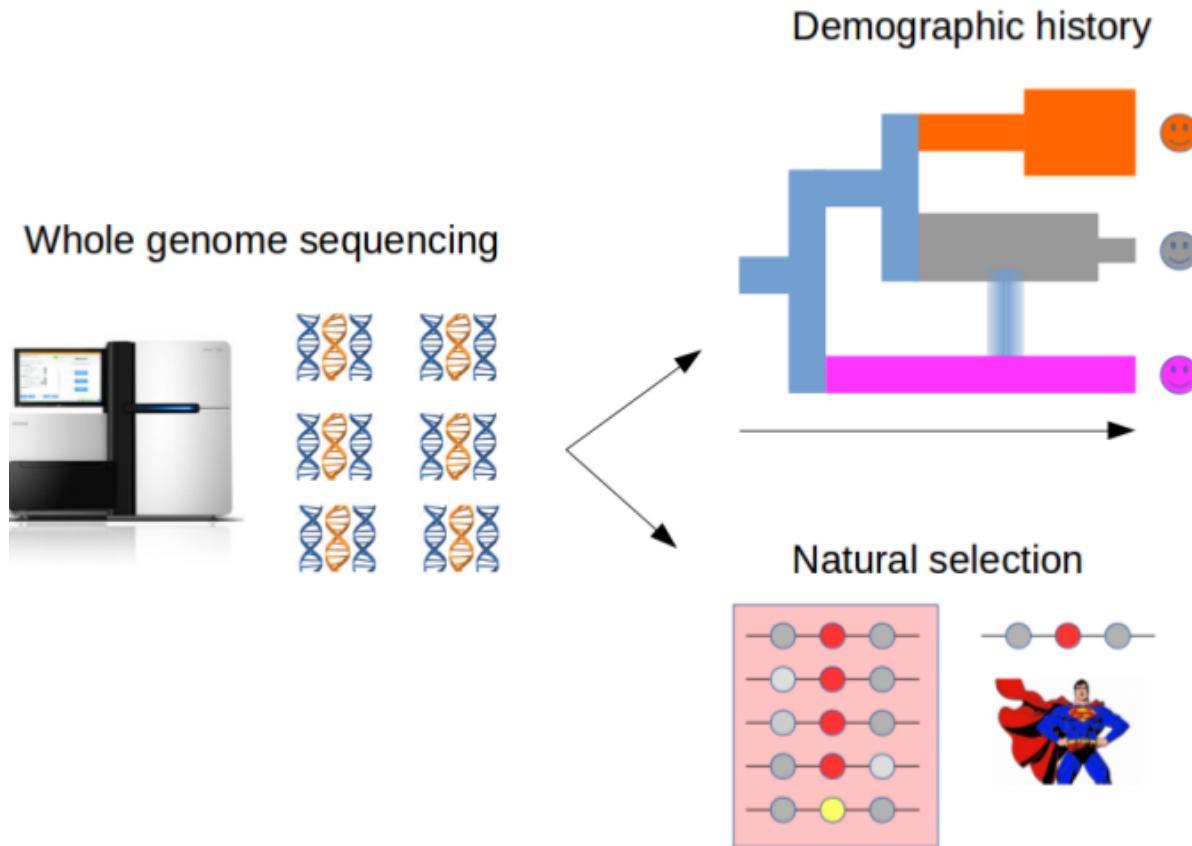


Detecting natural selection from (low depth) genomic data

Matteo Fumagalli

August 10th 2018

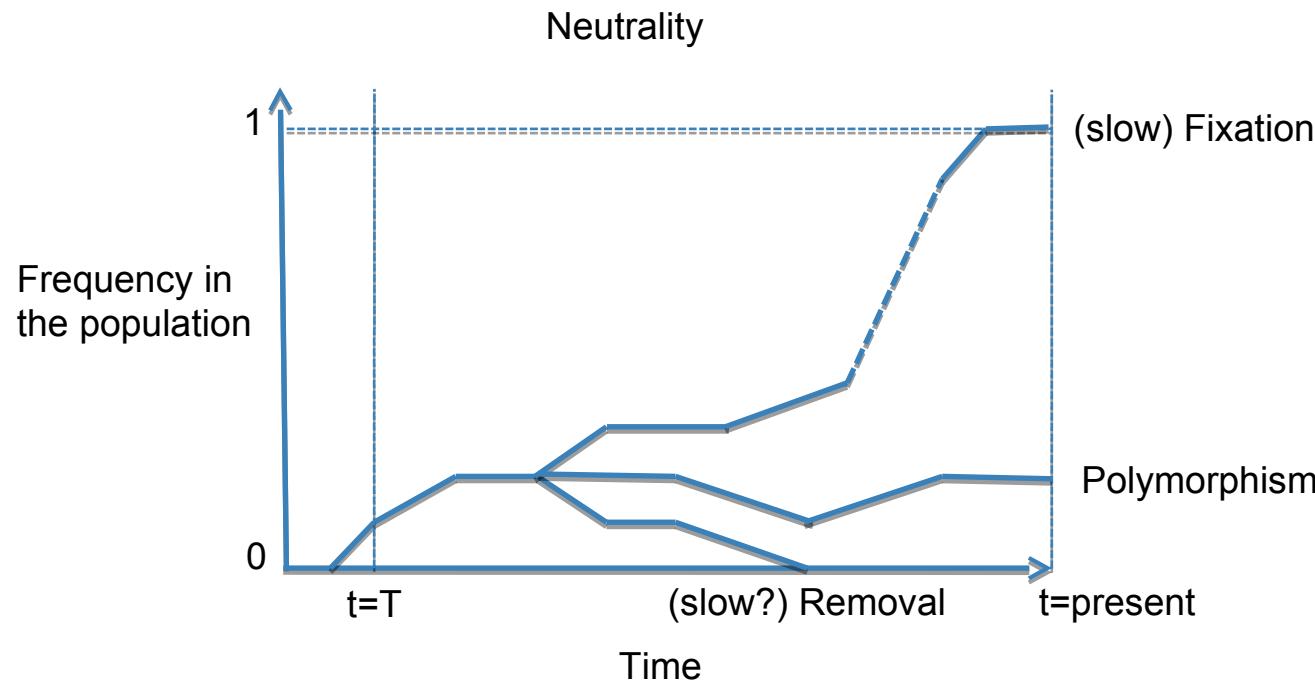
Bioinformatics for Adaptation



Natural selection

Heritable traits that increase the fitness of the become more common.

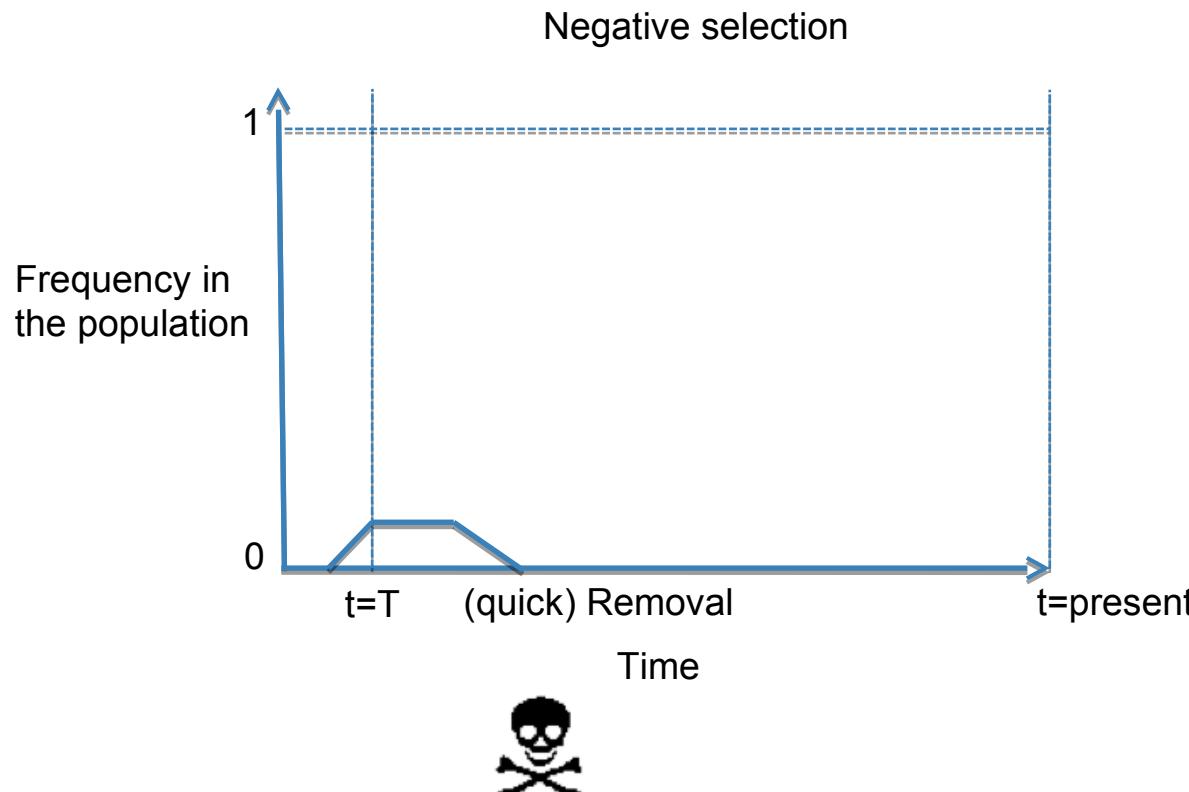
- 1) Mutations arise randomly and evolve according to their effect on the fitness of the carrier



Natural selection

Heritable traits that increase the fitness of the become more common.

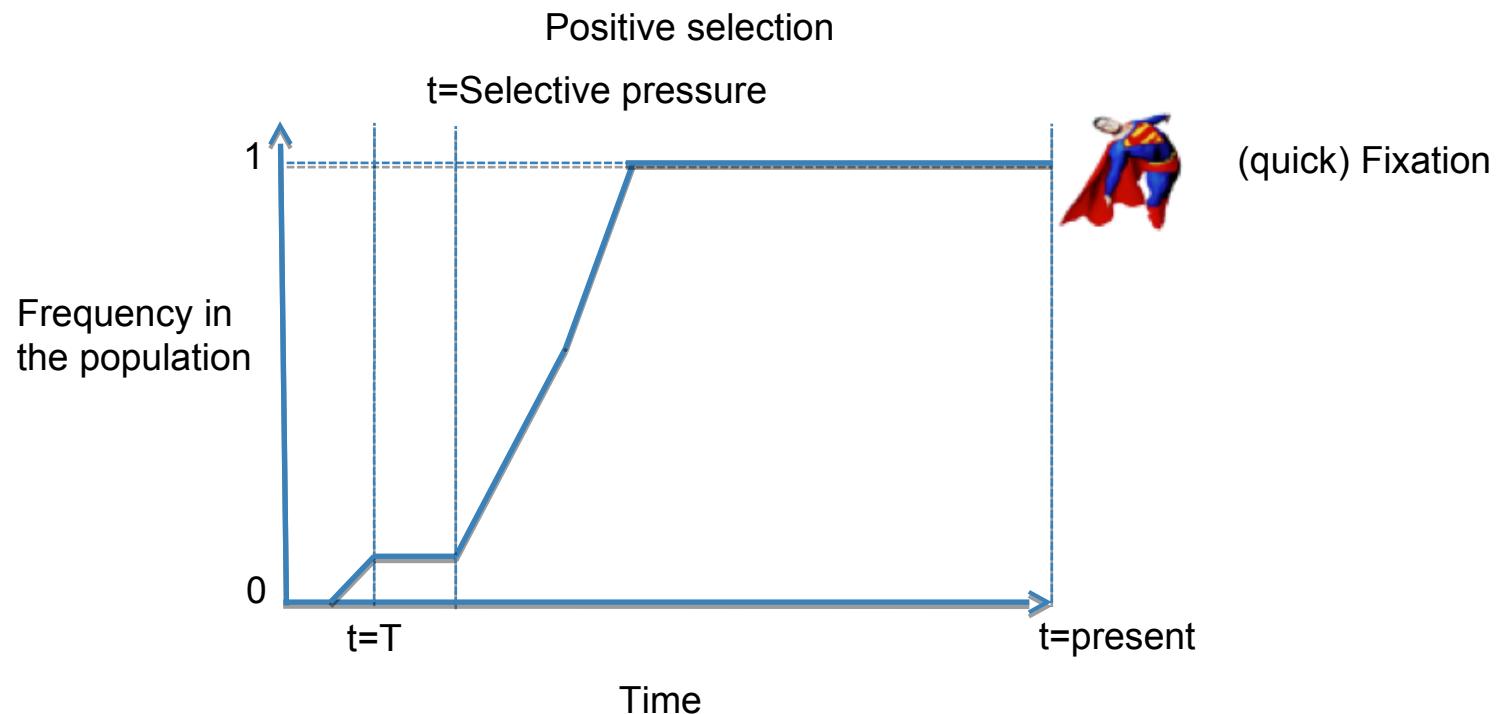
- 1) Mutations arise randomly and evolve according to their effect on the fitness of the carrier



Natural selection

Heritable traits that increase the fitness of the become more common.

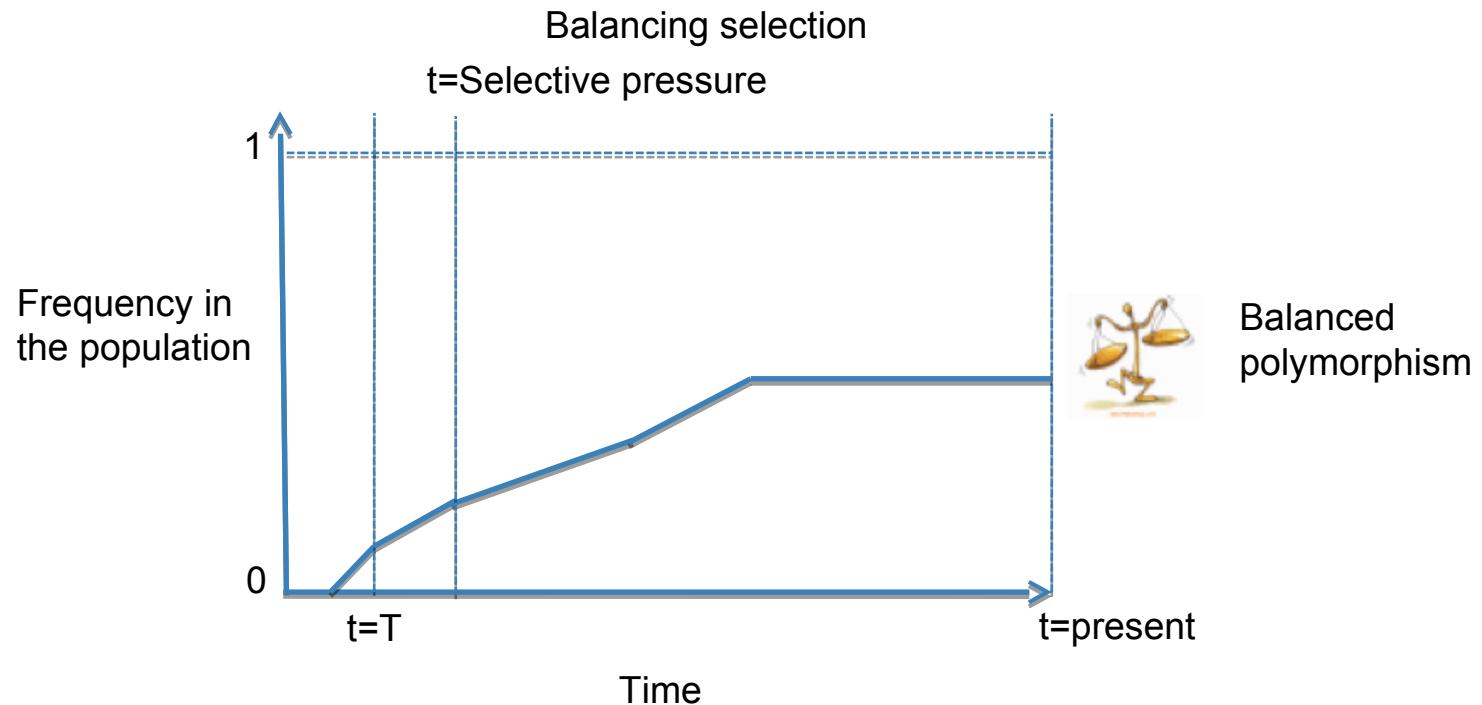
- 1) Mutations arise randomly and evolve according to their effect on the fitness of the carrier



Natural selection

Heritable traits that increase the fitness of the become more common.

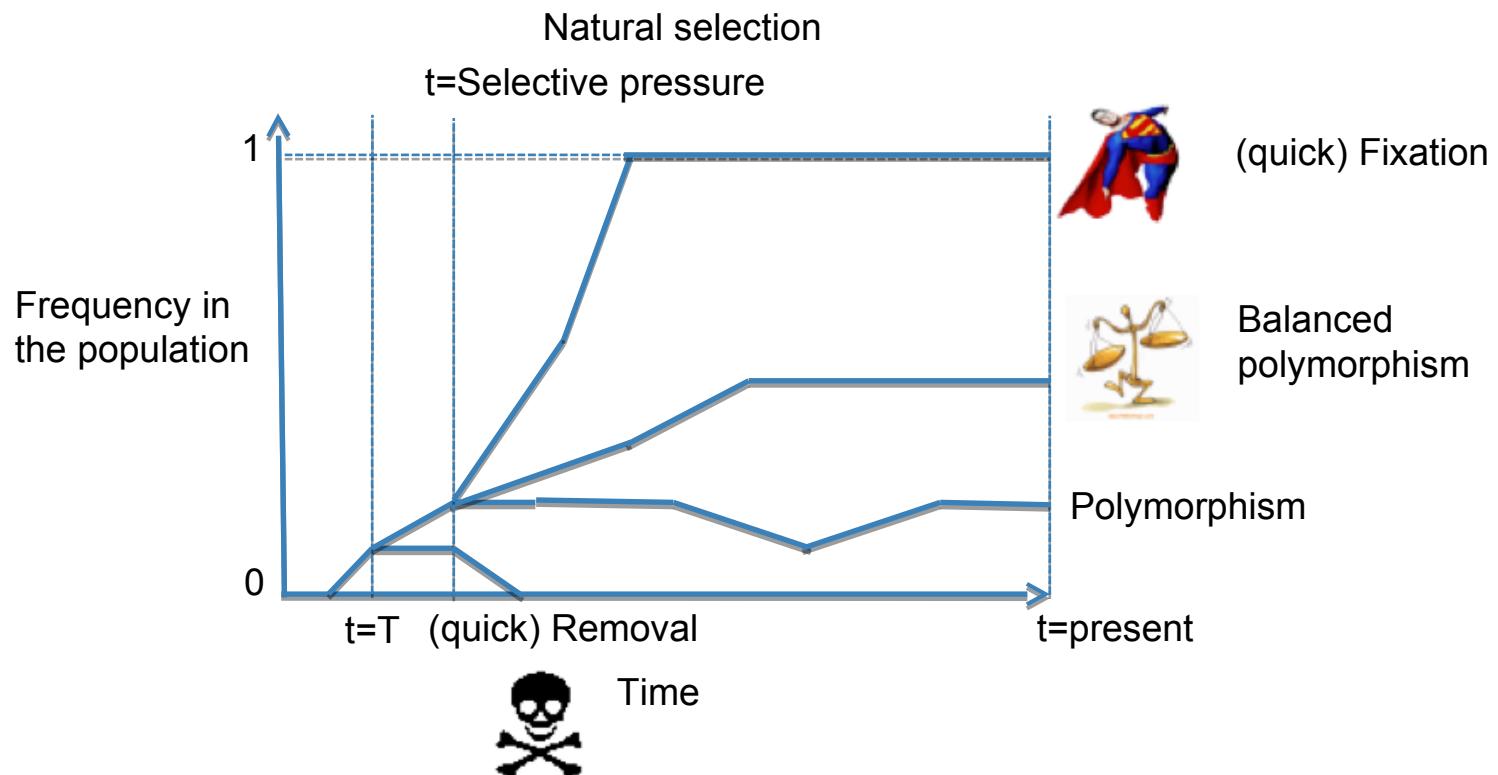
- 1) Mutations arise randomly and evolve according to their effect on the fitness of the carrier



Natural selection

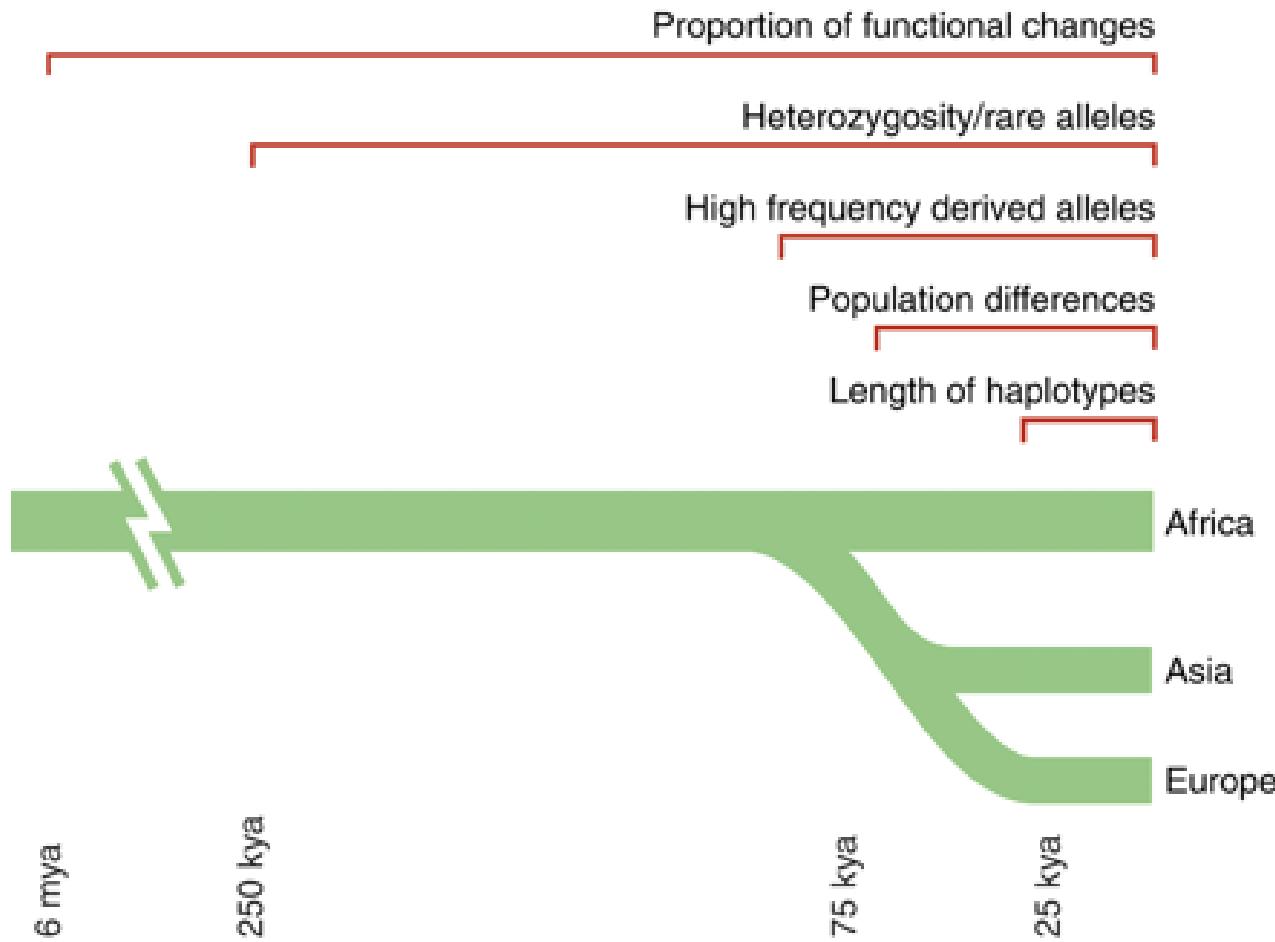
Heritable traits that increase the fitness of the become more common.

