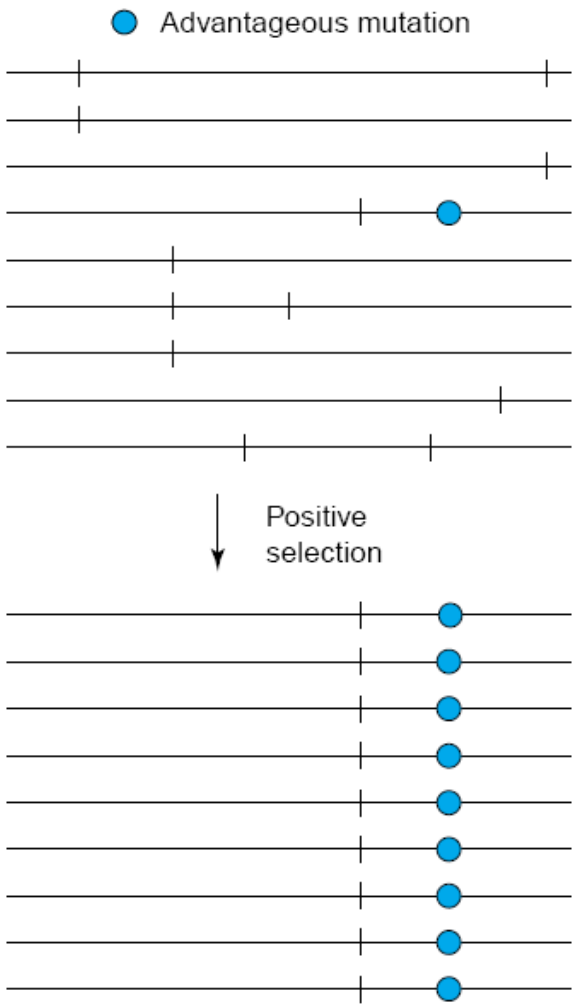
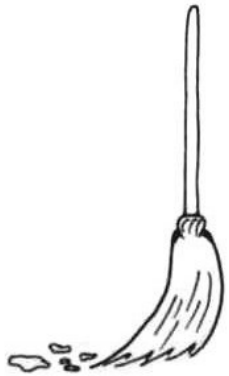
Detection of selection from molecular data

Recent positive selection

Selective sweep

- Reduction of genetic variability around positive mutation.
- Increase of linkage disequilibrium around positive mutation.
- Changes in allele frequency spektra
- Selection not much longer than ~ Ne generations ago (in humans ~ 250 000 years).

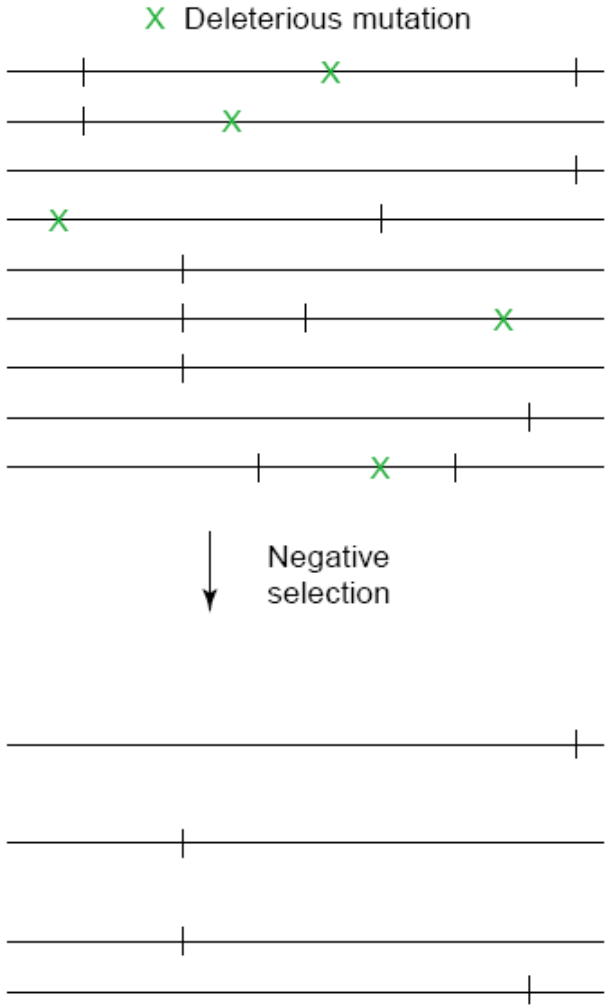




Recent negative selection

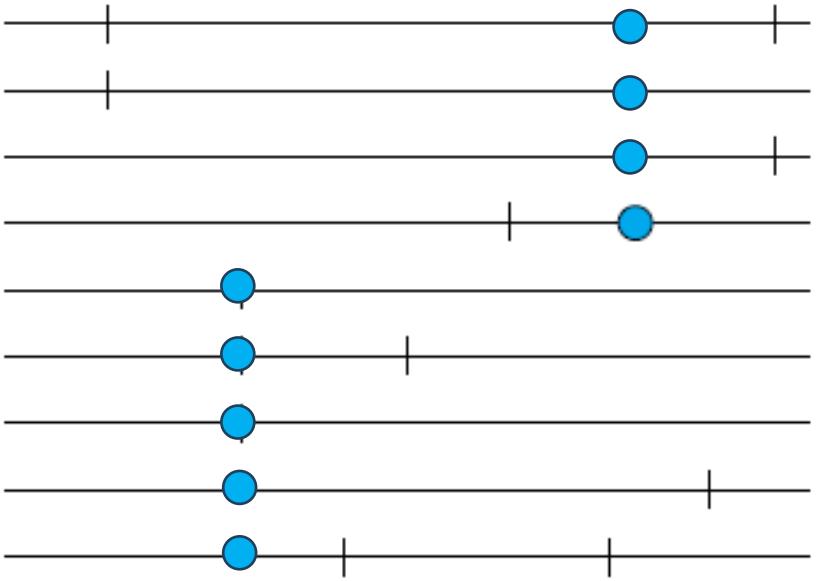
Background selection

- Reduction of genetic variation and change in allele frequency spectra around the negative mutation, but not so marked as in case of positive selection.



Balancing selection

- Increases levels of genetic variation
- Maintain relatively high frequecies of alternative alleles.



Methods of detection of recent positive selection (selective sweep)

Hudson-Kreitman-Aguadé (HKA) test

$\theta = 4N_e\mu$

$D = 2\mu t$

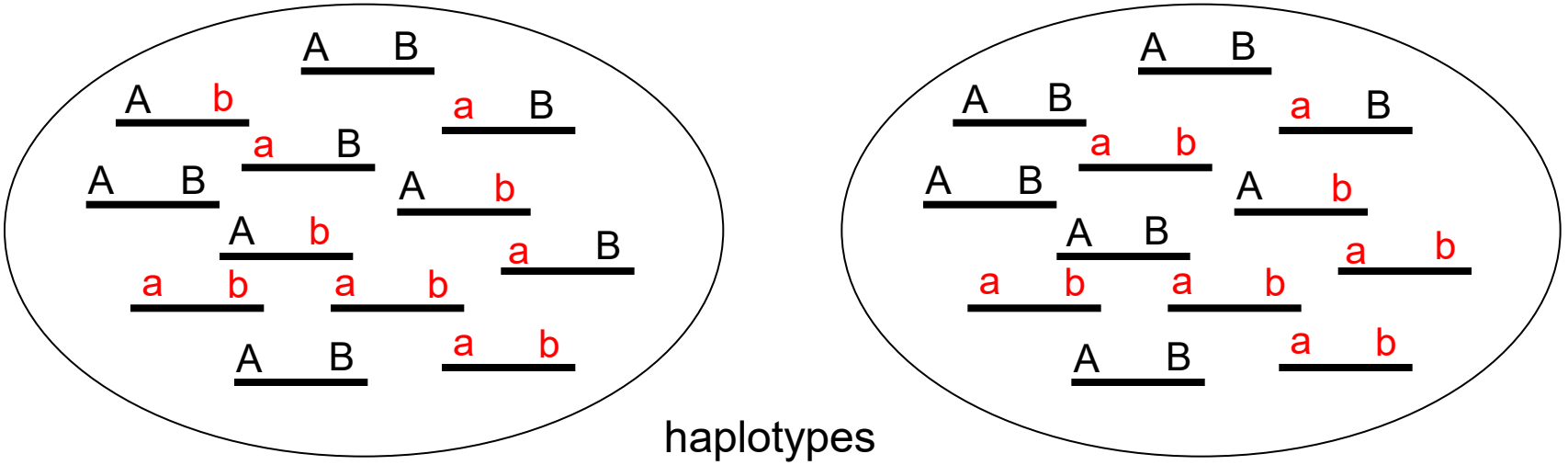
- Compares levels of within species polymorphism (θ) and between species divergence (D) in multiple loci.
- For neutral sequences θ/D ratio should be constant.
- Recent positive selection reduces θ, but does not affect D.
- Positive HKA test could be caused by selection for linked gene with the studied gene.

