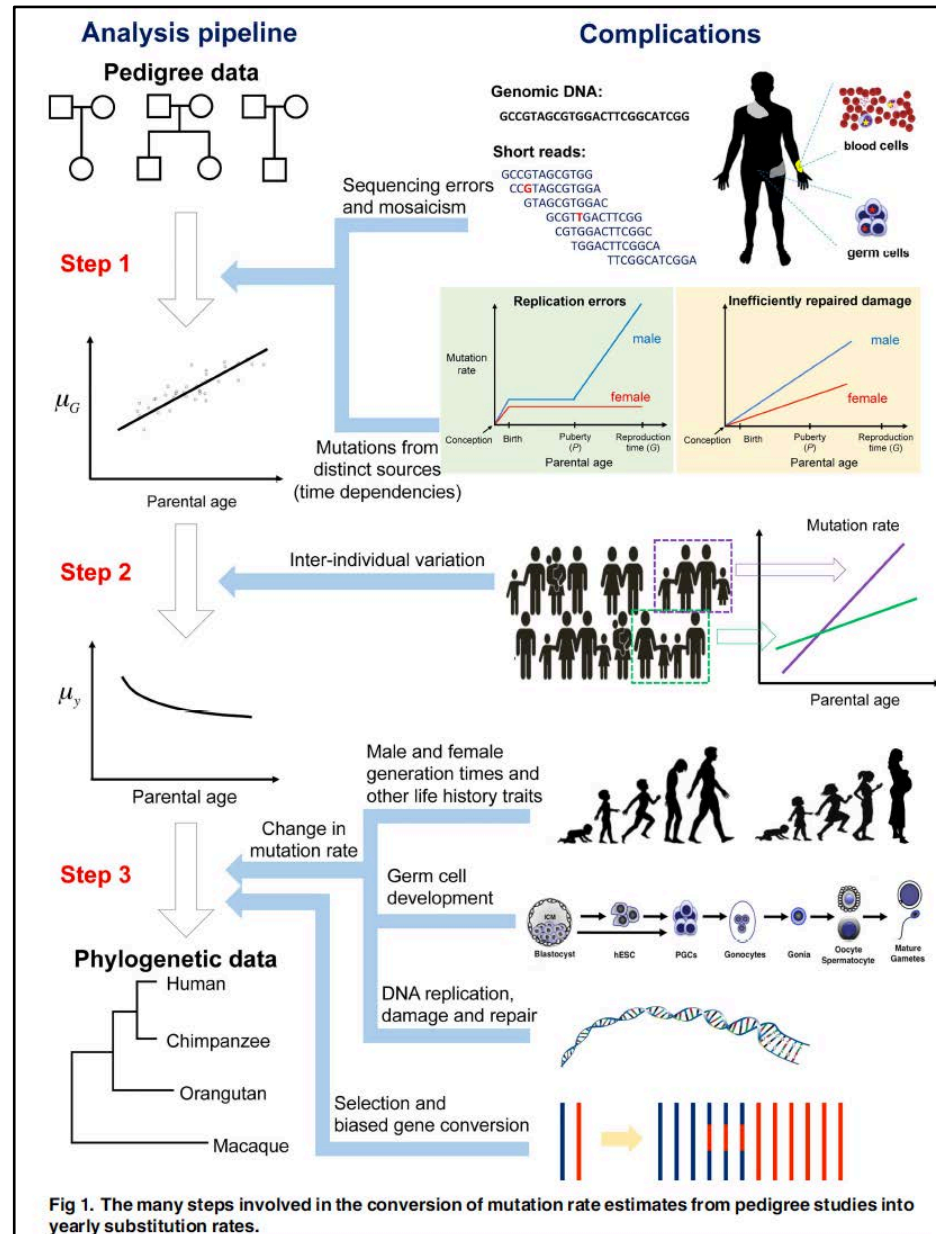
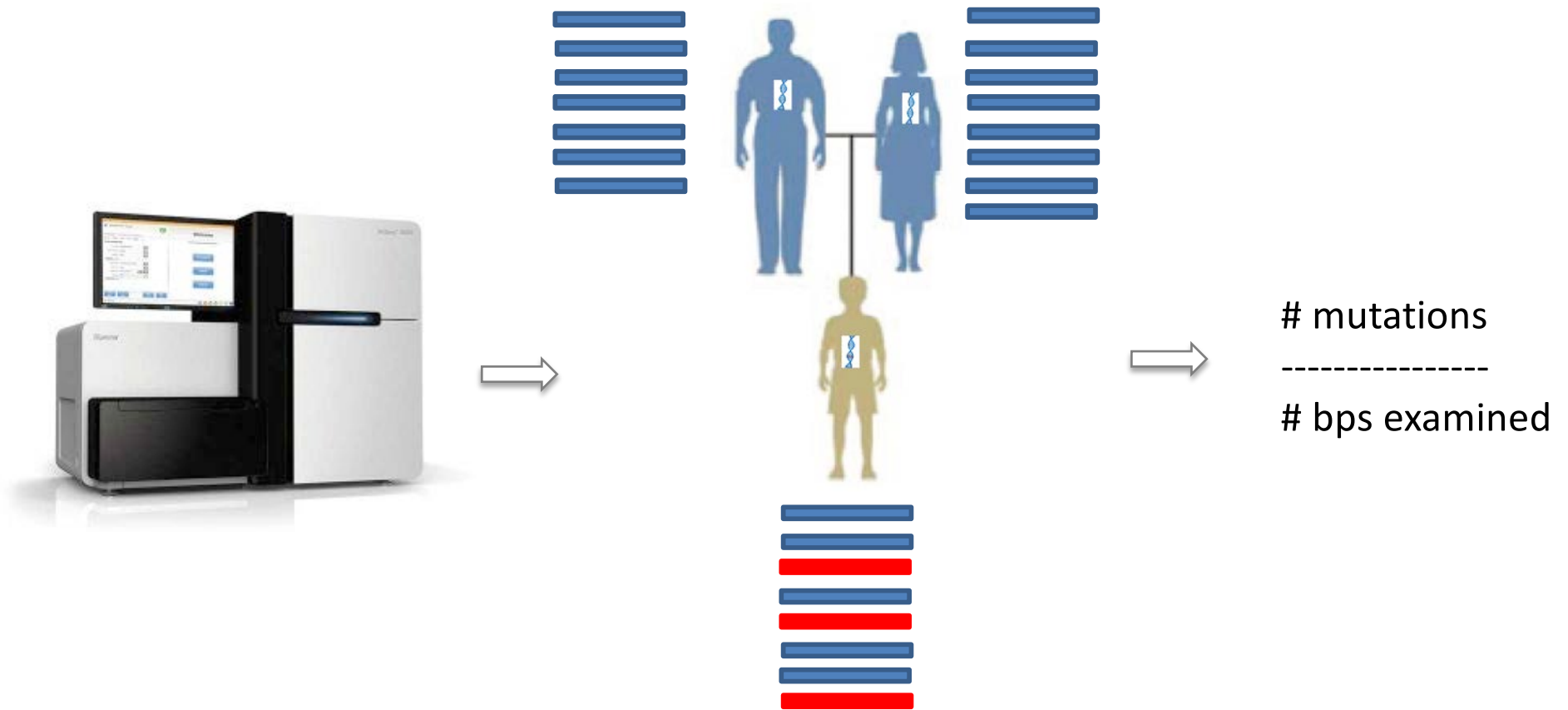
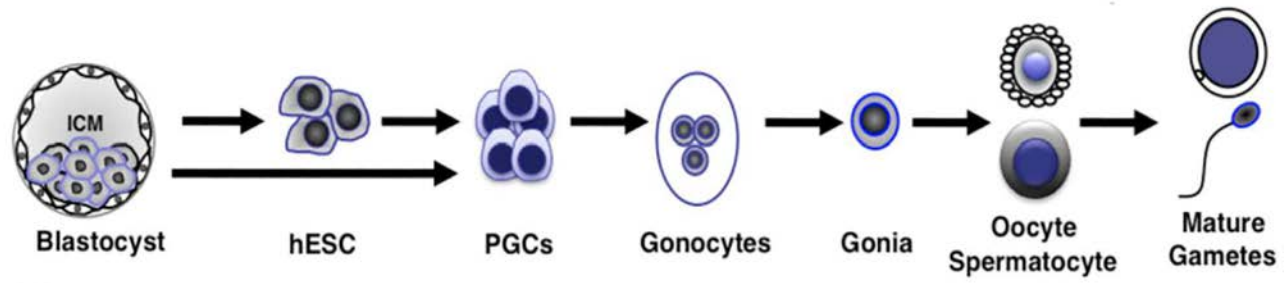


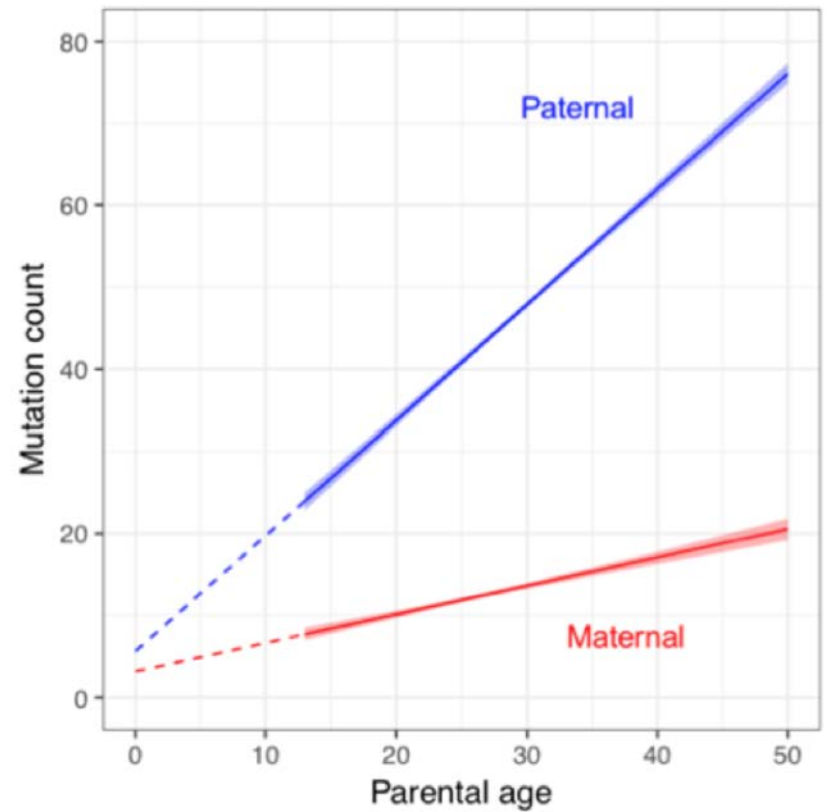
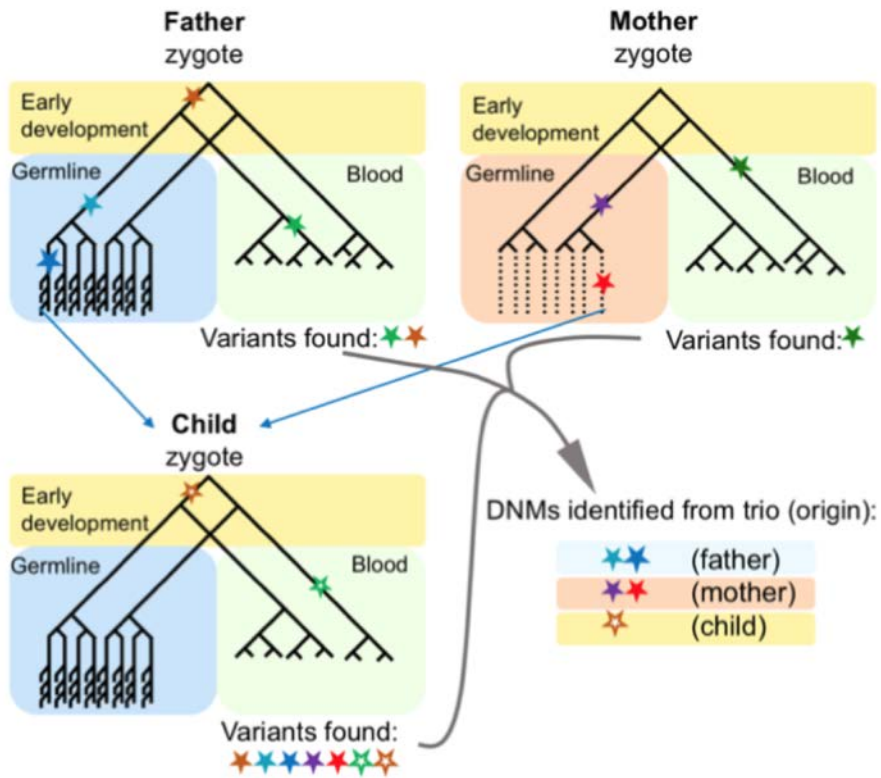
Evolution des mutations germinales chez les primates et datation de la spéciation humaine

