Neutrality and some of its deviations

Ryan Hernandez

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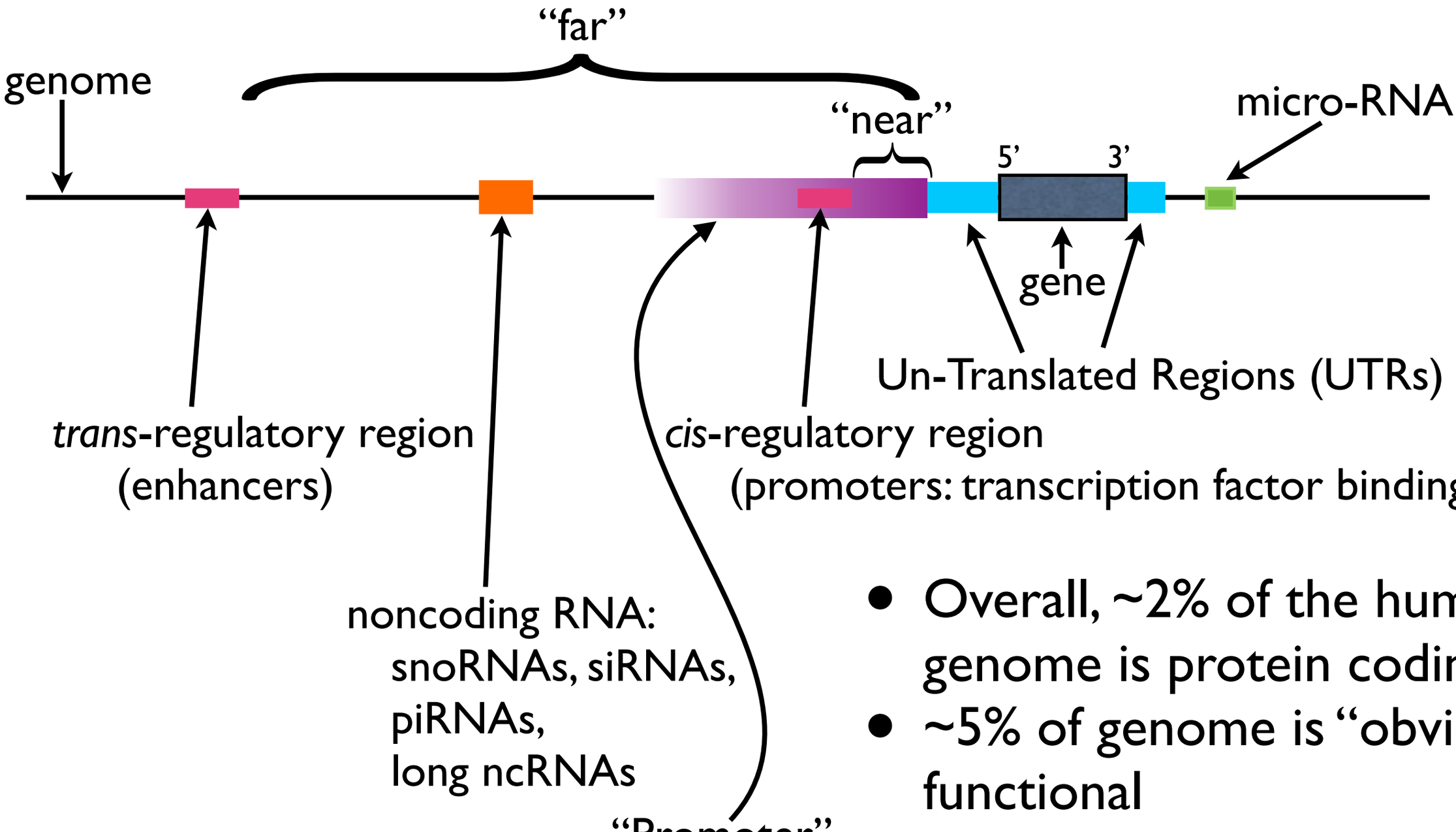
Goals

- Learn about the population genetics view of the life cycle
- A few Pop Gen summary statistics
- Revisit Hardy-Weinberg Equilibrium - Assumptions & violations

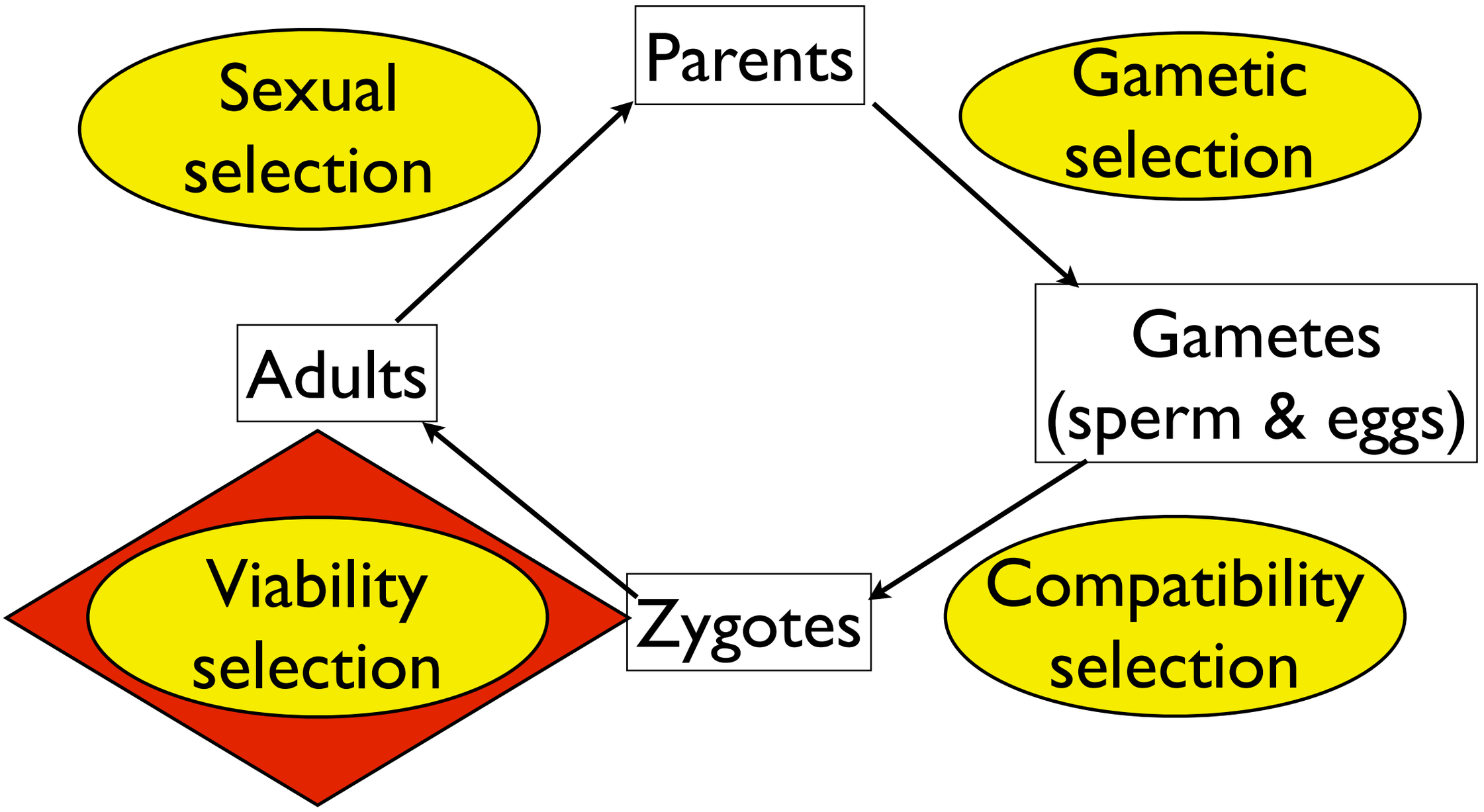
Basic Biology of Human Genome

Functional non-coding mutations



- Overall, ~2% of the human genome is protein coding
- ~5% of genome is "obviously" functional
- ~80% of genome has "functional activity"

Life Cycle

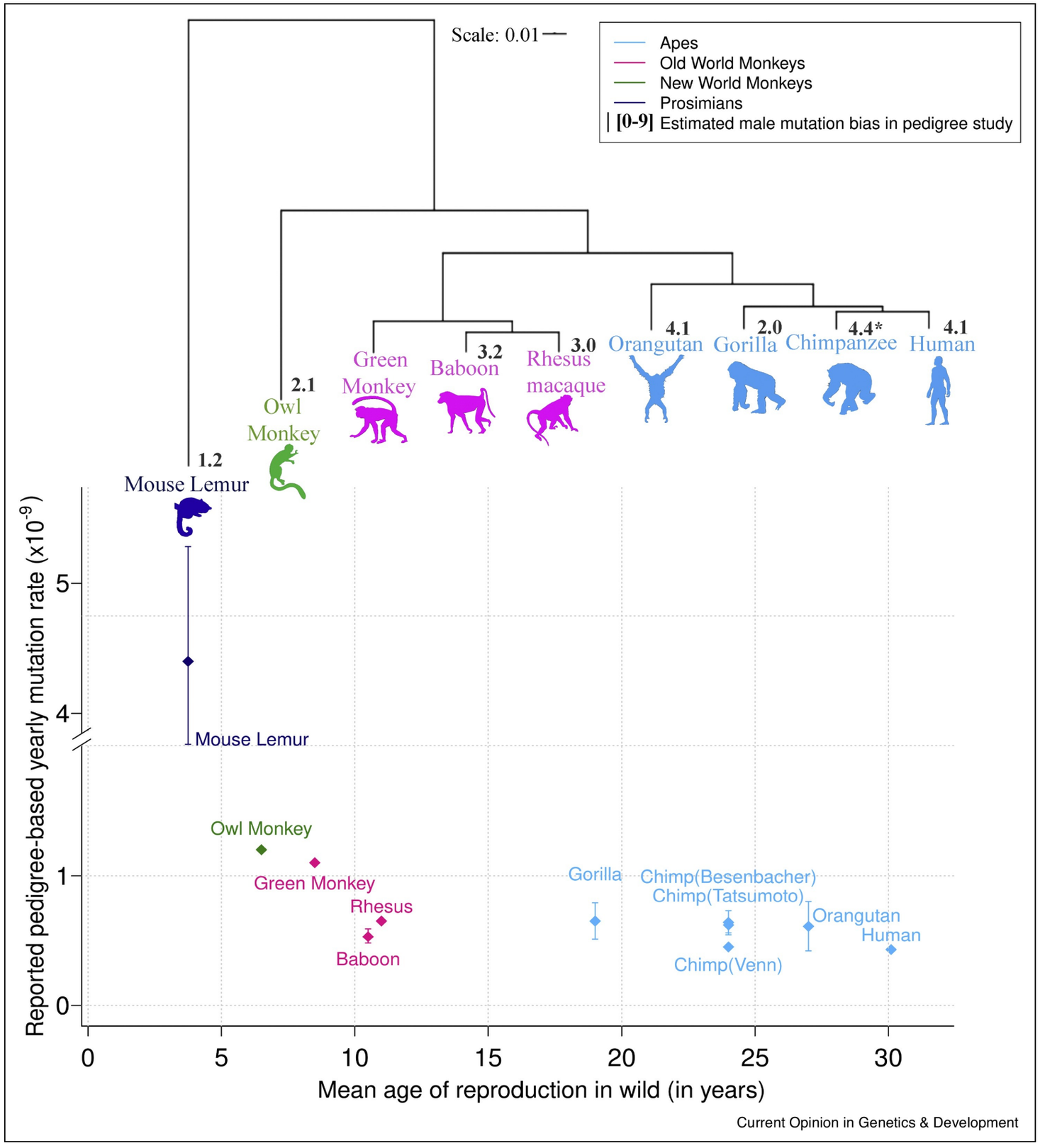

Parents
Sexual selection
Gametic selection
Gametes (sperm & eggs)
Compatibility selection
Zygotes
Viability selection
Adults

Modern Human Genomics:
A case for rare variants?

$$1.1\times10^{-8} \times 6\times10^{9} = 66 \text{ [muts / person]}$$

$$\frac{\begin{array}{r} 66 \text{ [muts/p]} \\ \times\ 130\text{M [p/y]} \\ \div\ \ \ 3\text{B [bp]} \end{array}}{2.86 \text{ muts/bp/yr}}$$

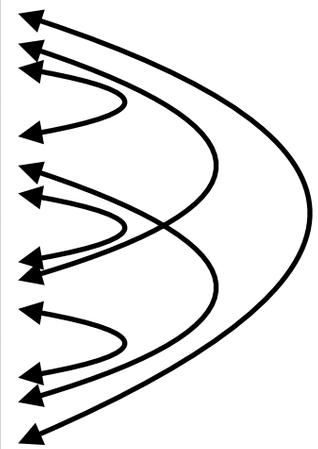
Mutation Rate Evolution in Primates



Chintalapati & Moorjani (Curr Op G&D, 2020)

Sequencing Data

Chromosome	SNP 1	SNP 2	SNP 3	SNP 4	SNP 5	SNP 6
1	A	C	A	G	C	C
2	A	T	G	A	C	T
3	G	T	G	A	T	T
4	A	C	G	A	C	T



# Pairwise differences	3	4	3	3	3	3

π = average pairwise diversity

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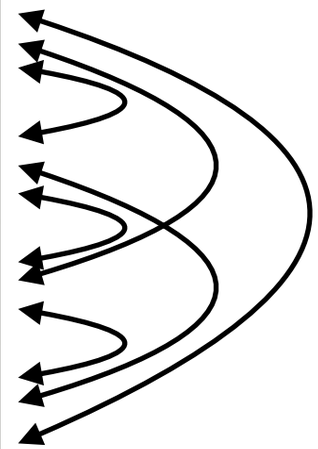