- 1) Mutations arise randomly and evolve according to their effect on the fitness of the carrier

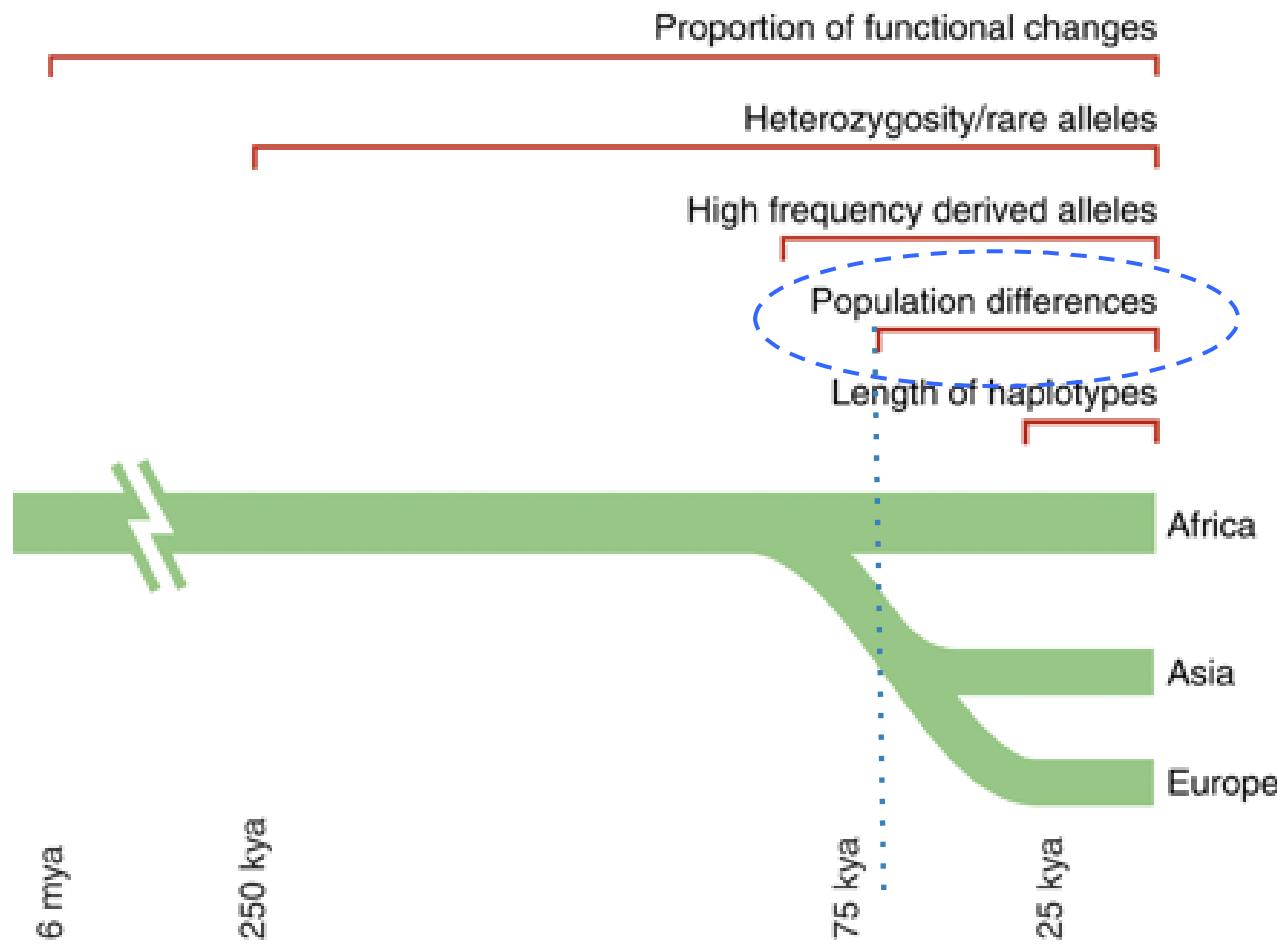


- 2) Sites targeted by natural selection are likely to harbour **functionality**

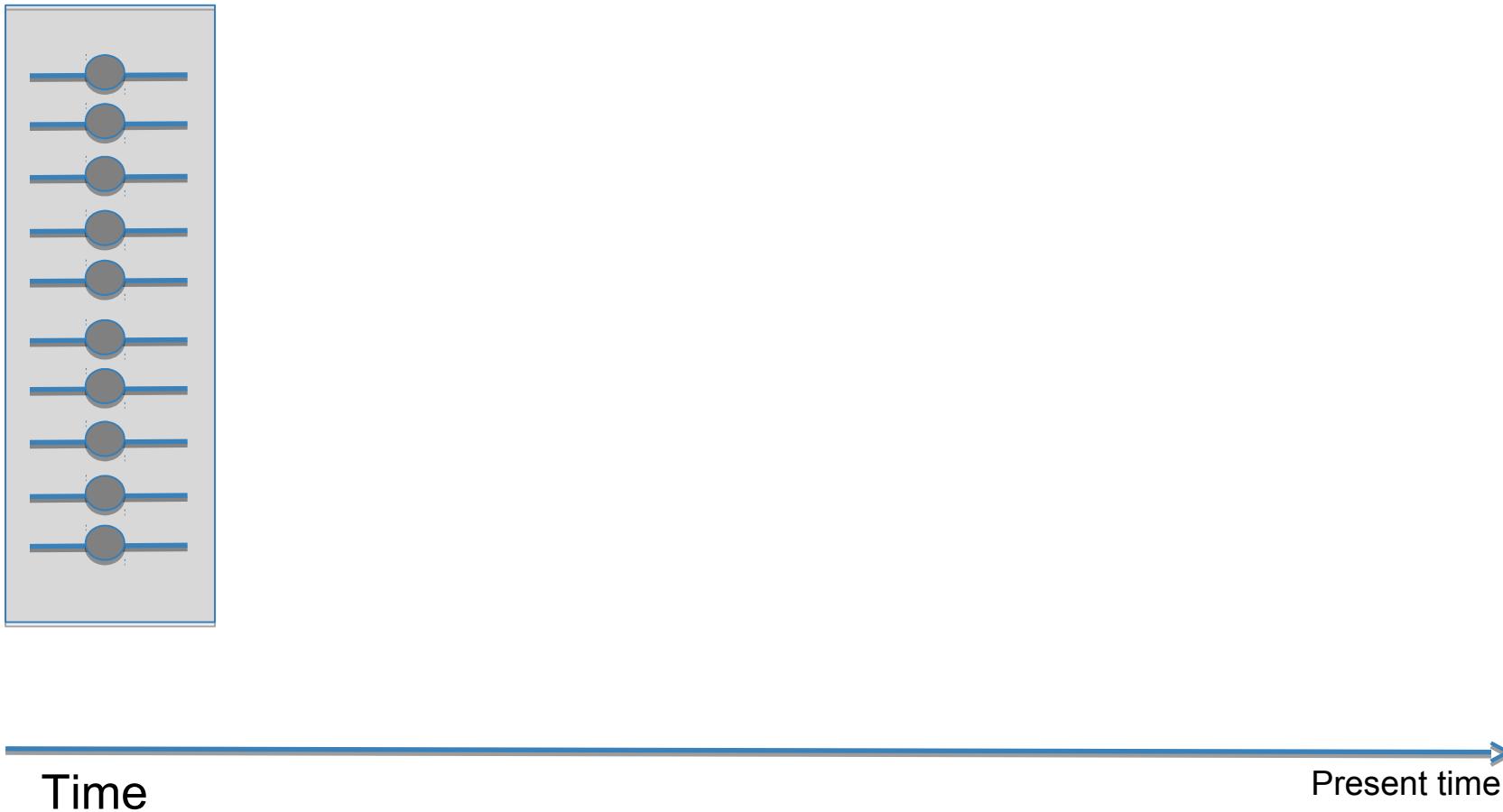
Methods to infer recent selection



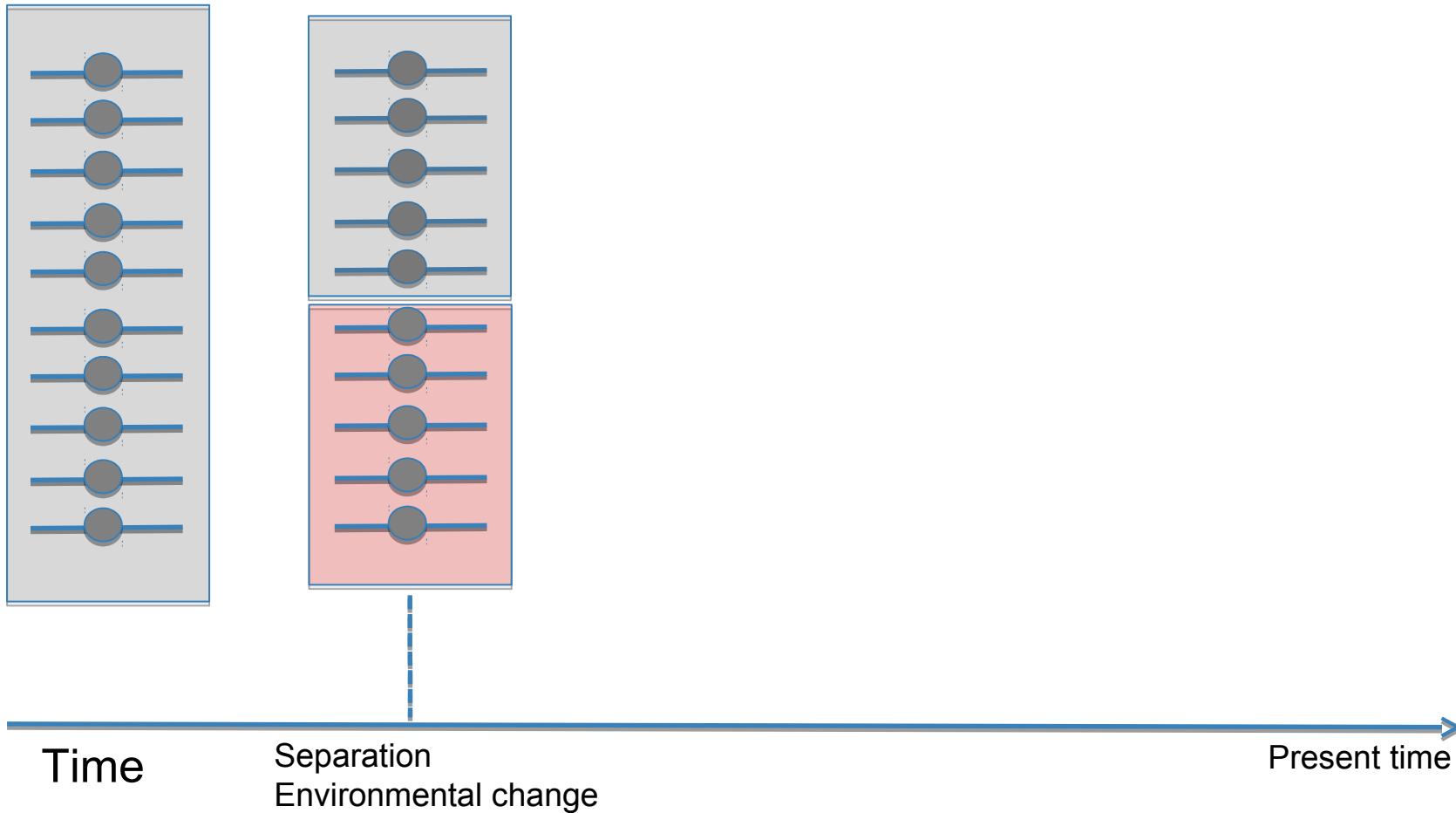
Methods to infer recent selection



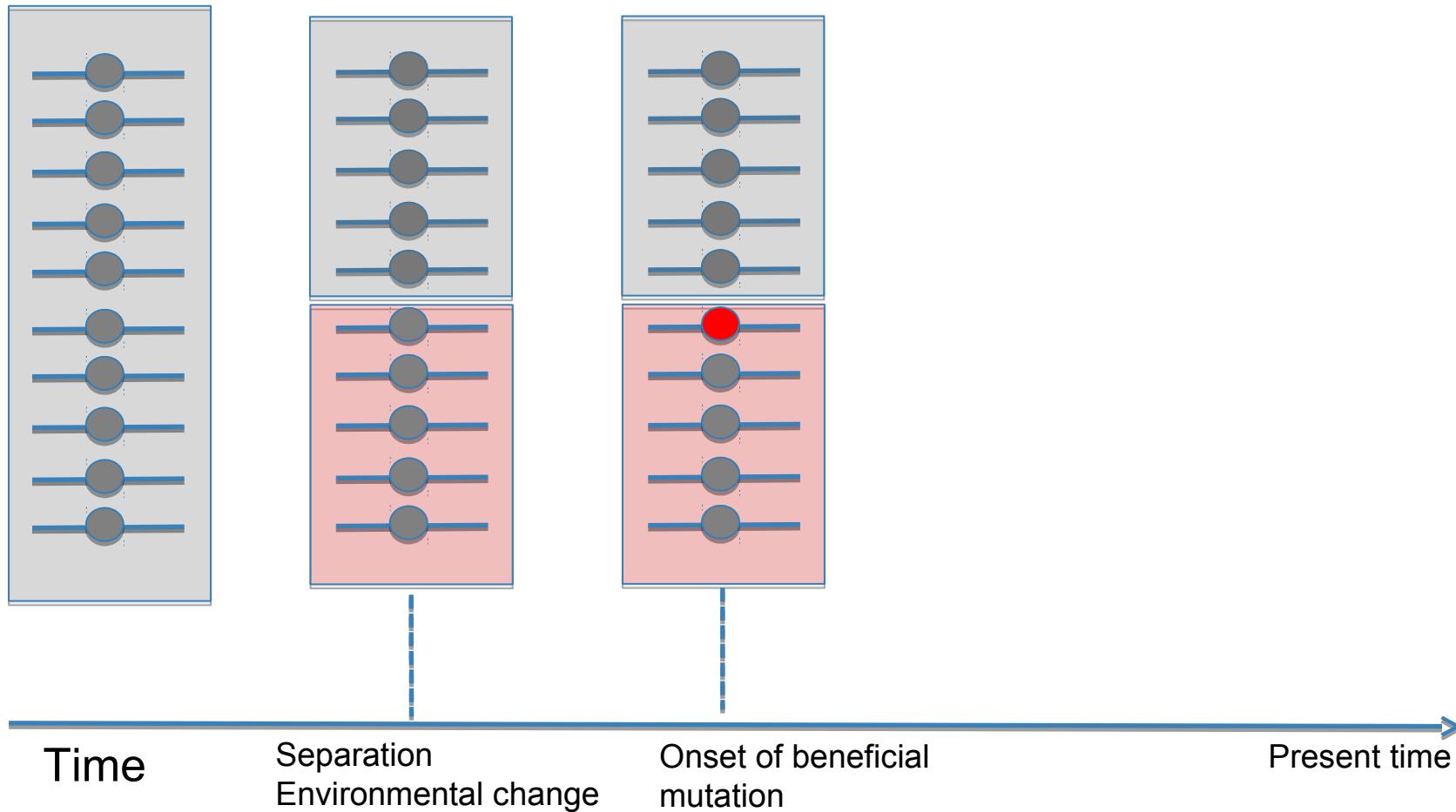
Allele frequency differentiation



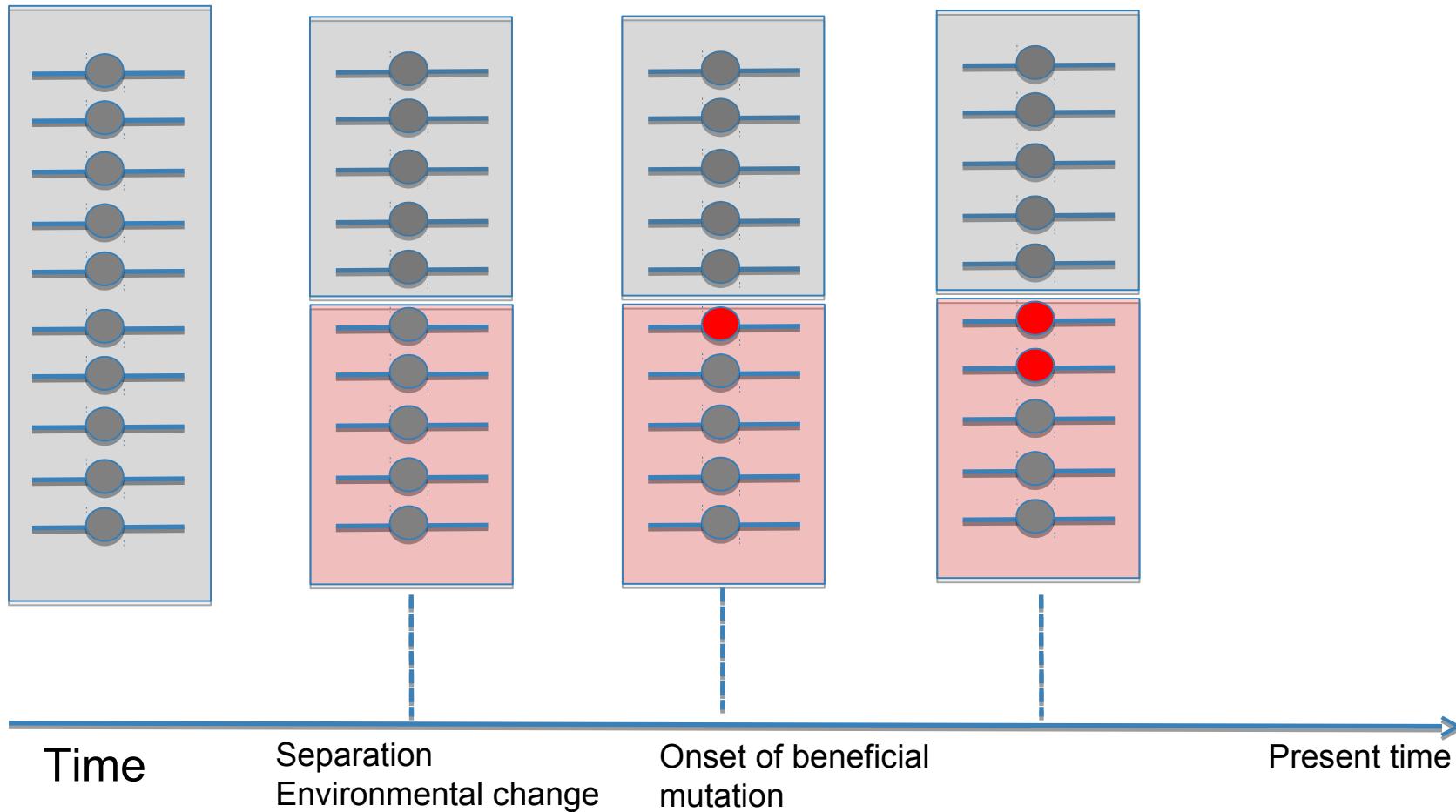
Allele frequency differentiation



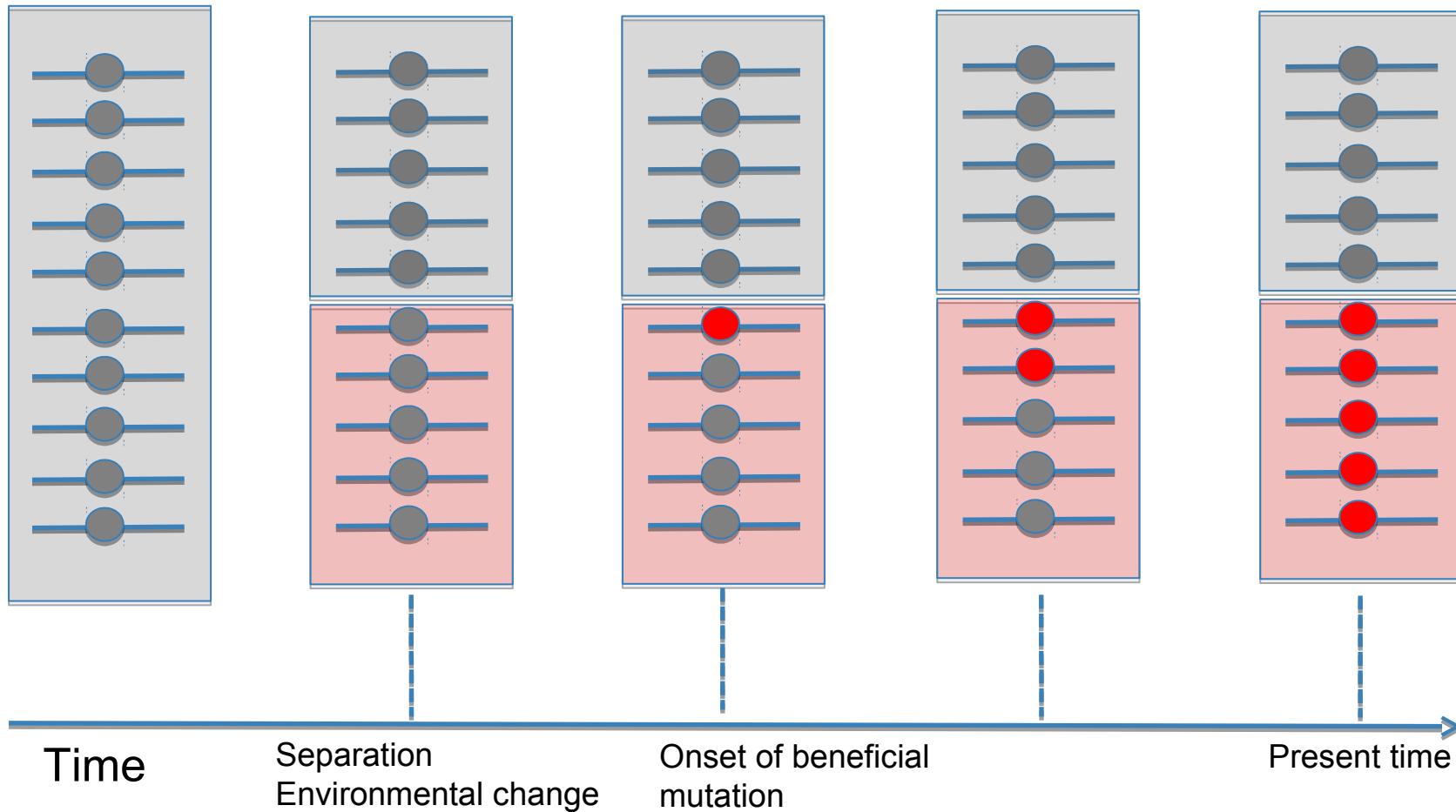
Allele frequency differentiation



Allele frequency differentiation



Allele frequency differentiation



$$F_{ST}$$

Common measure for quantifying population subdivision.

$$F_{ST} = H_B / (H_W + H_B)$$

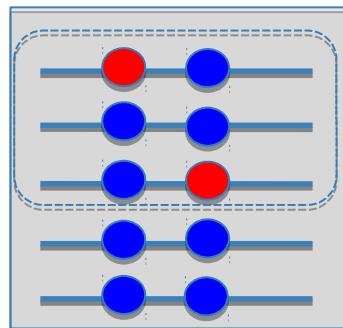
H_B : between populations

H_W : average within populations

- if $H_W \ll H_B$ then $F_{ST} \sim 1$
- if $H_B = 0$ then $F_{ST} = 0$

Haplotype-based F_{ST}

F_{ST} based on haplotype differentiation between populations

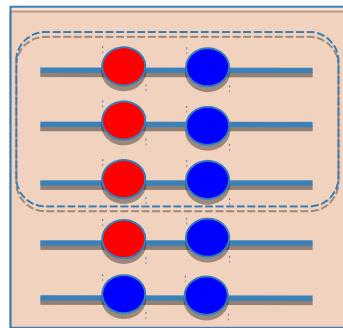


A
B
C

$$F_{ST} = 1 - (H_W / H_B)$$

Within populations

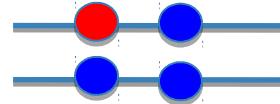
Between populations



D
E
F

What is the variation within populations?

e.g. A vs B



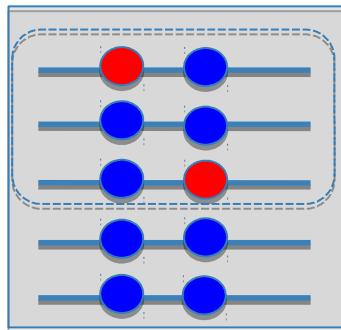
The differ by 1 site

Haplotype-based F_{ST}

$$F_{ST} = 1 - (H_W / H_B)$$

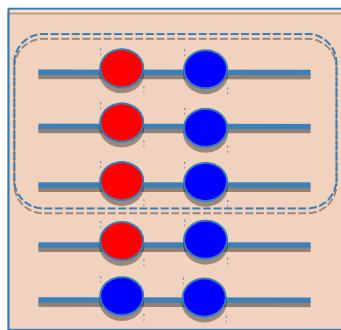
Within populations

Between populations



What is the variation within populations?

A	B	Mean=?
A	C	
B	C	



D	E	Mean=?
D	F	
E	F	

H_W is the average within-populations: ?

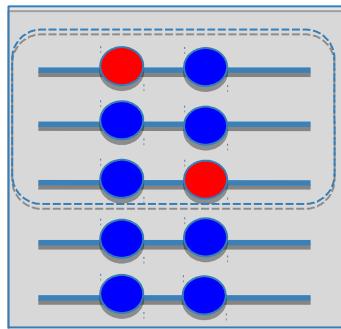
