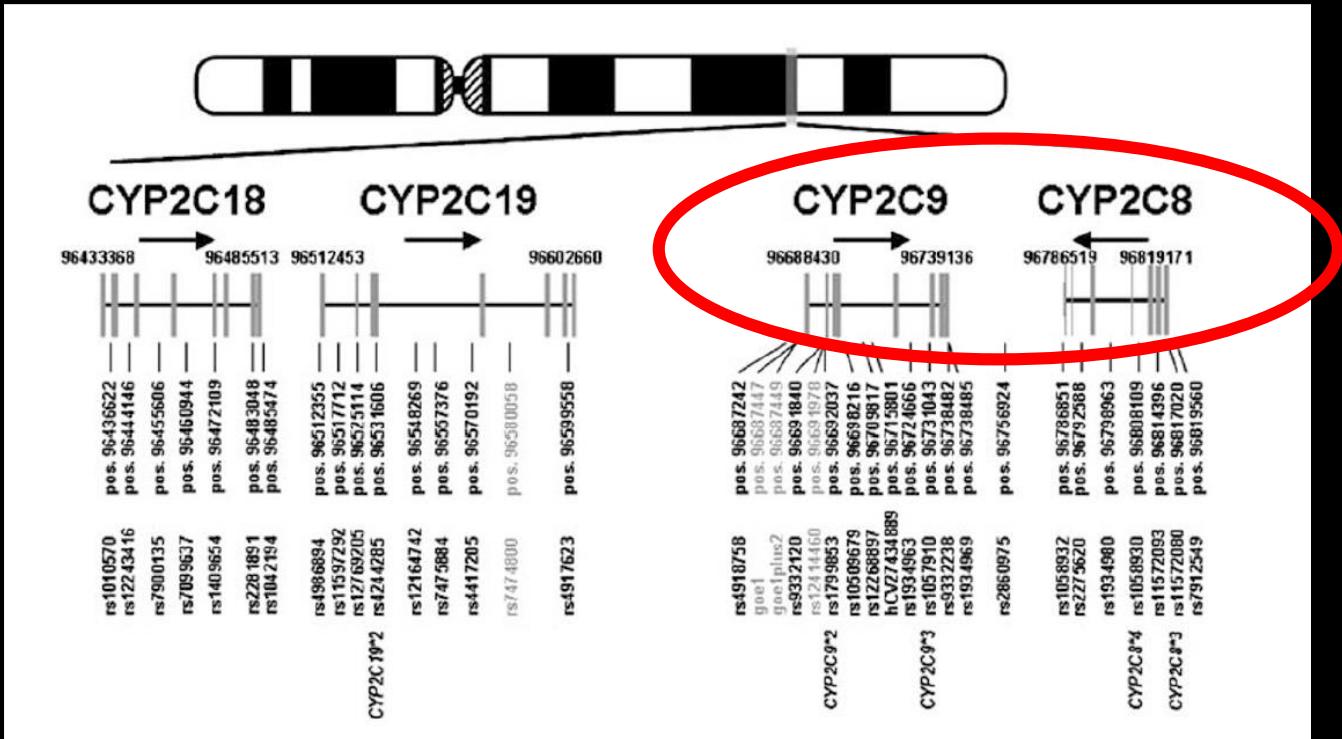


From: <https://www.britannica.com/science/ovulation>.

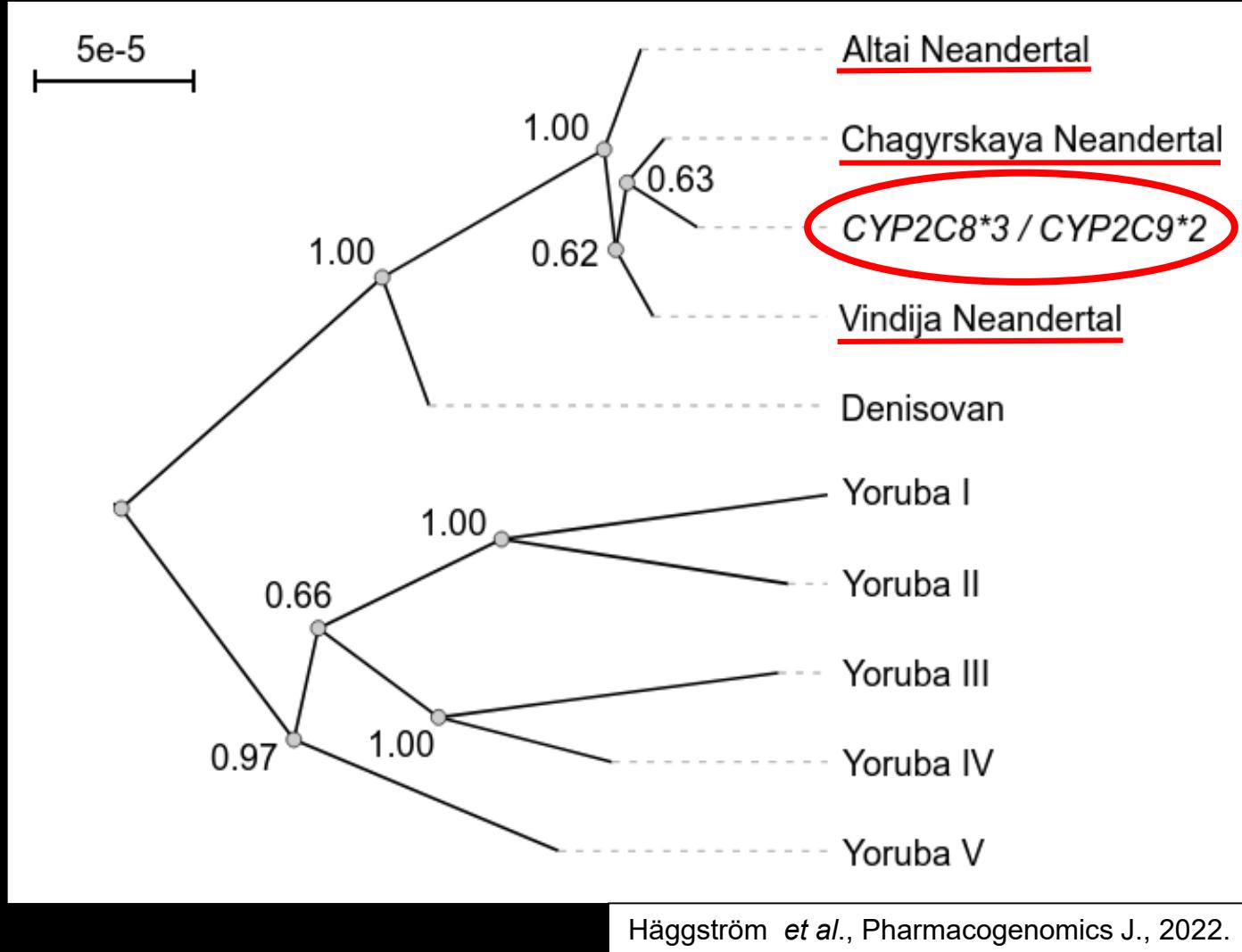
**FIGURE 2****PRISM trial data on live birth >34 weeks by the number of previous miscarriages**

CI, confidence interval; PRISM, Progesterone In Spontaneous Miscarriage.

Coomarasamy et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol 2020.



Vormfelde et al., Pharmacogenomics J., 2007.



# "Neandertal" CYP2C8\*3

	CYP2C8*1/*1	CYP2C8*1/*3	CYP2C8*3/*3	Overall individuals
Number of subjects	9 <sup>a</sup>	10 <sup>b</sup>	6 <sup>c</sup>	25
$C_{max}$ (mg litre $^{-1}$ )	20.6 (14.4–27.0)	25.3 (18.5–32.1)	15.2 (7.6–22.9)	21.2 (17.5–24.9)
$T_{max}$ (hours)	1.0 (0.6–1.3)	1.42 (0.91–1.94)	2.1 (1.6–2.6)[0.58–1.70, $P < 0.001$ ]	1.41 (1.11–1.71)
AUC (mg.h litre $^{-1}$ )	59.4 (35.8–83.0)	101.4 (80.1–122.7)[12.59–71.37, $P < 0.008$ ]	105.6 (65.0–146.3)[3.71–88.77, $P < 0.036$ ]	87.3 (71.8–102.8)
$t_{1/2}$ (hours)	2.0 (1.8–2.2)	4.2 (1.9–6.5)[0.10–4.44, $P < 0.05$ ]	9.0 (7.8–10.2)[5.74–8.15, $P < 0.001$ ]	4.56 (3.16–5.97)
Clearance (litres h $^{-1}$ )	3.5 (2.5–4.4)	2.2 (1.6–2.8)[0.23–2.34, $P < 0.02$ ]	2.1 (1.3–2.9)[0.30–2.49, $P < 0.03$ ]	2.63 (2.15–3.11)

Values are mean (95% confidence intervals) data. Cmax, maximum concentration. Tmax, time required to reach peak concentration. AUC, area under the concentration–time curve. t1/2, plasma half-life.

Br J Clin Pharmacol 59:62–68 (2004).



# Ibuprofen

# "Neandertal" CYP2C9\*2

Recommended daily warfarin doses (mg/day)	
CYP2C9*1/*1	CYP2C9*2/*2
5–7	3–4

Adapted from Johnson *et al.* (2011) *Clin Pharmacol Ther.* 90(4):625-9.



# The Corona Virus Pandemic



World Health Organization

Search by Country, Territory, or Area

Covid-19 Response Fund



Donate

WHO Coronavirus (COVID-19) Dashboard

[Overview](#)