# Pairwise differences	3	4	3	3	3	3
# Compared	6	6	6	6	6	6

π = average pairwise diversity

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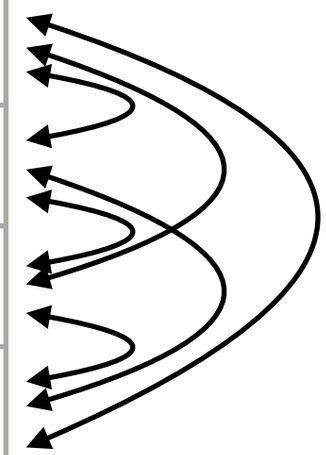
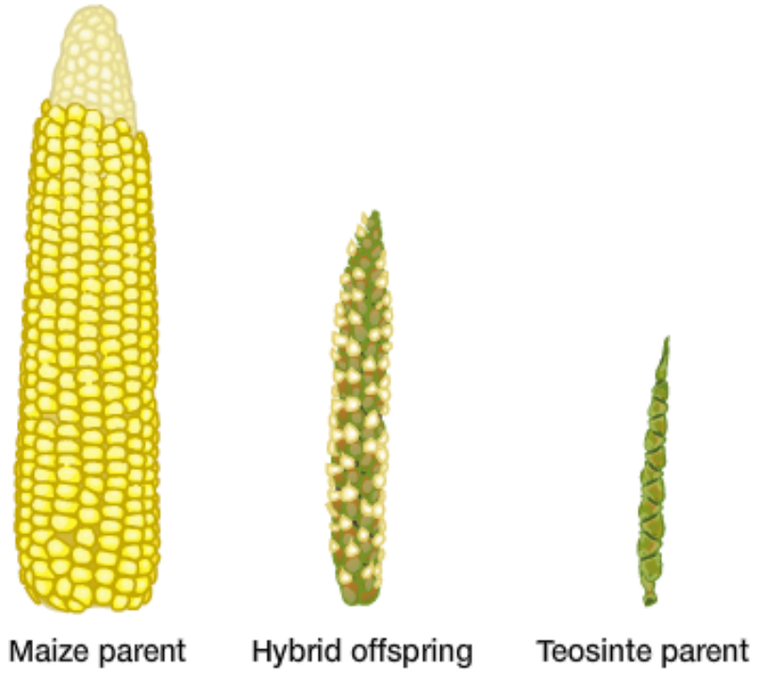
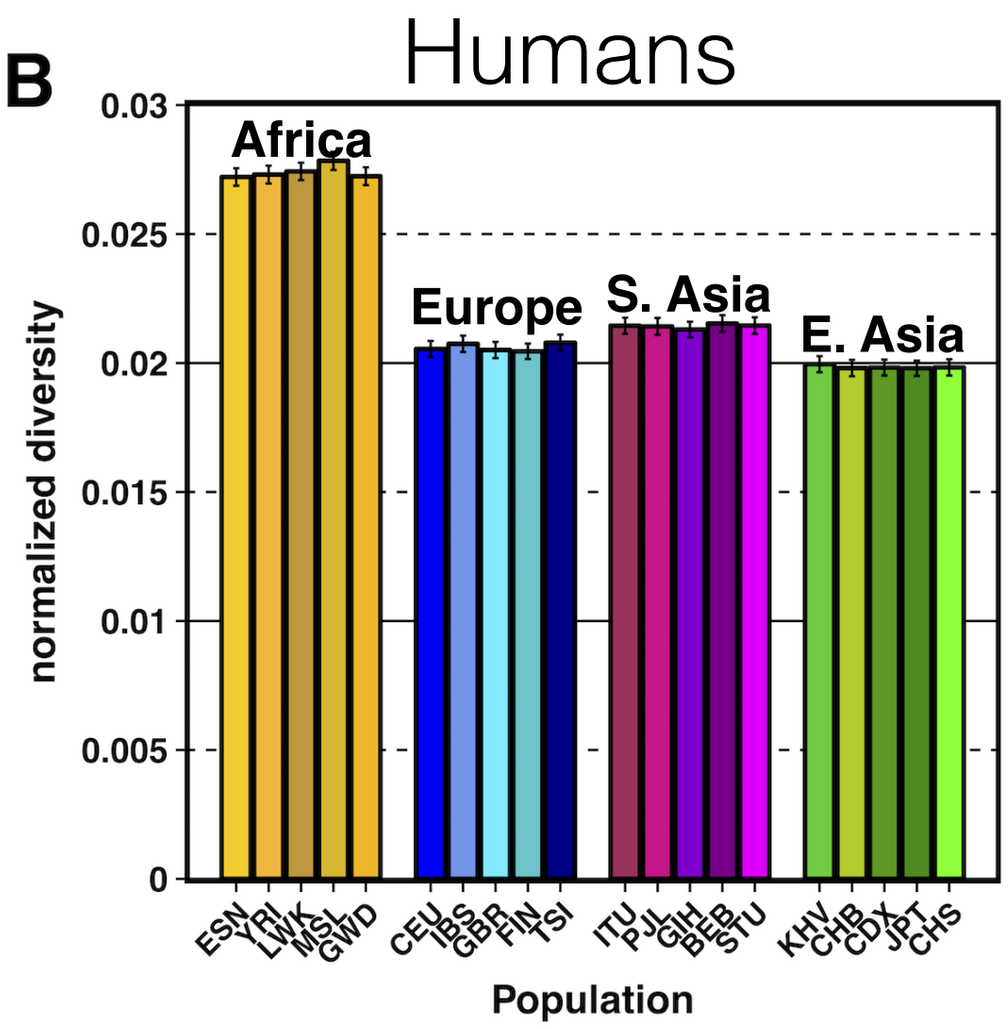


# Pairwise differences	3	4	3	3	3	3
# Compared	6	6	6	6	6	6
Avg. Pairwise Diff	0.5	0.67	0.5	0.5	0.5	0.5

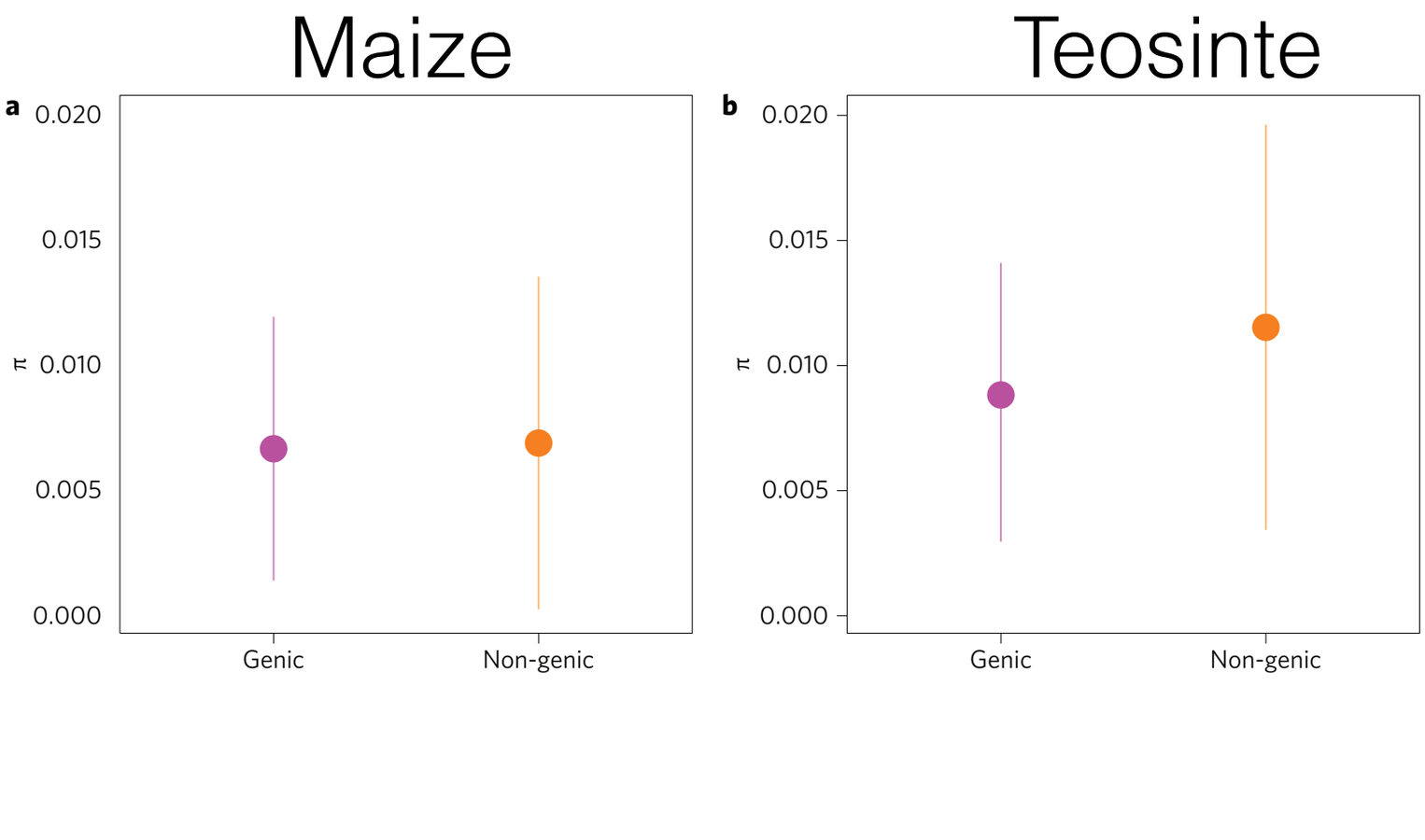
Number of variants: 6 SNPs
Diversity (π): 3.1667/L

Diversity Across Populations





Torres, et al. (2018)



Beissinger, et al. (2016)

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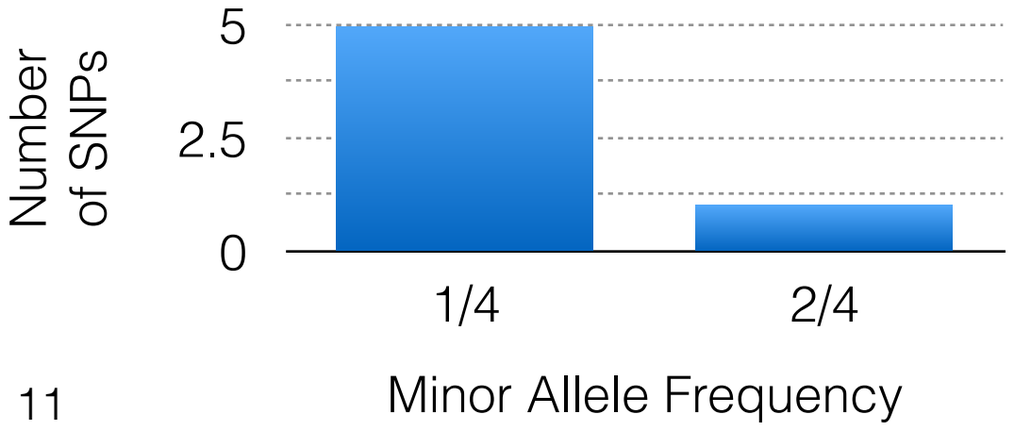
3	G	T	G	A	T	T
4	A	C	G	A	C	T
Minor Allele	G	T	A	G	T	C
MAF	0.25	0.5	0.25	0.25	0.25	0.25

MAF	5	1



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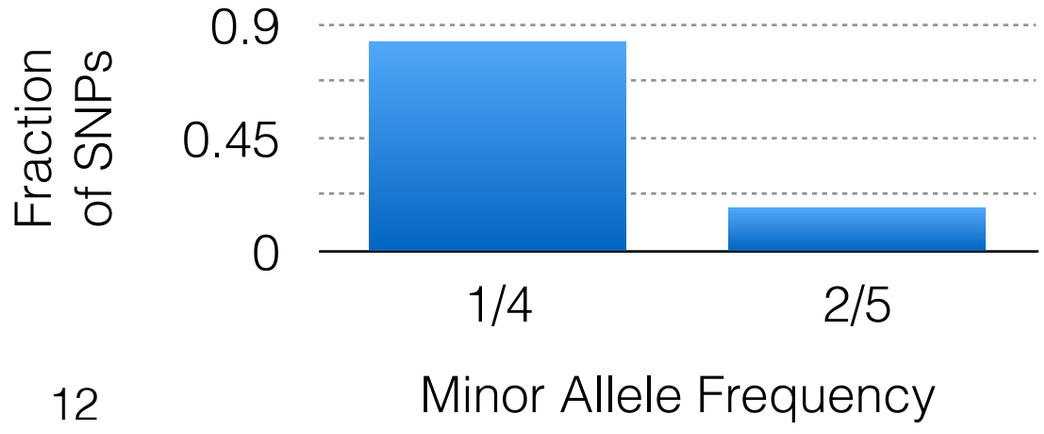

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Chimp	A	C	A	G	C	T

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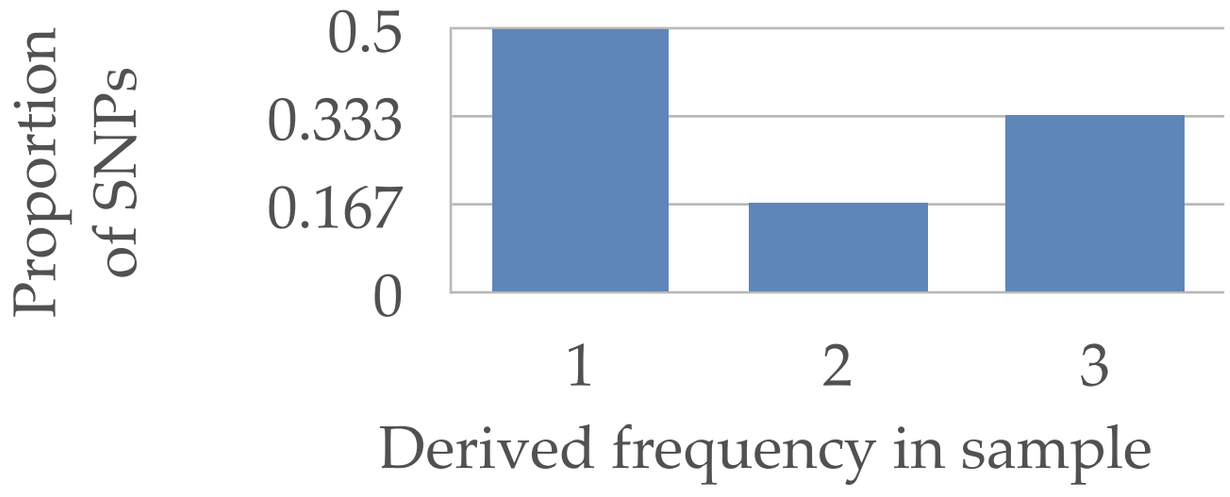
3	G	T	G	A	T	T
4	A	C	G	A	C	T

