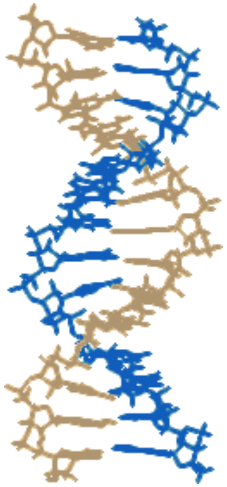
SISG 2022 - Module 2

Introduction to Genetics and Genomics

Molecular Evolution



12:15pm EDT, Tuesday, July 12th

Joe Lachance and Greg Gibson

joseph.lachance@biology.gatech.edu

Functional DNA

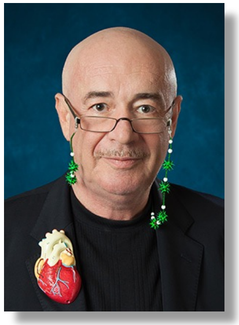
- What does it mean to say that a part of the genome is functional?

- What fraction of the human genome is functional?

ENCODE and the debate about functionality

- ENCODE refers to the **enc**yclopedia **o**f **D**NA **e**lements
- ENCODE: functional elements encode a defined product or display a reproducible biochemical signature
- Evolutionary conservation is another way to infer functional DNA

- Ewan Birney: "80% of the human genome has a biochemical function"



- Dan Graur: "An example of function that fits the ENCODE definition: shoes binding to chewing gum"
- 10-15% might be a better estimate

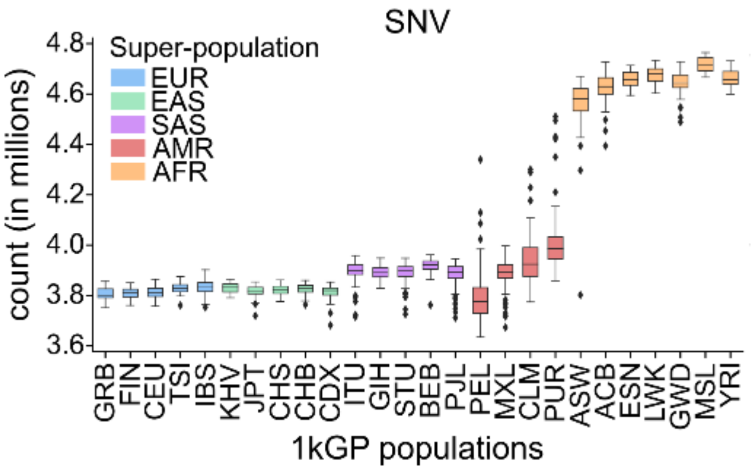
Junk DNA and the evolution of genomes

- **Junk DNA** refers to sequences that have no known function
- Species with small population sizes tend to have more junk DNA
- Genomes are not static – they change over evolutionary timescales
- Junk DNA can be repurposed

Image: Disney · PIXAR

SNPs

- **SNVs** refer to Single Nucleotide Variants (e.g., **A** or **G**), and when minor allele frequencies are above 1% these variants are called **SNPs** (Single Nucleotide Polymorphisms)



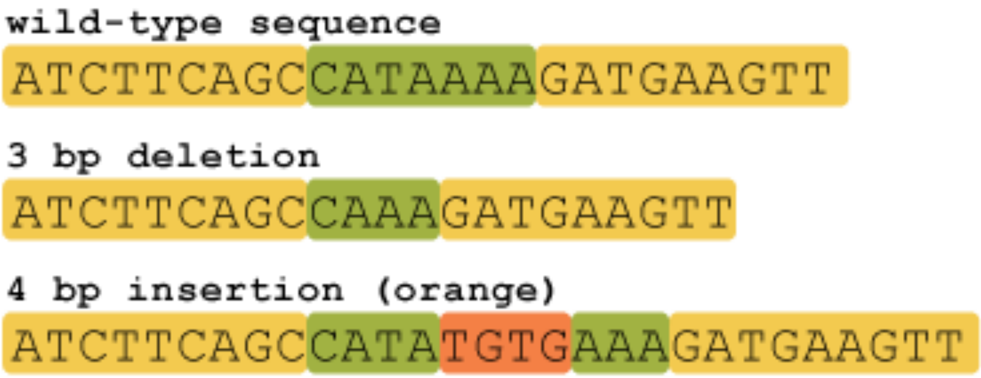
- Each human genome has between 3.8 million to 4.7 million SNVs
  - Genotyping error might overestimate counts of heterozygous sites
  - African genomes contain more genetic diversity than non-African genomes

- Most SNPs are biallelic (they have two alleles)

- More than 660 million polymorphisms are known at present (dbSNP)

Figure from Byrska-Bishop et al. (bioRxiv)

Indels



wild-type sequence

ATCTTCAGCCATAAAAGATGAAGTT

3 bp deletion

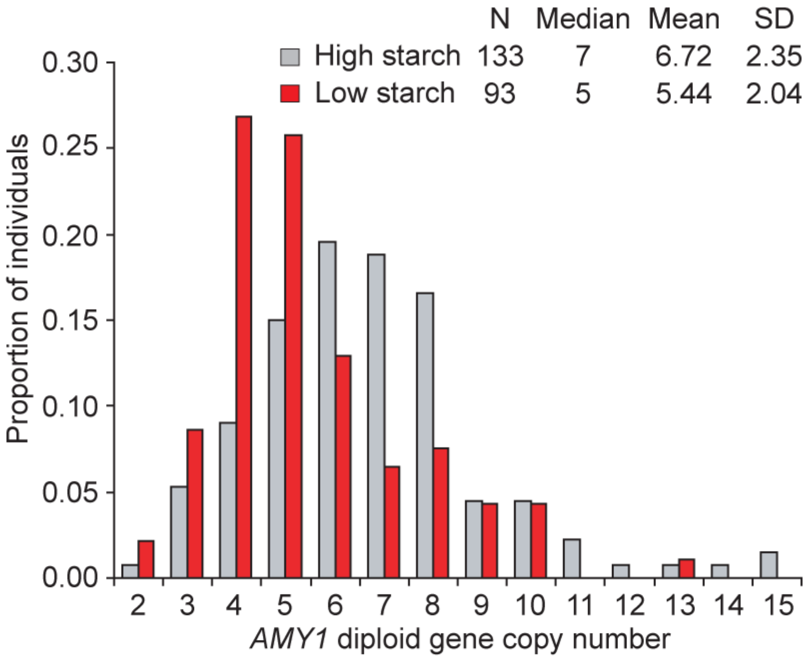
ATCTTCAGCCAAAGATGAAGTT

4 bp insertion (orange)

ATCTTCAGCCATATGTGAAAGATGAAGTT

- **In**sertions or **del**etions (indels)
- Human genomes have between 540k and 625k indels
- Most indels are small
- Indels in coding regions tend to be multiples of 3bp. Why?