Measures

Table View

Data

More Resources

Cases

Total

**175,469**

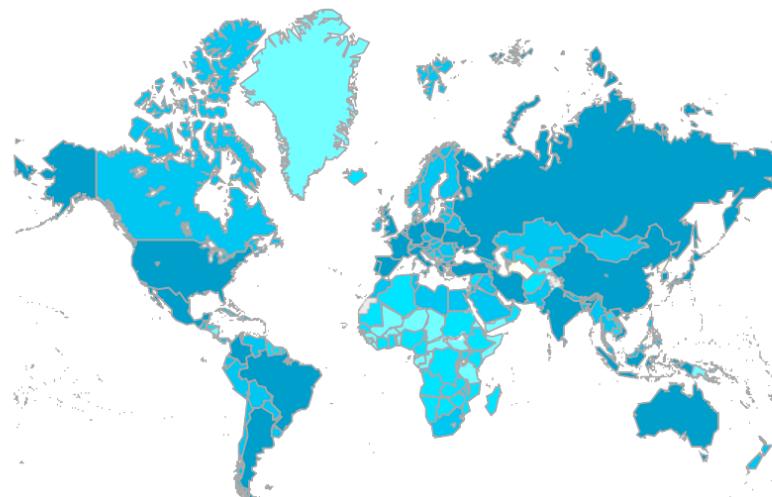
new cases in last 24hrs

**635,229,101**

cumulative cases

**6,602,552**

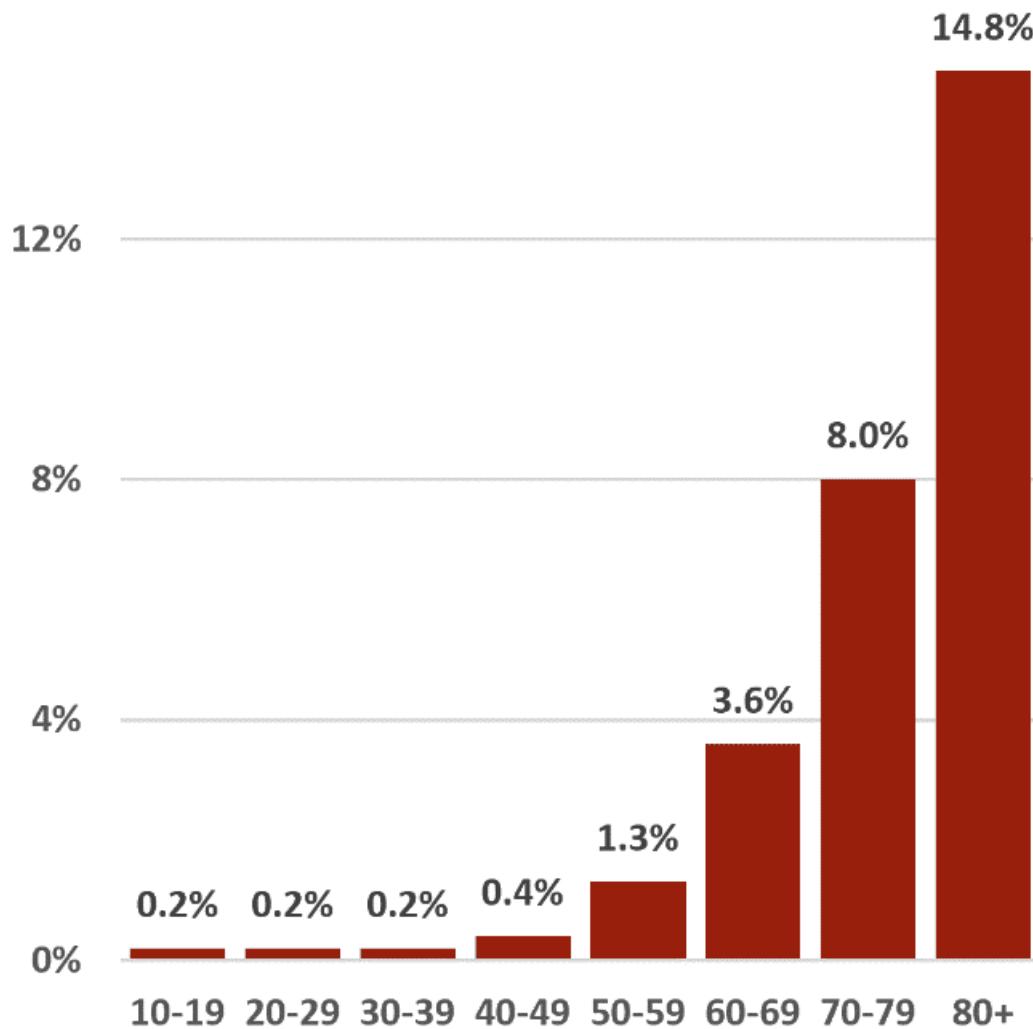
cumulative deaths



Download Map Data

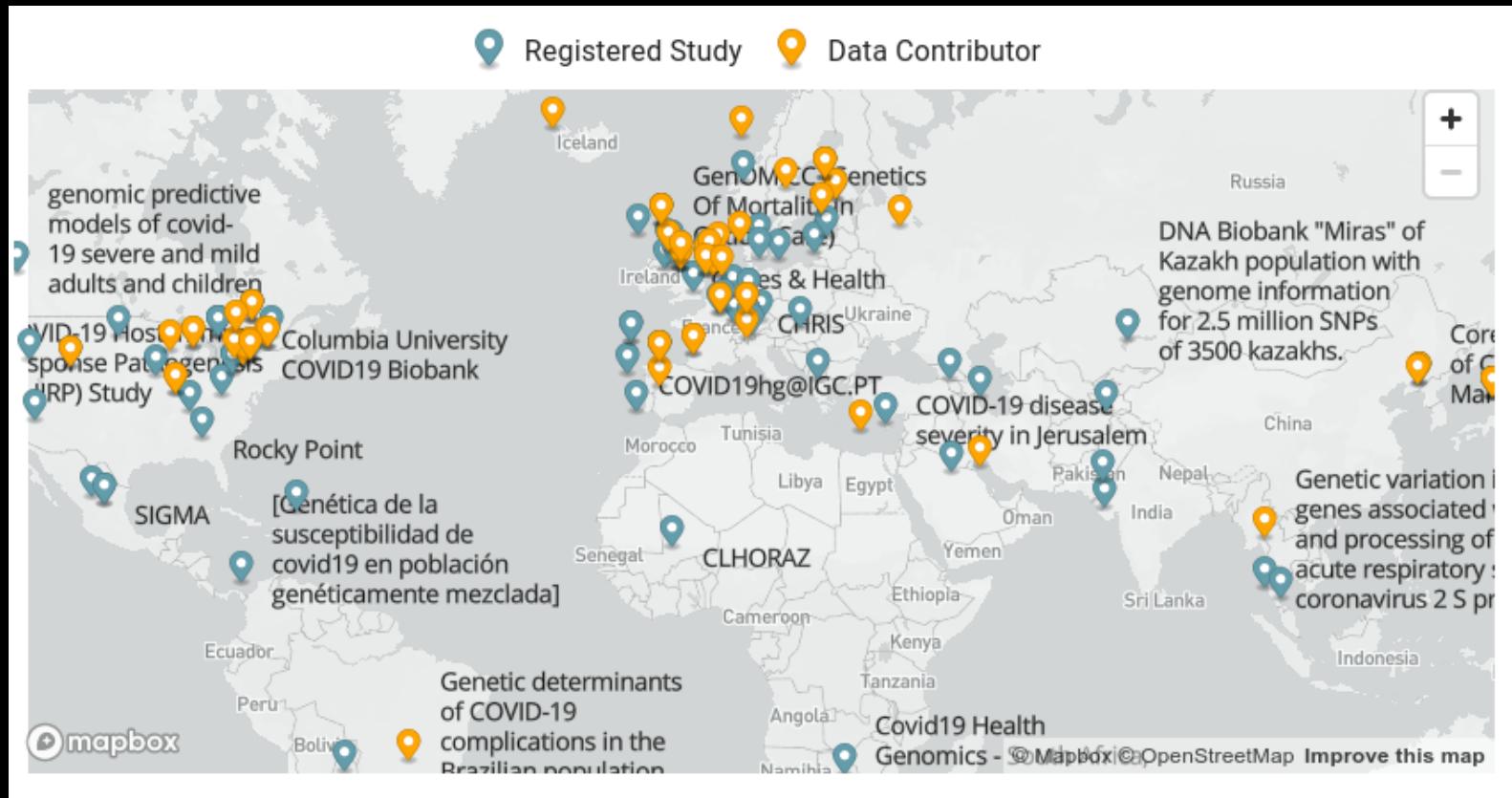
Globally, as of **5:37pm CET, 22 November 2022**, there have been **635,229,101 confirmed cases** of COVID-19, including **6,602,552 deaths**, reported to WHO. As of **16 November 2022**, a total of **12,943,741,540 vaccine doses** have been