	θ	D
Lokus 1	θ_1	D_1
Lokus 2	θ_2	D_2
Lokus 3	θ_3	D_3
Lokus 4	θ_4	D_4

Software: http://genfaculty.rutgers.edu/hey/software#HKA

Linkage disequilibrium

- Certain combinations of allels in two or more loci occur in higher frequencies than we would expect based on their random combination.



haplotypes

AB…. 25%
ab…. 25%
aB…. 25%
Ab…. 25%

LINKAGE EQUILIBRIUM

AB…. 40%
ab…. 40%
aB…. 10%
Ab…. 10%

LINKAGE DISEQUILIBRIUM

Linkage disequilibrium (D)

D = observed – expected frequency of haplotypes

Expected frequencies of haplotypes (i.e. random combinations) are given only by allele frequencies.

haplotype	**expected frequency**	
AB	p_1q_1	8%
ab	p_2q_2	48%
Ab	p_1q_2	32%
aB	p_2q_1	12%

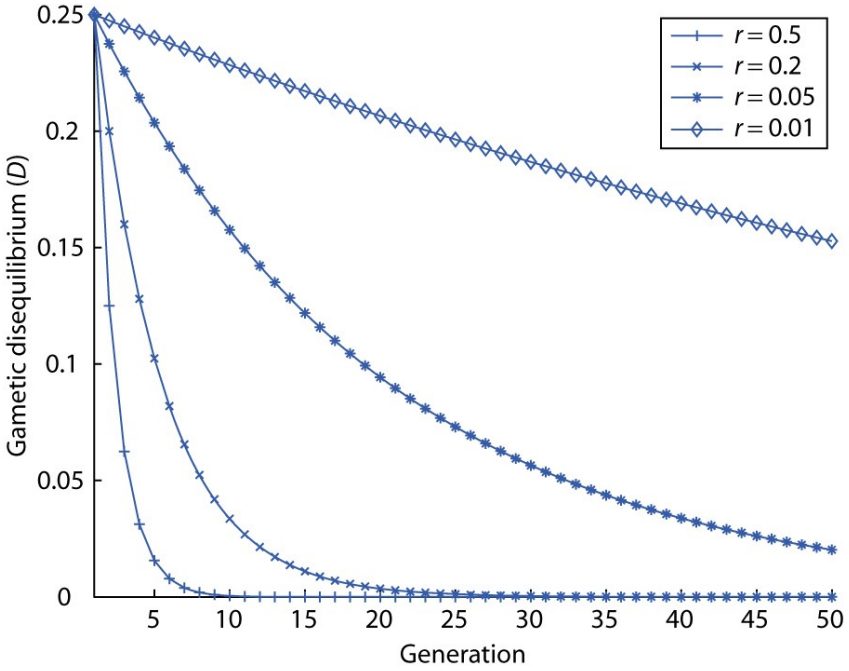
p_1 … frequency of A 40%
p_2 … frequency of a 60%
q_1 … frequency of B 20%
q_2 … frequency of b 80%

D = 0	linkage equilibrium
D > 0 či D < 0	linkage disequilibrium

D’ = D / Dmax mezi 0 a 1

Linkage disequilibrium (D)

- The level of linkage disequilibrium depends inversely on recombination rate (r) and effective population size (N_e).
- Lower levels of linkage disequilibrium in larger populations.
- Linkage disequilibrium between loci tend to decay with time (as recombination events accumulate between loci).

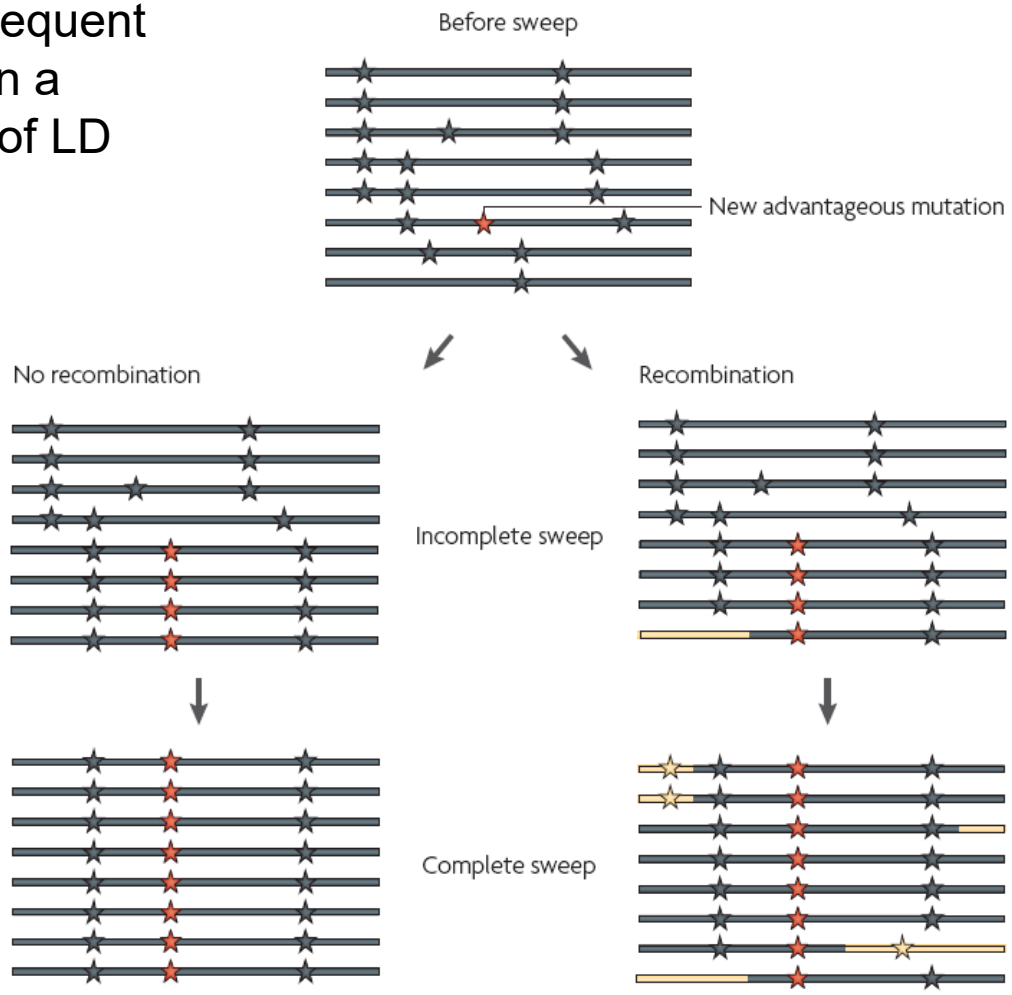


$$D = \frac{1}{4N_e r}$$

Population recombination rate

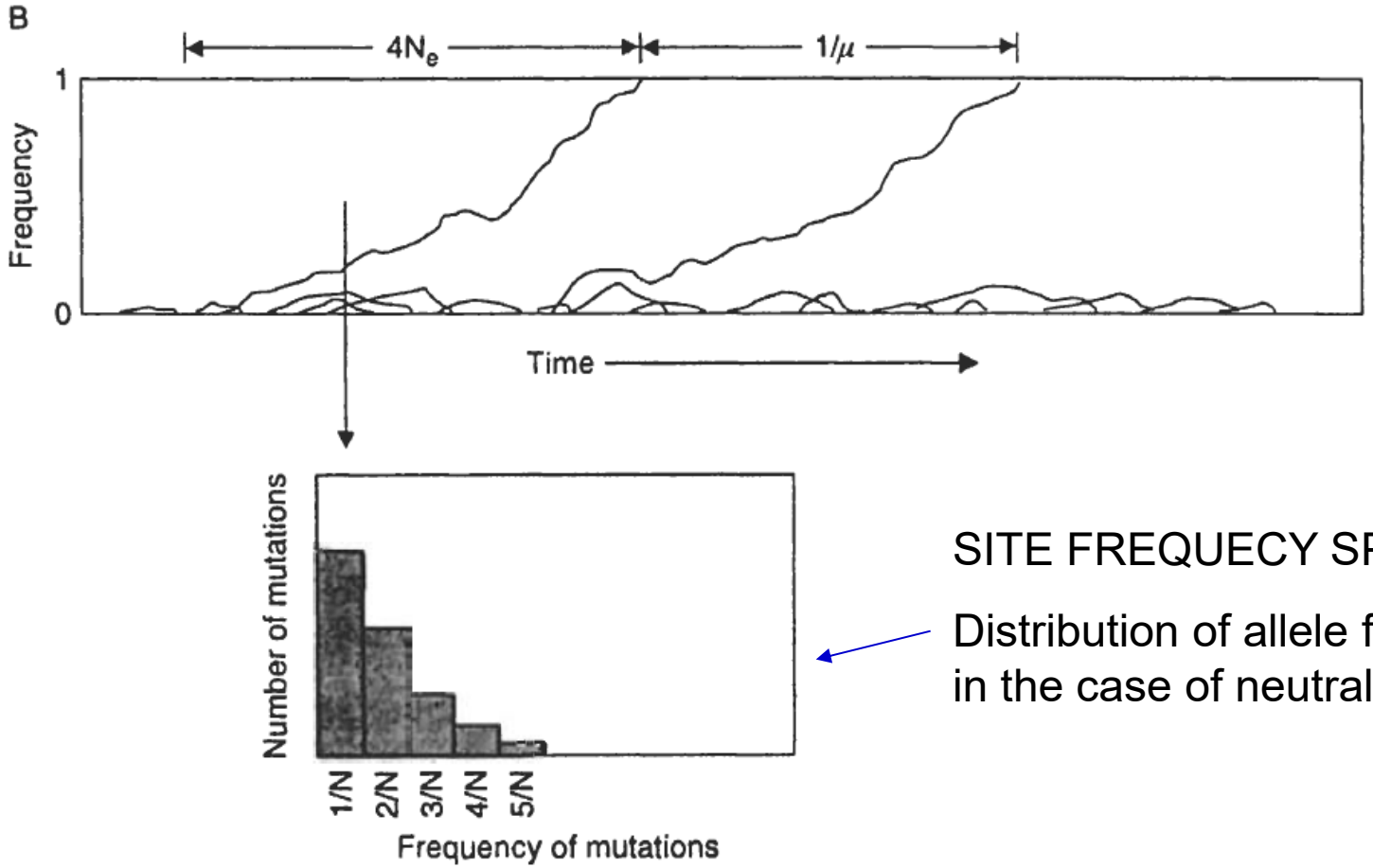
Detection of recent positive selection based on levels of linkage disequilibrium (LD)

- Ideally detection of relatively frequent haplotype (or haplotype fixed in a subpopulation) with high level of LD compared to other haplotypes.



