



Evolución Molecular

Evolución 2023

Secuencias de ADN

- Mejor visión de variabilidad genética
 - No hay alelos ocultos
- Teoría neutralista es modelo nulo
- Desviaciones por:
 - Fuerzas evolutivas
 - Demográficos
 - Cuellos de Botella
 - Mezcla poblacional
 - Expansión



Moto Kimura

Teoría Neutralista y quasi-neutralista

Diversidad en ciertos *loci* no existe por selección balanceadora sino por la acción combinada de las mutaciones neutras y de la deriva génica

Mutaciones deletéreas se eliminan rápido

Mutaciones ventajosas muy raras

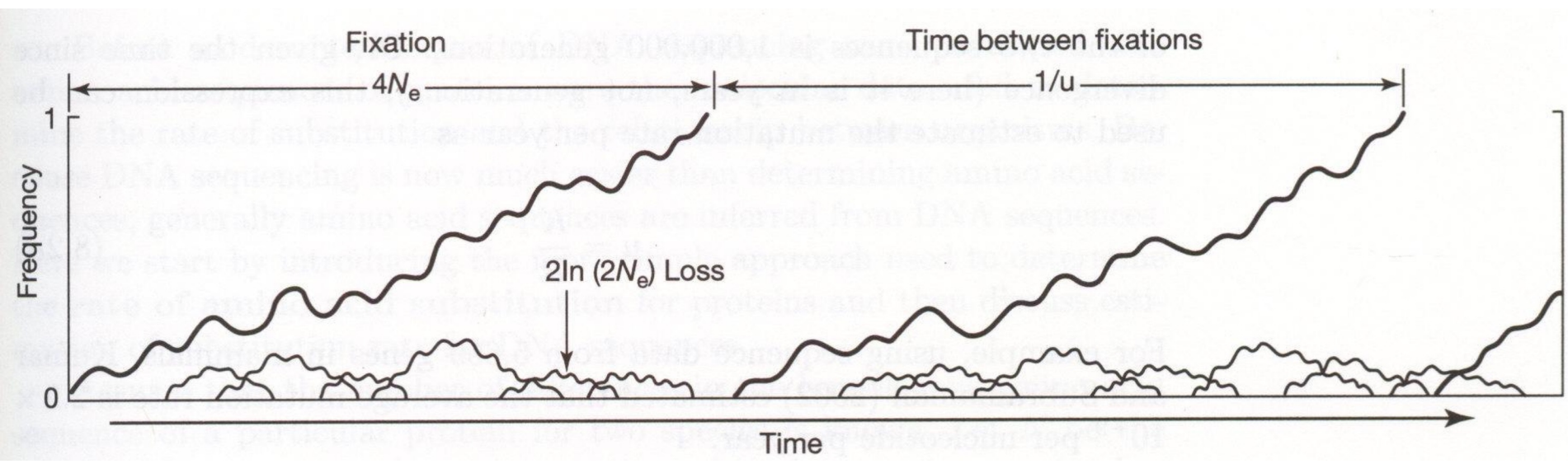
Variación observada es neutra

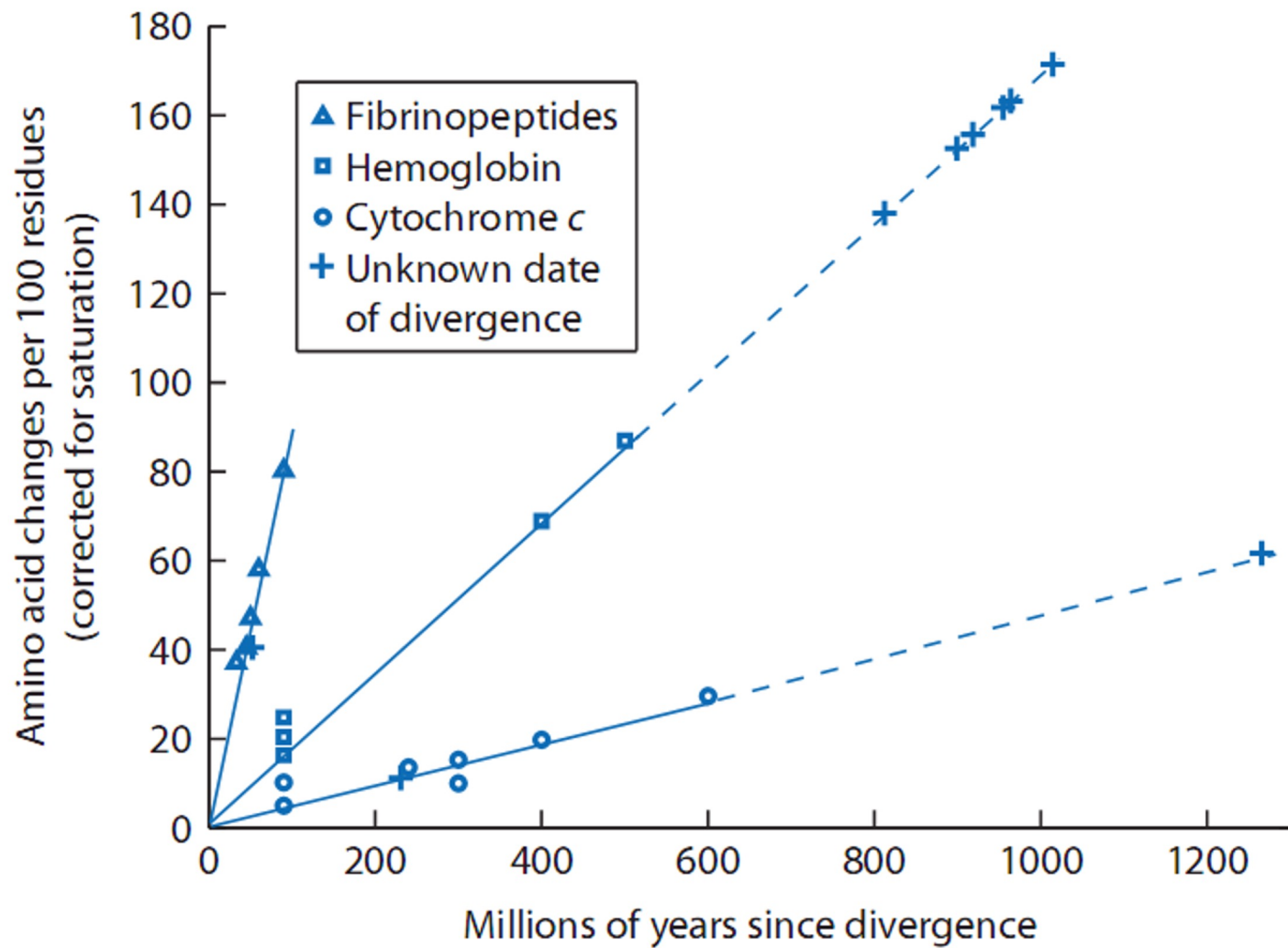
Deriva predomina cuando

$$s < \frac{1}{2N_e}$$



Tomoko Ohta





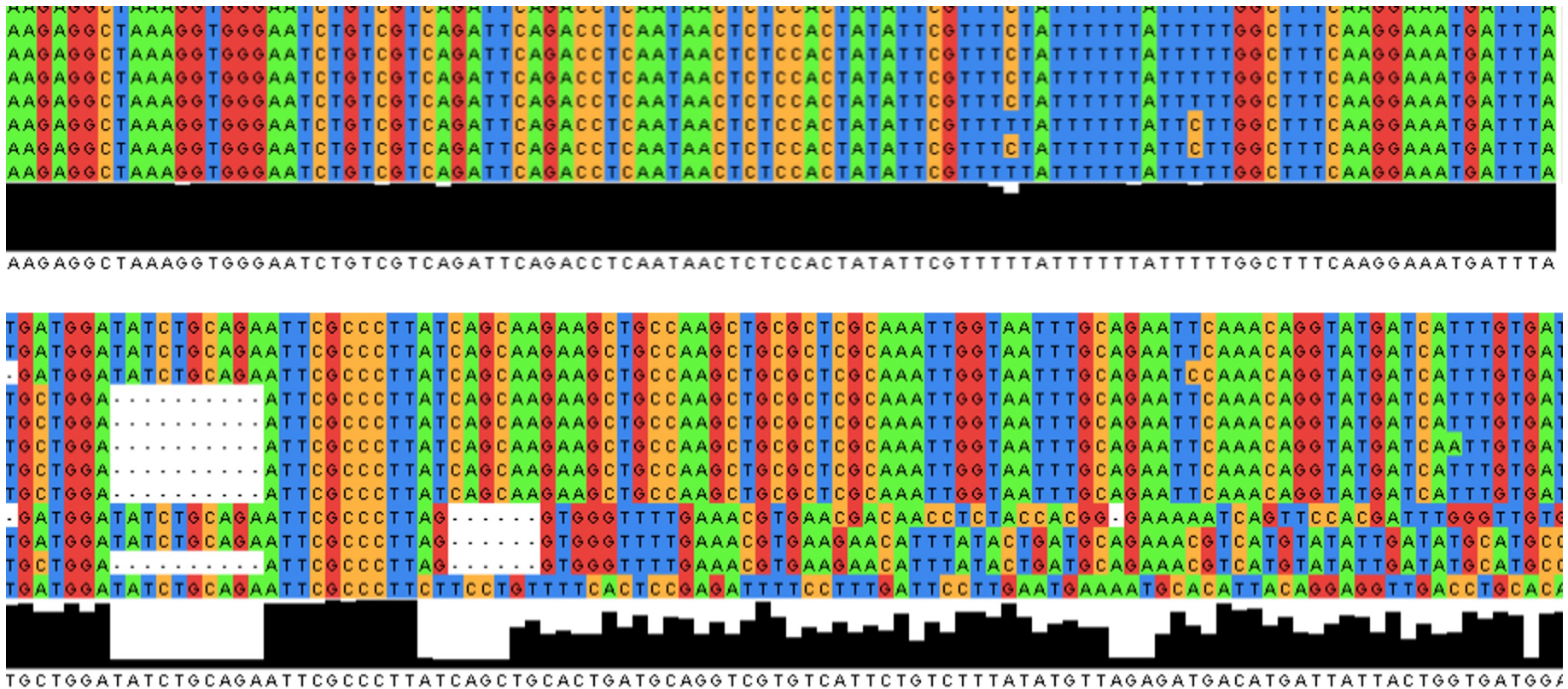
Procedimientos

- Obtener secuencias específicas o genomas