## COVID-19 Mortality Rate by Age

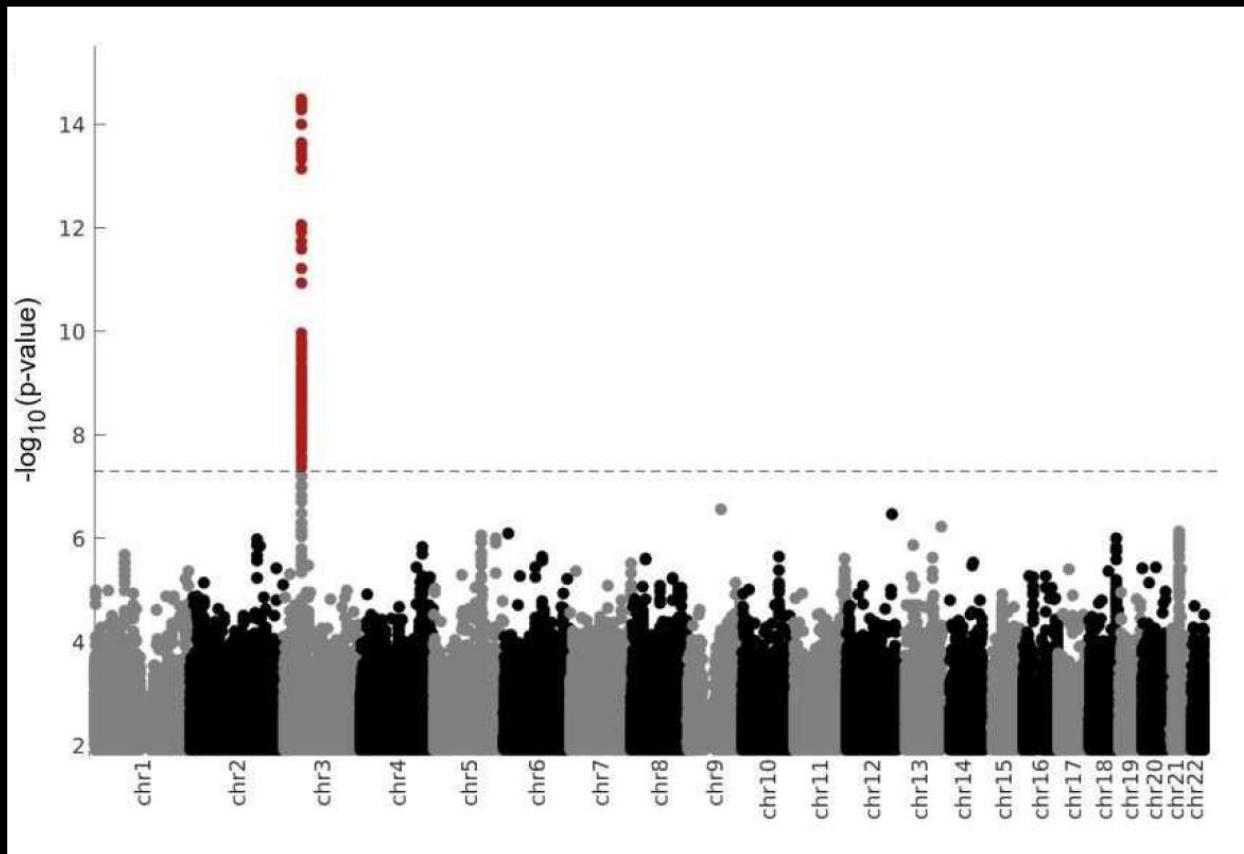


Source: CDC

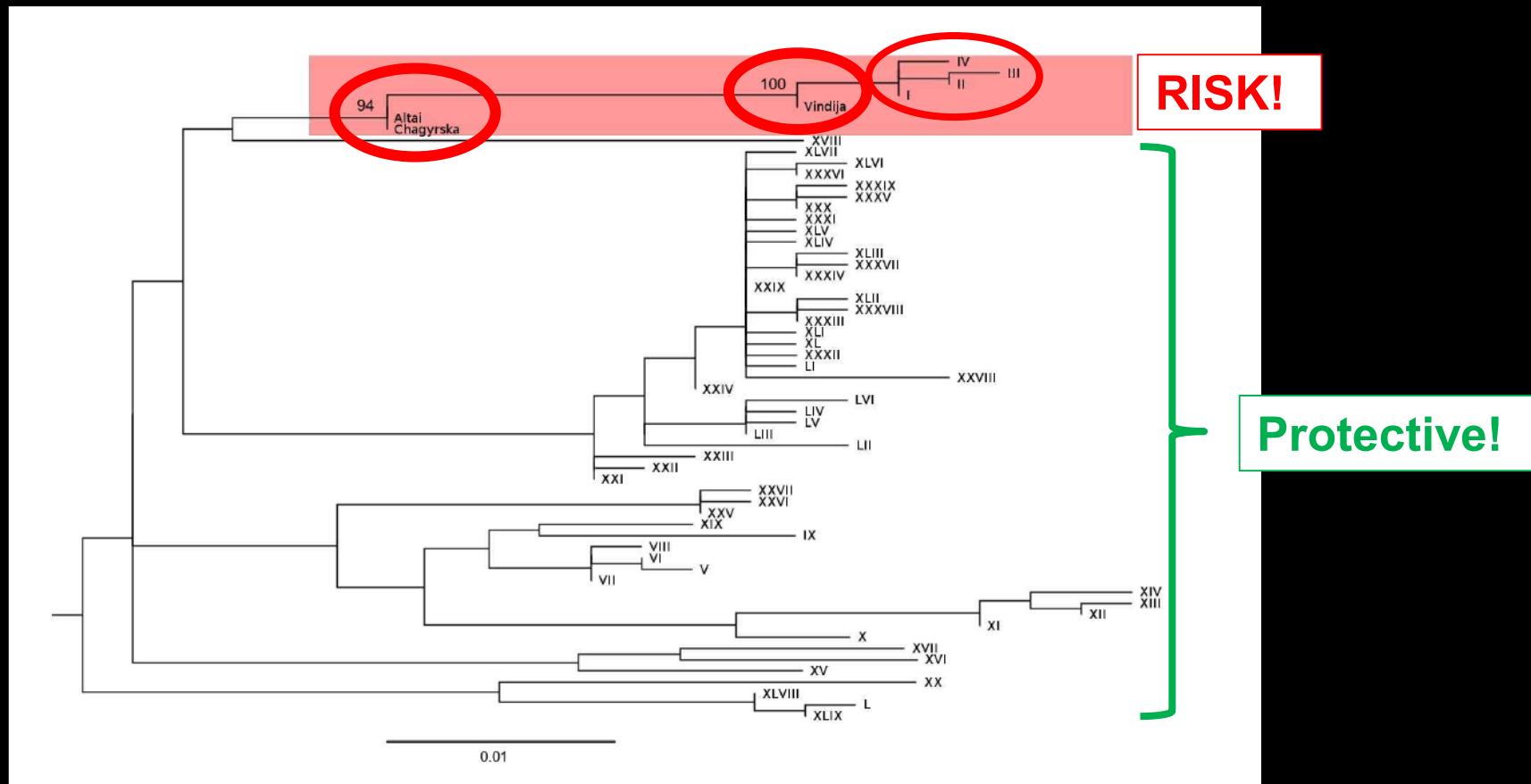
# The Covid-19 Host Genetics Initiative



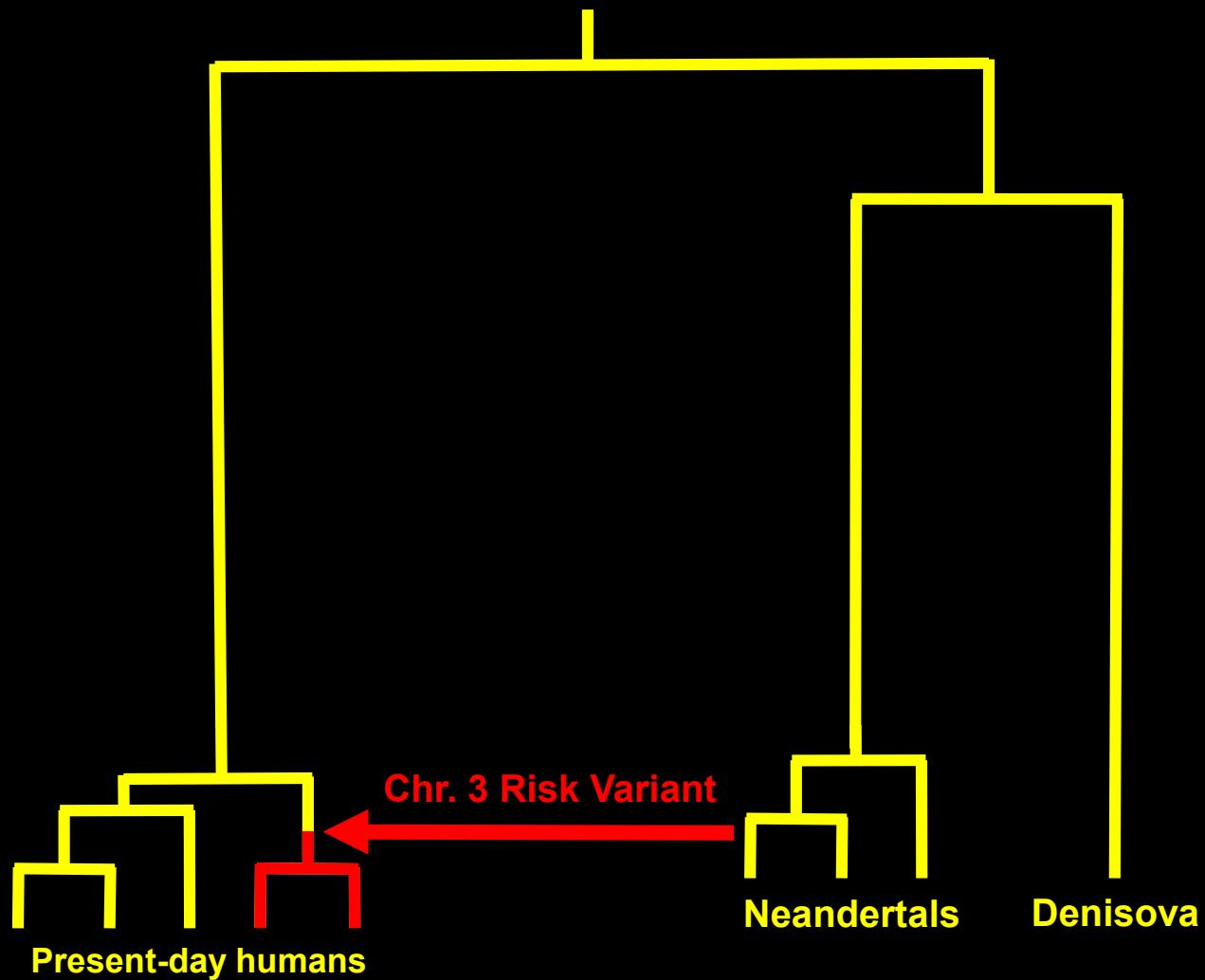
# Genome-wide associations for severe COVID-19

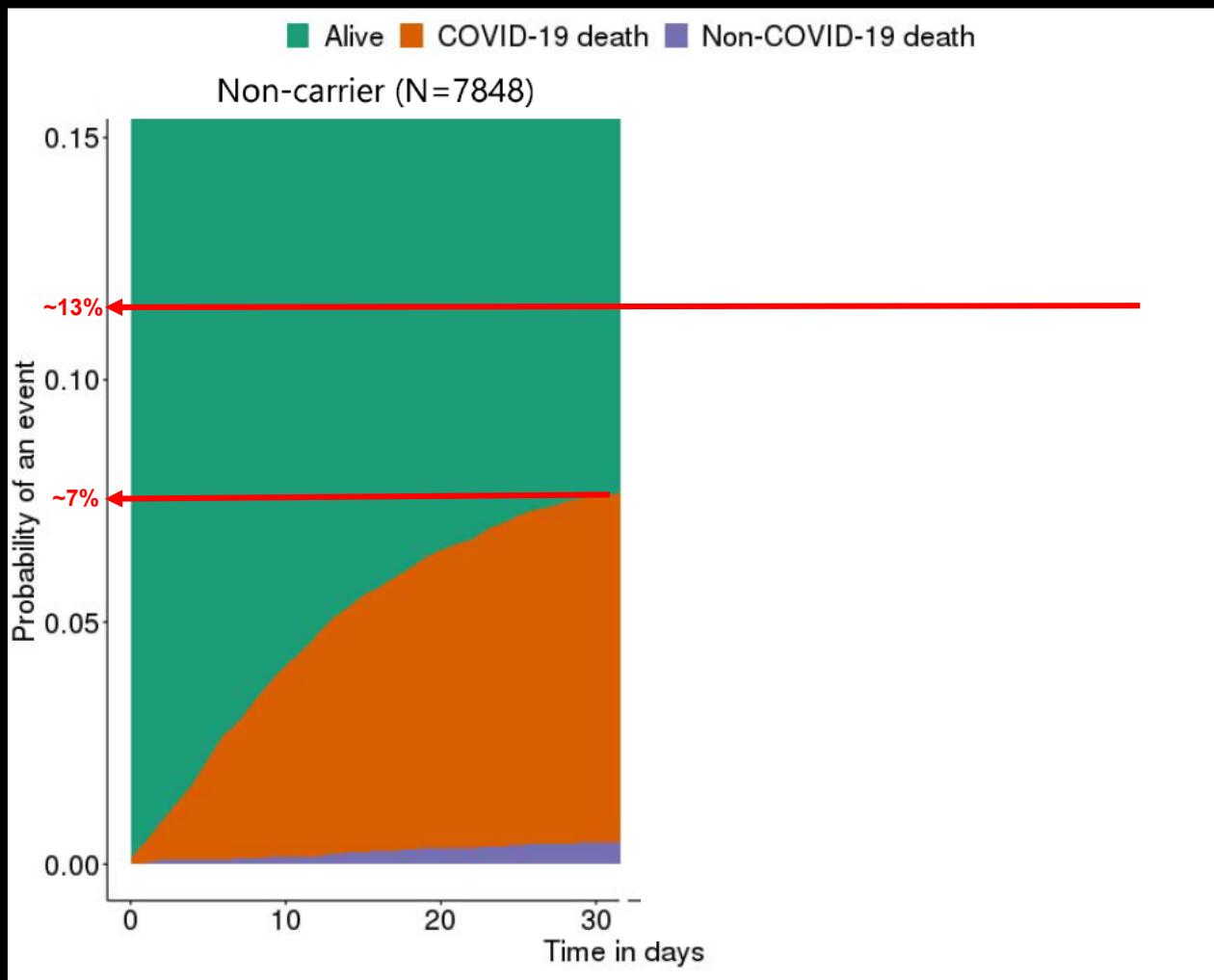


Modified from COVID-19 Host Genetics Initiative (<https://www.covid19hg.org/>)