Haplotype-based F_{ST}

$$F_{ST} = 1 - (H_W / H_B)$$

Within populations

Between populations

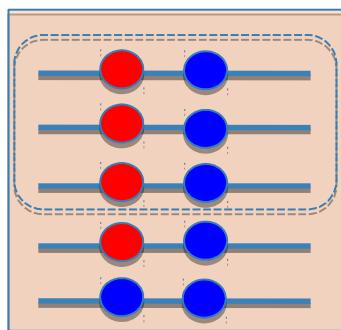
What is the variation within populations?



A
B
C

A	B	1
A	C	2
B	C	1

Mean=4/3



D
E
F

D	E	0
D	F	0
E	F	0

Mean=0/3

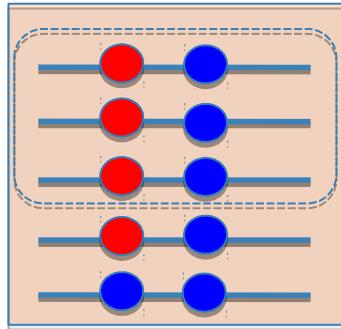
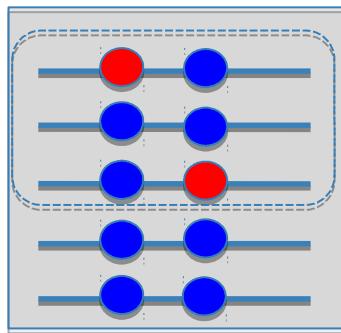
H_W is the average within-populations: $(4/3+0/3)/2=2/3$

Haplotype-based F_{ST}

$$F_{ST} = 1 - (H_W / H_B)$$

Within populations

Between populations



What is the variation between populations?

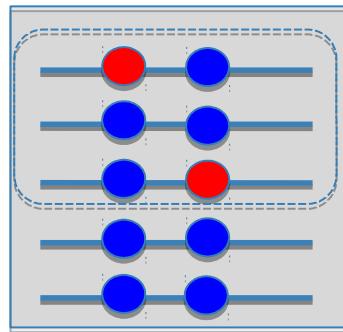
A	D	0
A	E	0
A	F	0
B	D	1
B	E	1
B	F	1
C	D	2
C	E	2
C	F	2

Mean=9/9

H_B is the average between-populations: $9/9=1$

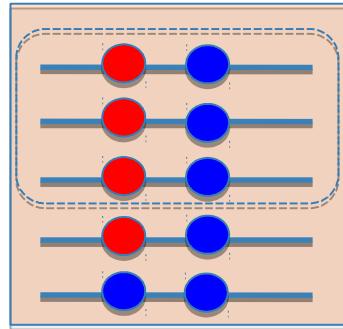
Haplotype-based F_{ST}

F_{ST} based on haplotype differentiation between populations



A
B
C

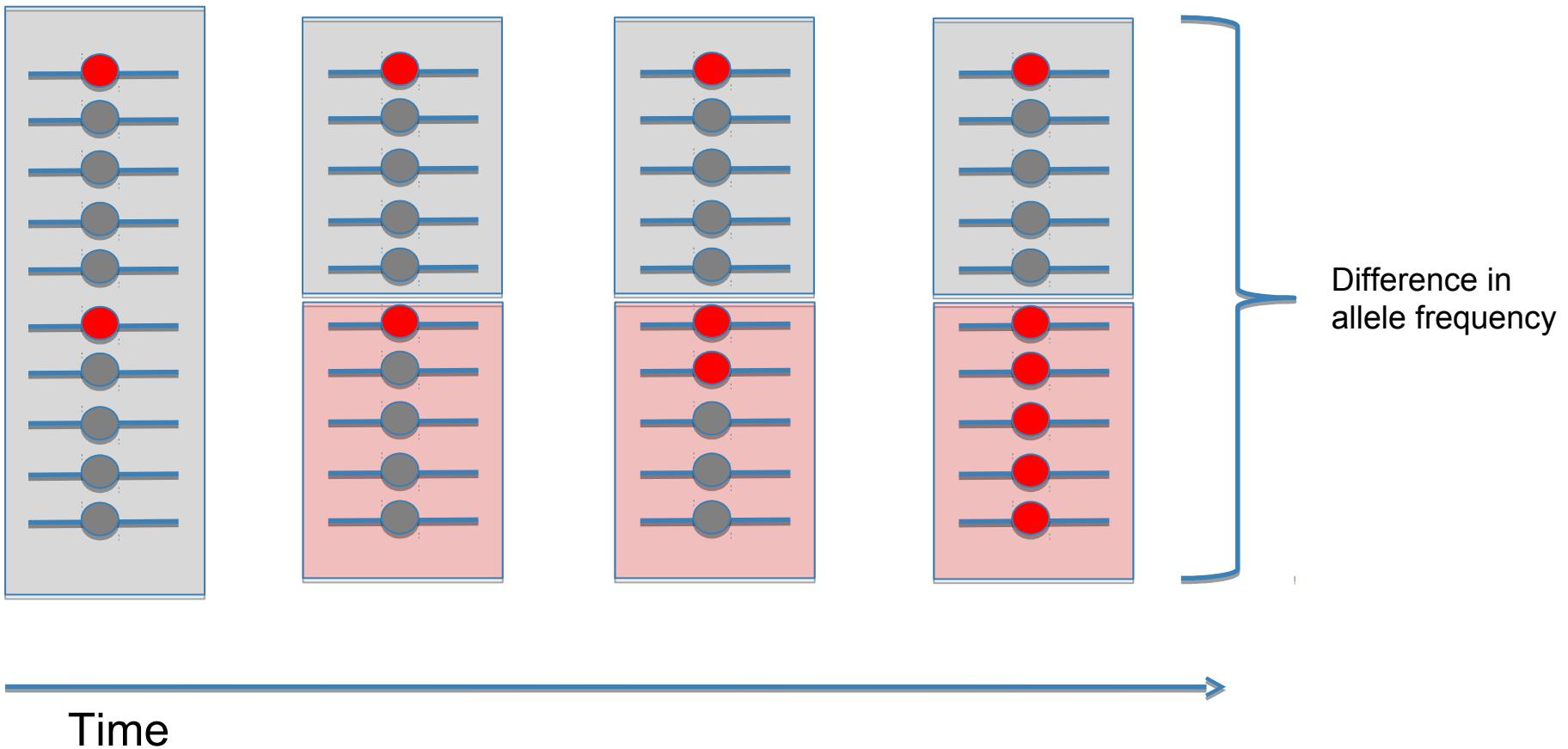
$$F_{ST} = 1 - (H_W / H_B) = 1 - ((2/3)/1) = 1/3 \sim 0.33$$



D
E
F

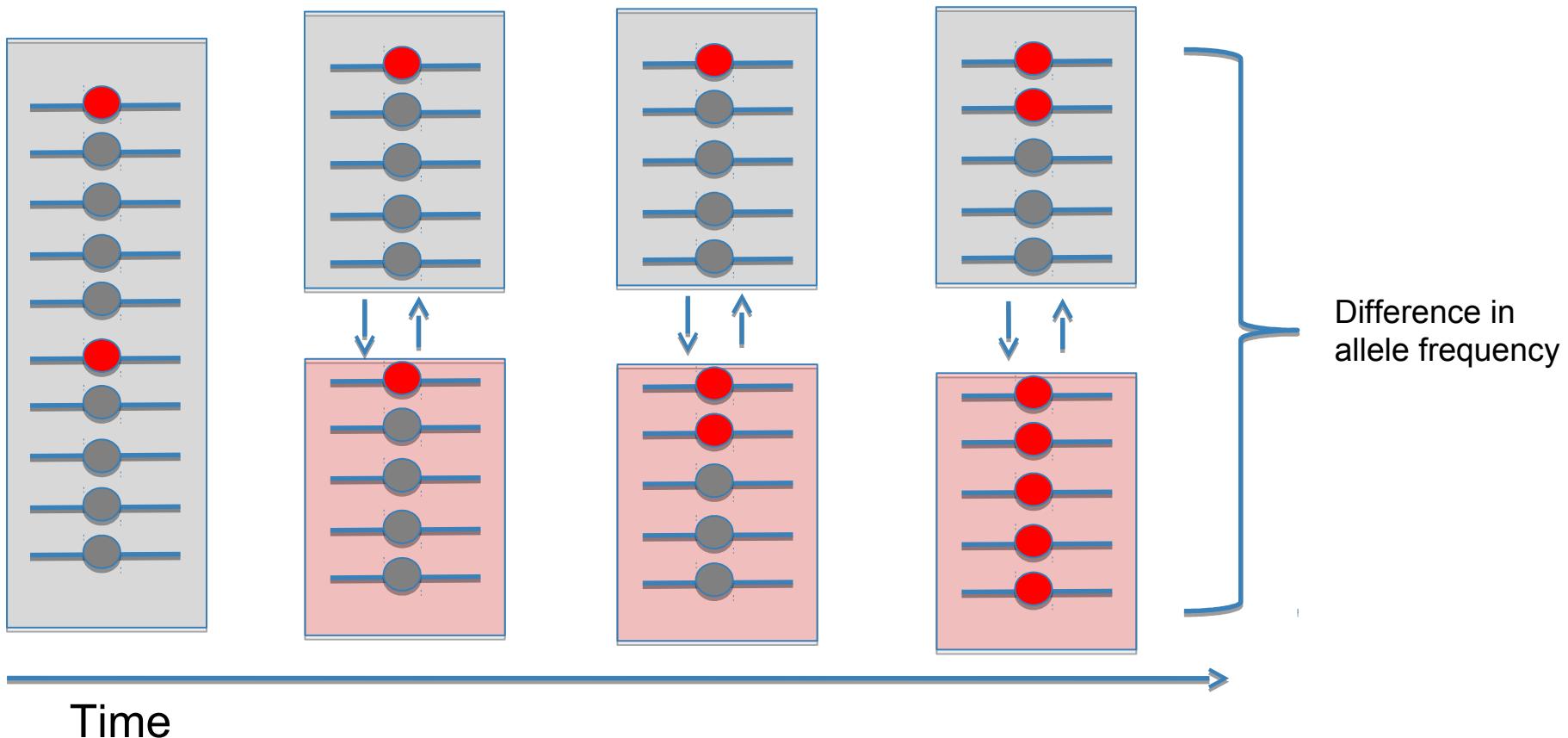
Allele frequency differentiation

From standing variation



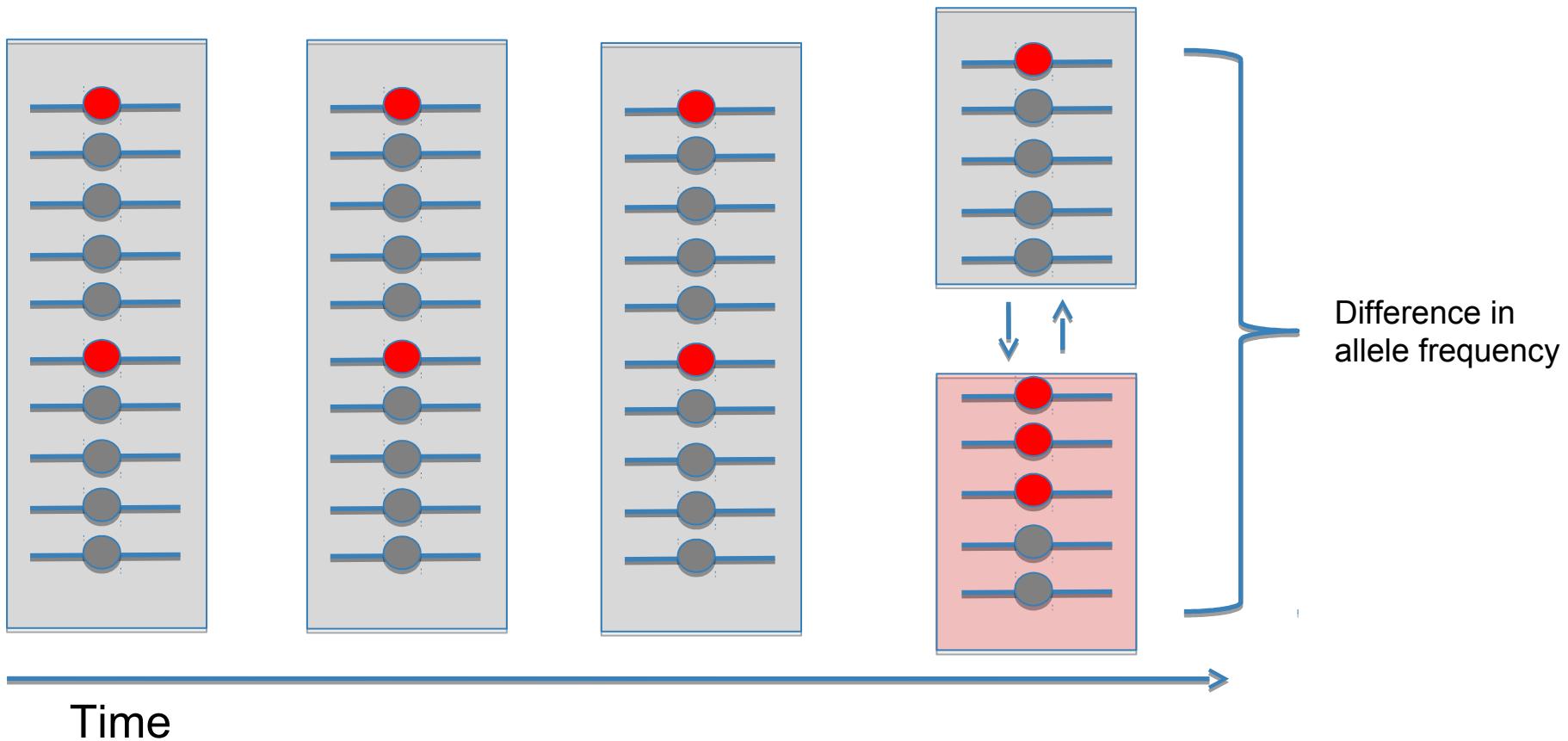
Allele frequency differentiation

With migration



Allele frequency differentiation

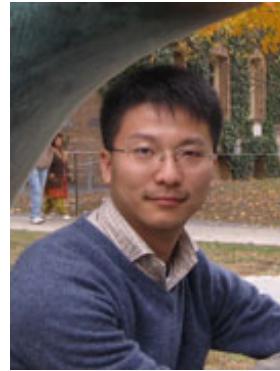
With recent divergence



Population genetic differentiation



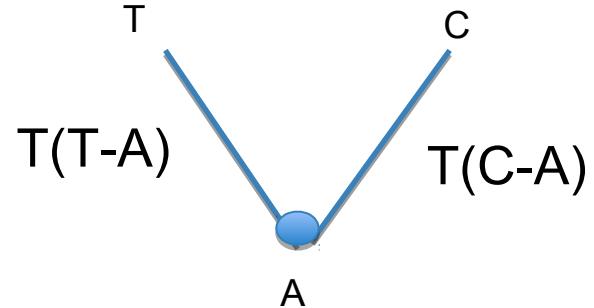
T



C

$$F_{ST}(\text{T-C})$$

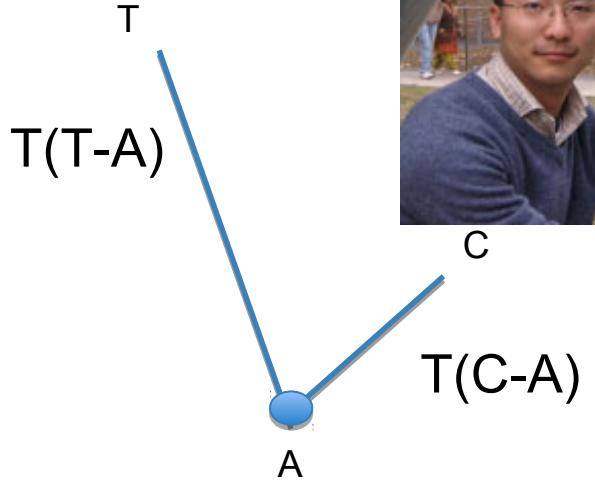
Population genetic differentiation



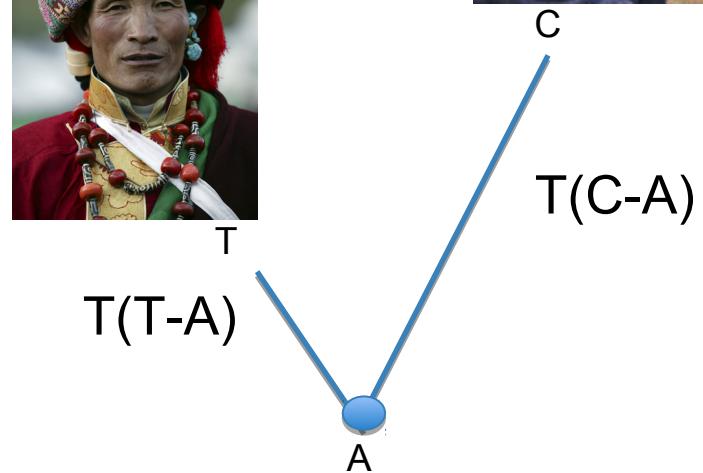
$$F_{ST}(T-C) \sim T(T-A-C)$$

Population genetic differentiation

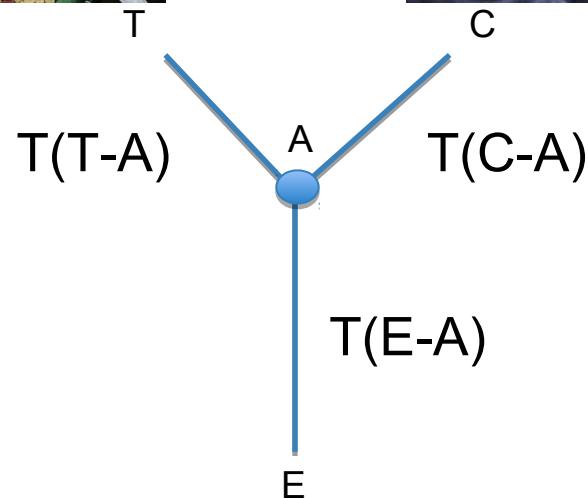
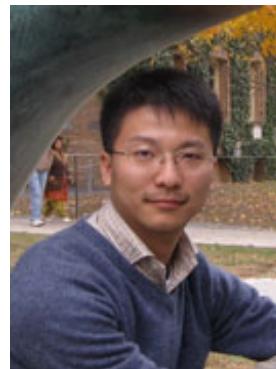
$$F_{ST}(T-C) \sim T(T-A-C)$$