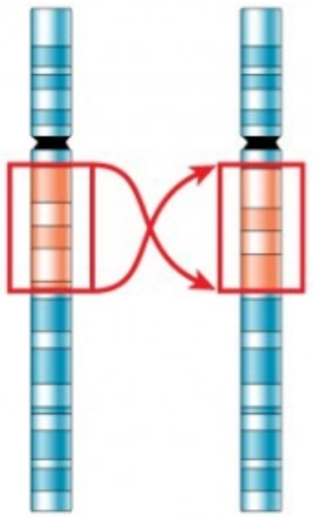
CNVs



	N	Median	Mean	SD
□ High starch	133	7	6.72	2.35
🟥 Low starch	93	5	5.44	2.04

- **CNV**: copy number variation
- Data from Perry et al. (*Nature Genetics*, 2007)
- Humans with high starch diets have more copies of *amylase genes*

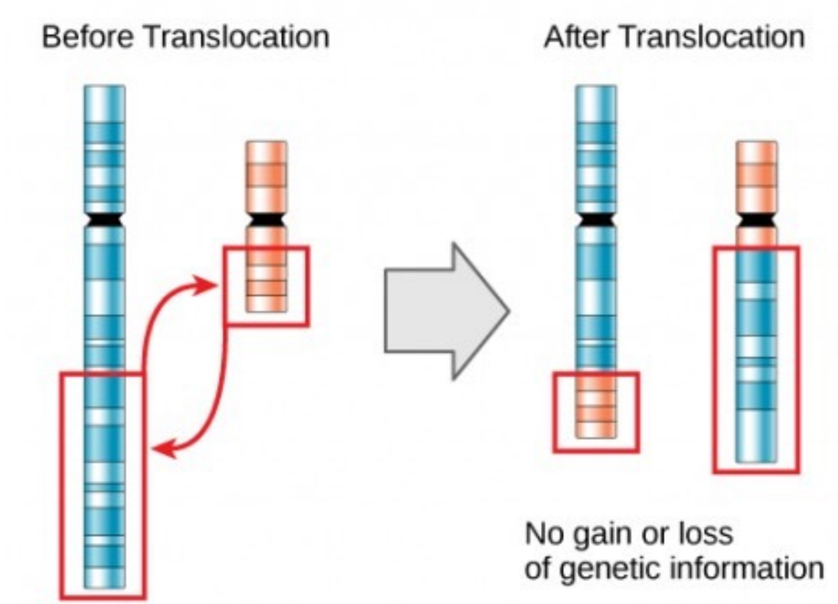
Inversions



- **Inversions** are chromosomal rearrangements in which a segment of a chromosome is reversed from end to end

- Inversions inhibit recombination (crossover products are not recovered)

Translocations



- **Translocations** are chromosomal rearrangements in which genetic material is exchanged between chromosomes

- Can cause genes to be mis-regulated and problems during meiosis

Translocation example

- Philadelphia chromosome

- Reciprocal translocation between chromosome 9 and 22 (in humans)

- Causes chronic myelogenous leukemia (CML)

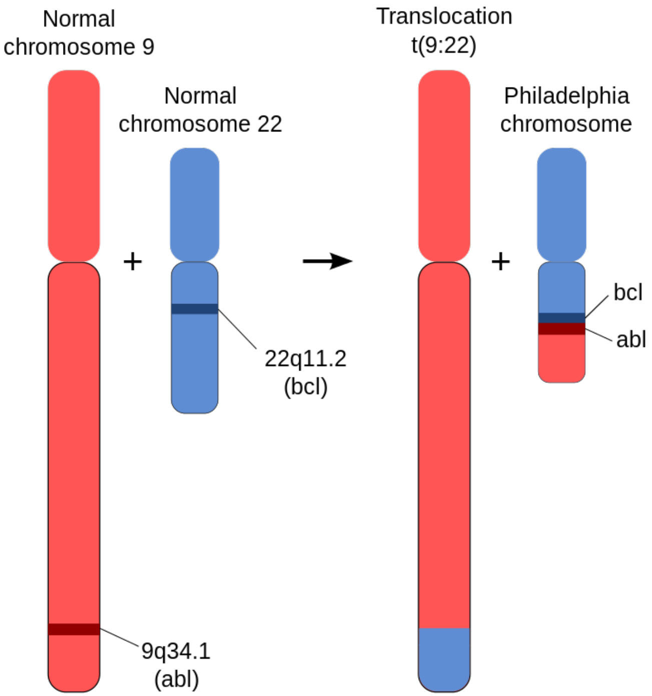
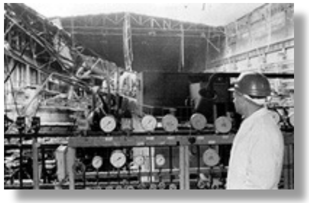


