A Draft Version of the Neandertal Genome

Svante Pääbo
Max Planck Institute for Evolutionary Anthropology
Leipzig, Germany

The Neandertal Genome Project

Croatian Academy of Sciences and Arts
Berlin-Brandenburg Academy of Sciences
The Max Planck Society

454 Life Sciences/Roche
Branford, CT, USA

Jason Affourtit
Jani Simons
Lei Du
Michael Egholm
Jonathan Rothberg

Museo Nacional de
Ciencias Naturales, Madrid

Javier Fortea
Carles LaLueza-Fox
Marco de la Rasilla
Antonio Rosas

LVR-Landesmuseum, Bonn

Ralf Schmitz

MPI-EVA
Leipzig, Germany

Ed Green
Johannes Krause
Adrian Briggs
Tomislav Maricic
Janet Kelso
Susan Ptak
Svante Pääbo

Inst. of Quaternary Geology
& Palaeontology &
HAZU, **Zagreb, Croatia**

Maja Paunovic
Dejana Brajkovic
Jadranka Mauch Lenardic
Pavao Rudan
Zeljko Kucan
Ivan Gusic

The Neandertal Genome Project

Croatian Academy of Sciences and Arts
Berlin-Brandenburg Academy of Sciences
The Max Planck Society

454 Life Sciences/Roche
Branford, CT, USA

Michael Egholm

LVR-Landesmuseum,
Bonn

Ralf Schmitz

MPI-EVA
Leipzig, Germany

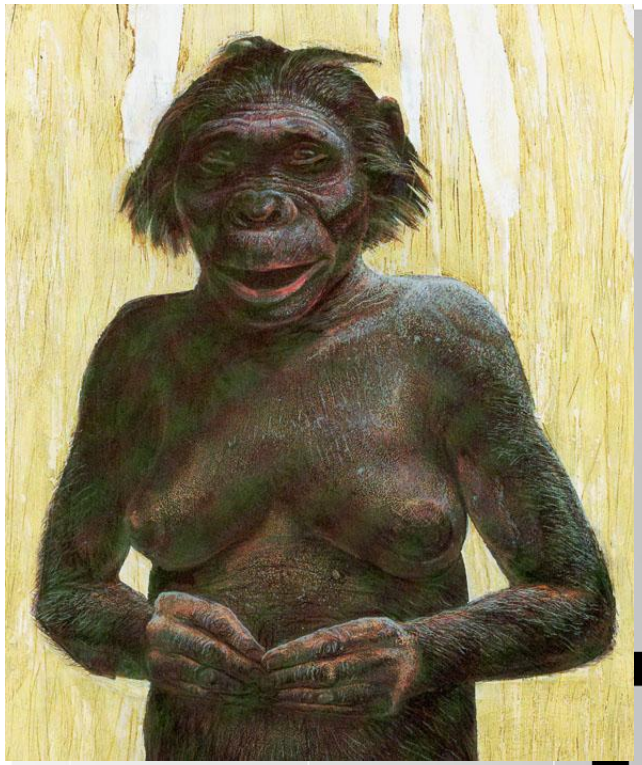
Ed Green
Udo Stenzel
Adrian Briggs
Tomislav Maricic
Janet Kelso
Svante Pääbo

Jean-Jacques Hublin

Inst. of Quaternary Geology
& Palaeontology &
HAZU, Zagreb, Croatia

Pavao Rudan
Zeljko Kucan
Ivan Gusic

Max Planck Institute for Evolutionary Anthropology Leipzig



PREMIERS HOMININES

Ardipithecus

Orrorin tugenensis

Sahelanthropus tchadensis

AUSTRALOPITHECUS

A. africanus

A. afarensis

A. anamensis

A. garhi

Kenyanthropus platyops

PARANTHROPUS

P. aethiopicus

P. boisei

P. robustus

HOMO

H. floresiensis

H. ergaster/ erectus

H. habilis

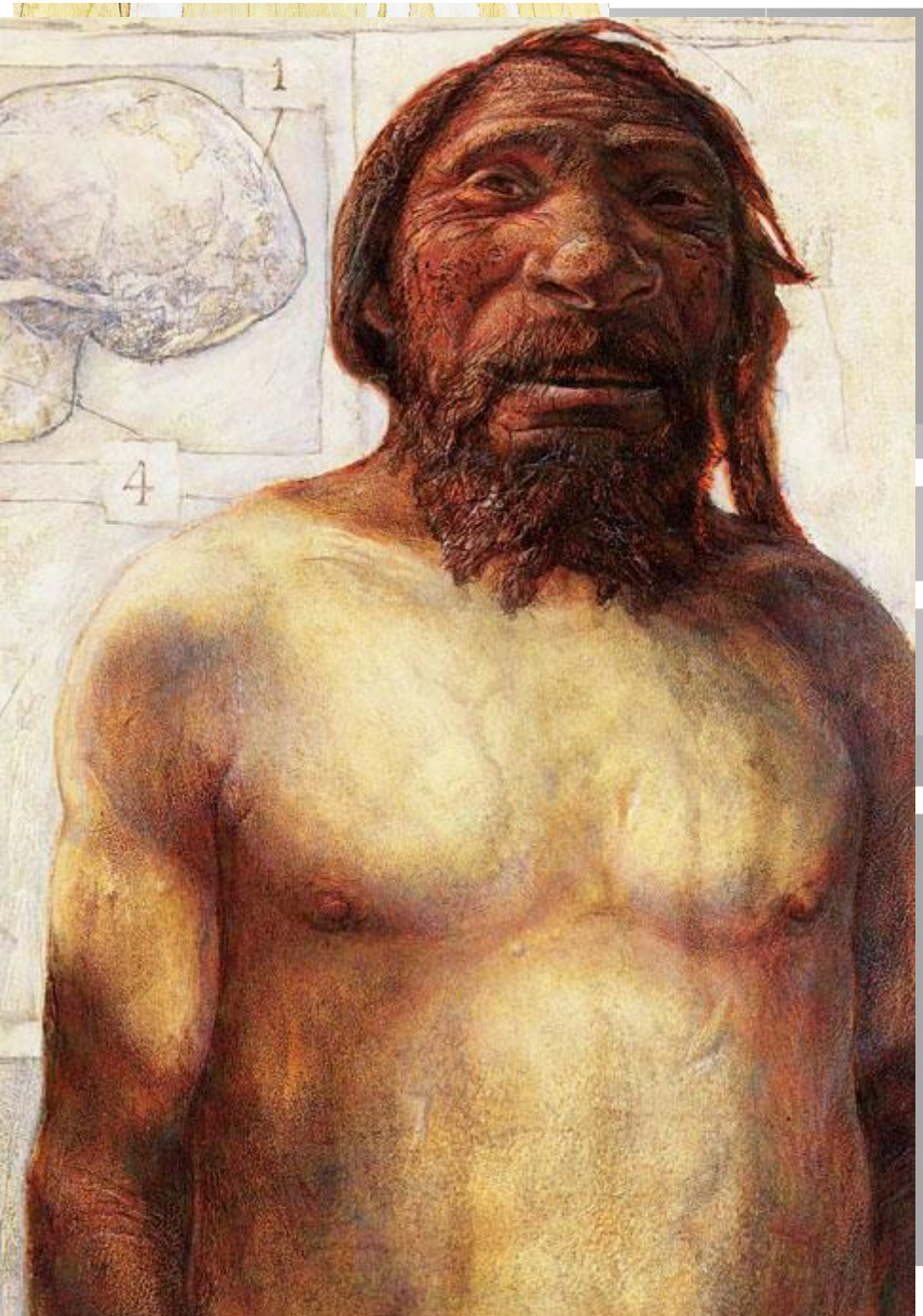
H. sapiens

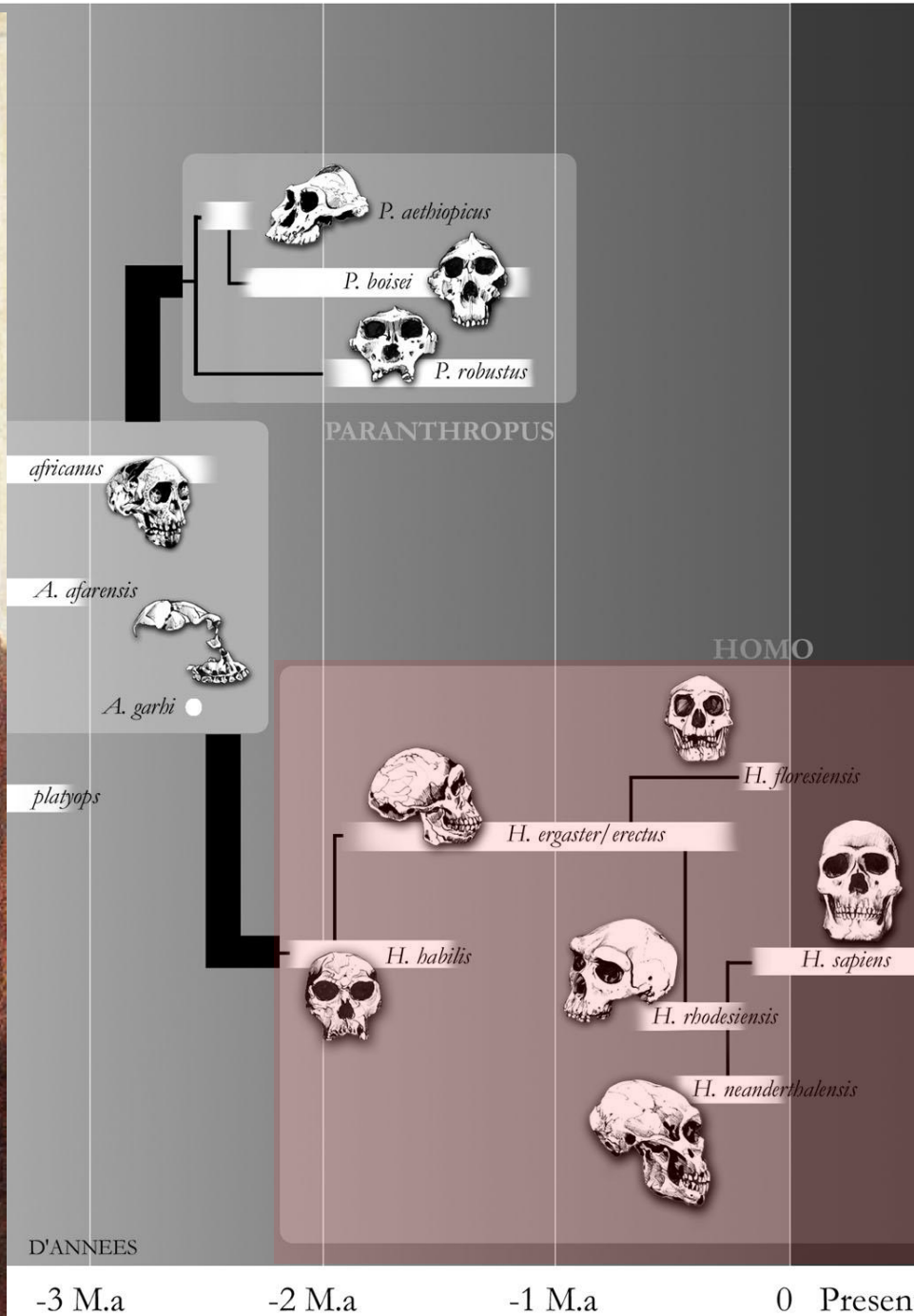
H. rhodesiensis

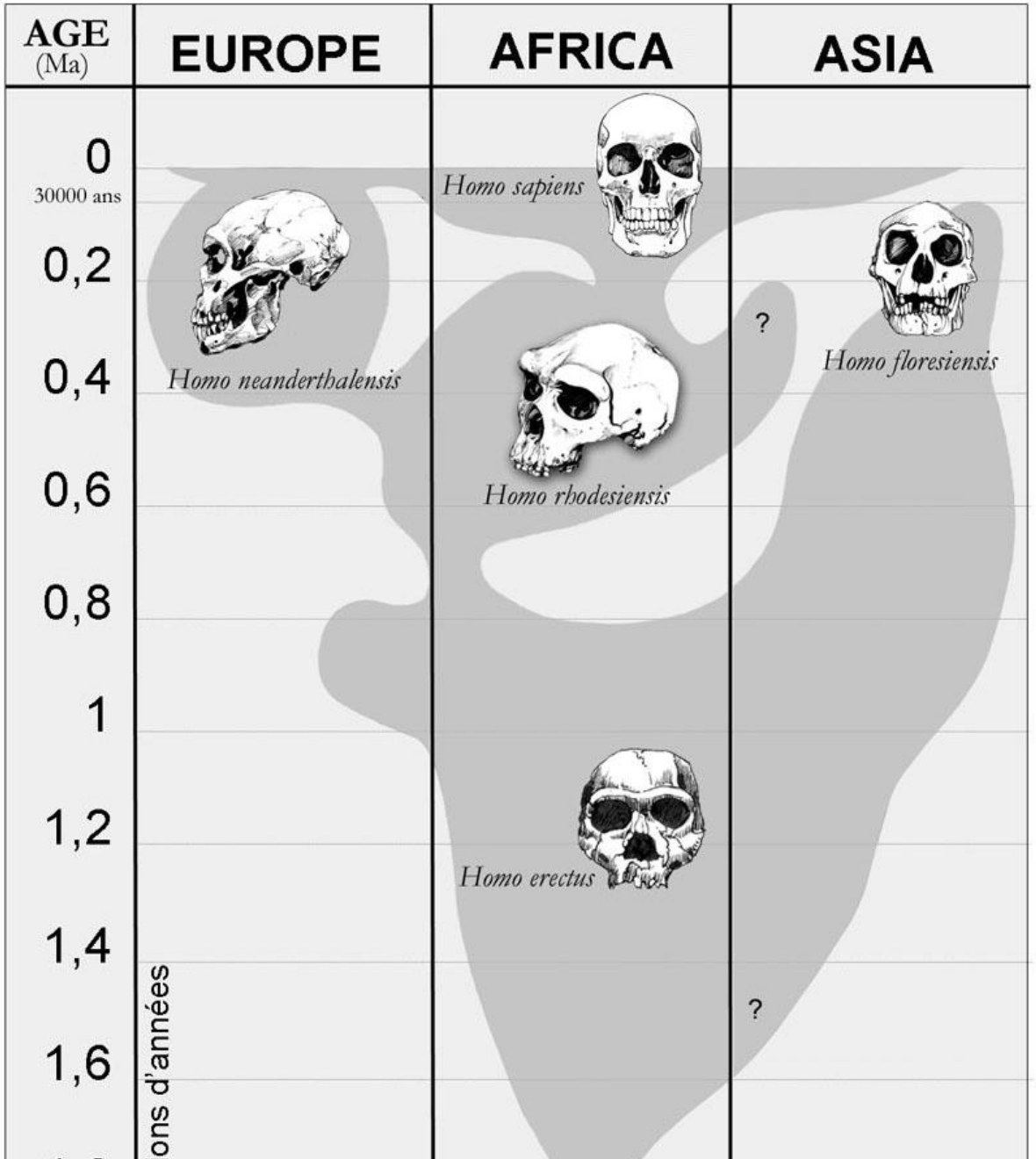
H. neanderthalensis

M.a = MILLIONS D'ANNEES

-7 M.a -6 M.a -5 M.a -4 M.a -3 M.a -2 M.a -1 M.a 0 Presen


1
4


P. aethiopicus
P. boisei
P. robustus
PARANTHROPUS
africanus
A. afarensis
A. garhi
platyops
HOMO
H. floresiensis
H. ergaster/ erectus
H. habilis
H. sapiens
H. rhodesiensis
H. neanderthalensis
D'ANNEES
-3 M.a
-2 M.a
-1 M.a
0 Presen


AGE
(Ma)
EUROPE
AFRICA
ASIA
0
30000 ans
0,2
0,4
0,6
0,8
1
1,2
1,4
1,6
Homo sapiens
Homo neanderthalensis
Homo rhodesiensis
Homo erectus
Homo floresiensis
?
?
ons d'années

Neandertals geographical distribution

Neandertals / Homo sapiens
(separation ca 0.5 my BP)