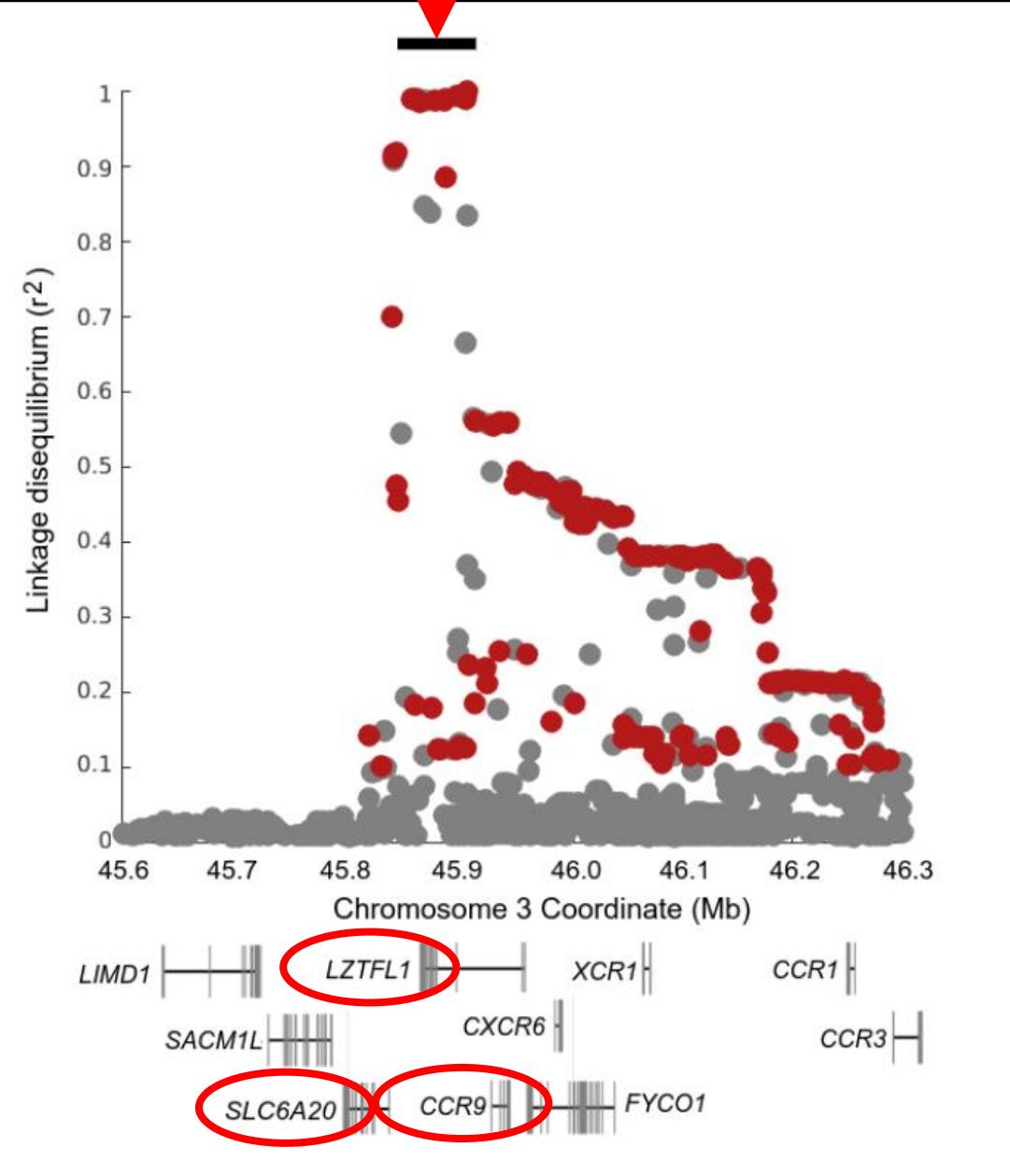


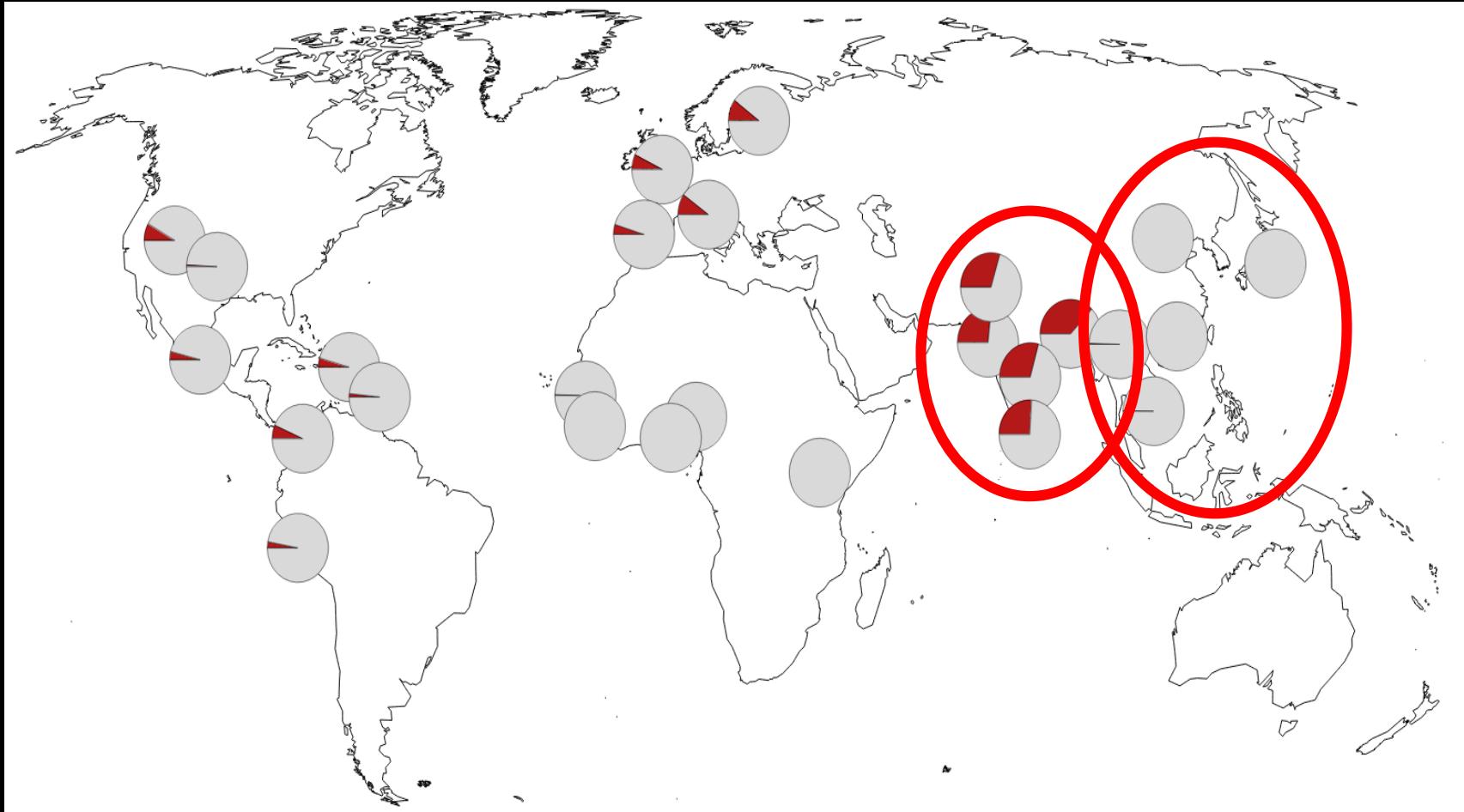
Zeberg & Pääbo, Nature, 2020.





Nakanishi *et al.*, J. Clin. Invest., 2021.





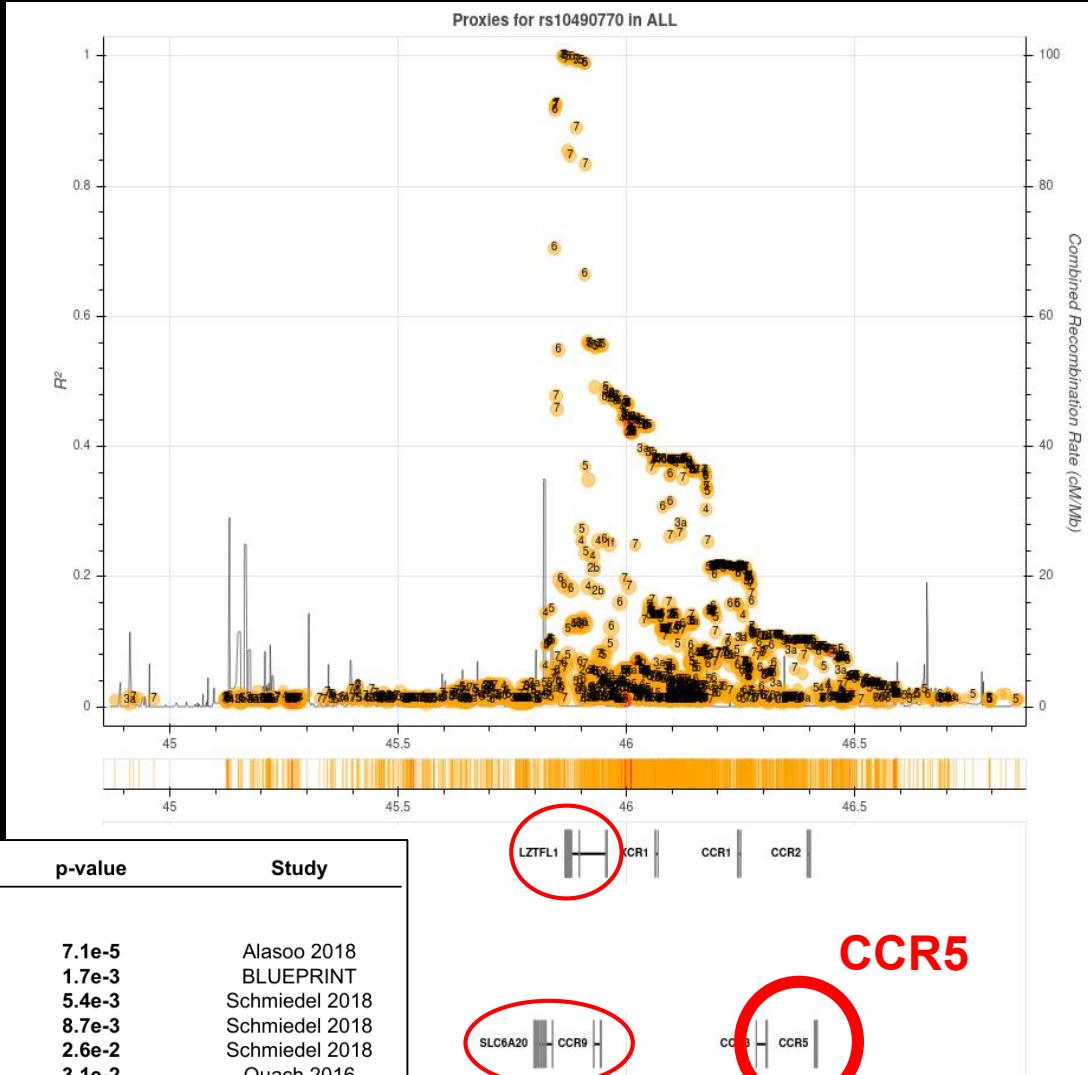
Zeberg & Pääbo, Nature, 2020.