Molly Przeworski

Cours #2







~10⁻⁸

Paternal
age effect

~75% mutations
paternal

Table 1. Estimates of mutation rates from pedigree studies.

Study	Reported mutation rate per bp per generation (x10 ⁻⁸)	Mean paternal age in study (in years)	Mutation rate at paternal age of 30 years (x10 ⁻⁸) [†]	Paternal age effect reported as the increase in number of mutations for each year of father's age	Callable genome in Gb (reported false negative rate [FNR] in %)	Sample size	Mean sequence coverage	Fraction of CpG transitions [‡]
Chimpanzee pedigree study:								
Venn 2014 [#] [40]	1.20	24.3 ^a	1.51	3.00	2.4 (13.4 ^b)	6	34.4 ^b	0.239 (0.183–0.296)
Human pedigree studies:								
Roach 2010 ^{§,c} [39]	1.10 (0.68–1.70)	—	—	—	1.8 (5.0)	2	61.3 ^b	0.178 (0.037–0.320)
Conrad 2011 (CEU) [41]	1.17 (0.88–1.62)	—	—	—	2.5 (5.0)	1	29.3	0.146 (0.046–0.246)
Conrad 2011 (YRI) [41]	0.97 (0.67–1.34)	—	—	—	2.5 (3.5)	1	29.2	0.114 (0.009–0.220)
Campbell 2012 [42]	0.96 (0.82–1.09)	26.3	—	—	2.2 (1.7) ^b	5	13.0	0.165 (0.110–0.220)
Kong 2012 [15]	1.20	29.7	1.21	2.01	2.6 (2.0)	78	30.0	0.173 (0.163–0.184)
Michaelson 2012 [43]	1.00	33.6	0.93	1.02	2.8 ^e (9.5)	10	30.0	0.128 (0.099–0.156)
Jiang 2013 [44]	—	34.4 ^e	—	1.50	—	32	30.0	0.162 (0.146–0.177)
Francioli 2015 [38]	—	29.4	—	1.20 [*]	2.1 (31.1)	250	13.0	0.165 (0.158–0.172)
Besenbacher 2015 [45]	1.27 (1.16–1.38)	28.4	1.3 ^d	2.00	—	10	50.0	0.201 (0.166–0.236)
Rahbari 2015 ^c [46]	1.28 (1.13–1.43)	29.8	1.29	2.87 (1.46–3.65) ^f	2.5 (—)	12	24.7	0.210 (0.180–0.240)
Yuen 2015 ^{§,g,c} [47]	1.18 ^h	34.1	1.08	1.19 [*]	2.5 (8.0) ⁱ	140	56.0	0.159 (0.151–0.167)
Wong 2016 ^{§, †} [48]	1.05	33.4	0.95	0.92	1.6 (13.0)	693	60.0	0.131 (0.127–0.135)
Goldmann 2016 ^{§, †} [49]	—	33.7	—	0.91	—	816	60.0	0.179 (0.175–0.182)

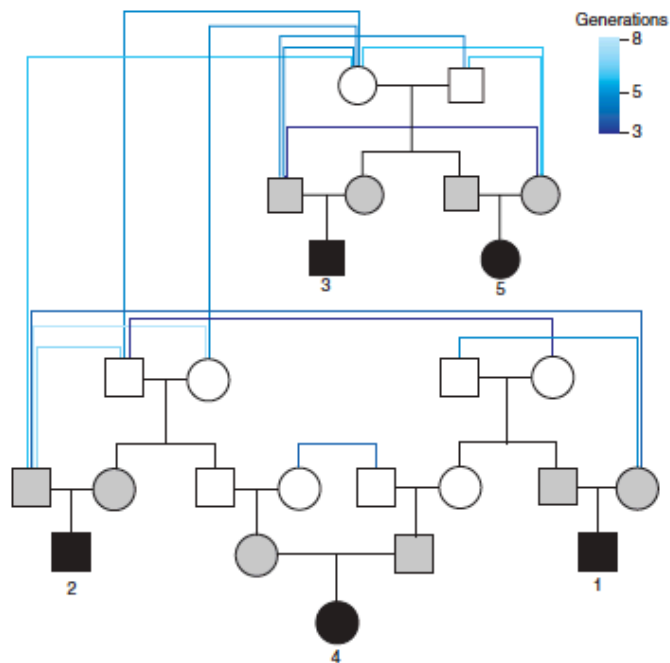
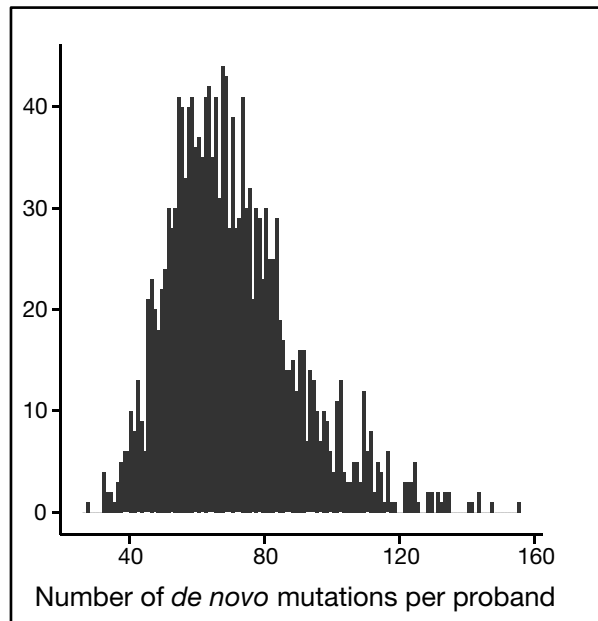


Figure 1 Relationship of sequenced individuals. Simplified pedigree showing the relationship between the 15 sequenced individuals. Black symbols represent the children in the five trios, and gray symbols represent their parents. Founders are connected by blue lines, with the shade of blue indicating the number of generations separating the connected individuals. For clarity, only the shortest relationships between each individual and the parents of that individual are shown. The color scale represents the number of generations separating the individuals, where darker blue indicates fewer generations and lighter blue indicates more generations.

From Campbell et al. 2012 Nat Gen

Parental influence on human germline *de novo* mutations in 1,548 trios from Iceland 2017

Hákon Jónsson¹, Patrick Sulem¹, Birte Kehr¹, Snaedis Kristmundsdottir¹, Florian Zink¹, Eirikur Hjartarson¹, Marteinn T. Hardarson¹, Kristjan E. Hjorleifsson¹, Hannes P. Eggertsson¹, Sigurjon Axel Gudjonsson¹, Lucas D. Ward¹, Gudny A. Arnadottir¹, Einar A. Helgason¹, Hannes Helgason¹, Arnaldur Gylfason¹, Adalbjorg Jonasdottir^{1,2}, Aslaug Jonasdottir¹, Thorunn Rafnar¹, Mike Frigge¹, Simon N. Stacey¹, Olafur Th. Magnusson¹, Unnur Thorsteinsdottir^{1,2}, Gisli Masson¹, Augustine Kong^{1,3}, Bjarni V. Halldorsson^{1,4}, Agnar Helgason^{1,5}, Daniel F. Gudbjartsson^{1,3} & Kari Stefansson^{1,2}