A Draft Version of the Neandertal Genome

Svante Pääbo

Max Planck Institute for Evolutionary Anthropology
Leipzig, Germany

~5-7 Myr

~5-7 Myr

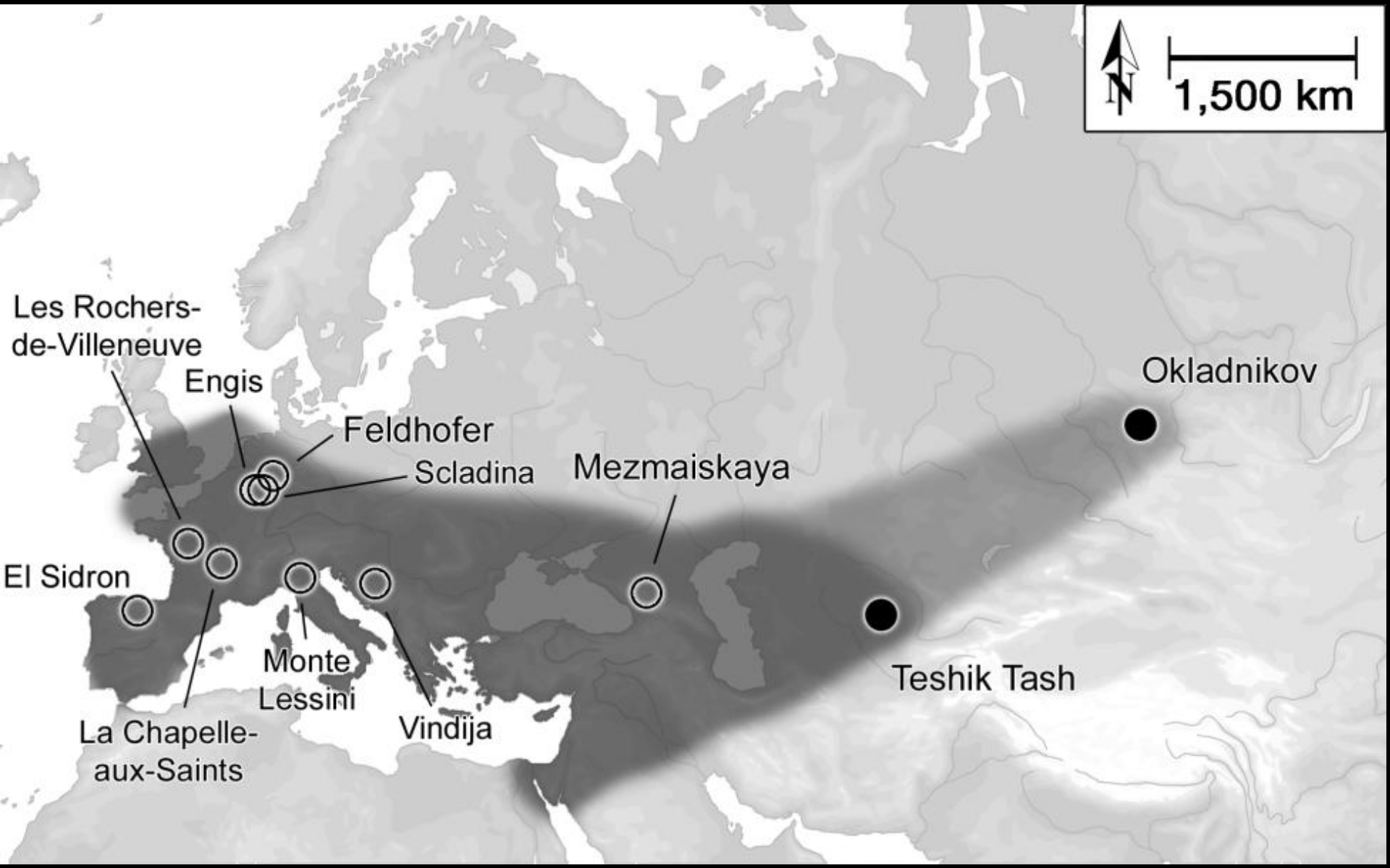
~0.3 Myr

~5-7 Myr

Catalogue of changes
Positive selection

~0.3 Myr



Krause *et al.*, Nature 2007

Krause *et al.*, Nature 2007

Vindija Cave, Croatia

Vi 33.16 (Vi 80); AMS date: 38, 310 +/- 2,130 BP

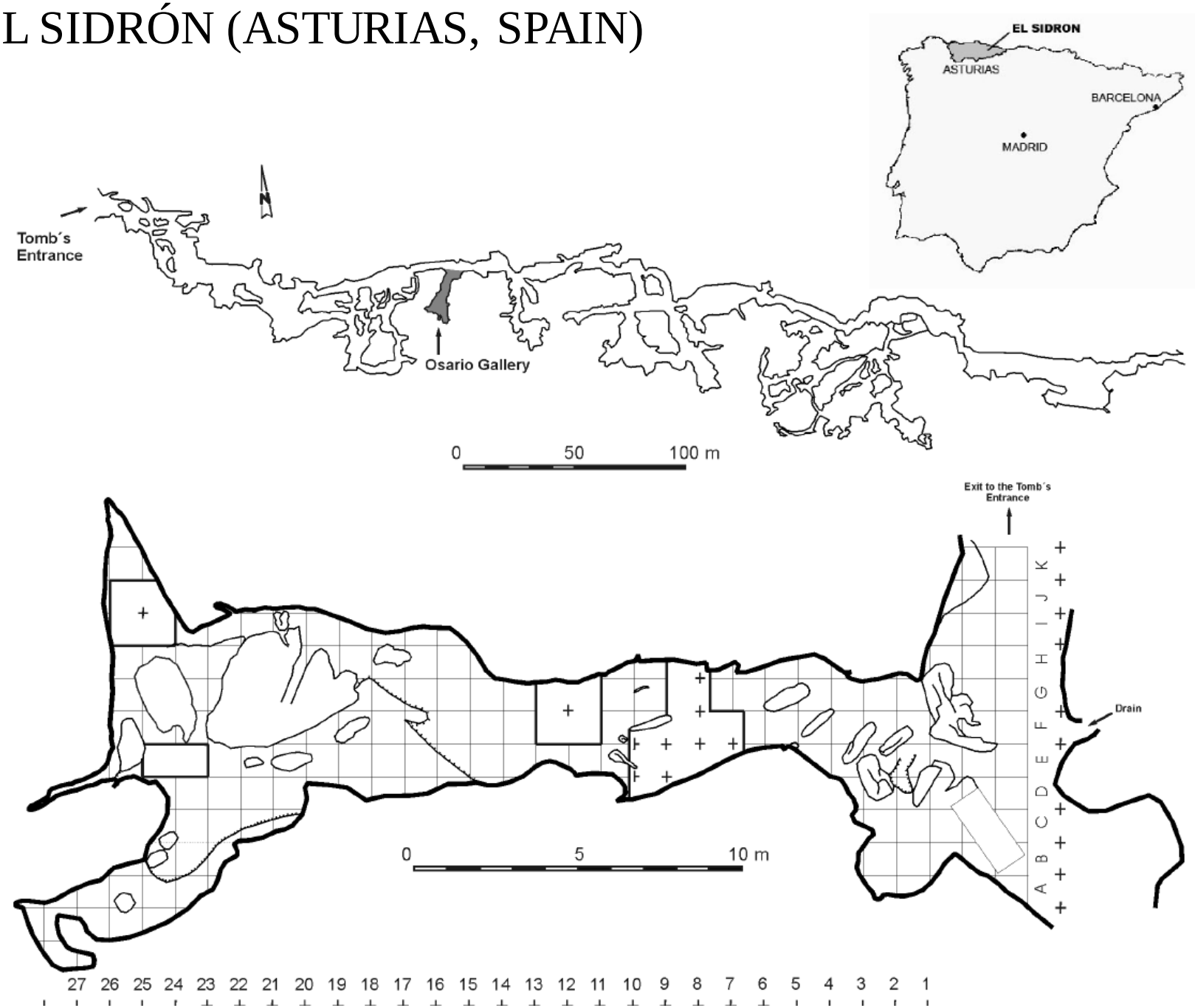
~200 DNA extracts from 70 fossils from 16 sites

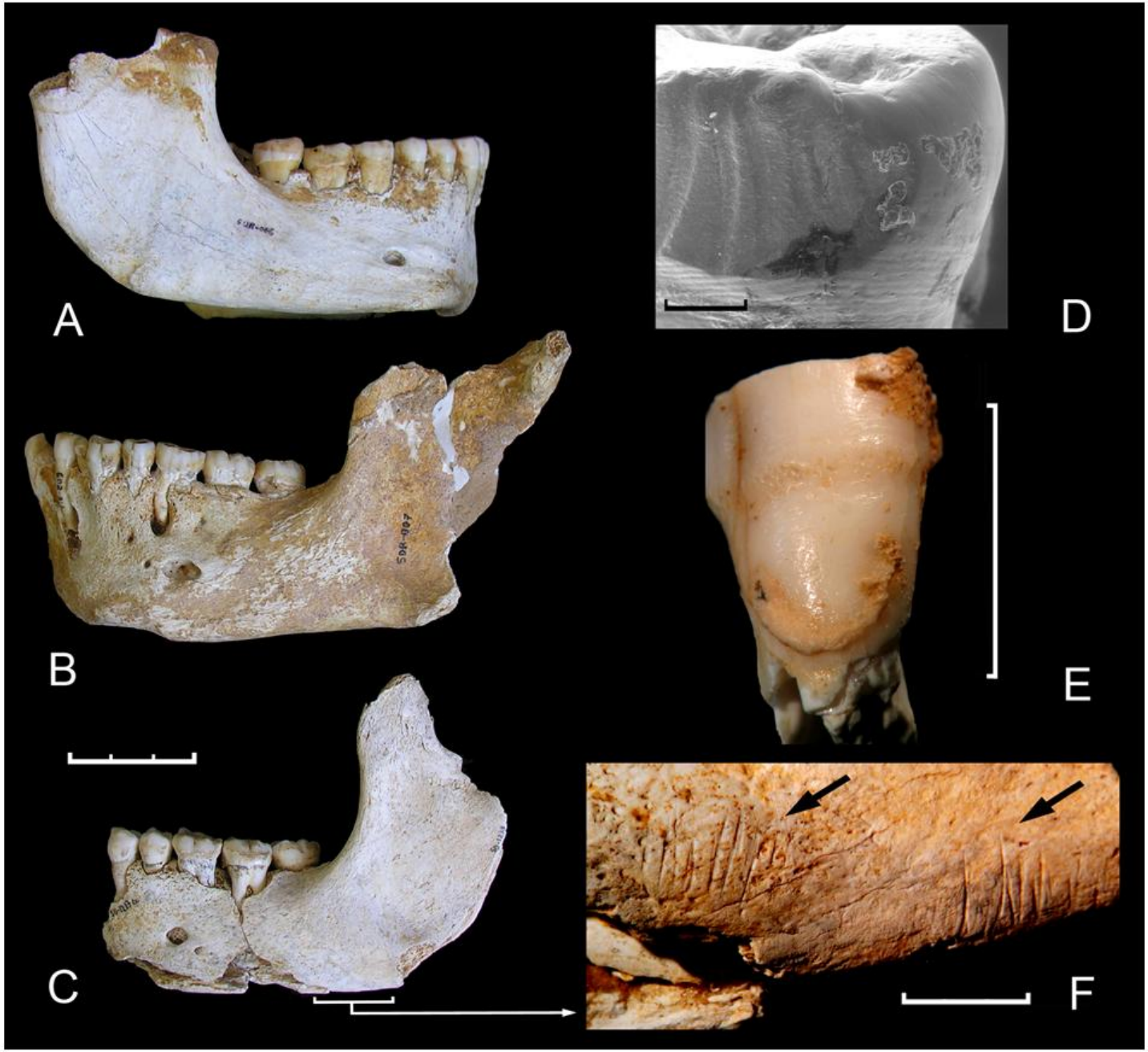
Krause *et al.*, Nature 2007

Krause *et al.*, Nature 2007

El Sidron, Asturias, Spain

EL SIDRÓN (ASTURIAS, SPAIN)





43,129+/-464 BP (cal.)

From Rosas *et al.*, PNAS 2006.

Sidron 1253


Coleman

Sidron 1253

Krause *et al.*, Nature 2007

Krause *et al.*, Nature 2007

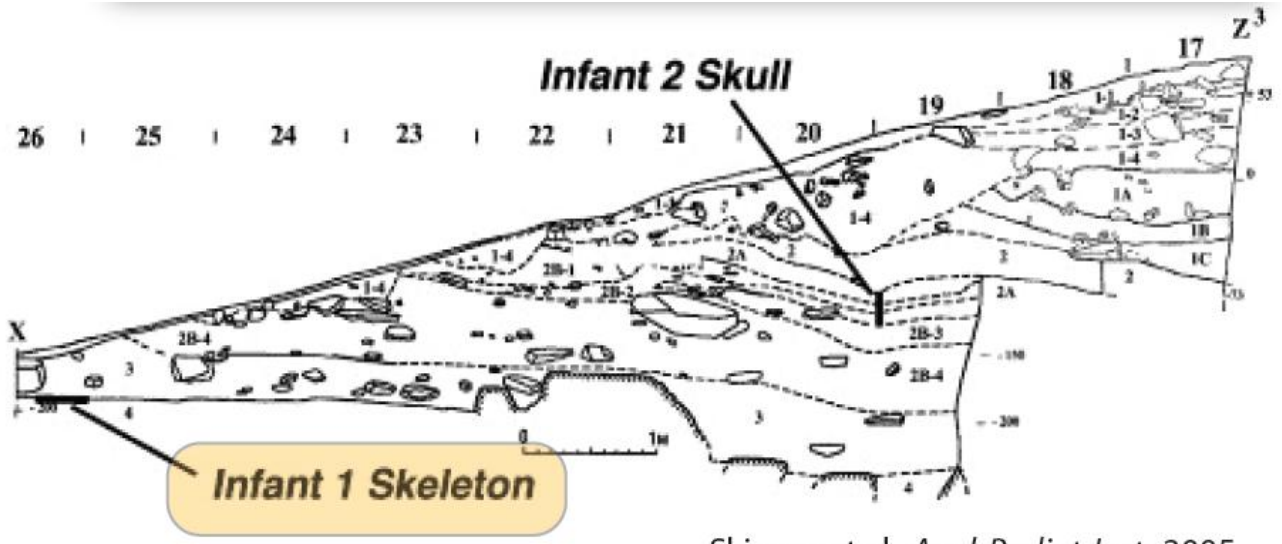
Feldhofer, Neandertal, Germany

~41,000 yrs B.P.

Krause *et al.*, Nature 2007

Krause *et al.*, Nature 2007


RUSSIA
Mezmaiskaya cave
BLACK SEA
GEORGIA
Kerch
Krasnodar
(Краснодар)
Armavir
(Армавир)
Stavropol'
(Ставрополь)
Novorossiysk
(Новороссийск)
Nevinnomyssk
Cherkessk
(Черкесск)
Pyatigorsk
(Пятигорск)
Kislovodsk
(Кисловодск)
Sochi
(Сочи)
Nal'chik
(Нальчик)
Vladikavkaz
(Владикавказ)
Sukhumi
Zugdidi
Senaki
Kutaisi
Poti
Samtredia
T'bilisi
Batumi
Bafra
Rustavi



Skinner et al., *Appl. Radiat. Isot.*, 2005

60,000 – 70,000 BP

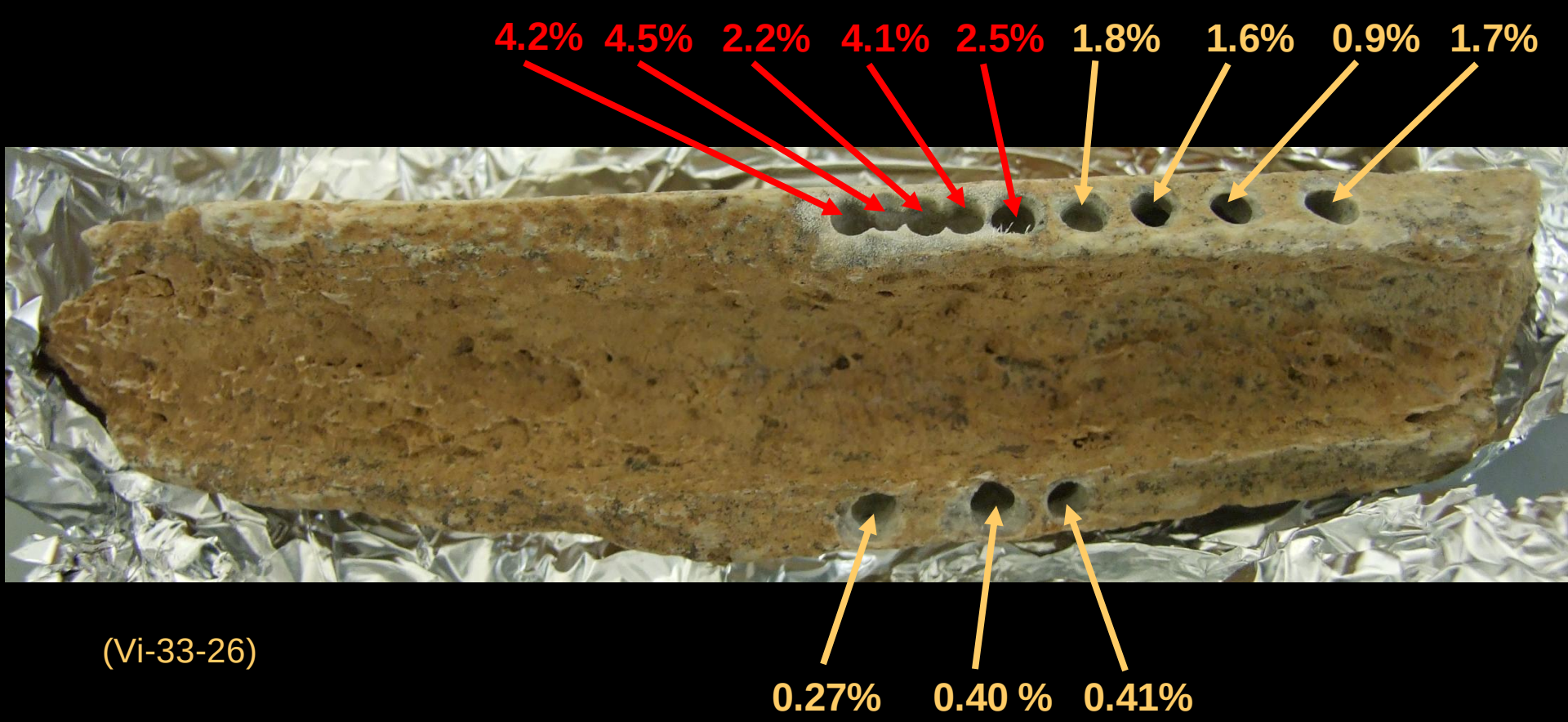
Ponce de León et al., 2008, PNAS


The Neandertal Genome Effort
Vi-11.34
Vi-33.10
Vi-33.11
Vi-33.15
Vi-33.17
Vi-33.16
Vi-33.19
Vi-33.20
Vi-33.22
Vi-33.23
Vi-33.25
Vi-33.26
Vi-33.28
Vi-33.29
Vi-33.30
Vi-33.31
Vi-33.36
Vi-33.38
Vi-33.39