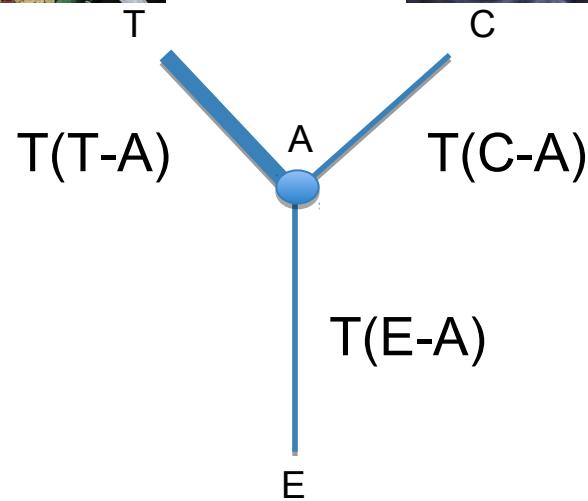
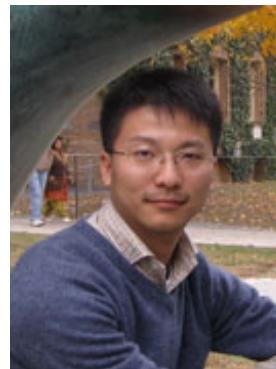
?



Population genetic differentiation



Population genetic differentiation

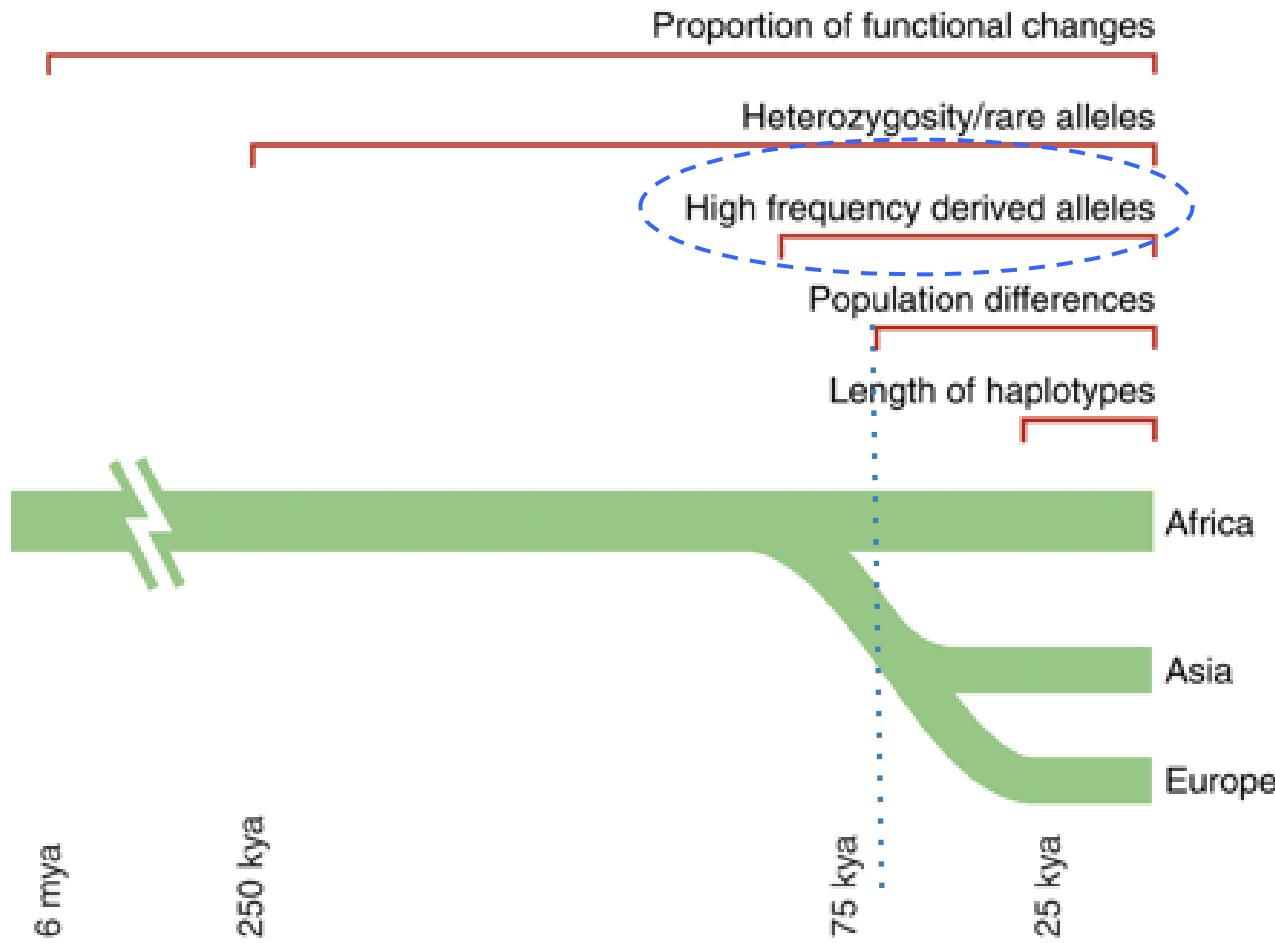


$$T(T-A-C) = -\log(1 - F_{ST}(T-C))$$

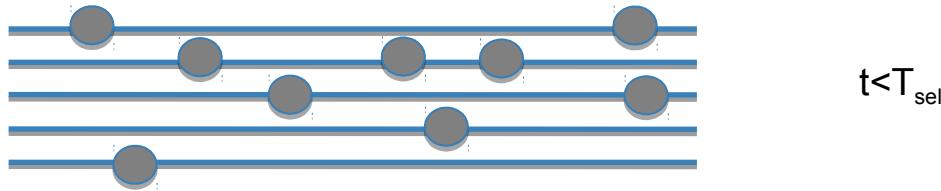
T(T-A)?



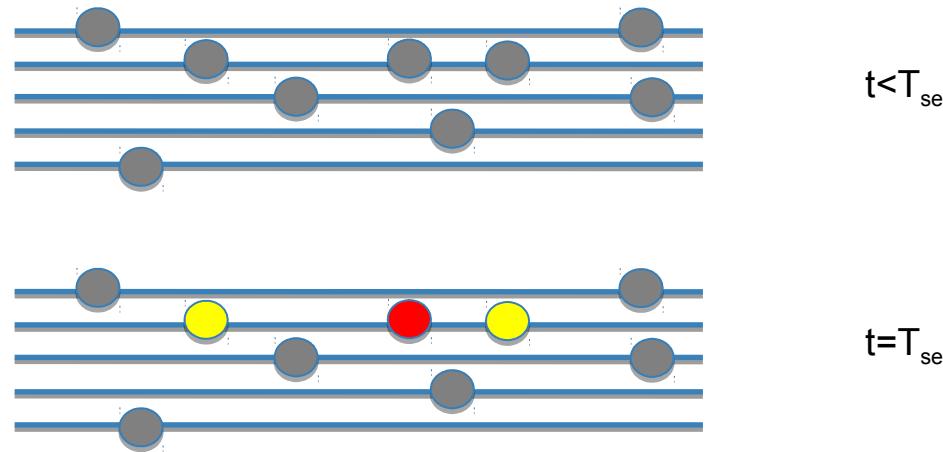
Methods to infer selection



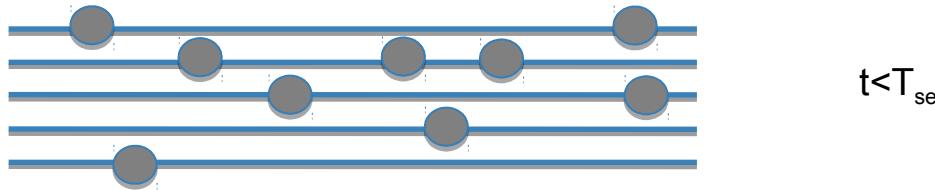
Positive selection: effect on haplotypes



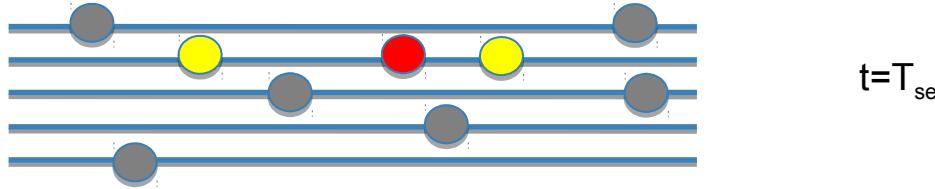
Positive selection: effect on haplotypes



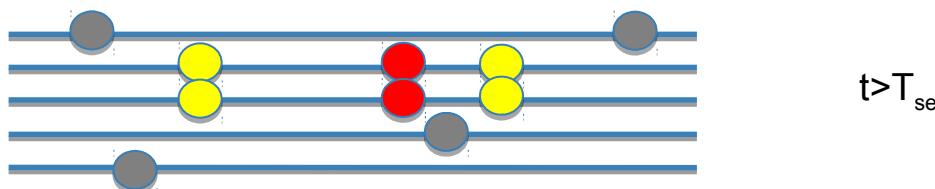
Positive selection: effect on haplotypes



$t < T_{\text{sel}}$

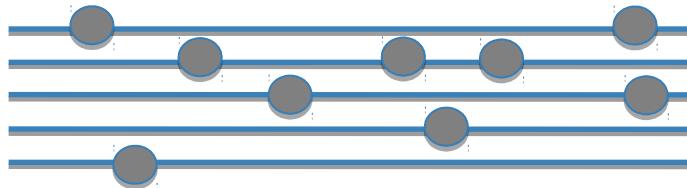


$t = T_{\text{sel}}$

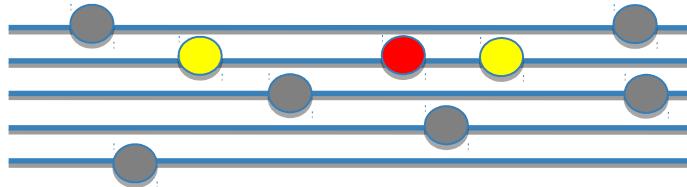


$t > T_{\text{sel}}$

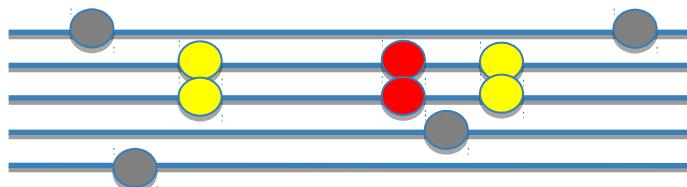
Positive selection: effect on haplotypes



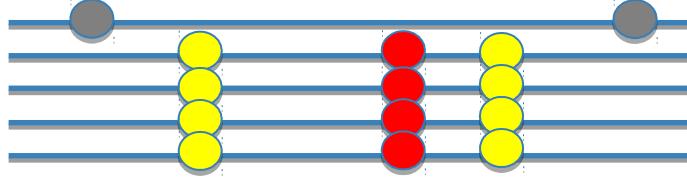
$t < T_{sel}$



$t = T_{sel}$



$t > T_{sel}$



$t \gg T_{sel}$

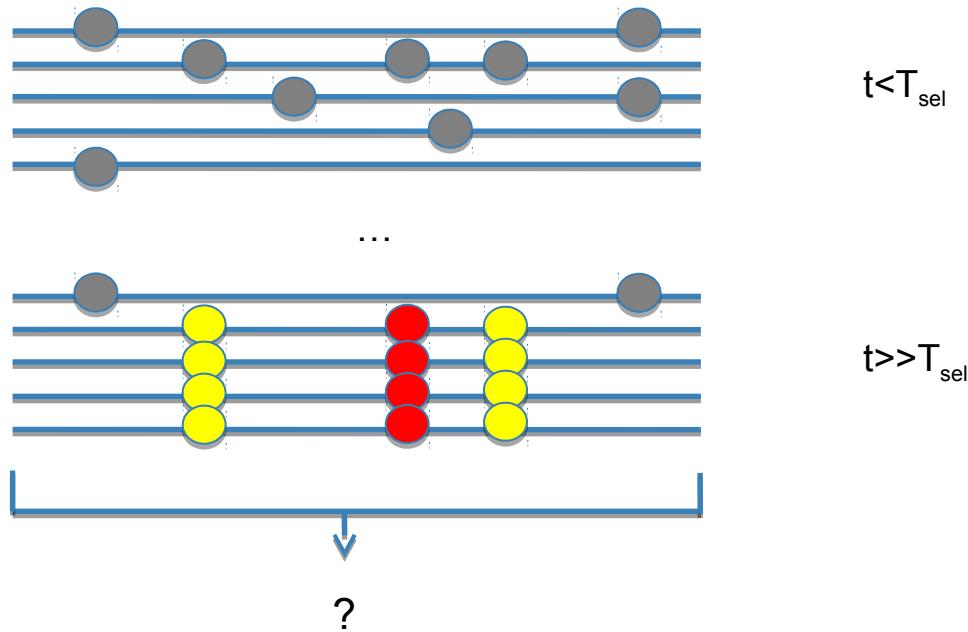
Selective sweep



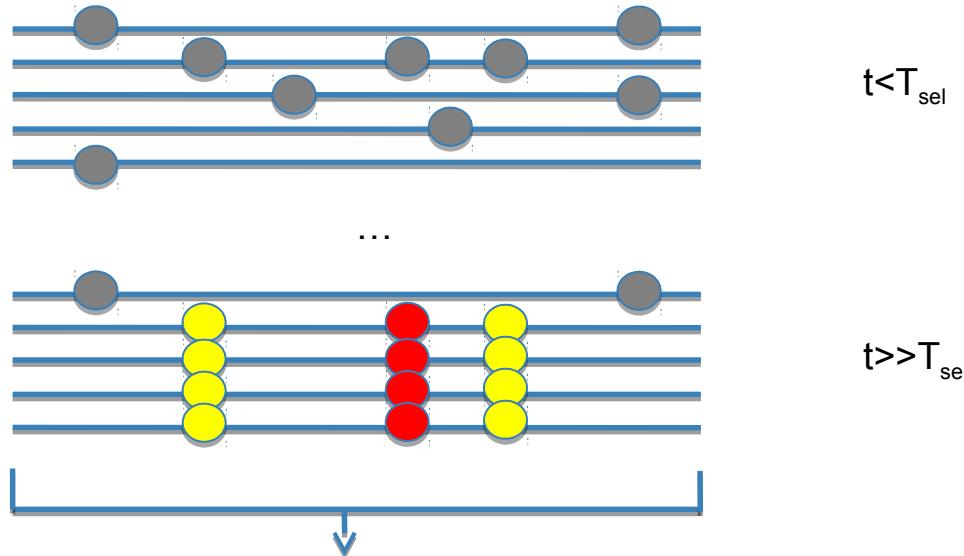
Genetic hitch-hiking



Positive selection

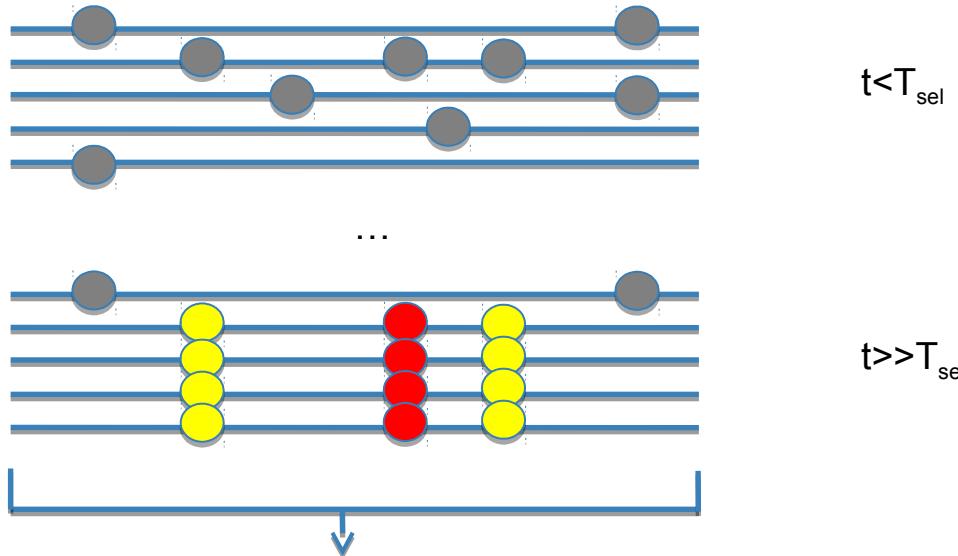


Positive selection



- Reduction of polymorphisms levels
(e.g. from 7 to 5 SNPs)

Positive selection



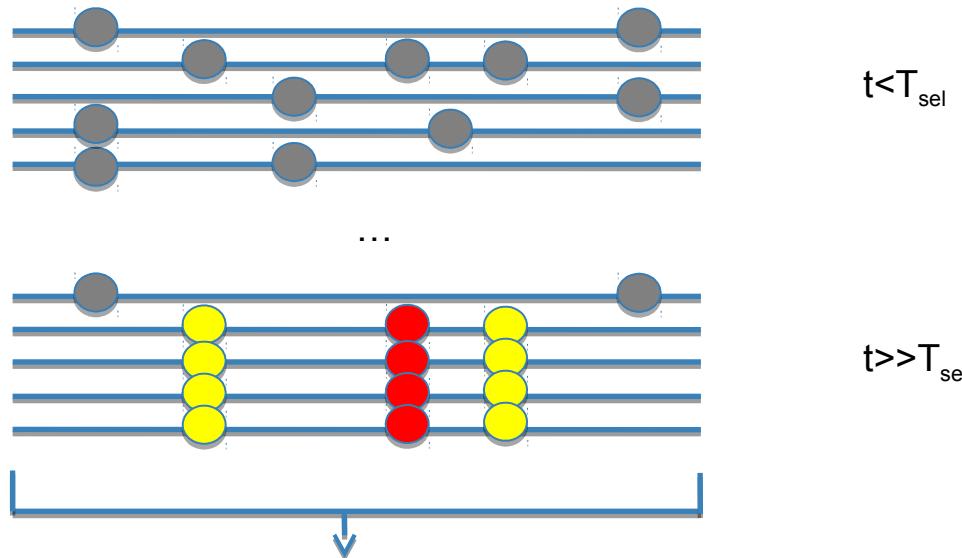
- Reduction of polymorphisms levels
(e.g. from 7 to 5 SNPs)

Nucleotide diversity index: Watterson's Theta
with K SNPs and n chromosomes

$$\theta_W = \frac{K}{a_n}$$

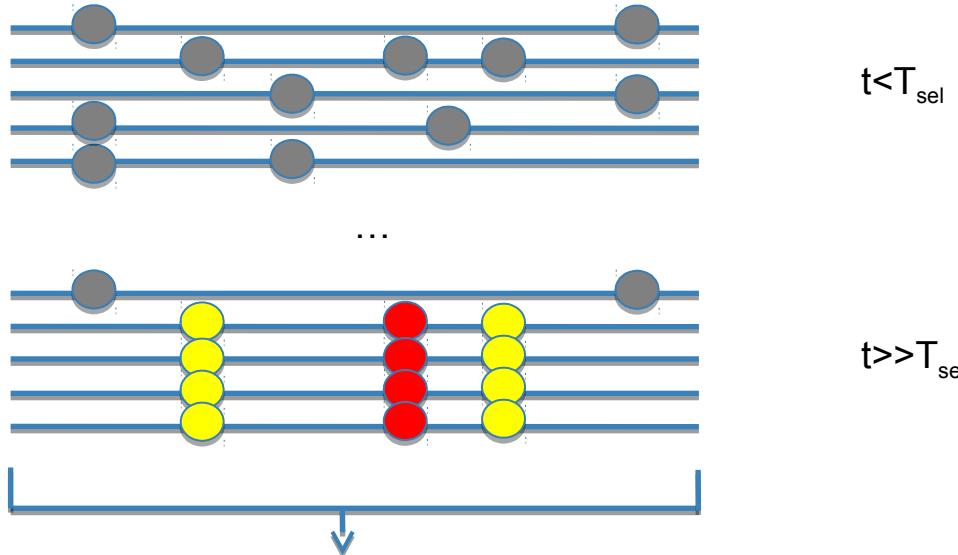
$$a_n = \sum_{i=1}^{n-1} \frac{1}{i}$$

Positive selection



- Reduction of polymorphisms levels (Theta)
- ?