Chimp	A	C	A	G	C	T
Derived count	1	2	3	3	1	1



Site-Frequency Spectrum (SFS)

Site-Frequency Spectrum

	*		*	*		*	*			*	*	*	*		*	*	*	*			*	*	*
1	C	A	T	T	C	G	A	A	G	C	G	A	T	C	A	G	G	C	T	A	T	A	
2	C	A	T	T	T	G	A	G	A	C	G	A	T	C	A	G	G	C	T	A	T	A	
3	C	G	T	T	T	G	A	G	A	C	G	A	T	T	A	G	G	C	C	A	T	A	
4	C	A	T	T	C	G	A	G	A	C	G	A	T	C	A	G	G	C	T	A	T	A	
outgroup	T	A	C	C	C	A	G	G	A	G	A	T	A	C	G	C	A	T	T	T	A	T	

= non-coding

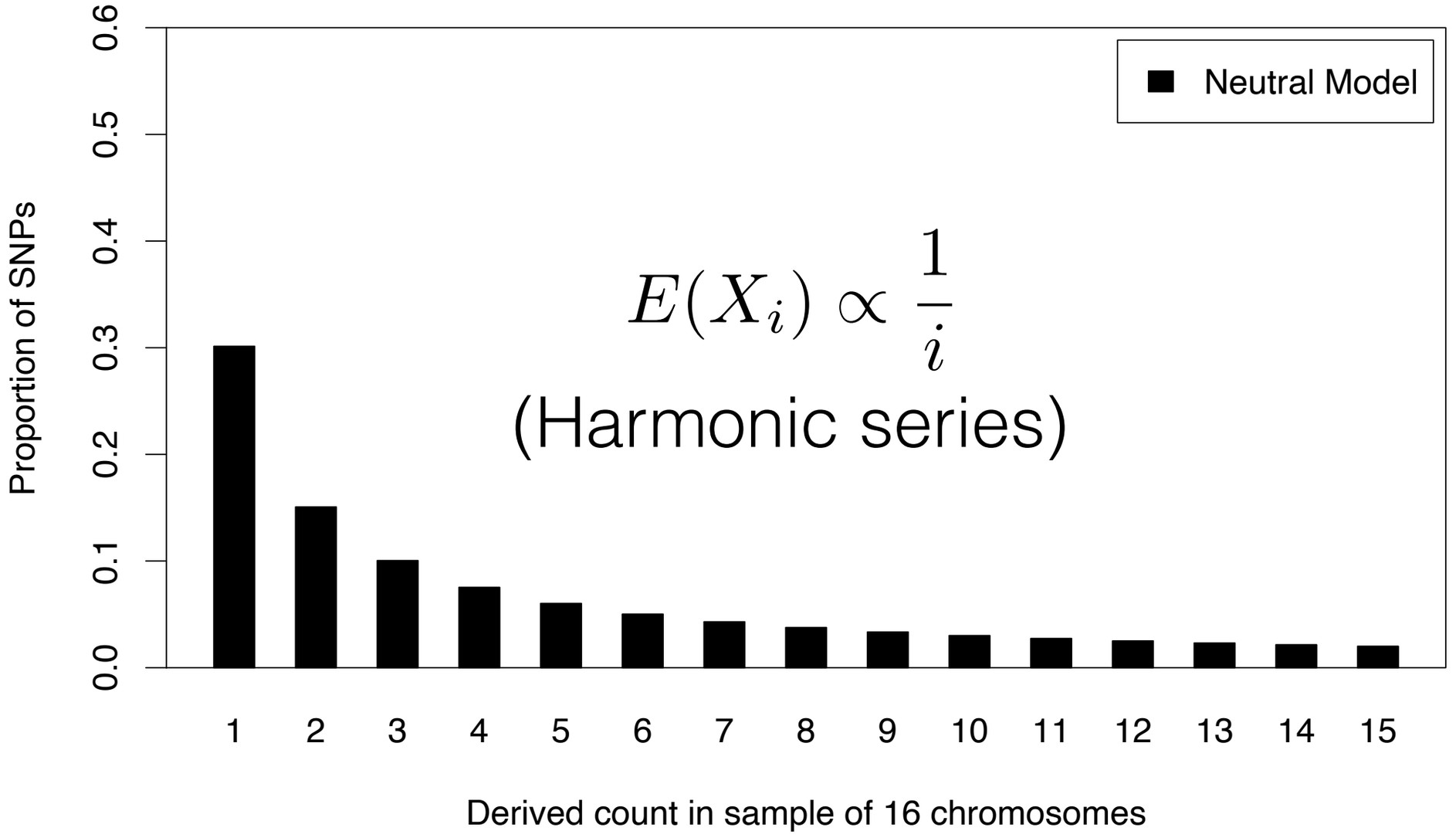
= synonymous

= nonsynonymous

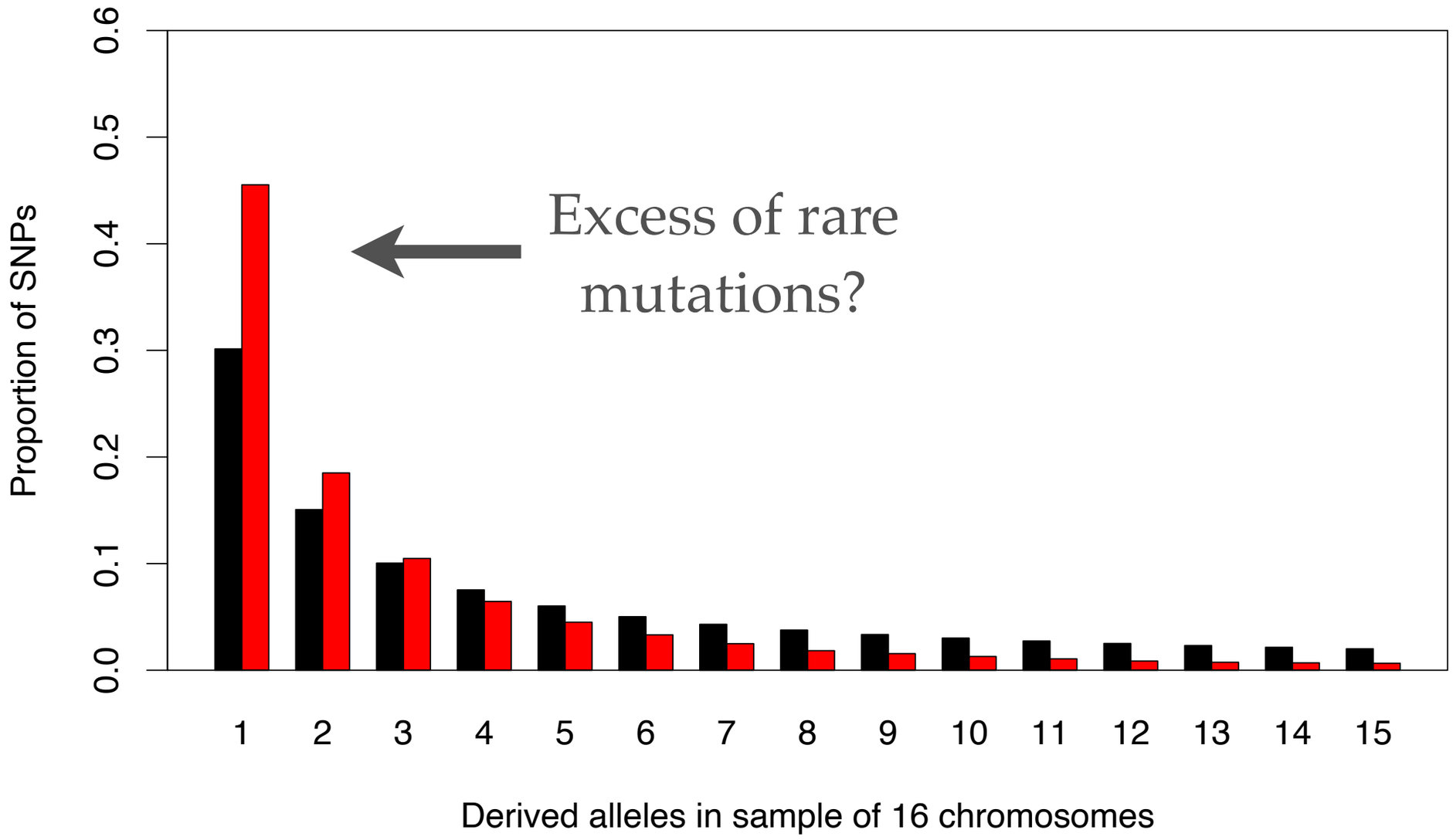
* - Substitution between species

Site-Frequency Spectrum

The proportion of derived mutations at each frequency in a sample of chromosomes



Site-Frequency Spectrum



What evolutionary forces could cause an excess of rare variants?

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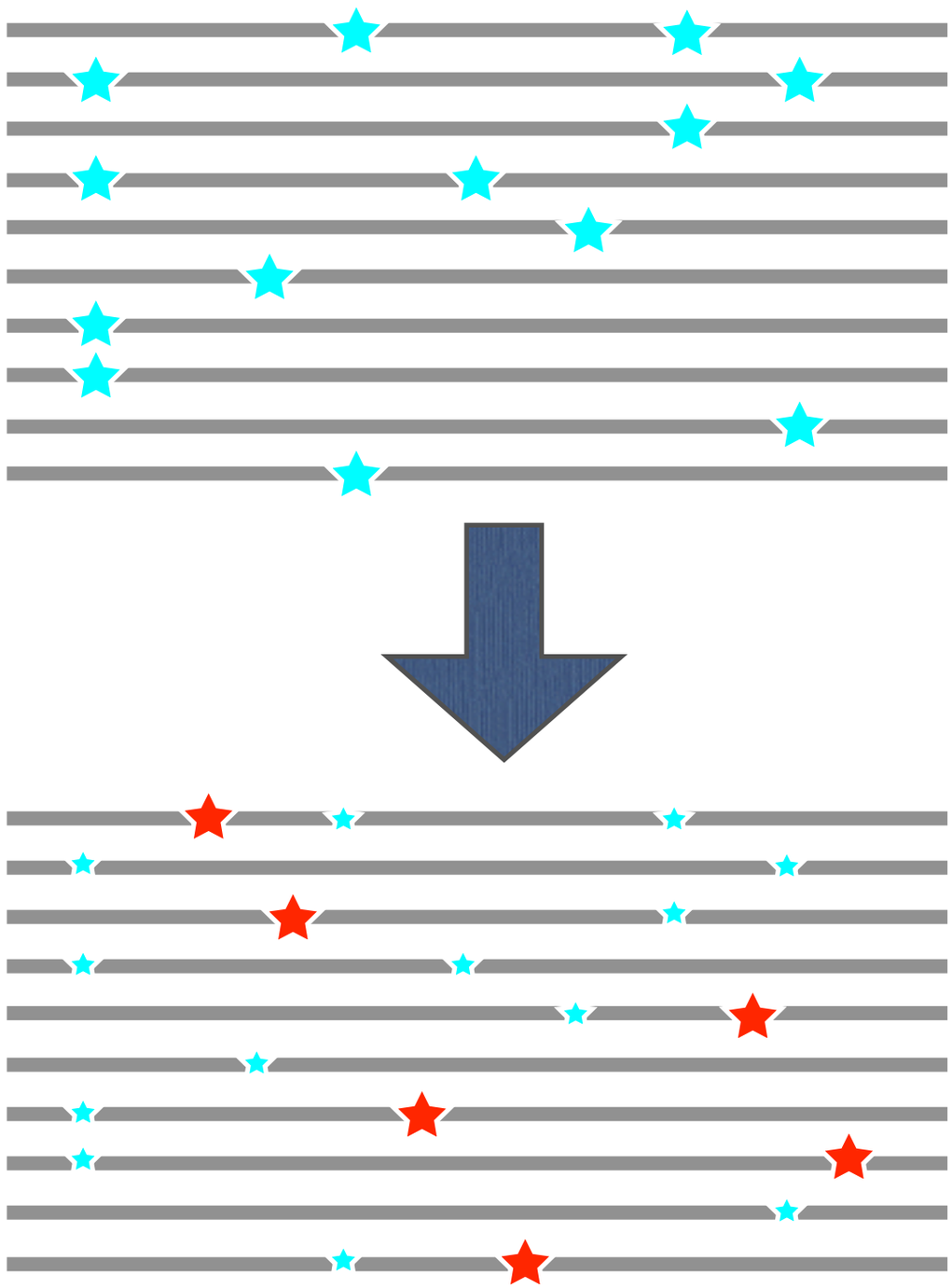
The Effect of Negative Selection