Image from Wikipedia

Causes of mutations

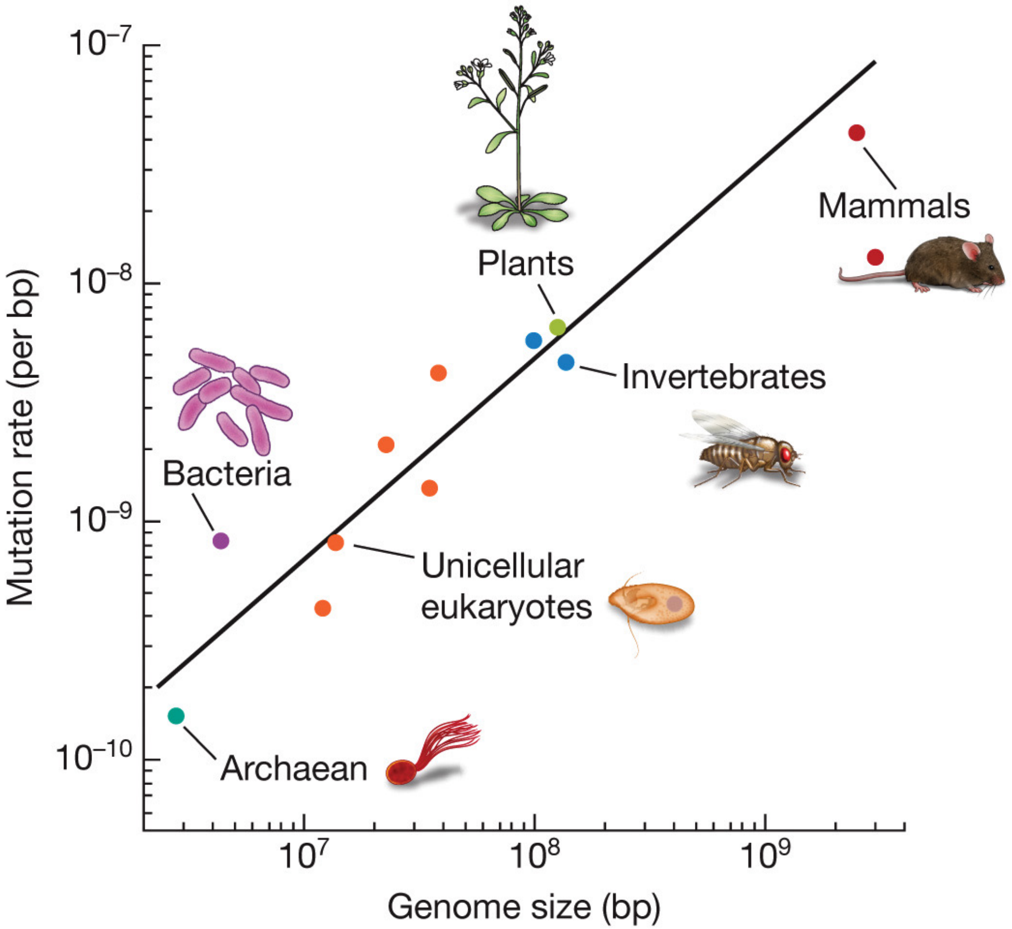
- DNA replication errors
- Chemical mutagens
  (think of the Ames test)
- Radiation (X-rays and UV)



- What are the evolutionary impacts of the Three Mile Island, Chernobyl, and Fukushima Daiichi disasters?

Image sources: Rick and Morty (Adult Swim) and NPR

Mutation rates vary widely across species



EVOLUTION 4e, Figure 4.15

Different estimates of mutation rates in humans

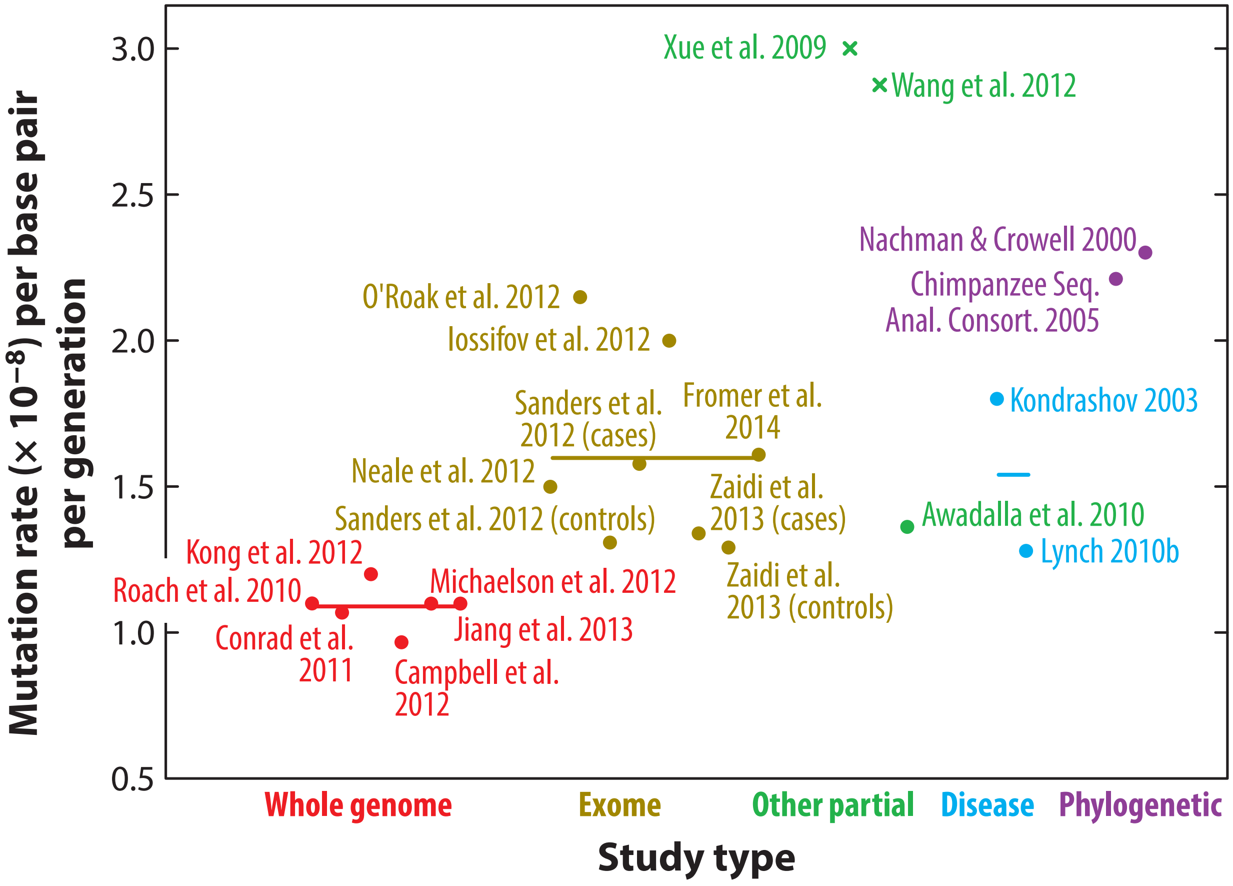


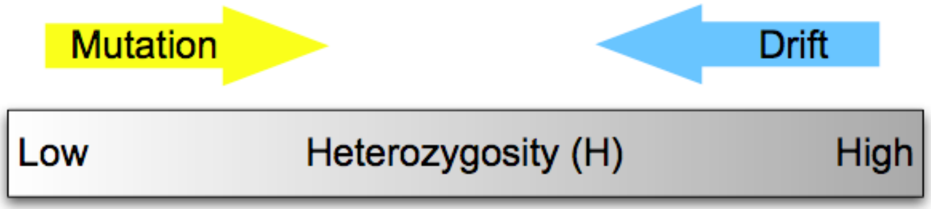
Figure from Ségurel et al. (*Annual Review of Genomics and Human Genetics*, 2015)

Neutral theory of molecular evolution

- Motoo Kimura (1968)
- Most polymorphisms are neutral (neither good nor bad)
- Examples of neutral variation:
  - Synonymous changes (codon change, but same amino acid)
  - Pseudogenes: “dead genes” that are no longer expressed
  - Intergenic DNA