Percent Hominid DNA

(Vi-33-26)

Percent Hominid DNA



(Vi-33-26)

Technical developments

Technical developments

Maximization of yields

Technical developments

Maximization of yields

Amplification of sequencing libraries

Technical developments

Maximization of yields

Amplification of sequencing libraries

Elimination of human contamination

Technical developments

Maximization of yields

Amplification of sequencing libraries

Elimination of human contamination

Understanding chemical modifications

Technical developments

Maximization of yields

Amplification of sequencing libraries

Elimination of human contamination

Understanding chemical modifications

Improved comparison to human genome

Technical developments

Maximization of yields

Amplification of sequencing libraries

Elimination of human contamination

Understanding chemical modifications

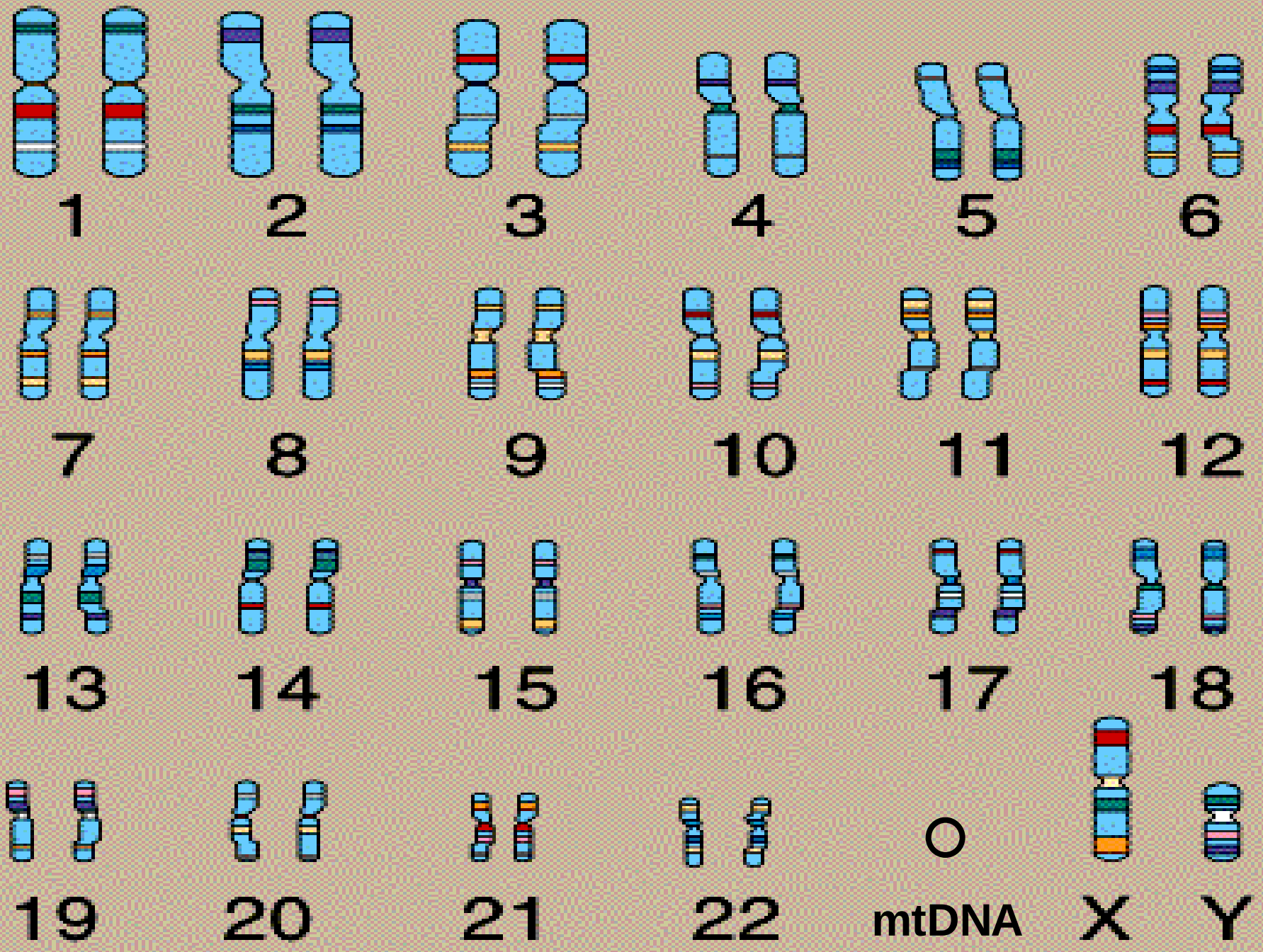
Improved comparison to human genome

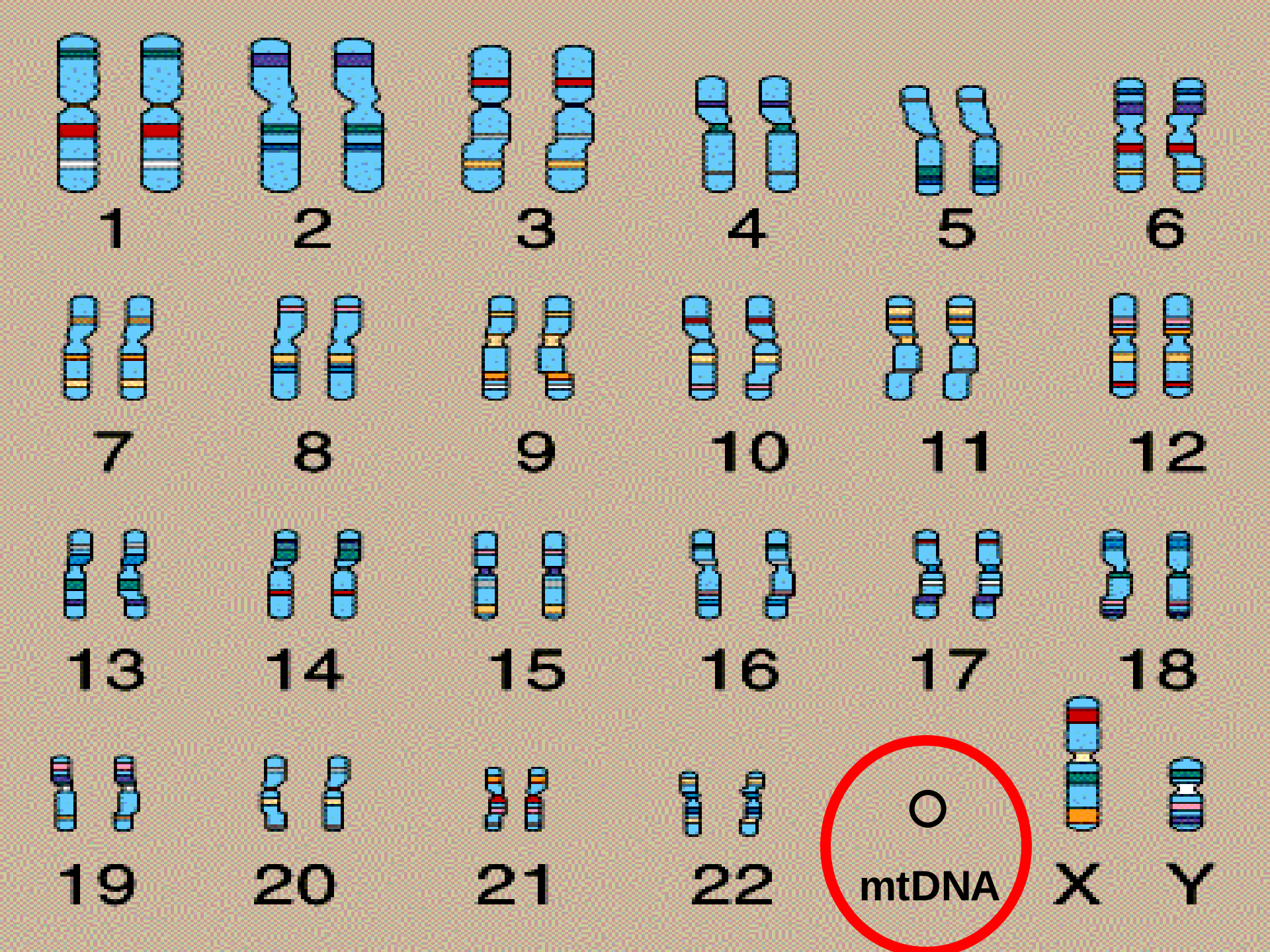
Better sequencing technology

Vindija	**~ 3,700Mb**
Type specimen	~ 2Mb
El Sidron	~ 5Mb
Mezmaiskaya	~ 20Mb

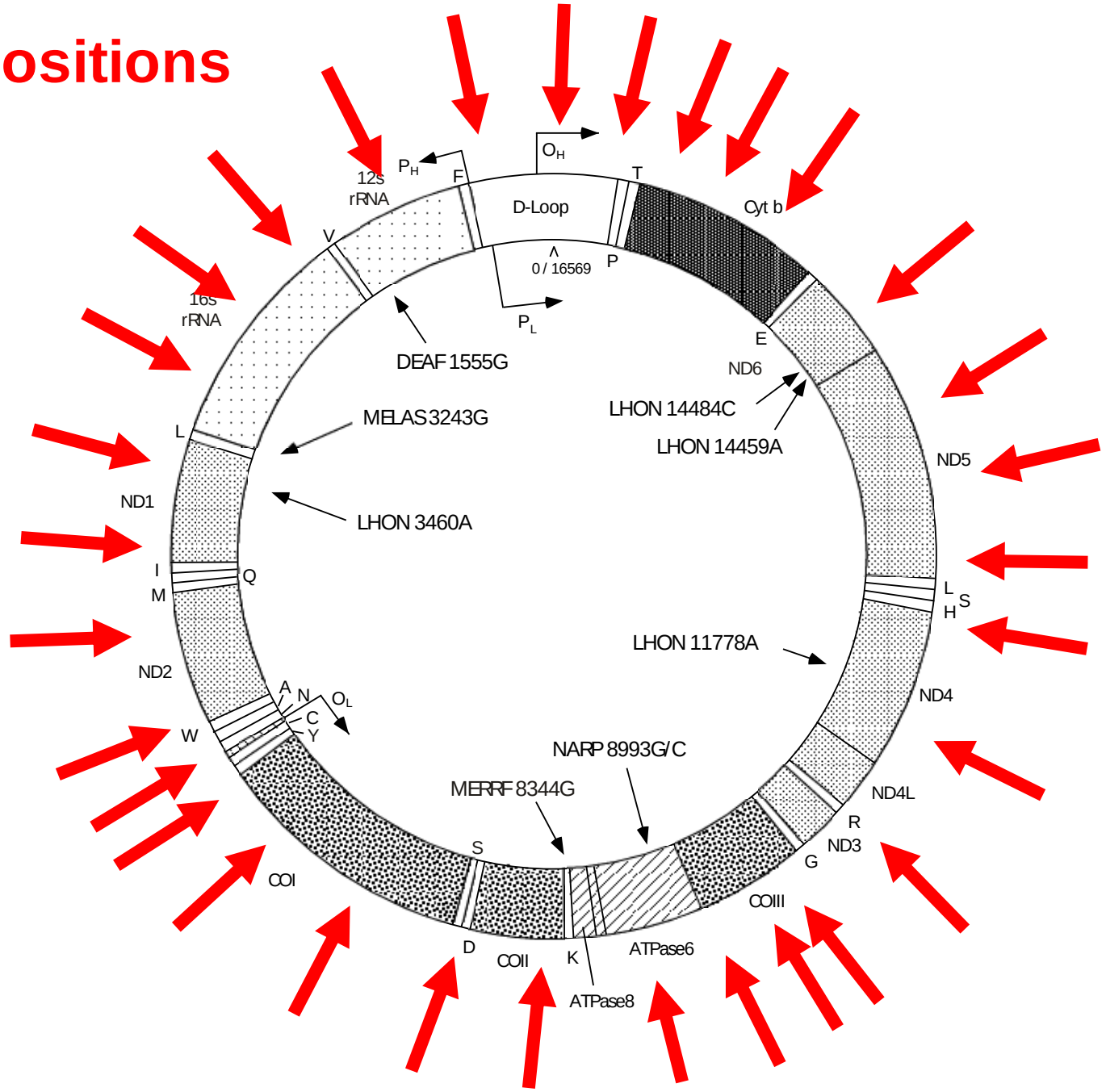
~ 1.2-fold coverage of the Neandertal Genome