Tajima's D test

- Based on distribution of allele frequencies

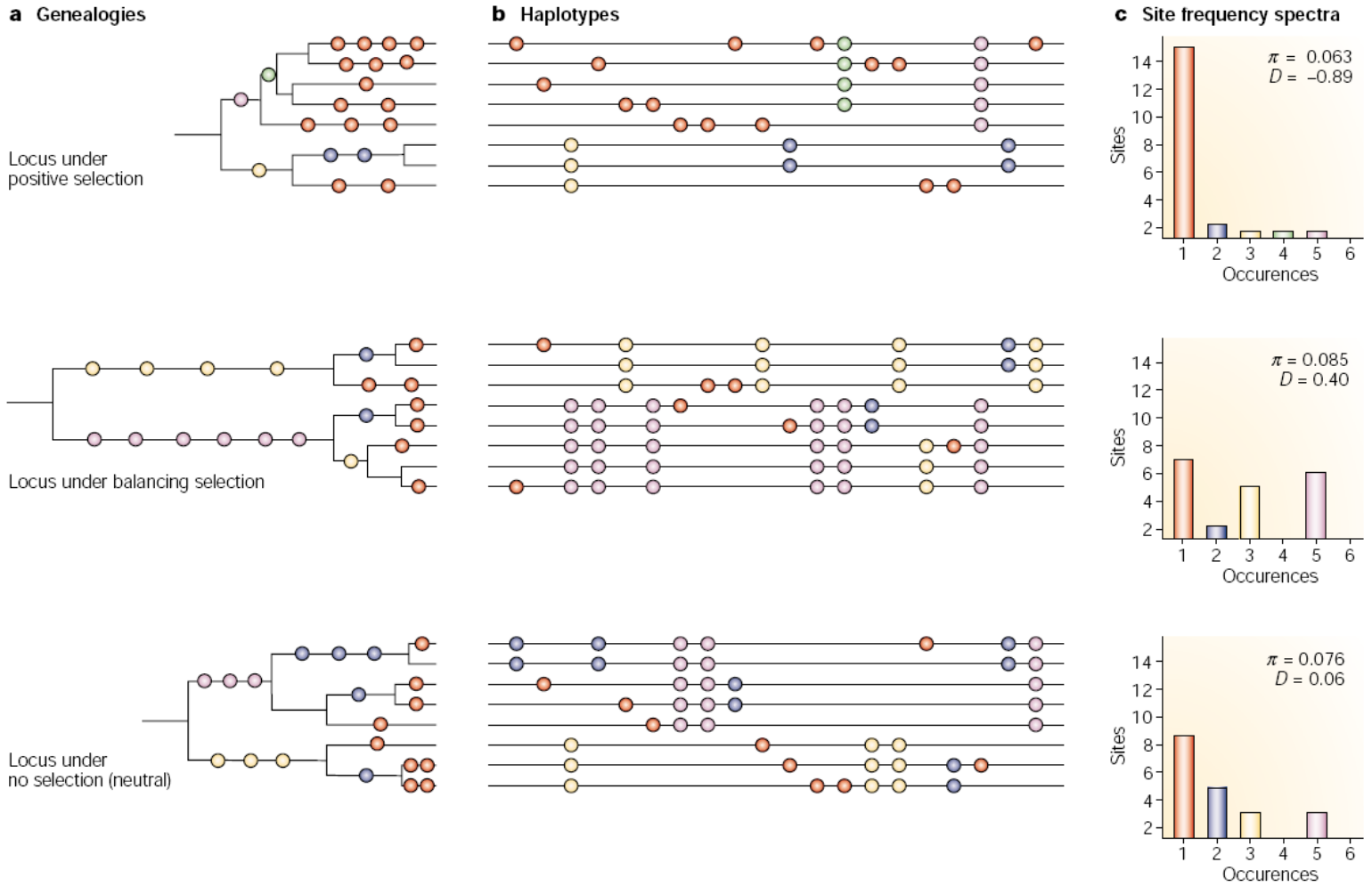


SITE FREQUECY SPECTRUM

Distribution of allele frequencies in the case of neutrality.

Tajima's D test

- Positive and negative selection leads to increased proportion of rare alleles.
  Balancing selection leads to the increased proportion of relatively frequent alleles.



Tajima's D test

- **Tajima's D = (π - θ)/SD (π - θ)**
- For neutral sequences: θ = π. D = 0.
- **Relatively more rare allels θ > π. D < 0. (positive or negative selection)**

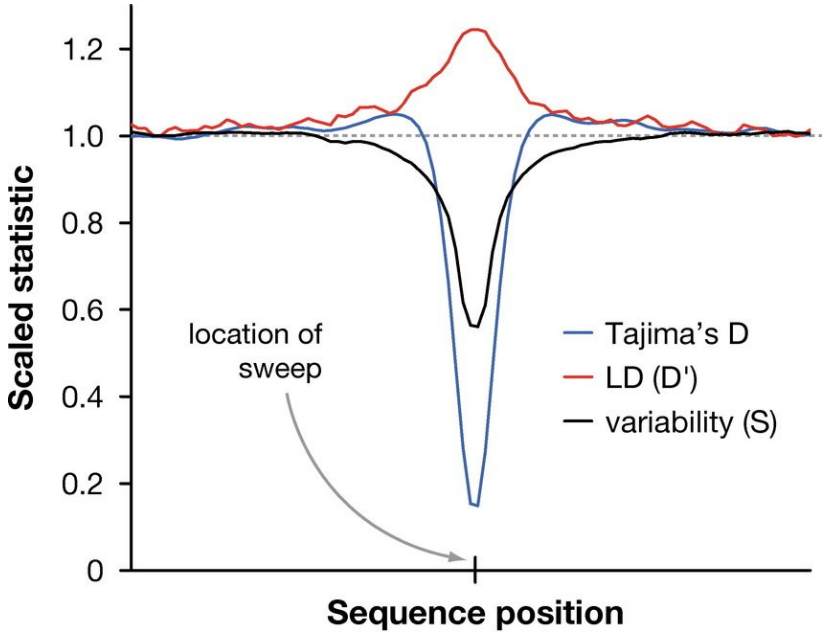
  Relatively more frequent allels π > θ. D > 0. (balancing selection)

Population expansion has similar effect on allele frequency spectrum as positive and negative selection.

Bottle-neck has similar effect as balancing selection.

How to differentiate the effect of selection and demographic factors?

SweepFinder



Nielsen R. 2005.
Annu. Rev. Genet. 39:197–218

RASMUS NIELSEN

SweepFinder

SweepFinder is a program implementing the method described in Nielsen et al. 2005. Genomic scans for selective sweeps using SNP data. Genome Research 1566-1575. It can be used to detect the location of a selective sweep based on SNP data. It will also estimate the frequency spectrum of observed SNP data in the presence of missing data.

MOLECULAR ECOLOGY

Molecular Ecology (2016) **25**, 142–156 doi: 10.1111/mec.13351

DETECTING SELECTION IN NATURAL POPULATIONS: MAKING SENSE OF GENOME SCANS AND TOWARDS ALTERNATIVE SOLUTIONS

Detecting recent selective sweeps while controlling for mutation rate and background selection

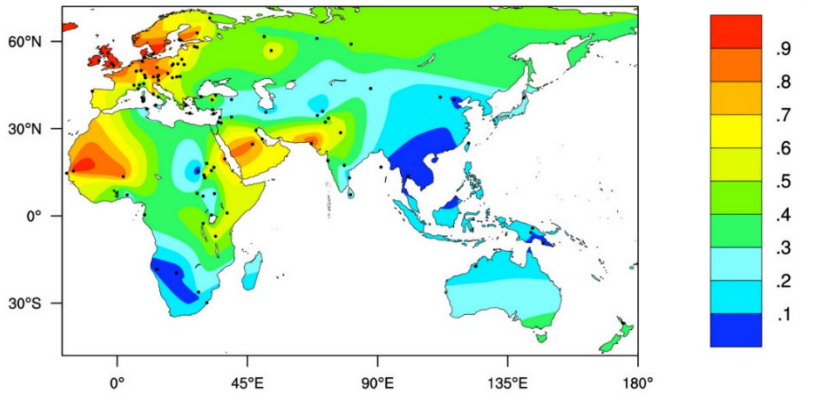
CHRISTIAN D. HUBER,*†‡ MICHAEL DEGIORGIO,§¶ INES HELLMANN** and RASMUS NIELSEN††

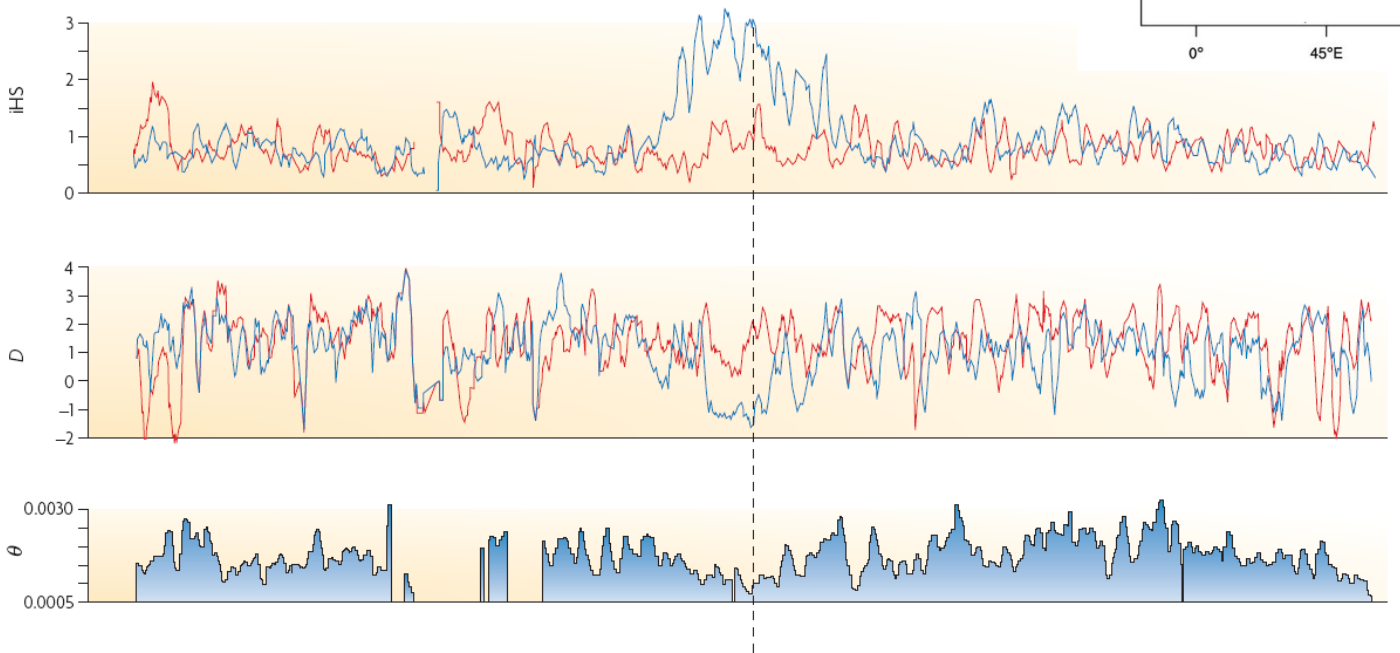
Selective sweeps in human genome

Lactase persistence

- Several independent mutations in LCT gene, allows digestion of milk in adulthood.
- Connected with the spread of parstoral farming.
- s ~1,4-15%

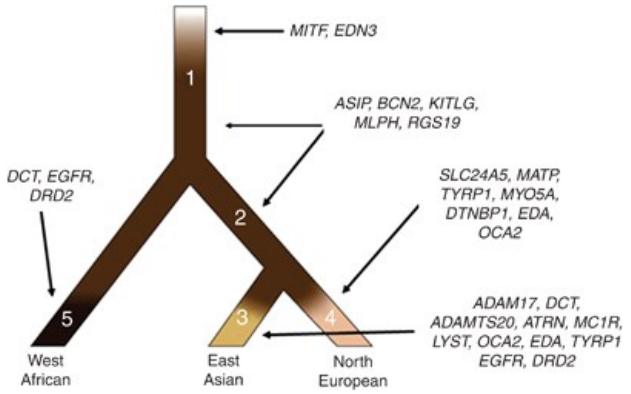
Occurrence of lactase persistence





Skin color

- Genes affecting skin color in humans: HERC2, SLC45A2, TYR
- Selection for lighter skin in Europe.
- s ~ 2–10%