Approximately 11 million  
extra deaths...  
South Asia: ~50% carriers  
Europe: ~16% carriers



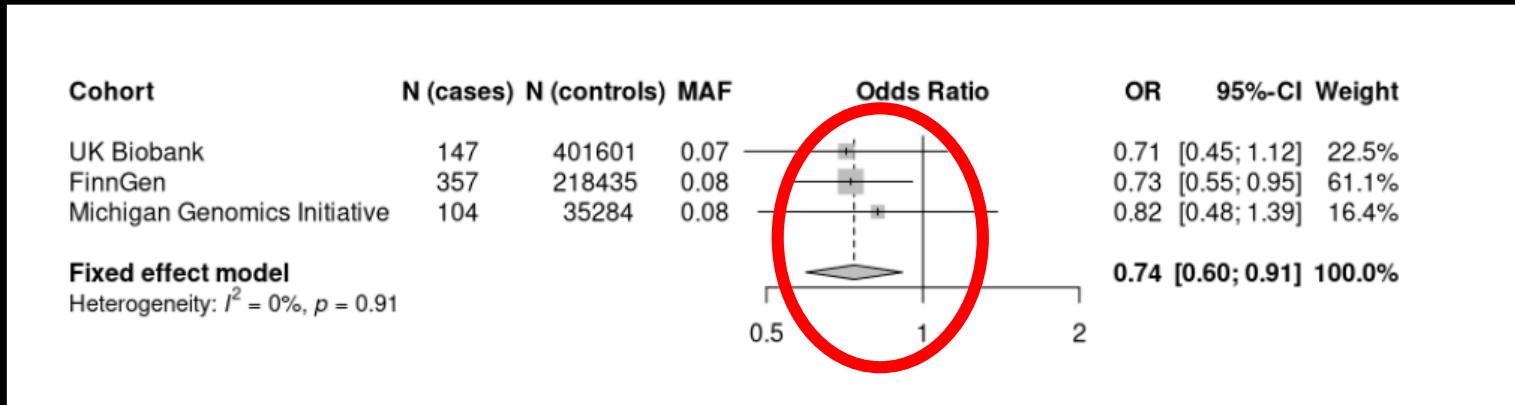
Hugo Zeberg

# The COVID risk variant downregulates CCR5!



eQTL Cat.	NES (eQTL Cat.)	p-value	Study
Macrophages	↓	-1.15	7.1e-5 Alasoo 2018
Monocytes	↓	-0.59	1.7e-3 BLUEPRINT
Memory T-follicular helper cells	↓	-1.09	5.4e-3 Schmiedel 2018
Memory T helper 2 cells	↓	-0.76	8.7e-3 Schmiedel 2018
Memory T helper 1 cells	↓	-0.34	2.6e-2 Schmiedel 2018
Monocytes	↓	-0.31	3.1e-2 Quach 2016
CD8+ T cells	↓	-0.69	5.3e-2 Schmiedel 2018
Macrophages	↓	-0.24	5.5e-2 Nedelec 2016
Memory T helper 1/17 cells	↓	-0.24	1.5e-1 Schmiedel 2018
NK cells	↓	-0.42	1.6e-1 Schmiedel 2018
Monocytes	↓	-0.20	2.1e-1 Schmiedel 2018
CD16+ Monocytes	↓	-0.45	3.4e-1 Schmiedel 2018
T cells	↓	-0.16	4.0e-1 BLUEPRINT
Memory T regulatory cells	↓	-0.07	6.2e-1 Schmiedel 2018
T cells	↓	-0.07	6.6e-1 GENCORD
T regulatory cells	↓	-0.10	7.4e-1 Schmiedel 2018
Memory T helper 17 cells	↓	-0.004	9.8e-1 Schmiedel 2018

# Risk of HIV infection in chr. 3 risk variant carriers



Zeberg, PNAS, 2022.

**26% reduced risk  
of HIV transmission!**

# The chromosome 3 locus

- Increased risk for severe covid
- Decreased risk for HIV infection

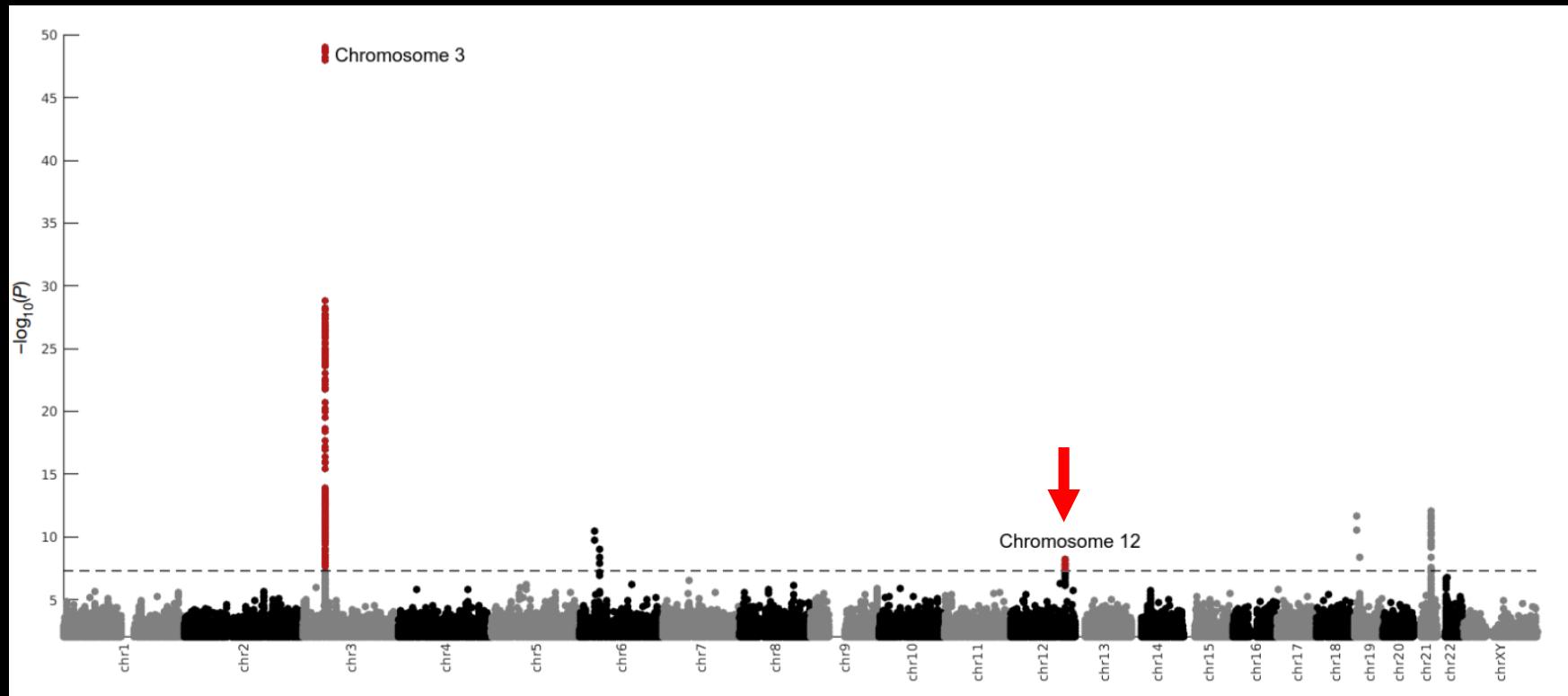


A double-edged sword



A multi-edged sword...





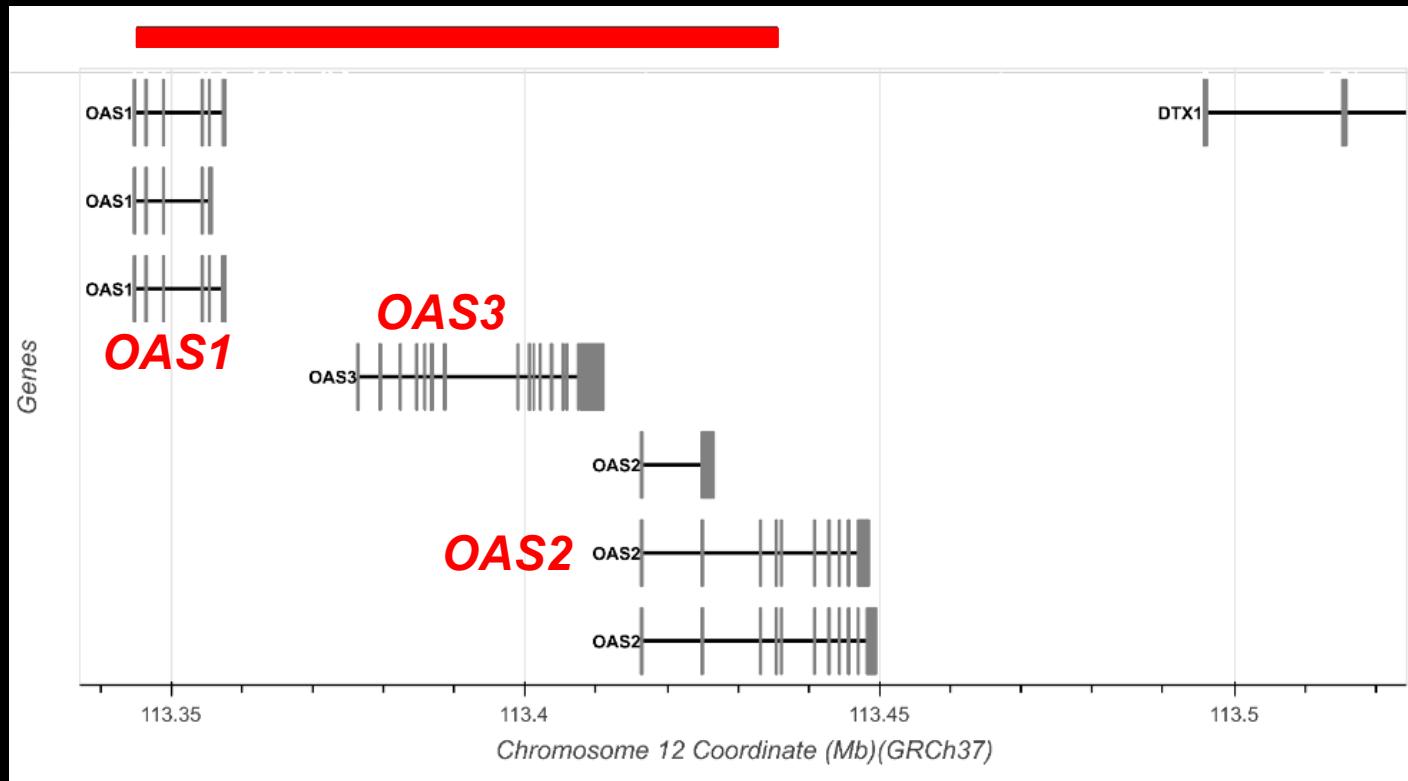
First reported by Pairo-Castineira *et al.* Nature (2020)