Neutral theory of molecular evolution

- A balance exists between a decrease in variation due to random chance (genetic drift) and an increase in variation due to mutation



$$\hat{H} = \frac{4N_e\mu}{1 + 4N_e\mu}$$

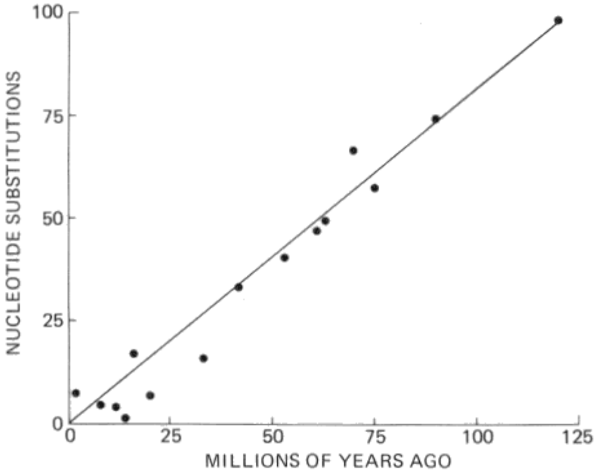
- Large populations have more genetic variation than small populations
- Highly mutable parts of genomes contain more genetic variation
- The neutral theory provides a null hypothesis for studies of molecular evolution

Neutral-selectionist debate

- What is more important: neutral evolution or natural selection?
- Historical: Motoo Kimura (neutral) vs. John Gillespie (selection)
- Modern day: Jeff Jensen (neutral) vs. Matt Hahn (selection)

Image of the Legislative Yuan in Taiwan: BBC/AFP

Molecular clock



$$d = 2\mu t$$

d = divergence (proportion of sites)

μ = mutation rate

t = time (generations)

- Mutations at neutral sites accumulate in a clocklike fashion (but not like a metronome!)
- Genetic data can be used to infer divergence times between species
- First proposed by Zuckerlandl and Pauling in 1962

Image from Shutterstock

D_n/D_s ratios and MK tests

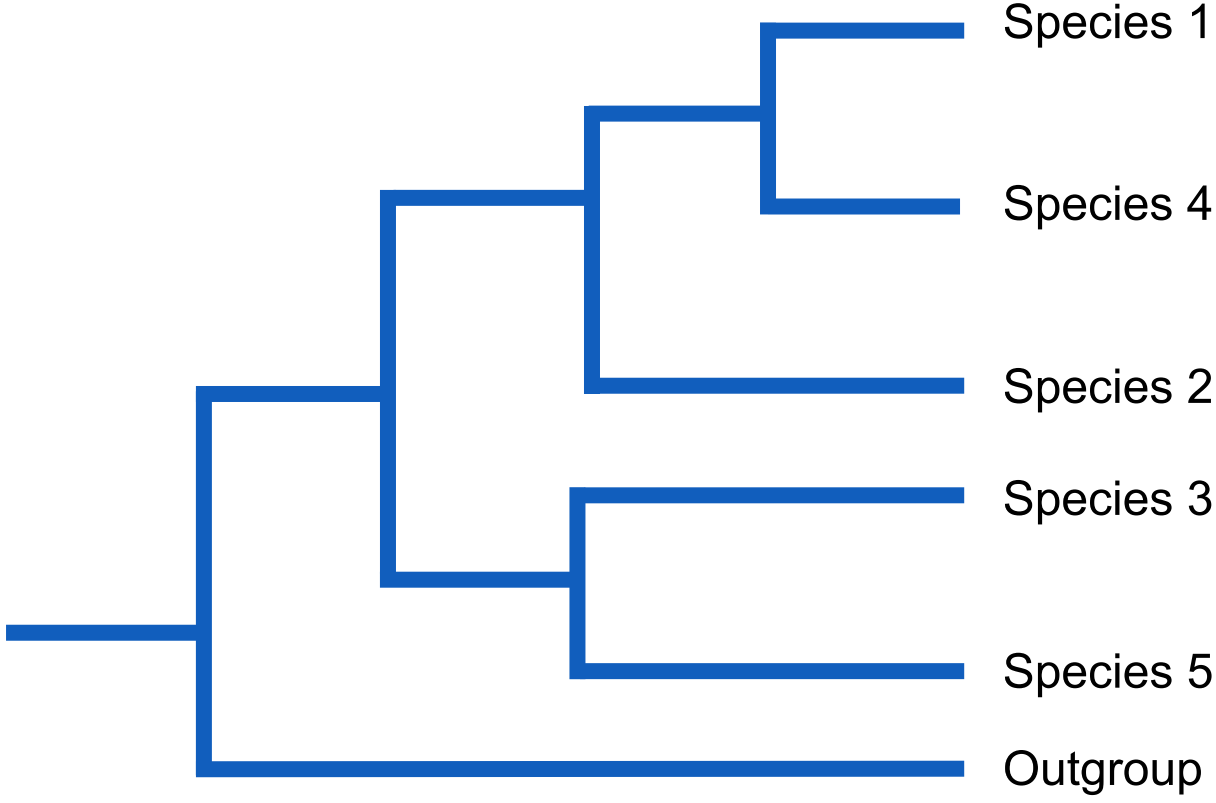
	Fixed differences between species	**Polymorphic within species**
Nonsynonymous (a.a. change)	D_n	P_n
Synonymous (no a.a. change)	D_s	P_s