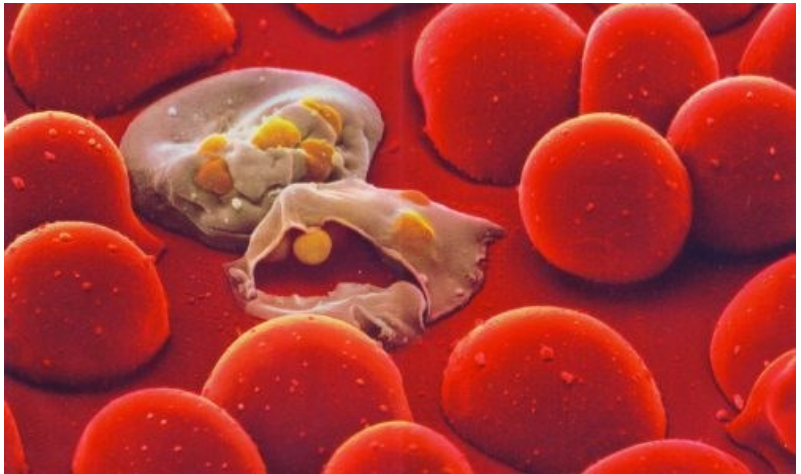
Source: Chaplin G.©, *Geographic Distribution of Environmental Factors Influencing Human Skin Coloration*, American Journal of Physical Anthropology 125:292–302, 2004; map updated in 2007.

Local adaptations

Inuits in Greenland

- Selective sweeps around genes FADS1, FADS2. Desaturases, metabolism of fatty acids.

Resistance against malaria



- Mutations in genes GYPA and GYPB coding for receptors on the red blood cells, *Plasmodium falciparum* uses to get into the cells.

Detection of genes for local adaptations based on levels of genetic differentiation

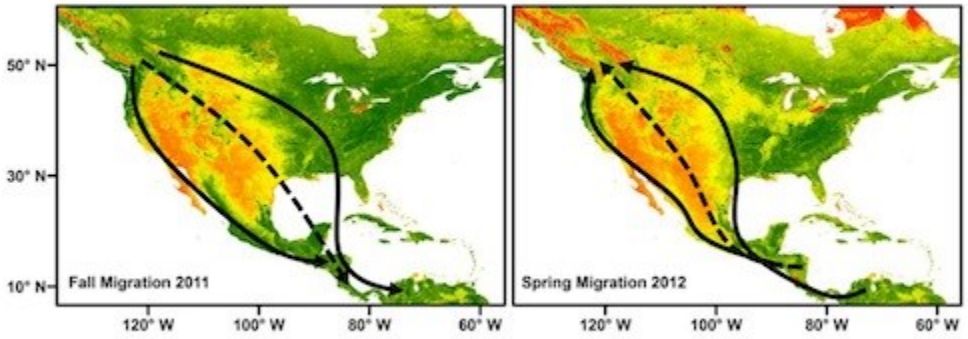
- Genes for local adaptations have increased levels of genetic differentiation (F_{ST}) between populations.

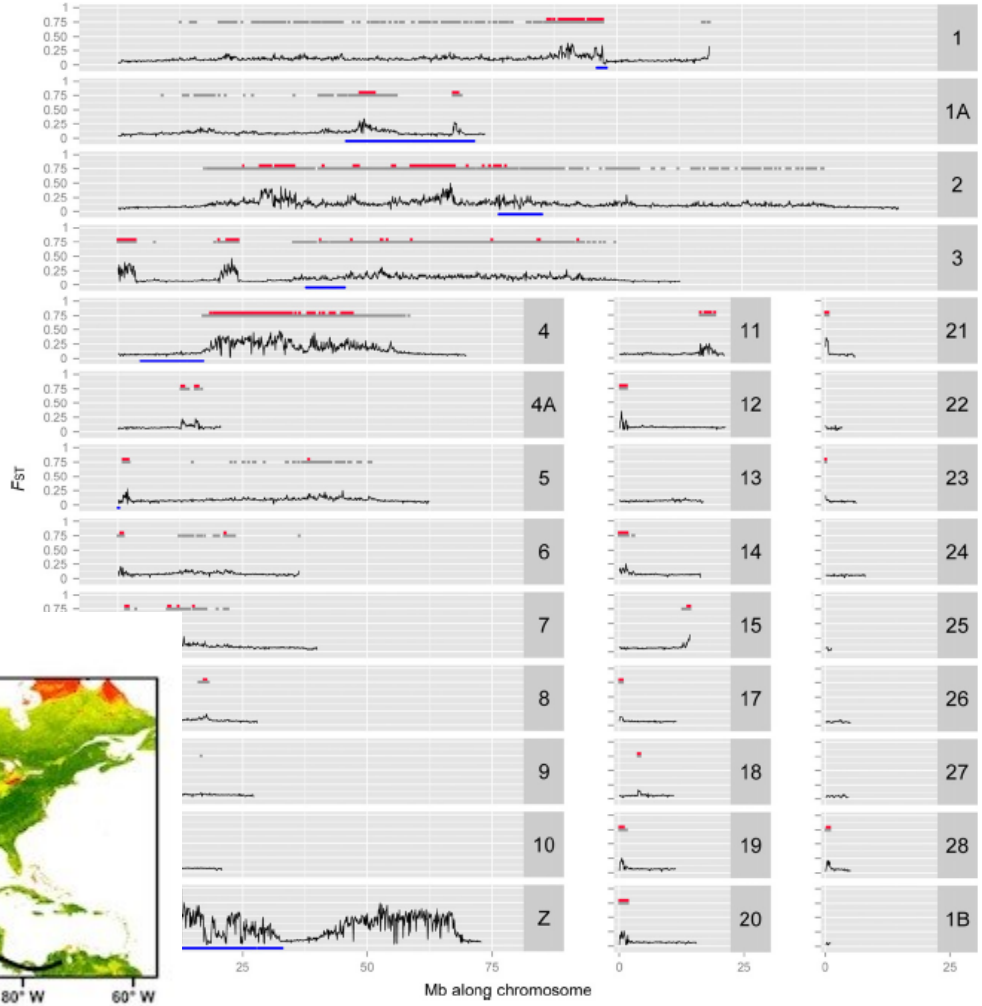
Genomic islands of increased F_{ST}

- Positive selection leads to incresed differences in allele frequencies between populations.

Islands of differentiation in Swainson's thrush

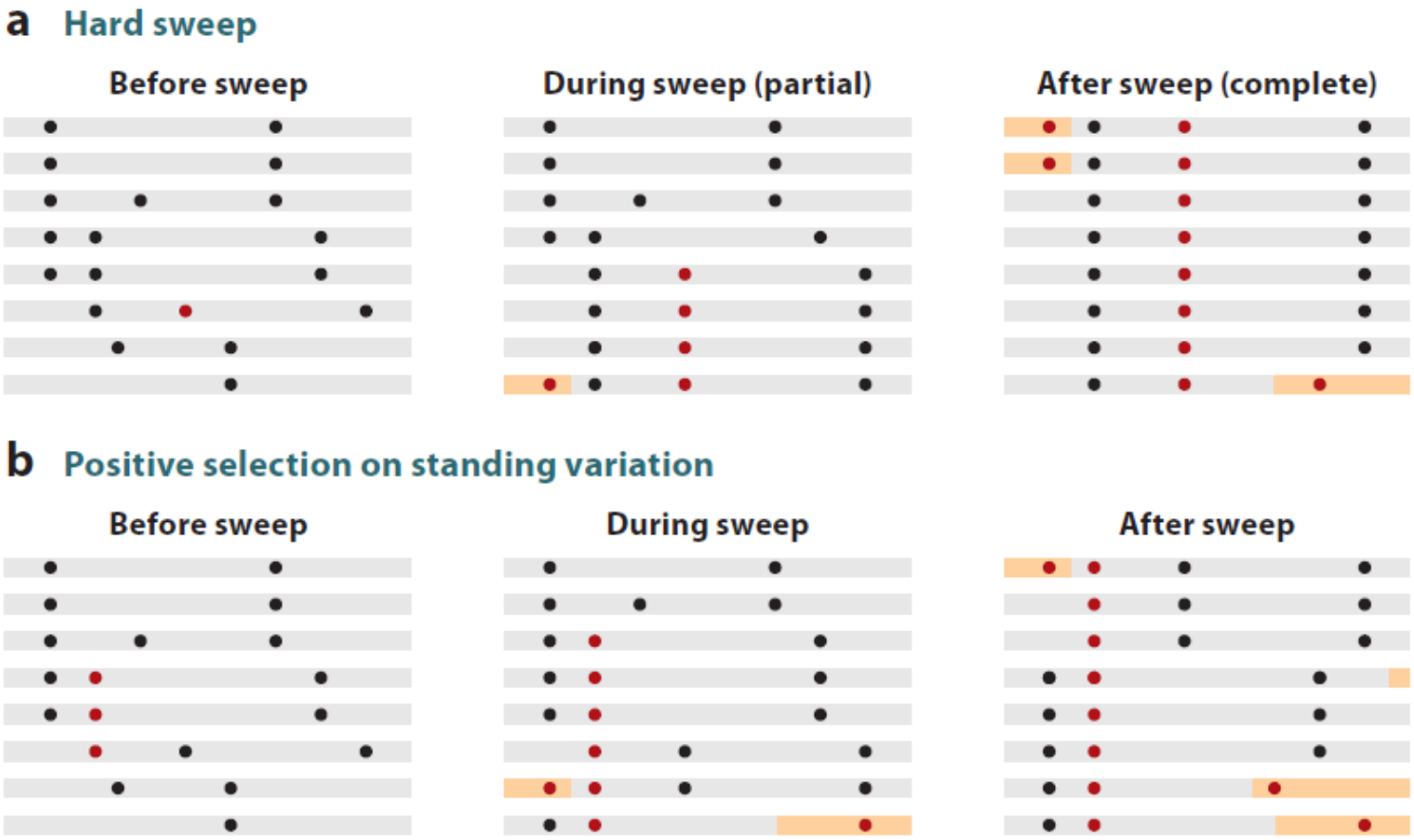
- Different migration routes





Delmore et al. 2015

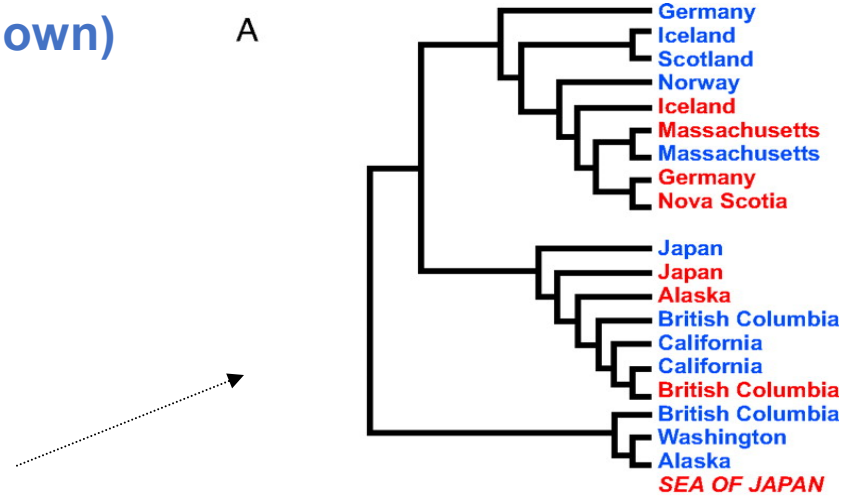
Adaptation from standing genetic variation (soft selective sweep)