Chromosomes in a population

The Effect of Negative Selection

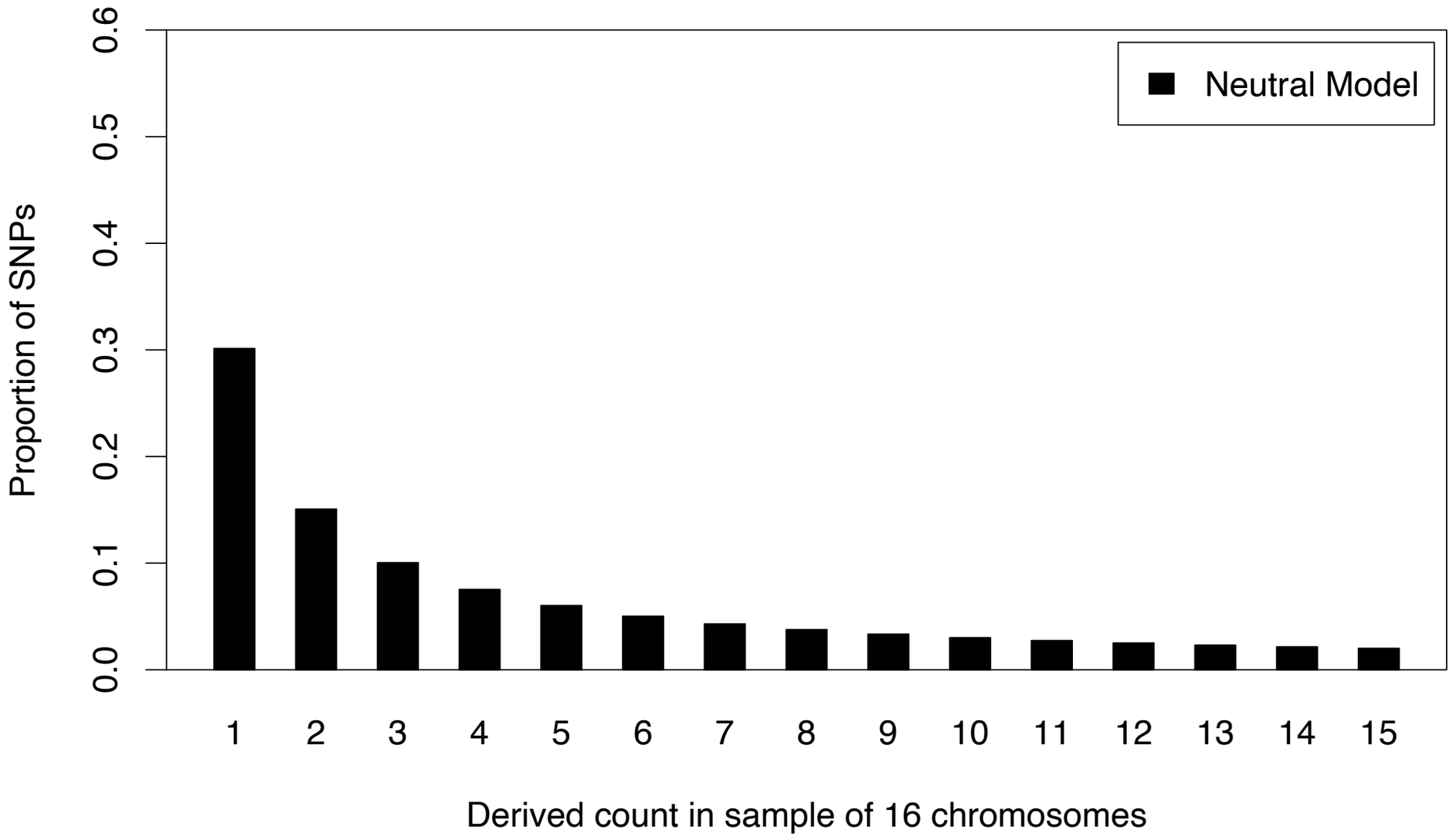
Chromosomes in a population with standing variation



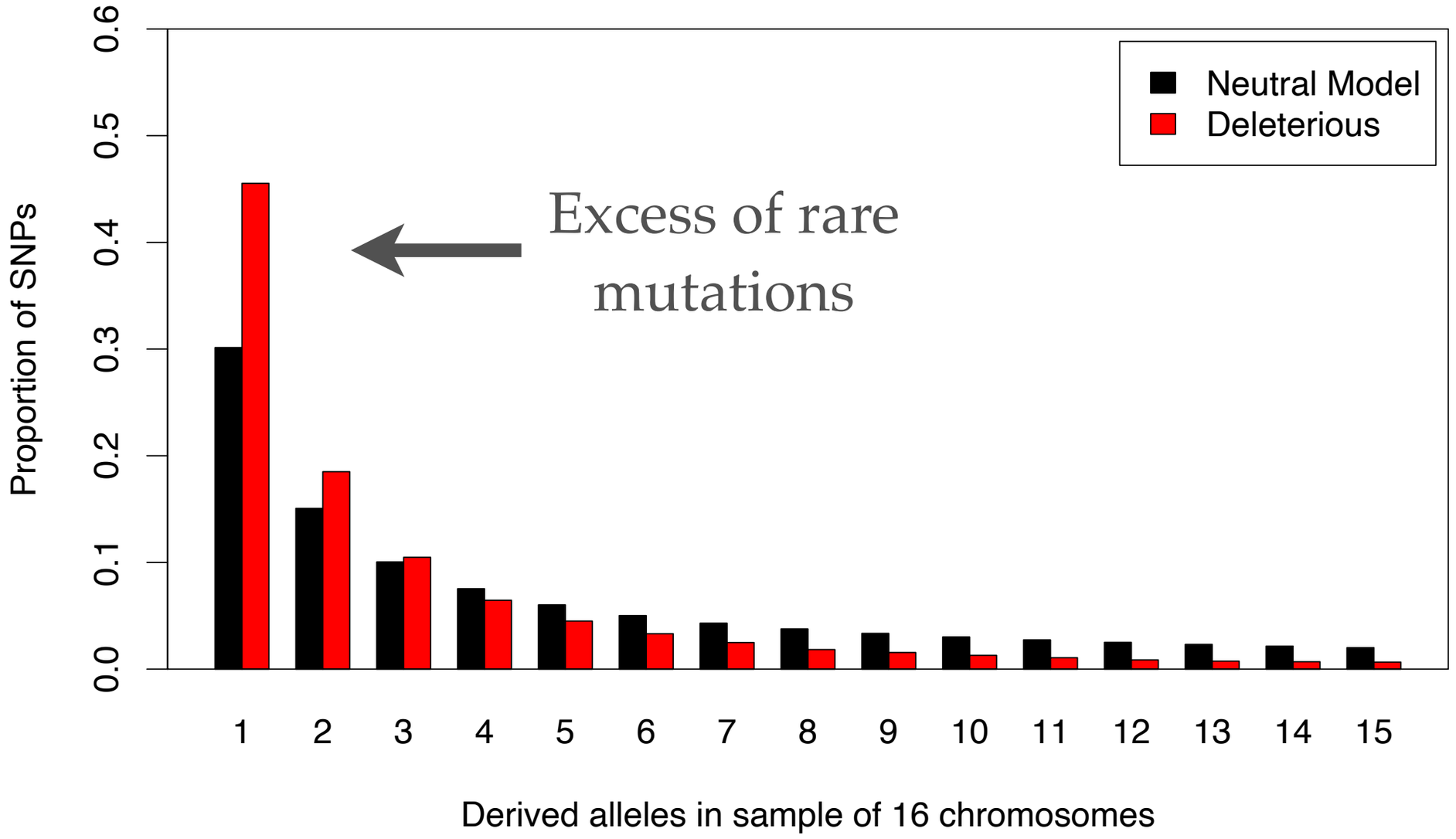
Deleterious mutations will arise in the next generation

Negative selection: the action of natural selection purging deleterious mutations.

Site-Frequency Spectrum

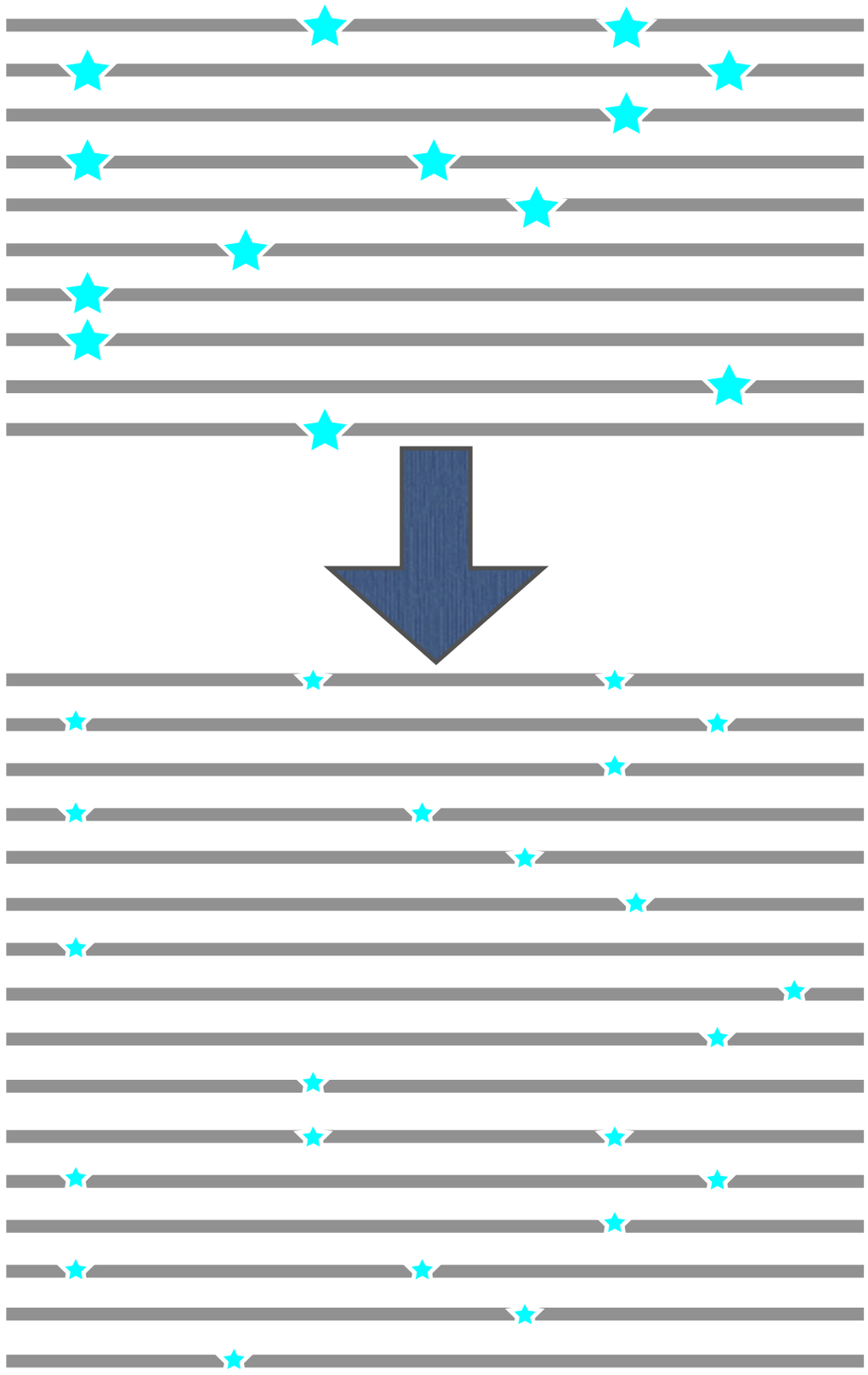


Site-Frequency Spectrum



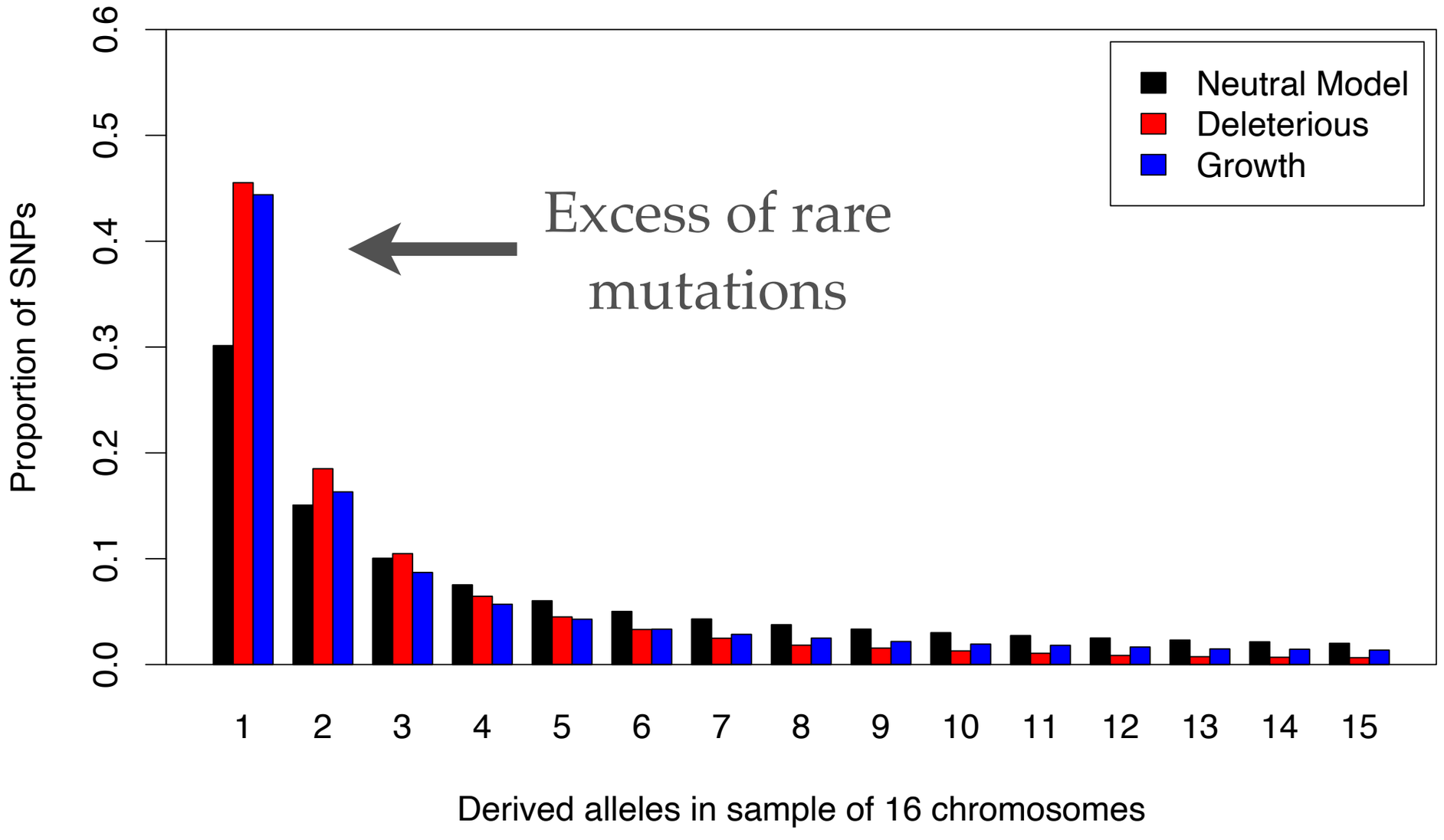
The Effect of Population Growth

Chromosomes in a population with standing variation



Population Growth: introduction of new (rare) variants.