- Alineamiento
- Estudio de Polimorfismo y Divergencia
 - Entre spp
 - Entre individuos
 - Entre genes



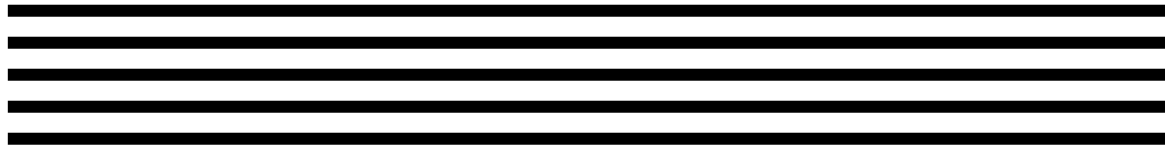
Alineamiento

- Primer paso para análisis de secuencias es alineamiento
 - Varias técnicas
 - ClustalX - Muscle - MAFFT – COFFEE – SAM – BWA - Bowtie



TAAAGATATTGGAAC TTTATATTTTATTTTTGGAGCT

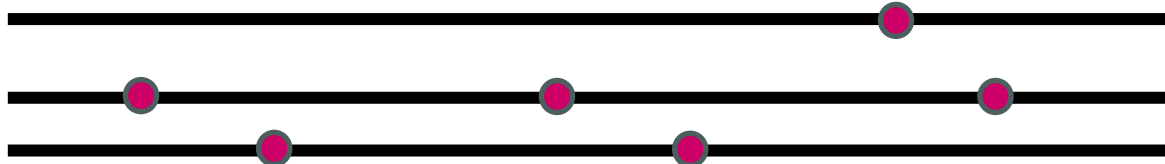
TAAAGATATTGGAAC TTTATATTTTATTTTTGGAGCT



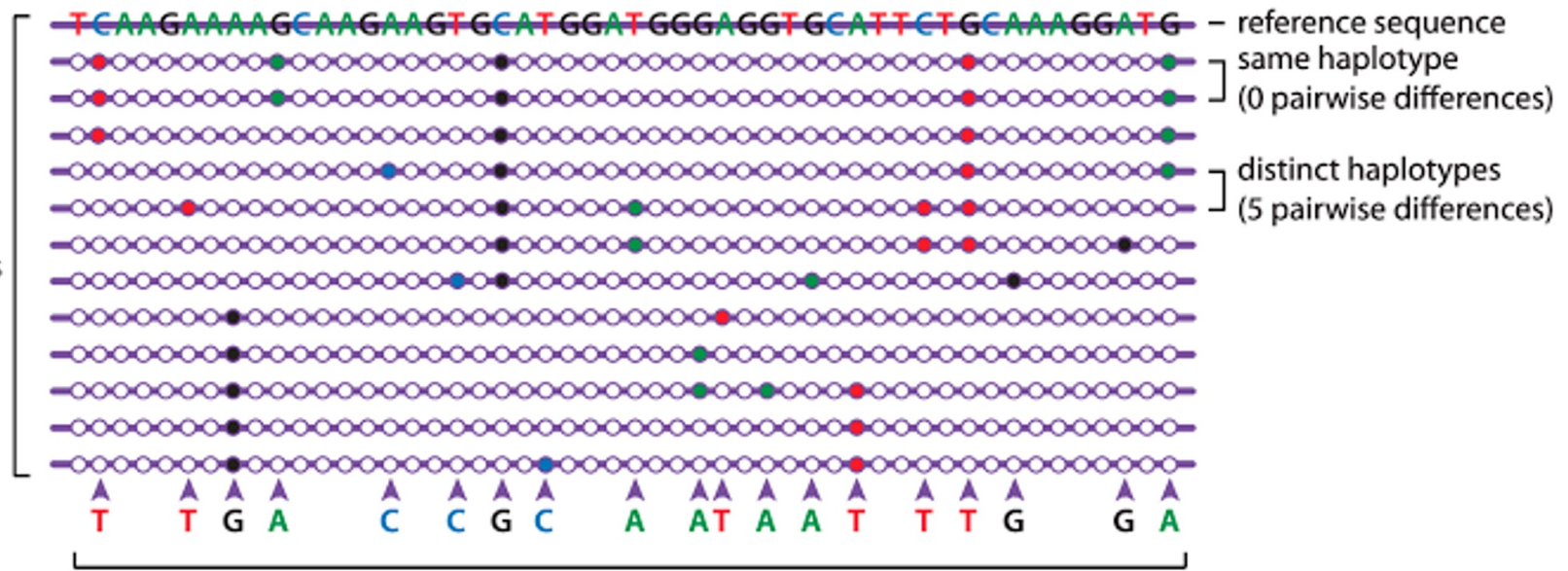
TAACGATATTGGAAC TTTATATTTTATTTTTGGAGCT



TAAAGATATTGGAAC TTTATATTTTATTGTTGGAGCT



n 13 samples
= 12 haplotypes



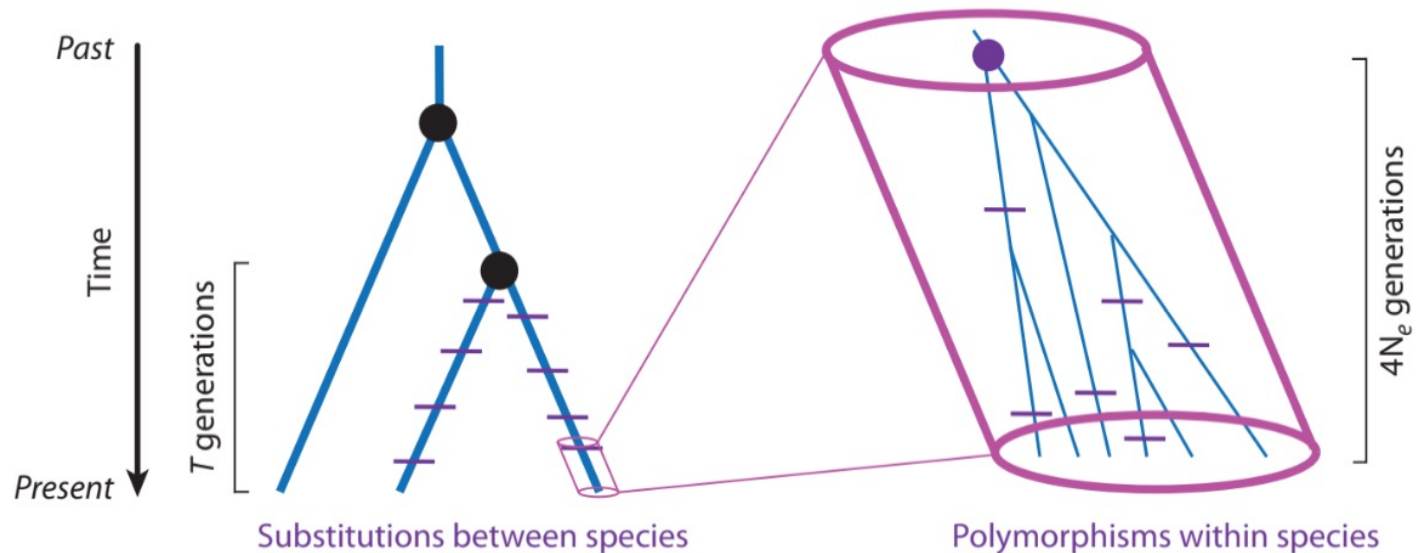
L 50 total sites
= 31 monomorphic sites
S 19 segregating sites
=

○ same nucleotide as reference
●●● different nucleotide from reference

Divergencia y Polimorfismo

Ocurre por substitución entre secuencias

(A)