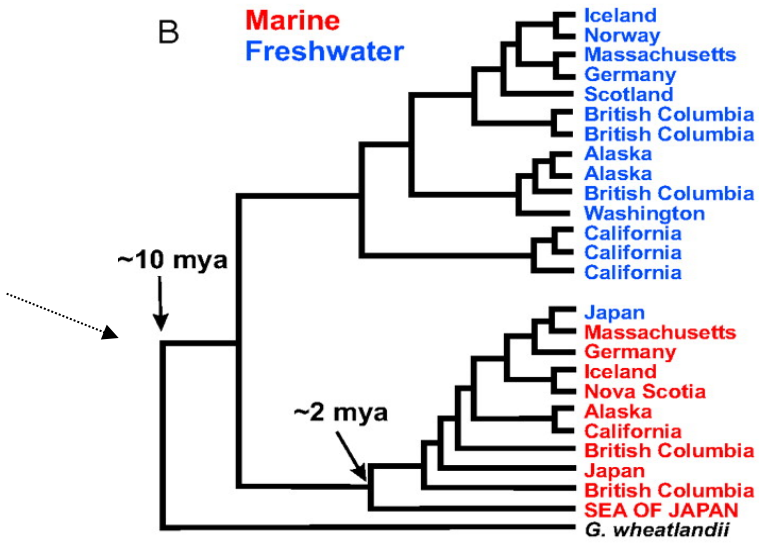
Fu and Akey, 2013

Adaptation from standing genetic variation and paralel evolution

Three spine stickleback
marine form (up) a **freshwater form (down)**



- Freshwater form arose multiple times independely by colonization of new rivers.

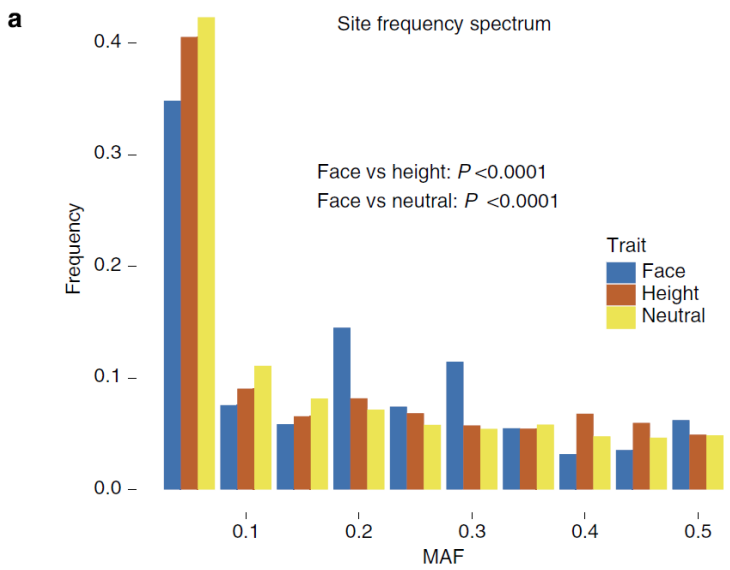


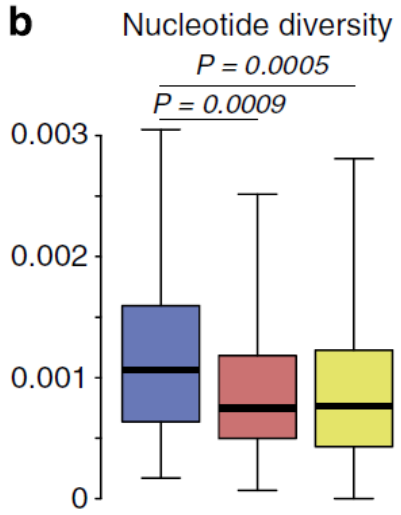
- Phylogeny based on *Ectodisplasin* (*Eda*) gene underlying some differences between forms.
- The same pattern holds for other genes underlying phenotypic differences between forms. These genes often in inversions.

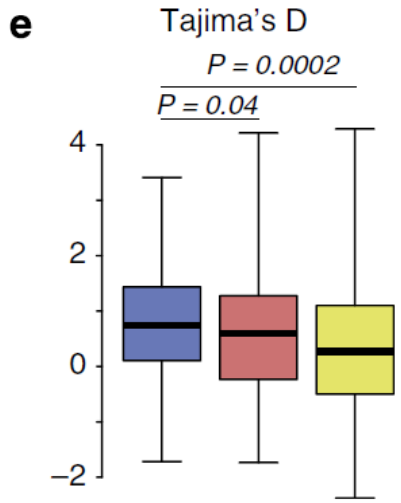
Jones et al. Nature. 2012

Balancing selection

Maintains variability in human faces





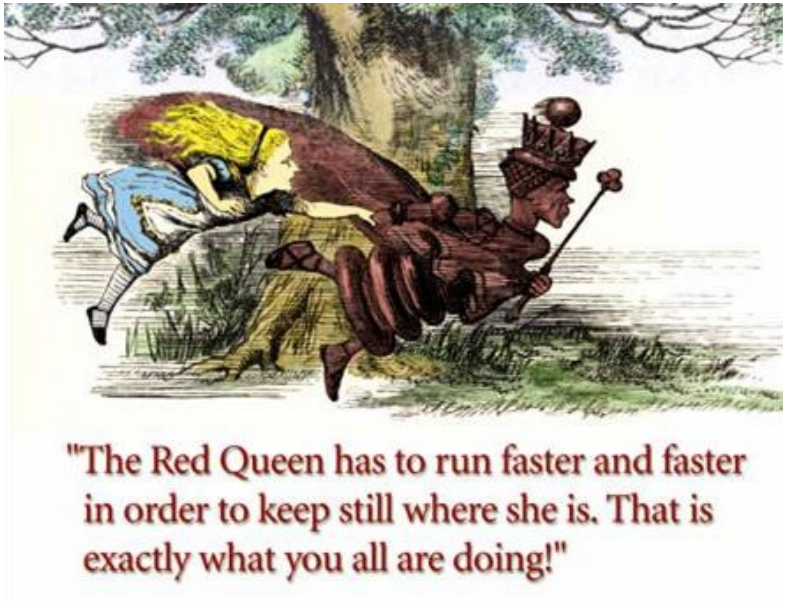


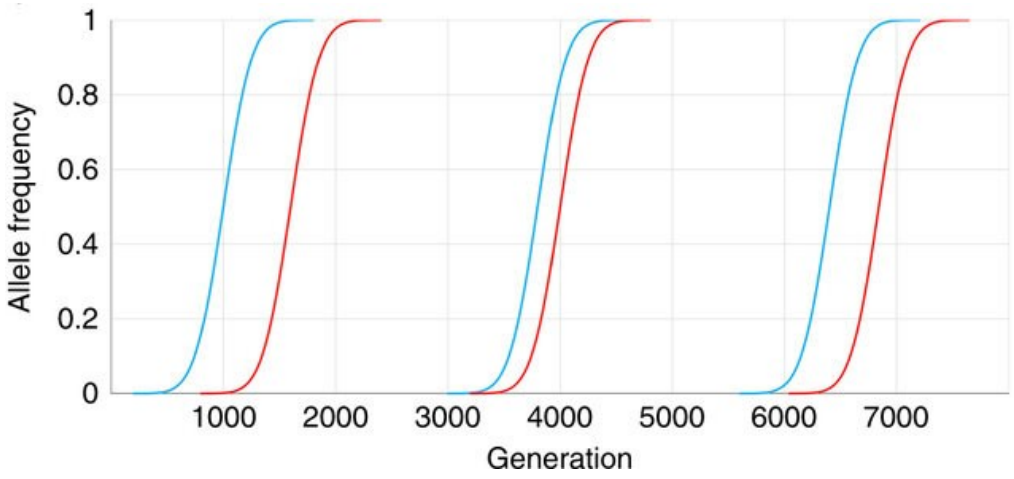
Sheeman and Nachman. 2014. Nature.

Detection of reccurent positive selection

Repeated fixation of advantageous mutations in the same locus increases the ratio between non-synonymous substitutions (K_A) and synonymous substitutions (K_S).

$K_A/K_S = 1$ neutral evolution
$K_A/K_S > 1$ positive selection





Detection of long-term negative selection

Longterm negative selection decreases the ratio between non-synonymous substitutions (K_A) and synonymous substitutions (K_S).