Mutation rate per « generation »:
 $\sim 1.3 \times 10^{-8}$ at age 30

\Rightarrow Mutation rate per year:
 $\sim 4.3 \times 10^{-10}$

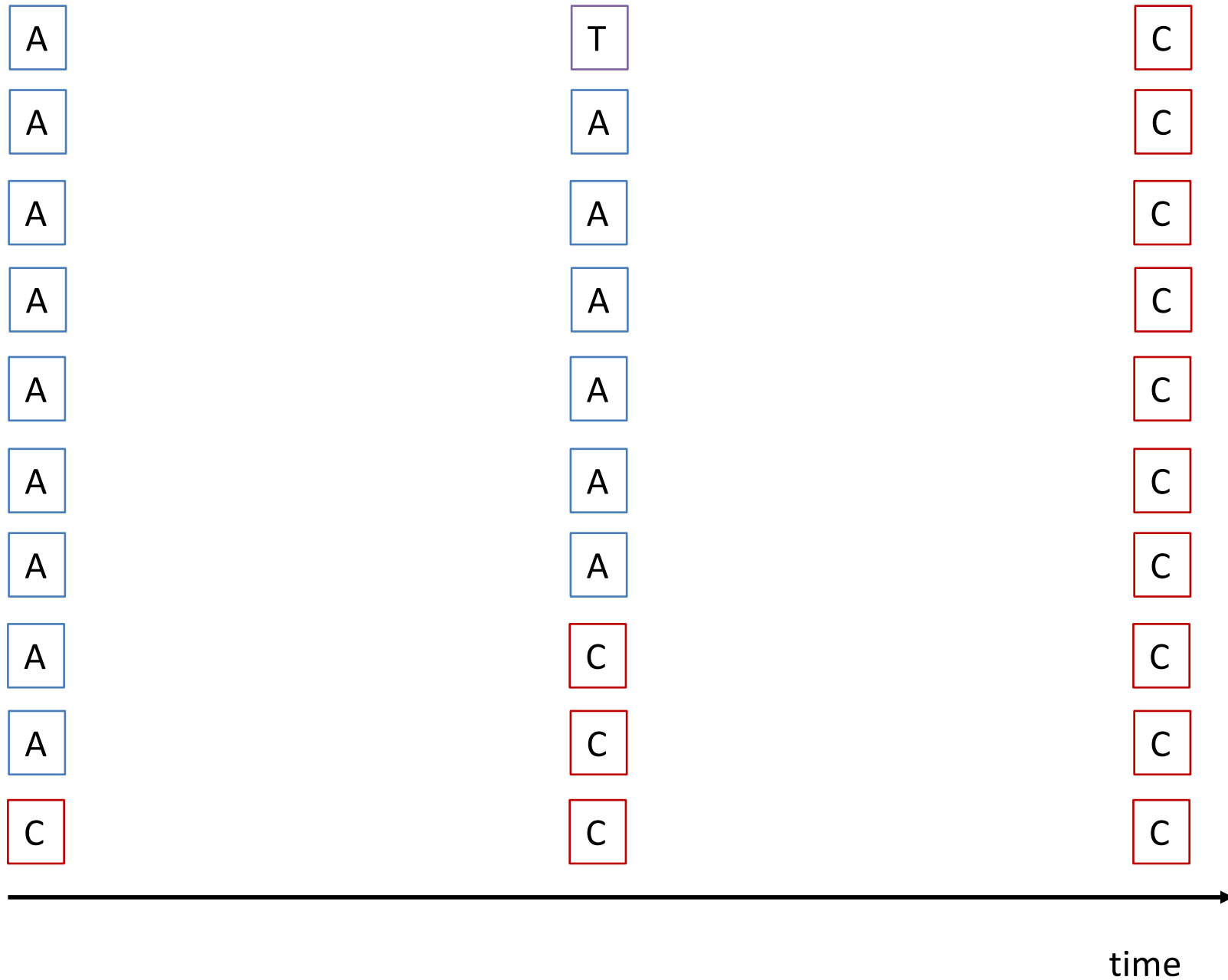


Neutral theory of molecular evolution

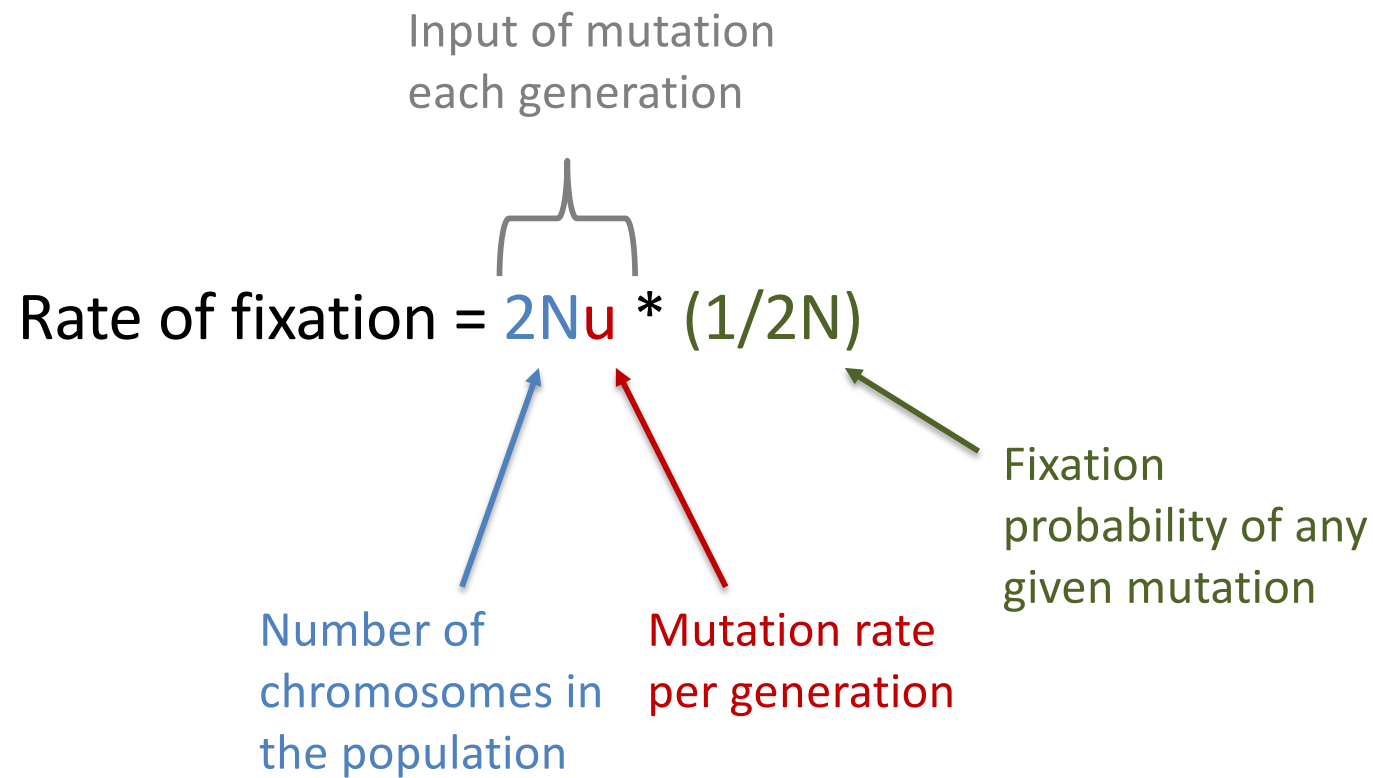


- ❖ Kimura 1968; King and Jukes 1969; Ohta 1973
- ❖ Claims:
 - Most of the observed molecular polymorphisms and substitutions are neutral (does NOT claim that most mutations are neutral).
 - Adaptation is rare and has negligible effects on polymorphism and divergence.
 - If mutations are neutral, the fixation (substitution rate) = the mutation rate
- ❖ Extended to the “nearly neutral theory” by T. Ohta

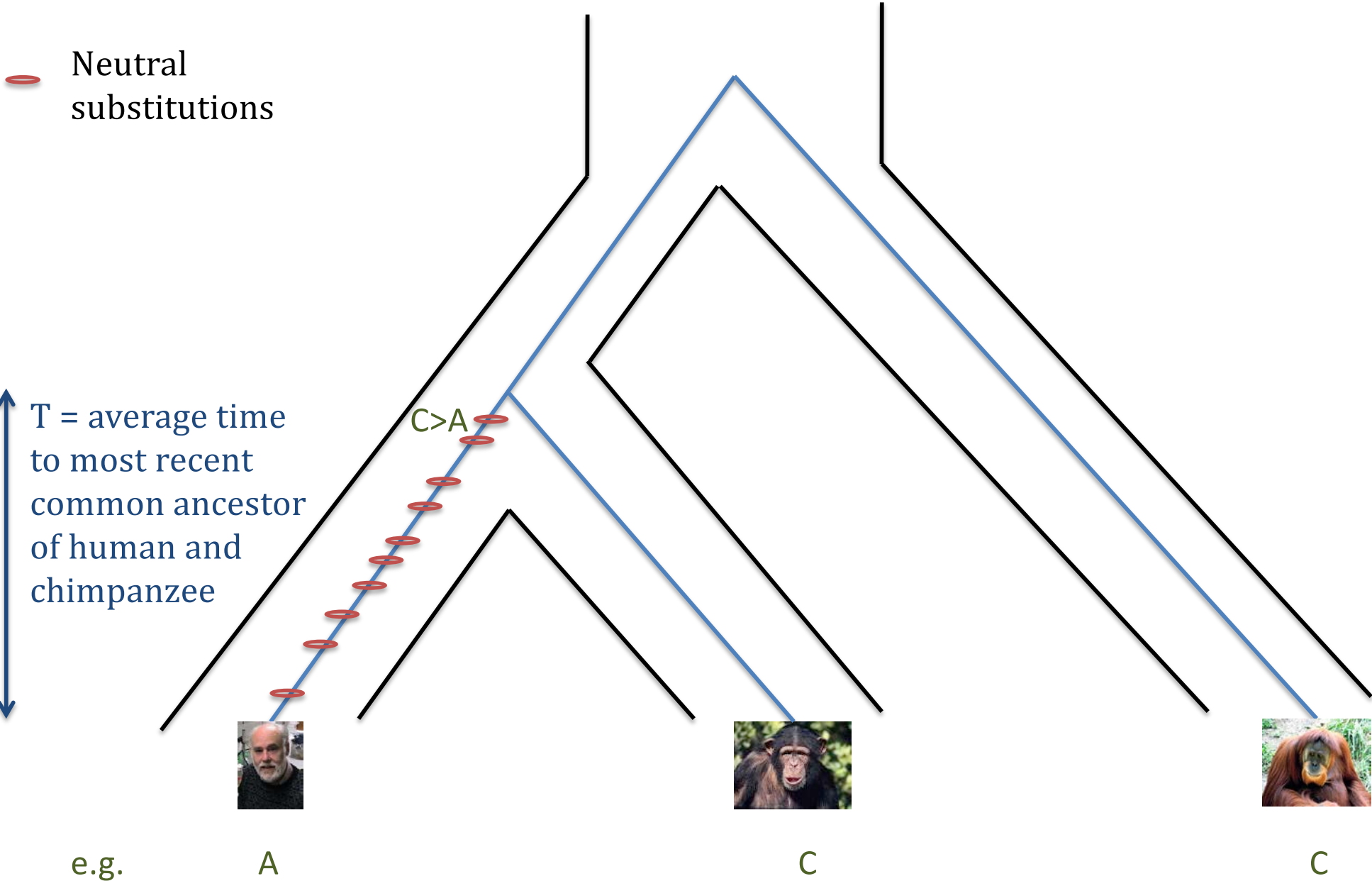
Fixation probability = $1/2N$, where N number of diploid individuals