Contamination estimates


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y

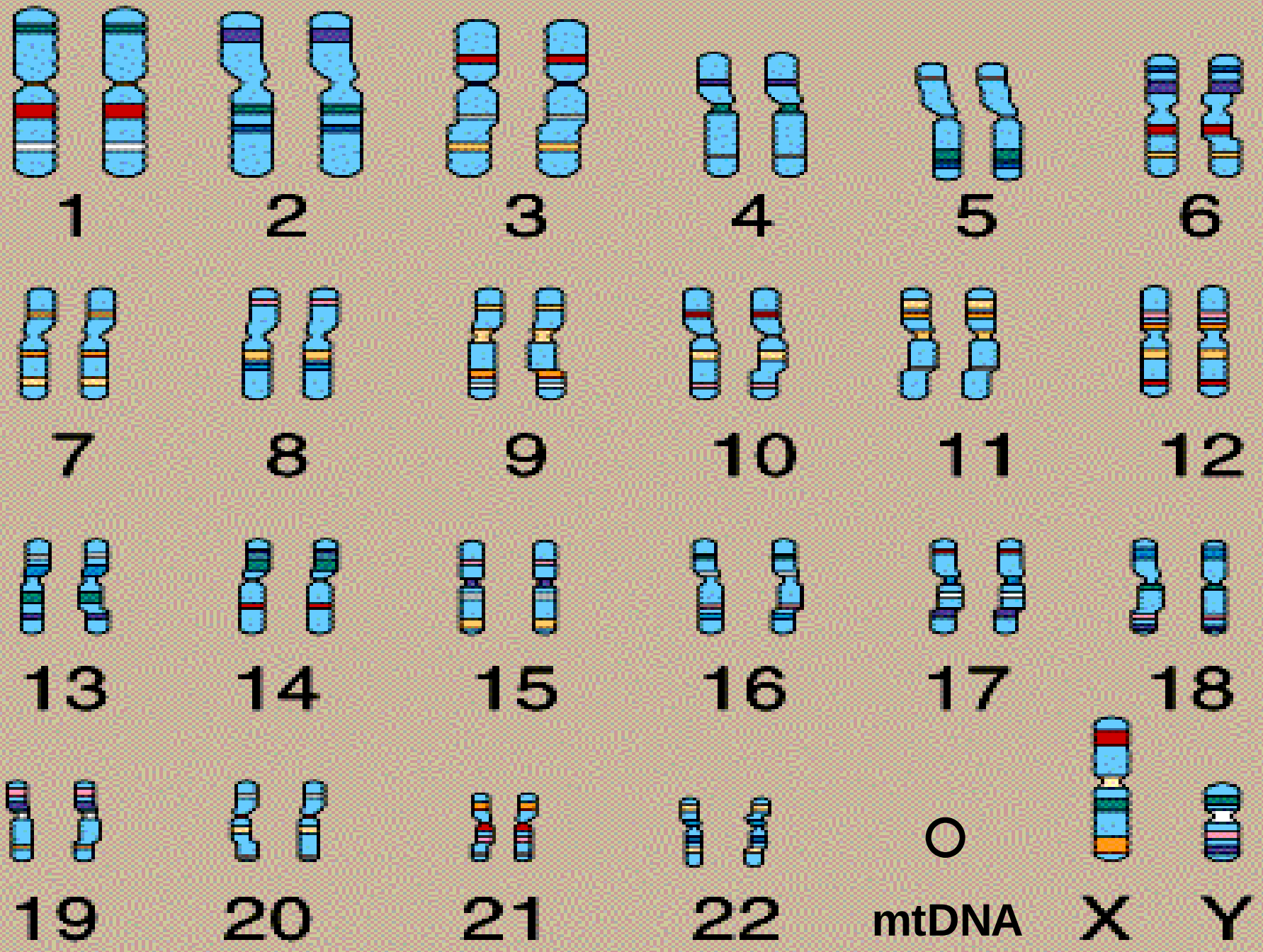

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y

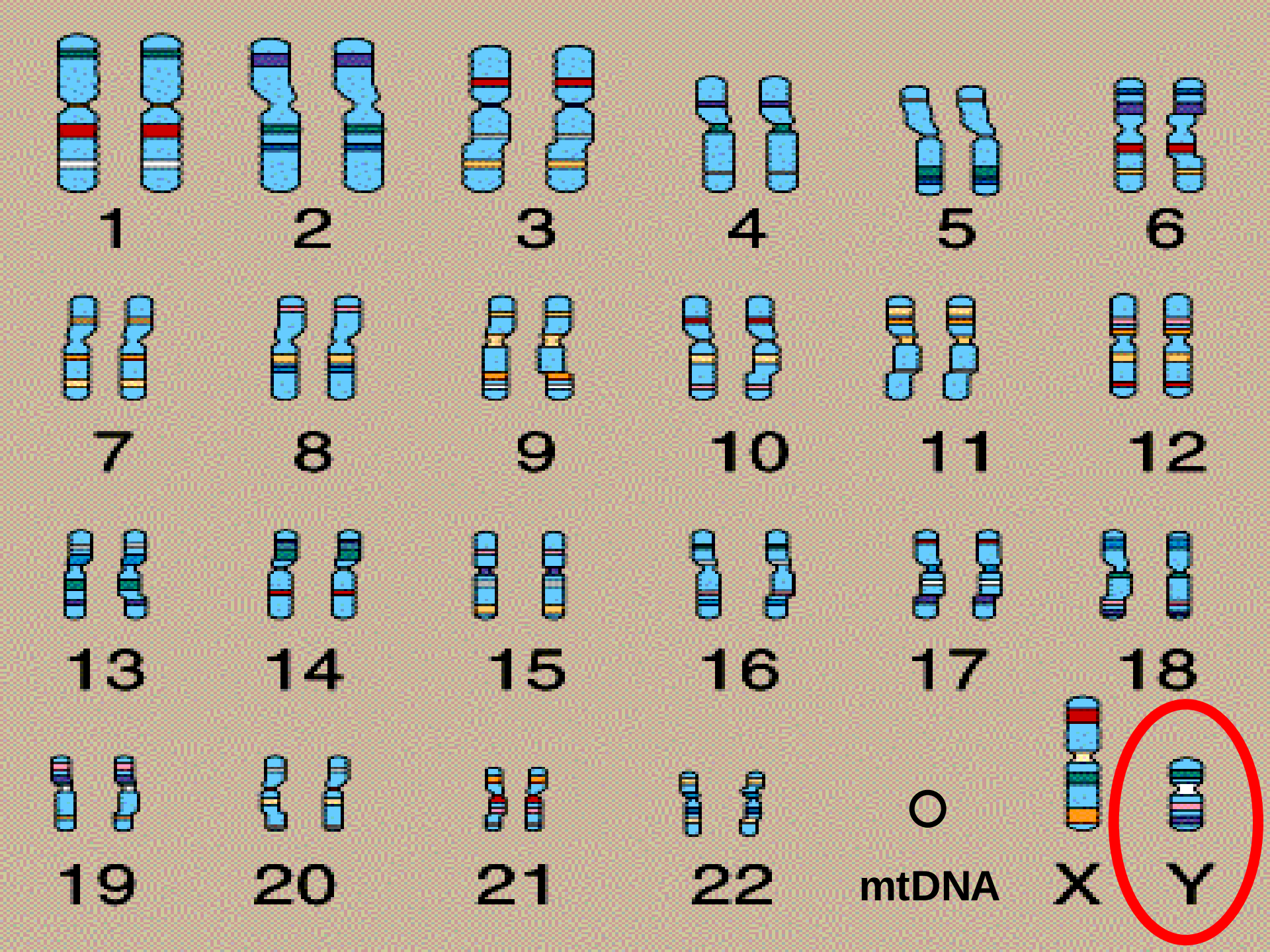
133 positions



Mitochondria contamination estimate

Bone	Human	Neandertal	Contamination rate
Vi33.16/1	9	1,928	0.5% (0.2% - 0.9%)
Vi33.16	11	5,827	0.2% (0.1% - 0.3%)
Vi33.26	5	1,488	0.3% (0.1% - 0.8%)
Total	**25**	**9,243**	**0.3% (0.2% - 0.4%)**

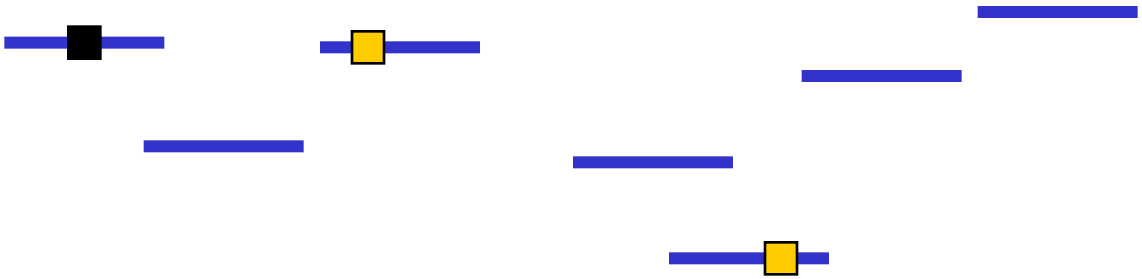

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y

Y chromosome contamination estimate

sample	total sequences	in Y-unique regions	expected in Y-unique regions	contamination rate
Vi33.16/1	1,078,815	0	19	0% (0% - 17.6%)
Vi33.16	12,250,471	2	215	0.9% (0.1% - 3.3%)
Vi33.26	8,342,262	0	146	0% (0% - 2.5%)
Total	**21,671,548**	**2**	**380**	**0.5% (0.1% - 1.9%)**

Human genome



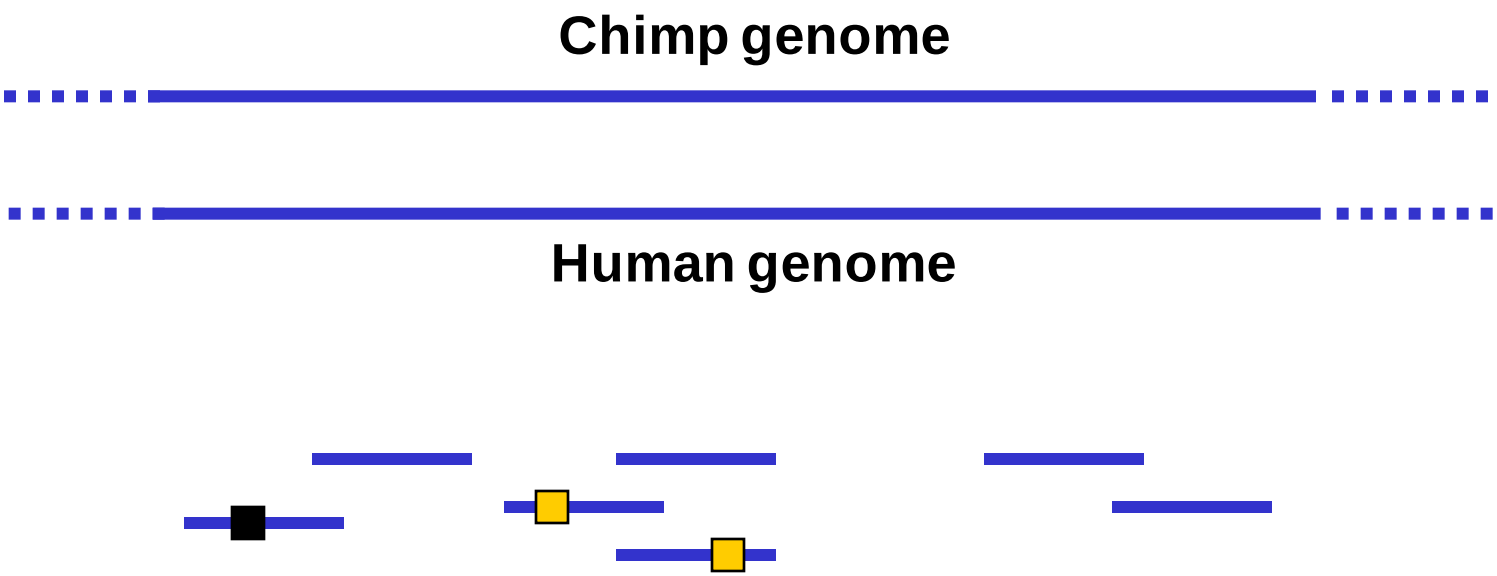
Neandertal genome
(One-fold coverage)

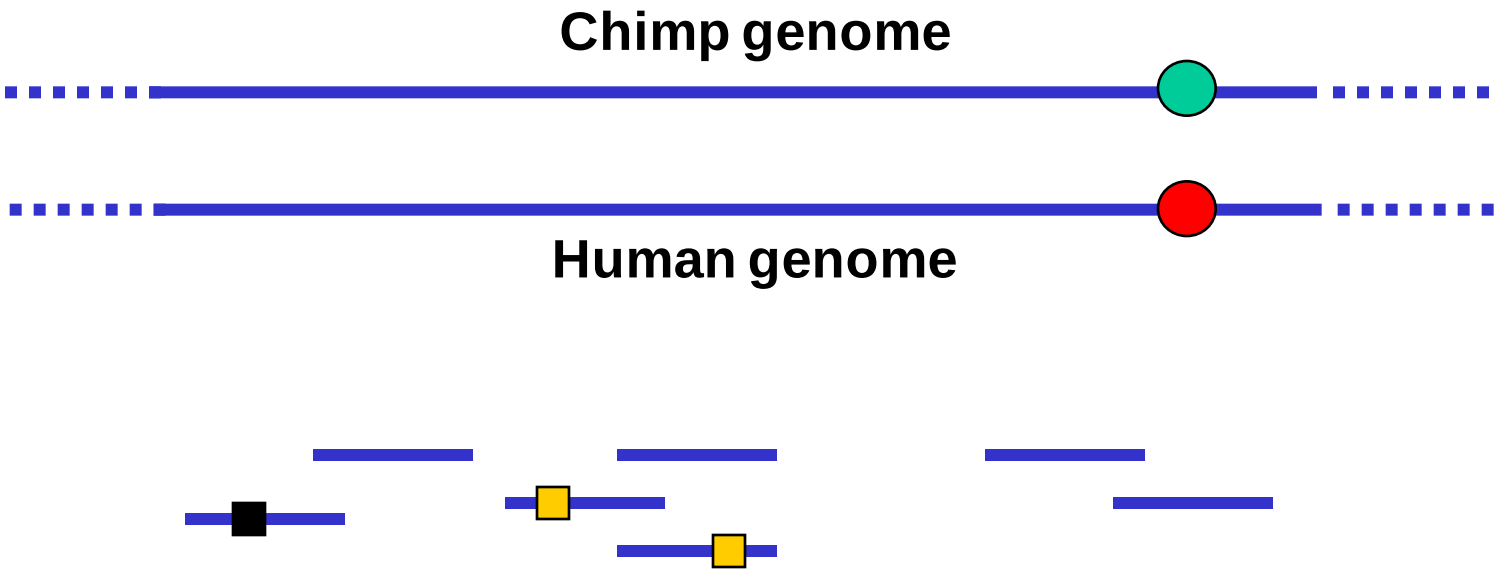
Human genome

~ 63%

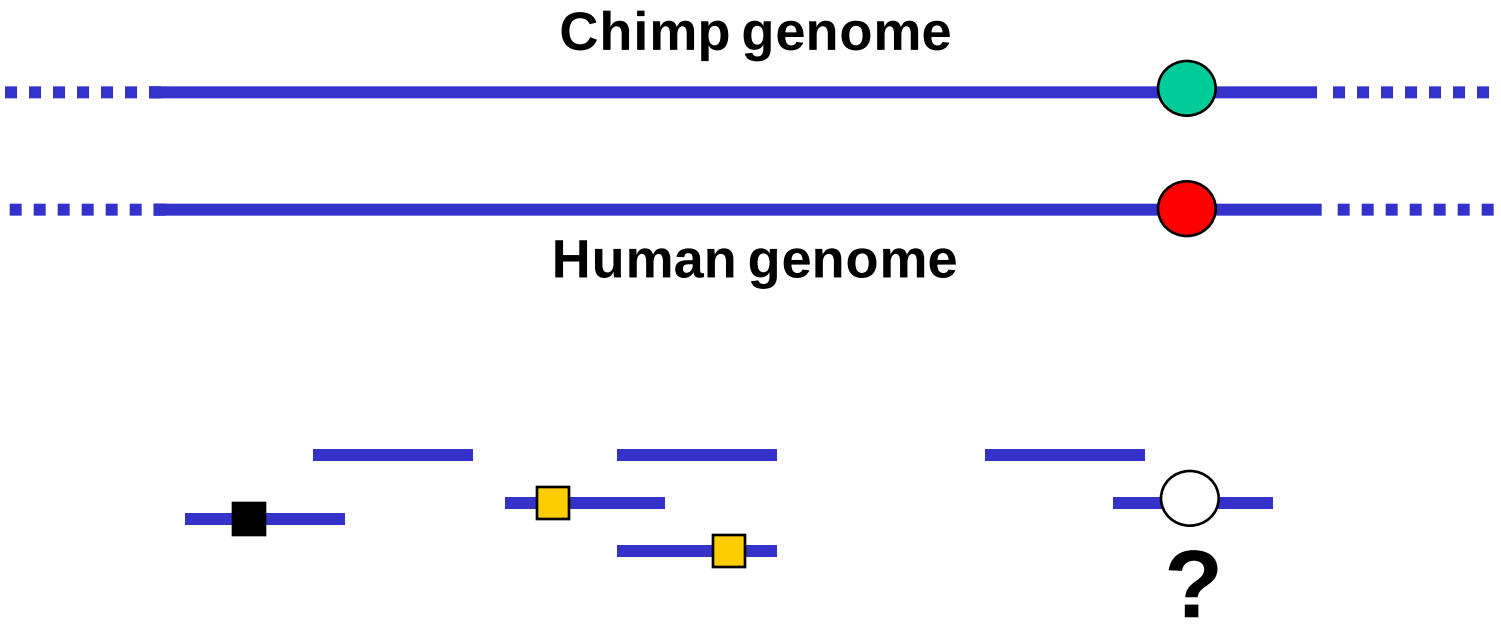
Neandertal genome
(One-fold coverage)

Catalogue of changes


Chimp genome
Human genome
Neandertal genome
(One-fold coverage)



Neandertal genome
(One-fold coverage)



Neandertal genome
(One-fold coverage)

Human	…1111111111111111111111111111111…
Neandertal	…1111111111111110111111111111110111…
Chimp	…0000000000000000000000000000000…

Human …1111111111111111111111111111111111…

Neandertal …1111111111111111011111111111101111…

Chimp …0000000000000000000000000000000000…

~6.5 Myr




~6.5 Myr

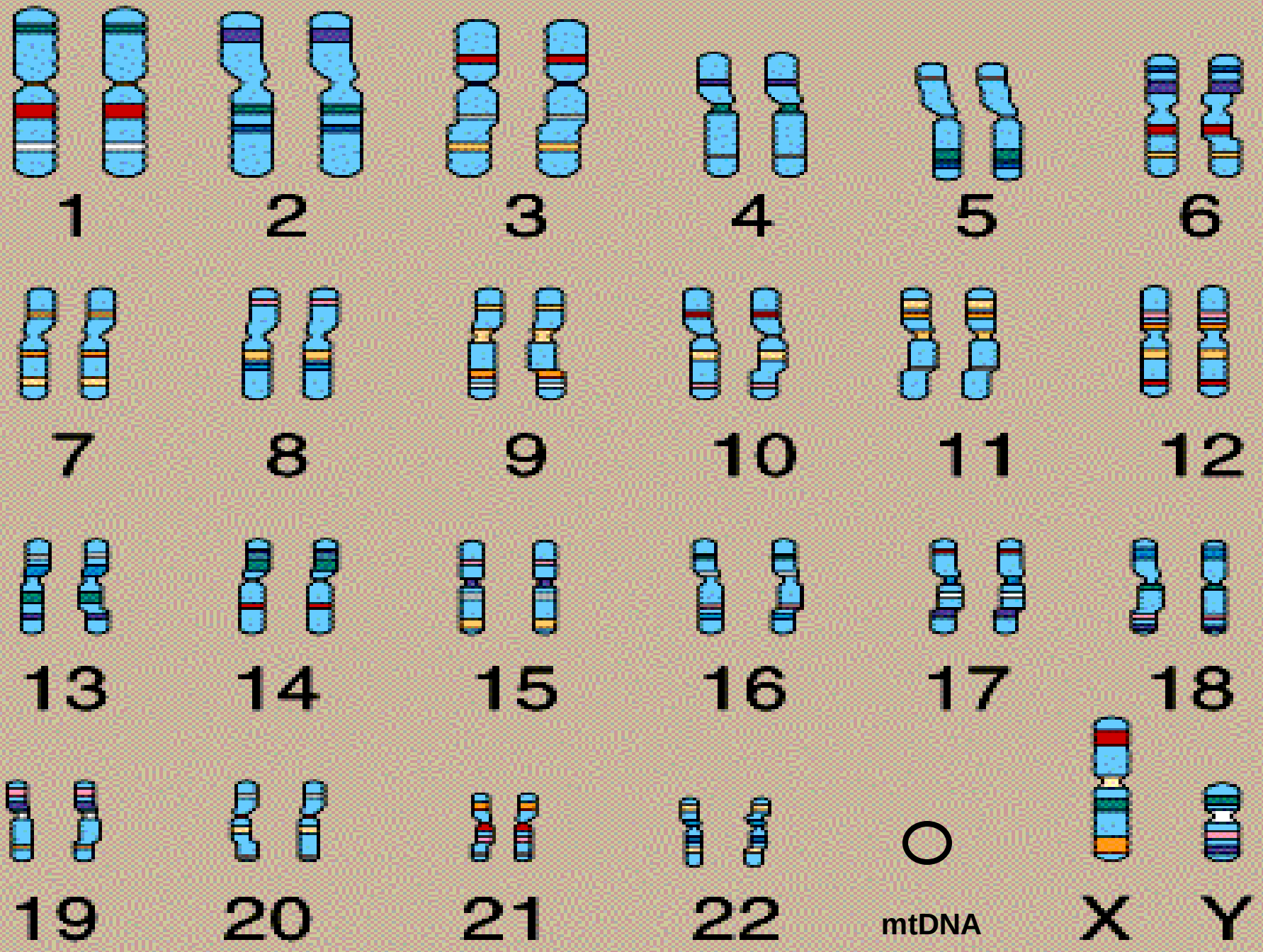
12.8%?