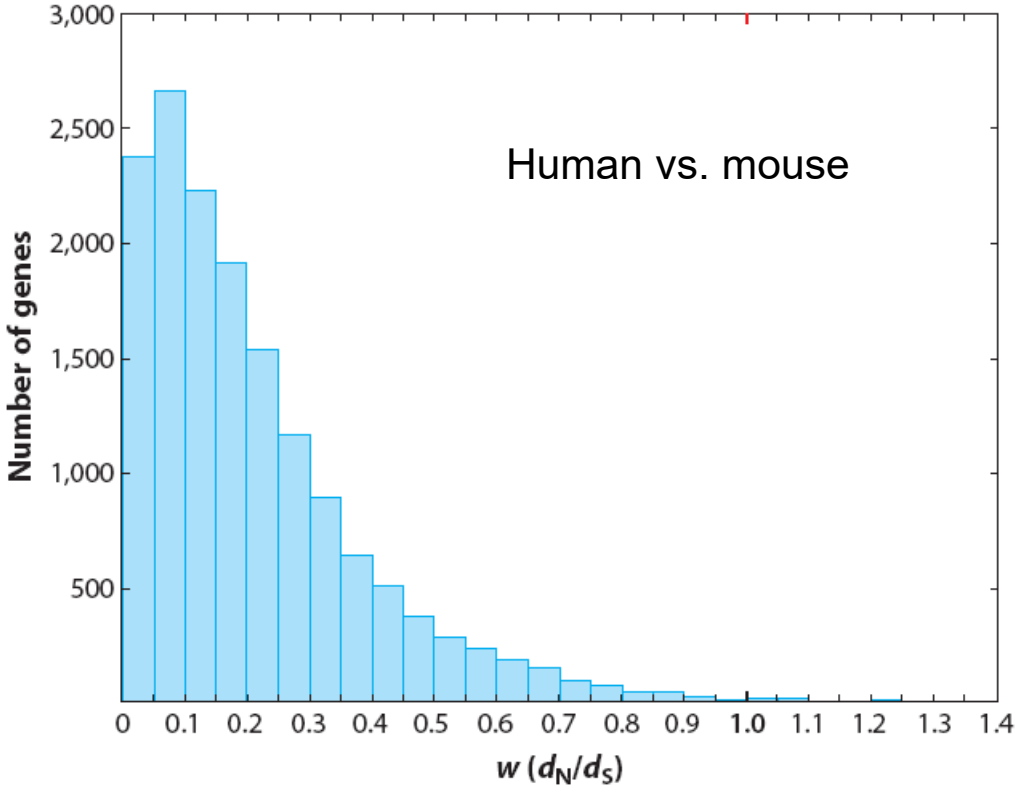
$K_A/K_S = 1$ neutral evolution
$K_A/K_S < 1$ negative selection

Ultra conserved genetic elements: extremely low substitution rate for non-synonymous substitutions.

K_A/K_S test (d_N/d_S test)

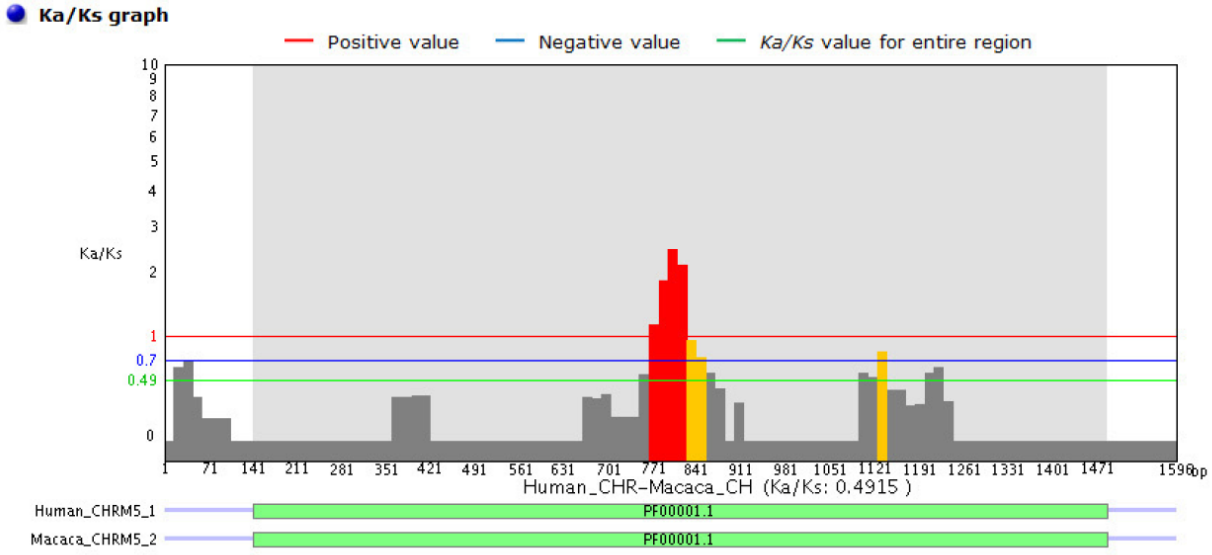
- Most genes have K_A/K_S <<1.
  Under negative selection.

- Genes with high K_A/K_S often associated with **reproduction**, **imunity**, in mammals in **olfactory sense** (e.g. OBP genes).



K_A/K_S test – site specific analysis

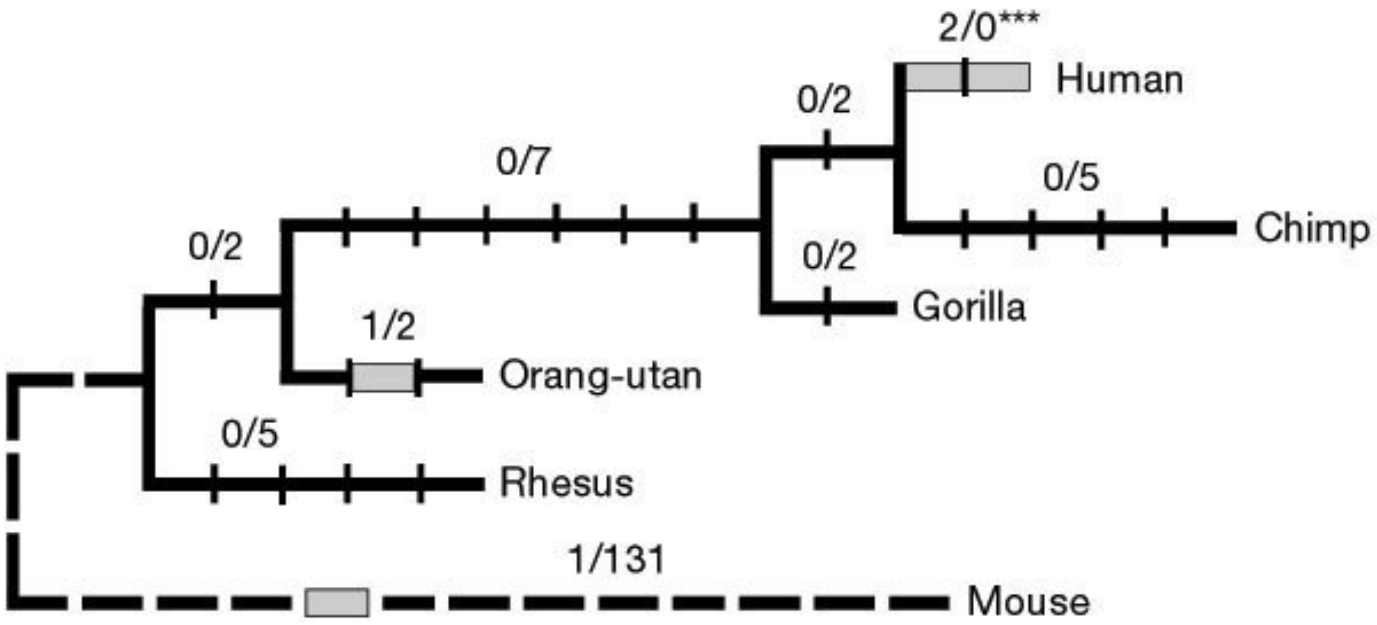
- Sliding window analysis – allows to calculate K_A/K_S for different parts of the genes.
- K_A/K_S can be calculated for individual codons if we compare multiple species.



K_A/K_S test – lineage specific analysis

FOXP2 gene for speach, positive selection in human lineage

No. of nonsynonymous/ synonymous substitutions.



Enard W. 2002. Nature

McDonald-Kreitman (MK) test

- Compares numbers of nonsynonymous and synonymous substitutions within species (P) and between species (D) for individual genes.
- Neutral genes Ds/Ps = Dn/Pn.
- Positively selected genes Dn/Pn >> Ds/Ps.

	D	P
Synonymous	Ds	Ps
Nonsynonymous	Dn ↑	Pn

Positive selection

MK test allows to estimate proportion of aminoacid substitutions driven by positive selection (α).

Organisms with higher Ne have higher α.
Selection in larger populations is more efficient.

- Drosophila (Ne ~ 10^6) α > 50%
- Mus musculus castaneus (Ne ~ 5 x 10^5) α ~ 40-60%
- Populus tremula (Ne ~ 10^5) α ~ 30-40%
- Mus musculus domesticus (Ne ~ 10^5) α ~ 13%
- Human (Ne ~ 10^4) α ~ 10 – 20%

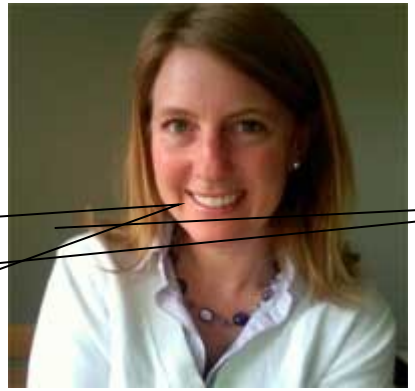
Genetic basis of adaptations

Importance of coding vs. regulatory changes

Sean B. Carroll

Mutations in regulatory regions of genes are more important.

Most so far detected mutations underlying adaptations are in coding regions of the gene.