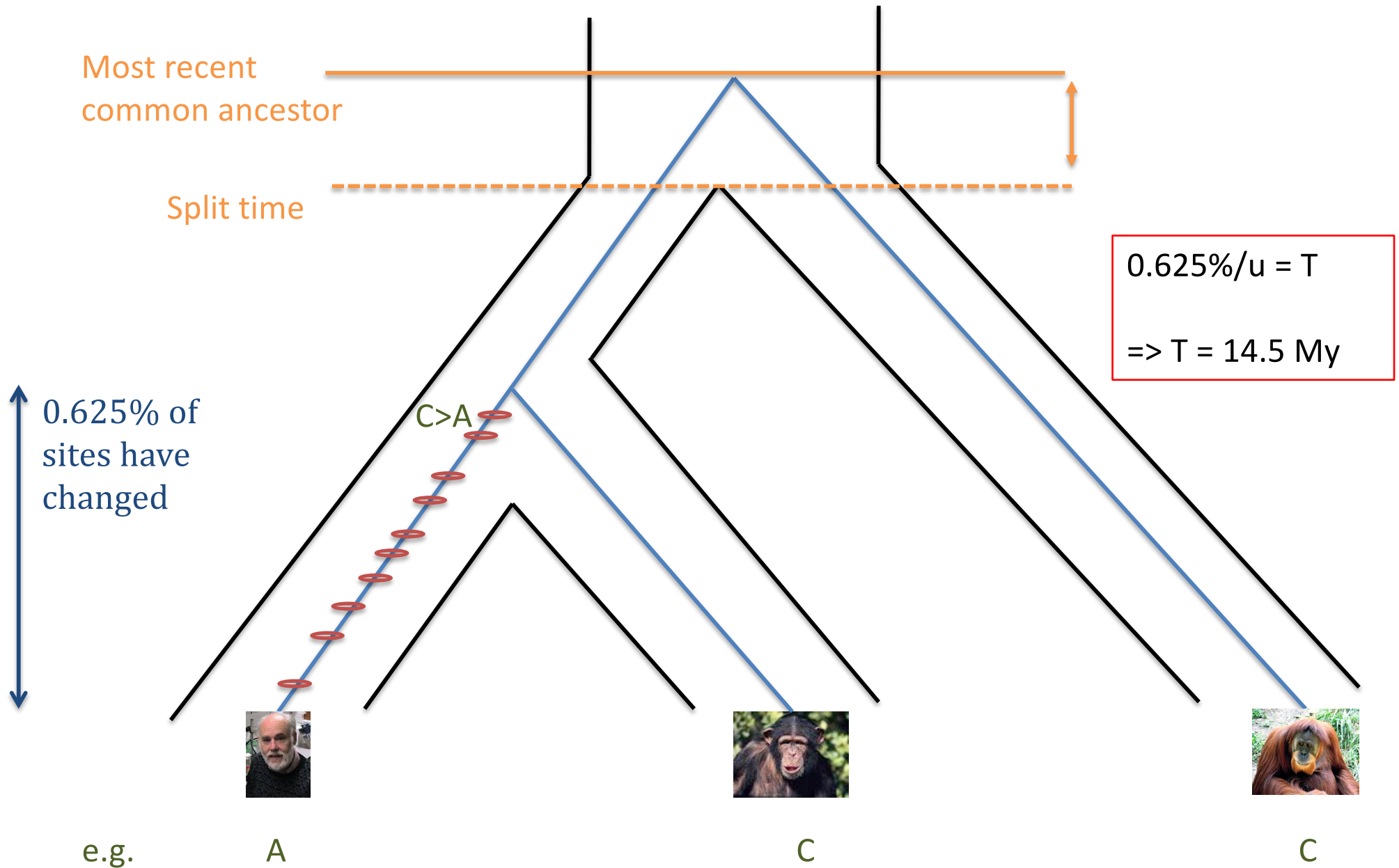
Rate of fixation = rate of mutation



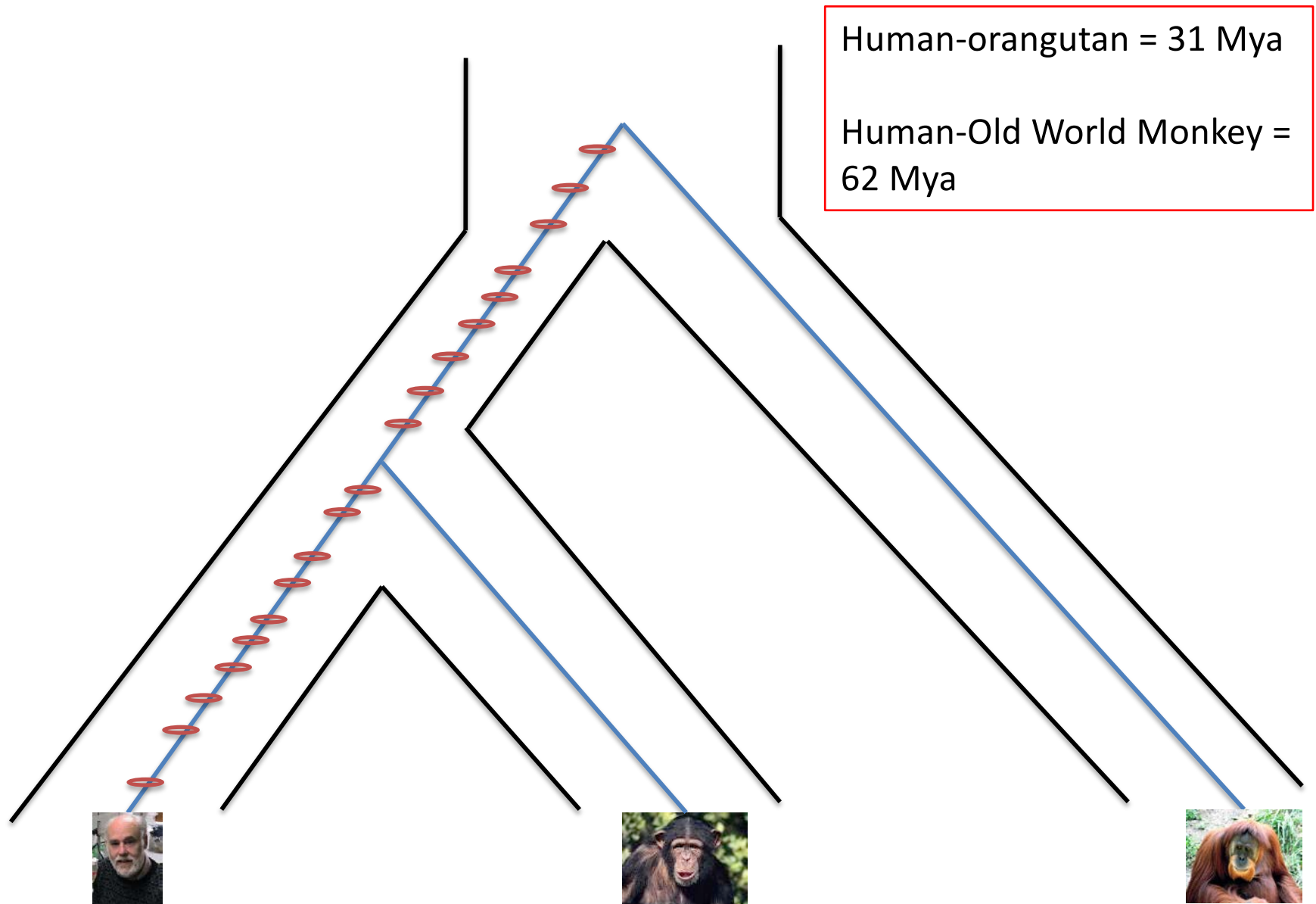
The phylogenetic approach



The phylogenetic approach



Suspiciously old estimates



The phylogenetic approach

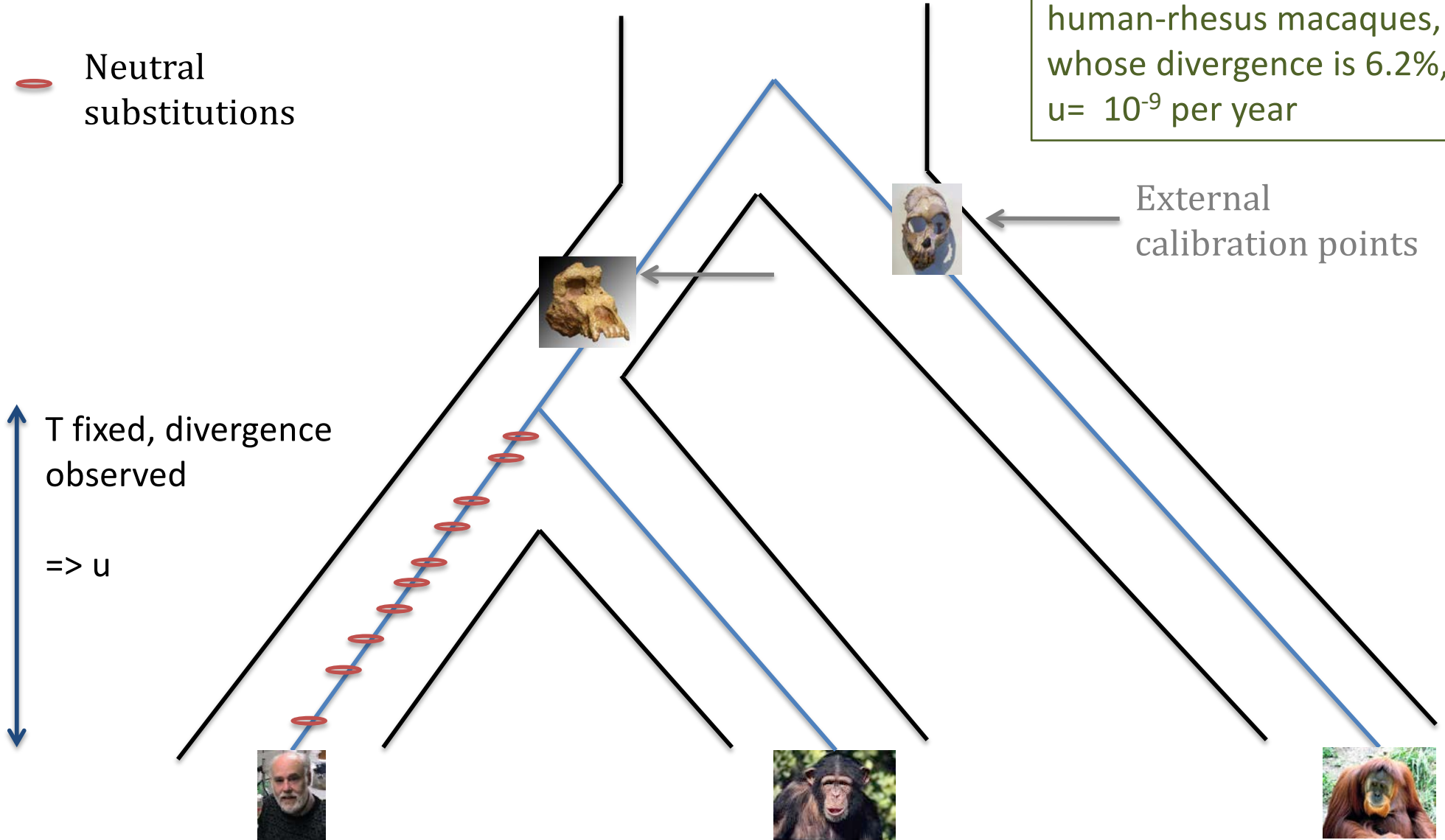
Using $T=30$ Mya for human-rhesus macaques, whose divergence is 6.2%, $u= 10^{-9}$ per year