Modified from COVID-19 HGI

# Neandertals

Chr	Pos	rsid	P-value	LD (rs4766664)	Ref	Alt	Anc	Vindija	Altai	Chagyrskaya	Denisova
12	113362997	rs4766664	5.7e-09	1.00	T	G	T	T/T	T/T	T/T	G/G
12	113381956	rs2269899	7.9e-09	0.56	C	T	T	C/C	C/C	C/C	T/T
12	113380008	rs10735079	7.9e-09	0.75	G	A	A	G/G	G/G	G/G	A/A
12	113410316	rs10744791	1.3e-08	0.63	G	A	A	G/G	A/G	G/G	A/A
12	113372804	rs4767037	1.4e-08	0.98	A	C	A	A/A	A/A	A/A	C/C
12	113372866	rs1981557	1.4e-08	0.98	G	C	G	G/G	G/G	G/G	C/C
12	113372977	rs1981555	1.4e-08	0.98	G	A	G	-	-	-	-
12	113376913	rs7299132	1.5e-08	0.99	T	A	A	T/T	T/T	T/T	A/A
12	113357209	rs1131476	1.6e-08	0.92	G	A	G	G/G	G/G	G/G	A/A
12	113357442	rs2660	1.6e-08	0.92	G	A	G	G/G	G/G	G/G	A/A
12	113381695	rs7131998	1.8e-08	0.86	A	C	A	-	-	-	-
12	113406196	rs3937434	1.8e-08	0.63	A	G	G	-	-	-	-
12	113406460	rs2016831	1.8e-08	0.63	G	C	C	-	-	-	-
12	113374017	rs4767040	1.9e-08	0.98	G	C	G	G/G	G/G	G/G	C/C
12	113372961	rs1981556	1.9e-08	1.00	C	G	G	-	-	-	-
12	113406945	rs757405	1.9e-08	0.63	T	A	A	T/T	A/T	T/T	A/A
12	113373563	rs3759376	1.9e-08	1.00	A	G	G	A/A	A/A	A/A	G/G
12	113409413	rs4767045	1.9e-08	0.63	C	T	T	T/T	T/T	C/C	T/T
12	113402899	rs4767044	2.0e-08	0.63	C	A	A	C/C	C/C	C/C	A/A
12	113373588	rs3759375	2.0e-08	1.00	A	G	G	A/A	A/A	A/A	G/G
12	113386950	rs2285932	2.0e-08	0.63	T	C	C	T/T	T/T	T/T	C/C
12	113375036	rs7132797	2.1e-08	0.98	A	C	A	A/A	A/A	A/A	C/C
12	113392182	rs7310667	2.1e-08	0.31	A	G	A	-	-	-	-
12	113381376	rs6489882	2.2e-08	0.97	G	A	A	A/A	A/A	A/A	A/A
12	113377822	rs6489879	2.3e-08	0.99	G	A	G	G/G	G/G	G/G	A/A
12	113379123	rs7311182	2.3e-08	0.99	T	C	C	-	-	-	-
12	113405181	rs1557866	2.4e-08	0.63	A	C	C	A/A	A/A	A/A	C/C
12	113380271	rs6489880	2.4e-08	0.99	C	T	T	-	-	-	-
12	113364382	rs4767033	2.4e-08	1.00	T	A	A	T/T	T/T	T/T	A/A
12	113378081	rs4238033	2.4e-08	0.99	T	A	A	T/T	T/T	T/T	A/A
12	113375983	rs1156361	2.6e-08	1.00	T	C	C	T/T	T/T	T/T	C/C
12	113372539	rs7966314	3.1e-08	0.98	A	G	A	A/A	A/A	A/A	G/G
12	113408208	rs2010604	3.2e-08	0.52	G	C	C	G/G	G/G	G/G	G/G
12	113374748	rs10774679	3.3e-08	0.44	C	T	C	C/C	C/C	C/C	C/C
12	113385000	rs10850103	3.3e-08	0.63	A	T	T	A/A	T/A	A/A	T/T
12	113376320	rs3815178	3.3e-08	0.99	C	T	C	C/C	C/C	C/C	T/T
12	113376388	rs1859330	3.4e-08	0.53	G	A	G	G/G	G/G	G/G	A/A
12	113381217	rs6489881	3.6e-08	0.75	A	T	A	A/A	A/A	A/A	T/T
12	113380708	rs7977345	3.7e-08	0.75	A	T	T	A/A	A/A	A/A	T/T
12	113379039	rs7955267	3.7e-08	0.75	C	T	C	-	-	-	-
12	113382977	rs2384074	3.7e-08	0.66	C	T	C	-	-	-	-
12	113396010	rs10744789	4.1e-08	0.35	T	C	C	-	-	-	-
12	113371646	rs9971885	4.2e-08	1.00	A	C	C	-	-	-	-
12	113378677	rs4767041	4.3e-08	0.75	G	A	G	-	-	-	-
12	113367422	rs2384072	4.6e-08	1.00	T	C	T	T/T	T/T	T/T	C/C
12	113366899	rs7306205	4.6e-08	1.00	A	G	A	A/A	A/A	A/A	G/G
12	113367309	rs1859336	4.7e-08	1.00	C	T	C	C/C	C/C	C/C	T/T
12	113364633	rs4766667	4.8e-08	1.00	G	A	G	-	-	-	-
12	113370966	rs1859333	4.9e-08	1.00	T	C	C	T/T	T/T	T/T	C/C
12	113368079	rs6489877	4.9e-08	0.99	A	G	A	-	-	-	-
12	113363408	rs6489866	4.9e-08	1.00	A	G	A	-	-	-	-

Protective!

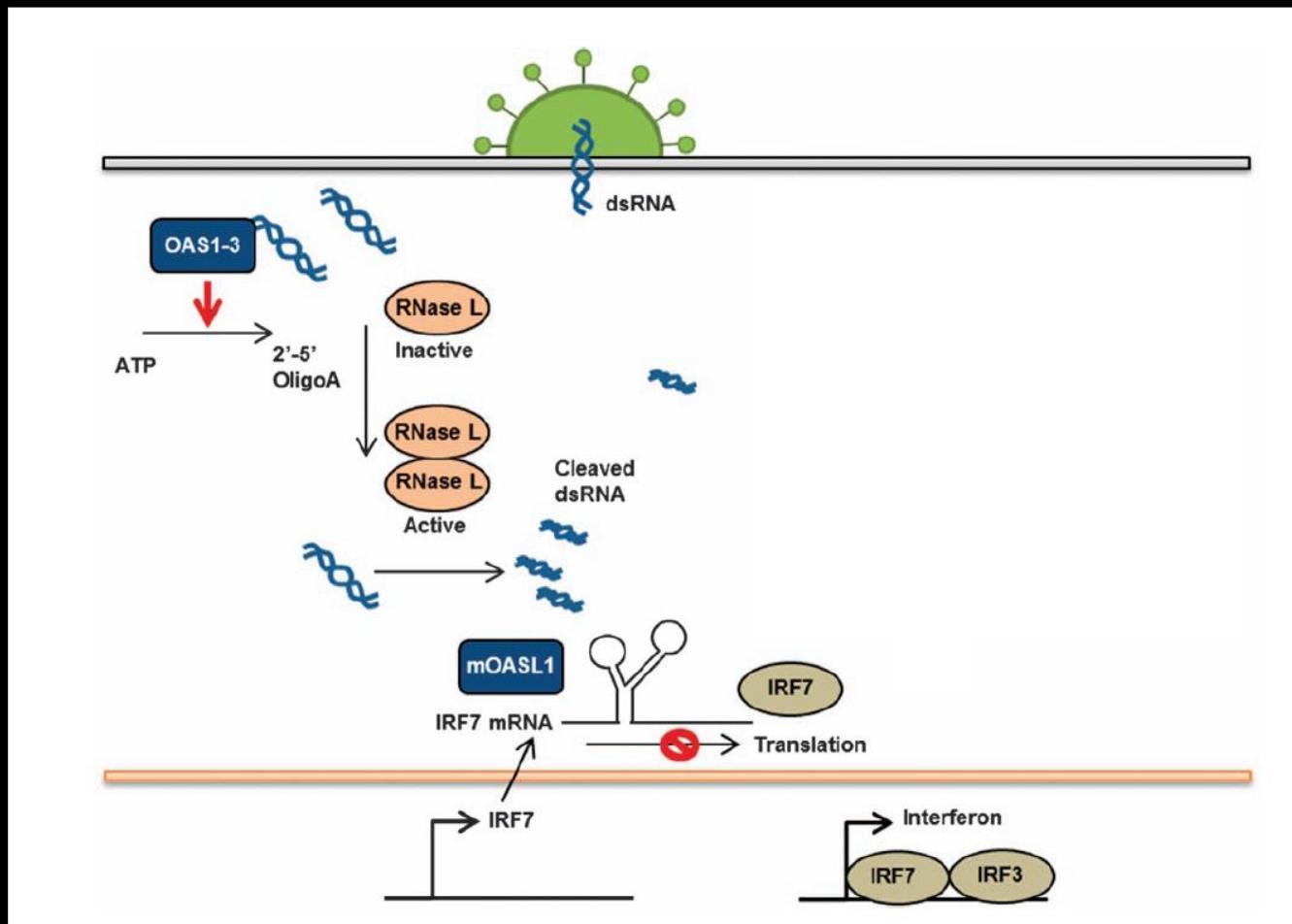


Zeberg and Pääbo, PNAS 2021.

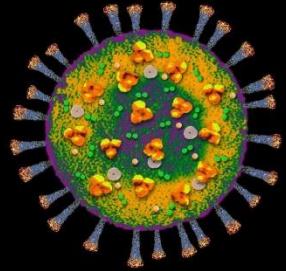
# Also protective against SARS-CoV-1!

Hamano *et al.* BBRC (2005)

# OAS 1-3



Modified from Choi *et al.*, Exp. & Mol. Med. 2015.

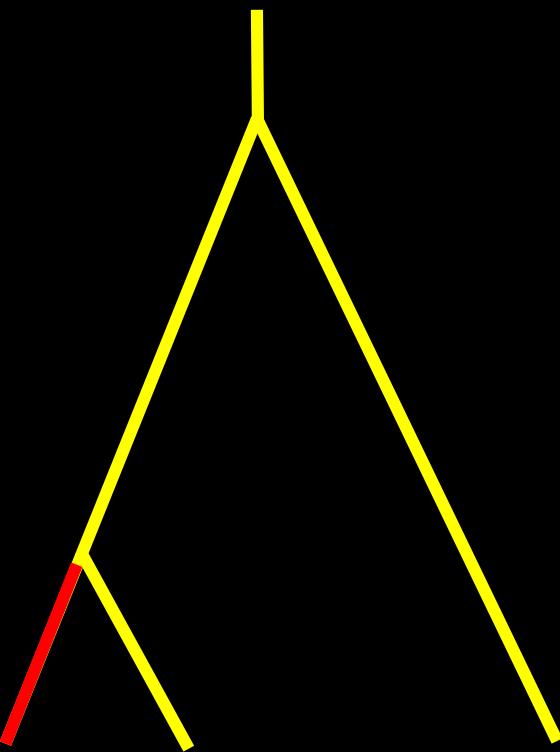


# Effect sizes

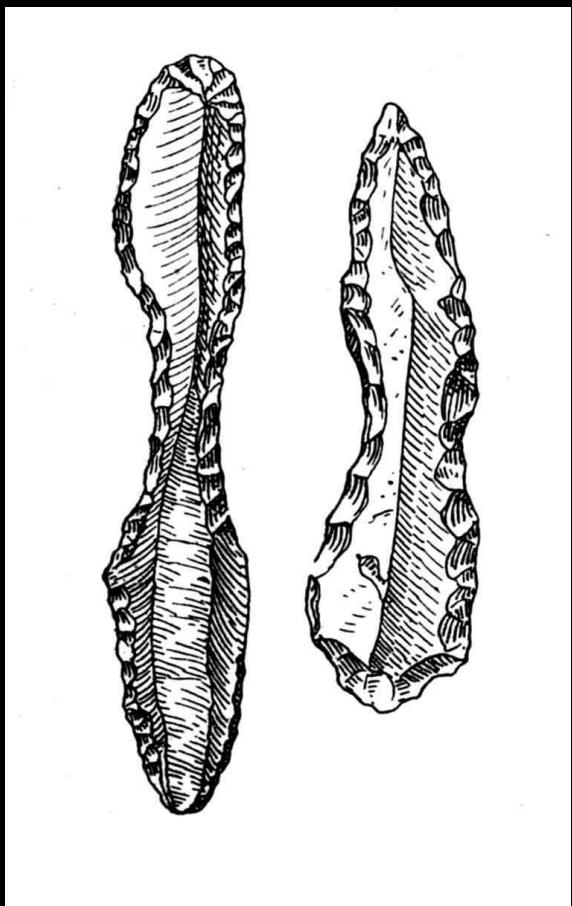
(under the rare disease assumption)