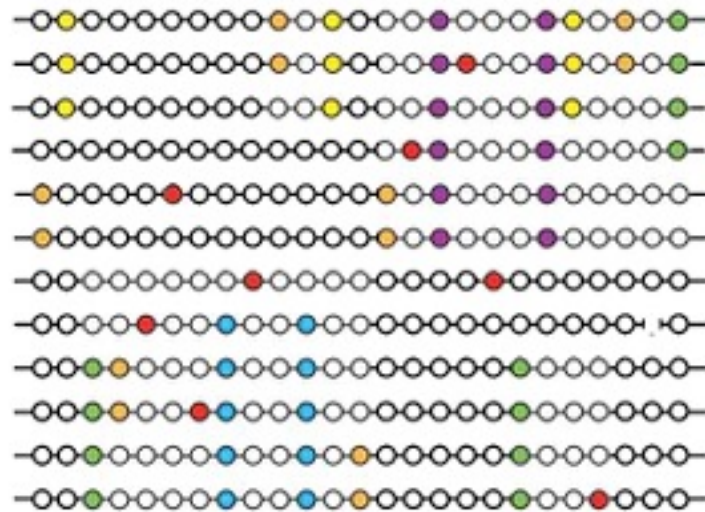


Polimorfismo

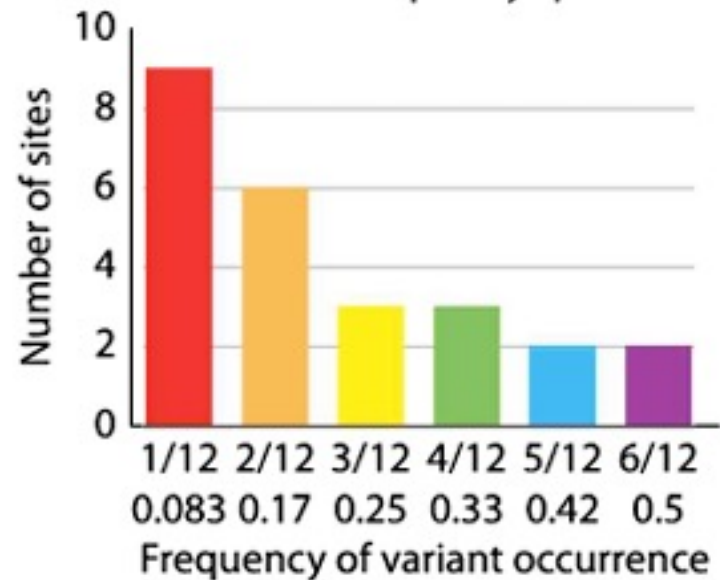
Espectro de frecuencias alélicas

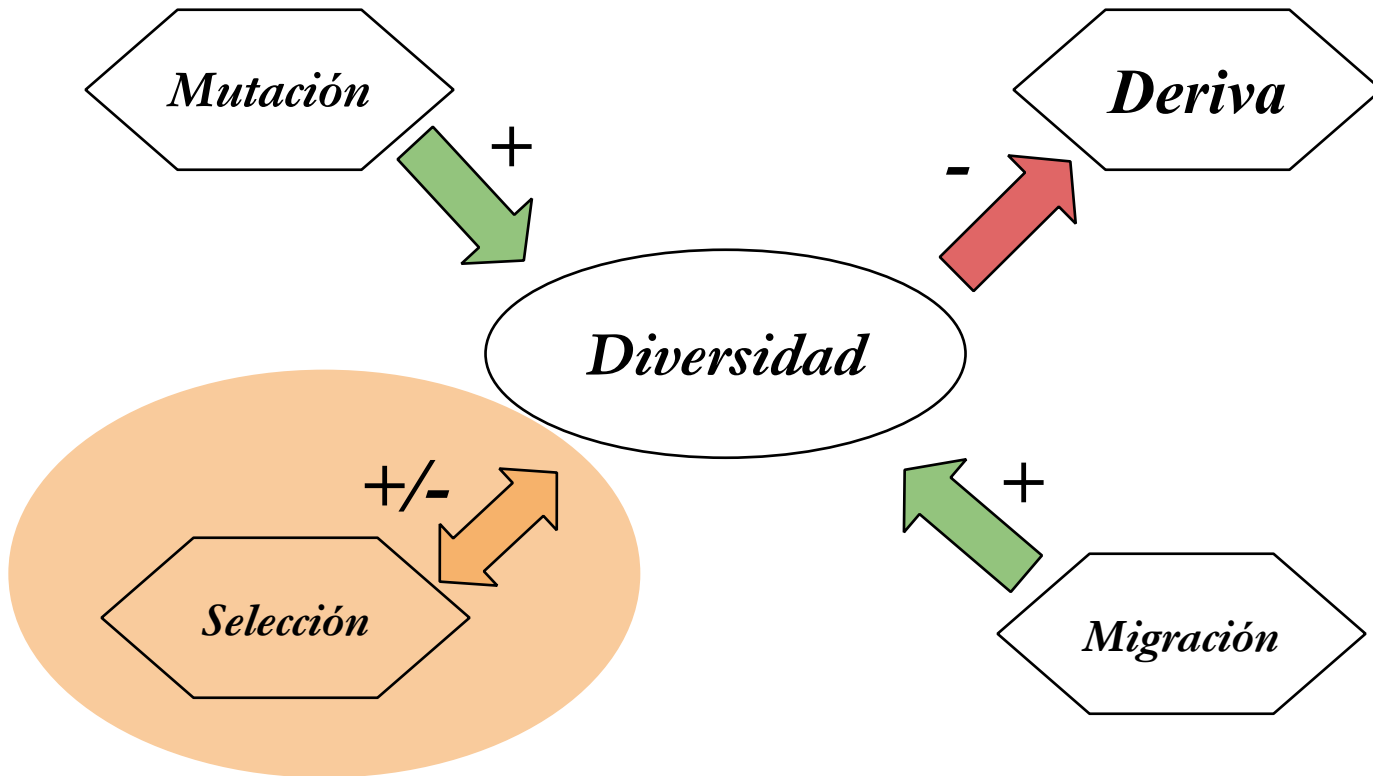


Polymorphic sites among haplotypes of the locus



Folded site frequency spectrum





Selección **positiva** y **negativa**

Selección **negativa** o purificadora es la que elimina alelos deletéreos

Selección **positiva** es la selección que aumenta la frecuencia de un alelo ventajoso en la población

Barrido de Selección

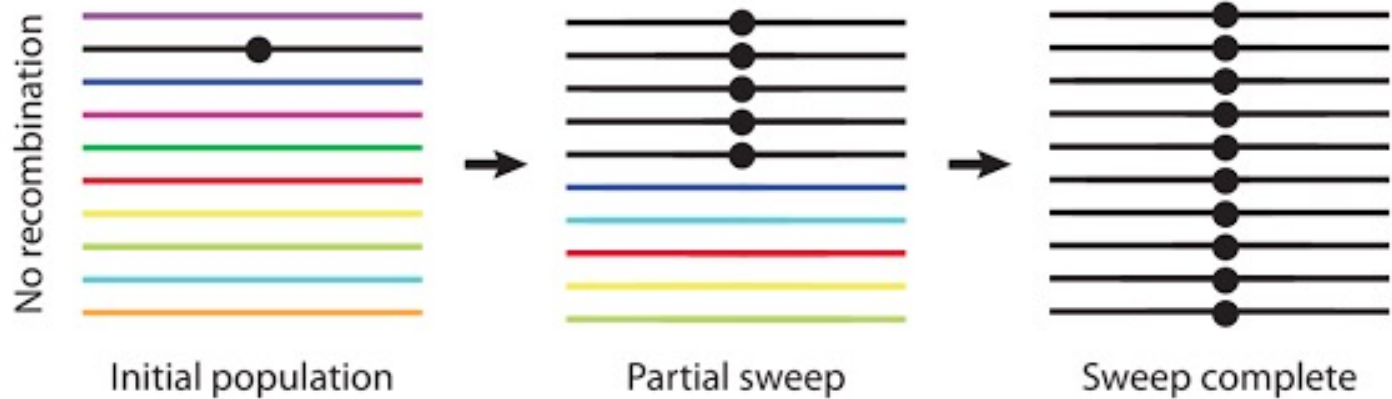


Figure 7.1 Hard selective sweep from a new beneficial mutation.