○ Neutral substitutions

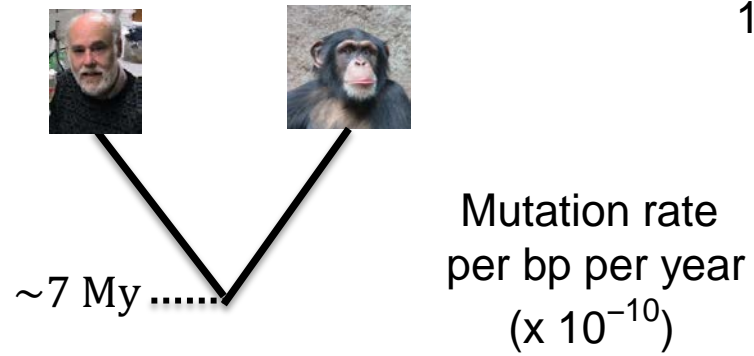
External calibration points

T fixed, divergence observed

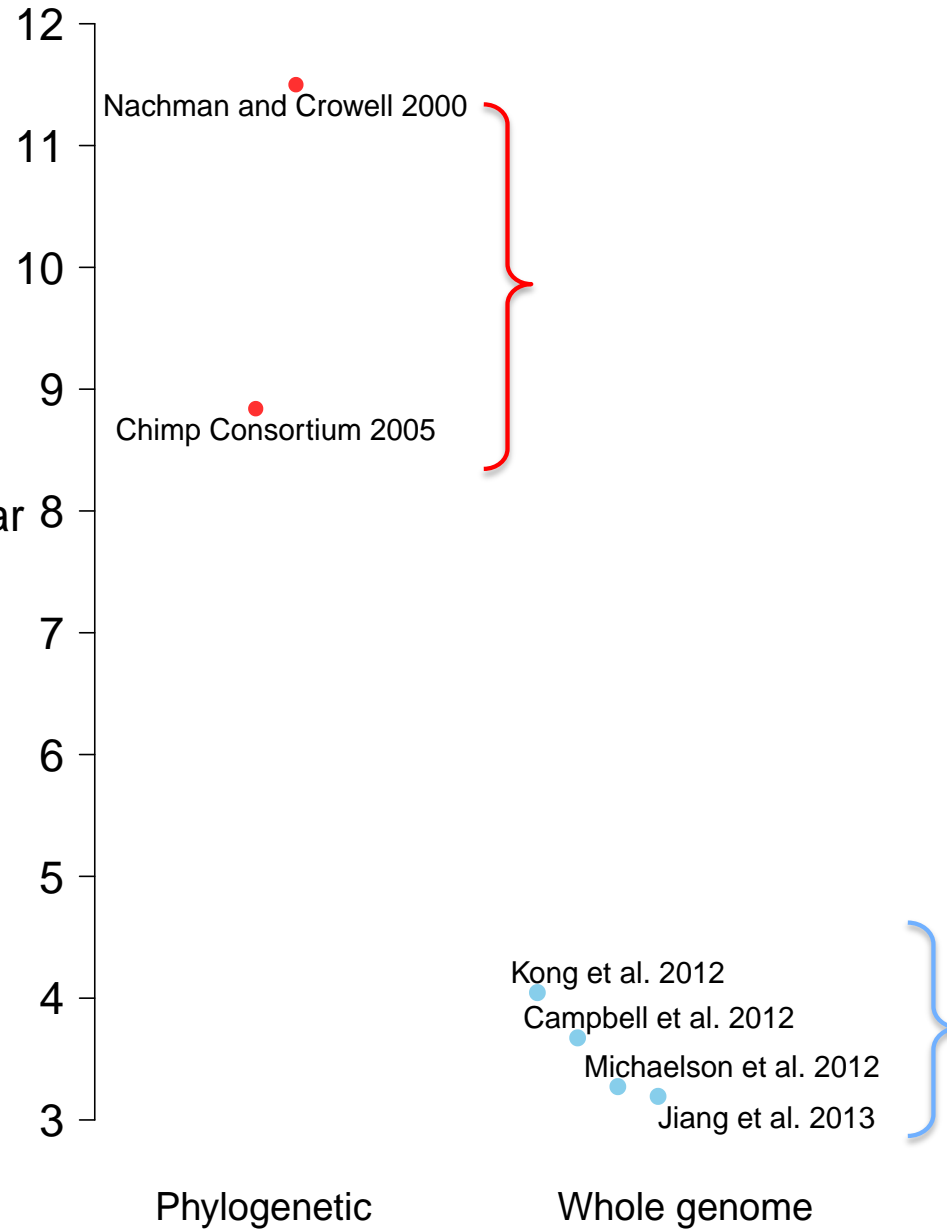
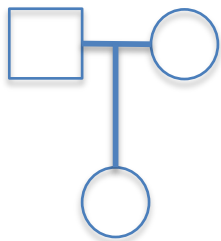
=> u