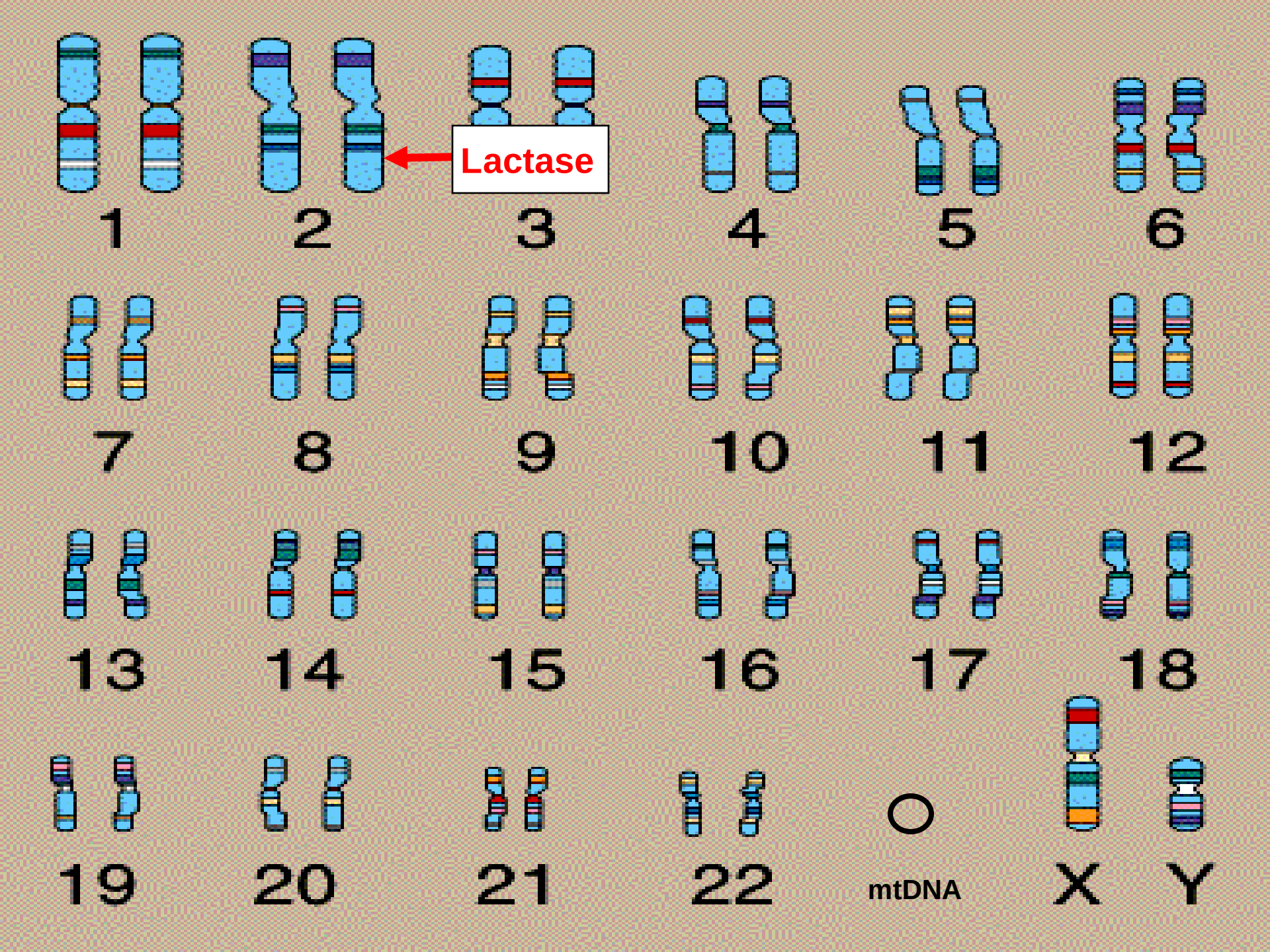
Divergence

		x 6.5 MY
Neandertal:	**12.8%**	**830,000 yrs**

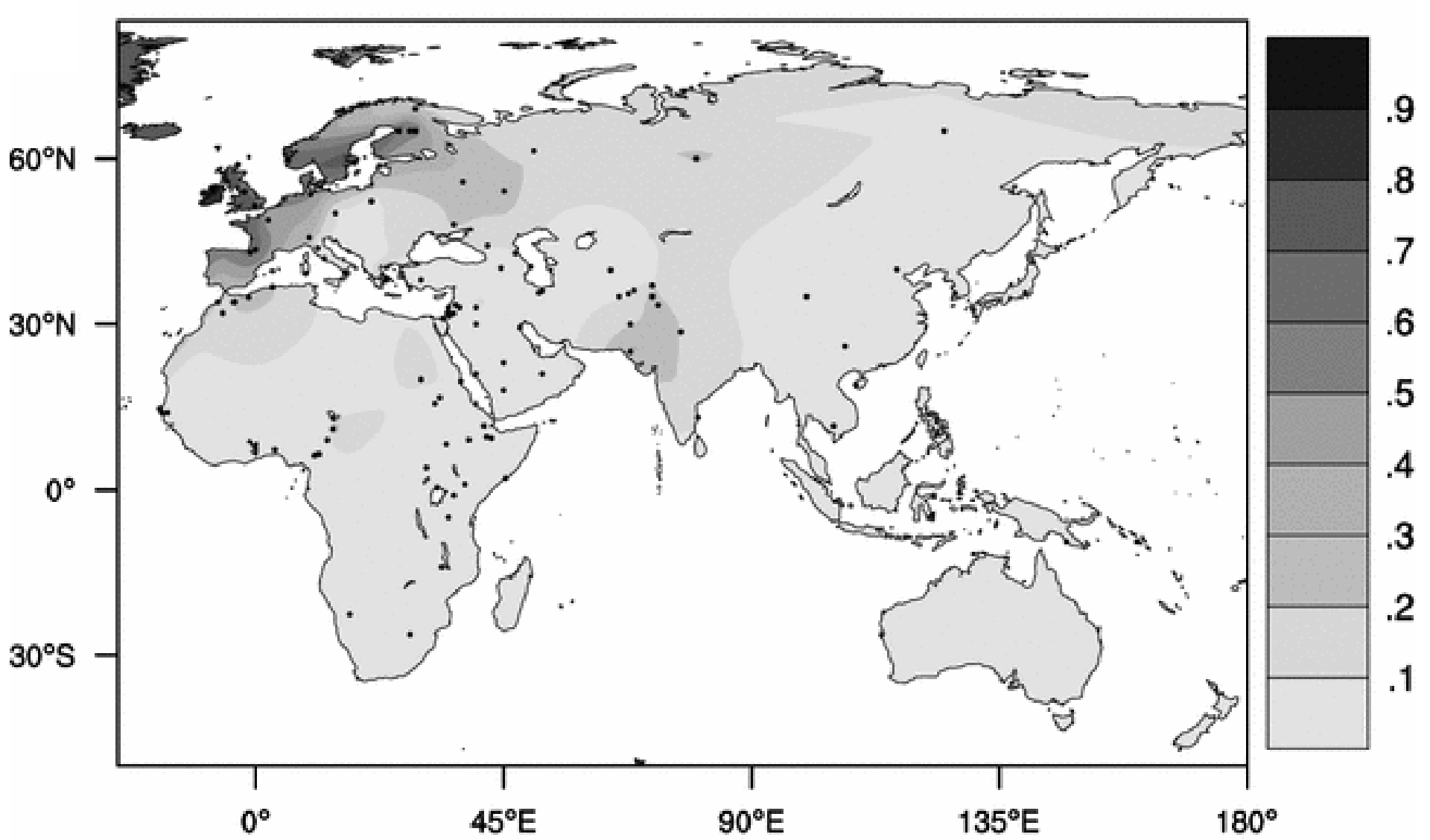
Divergence

		x 6.5 MY
Neandertal:	**12.8%**	**830,000 yrs**
French:	**8.1%**	**529,000 yrs**
Han:	**8.6%**	**558,000 yrs**
Mbuti:	**10.5%**	**682,000 yrs**
San:	**10.7%**	**694,000 yrs**