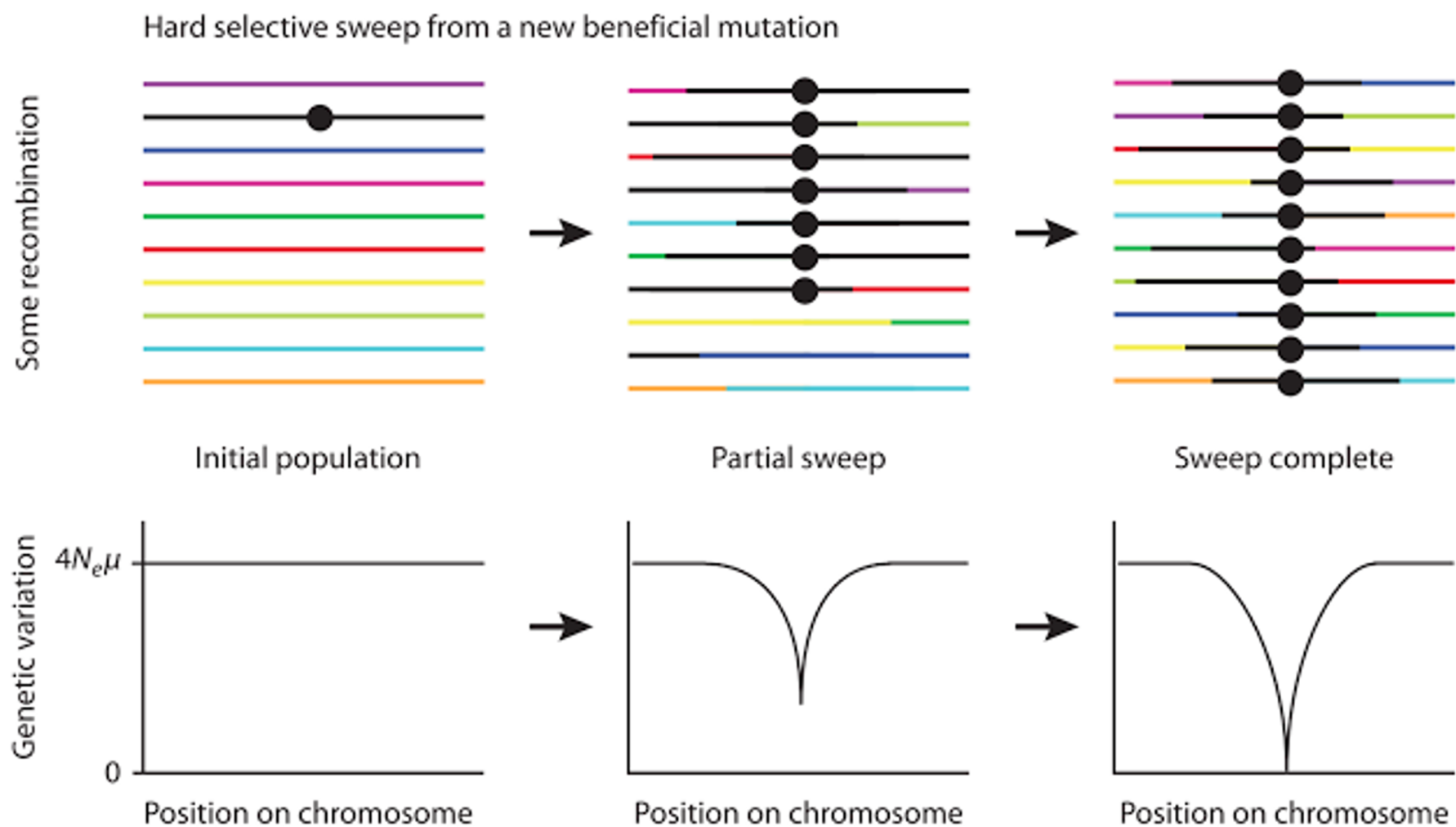
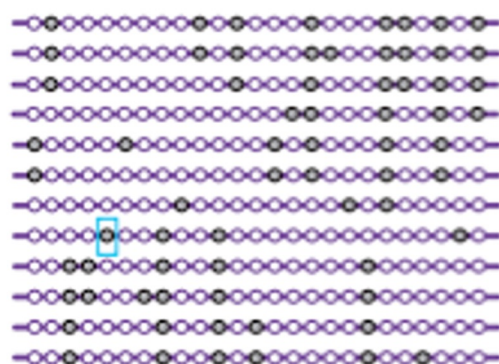


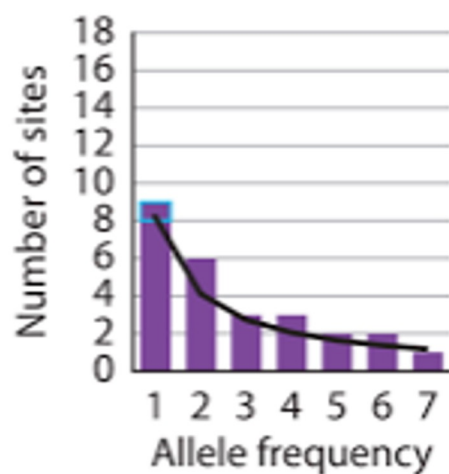
Figure 7.4 Hard selective sweep in the presence of recombination.

Neutrality

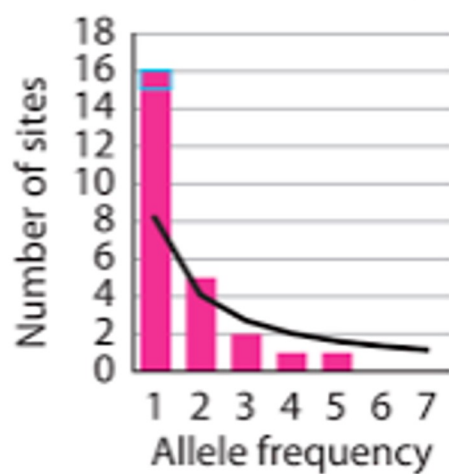
Polymorphic sites among haplotypes of the locus



Site frequency spectrum



Positive selection



Tolerancia a la lactosa (LCT)

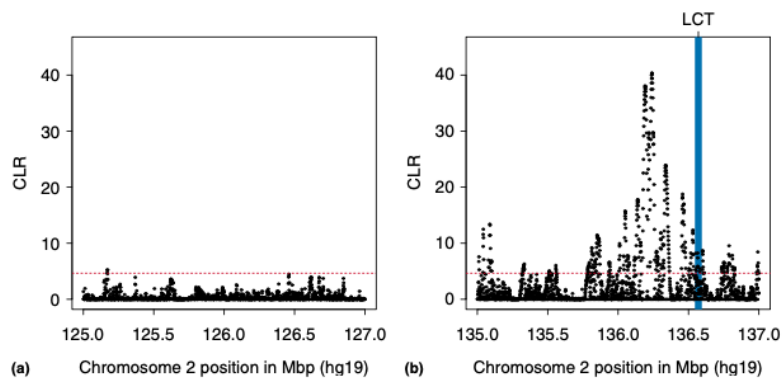


Figure 4 CLR scores calculated across 102 European human genomes for (a) a putatively neutral region of chromosome 2 and (b) a region surrounding the LCT locus (bounded by blue box) on chromosome 2.