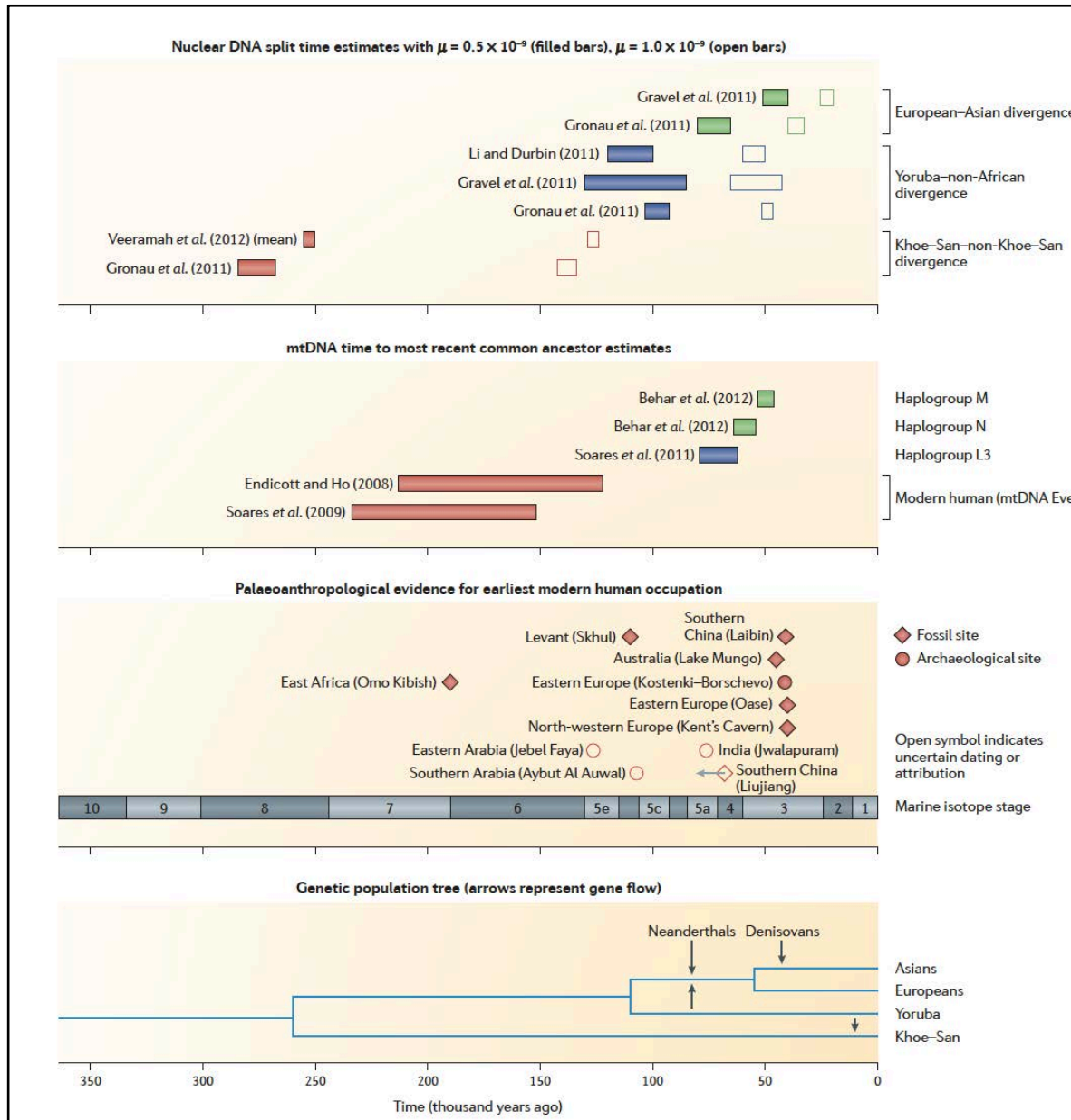


Phylogenetic Method

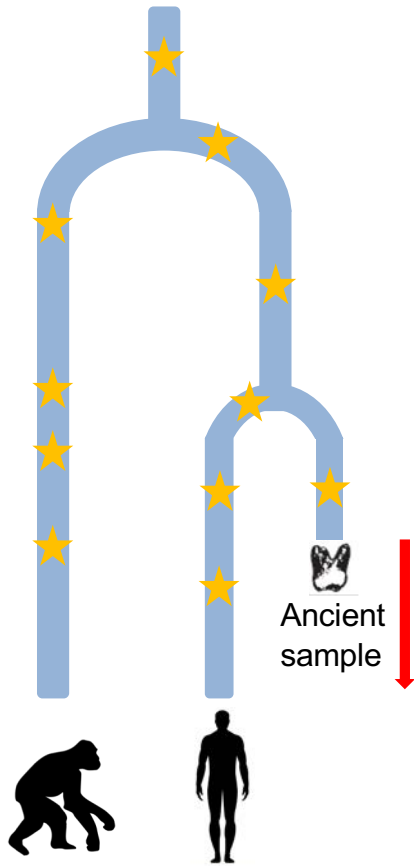


Pedigree-based Method

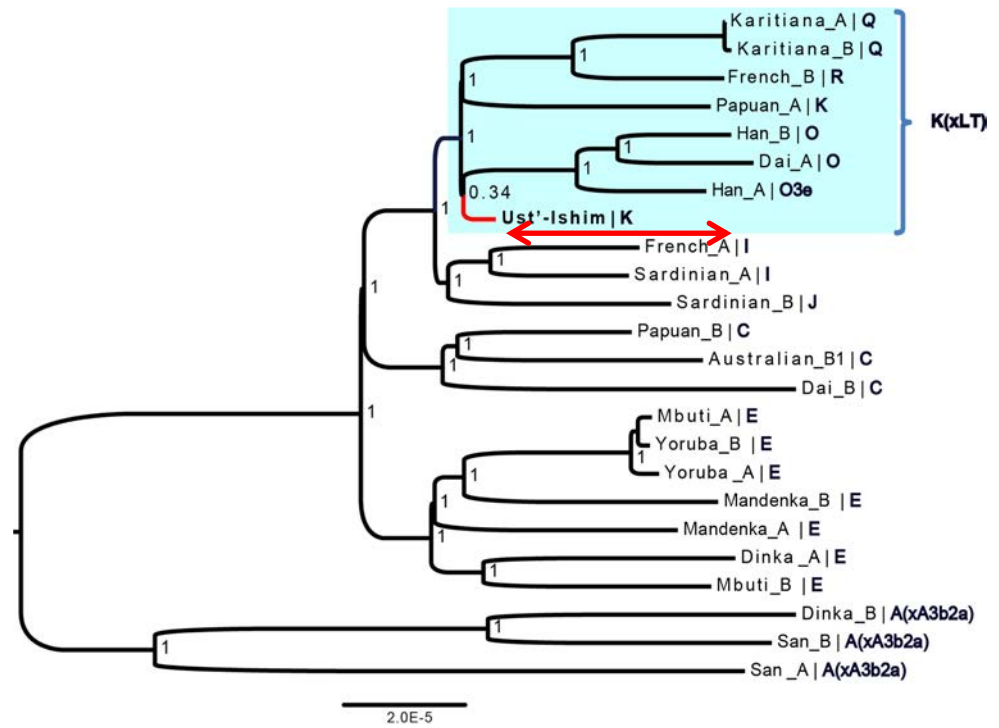




From Scally & Durbin 2012 NRG

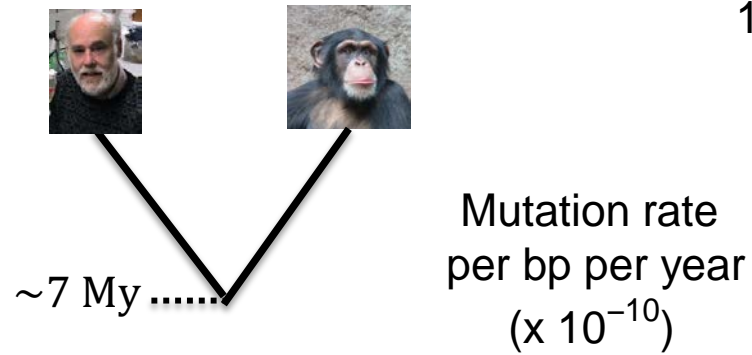


Phylogenetic tree of chromosome Y

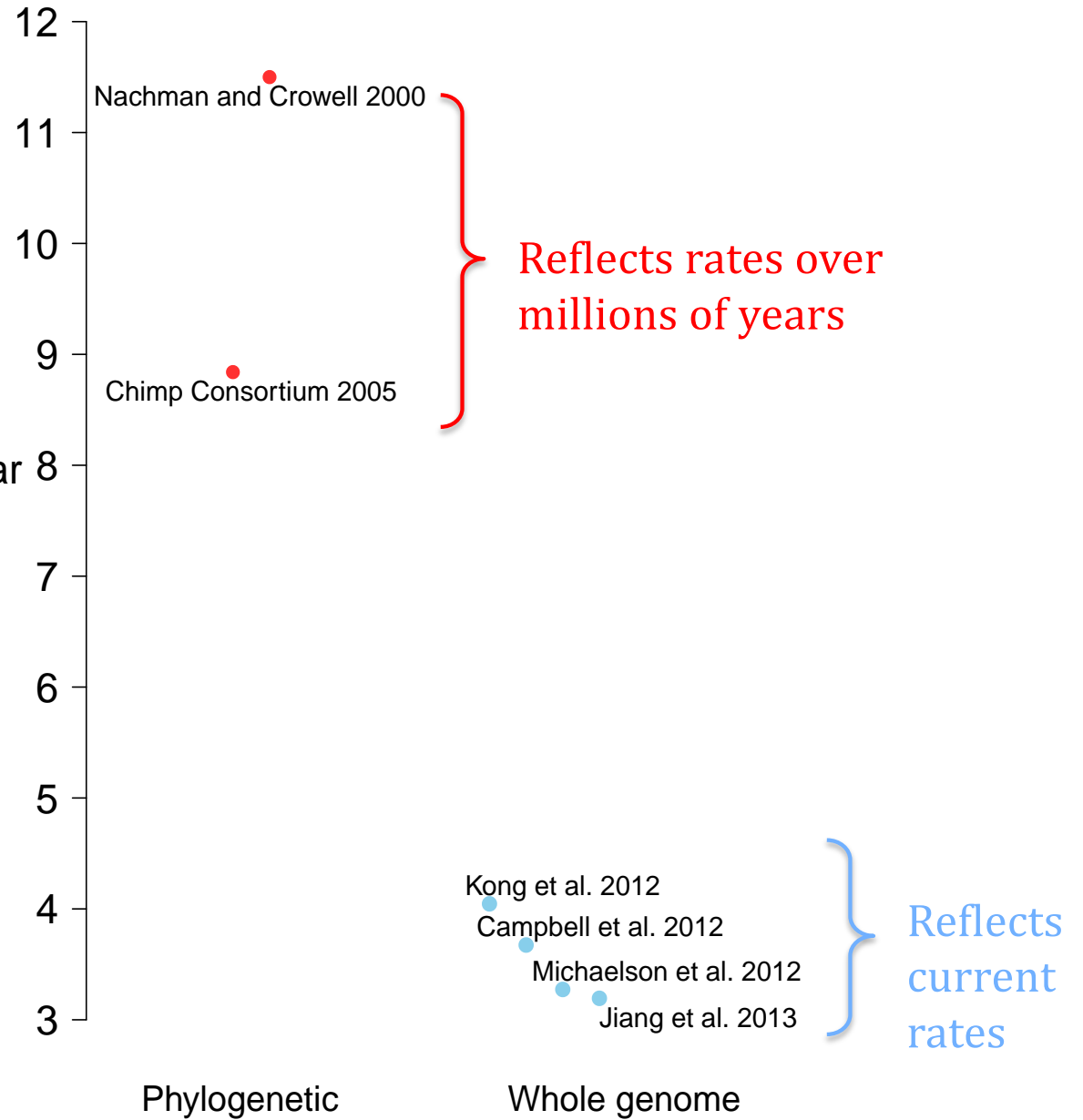
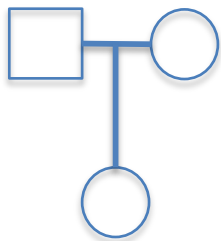


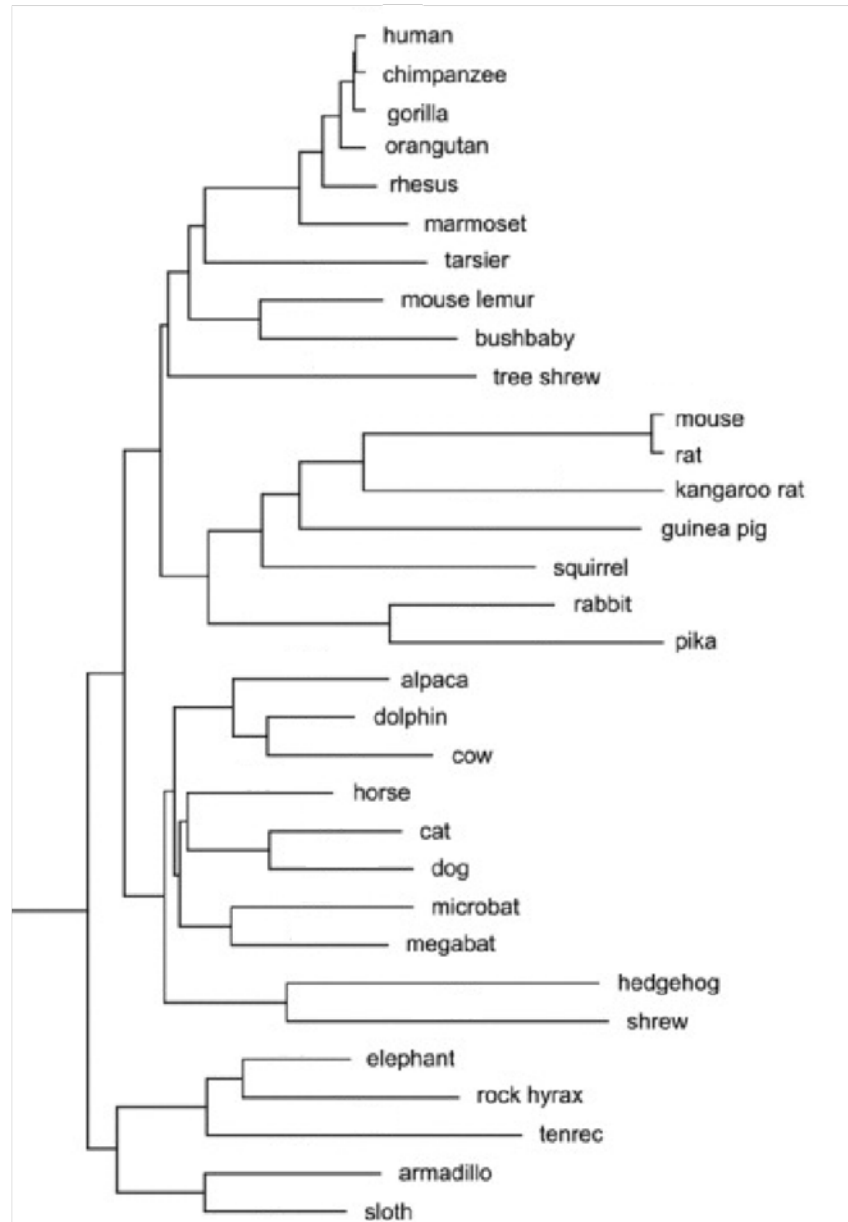
Fu et al., (2014)

Phylogenetic Method



Pedigree-based Method



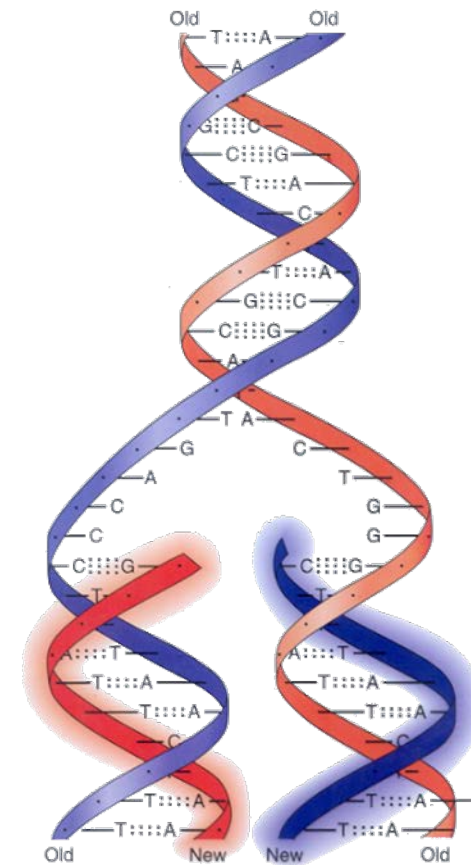


From Sayres et al. 2011 Evolution

The “generation time effect”

- ❖ Rodents have a substitution rate 2-3 times higher than primates.
- ❖ Rodents have a much shorter generation time (months) than primates (decades).