Site-Frequency Spectrum



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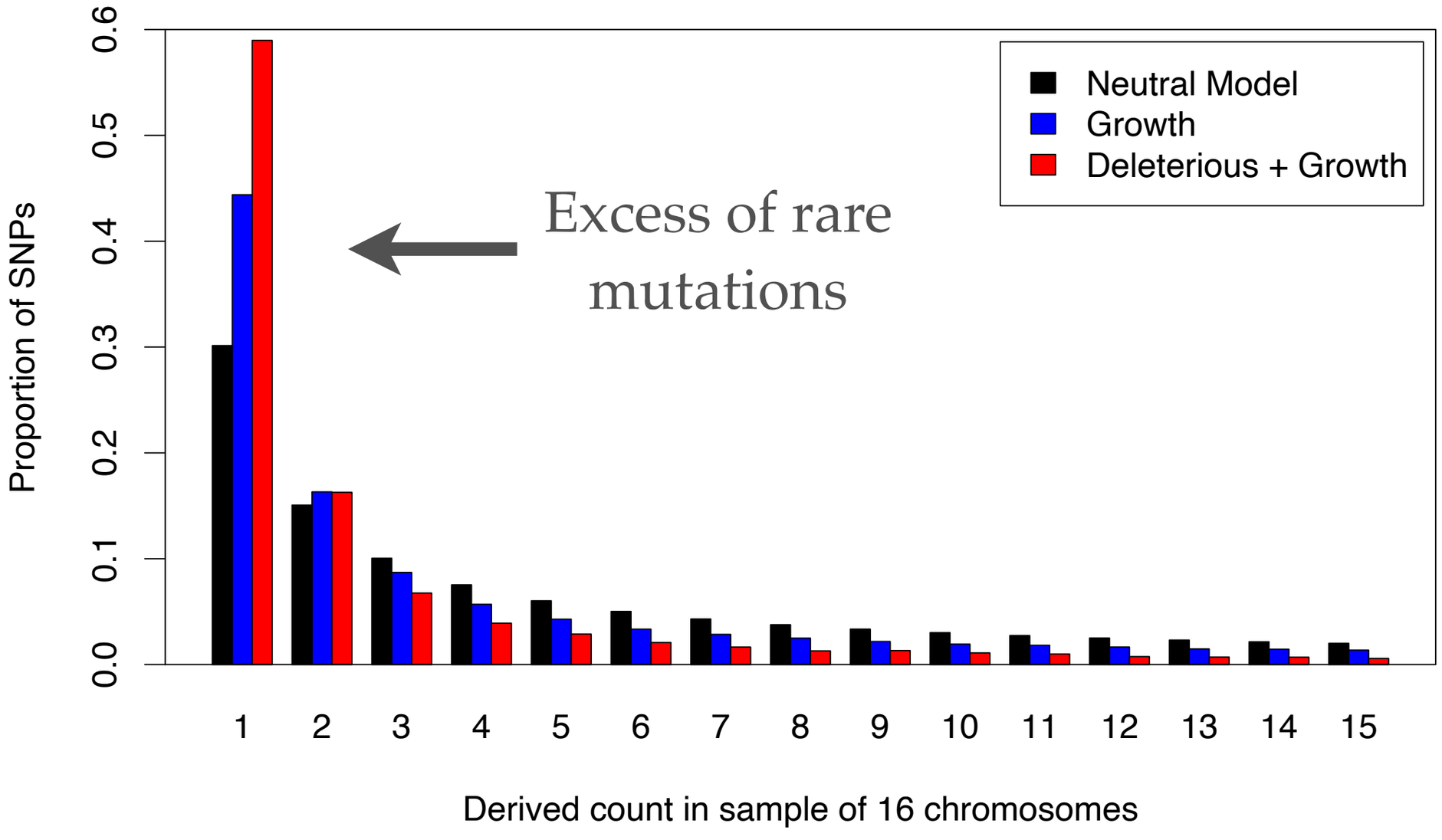
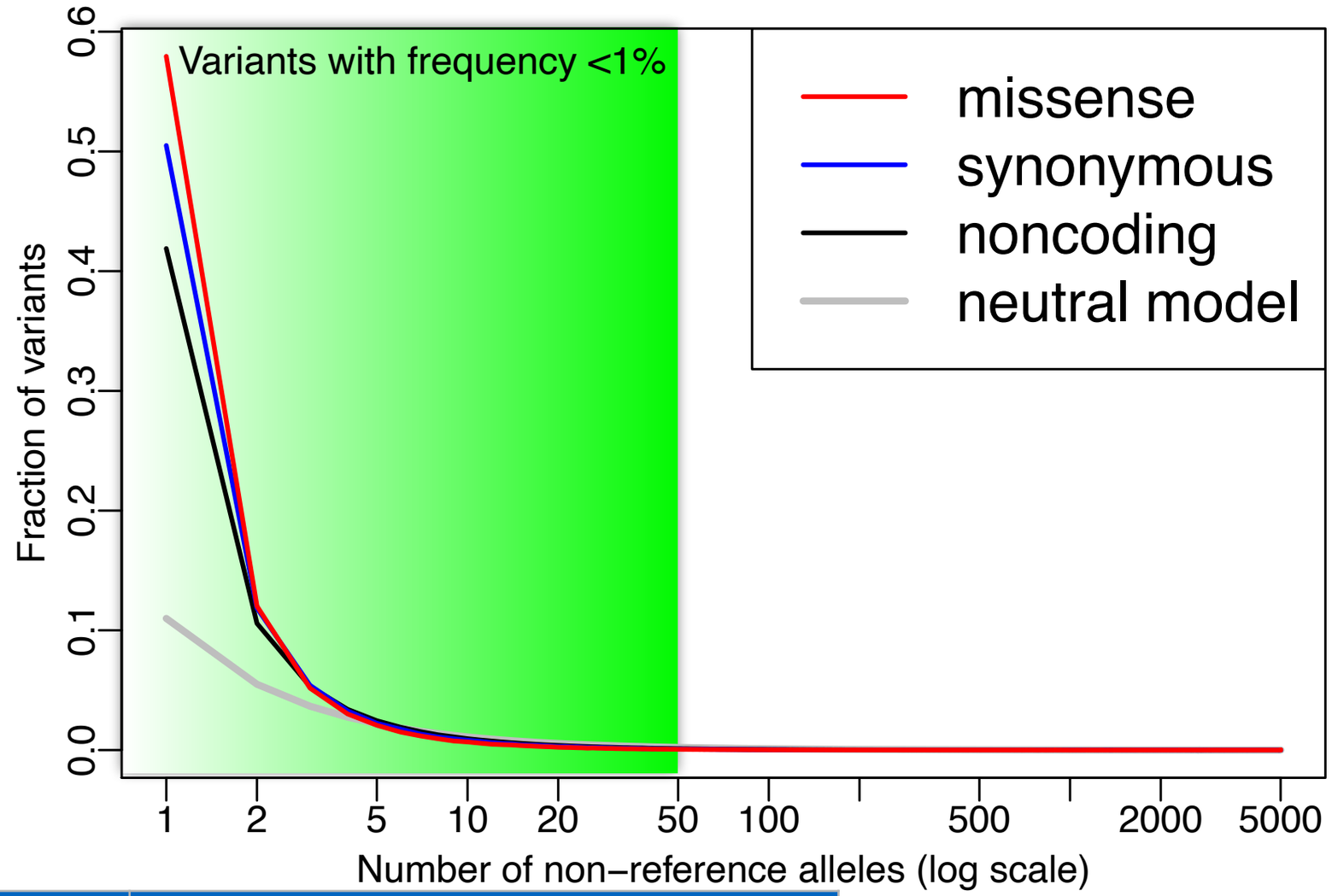
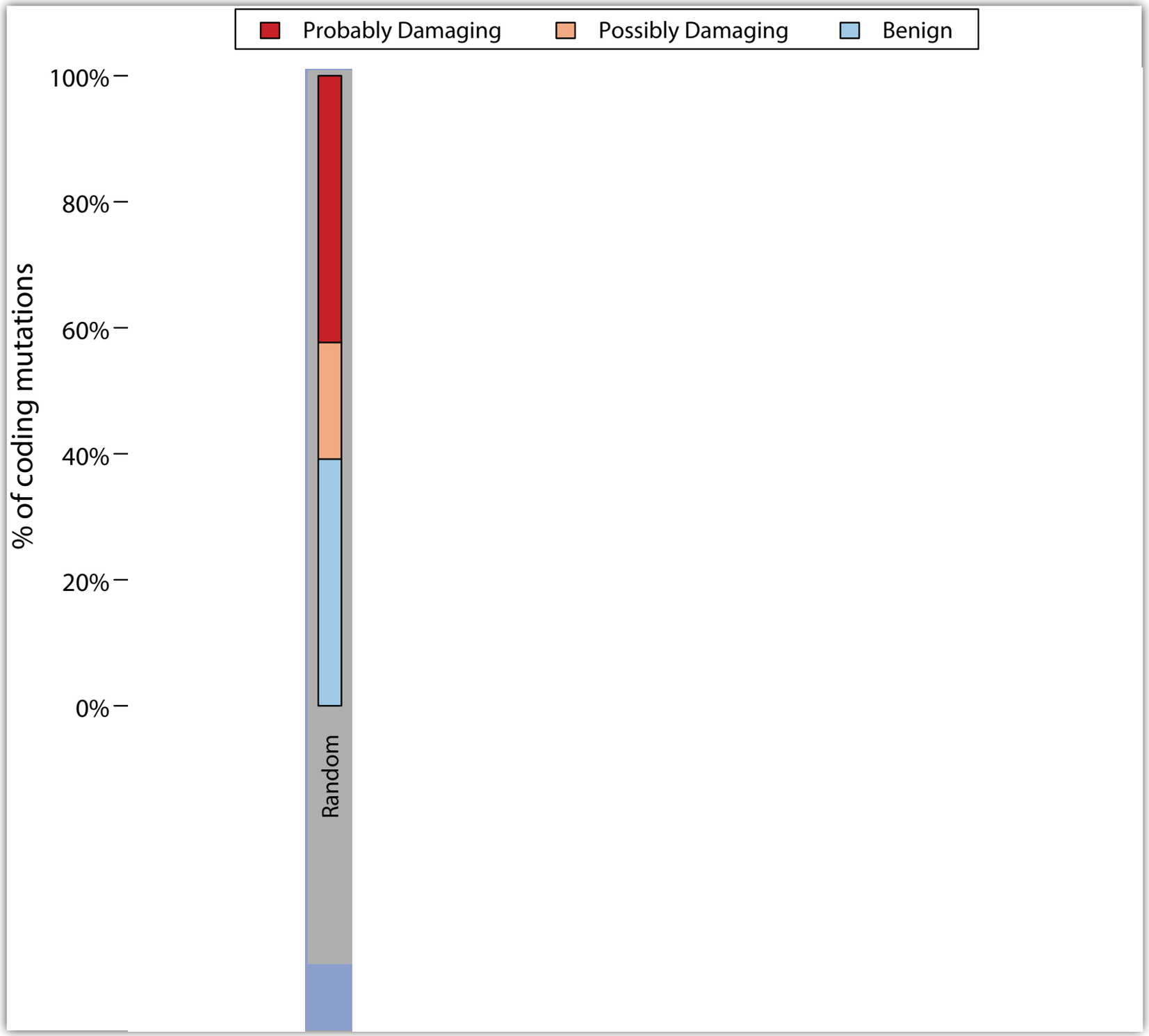