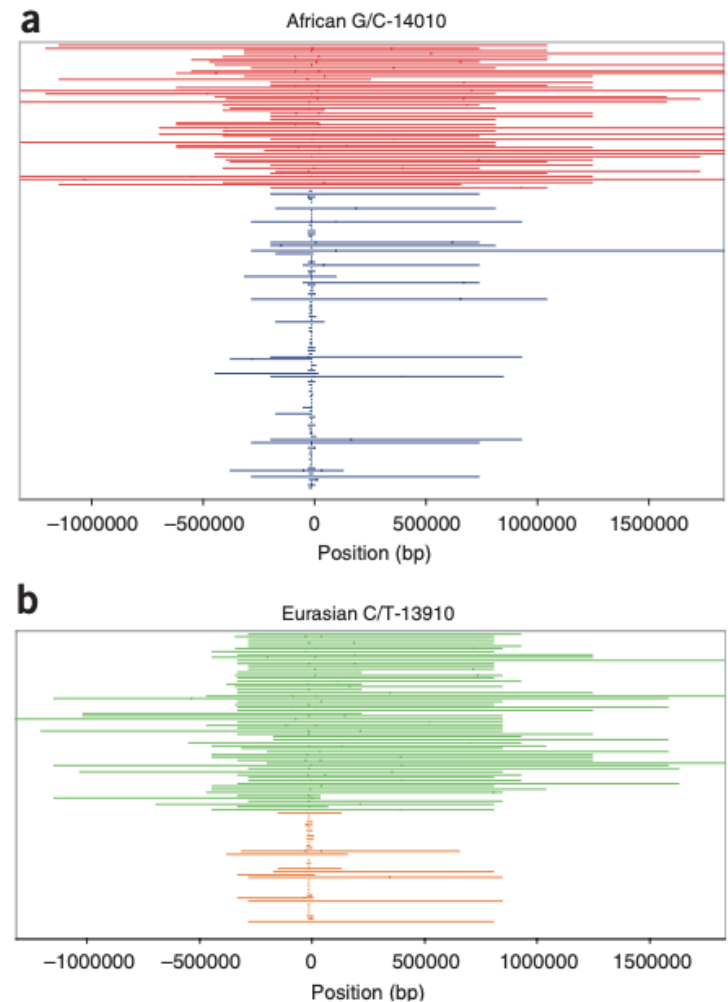
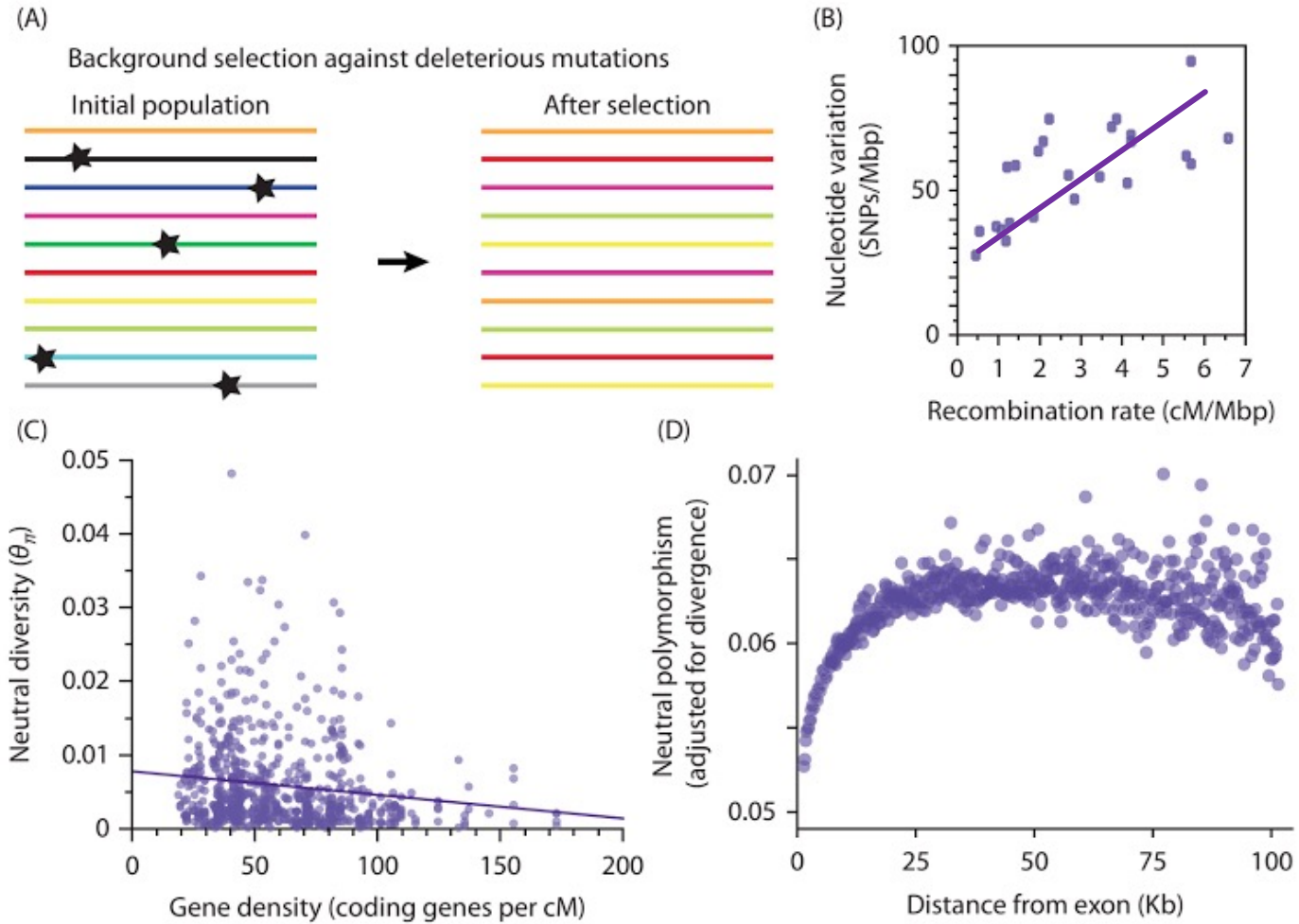
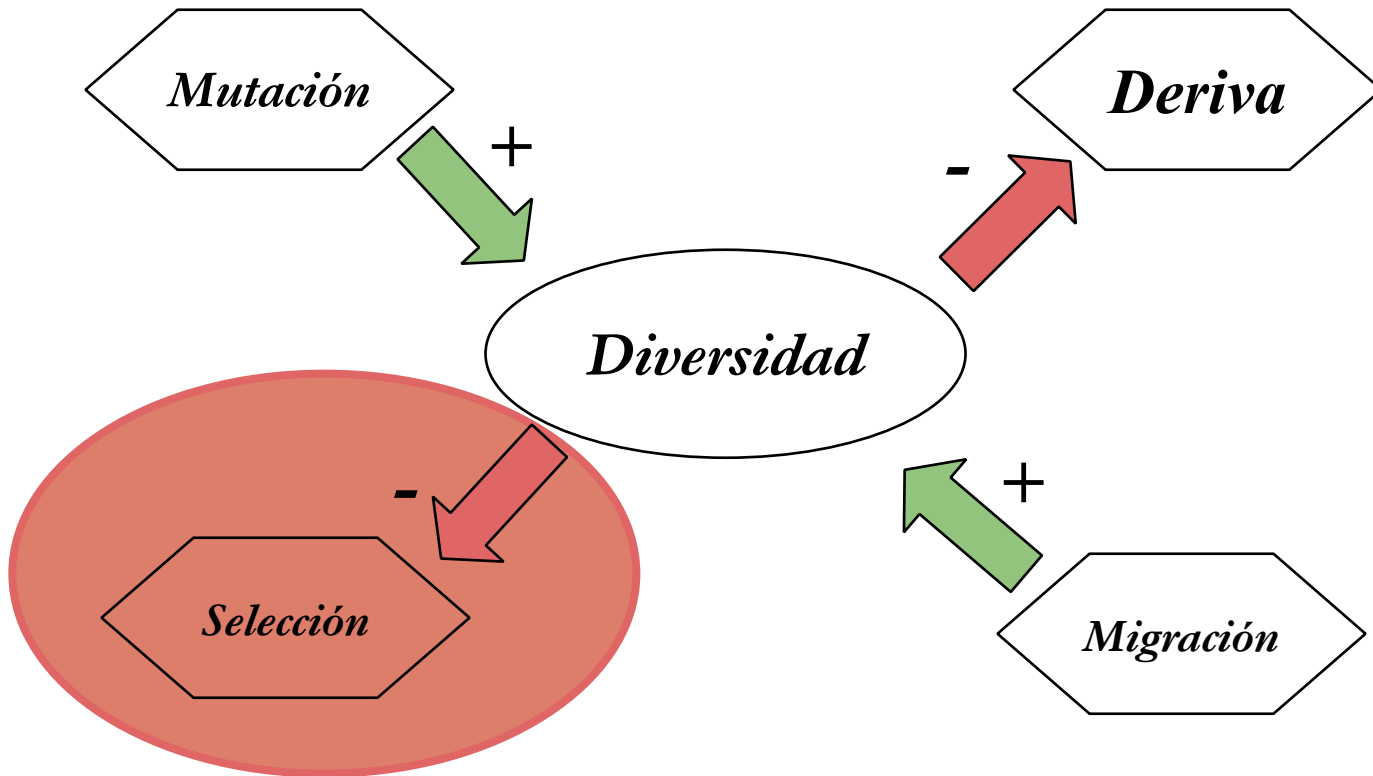


Figure 6 Comparison of tracts of homozygous genotypes flanking the lactase persistence-associated SNPs. (a) Kenyan and Tanzanian C-14010 lactase-persistent (red) and non-persistent G-14010 (blue) homozygosity tracts. (b) European and Asian T-13910 lactase-persistent (green) and C-13910 non-persistent (orange) homozygosity tracts, based on the data from ref. 14. Positions are relative to the start codon of *LCT*. Note that some tracks are too short to be visible as plotted.

Selección de fondo





Selección **Balanceadora**

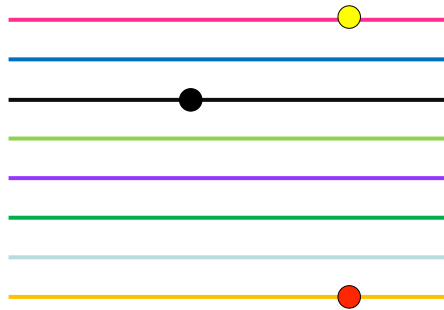
Proceso por el cual múltiples alelos están activamente presentes en el pool genético en frecuencias superiores a la esperada por mutación

¡Ventaja de heterocigota !