-> more cell divisions per unit time
-> more replication-driven mutations per unit time
-> a higher neutral substitution rate per unit time



Wu and Li 1984

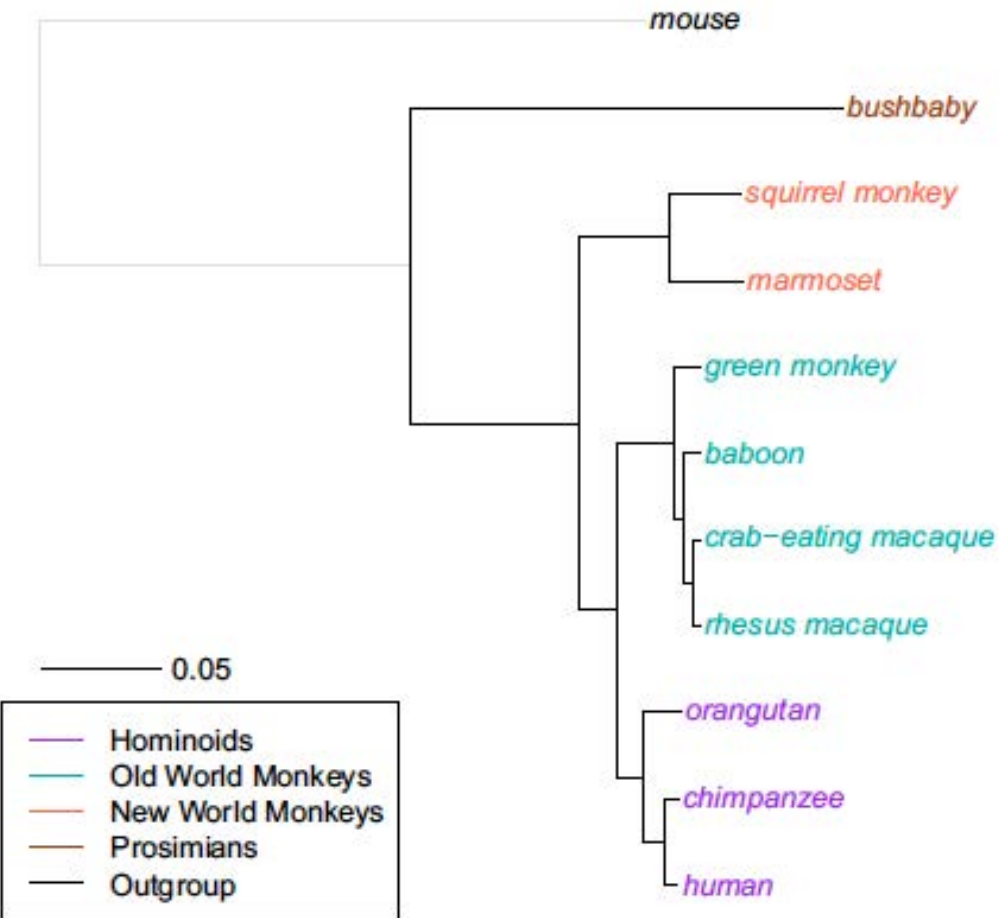
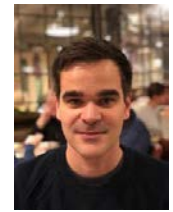


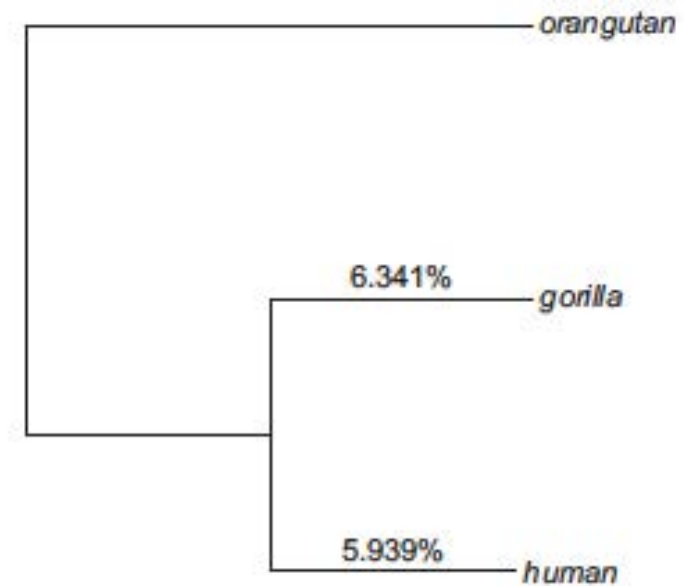
Fig. 1. Phylogenetic tree for 10 primates. Autosomal neutral substitution rates for 10 primates and an outgroup (mouse, shown in gray) from the



Priya
Moorjani



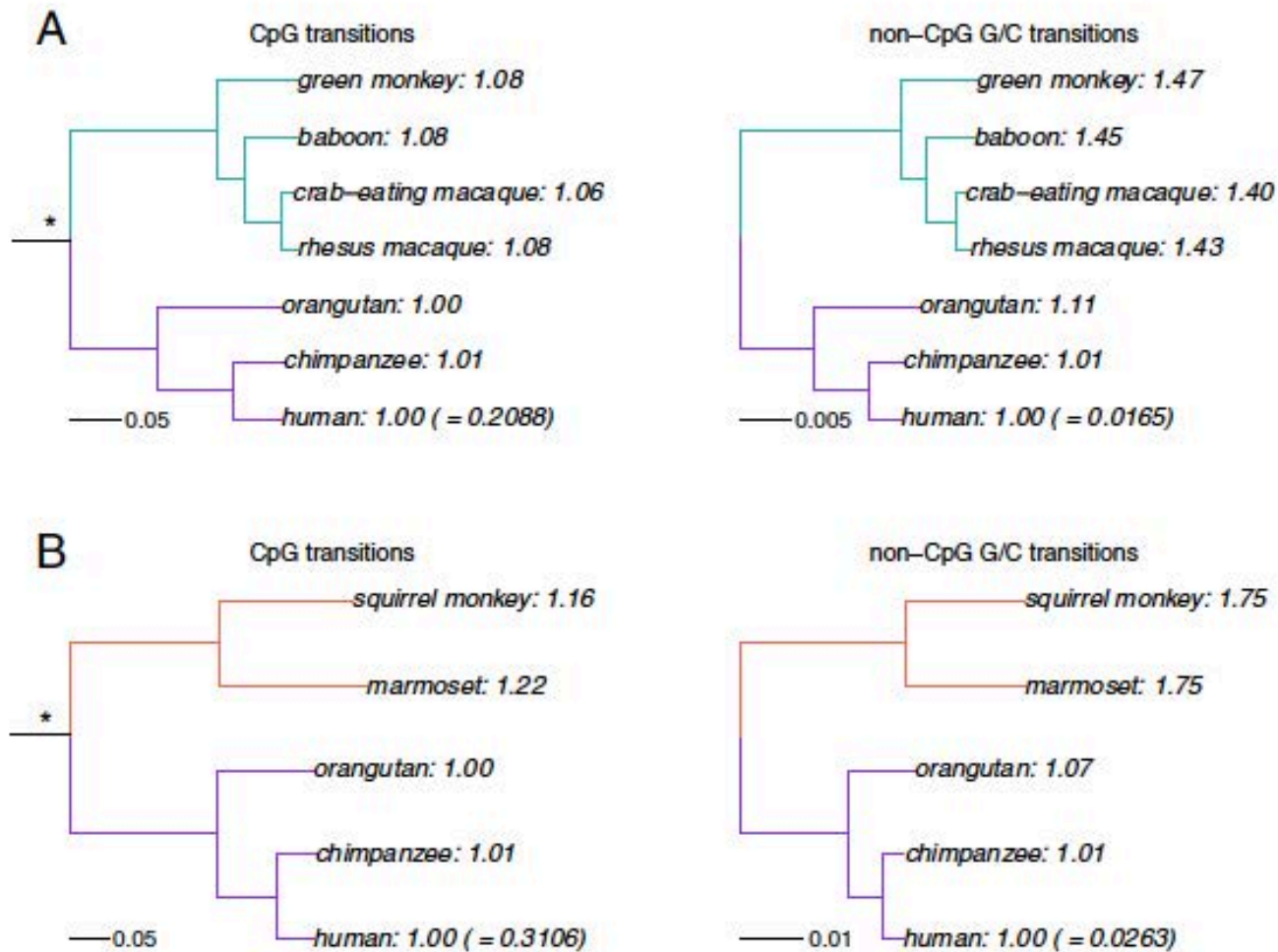
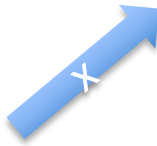
Eduardo
Amorim



Moorjani, Amorim et al. 2016 PNAS

See also Hwang and Green 2004 PNAS; Kim et al. 2006 Plos Gen

Human-chimpanzee
ancestor at ~12 My



Moorjani, Amorim et al. 2016 PNAS

See also Hwang and Green 2004 PNAS; Kim et al. 2006 Plos Gen

<i>Arabidopsis thaliana</i>	Plants	7.1×10^{-9}
<i>Pristionchus pacificus</i>	Invertebrates	2.0×10^{-9}
<i>Caenorhabditis elegans</i>	Invertebrates	1.5×10^{-9}
<i>Caenorhabditis briggsae</i>	Invertebrates	1.3×10^{-9}
<i>Drosophila melanogaster</i>	Invertebrates	3.2×10^{-9}
<i>Heliconius melpomene</i>	Invertebrates	2.9×10^{-9}
<i>Daphnia pulex</i>	Invertebrates	5.7×10^{-9}
Atlantic herring (<i>Clupea harengus</i>)	Teleosts	2.0×10^{-9}
Collared flycatcher (<i>Ficedula albicollis</i>)	Birds	4.6×10^{-9}
Mouse (<i>Mus musculus</i>)	Mammals	5.4×10^{-9}
Cattle (<i>Bos taurus</i>)	Mammals	9.7×10^{-9}
Chimpanzee (<i>Pan troglodytes</i>)	Mammals	1.2×10^{-8}
Human (<i>Homo sapiens</i>)	Mammals	1.2×10^{-8}

From Feng et al. 2017 Elife



Owl monkey:

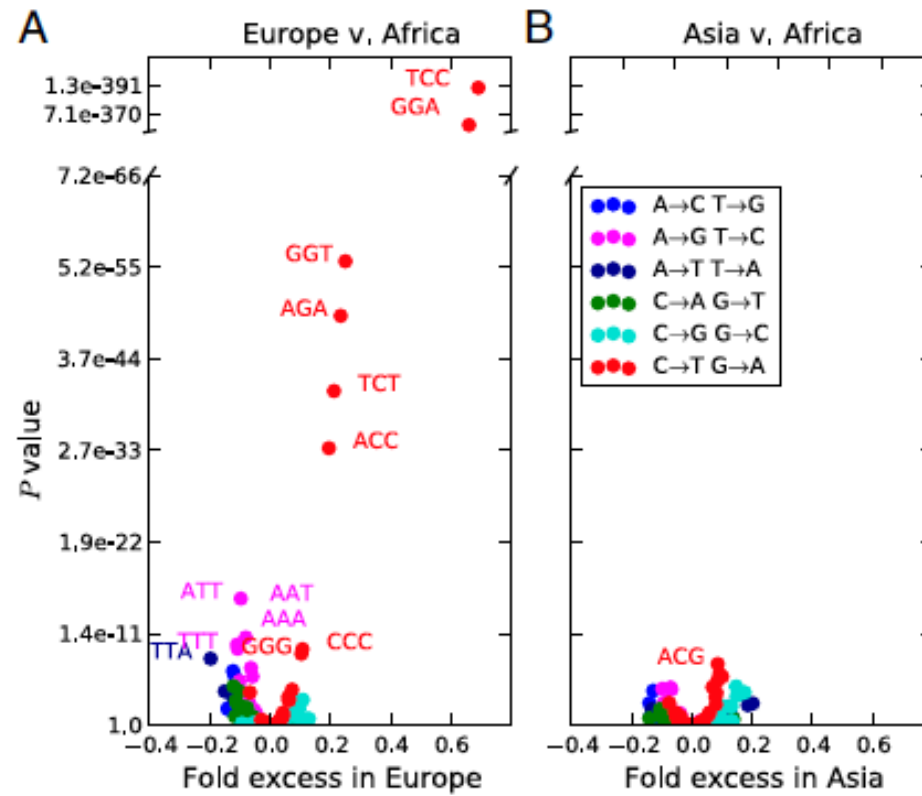
0.8×10^{-8} per bp per generation

Gen time ~ 6 years

$\Rightarrow 1.3 \times 10^{-9}$ per year, or ~ 3 higher than in humans...