Majority of human genetic variation is rare



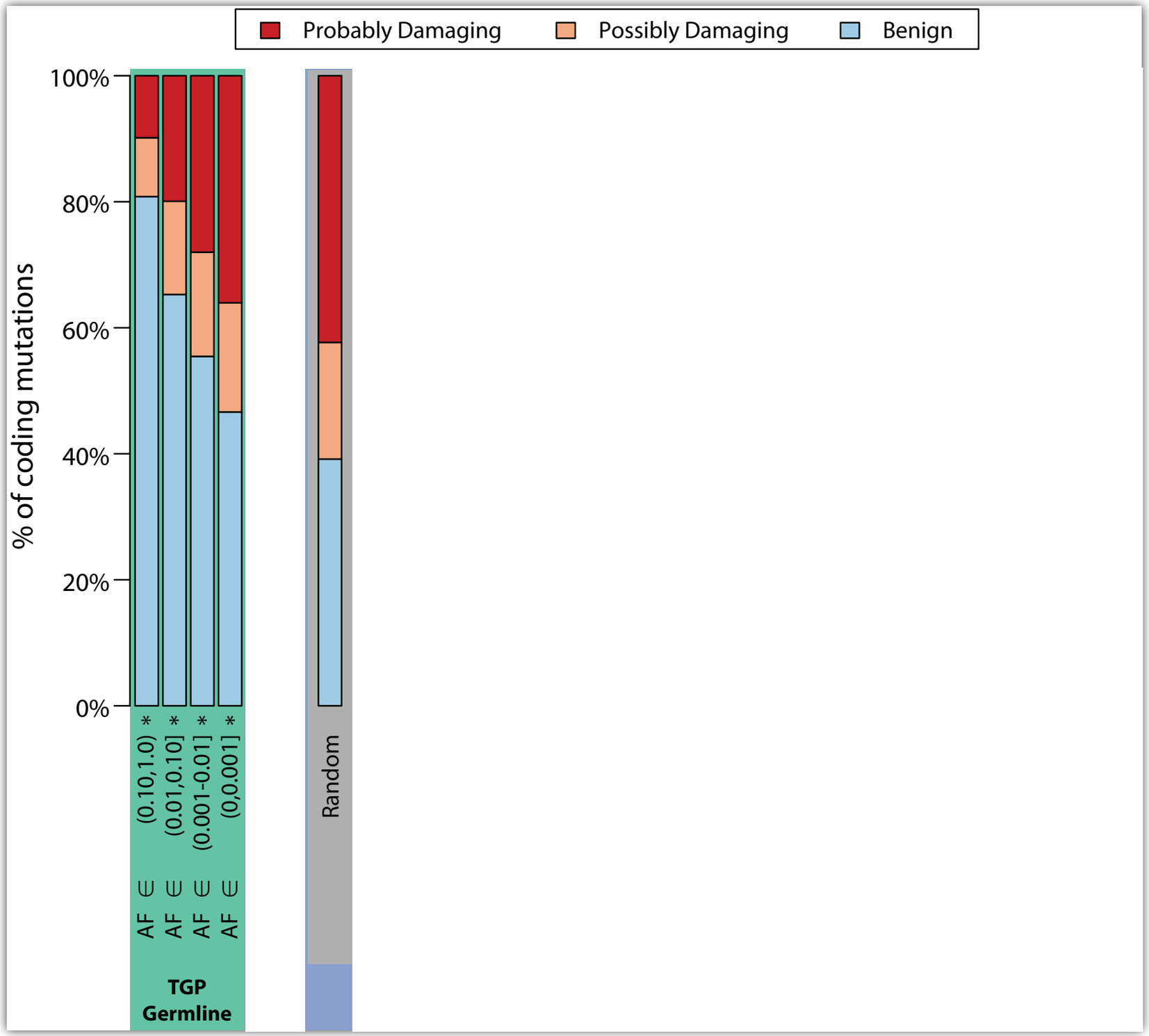
Class	Fraction of variants < 1%
Missense	92.6%
Synonymous	88.5%
Non-coding	82.3%

Observed Effect of Selection



PolyPhen2

Observed Effect of Selection



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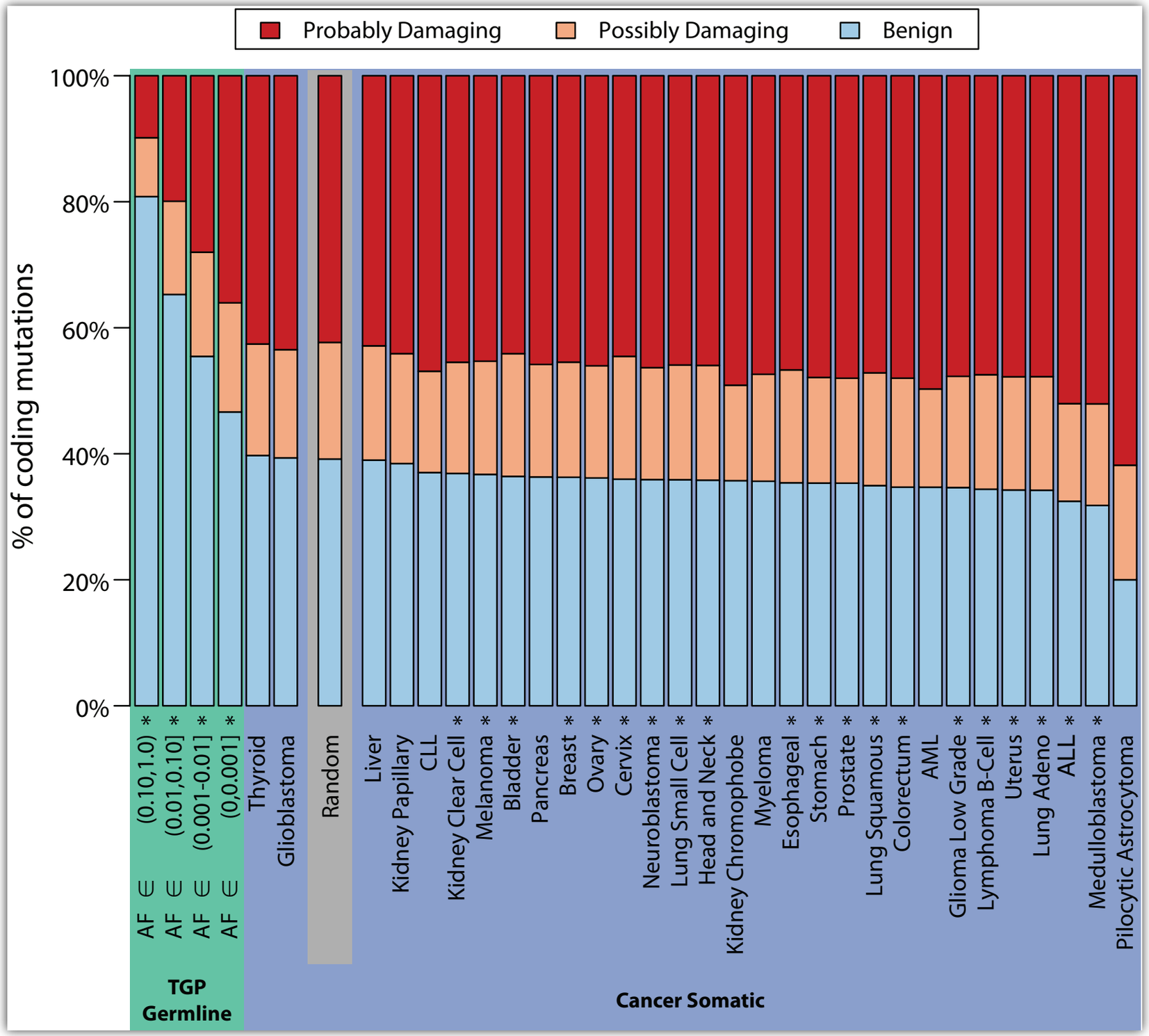
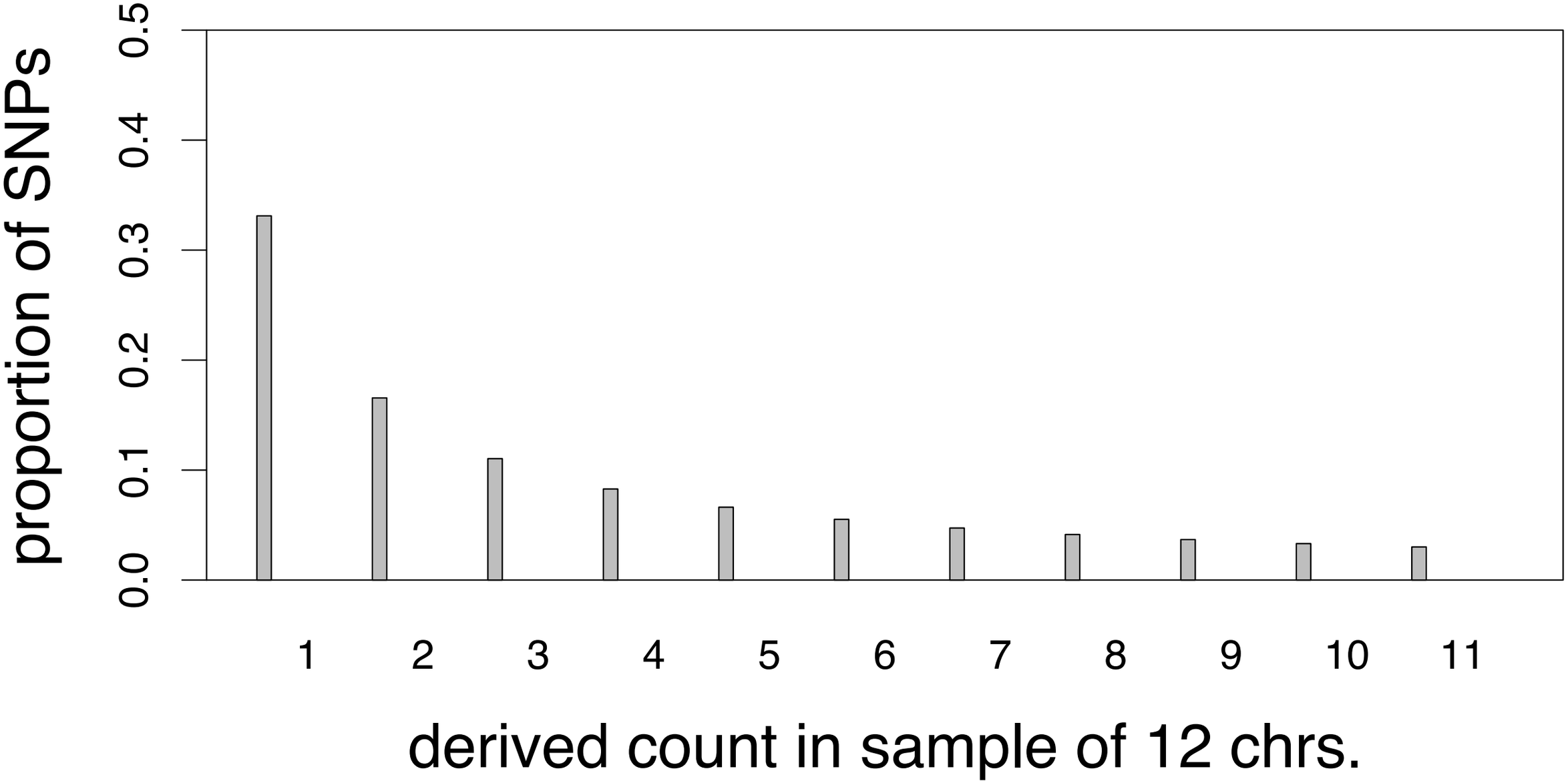


PolyPhen2

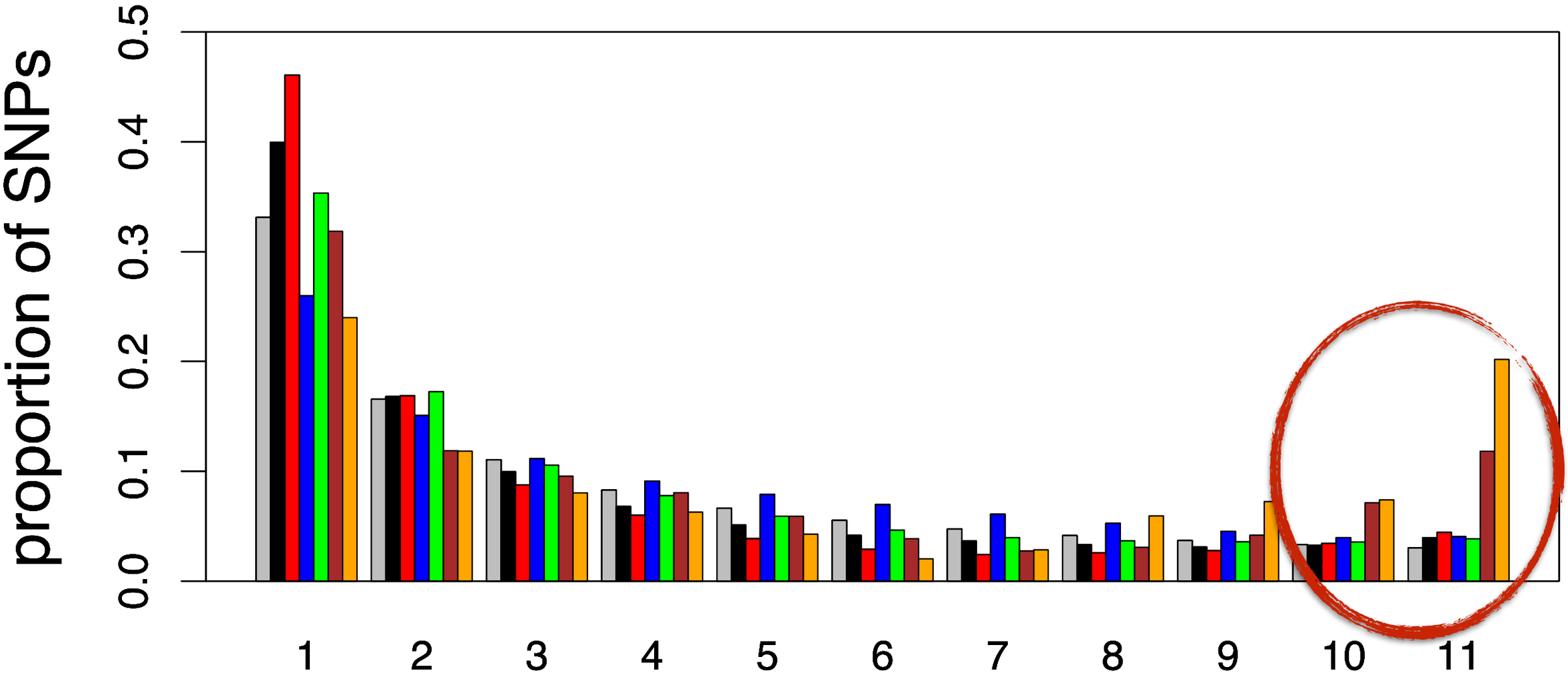
Site-Frequency Spectrum

- The proportion of SNPs at each frequency in a sample of chromosomes.