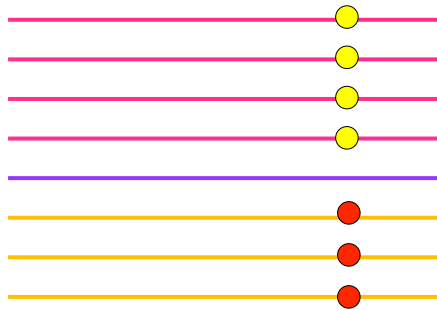
Selección dependiente de frecuencia

Selección varía espacio-tiempo

Selección Balanceadora



Población inicial



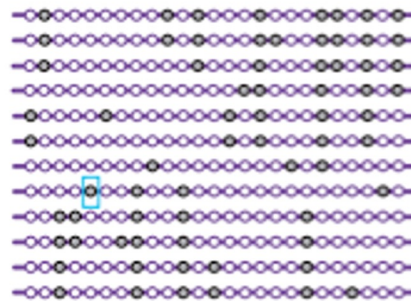
Selección



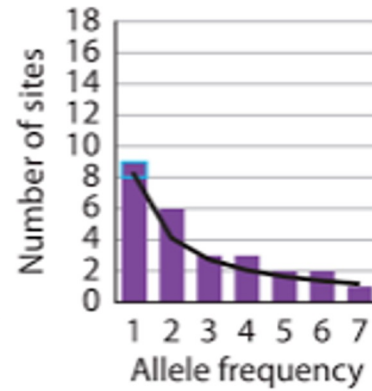
Después de selección

Polymorphic sites among haplotypes of the locus

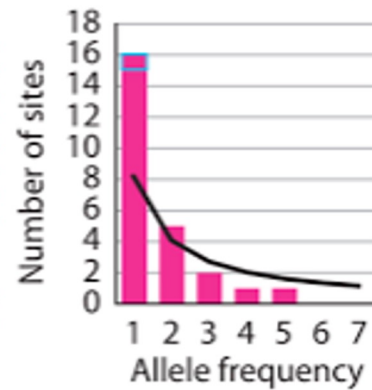
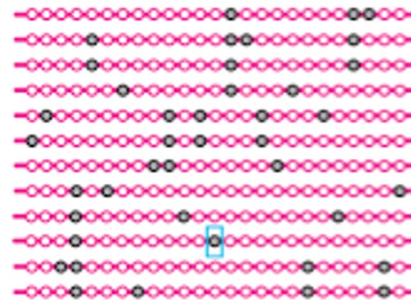
Neutrality



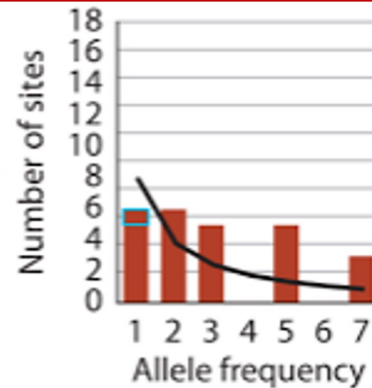
Site frequency spectrum

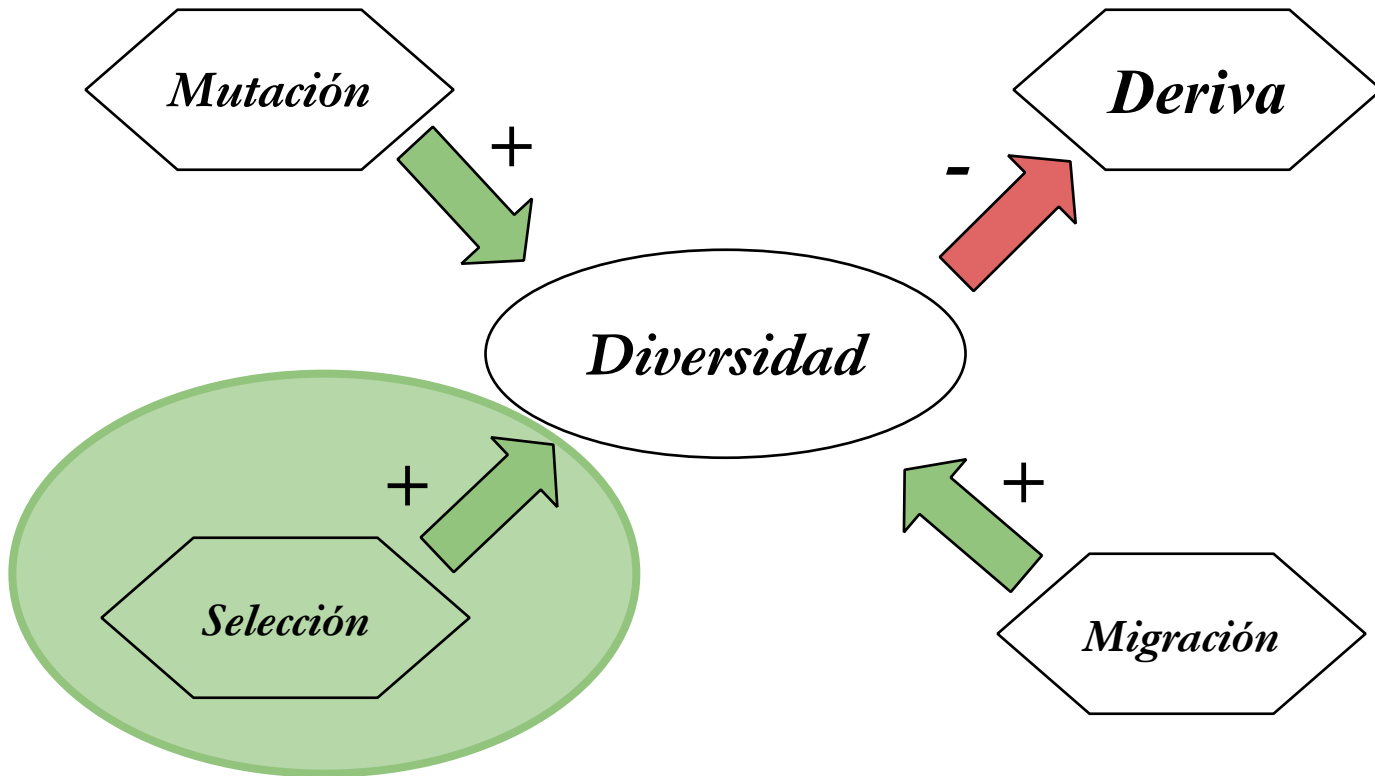


Positive selection

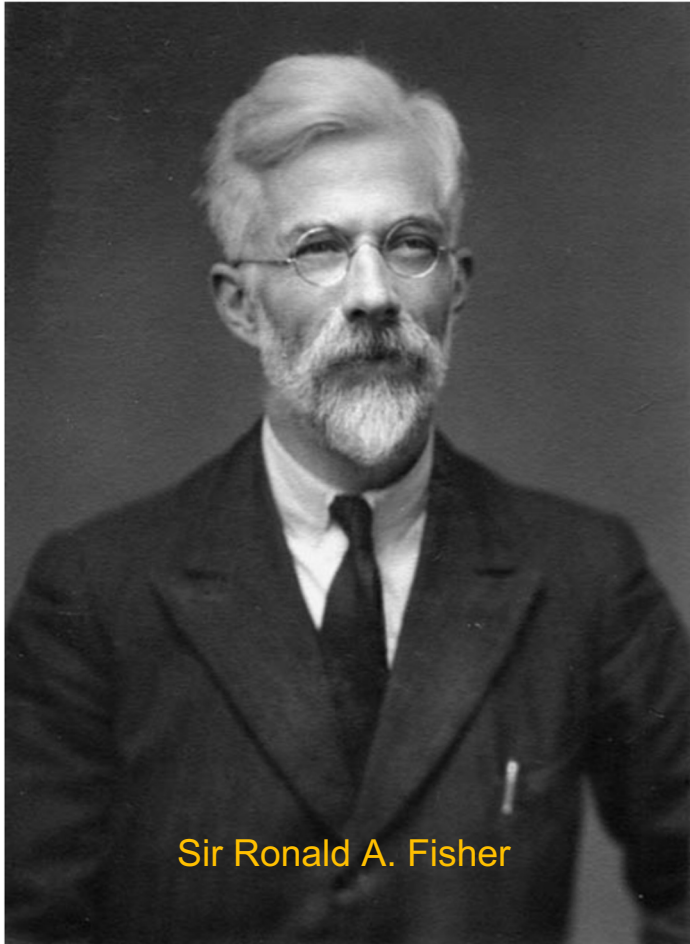


Balancing selection





Teorema fundamental de la selección natural

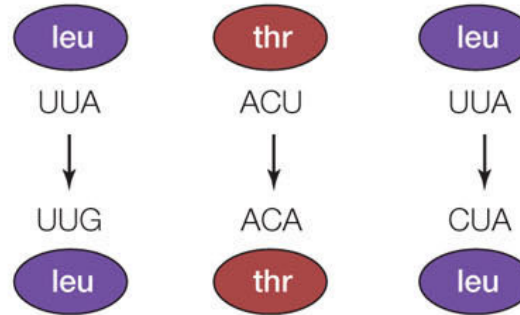


Sir Ronald A. Fisher

$$\Delta \bar{\omega} \propto \text{var}(\omega)$$

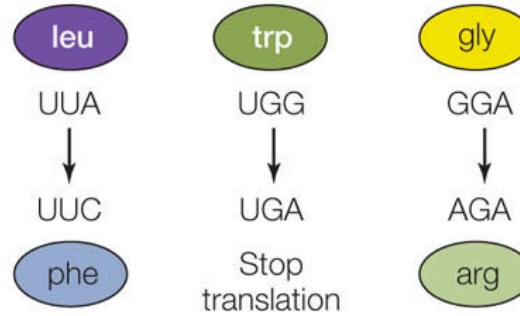
(A)

Synonymous
substitutions



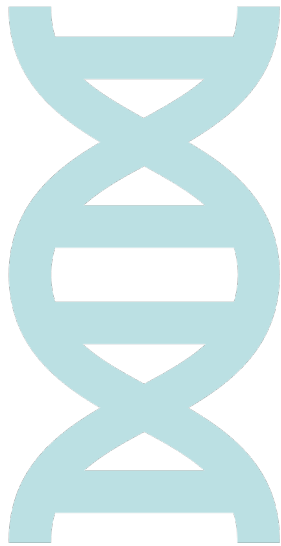
(B)

Nonsynonymous
substitutions



This substitution would result in an incomplete protein.