Hopi E. Hoekstra

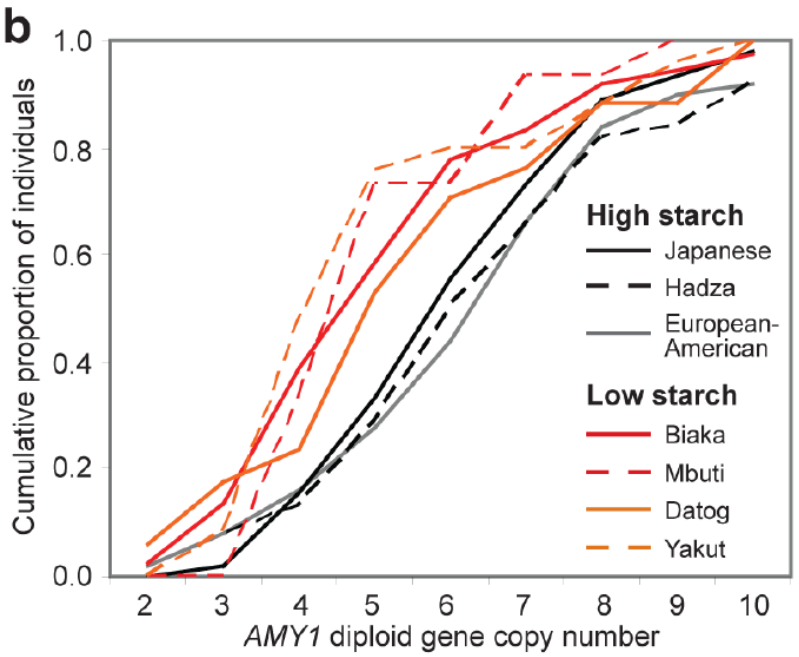
Jerry A. Coyne

Hoekstra HE and Coyne JA (2007).
The locus of evolution:evo devo and the genetics of adaptation. *Evolution.*

Adaptive evolution by gene duplications

Salivary amylase gene (*AMY1*)

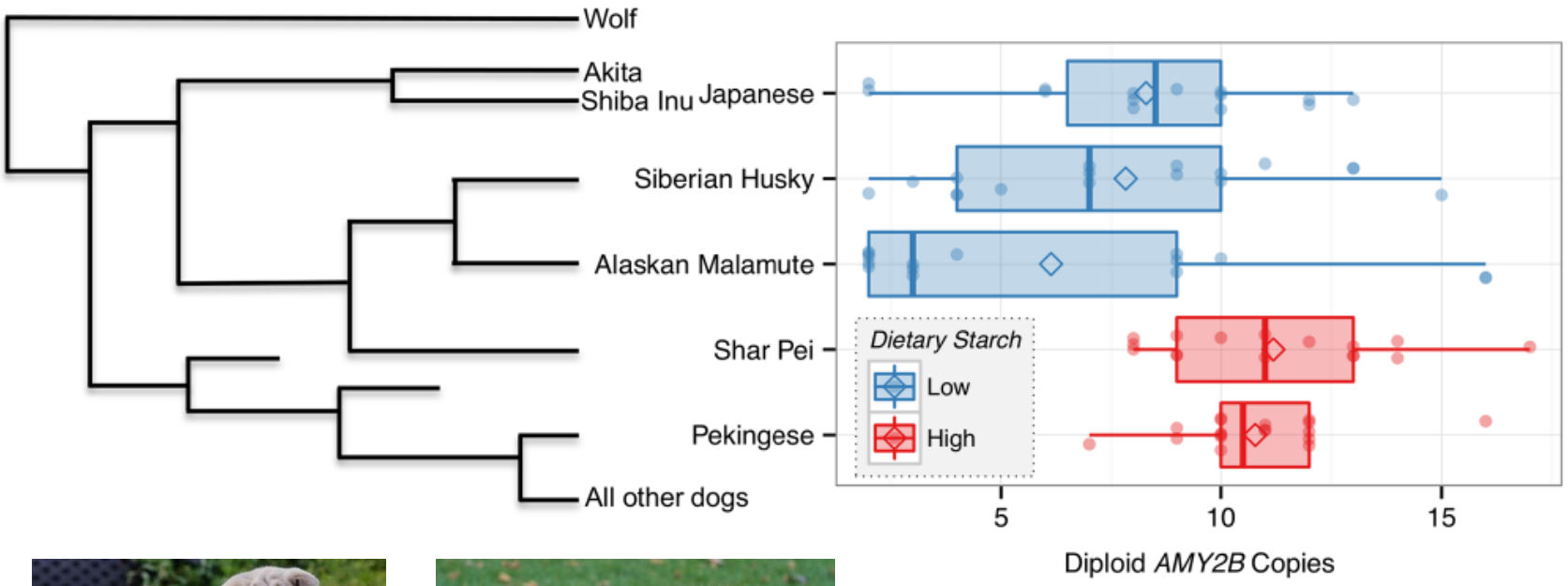
- Digest starch.
- One of the most variable gene in terms of gene copies in the genome.
- More copies of AMY1 gene more amylase enzyme in saliva.
- Populations with starch rich diet have higher number of AMY1 gen copies.



Perry et al. 2007, Nature Genetics

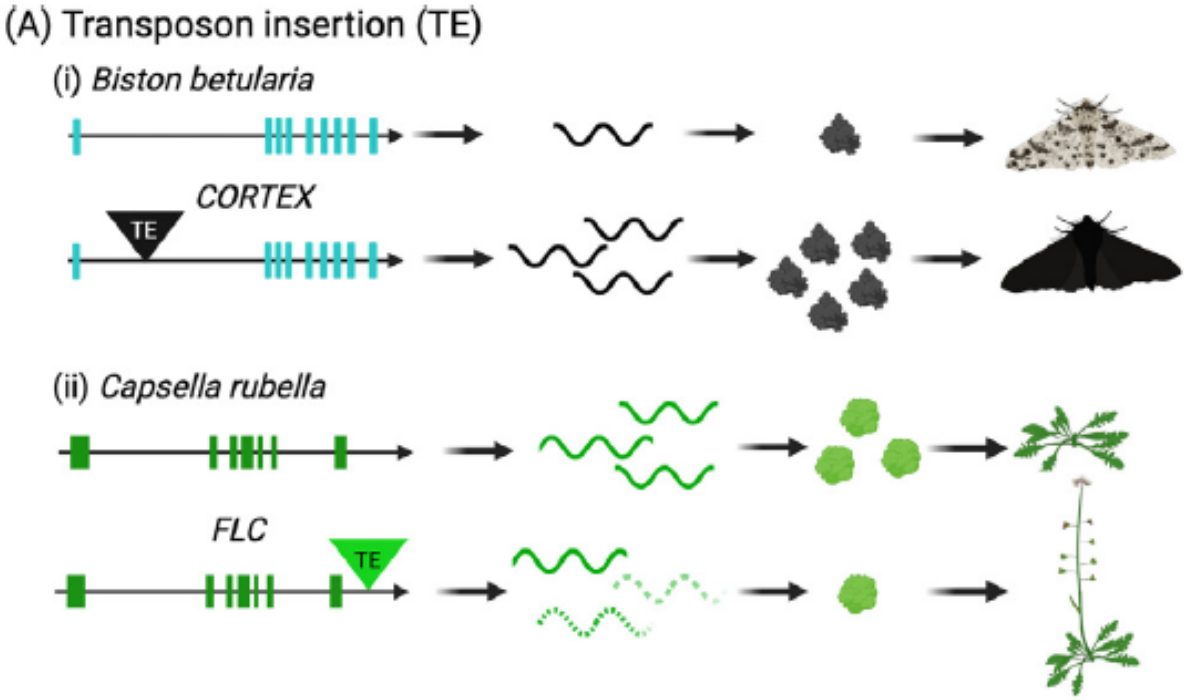
Number of AMY2B amylase gene copies is related to the diet of domestic dogs