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y

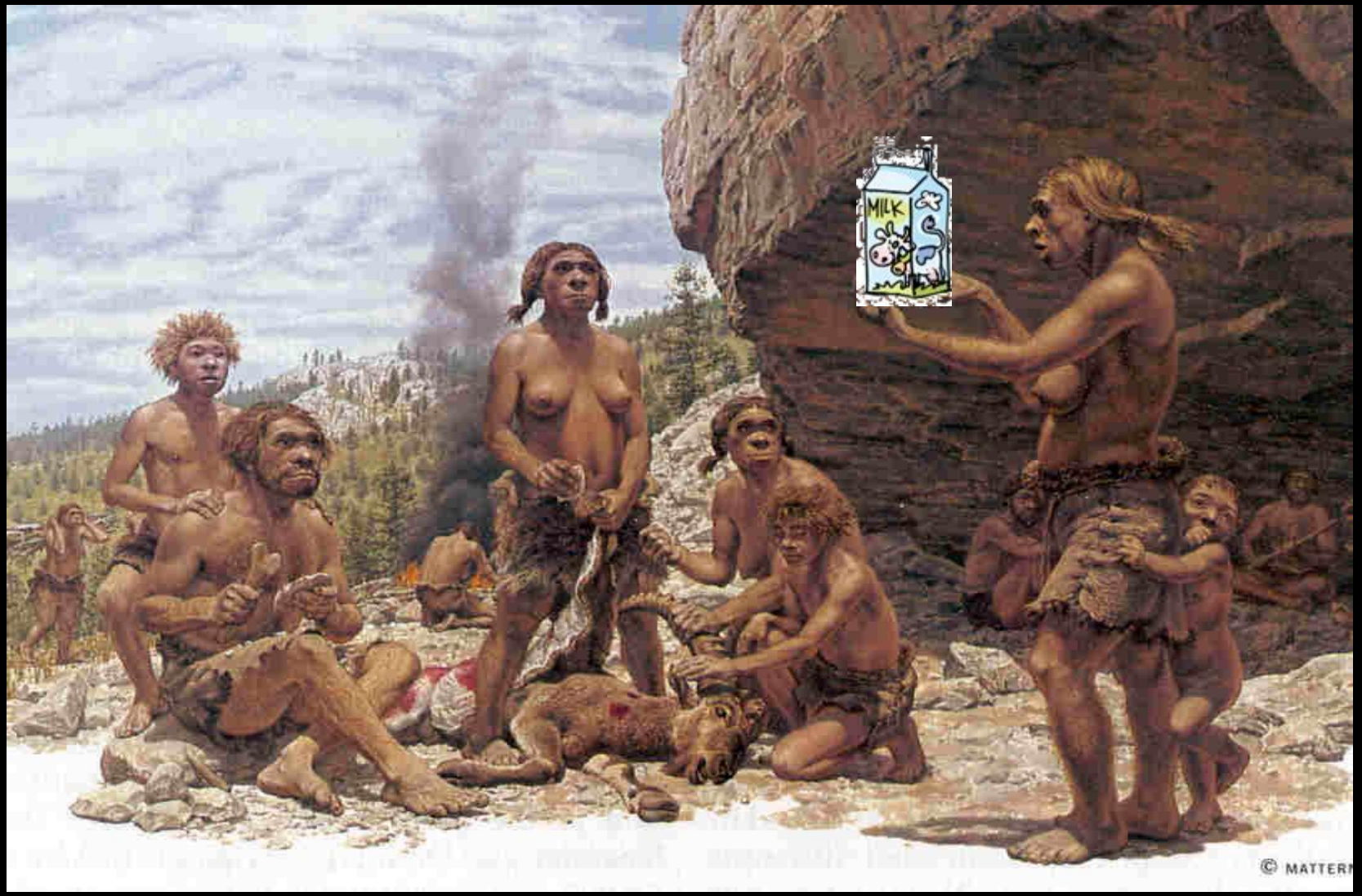

Lactase
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y

Distribution of *LCT (C-13910*T)*



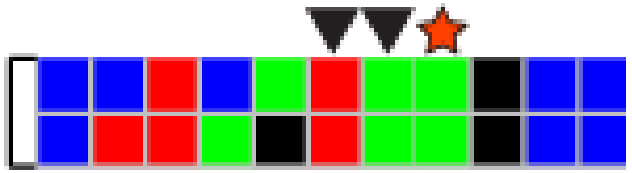
From Ingram *et al.*, 2008

Lactase persistence



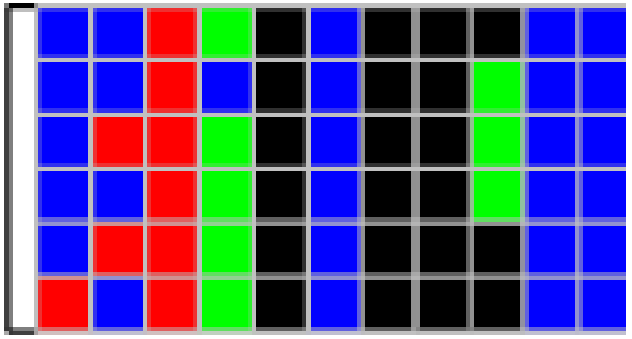
Lactase persistence

Lactase persistent chromosomes

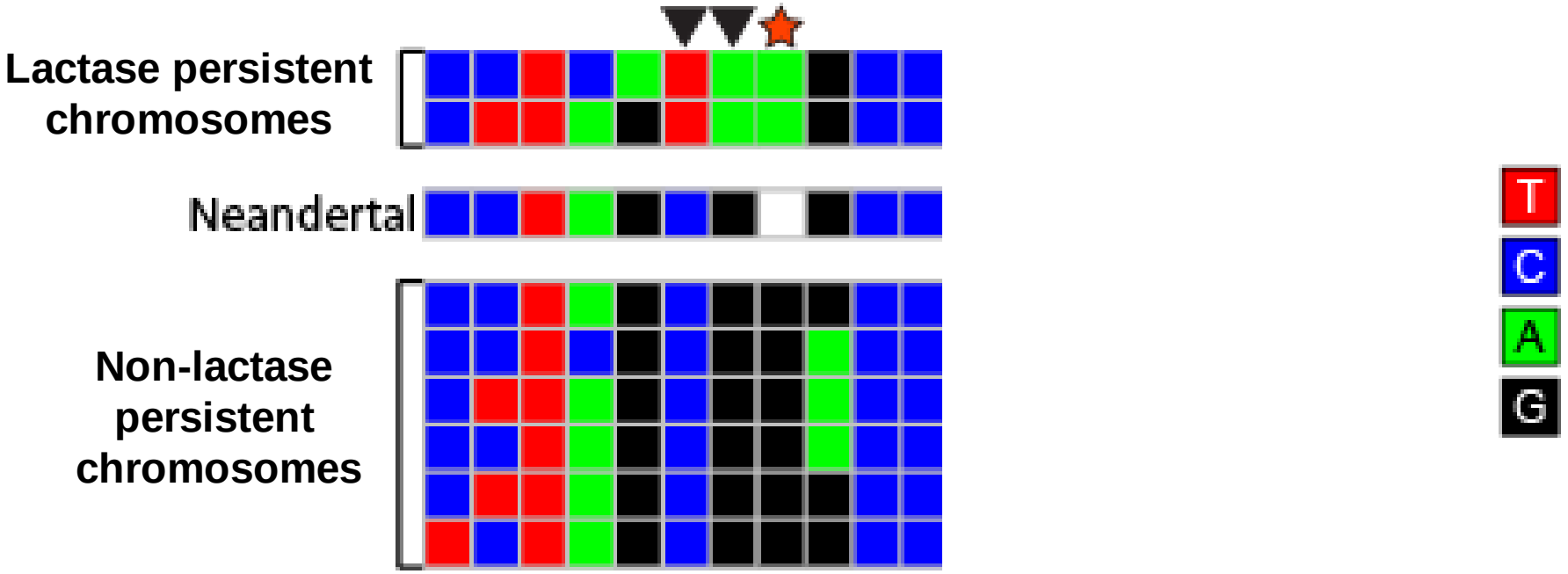


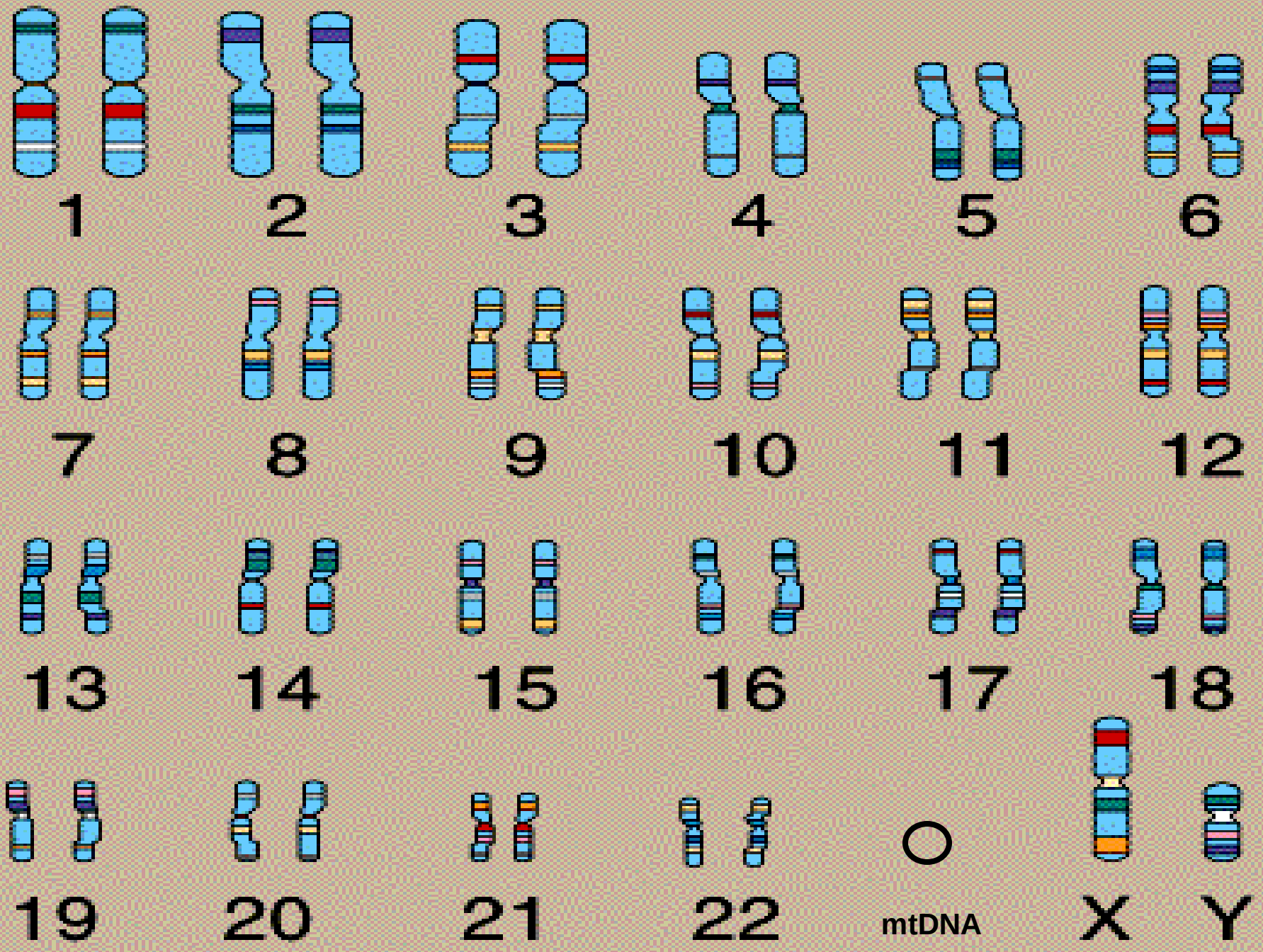
Neandertal

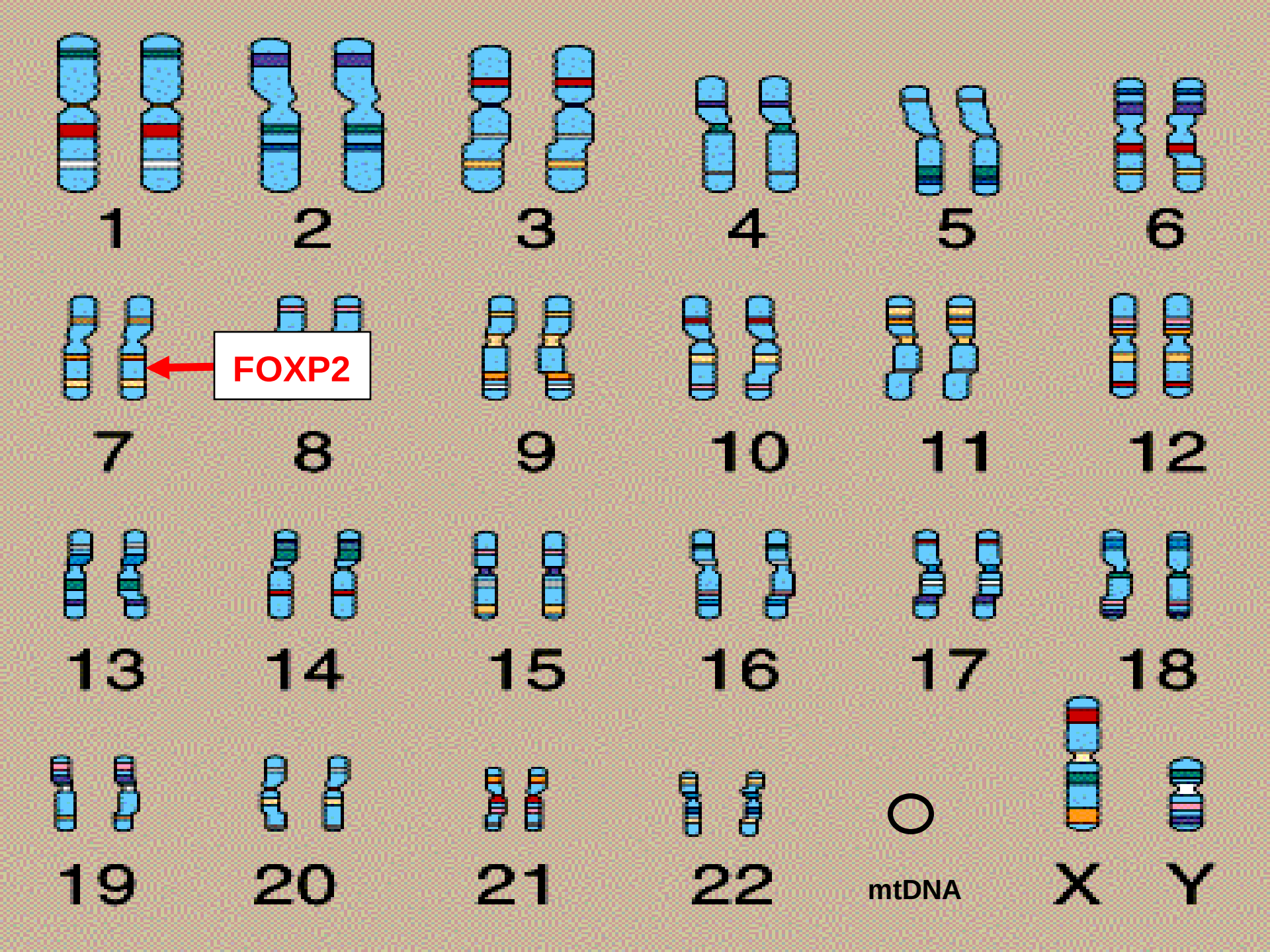
Non-lactase persistent chromosomes



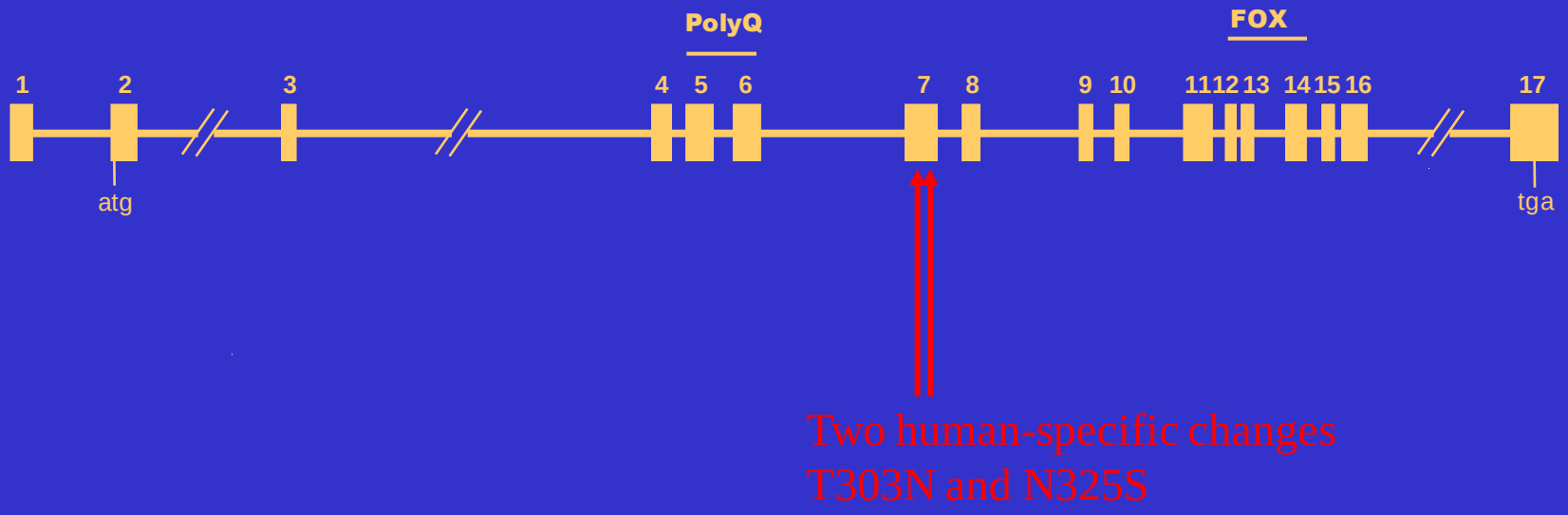
Lactase persistence




1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y


1
2
3
4
5
6
FOXP2
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mtDNA
X
Y