**Chromosome 3: ~ 100% increased risk per allele**

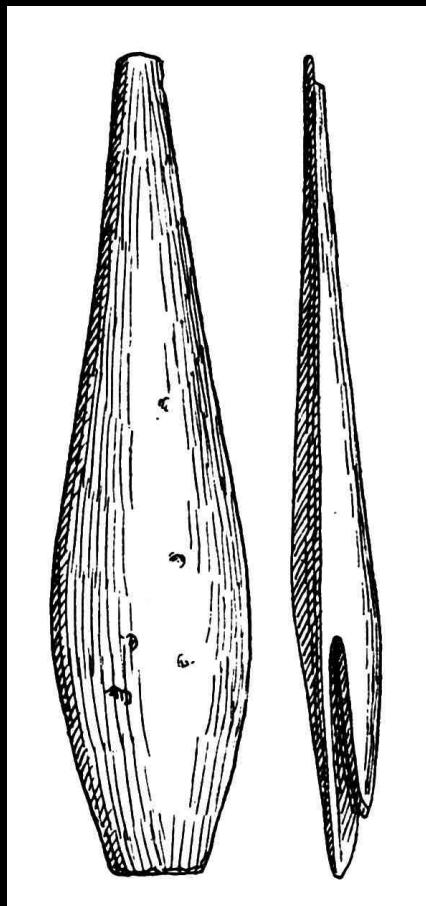
**Chromosome 12: ~ 23% decreased risk per allele**



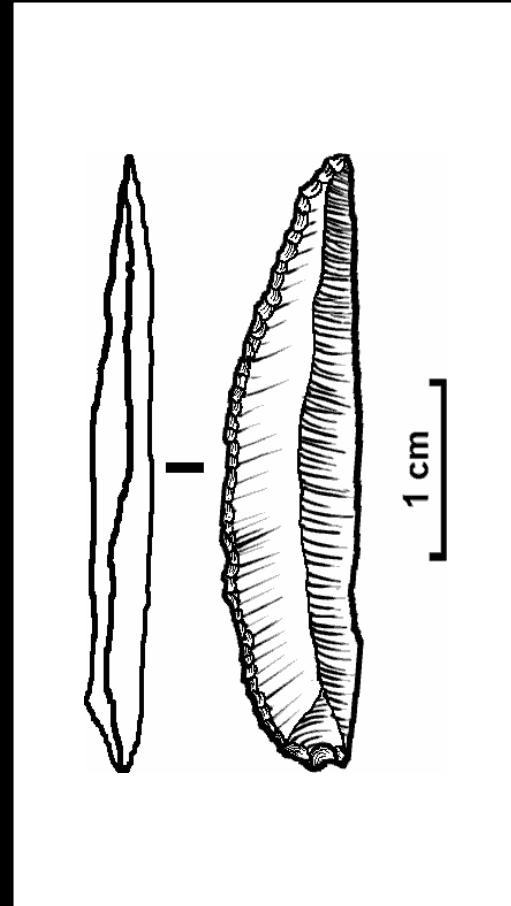
**Functions unique  
to modern humans?**