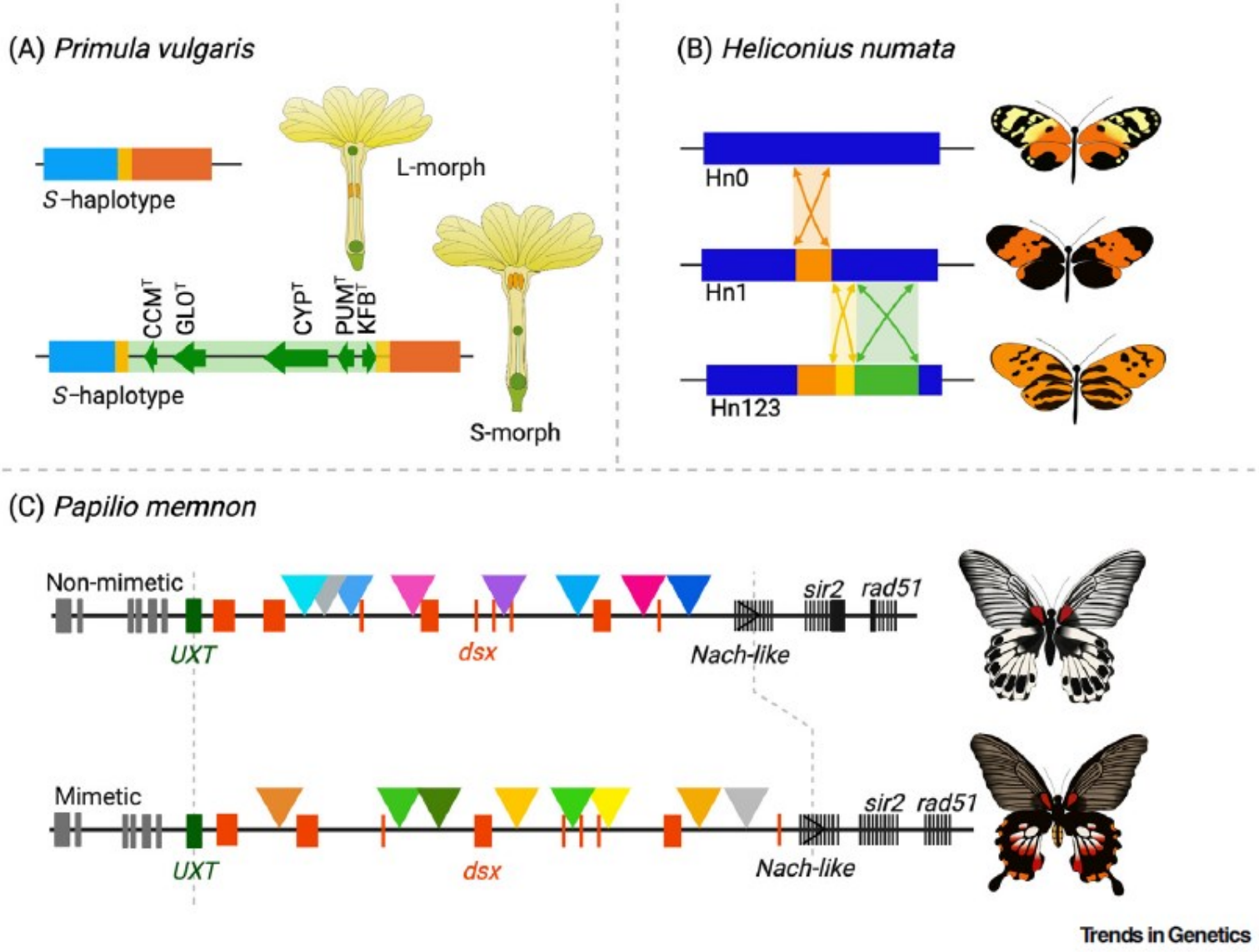

Reiter et al. 2016

The role of structural variations in adaptations



The role of structural variations in adaptations

Supergenes



Trends in Genetics

Adaptations underlied by epigenetic changes

nature ecology & evolution

ARTICLES

https://doi.org/10.1038/s41559-018-0569-4

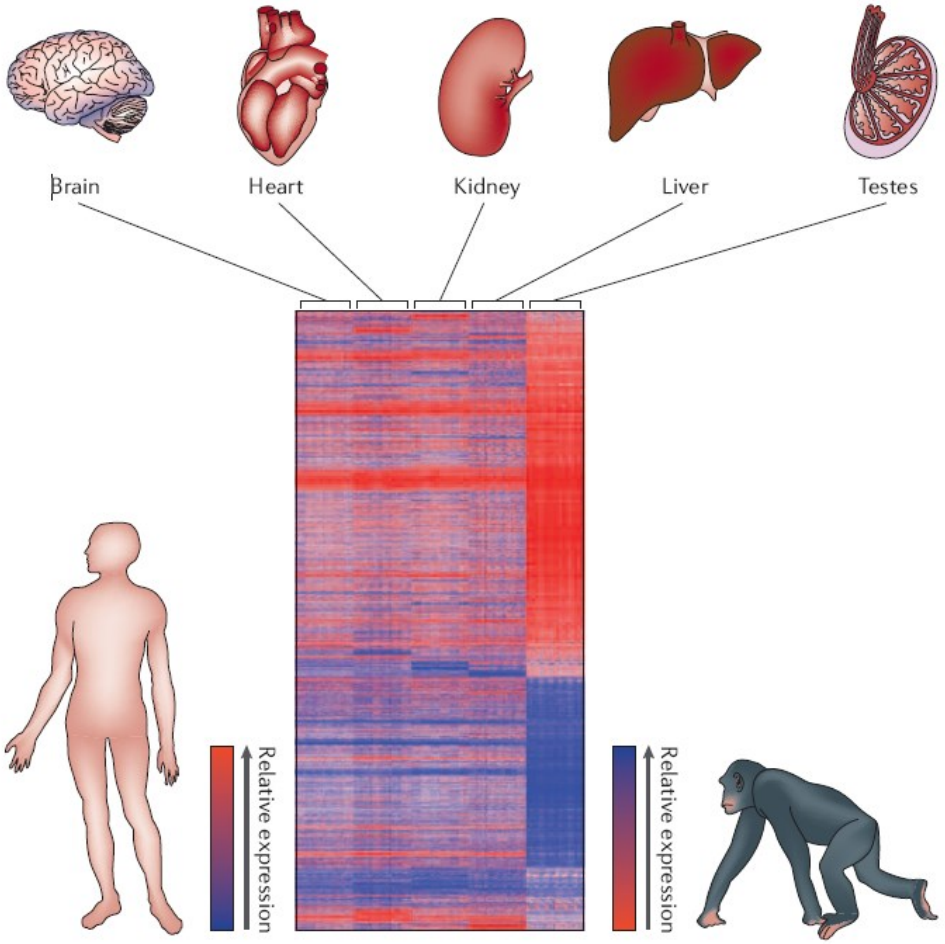
An epigenetic mechanism for cavefish eye degeneration

Aniket V. Gore[1*], Kelly A. Tomins[1], James Iben[2], Li Ma[3], Daniel Castranova[1], Andrew E. Davis[1], Amy Parkhurst[1], William R. Jeffery[3] and Brant M. Weinstein[1*]

Coding and non-coding mutations in DNA contribute significantly to phenotypic variability during evolution. However, less is known about the role of epigenetics in this process. Although previous studies have identified eye development genes associated with the loss-of-eyes phenotype in the Pachón blind cave morph of the Mexican tetra *Astyanax mexicanus*, no inactivating mutations have been found in any of these genes. Here, we show that excess DNA methylation-based epigenetic silencing promotes eye degeneration in blind cave *A. mexicanus*. By performing parallel analyses in *A. mexicanus* cave and surface morphs, and in the zebrafish *Danio rerio*, we have discovered that DNA methylation mediates eye-specific gene repression and globally regulates early eye development. The most significantly hypermethylated and downregulated genes in the cave morph are also linked to human eye disorders, suggesting that the function of these genes is conserved across vertebrates. Our results show that changes in DNA methylation-based gene repression can serve as an important molecular mechanism generating phenotypic diversity during development and evolution.

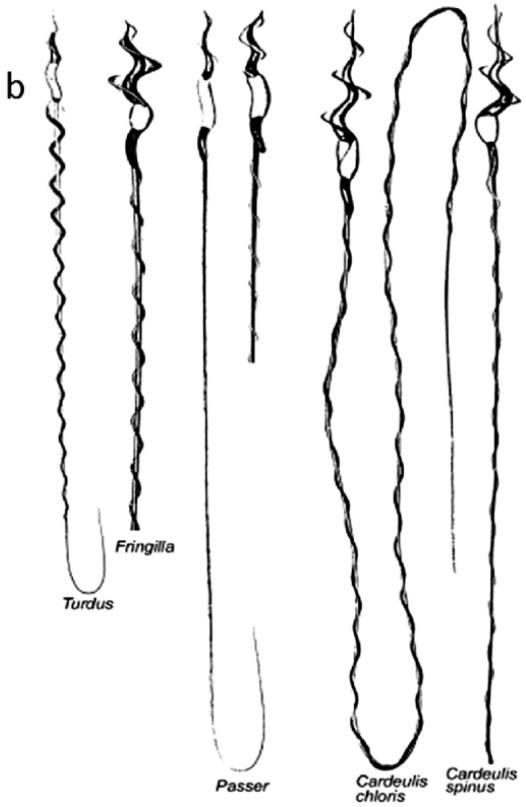
How to detect positive selection in gene expression data?

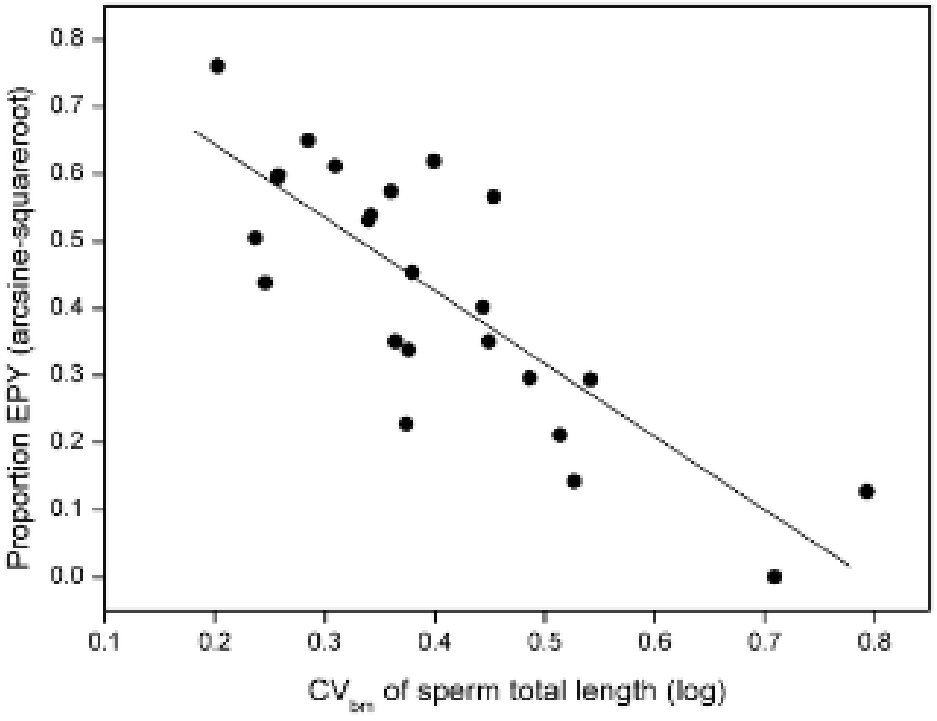
- Relatively higher divergence in expression between species compared to variability in expression within species.
- Expression in testes show cca 3-times higher divergence compared to variability within species than somatic tissues.



Khaitovich et al. 2006. Nat Rev Genet

Sperm Length Variation as a Predictor of Extrapair Paternity in Passerine Birds

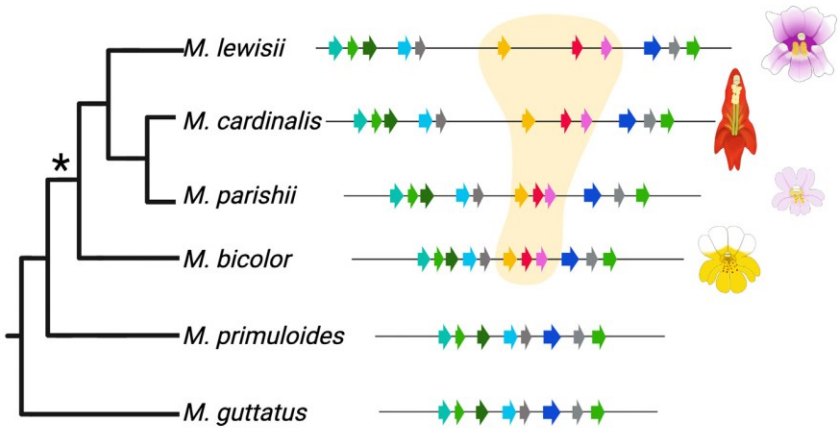




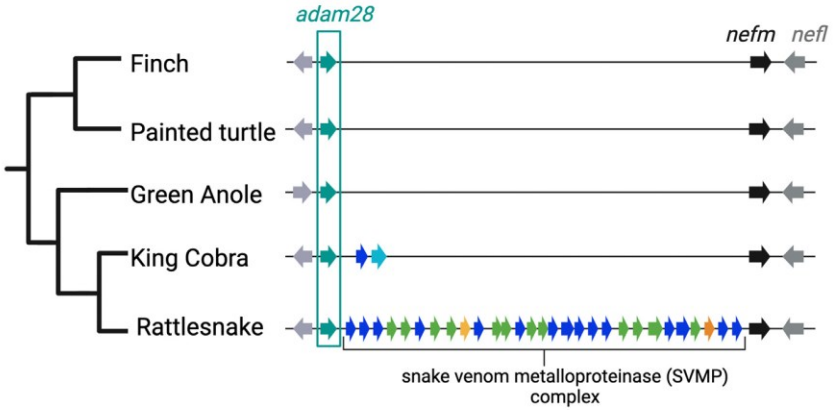
Lifjeld et al. 2010

Taxon-specific genes underlying adaptive traits

(A) *YUP-SOLAR-PELAN* in *Mimulus*



(B) Snake venom metalloproteinase (SVMP) genes in *Crotalus*



(C) Antifreeze glycoprotein (*AFGP*) genes in Antarctic notothenioid fish