The human *FOXP2* gene



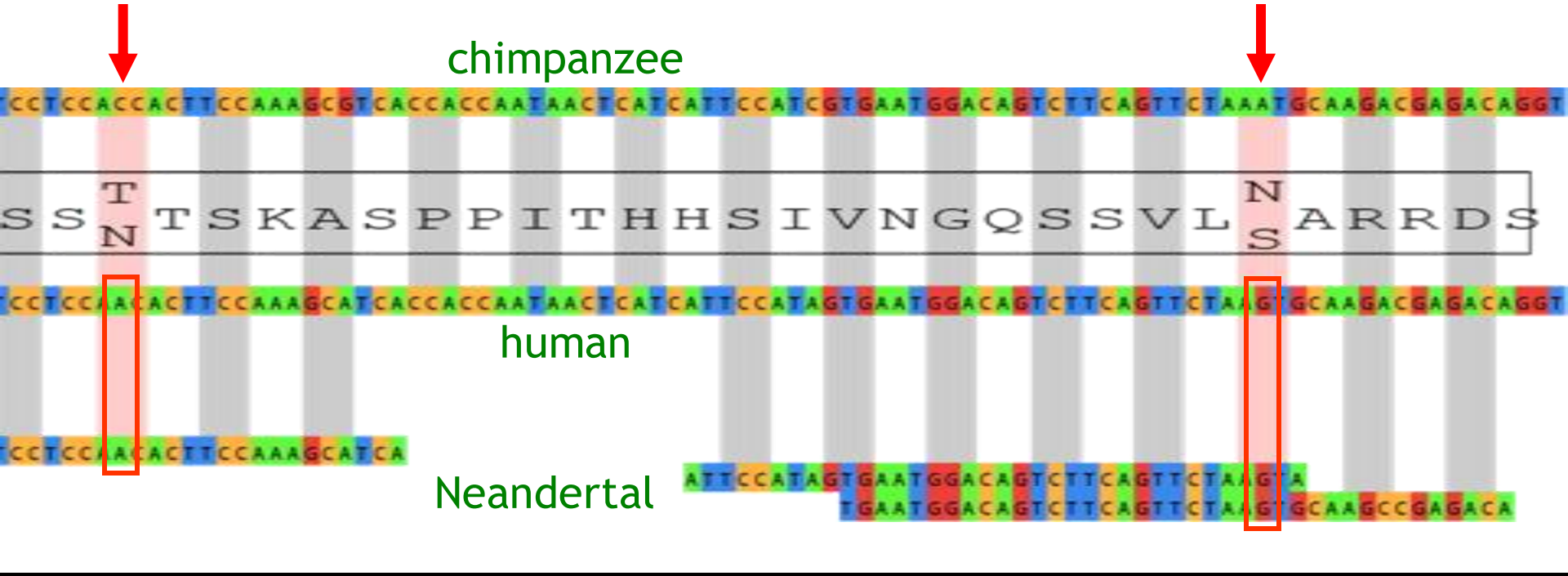
FOXP2 exon 7

chimpanzee

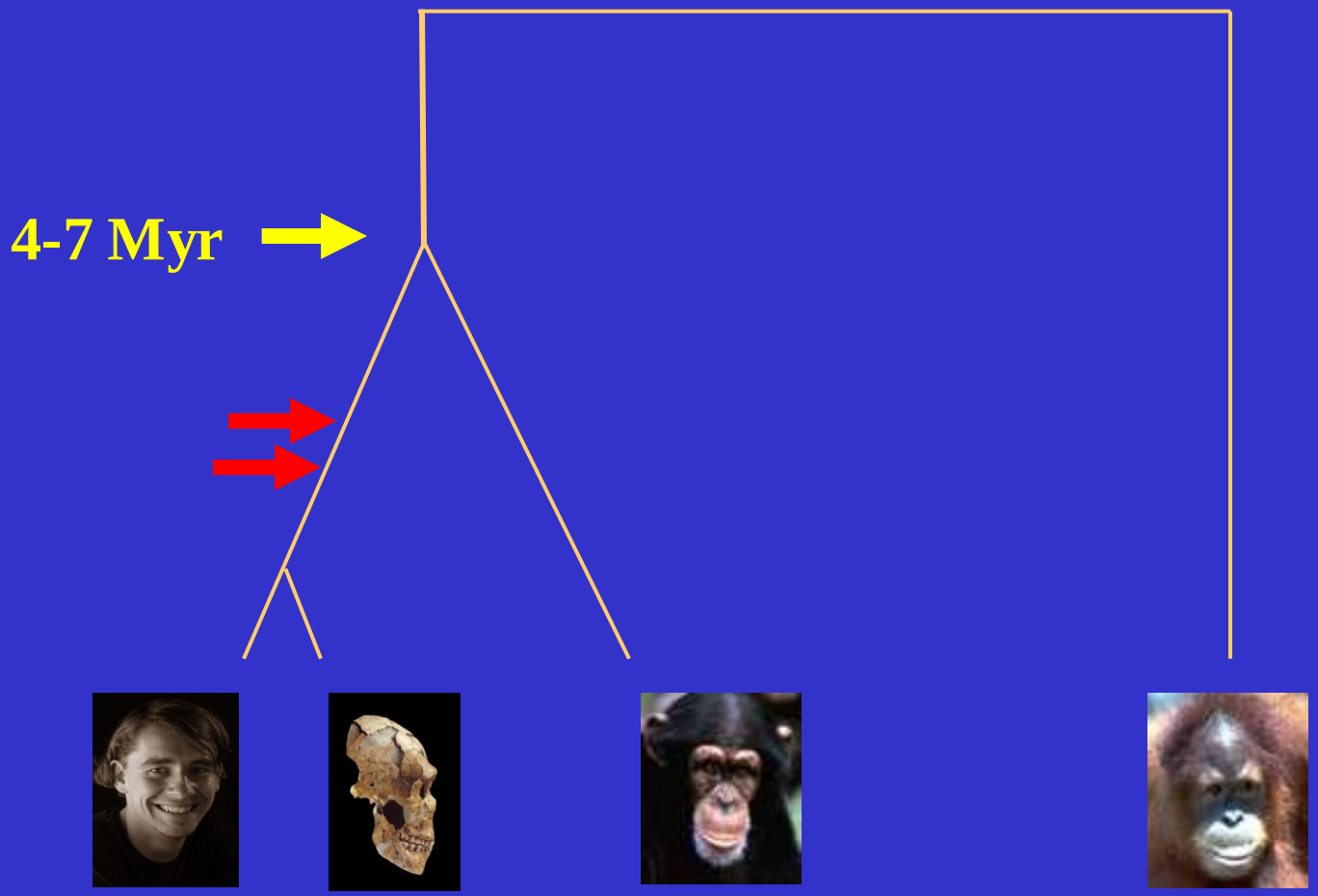
human

FOXP2 exon 7

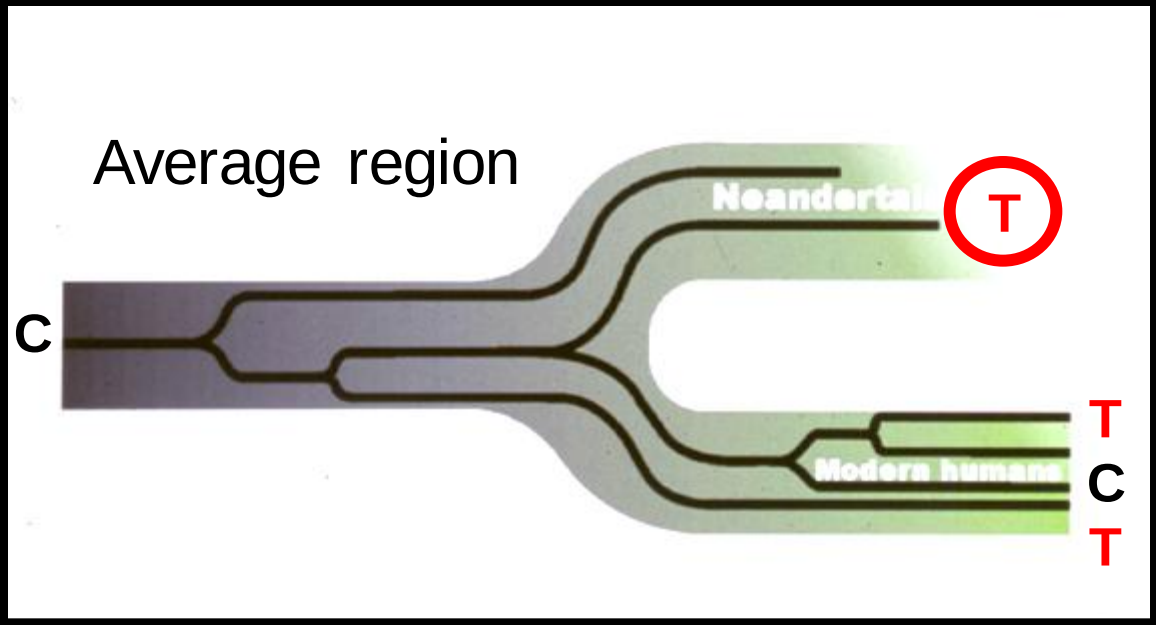
FOXP2 exon 7

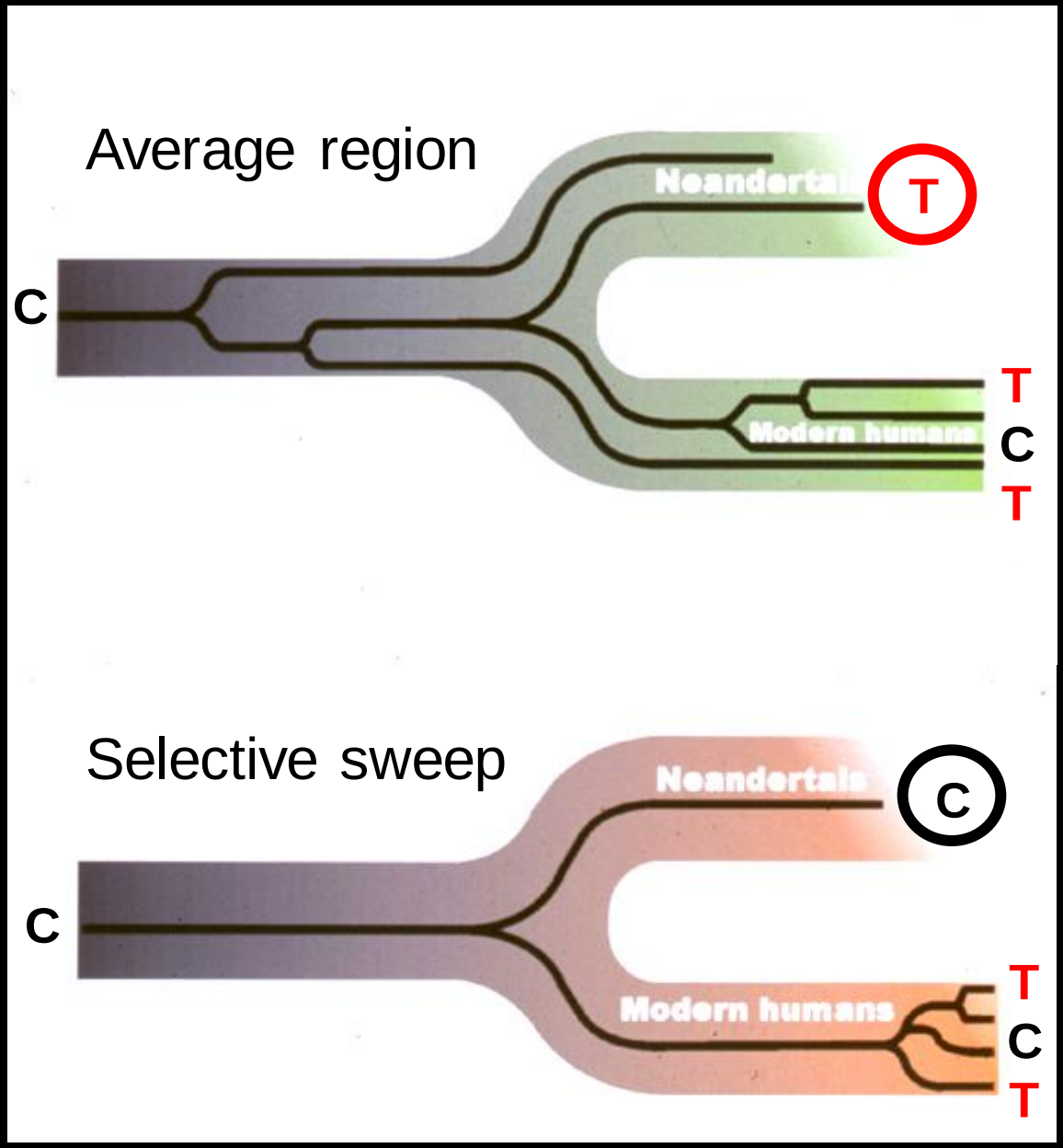

chimpanzee
S S T N T S K A S P P I T H H S I V N G Q S S V L N S A R R D S
human
Neandertal

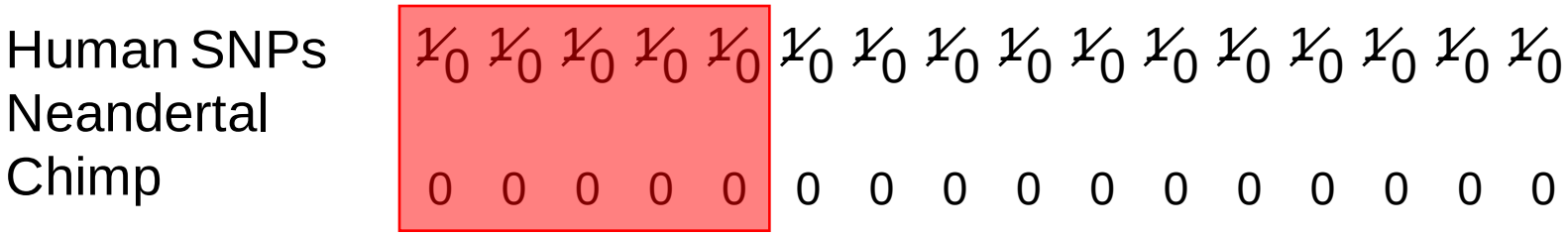
4-7 Myr


4-7 Myr

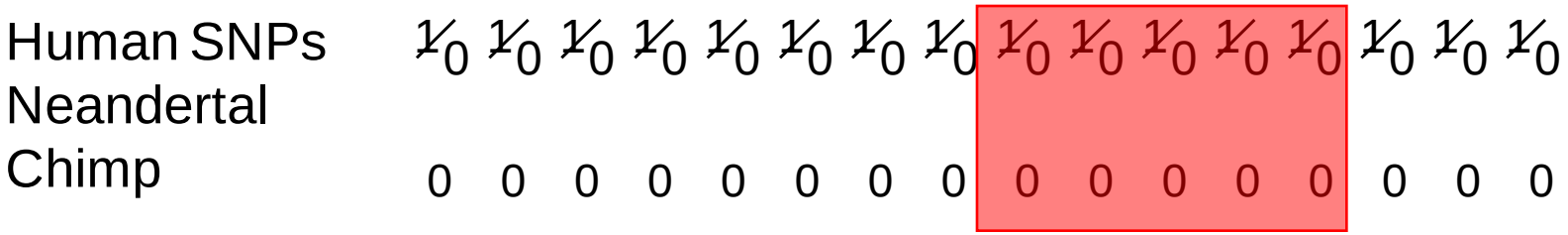
Positive Darwinian selection


Average region
Neandertal
T
C
Modern humans
T
C
T

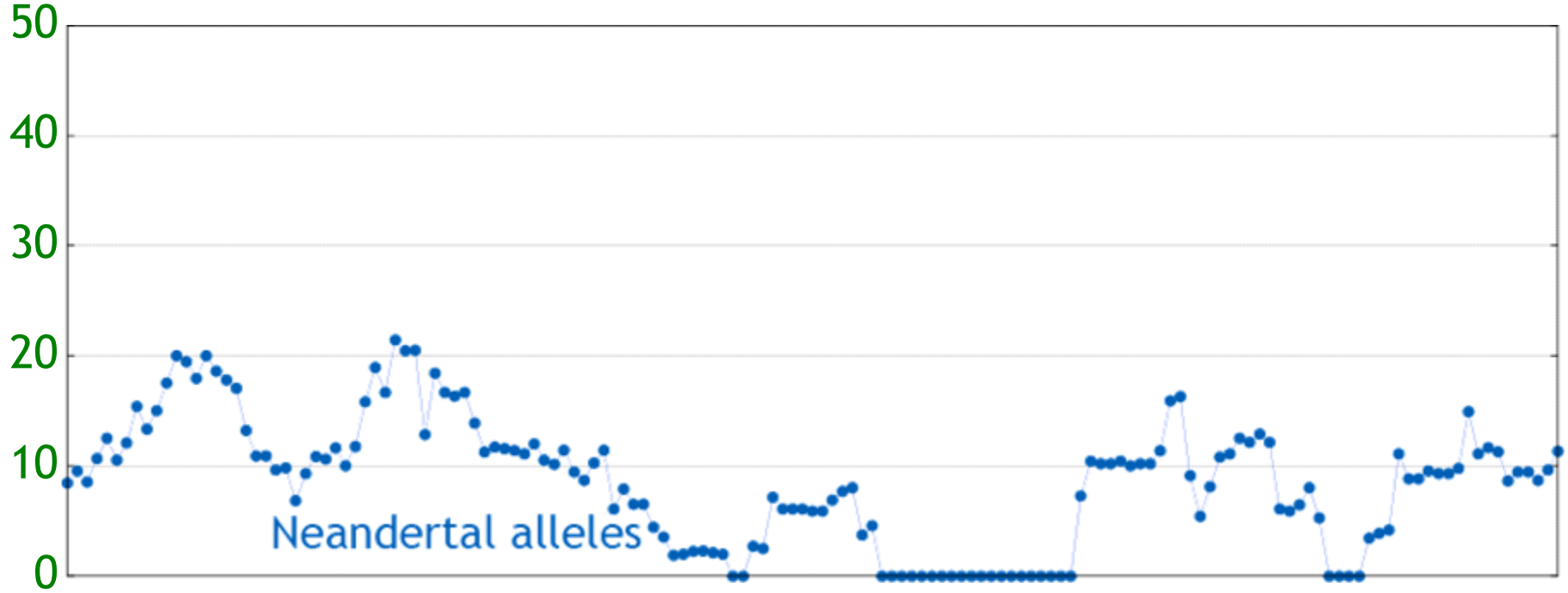

Average region
Neandertals
T
C
T
C
T
Modern humans
Selective sweep
Neandertals
C
C
T
C
T
Modern humans


Human SNPs
Neandertal
Chimp
1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0

Positive selection?