$$\text{Neutrality Index } (NI) = \frac{P_n/P_s}{D_n/D_s}$$

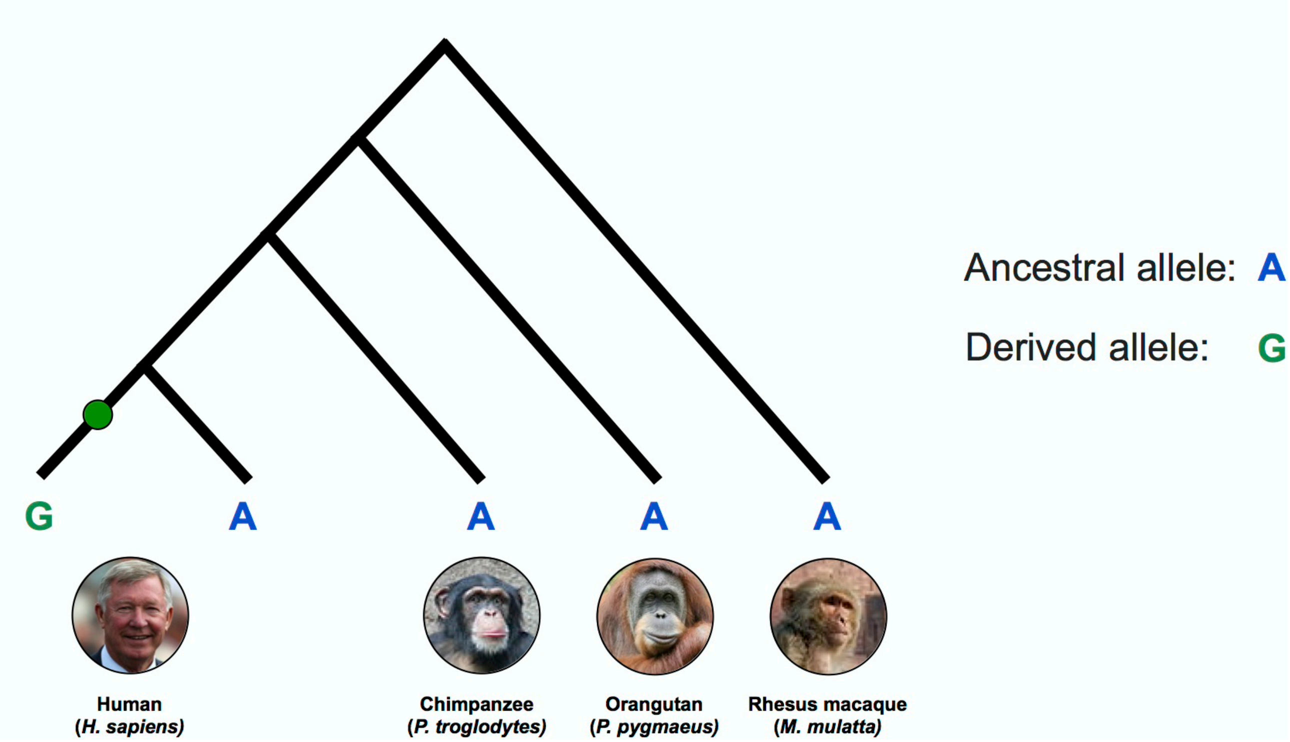
$$\begin{aligned} NI > 1 &\implies \text{negative selection} \\ NI < 1 &\implies \text{positive selection} \end{aligned}$$

- Comparative genomics can reveal which genes have been under selection
- Positively selected genes have an excess of nonsynonymous substitutions
- McDonald-Kreitman (MK) test compares fixed differences and polymorphisms

Phylogenies describe evolutionary relationships

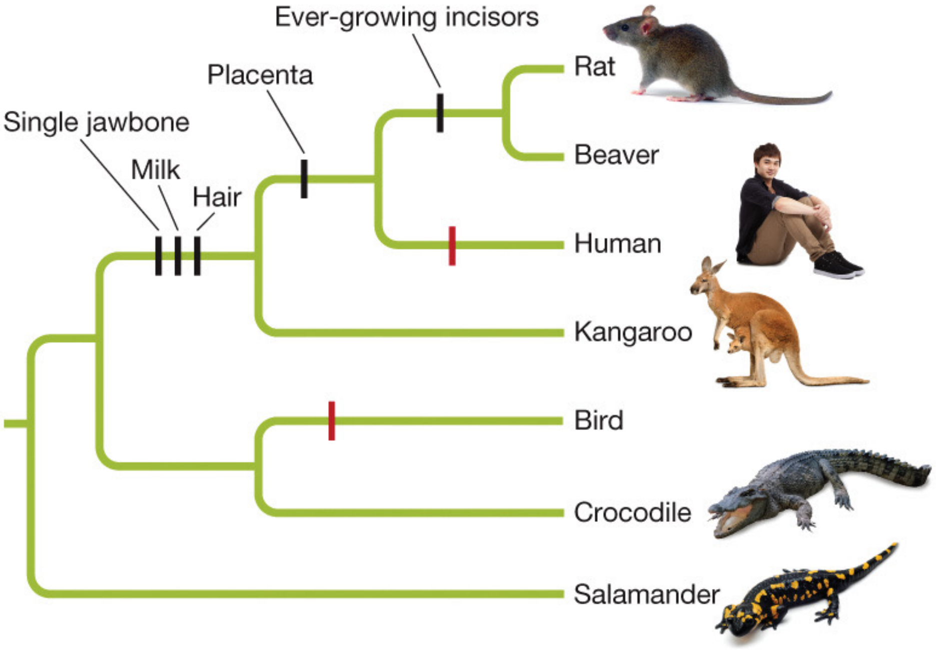


Ancestral vs. derived traits



- **Ancestral** traits are shared with related species
- **Derived** traits are due to recent mutations

Phylogenetically informative characters



- **Synapomorpy:** shared derived character

- Synapomorphies are phylogenetically informative characters

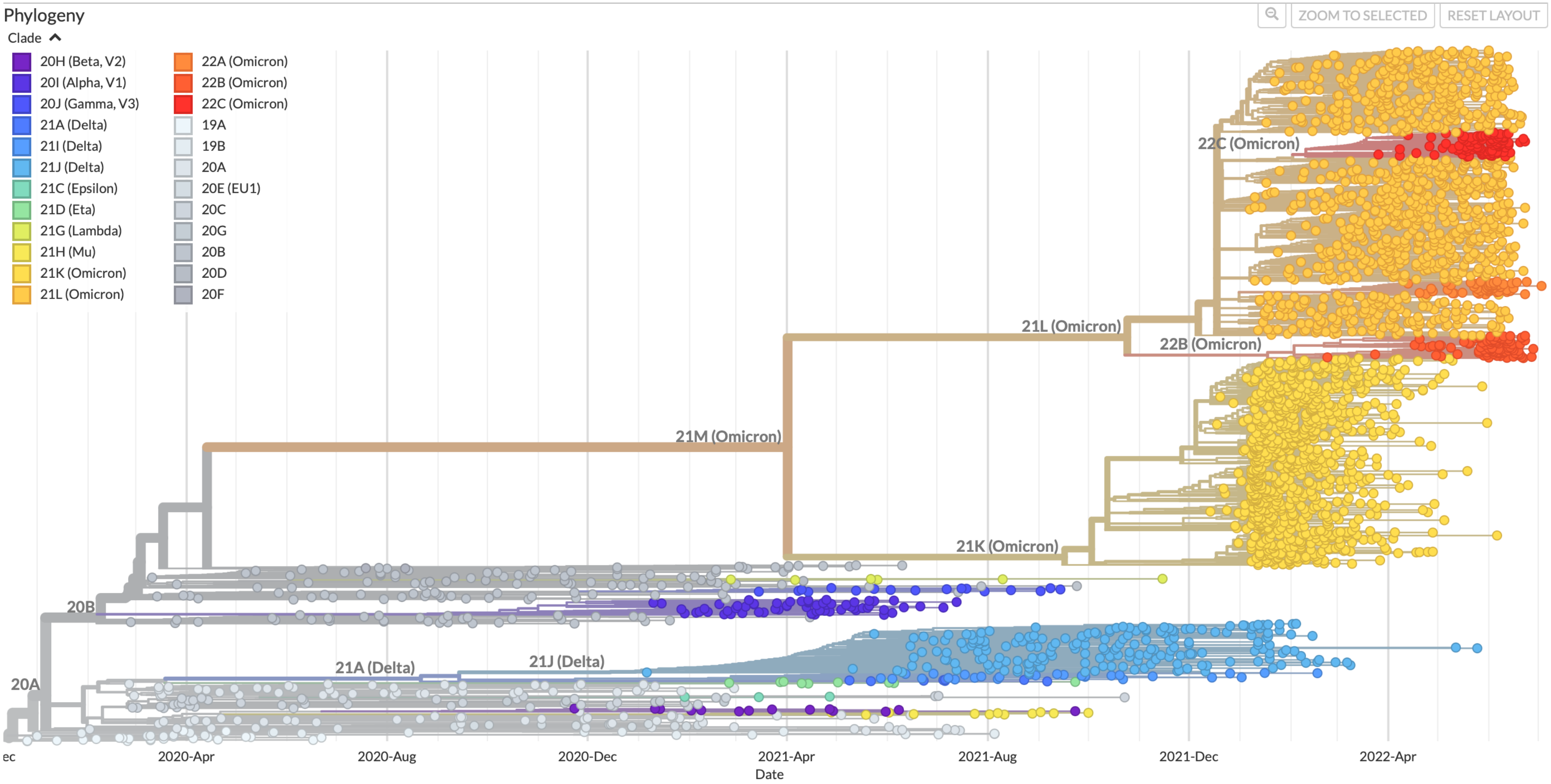
Figure from *Evolution 4e* (Sinauer Associates)