Site-Frequency Spectrum

- SNM
- AfAm (Human)
- Ch (RheMac)
- In (RheMac)
- Rufi (rice)
- Indica (rice)
- Japonica (rice)



What evolutionary forces could cause an excess of high frequency derived variants?

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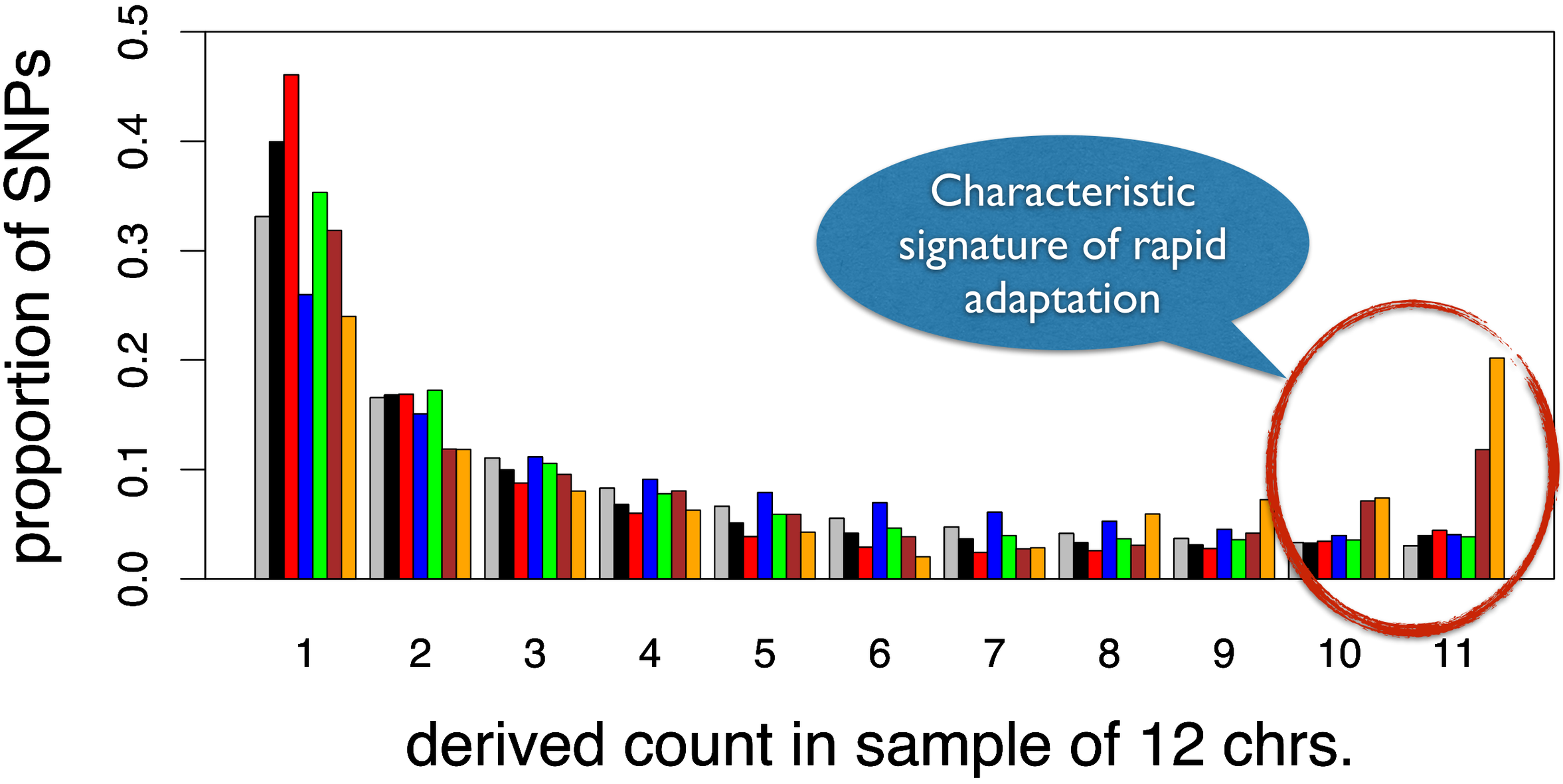
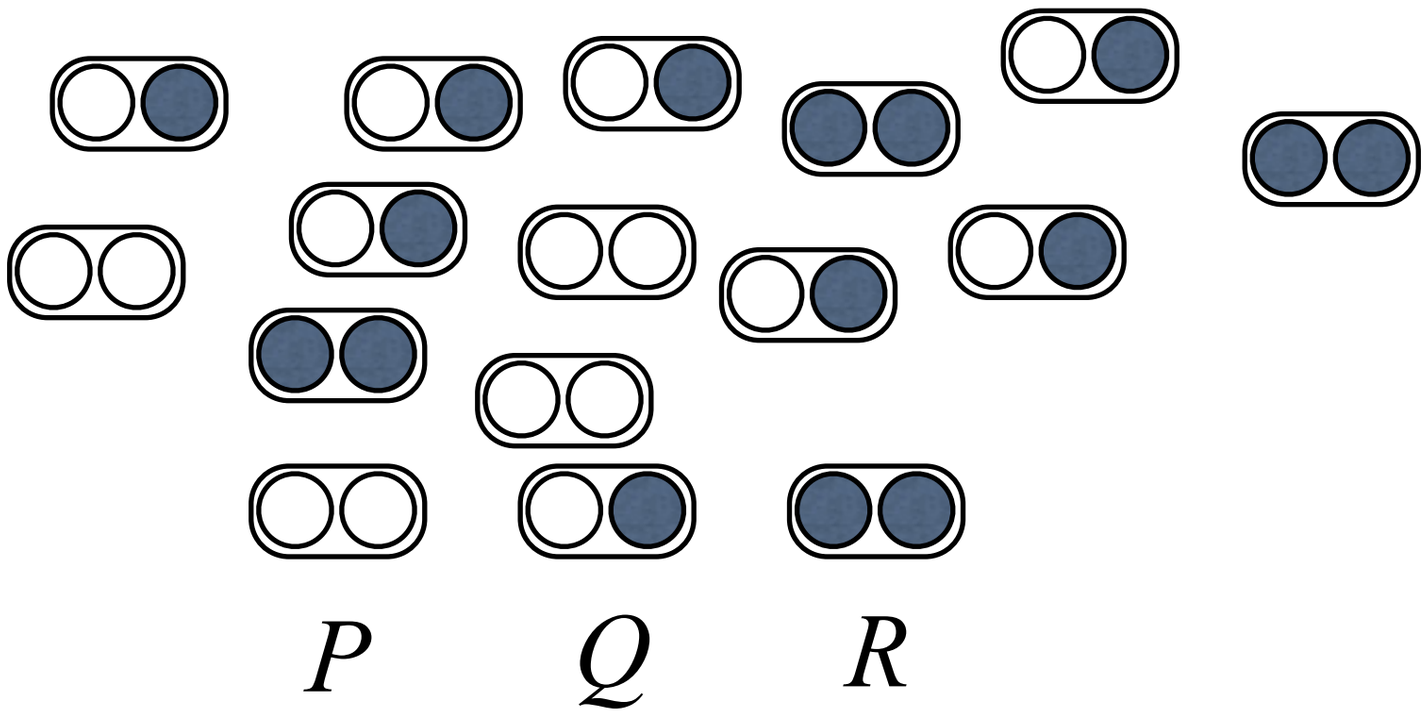


Population Genetics

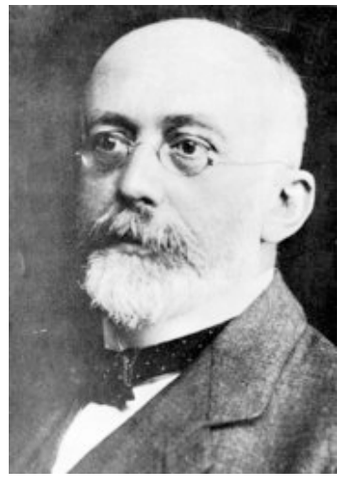
- Imagine a population of diploid individuals



- Principles of **random mating**:
  - Any two individuals are equally likely to mate and reproduce to populate the next generation.
  - Either chromosome is equally likely to be passed on.

Hardy-Weinberg Principle

Godfrey H. Hardy:
1877-1947



Wilhelm Weinberg:
1862-1937

What are the assumptions of the Hardy-Weinberg Principle?

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Hardy-Weinberg Principle

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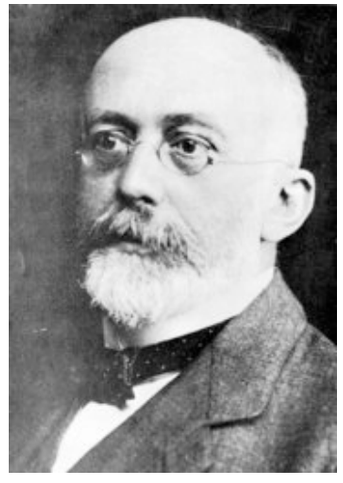


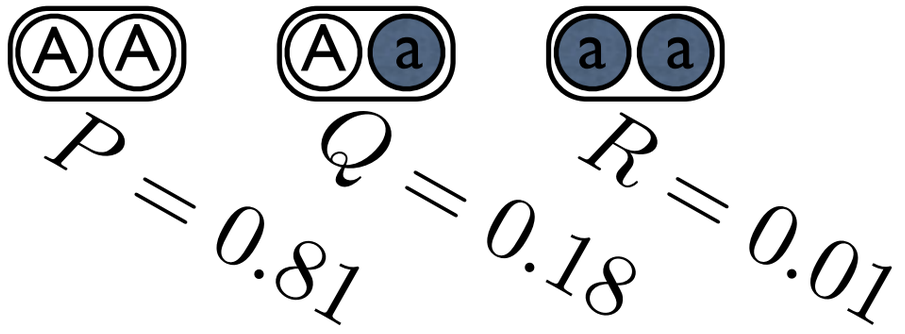
Wilhelm Weinberg:
1862-1937

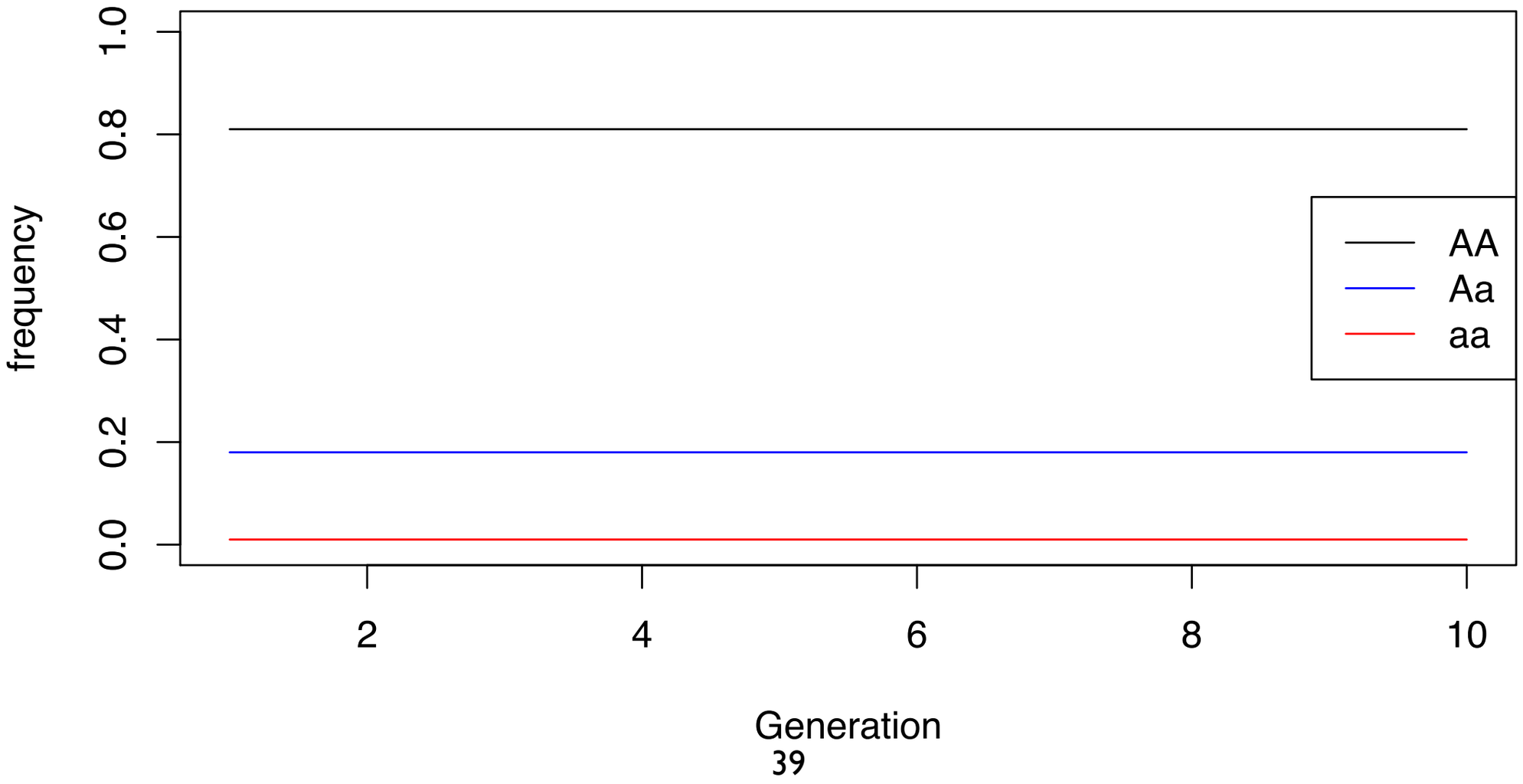
- **Assumptions:**
  - Diploid organism
  - Sexual reproduction
  - Non-overlapping generations
  - Only two alleles
  - Random mating
  - Identical frequencies in males/females
  - Infinite population size
  - No migration
  - No mutation
  - No natural selection
- **Conclusion 1:**
  Both allele AND genotype frequencies will remain constant at **HWE** generation after generation... forever!