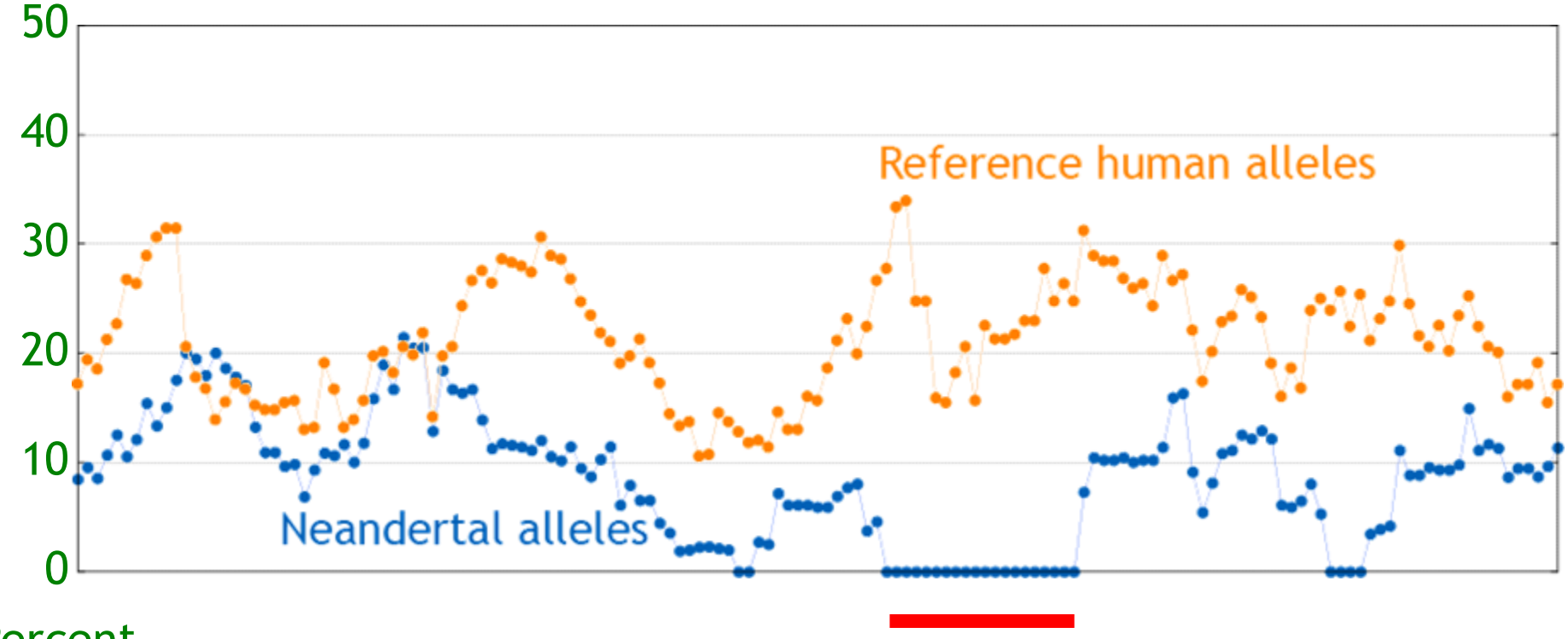
Derived allele frequency at human SNPs

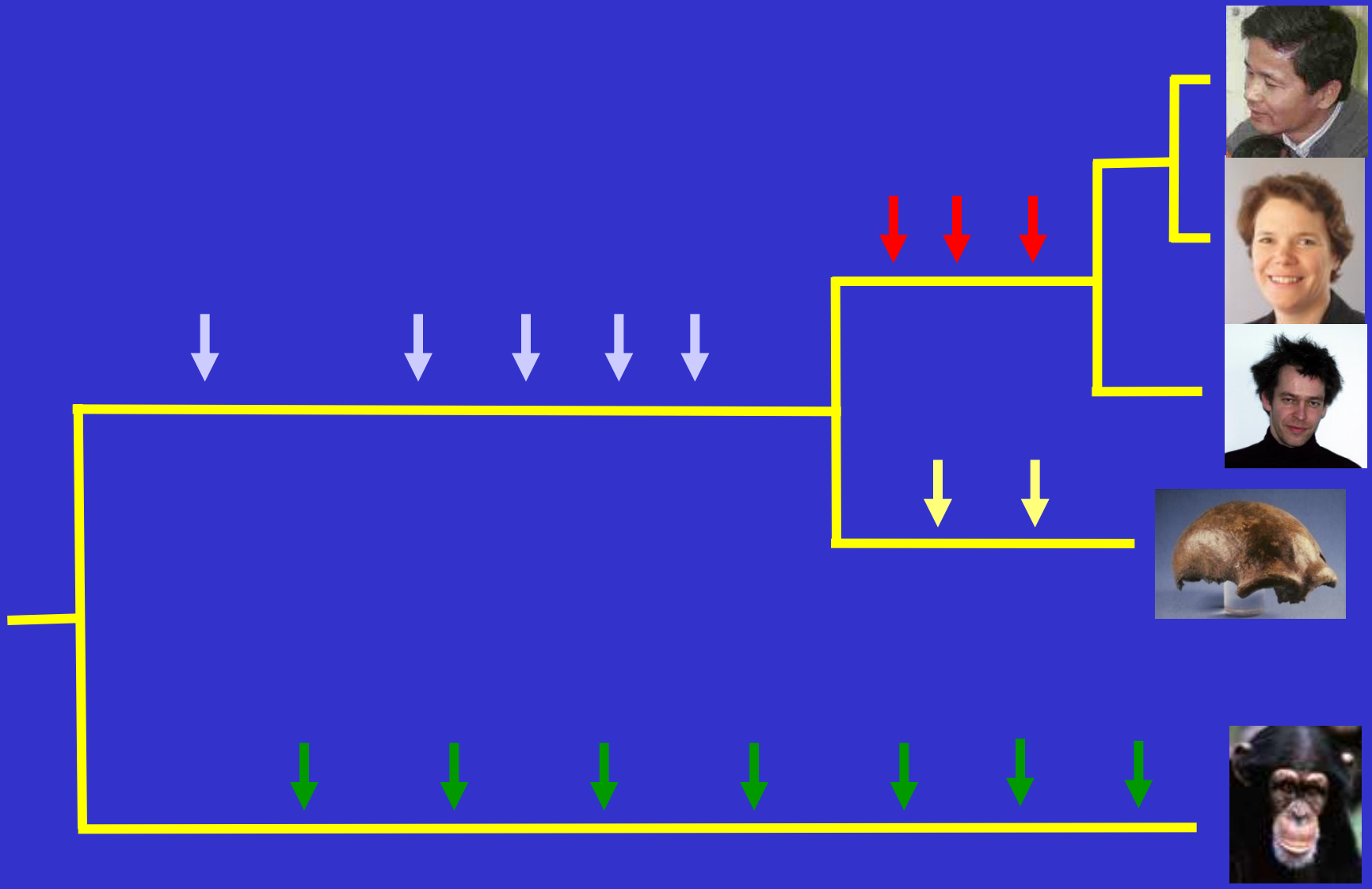


Percent derived allele

100 kb

Derived allele frequency at human SNPs

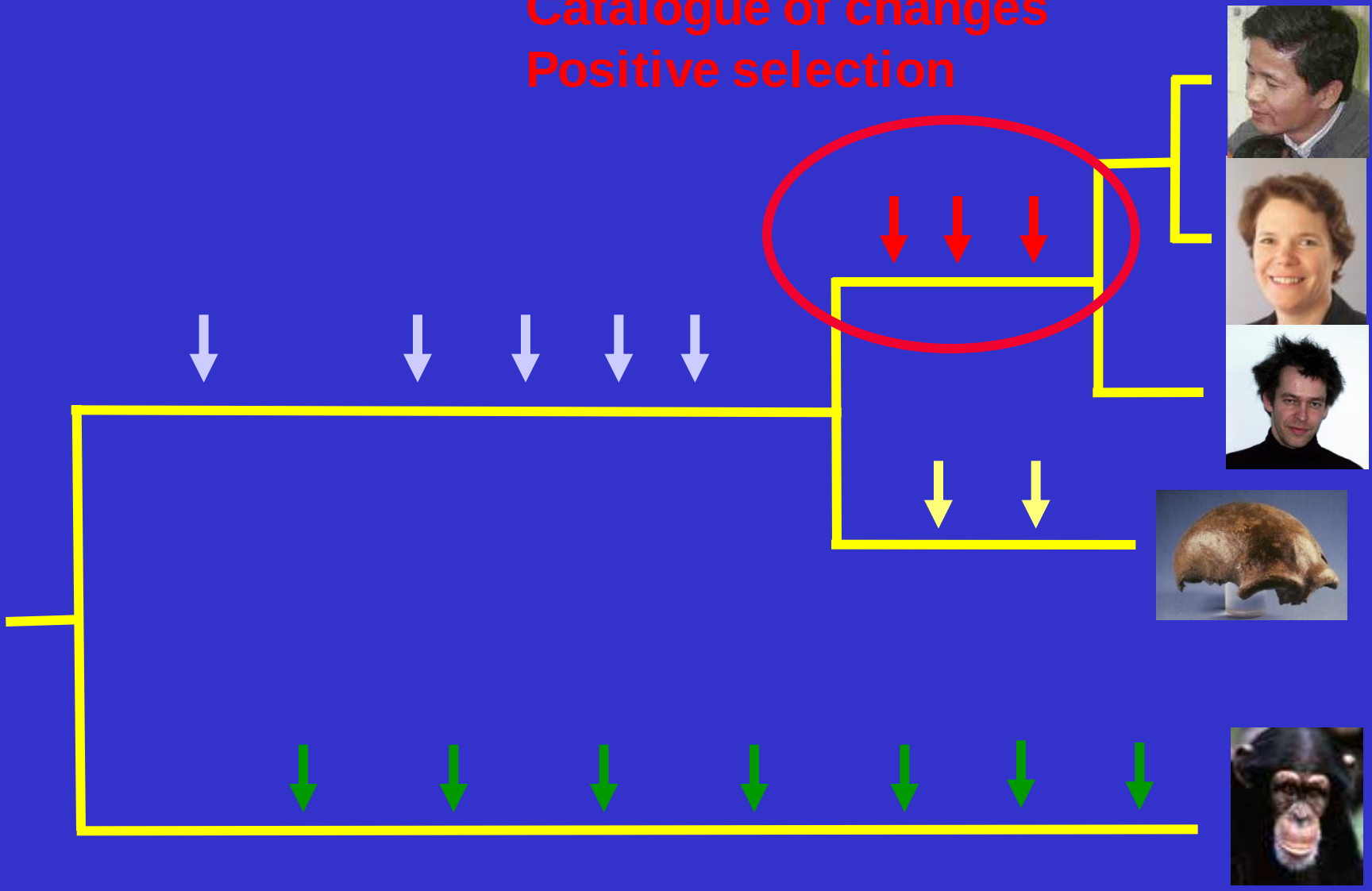




6 Myr

0.5 Myr

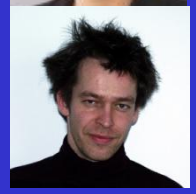
Catalogue of changes
Positive selection



6 Myr

0.5 Myr

Catalogue of changes
Positive selection



Neandertal-specific features

6 Myr

0.5 Myr


Ende

Journal of Human Evolution 55 (2008) 756–757

Contents lists available at ScienceDirect

Journal of Human Evolution

journal homepage: www.elsevier.com/locate/jhevol

News and Views

Suggested guidelines for invasive sampling of hominid remains

Jean-Jacques Hublin [a,*], Svante Pääbo [a], Anatoly P. Derevianko [b], Vladimir B. Doronichev [c], Liubov V. Golovanova [c], Martin Friess [d], Alain Froment [d], Almut Hoffmann [e], Ngalla Edward Jillani Kachache [f], Ottmar Kullmer [g], David Lordkipanidze [h], Marie-Hélène Moncel [i], Richard Potts [j], Jakov Radovcic [k], Yoel Zvi Rak [l], Michael Richards [a], Jesús Rodríguez Méndez [m], Antonio Rosas [n], Michael Schmauder [o], Ralf W. Schmitz [p], Patrick Semal [q], Tanya Smith [a], Mary Anne Tafuri [r], Ian Tattersall [s], Jean-François Tournepiche [t], Michel Toussaint [u], Sergey Vassiliev [v], Amélie Vialet [w], Tim White [x], Reinhard Ziegler [y]

[a] Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany
[b] Institute of Archaeology and Ethnography, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia
[c] ANO Laboratory of Prehistory, St. Petersburg, Russia
[d] Musée de l'Homme, Paris, France
[e] Museum für Vor- und Frühgeschichte, Staatliche Museen zu Berlin, Germany
[f] Palaeontology Department, National Museums of Kenya
[g] Forschungsinstitut Senckenberg, Frankfurt, Germany
[h] Georgian National Museum, Tbilisi, Georgia
[i] Département de Préhistoire, Muséum National d'Histoire Naturelle, Paris, France
[j] National Museum of Natural History, Smithsonian Institution, Washington D.C., USA
[k] Croatian Natural History Museum, Zagreb, Croatia
[l] Sackler School of Medicine, Tel Aviv University, Israel
[m] National Research Centre on Human Evolution, Burgos, Spain
[n] Museo Nacional de Ciencias Naturales, Madrid, Spain
[o] Rheinisches Landesmuseum Bonn, Germany
[p] Institut für Ur- und Frühgeschichte und Archäologie des Mittelalters, Universität Tübingen, Germany
[q] Institut Royal des Sciences Naturelles de Belgique, Bruxelles, Belgium
[r] Dipartimento di Biologia Animale e dell'Uomo, Universitá di Roma "La Sapienza", Italy
[s] Division of Anthropology, American Museum of Natural History, New York, USA
[t] Musée des Beaux-Arts d'Angoulême, France
[u] Direction de l'Archéologie, Ministère de la Région Wallone, Liège, Belgium
[v] Institute of Ethnology and Anthropology, Russian Academy of Sciences, Mosow, Russia
[w] Institut de Paléontologie Humaine, Paris, France
[x] Department of Integrative Biology, University of California, Berkeley, USA
[y] Staatliches Museum für Naturkunde, Stuttgart, Germany

Screening of Neandertal bones

No detectable Neandertal DNA:

Shanidar III (Iraq)
Krasny grot (Ukraine)
Zaskalnaya VI (Ukraine)
Sima de los Palomas (Spain)
Quina Negra (Spain)
Gibraltar (UK)
Tabun (Israel)
La Quina (France)

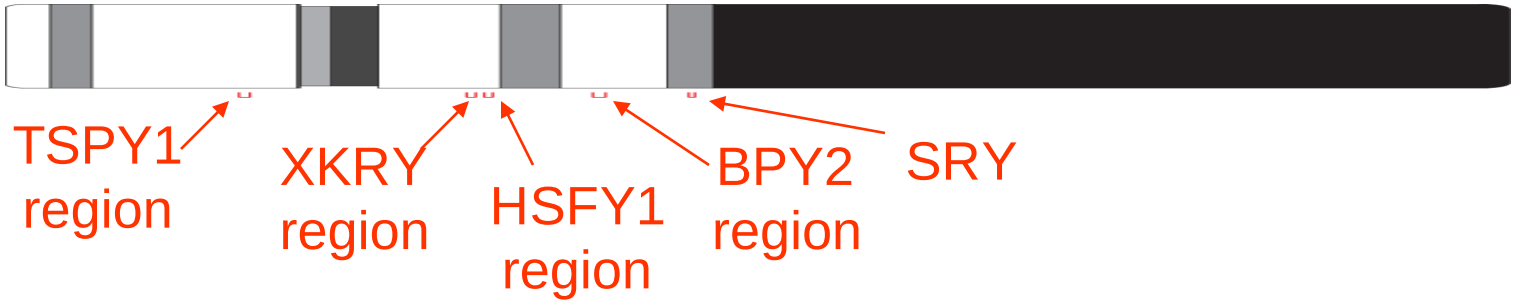
<1% Neandertal DNA:

Hohlenstein-Stadel (Germany)
Feldhofer (Germany)
El Sidron (Spain)
Mezmaiskaya (Russia)
La Chapelle (France)
Okladnikov (Russia)
Teshik Tash (Ushbekistan)

>1% Neandertal DNA:

Vindija (Croatia)

Y chromosome



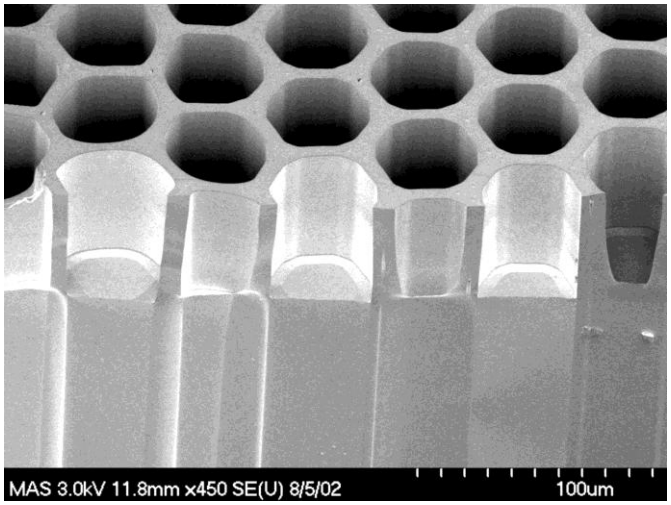
Total Y-unique sequence = 98,295 nt

www.roche-applied-science.com

Michael Egholm
michael.egholm@roche.com

February 12, 2009

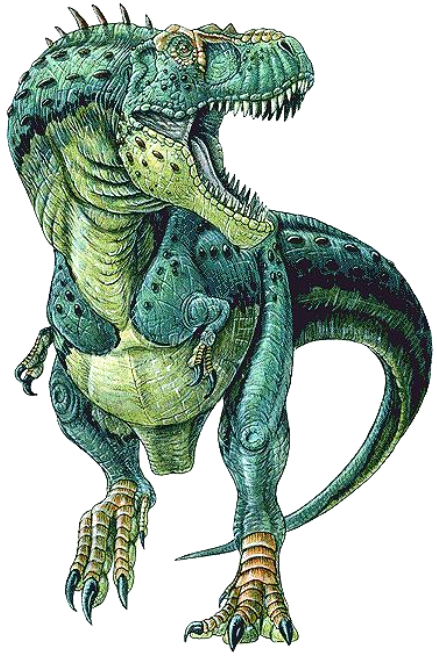
First NextGen Sequencer Anno 2005



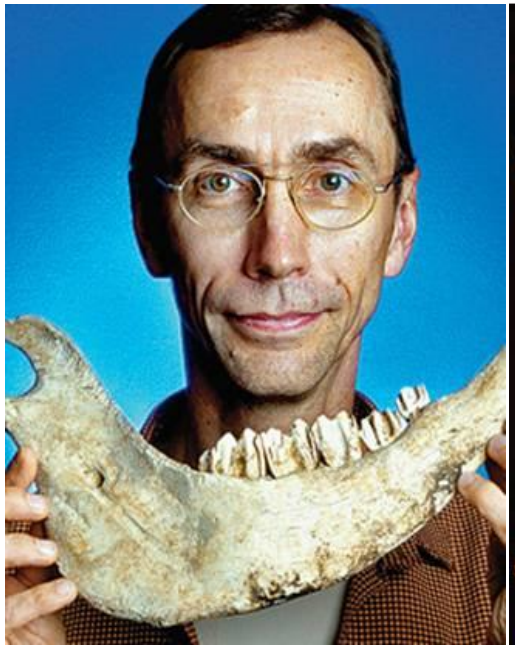
454 SEQUENCING

454's Road to the Neanderthal Project

Jonathan Rothberg
Founder of 454



T. rex

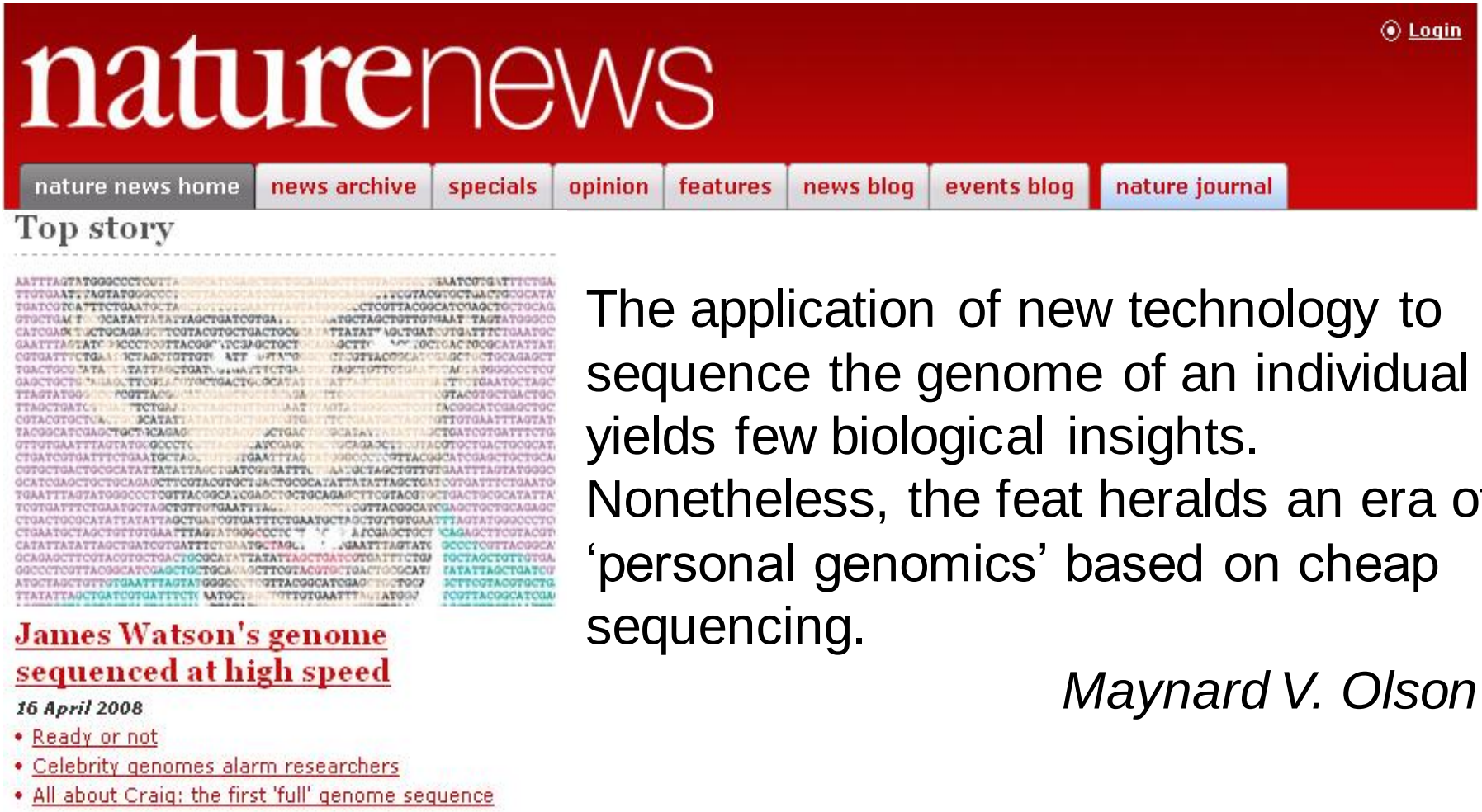


Svante Pääbo
MPI

Neanderthal

454 SEQUENCING

One is not enough



The application of new technology to sequence the genome of an individual yields few biological insights. Nonetheless, the feat heralds an era of 'personal genomics' based on cheap sequencing.

Maynard V. Olson

Acknowledgements

- Jonathan Rothberg
- Jan Simons
- Mike Ronan
- Jason Affourtit
- Eli Buglione
- Adam Burke
- Cynthia Turcotte
- Gerald Irzyk
- Joe Salem and the members of the 454 Sequencing Center production team
- All of 454


Roche