Genetic data can be used to build phylogenies

	Species **1**	Species **2**	Species **3**	Species **4**	Species **5**
Species **1**	0	3	7	1	7
Species **2**	3	0	7	3	7
Species **3**	7	7	0	6	2
Species **4**	1	3	7	0	7
Species **5**	7	7	2	7	0

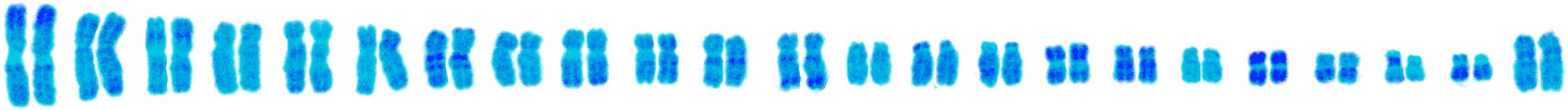
- Pairwise distance matrix calculated by counting the number of sites that differ between each pair of species

SARS-CoV-2 phylogenetics



Figures nextstrain.org

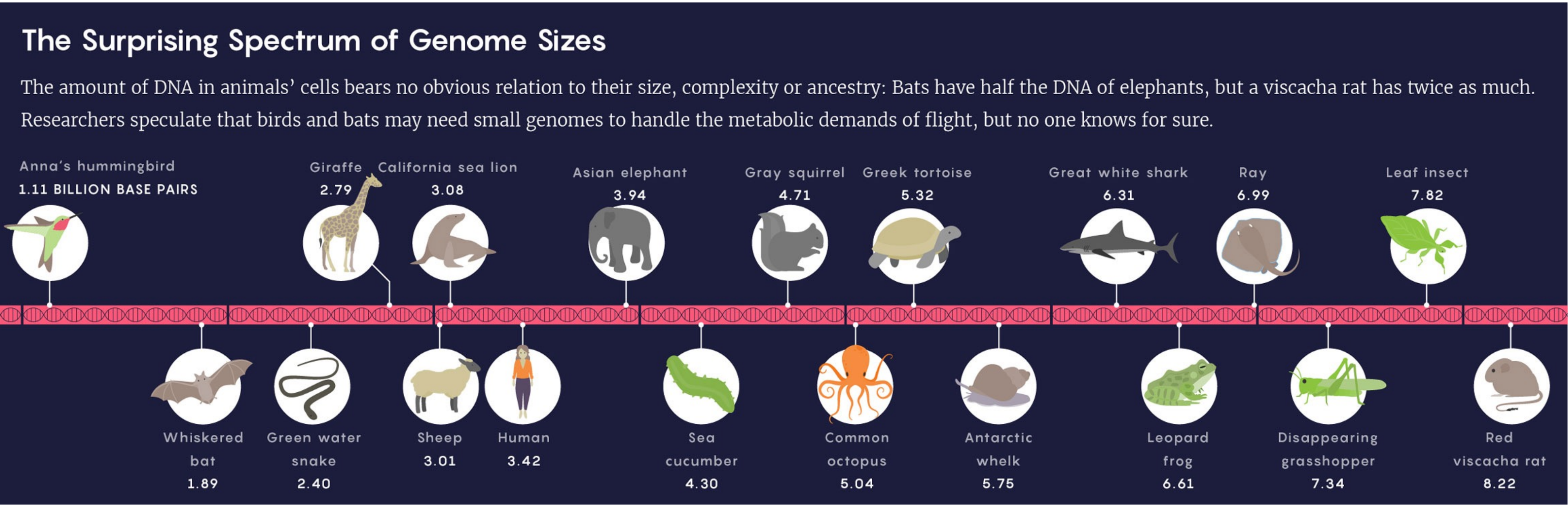
Variation in the number of chromosomes



- **Karyotype**: the number of chromosomes in the nucleus of a species

- Diploid (2N) chromosome numbers for different species
  - Human *(Homo sapiens*): 46
  - Chimpanzee (*Pan troglodytes*): 48
  - Jack jumper ant (*Myrmecia pilosula*): 2
  - Fern (*Ophioglossum reticulatum*): 1260
  - Ciliate (*Oxytricha trifallax*): 32000