Mutaciones sinónimas y no-sinónimas



Mutaciones sinónimas
Invisibles a selección

K_S : tasa de mutaciones sinónimas

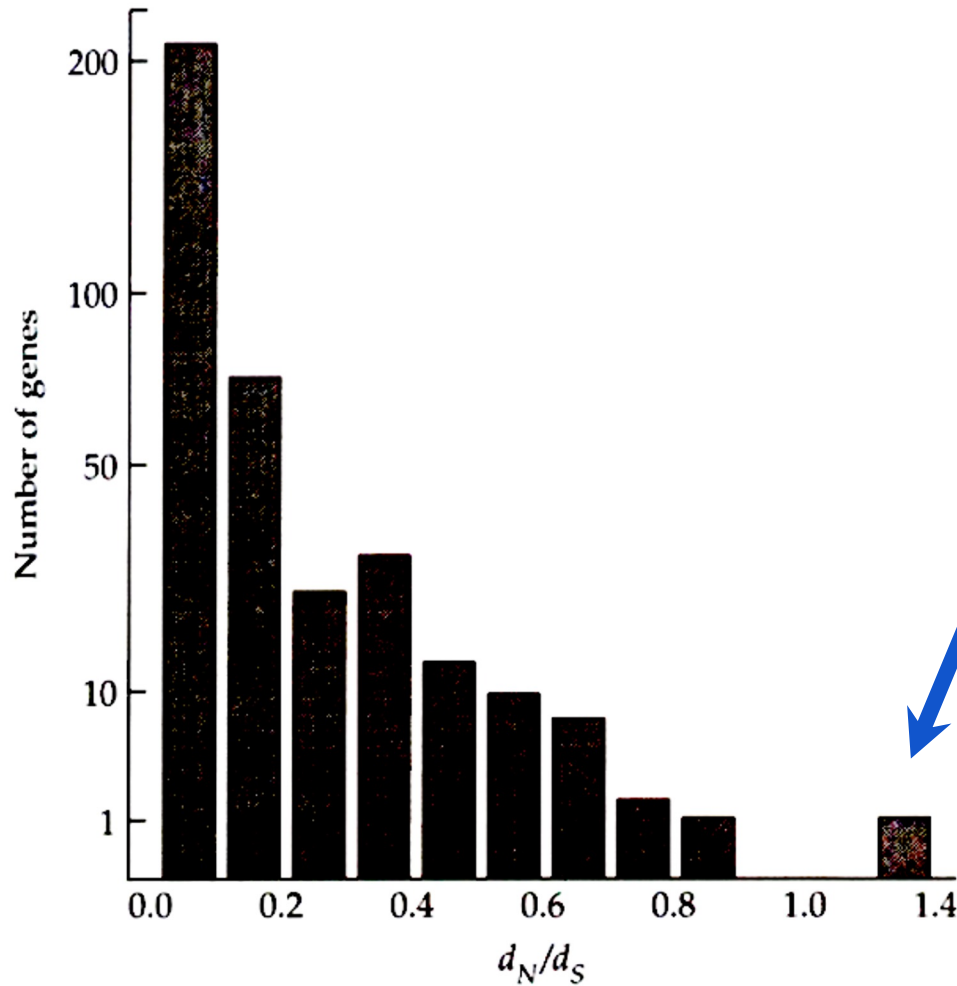
K_A : tasa de mutaciones no-sinónimas

$$\Omega = K_A/K_S$$

$\Omega > 1$: Selección positiva

$\Omega < 1$: Selección negativa

d_N/d_S para 363 genes ratones



Mayoría genes selección purificadora ($d_N/d_S < 1$)

Evidencia de selección dirigida en genes del sistema inmunológico

K_A / K_S en humanos

K_A / K_S promedio (13 454 genes) = 0.23

$K_A / K_S > 1$: 585 genes

Selección Negativa
($K_A / K_S < 1$)

Estructura celular
Motilidad
Citoesqueleto
Transporte vesicular
Transporte intercelular
Tráfico de membrana

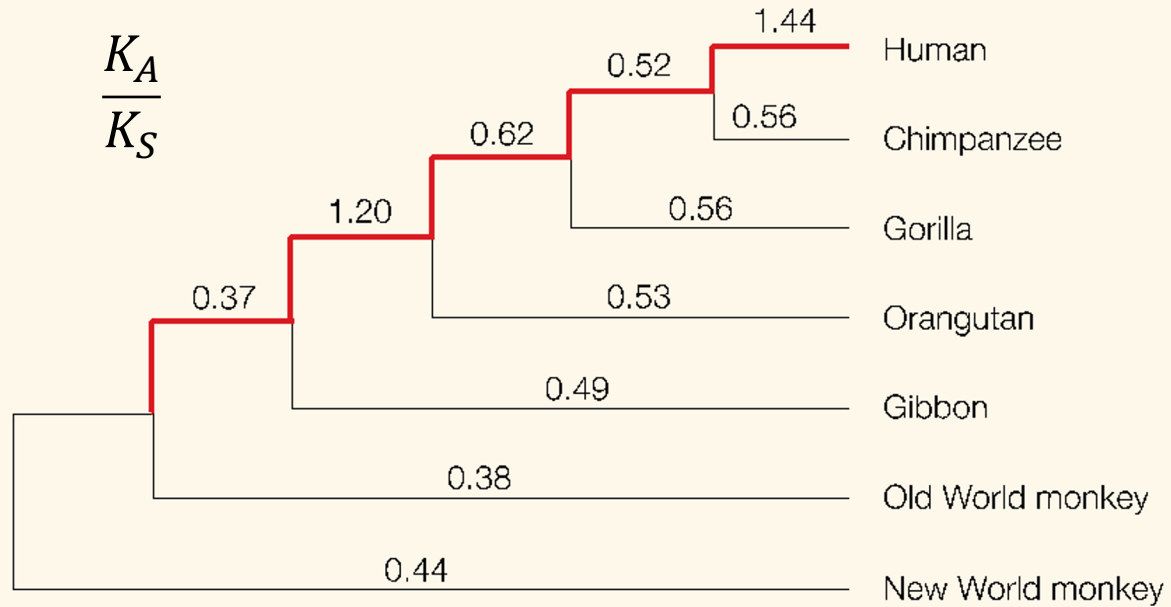
Selección Positiva
($K_A / K_S > 1$)

Apoptosis
Inmunológicos
Receptores
Inmunoglobulinas
Receptor nuclear hormonas
Kinasas
Factores de Transcripción