Aurignacian blades

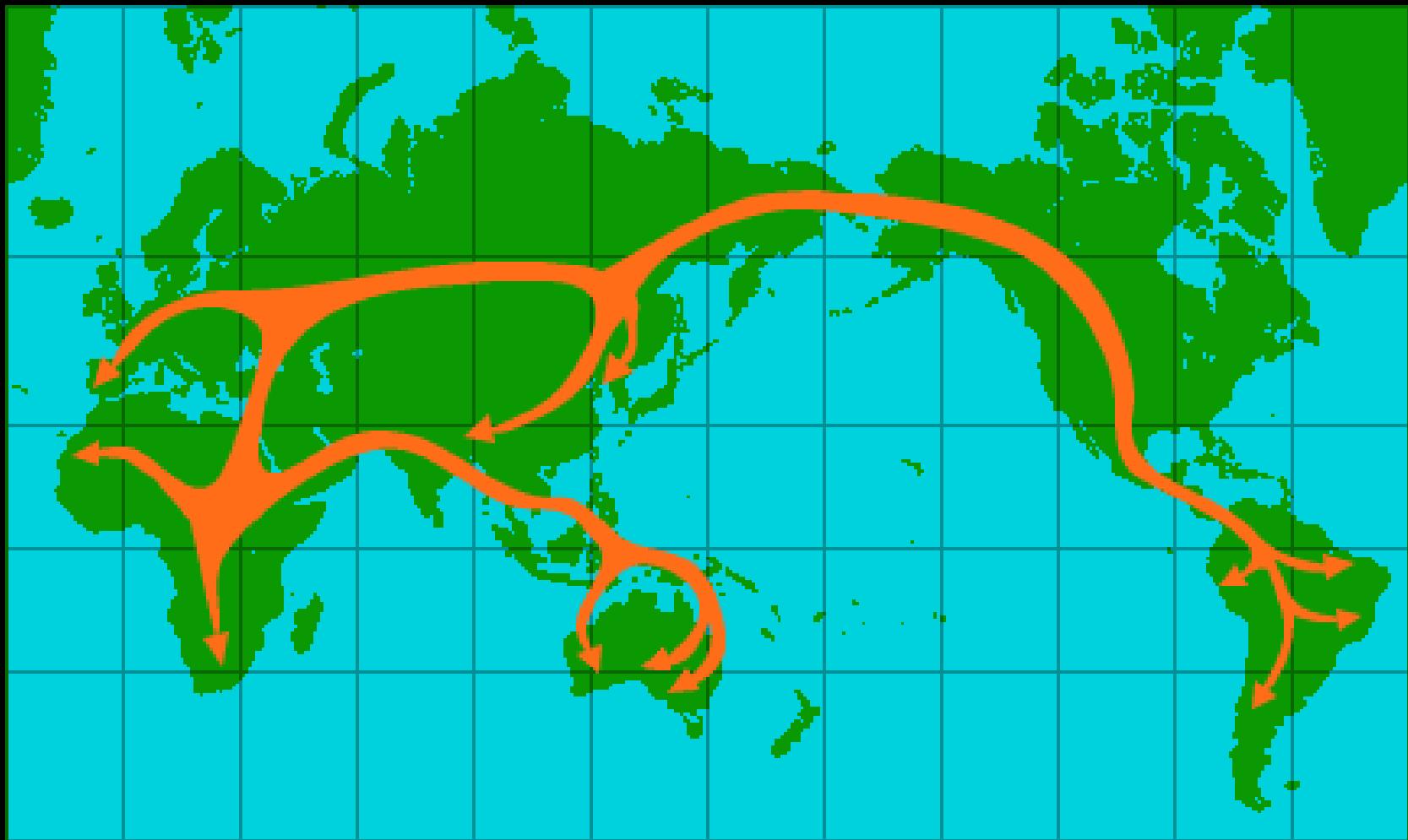


Bone points

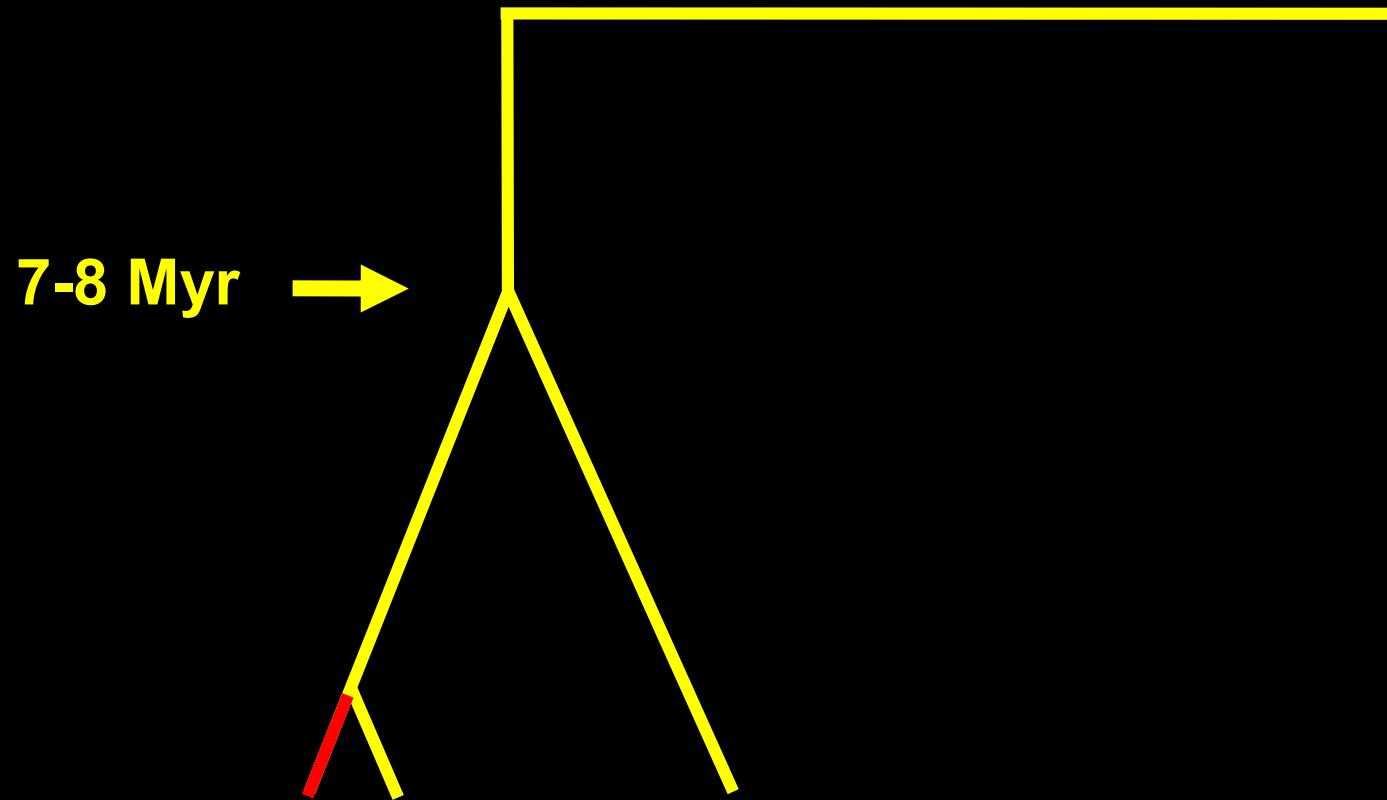


Bladelets





Slide after Prof. C. Wang, GU-CAS, Beijing



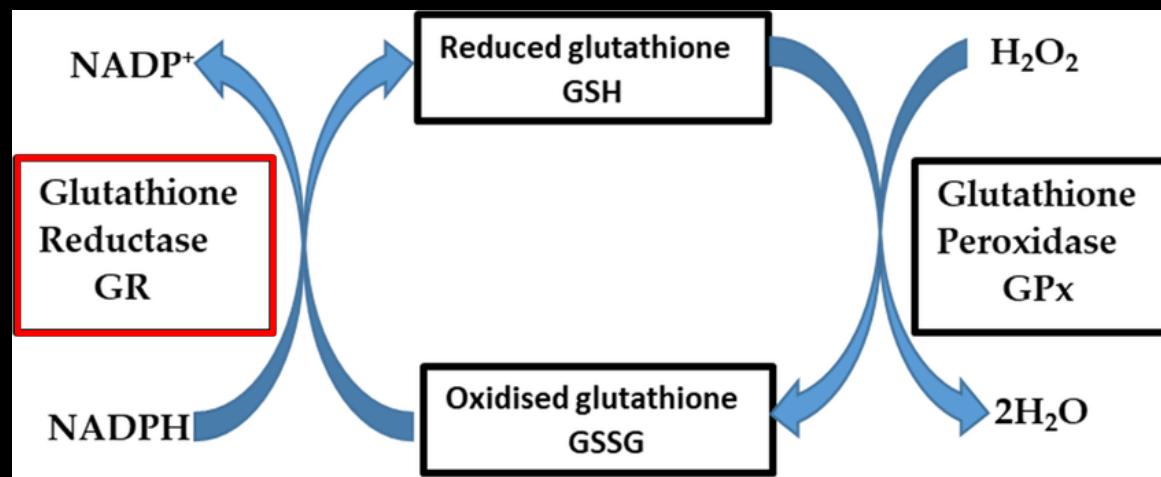
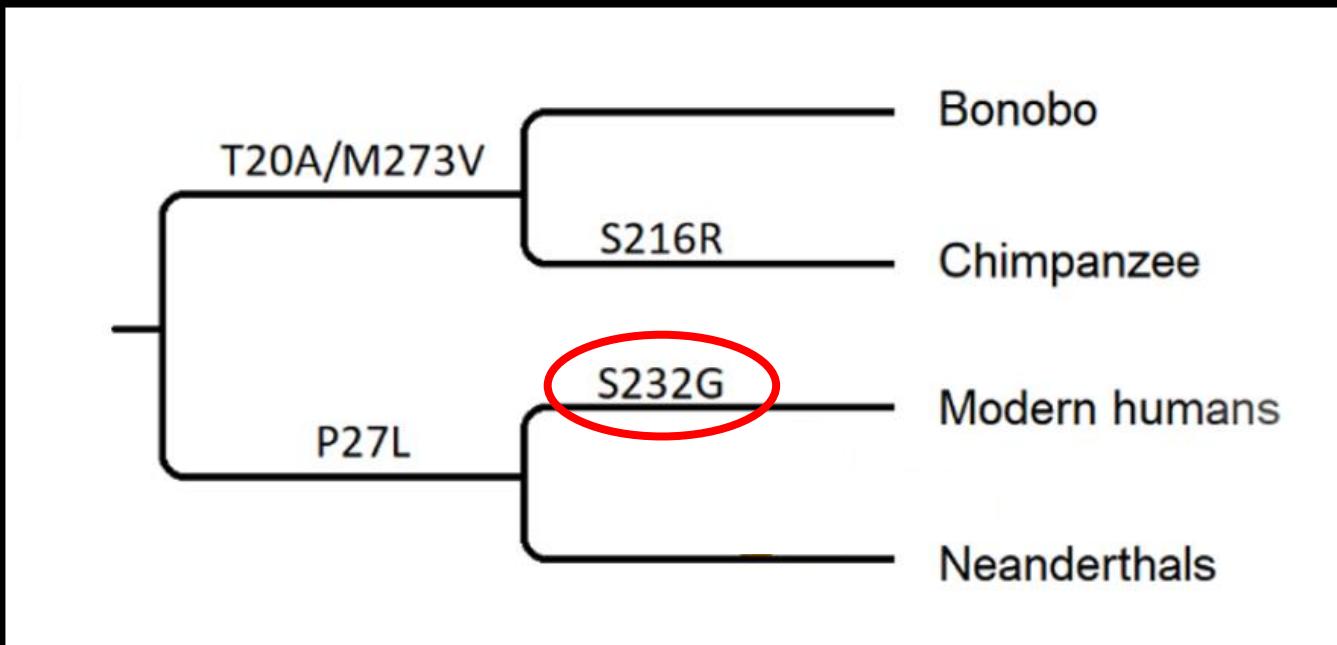
~30,000 single nucleotide changes

~100 small insertions and deletions

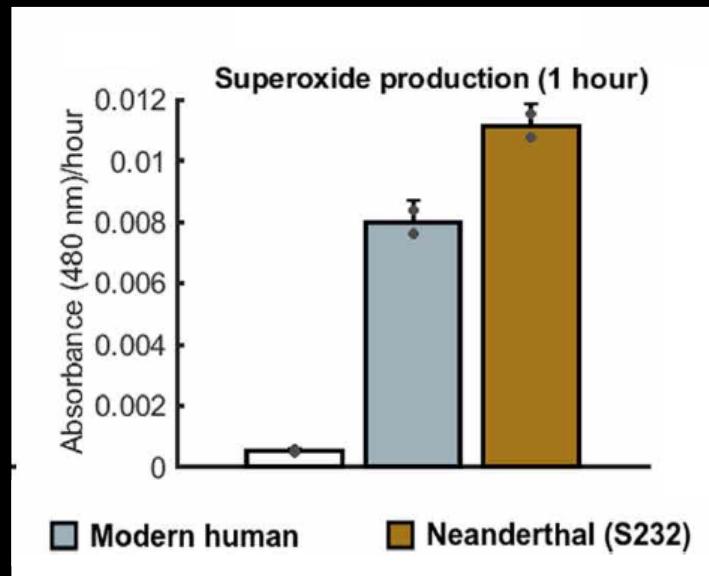
~3,000 regulatory regions (Ensembl)

~100 amino acids (CCDS)

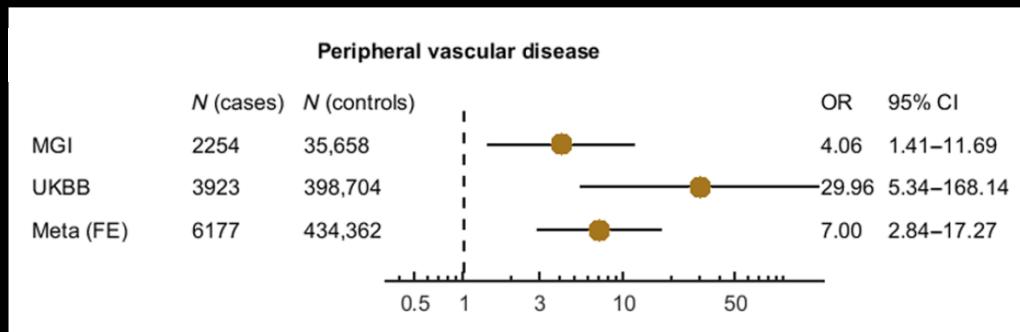
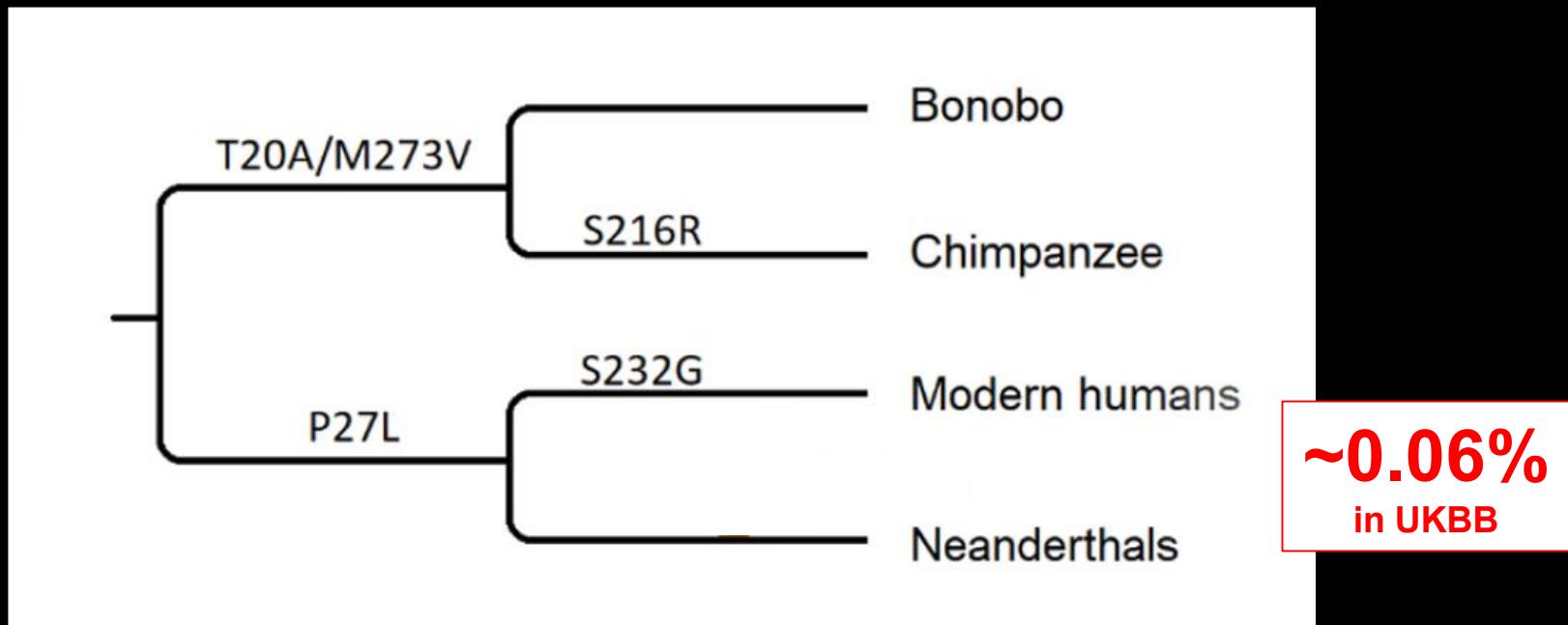
# Glutathione reductase



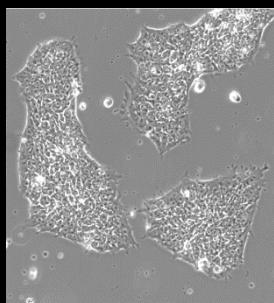
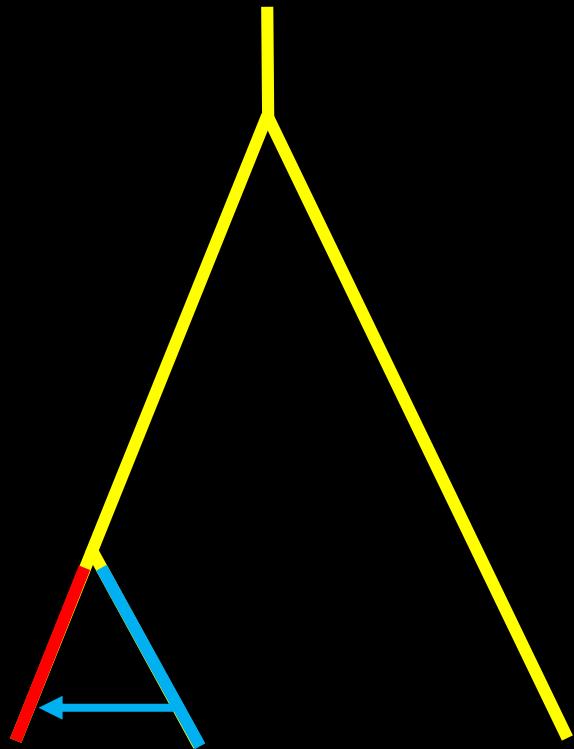
# Glutathione reductase



# Glutathione reductase



Coppo *et al.*, Sci Adv 2022.





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