Genome sizes vary greatly across species



The Surprising Spectrum of Genome Sizes

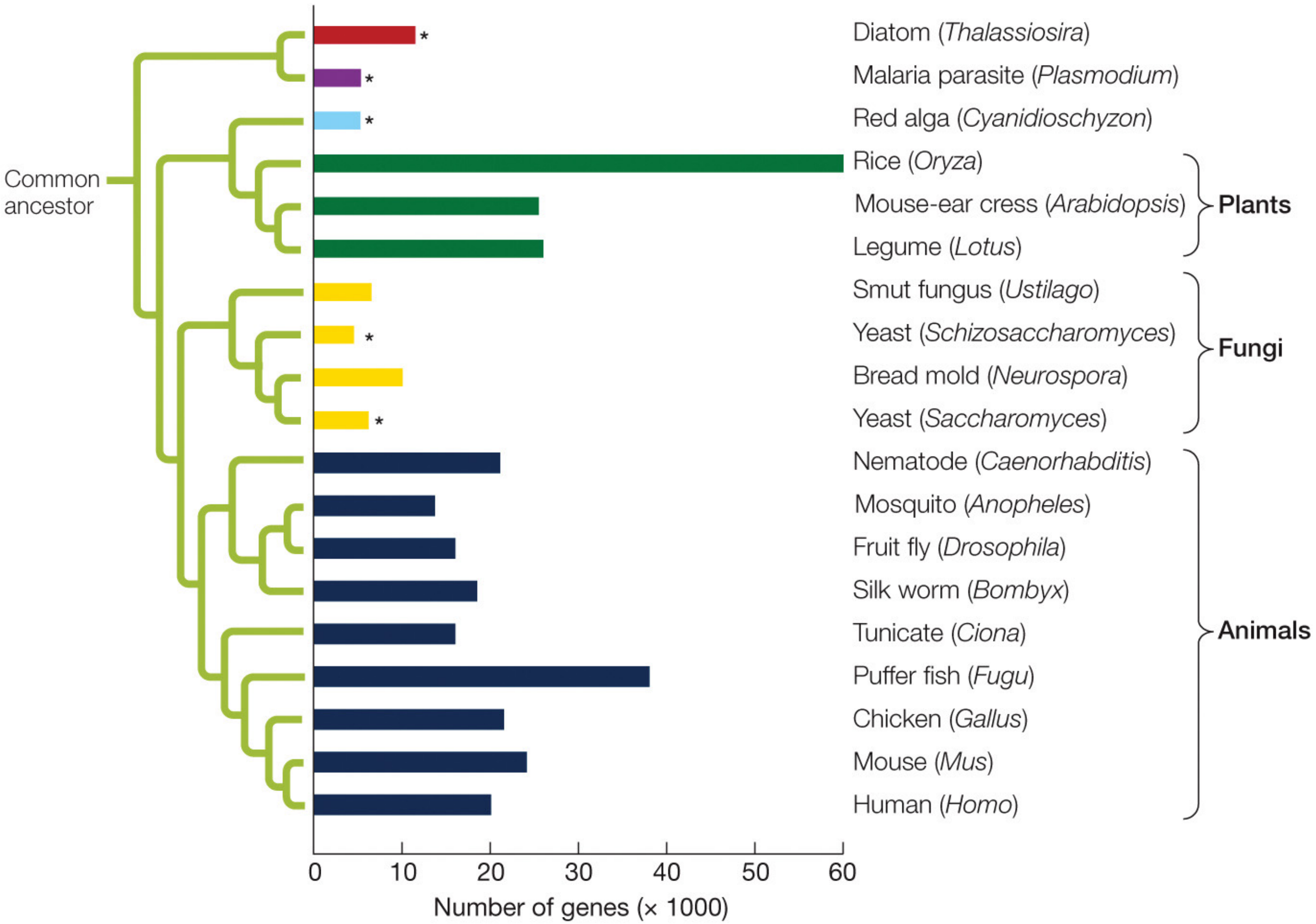
The amount of DNA in animals' cells bears no obvious relation to their size, complexity or ancestry: Bats have half the DNA of elephants, but a viscacha rat has twice as much. Researchers speculate that birds and bats may need small genomes to handle the metabolic demands of flight, but no one knows for sure.

- **C-value paradox**: complex organisms don't always have big genomes (C-value refers to the total amount of DNA in each genome)

- Why might this be the case?

Image source: Quanta Magazine (Lucy Reading-Ikkanda)