Positive selection

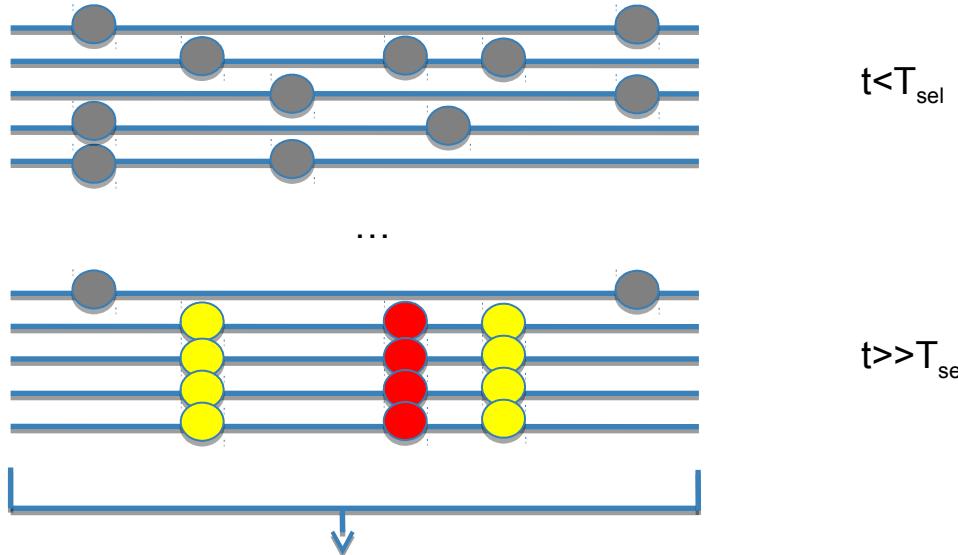


- Reduction of polymorphisms levels (Theta)
- Excess of low-frequency variants

Nucleotide diversity index: average pairwise nucleotide differences (π) with $k_{i,j}$ equal to the number of nucleotide differences between sequences i and j

$$\pi = \frac{\sum_{i=1}^{n-1} \sum_{j=i+1}^n k_{i,j}}{\binom{n}{2}}$$

Positive selection



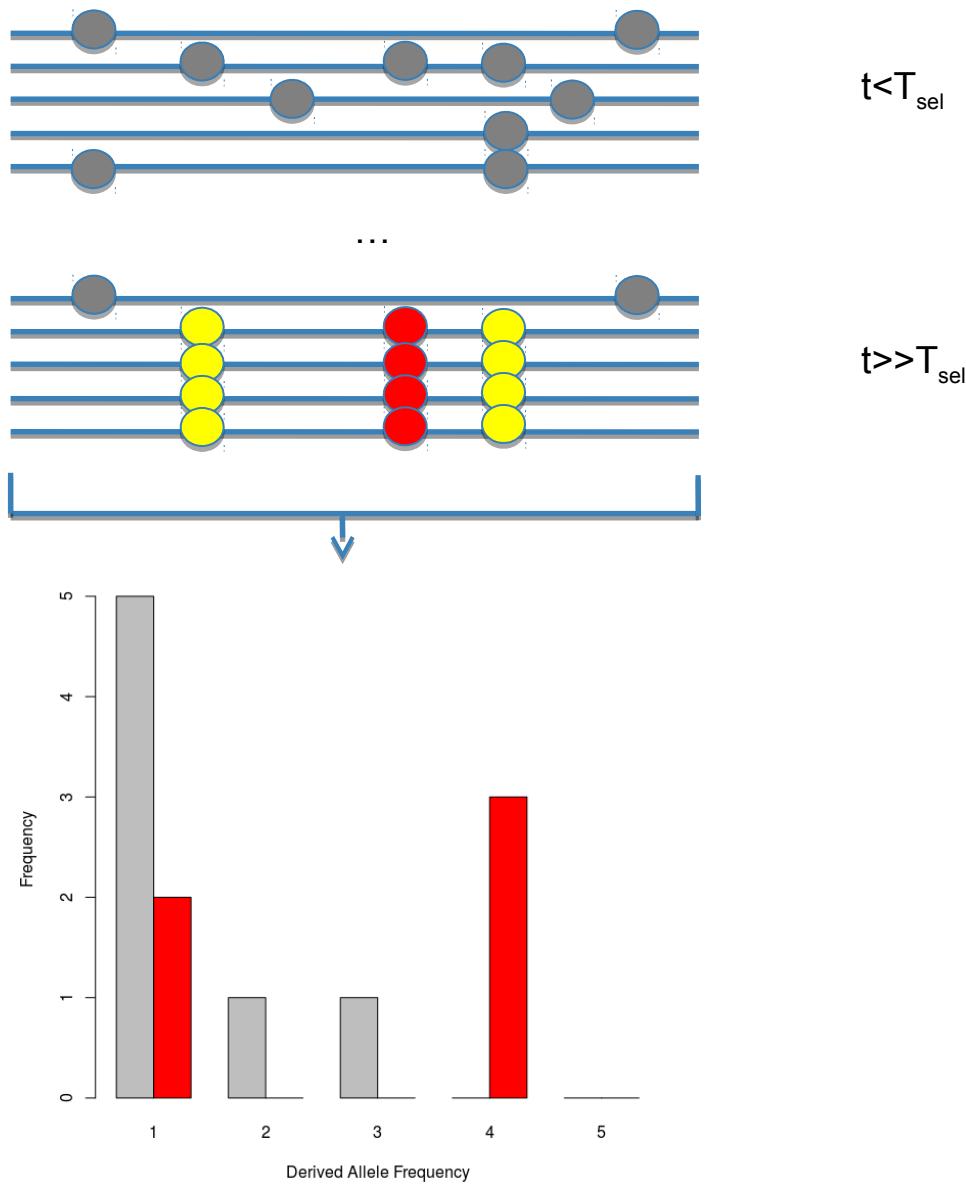
- Reduction of polymorphisms levels (Theta)
- Excess of low-frequency variants (Pi)

Under neutrality, Theta and Pi are expected to be the same.
Tajima's D measures their difference.

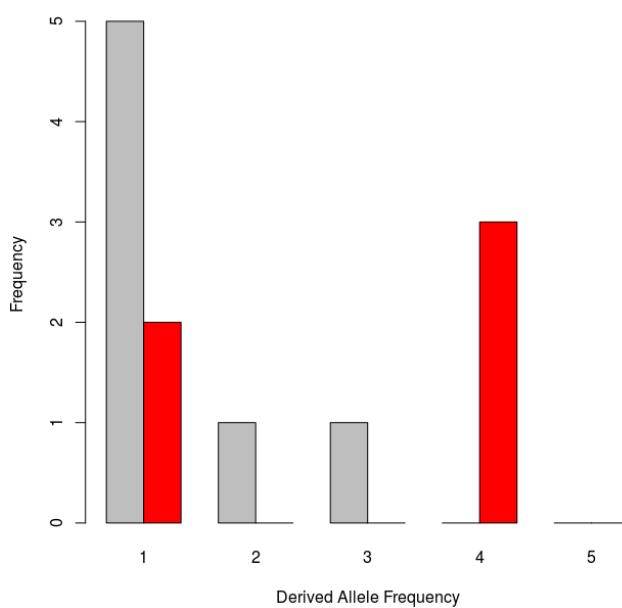
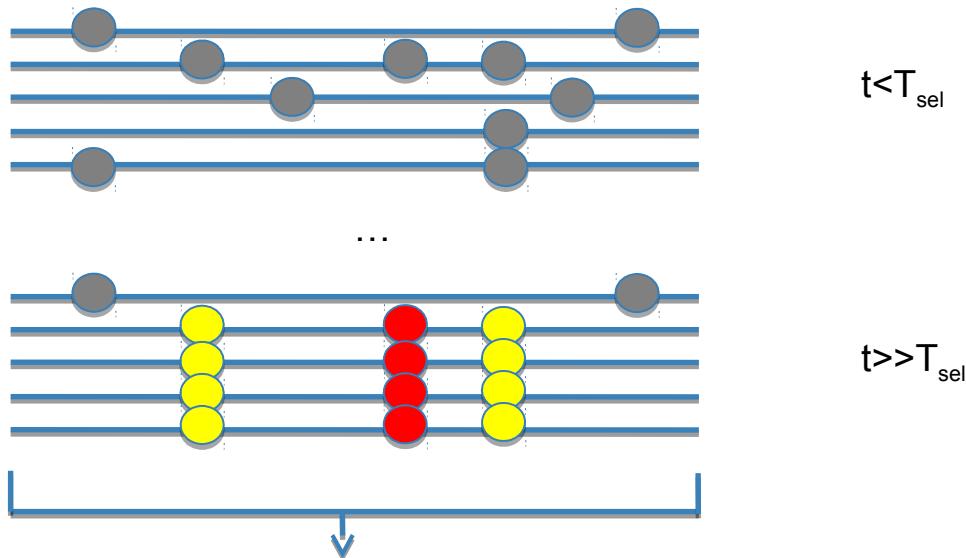
$$D = \frac{\pi - \theta_w}{\sqrt{\hat{V}(\pi - \theta_w)}}$$

$D < 0$ is suggestive of an excess of low-frequency variants

The Site Frequency Spectrum



The Site Frequency Spectrum



Tajima's D?

$$D = \frac{\pi - \theta_W}{\sqrt{\hat{V}(\pi - \theta_W)}}$$

$\downarrow \sim 0.33 = 1/3$

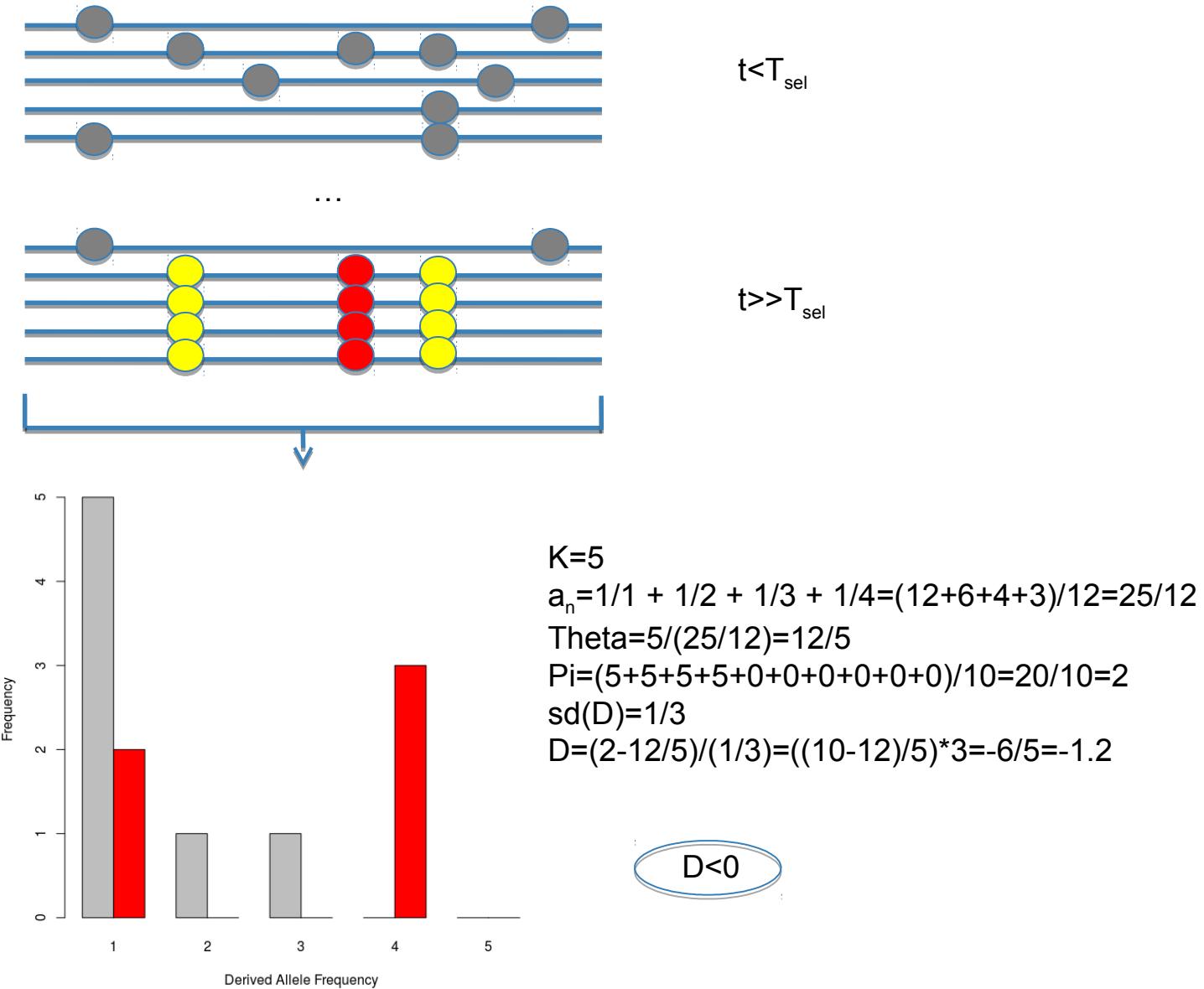
$$\theta_W = \frac{K}{a_n}$$

$$a_n = \sum_{i=1}^{n-1} \frac{1}{i}$$

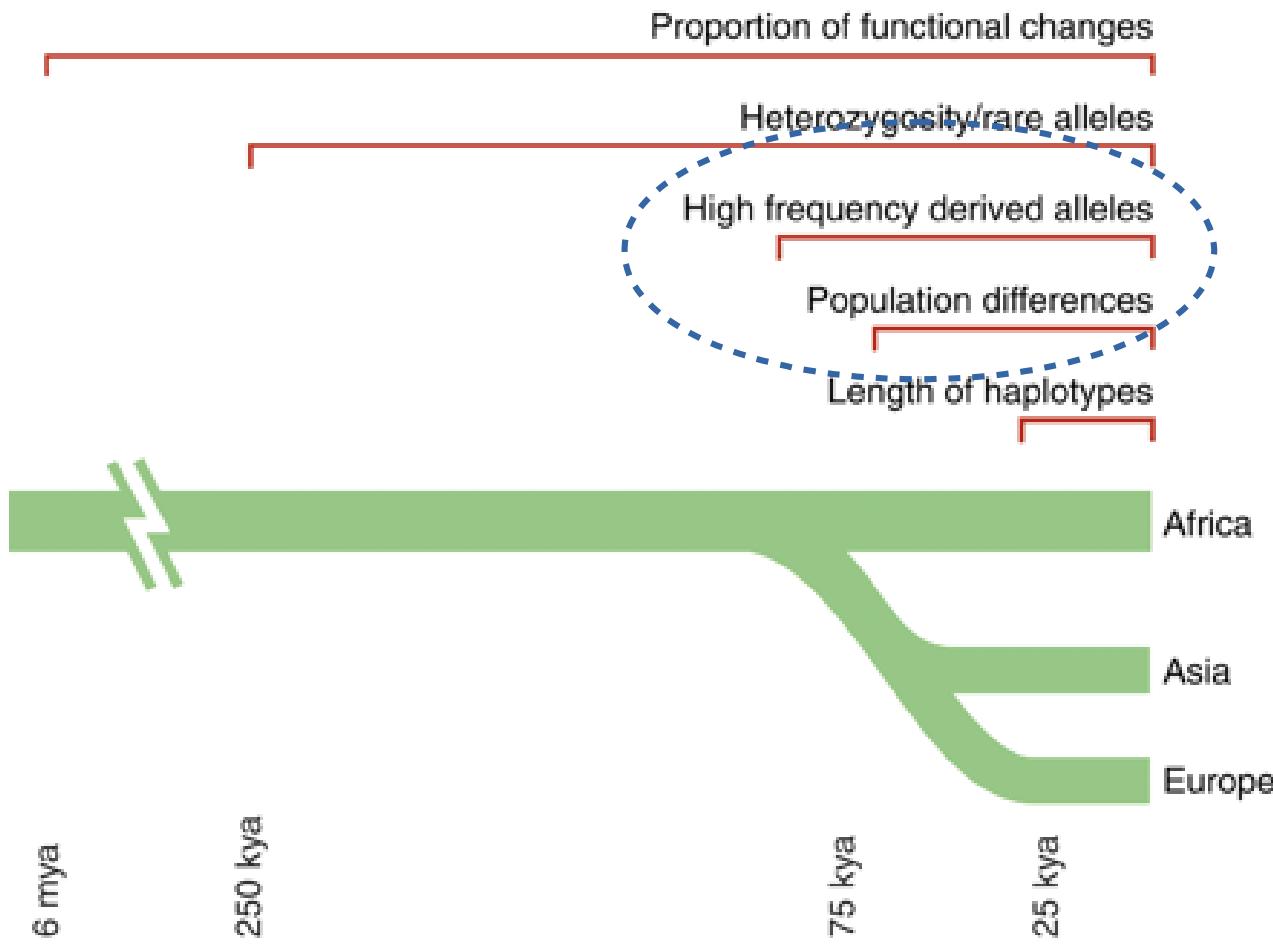
$$\pi = \frac{\sum_{i=1}^{n-1} \sum_{j=i+1}^n k_{i,j}}{n \choose 2}$$

$= 10$, the number of comparisons you need to make

The importance of being... The Site Frequency Spectrum



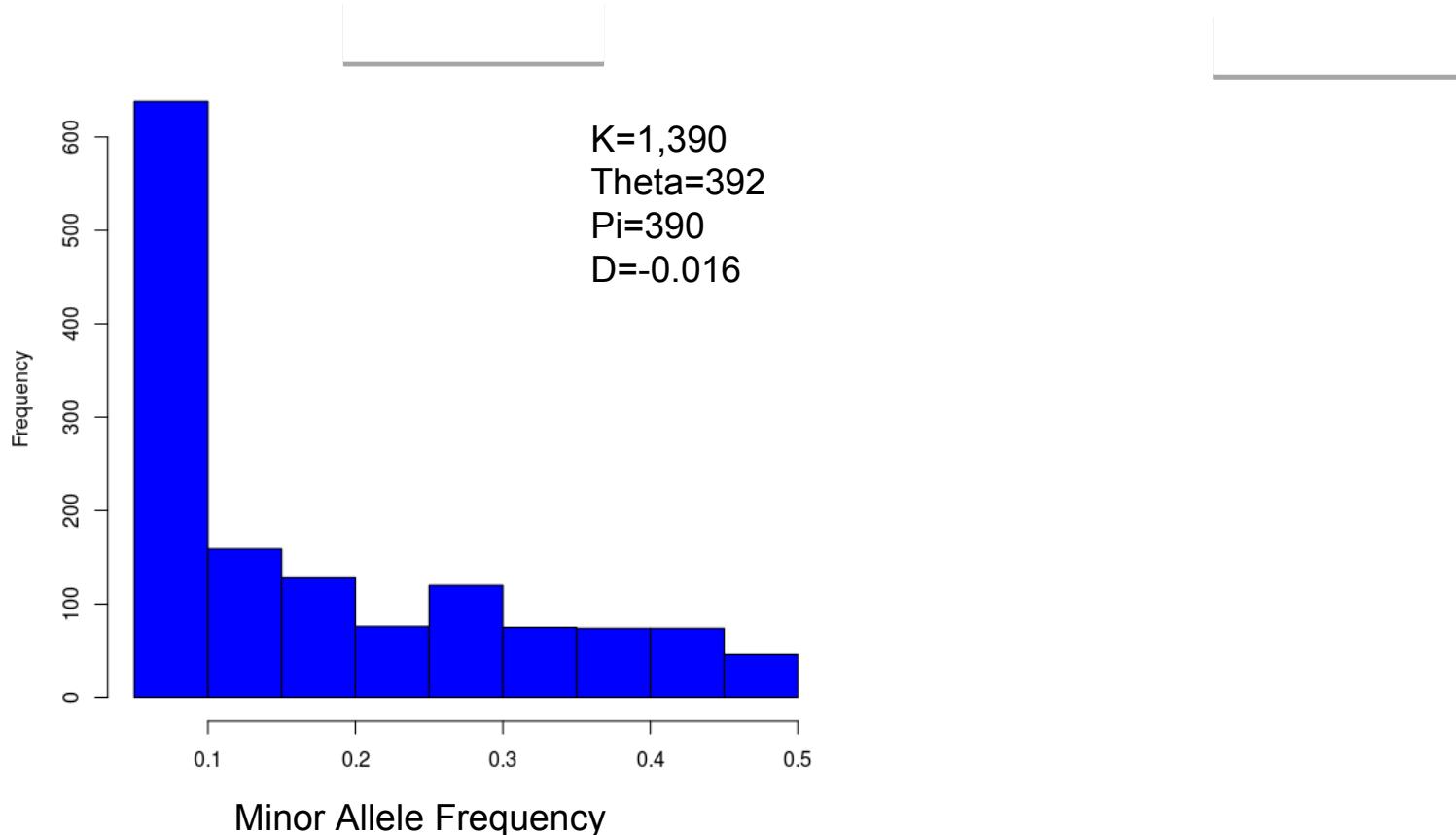
Inference of positive selection



How can we calculate these summary statistics from low-depth sequencing data?