Abnormal spindle-like microcephaly-associated

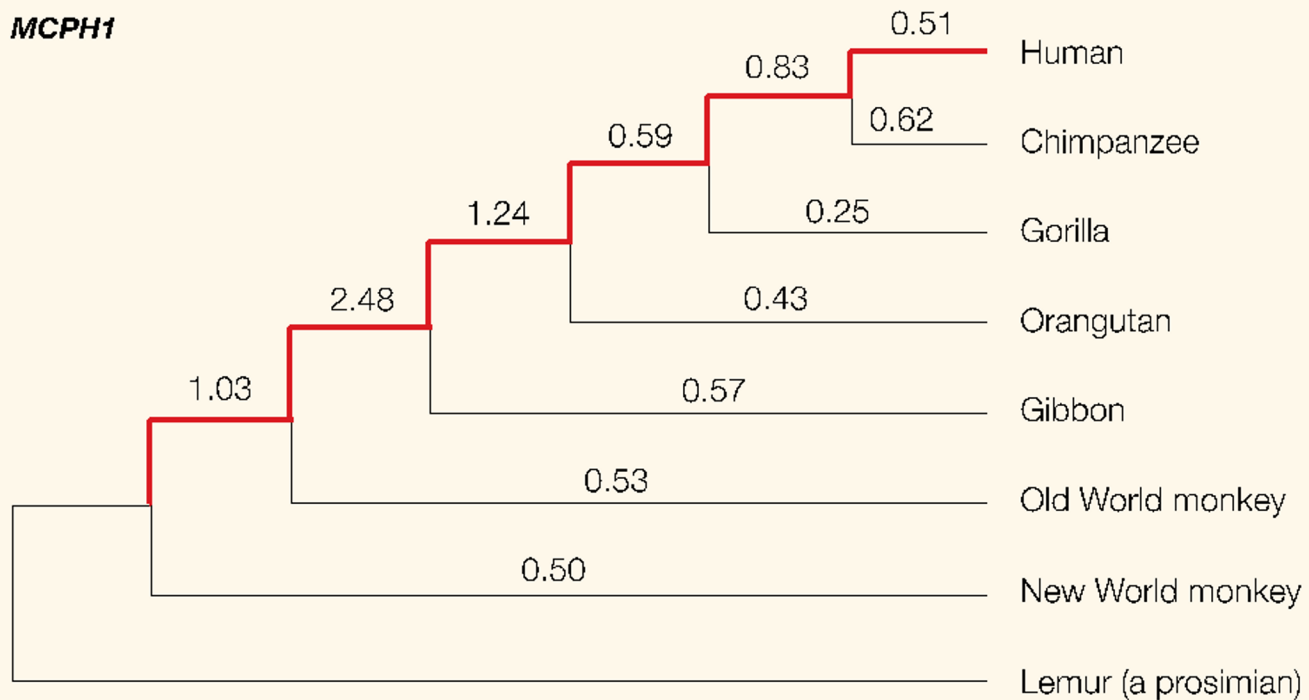
ASPM

$$\frac{K_A}{K_S}$$

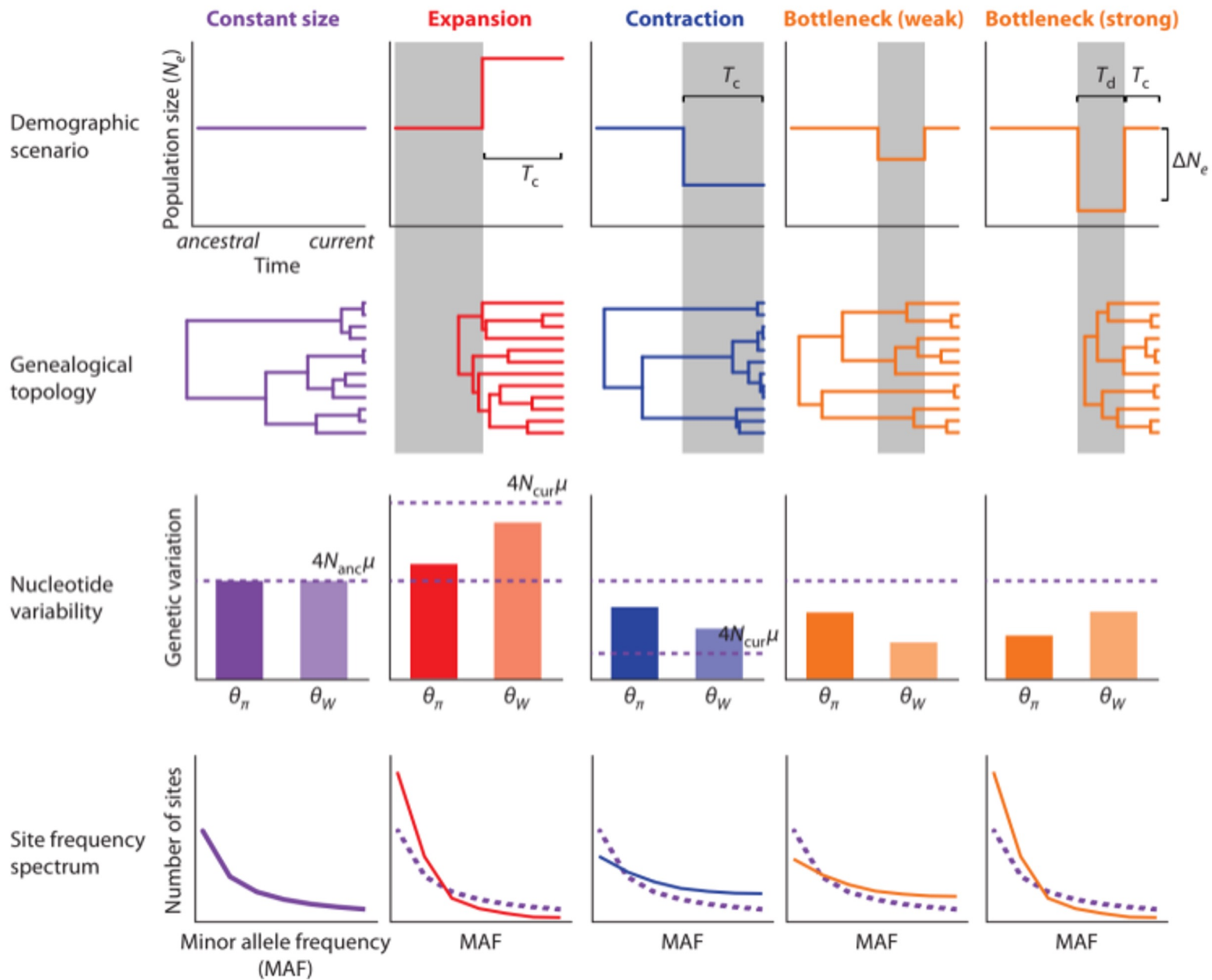


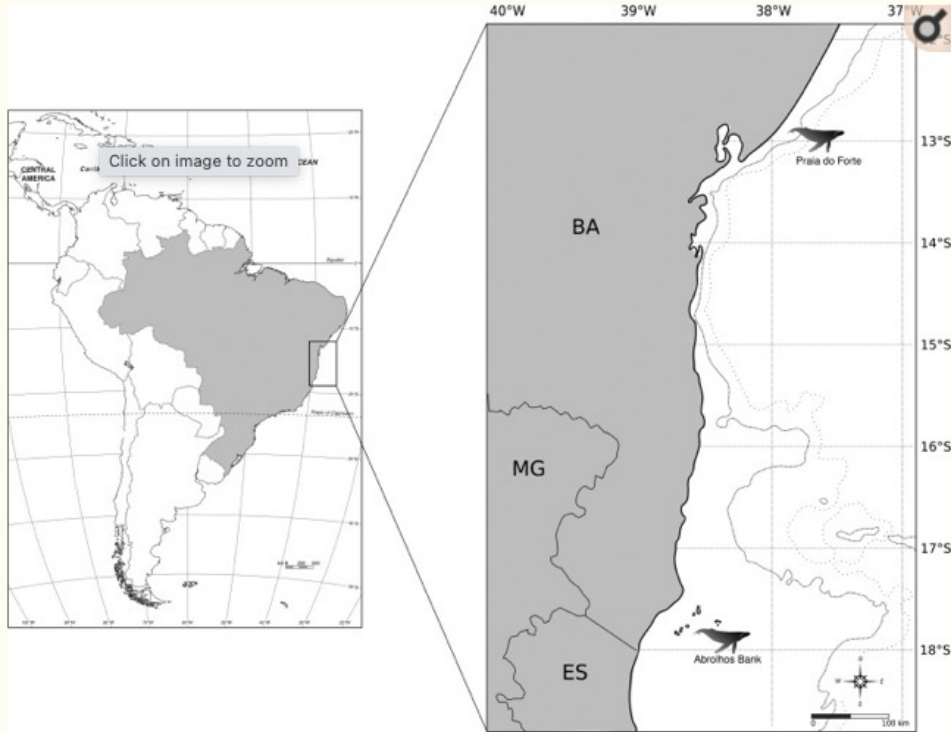
microcephaly, primary autosomal recessive 1

MCPH1



Gilbert et al. 2005





A

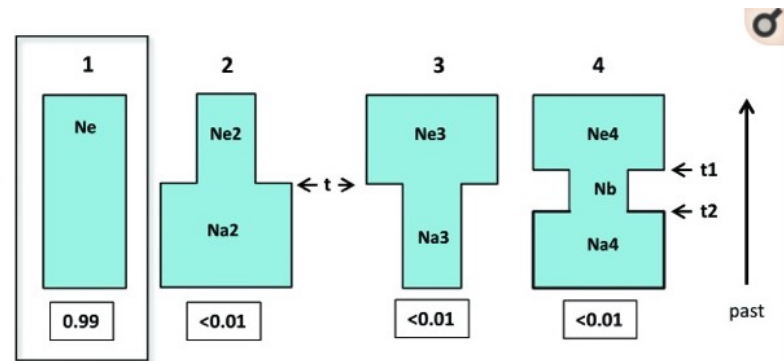


Table 7.1 Summary of the effects of selection and demography* on patterns of polymorphism and divergence.

Effect	Positive selection	Purifying selection	Balancing selection	Population expansion	Population contraction
Polymorphism	Lower	Lower	Higher	Lower	Lower
Genealogies	Shorter TMRCA	Shorter TMRCA	Longer TMRCA	Shorter TMRCA	Longer TMRCA
Site frequency spectrum	Excess of low-frequency variants, excess of high-frequency derived variants	Excess of low-frequency variants	Excess of intermediate-frequency variants	Excess of low-frequency variants	Excess of intermediate-frequency variants
Divergence	Higher K_A	Lower K_A	—	—	—

* relative to expectations from the standard neutral model for a single population of a historically constant size equal to the present-day size; TMRCA = Time to the Most Recent Common Ancestor