Numbers from Thomas et al. 2018 Curr Biol

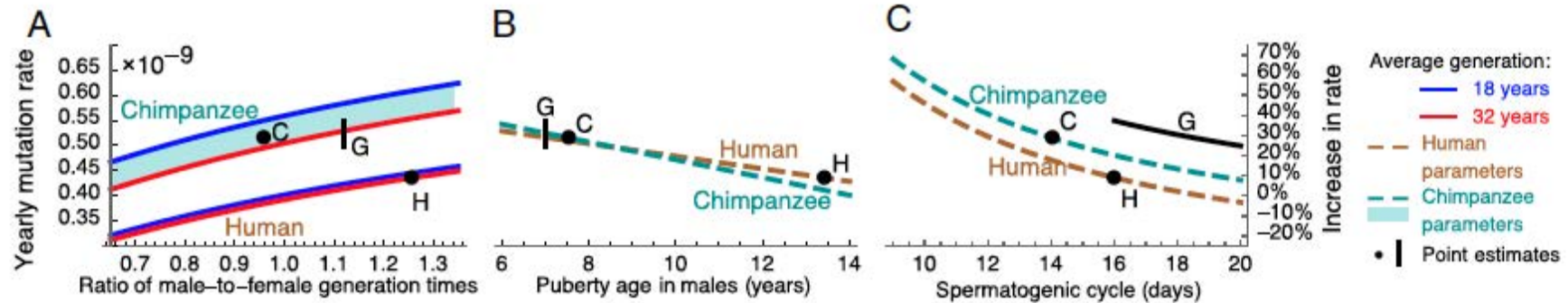
Simons Diversity Genome Project (2016 Nature): ~5% longer branches in non-African populations



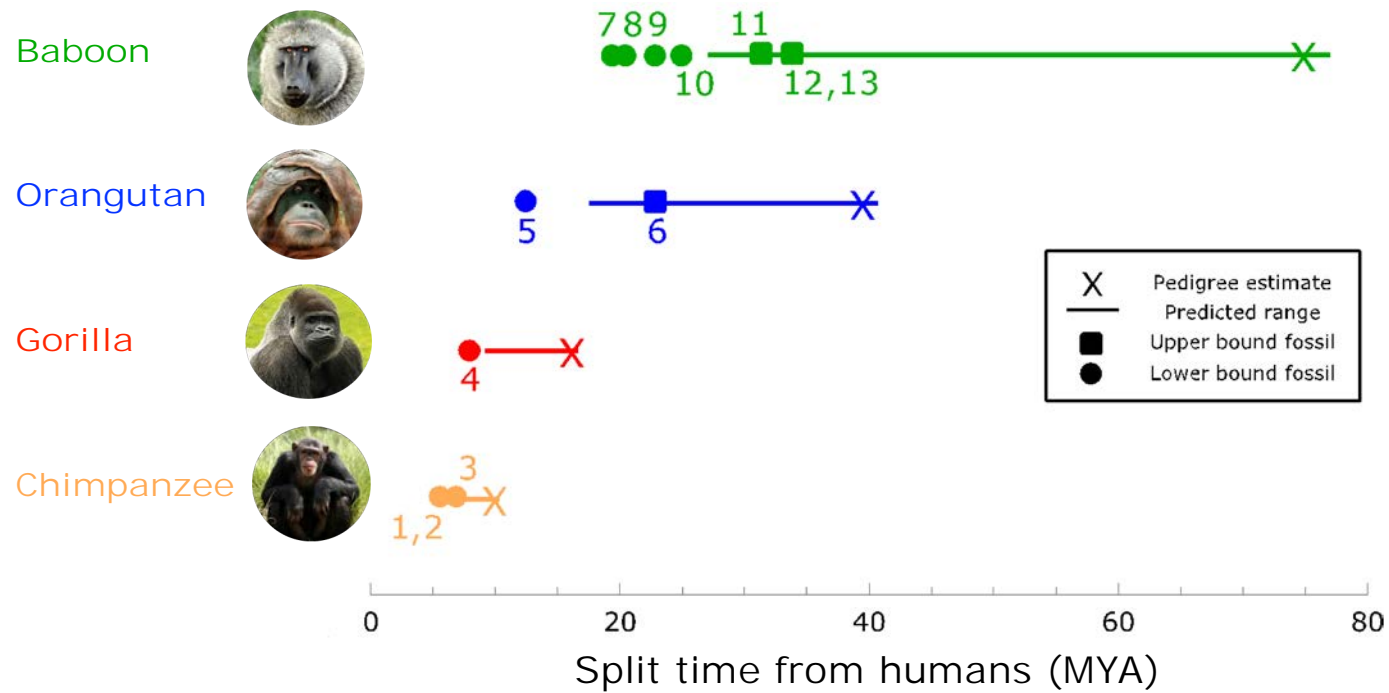
From Harris 2005 PNAS

Why do mutation rates evolve?

- Due to changes in generation times and onset of puberty



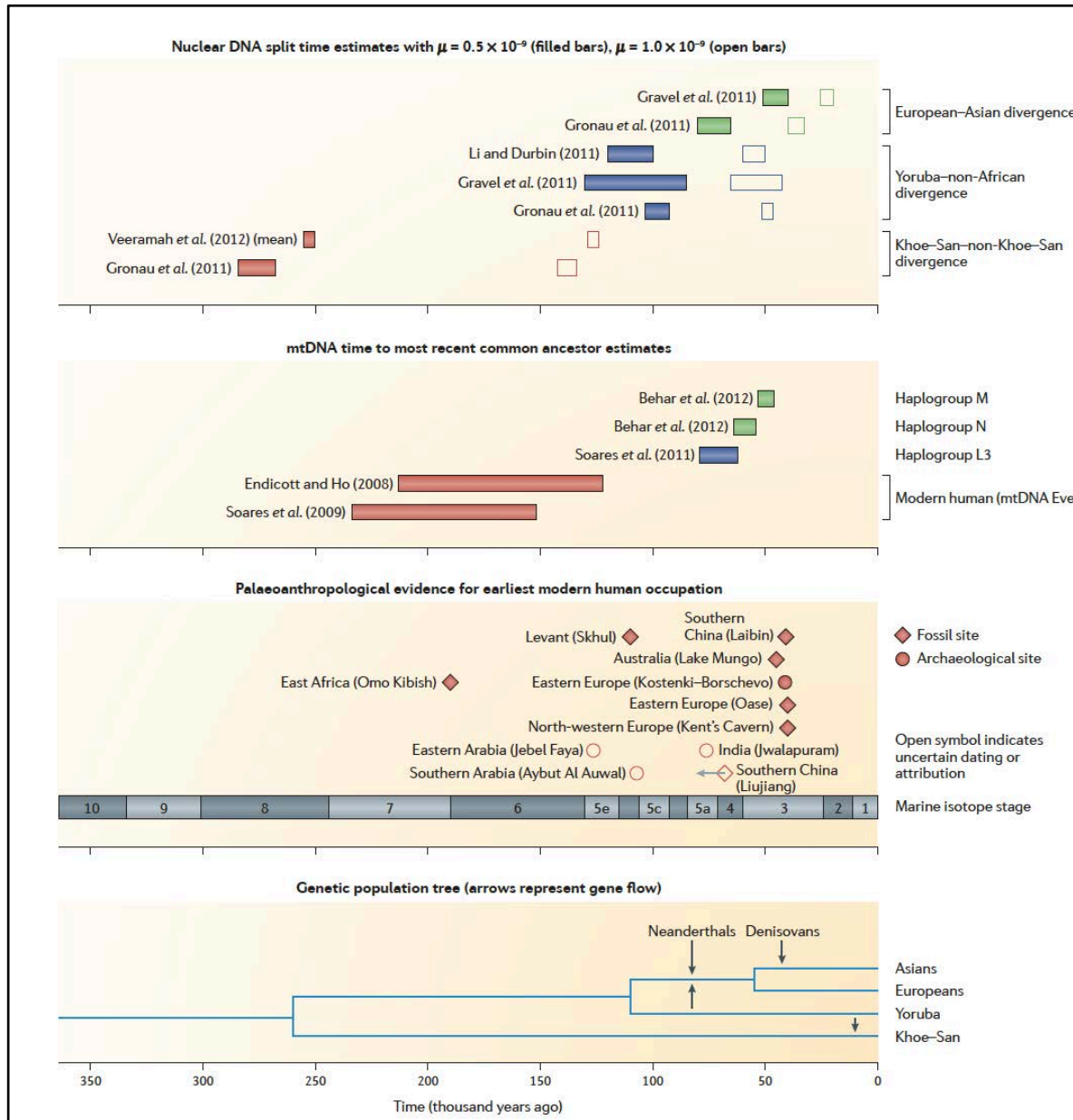
From Amster and Sella 2016 PNAS



- | | | | |
|-------------------|--------------------|--------------------|-----------------|
| 1 Orrorin | 5 Sivapithecus | 9 Proconsul | 13 CatoPithecus |
| 2 Ardipithecus | 6 Proconsul | 10 Nsungwepithecus | |
| 3 Sahelanthropus | 7 Victoriapithecus | 11 Propithecus | |
| 4 Chororapithecus | 8 Morotopithecus | 12 Oligopithecus | |

Summary

- Mutation rates estimated from pedigrees are only half those that seem to be suggested by the fossil record. In other words, current mutation rates seem to be suggesting split times between primate species that are too old.
- One possibility is that mutation rates per year evolve, and have slowed towards the present. Indeed we know that yearly mutation rates evolve across species and even across populations.
- However, the conversion between mutation and divergence is less obvious than it first seems. It depends on life history traits and in particular male to female generation time and the onset of puberty.
- Moving forward, we need direct estimates of mutation rates in multiple primates and populations, and more estimates of mutation rates from « missing divergence » of fossils.



From Scally & Durbin 2012 NRG