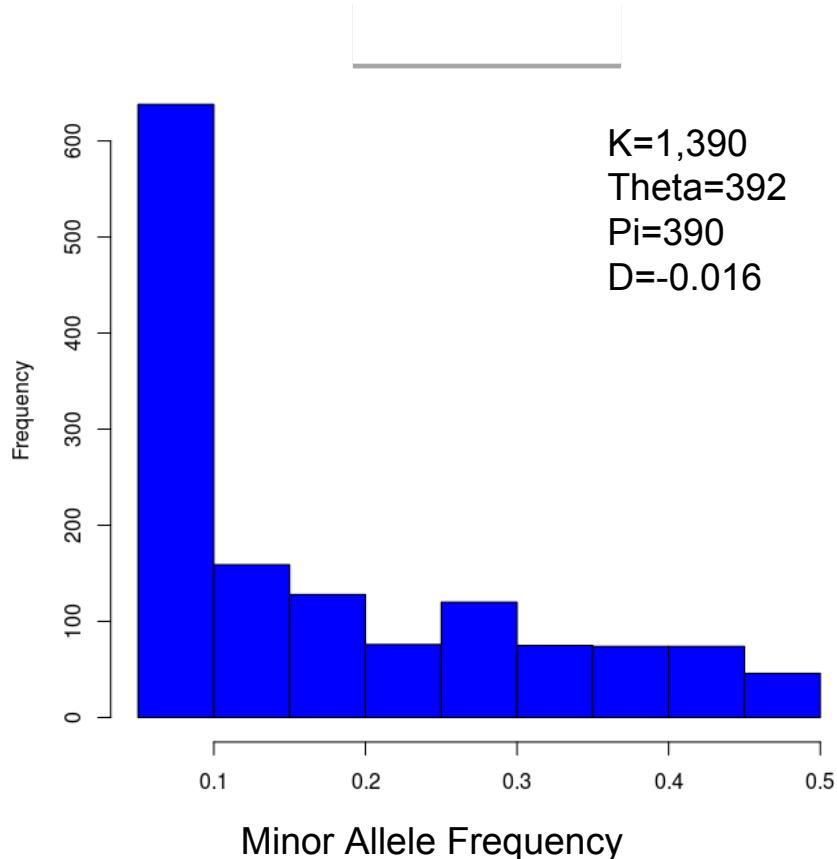
Confounding factor

$n=20$; $L=500\text{ kbp}$; no selection

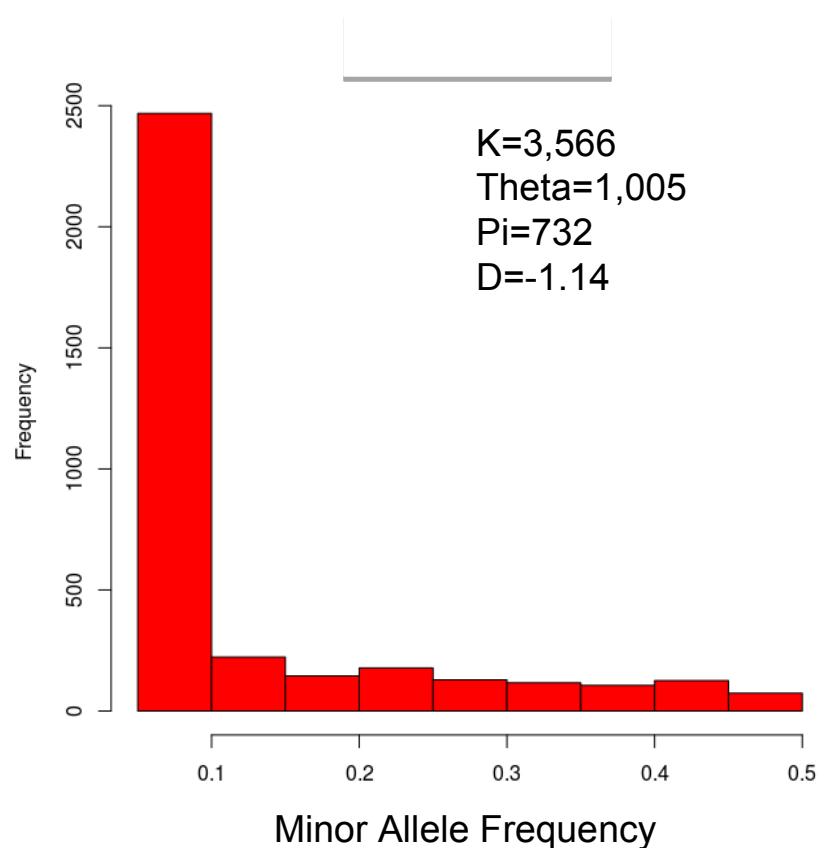


Confounding factor

n=20; L=500kbp; no selection

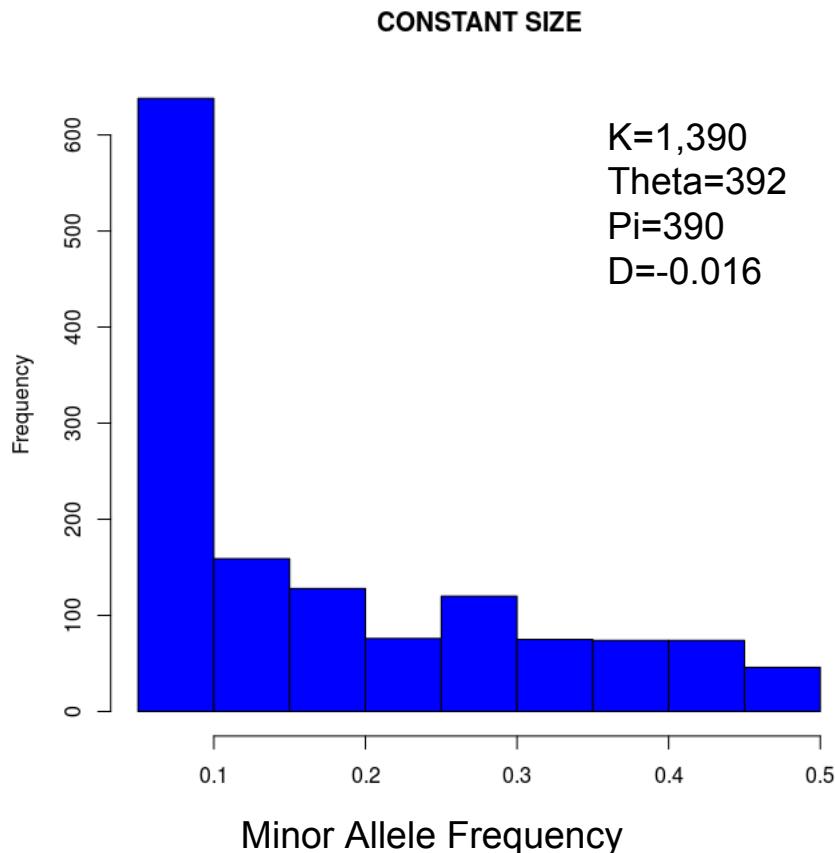


n=20; L=500kbp; no selection

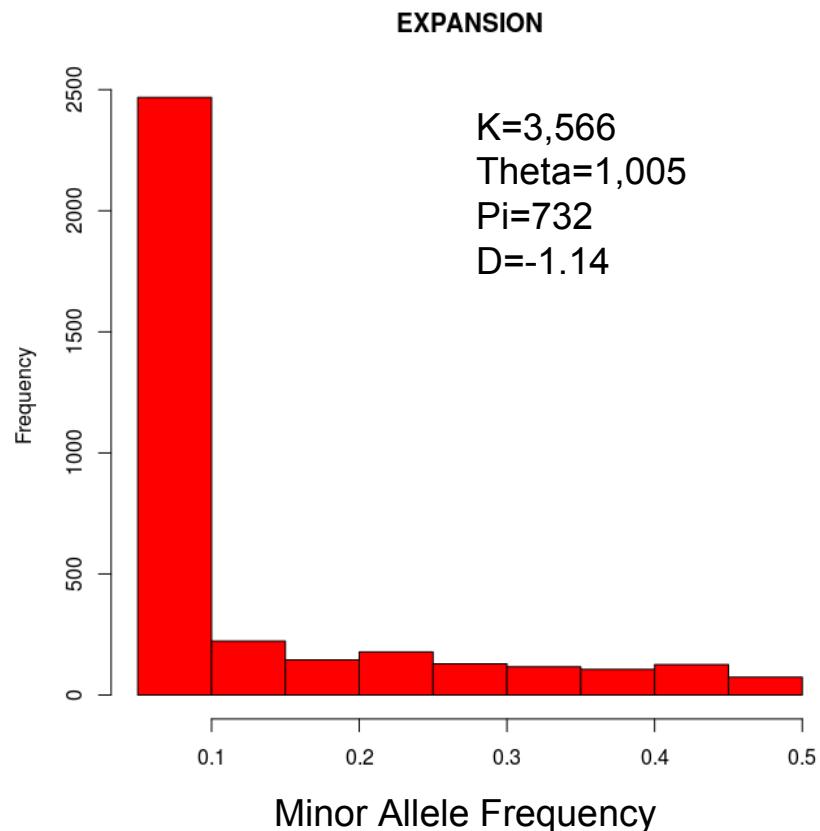


Demography matters!

n=20; L=500kbp; no selection



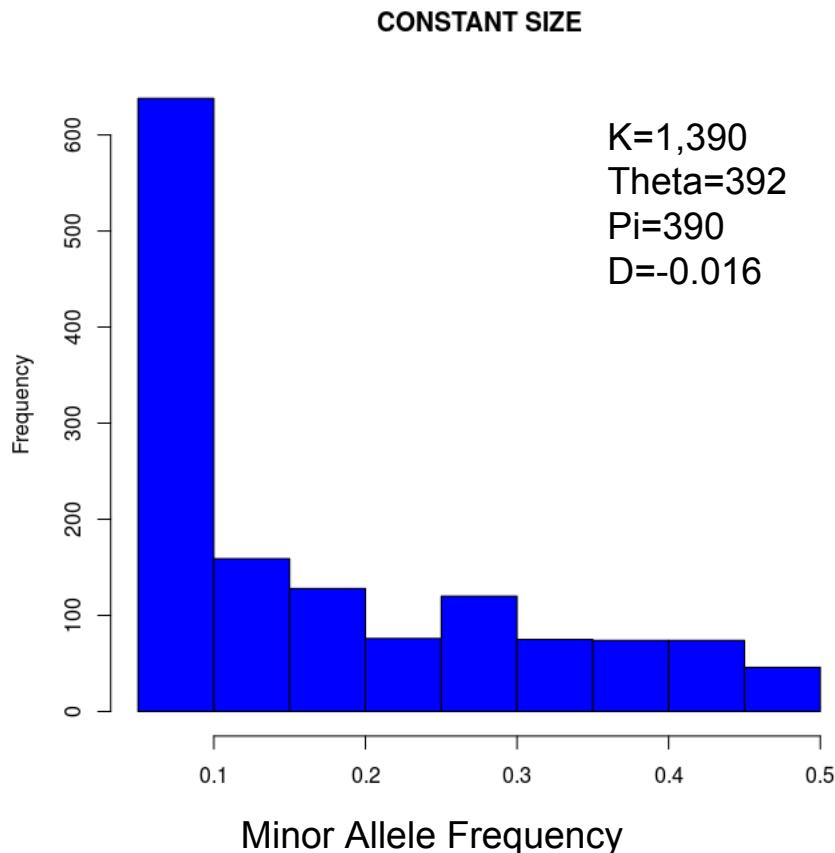
n=20; L=500kbp; no selection



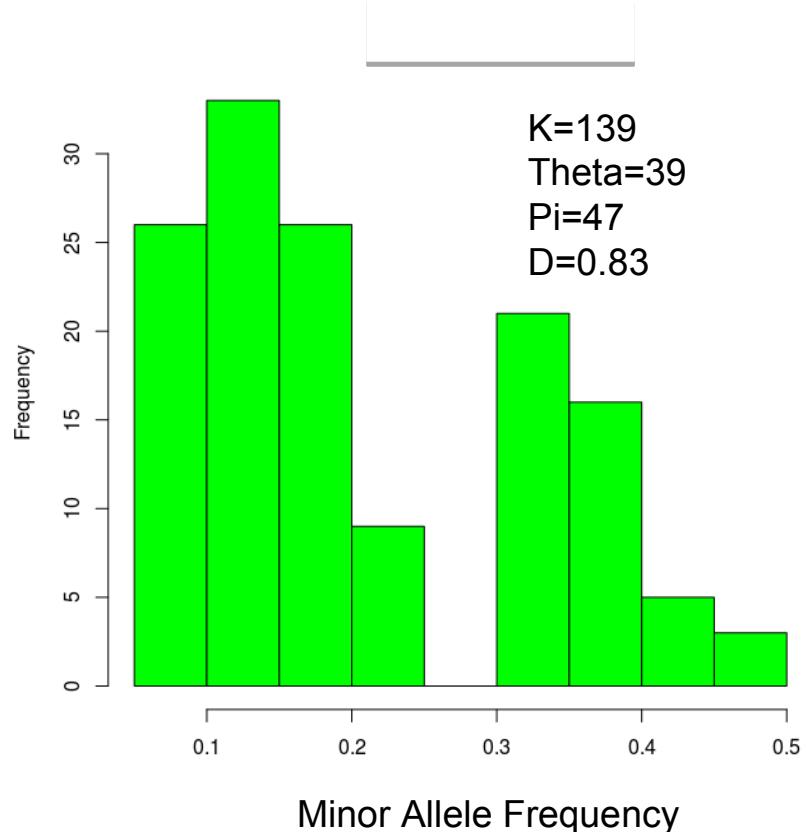
- Excess of segregating sites
- Excess of low-frequency variants
- SFS-derived summary statistics may fail to distinguish between the effects of demography and selection

Demography matters?

n=20; L=500kbp; no selection

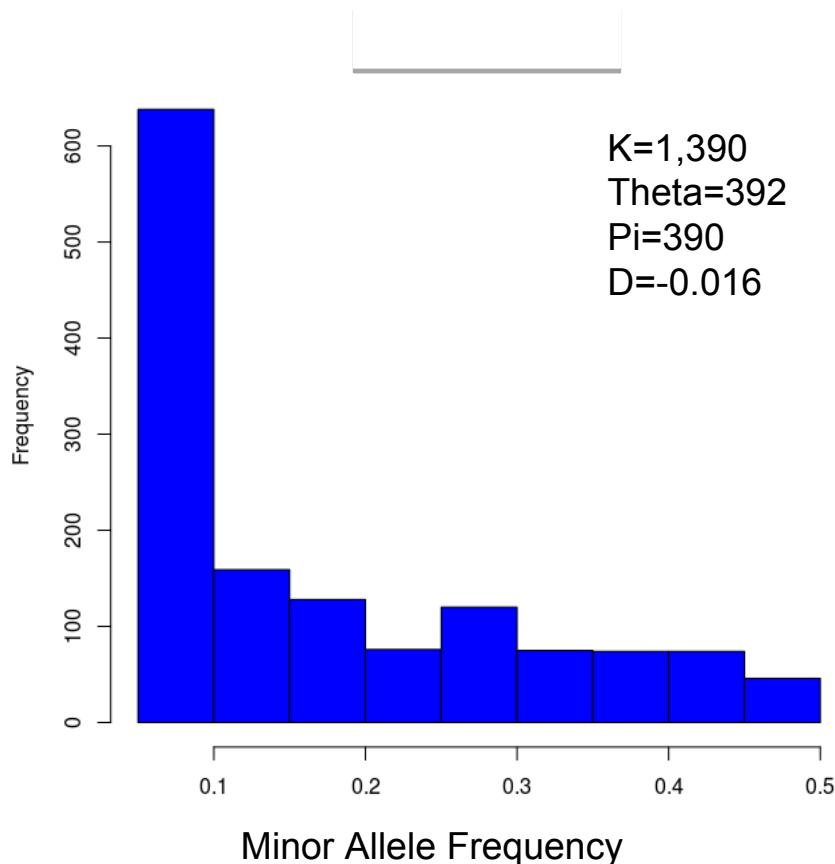


n=20; L=500kbp; no selection

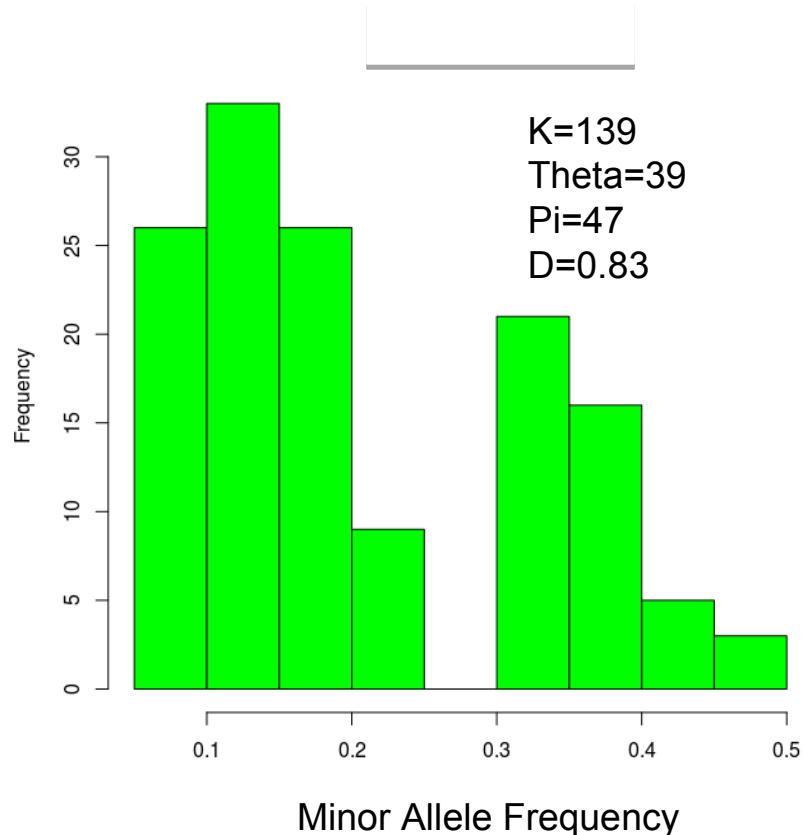


Demography matters!

n=20; L=500kbp; no selection



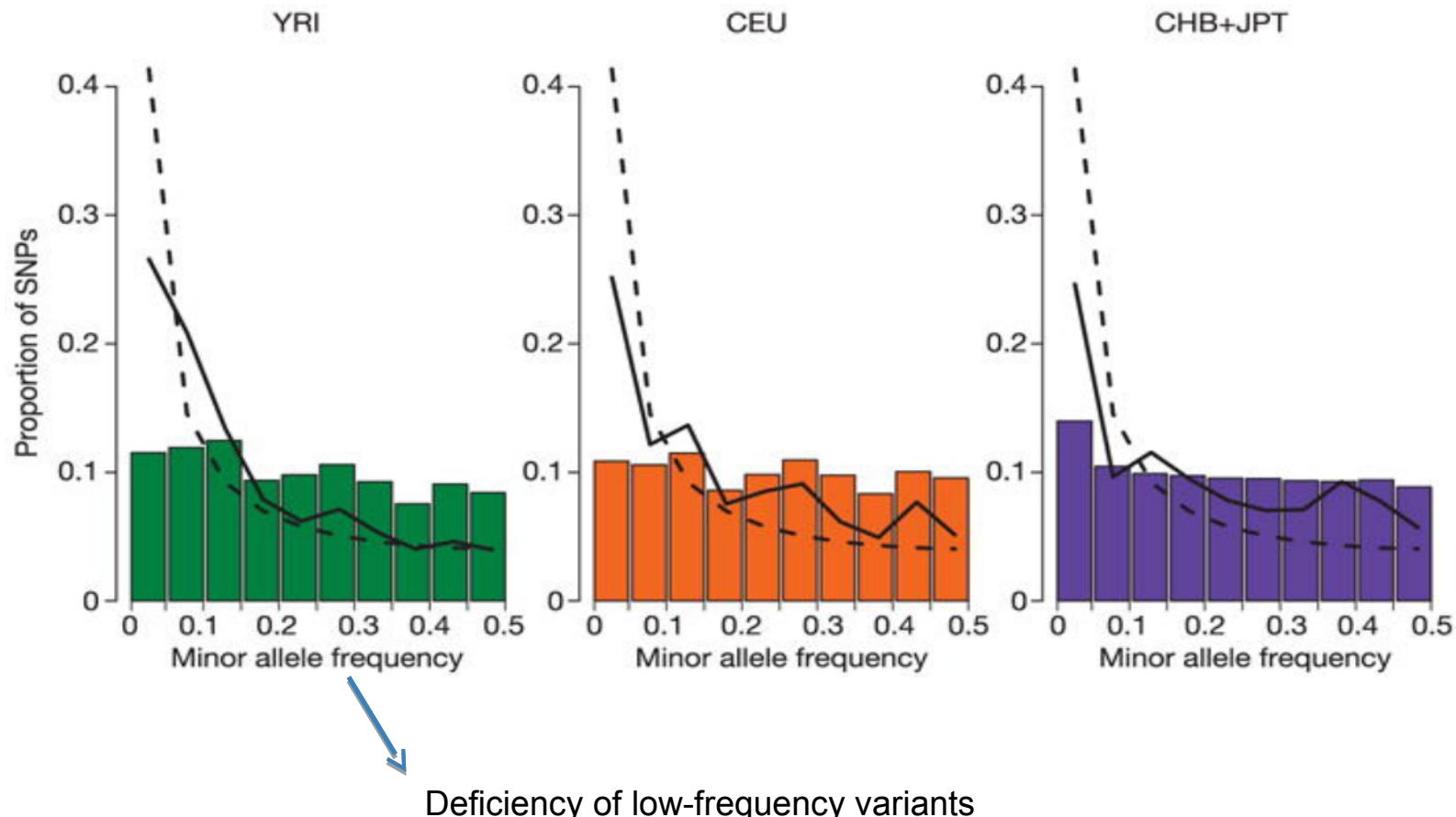
n=20; L=500kbp; no selection



- Depletion of segregating sites
- Excess of intermediate-frequency variants
- SFS-derived summary statistics may fail to distinguish between the effects of demography and selection