$$P=p^2$$
$$Q=2p(1-p)$$
$$R=(1-p)^2$$

Hardy-Weinberg Principle

- Imagine a population of diploid individuals





Hardy-Weinberg Principle

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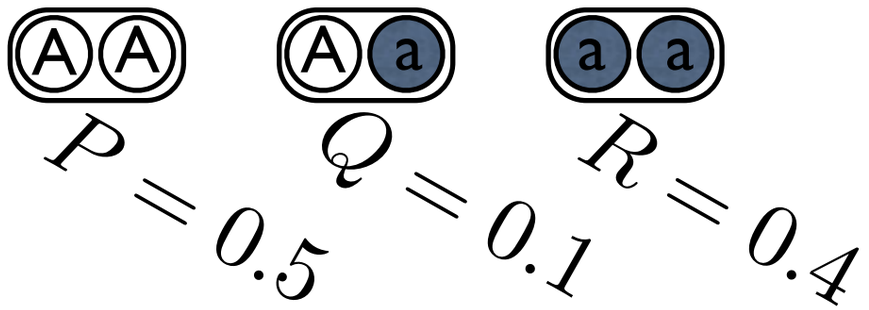
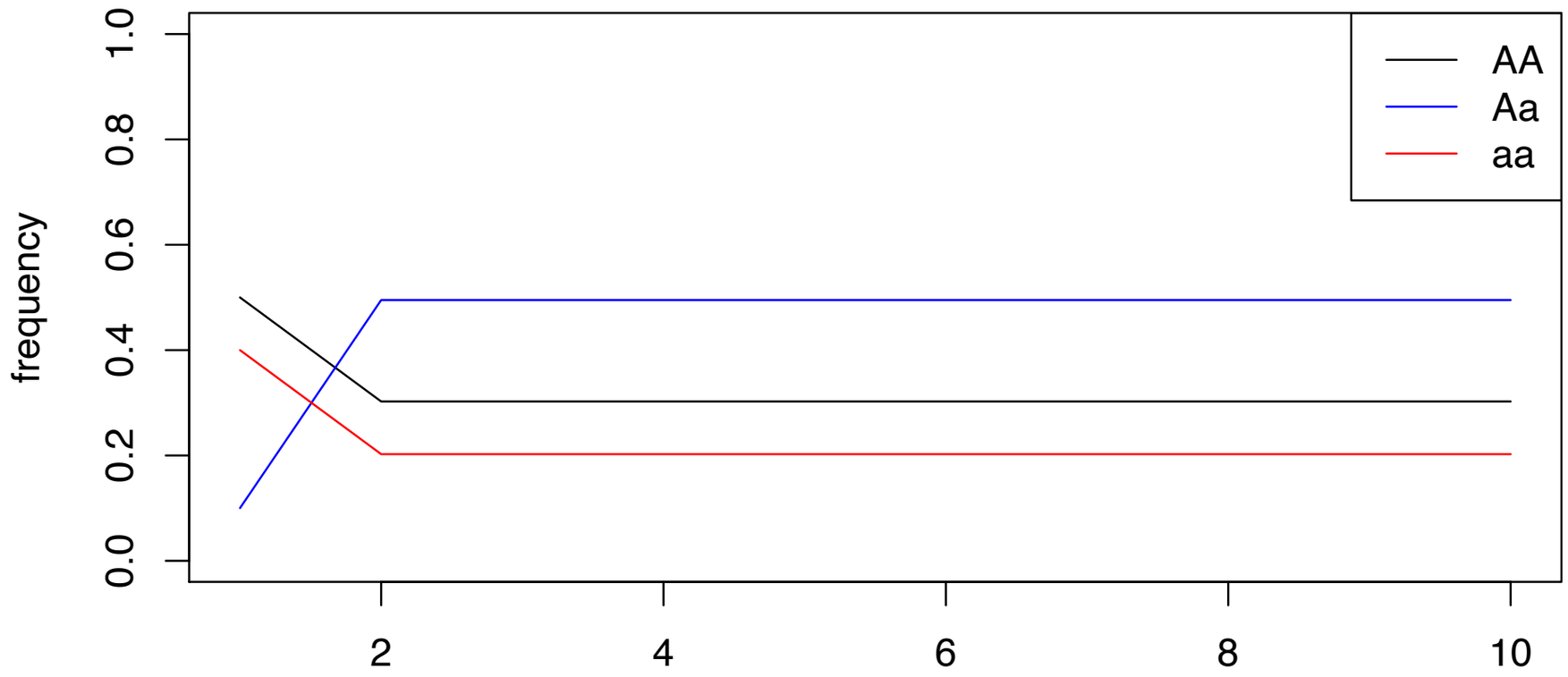


$$p = P + Q/2 = 0.55$$

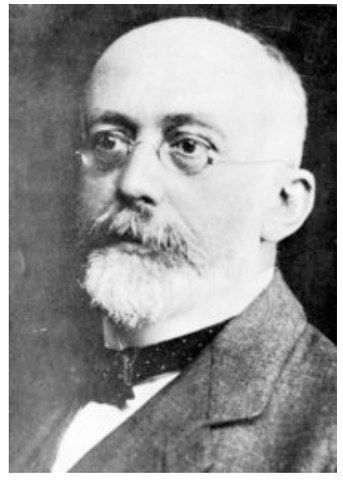
$$p^2 = 0.3025$$
$$2p(1-p) = 0.495$$
$$(1-p)^2 = 0.2025$$



- **Conclusion 2:** A single round of random mating will return the population to HWE frequencies!

Hardy-Weinberg Principle

Godfrey H. Hardy:
1877-1947



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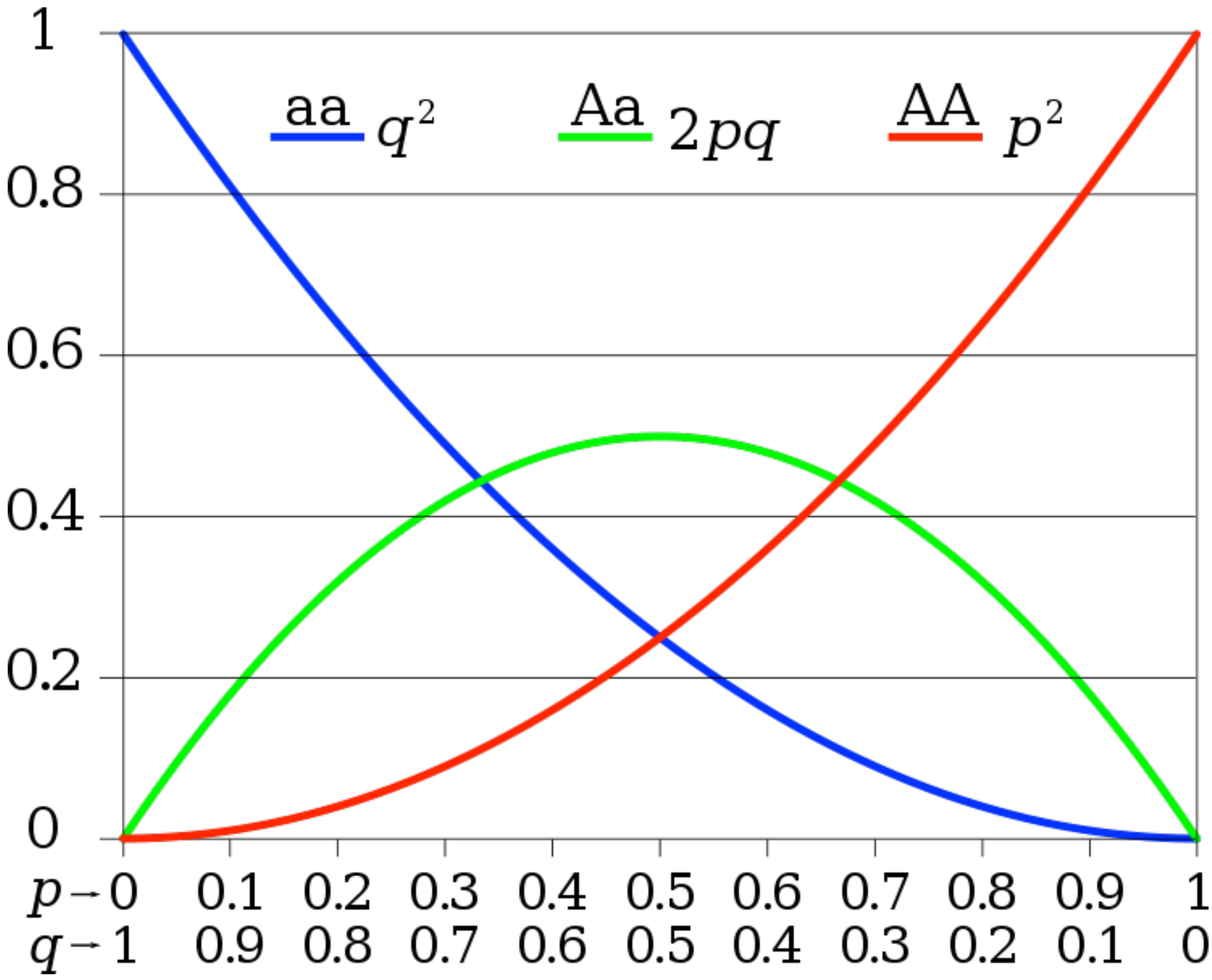
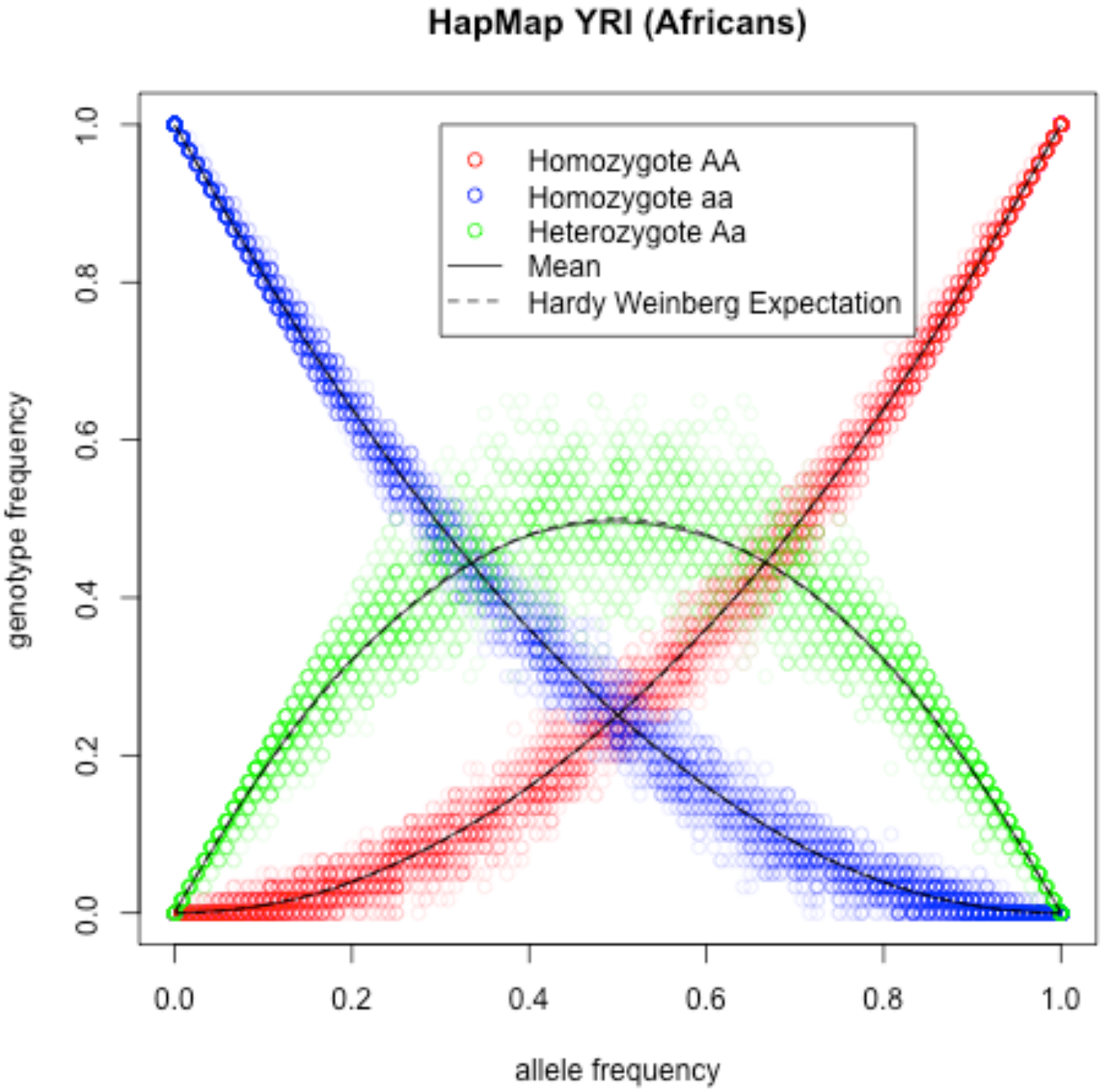
Hardy-Weinberg Equilibrium



Hardy-Weinberg Equilibrium



Graham Coop

Summary

- Hardy-Weinberg Equilibrium requires many assumptions, all of which are routinely violated in natural populations.
- Nevertheless, the vast majority of variants are in HWE.
    - Deviations almost always due to technical artifacts!
- Natural selection changes the expected allele frequency in the next generation.
    - But drift still acts in finite populations!