The number of protein coding genes varies by species



EVOLUTION 4e, Figure 14.2

Fates of duplicated genes

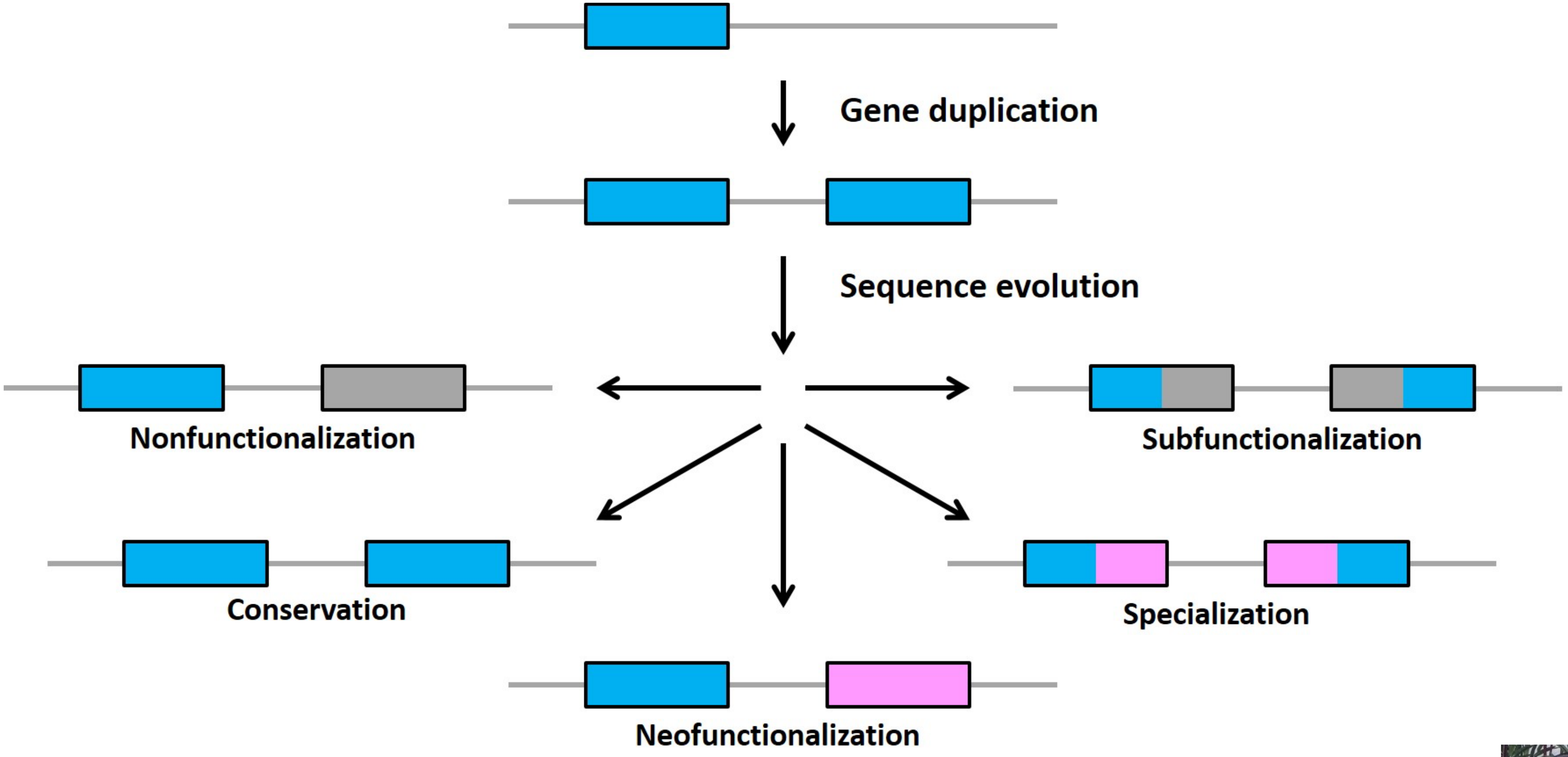
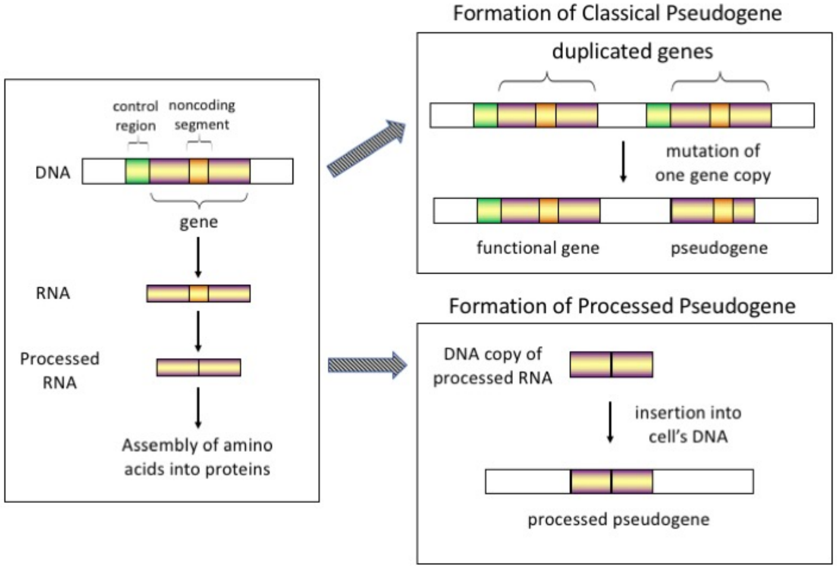


Figure from the Assis Lab at Florida Atlantic University

Pseudogenes


control region
noncoding segment
DNA
gene
RNA
Processed RNA
Assembly of amino acids into proteins
Formation of Classical Pseudogene
duplicated genes
mutation of one gene copy
functional gene
pseudogene
Formation of Processed Pseudogene
DNA copy of processed RNA
insertion into cell's DNA
processed pseudogene

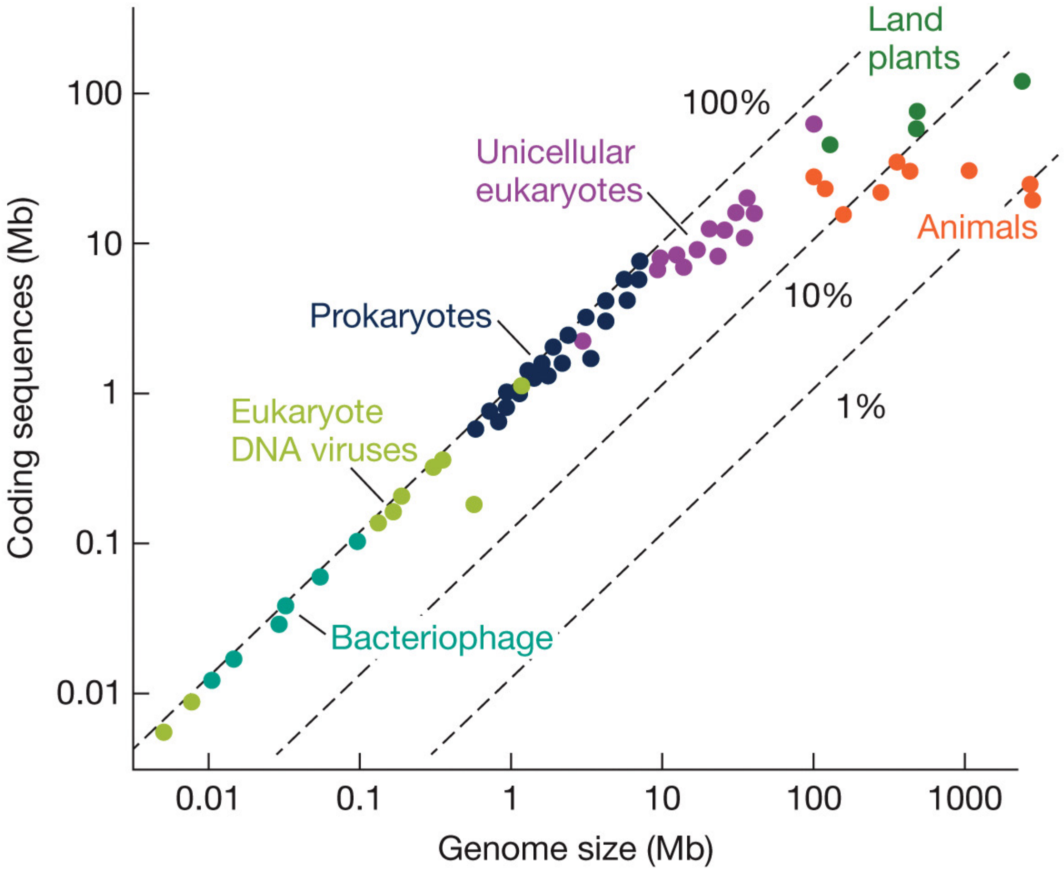
- **Pseudogenes** are nonfunctional versions of normal genes
  - Causes include mutations of premature stop codons

- Classical pseudogenes contain introns

- Processed pseudogenes do not contain introns (they are due to reverse transcription of mRNA into chromosomal DNA)

Image from Wikipedia

The coding fraction of genomes varies by taxa



EVOLUTION 4e, Figure 14.18
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- What might explain this pattern?