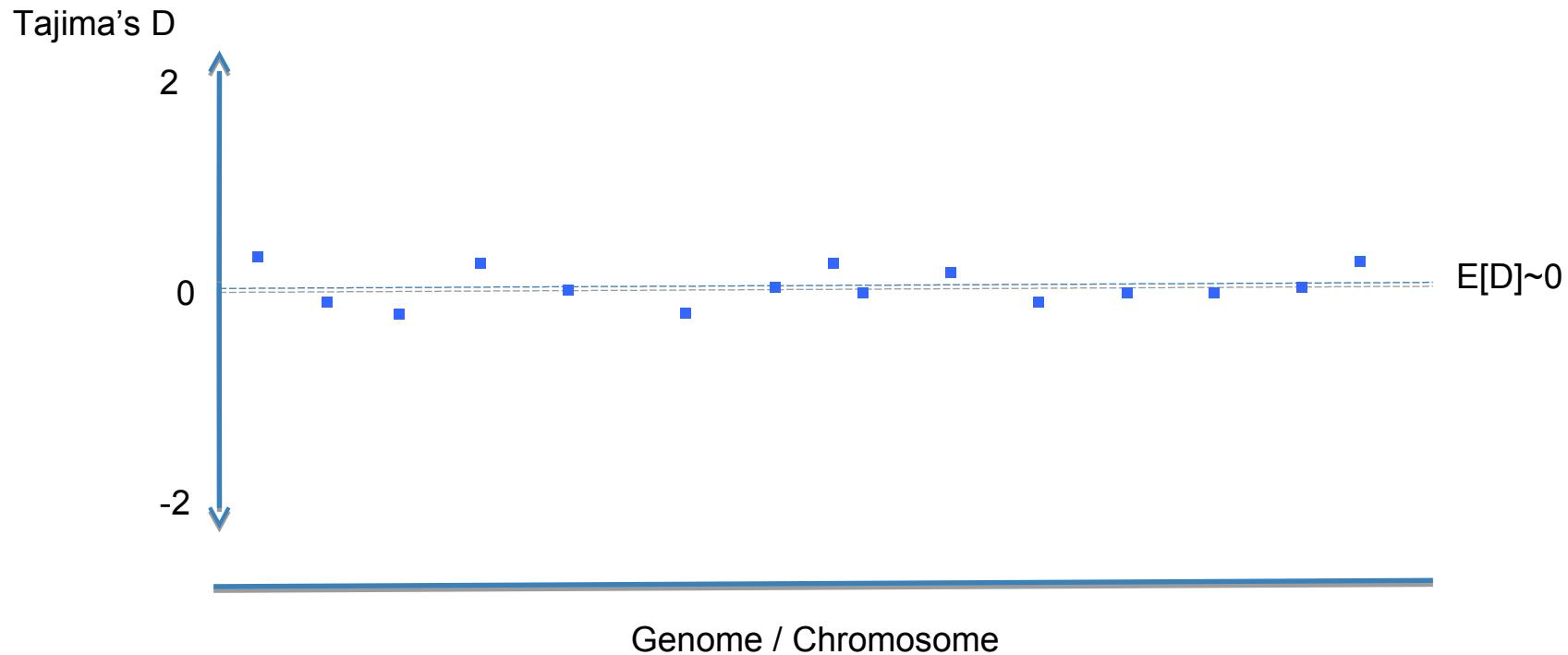
Experimental design matters?

The effect of ascertainment bias



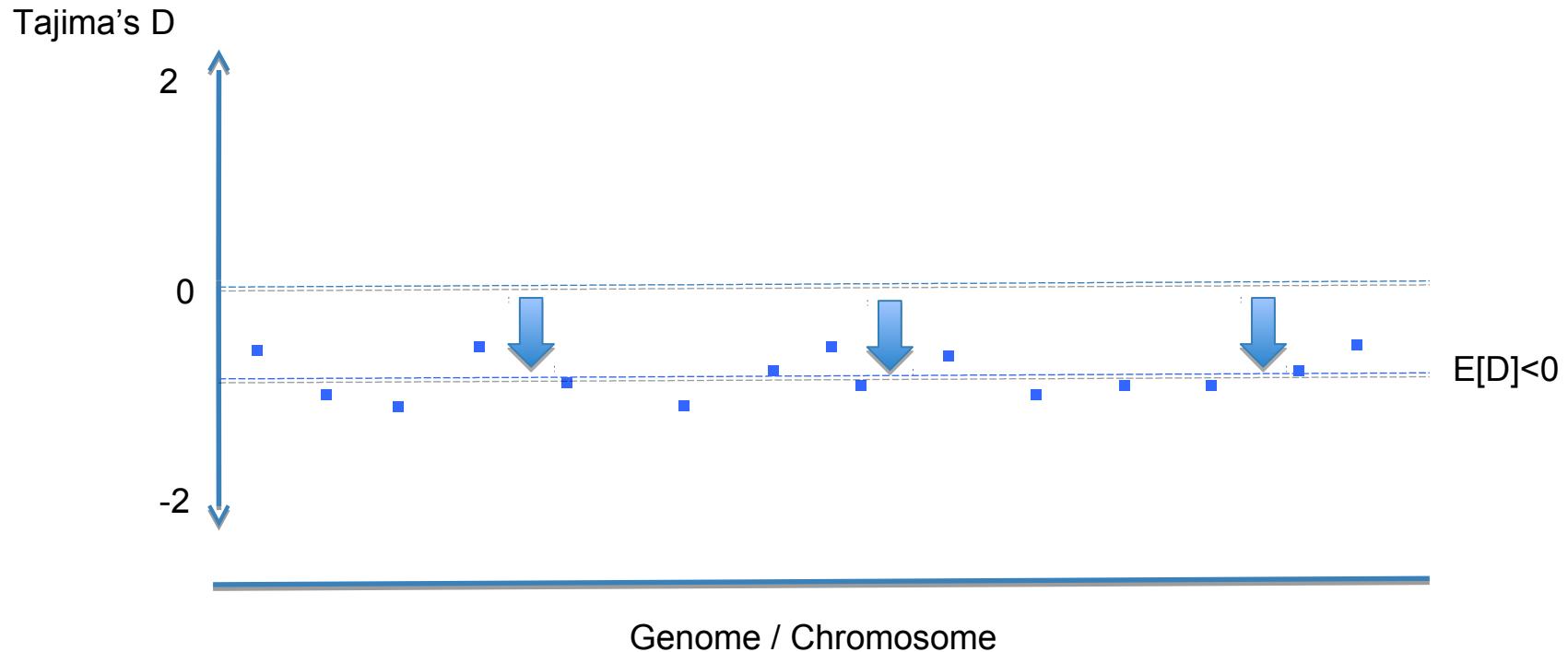
How to take neutral confounding factors into account?

Under constant population size:



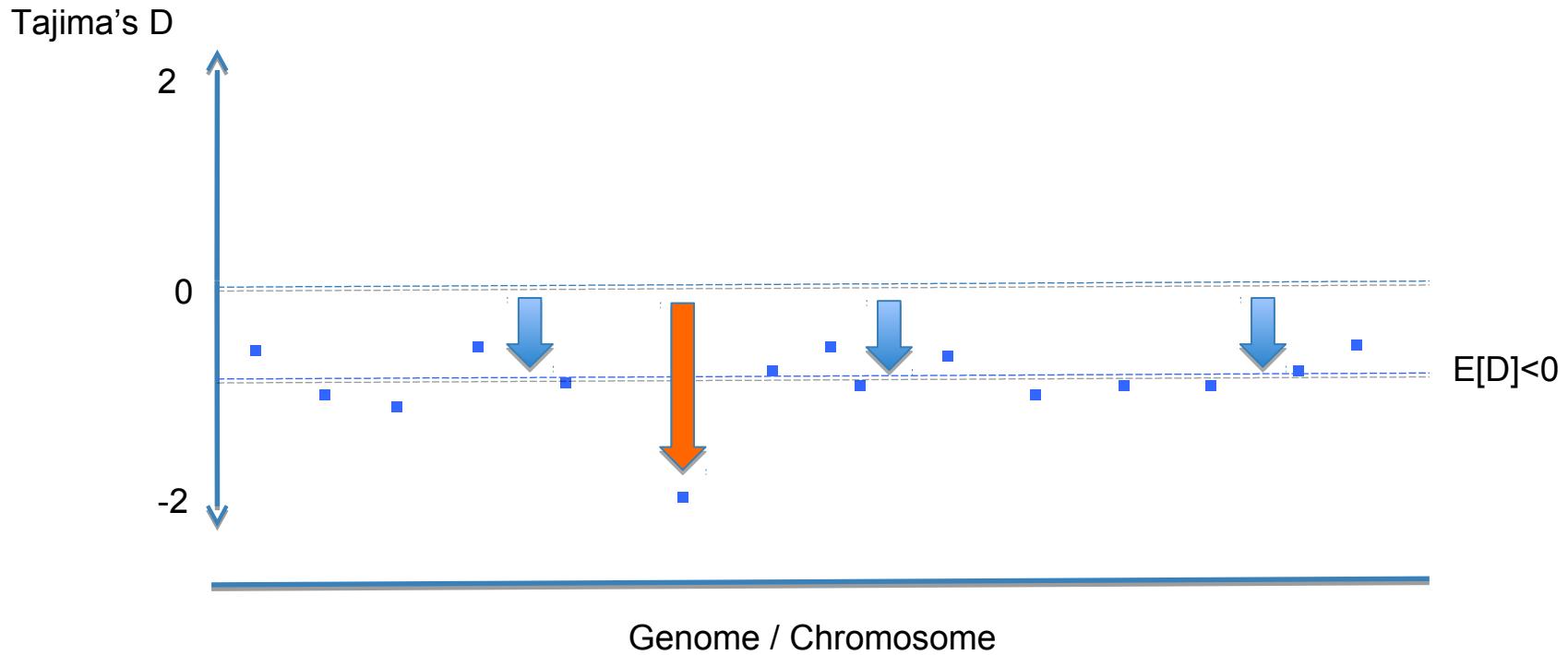
How to take neutral confounding factors into account?

Under expanding population size:



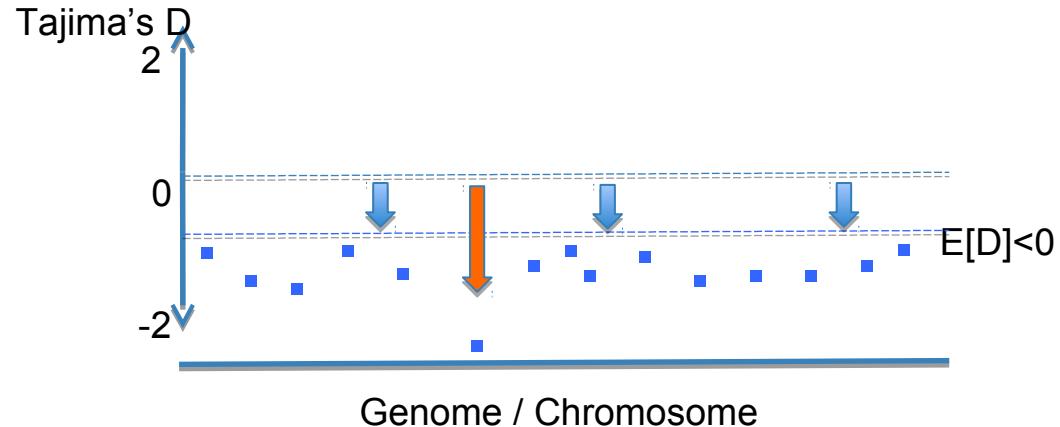
How to take neutral confounding factors into account?

Under expanding population size and positive selection:

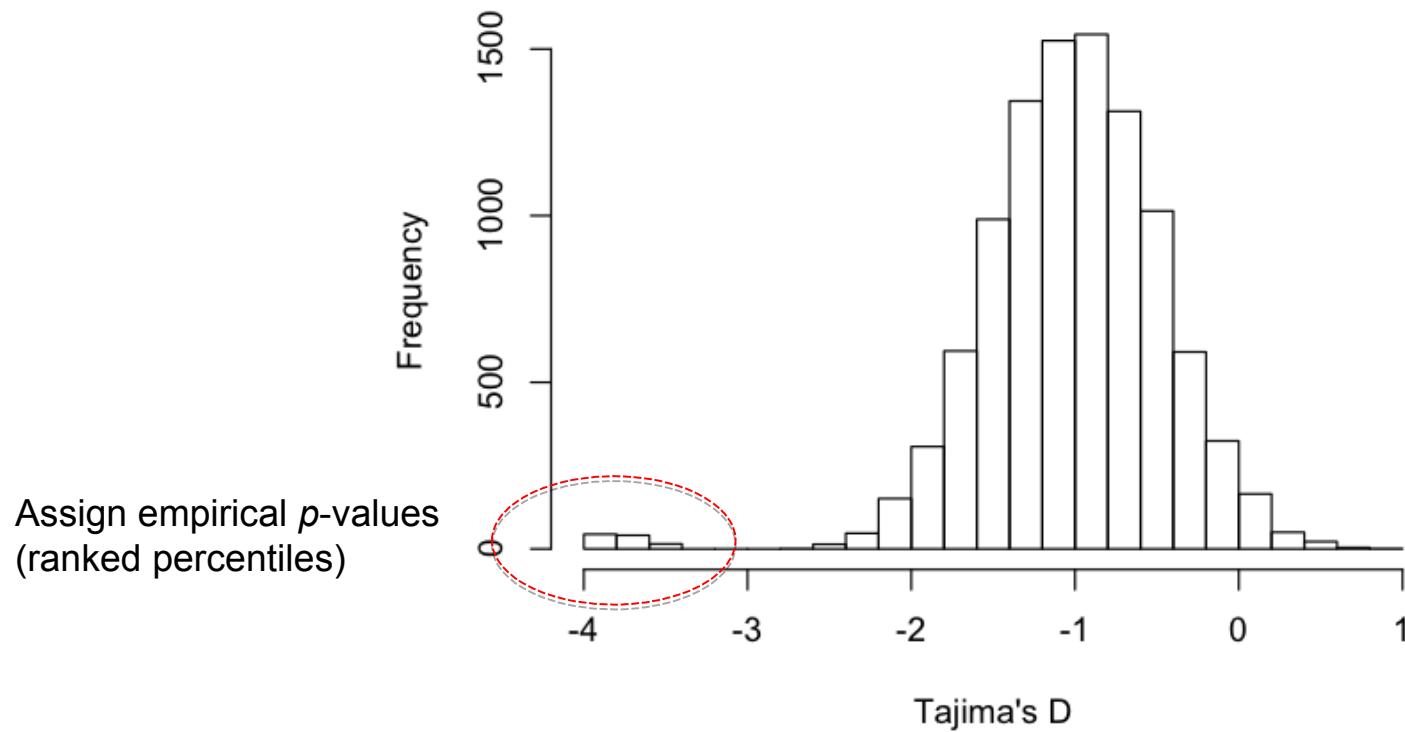


- Demography affects all loci equally, while selection changes local patterns

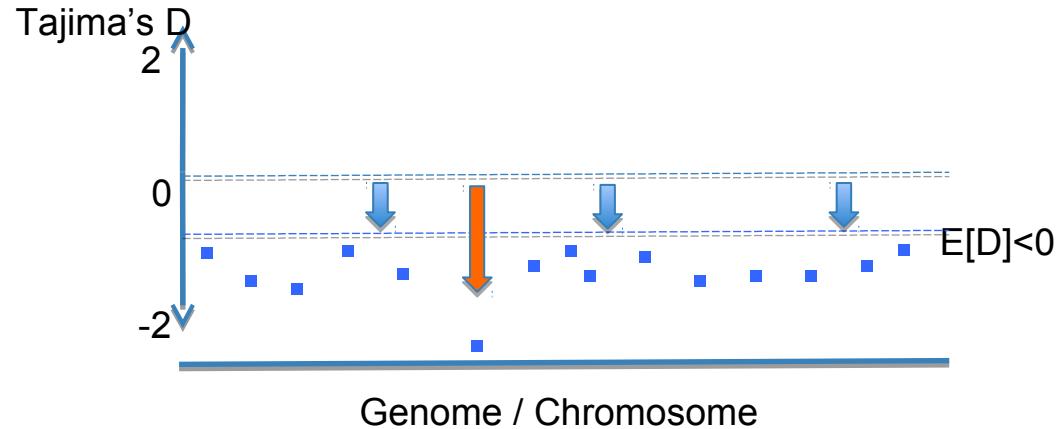
Outlier approach



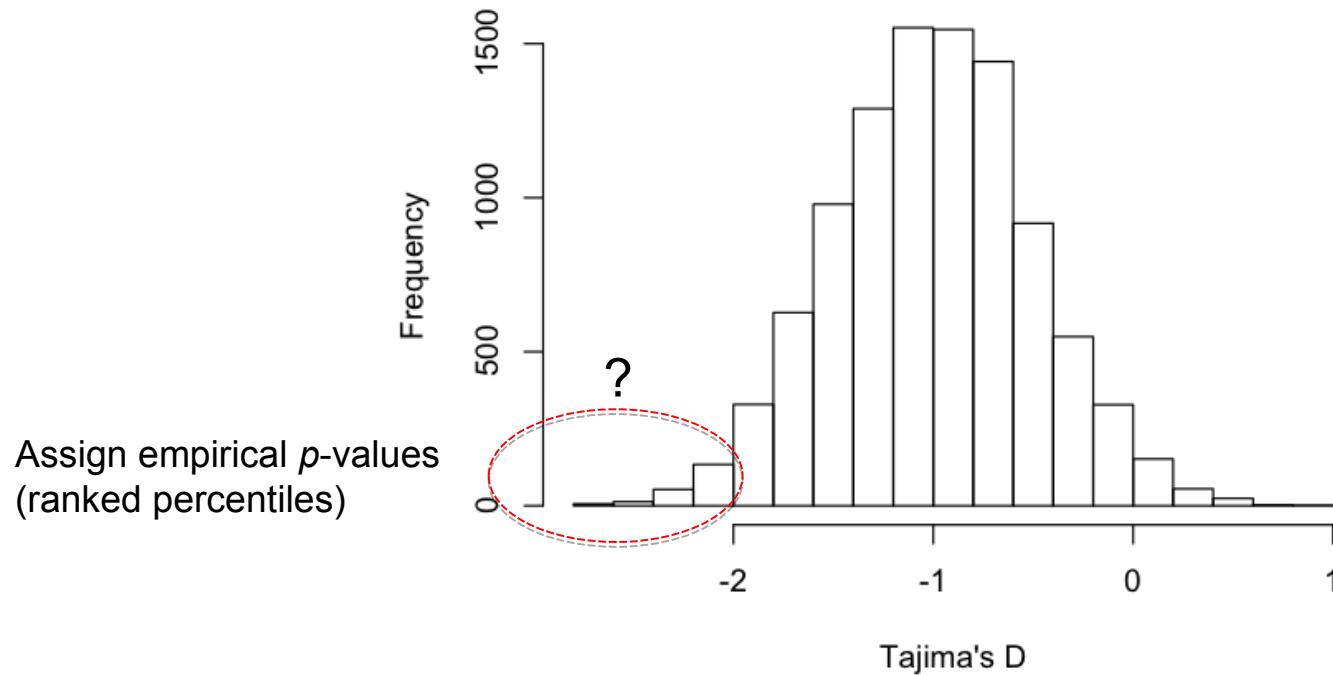
Empirical distribution



Outlier approach



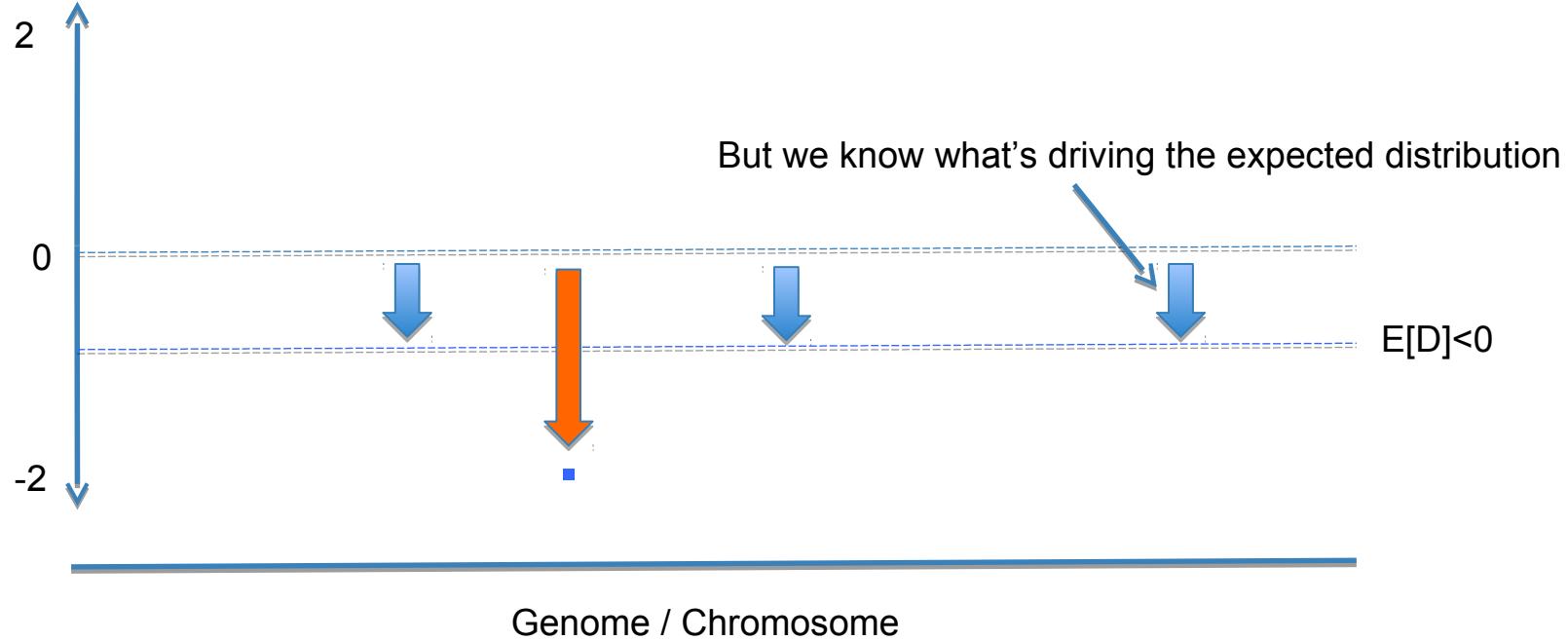
Empirical distribution



How to take neutral confounding factors into account?

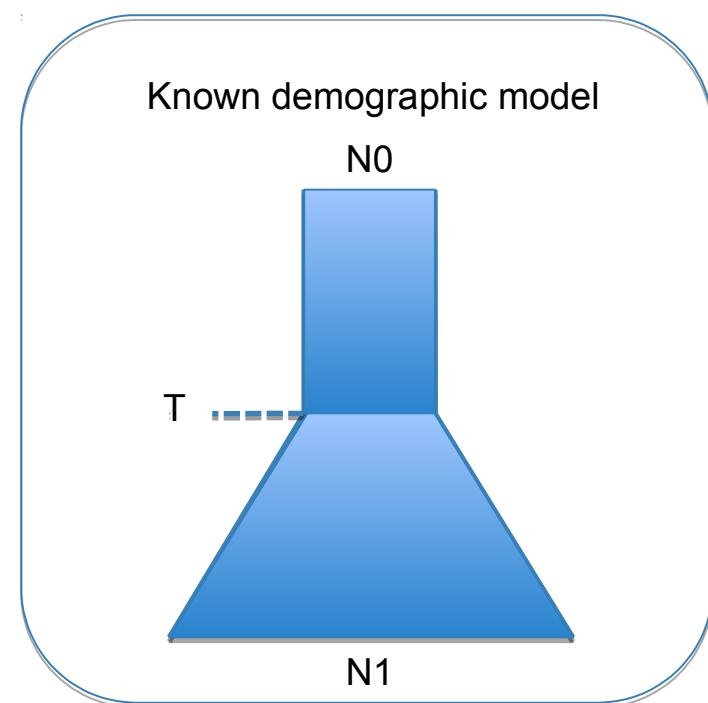
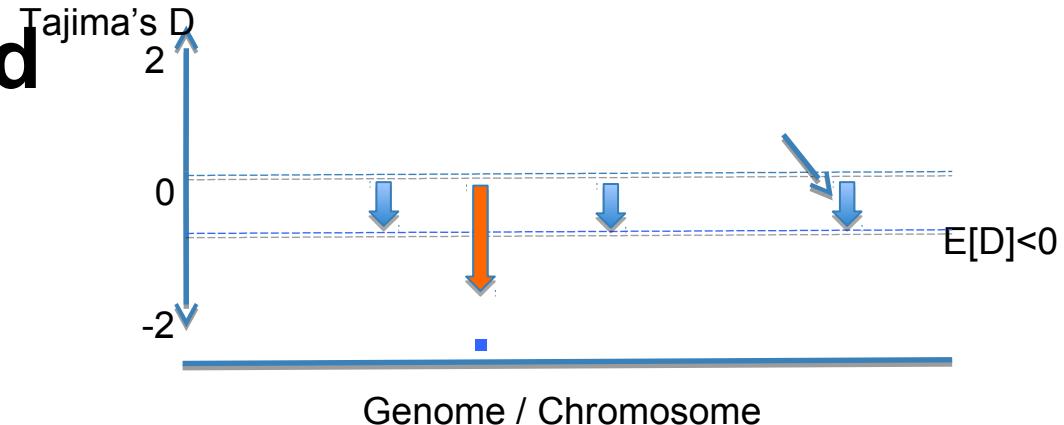
Under expanding population size and positive selection:

Tajima's D

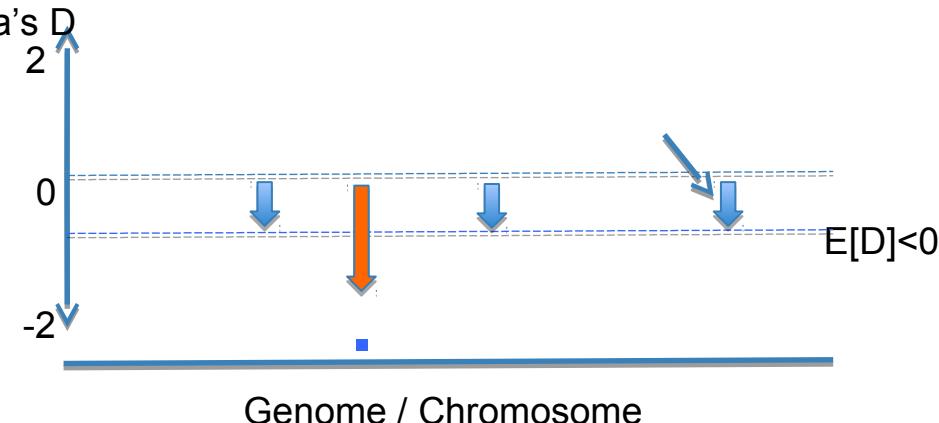


- Demography affects all loci equally, while selection changes local patterns
What should we do if we don't have genome-wide data?

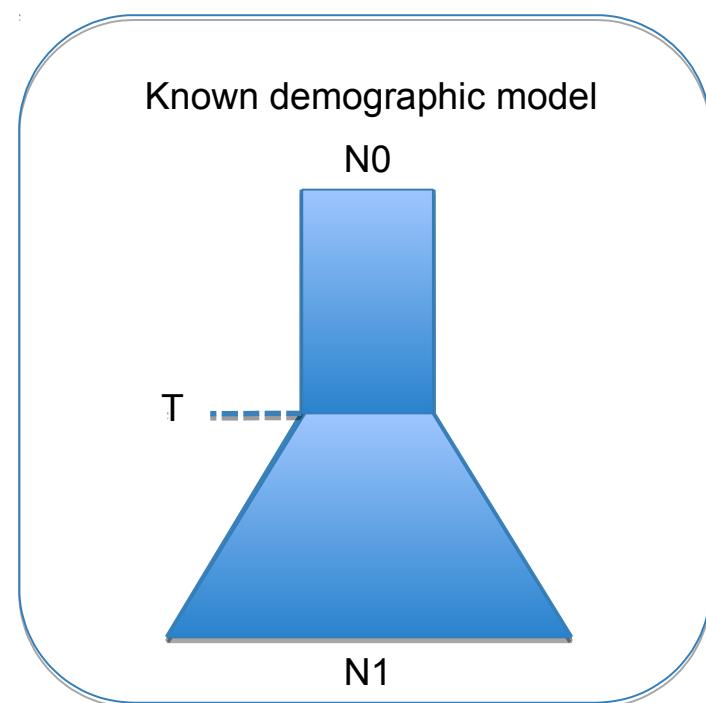
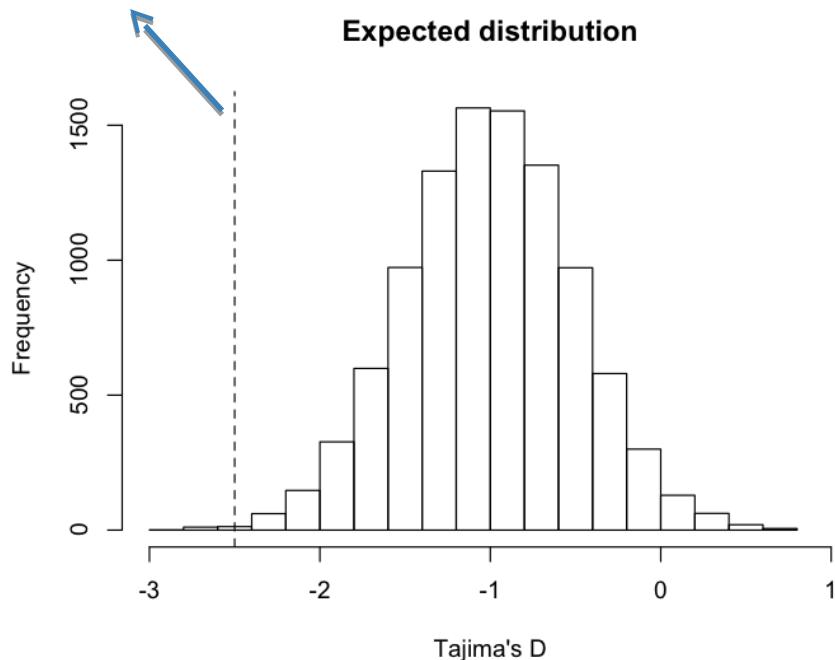
Simulations-based approach



Simulations-based approach

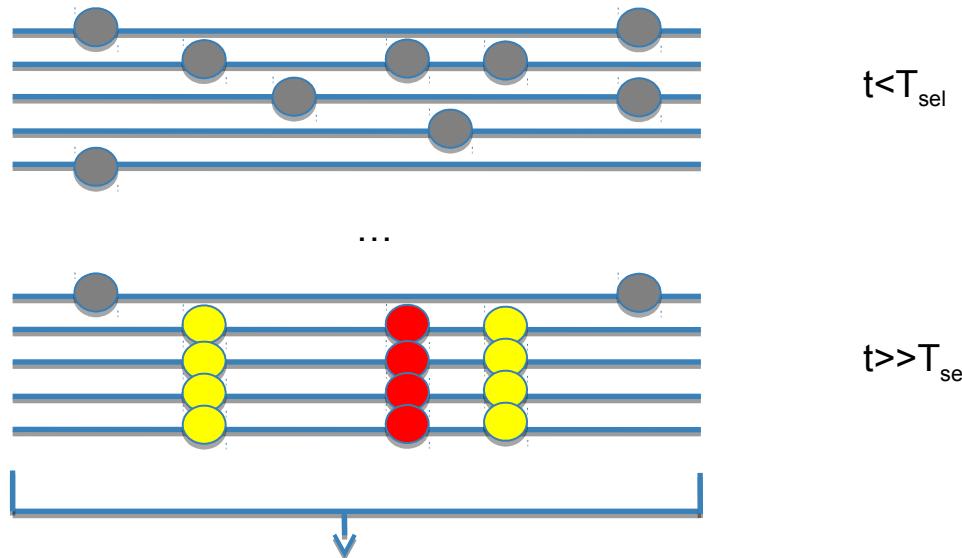


Assign p -values
(based on ranked percentile of observed value)



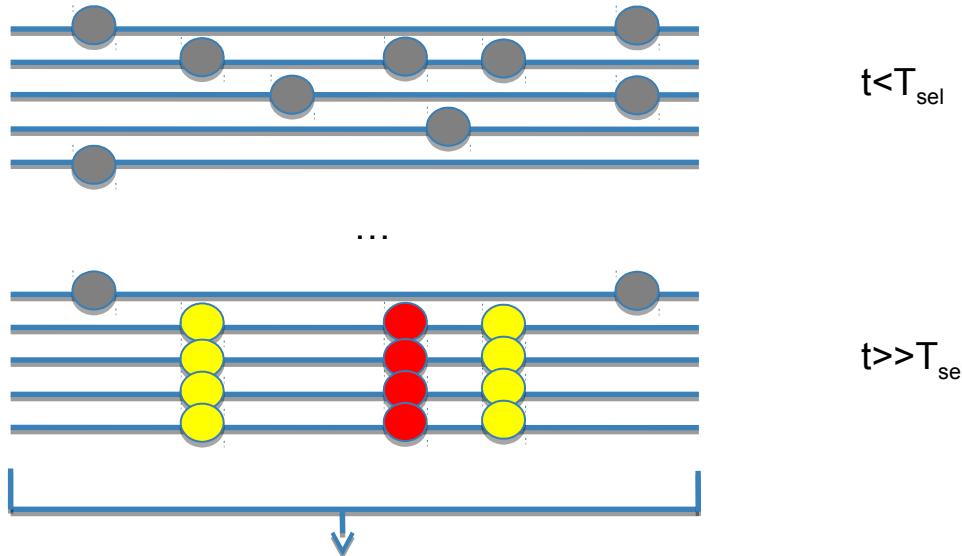
Let's assess statistical significance for our test of selection on EDAR.

Positive selection



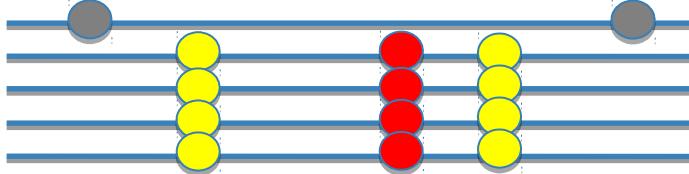
- Reduction of polymorphisms levels (Theta)
- Excess of low-frequency variants (Pi, Tajima's D, SFS)
- ?

Positive selection

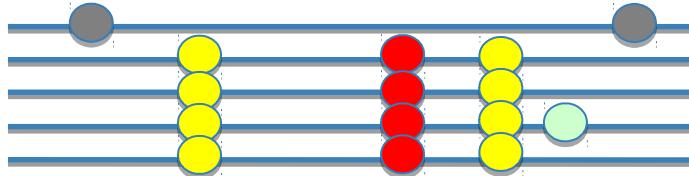


- Reduction of polymorphisms levels (Theta)
- Excess of low-frequency variants (Pi, Tajima's D, SFS)
- Extended haplotype homozygosity / Extended LD

Extended Haplotype Homozygosity

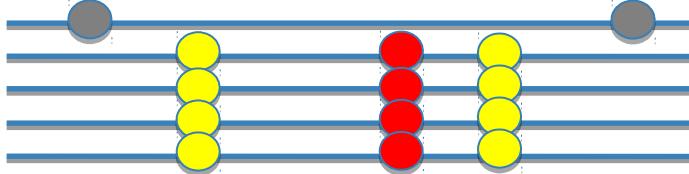


$t \gg T_{sel}$

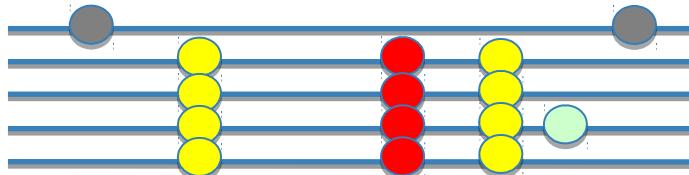


$t \gg \gg T_{sel}$

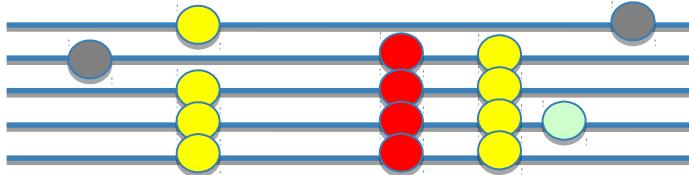
Extended Haplotype Homozygosity



$t >> T_{sel}$

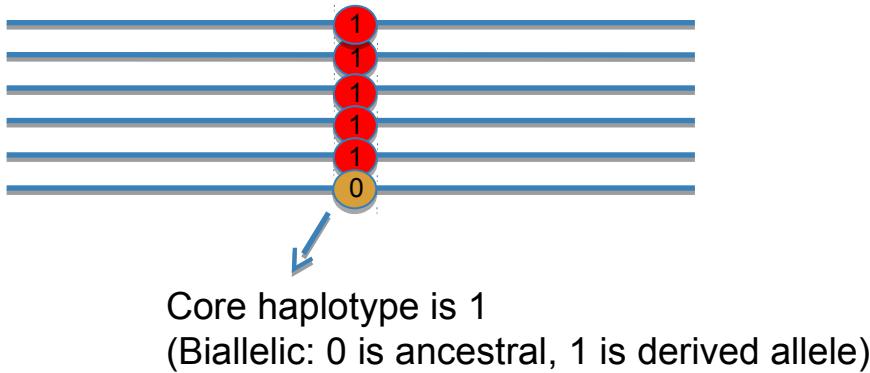


$t >>> T_{sel}$



$t >>> T_{sel}$

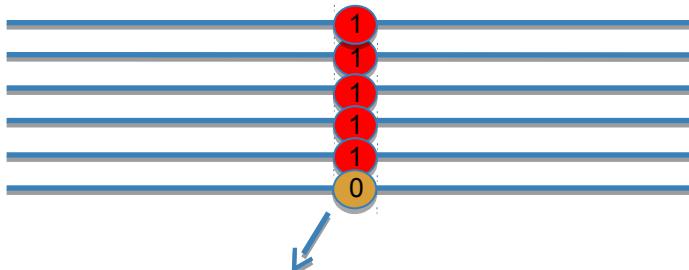
Extended Haplotype Homozygosity



$$EHH_c(x_i) = \sum_{h \in H_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}$$

Core SNP

Extended Haplotype Homozygosity



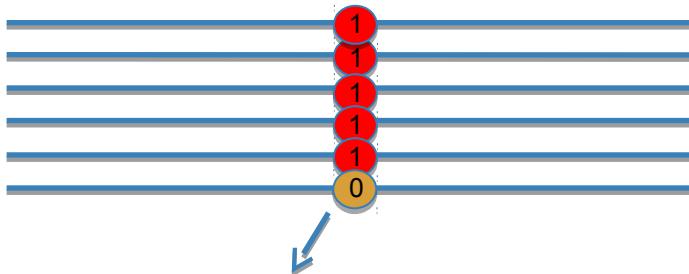
Core haplotype is 1
(Biallelic: 0 is ancestral, 1 is derived allele)

$$EHH_c(x_i) = \sum_{h \in H_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}$$

A blue arrow points from the left side of the equation towards the text below.

Until marker x_i
(starting from x_0)

Extended Haplotype Homozygosity

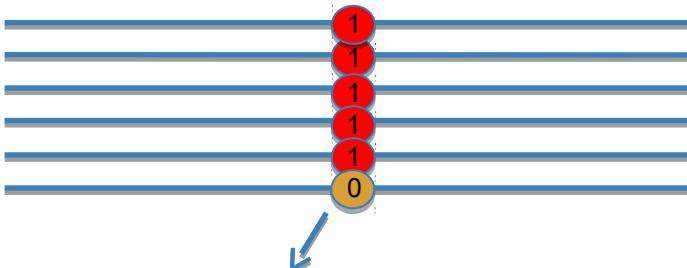


Core haplotype is 1
(Biallelic: 0 is ancestral, 1 is derived allele)

$$EHH_c(x_i) = \sum_{h \in H_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}$$

Sum across all unique haplotypes
carrying the core SNP

Extended Haplotype Homozygosity



Core haplotype is 1
(Biallelic: 0 is ancestral, 1 is derived allele)

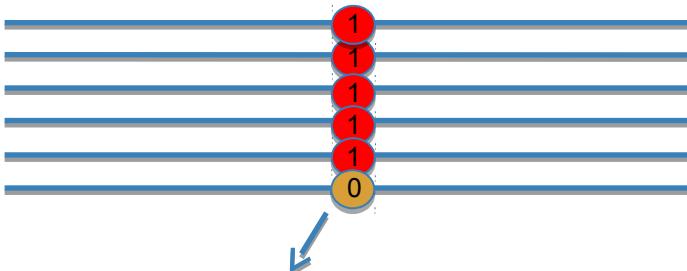
$$EHH_c(x_i) = \sum_{h \in H_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}$$

Sum across all unique haplotypes carrying the core SNP

n_h is haplotype frequency of h

n_h is haplotype frequency of the core SNP

Extended Haplotype Homozygosity



Core haplotype is 1
(Biallelic: 0 is ancestral, 1 is derived allele)

$$EHH_c(x_i) = \sum_{h \in H_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}$$

}

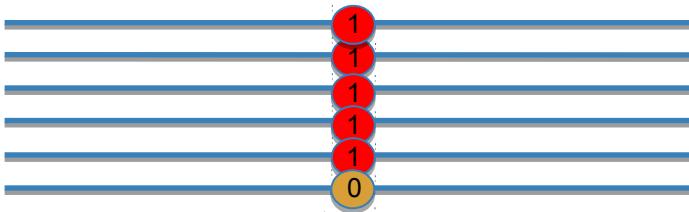
n_h is haplotype frequency of h

n_h is haplotype frequency of the core SNP

Sum across all unique haplotypes carrying the core SNP

$$EHH_c(x_i=0) = ?$$

Extended Haplotype Homozygosity



Core haplotype is 1
(Biallelic: 0 is ancestral, 1 is derived allele)



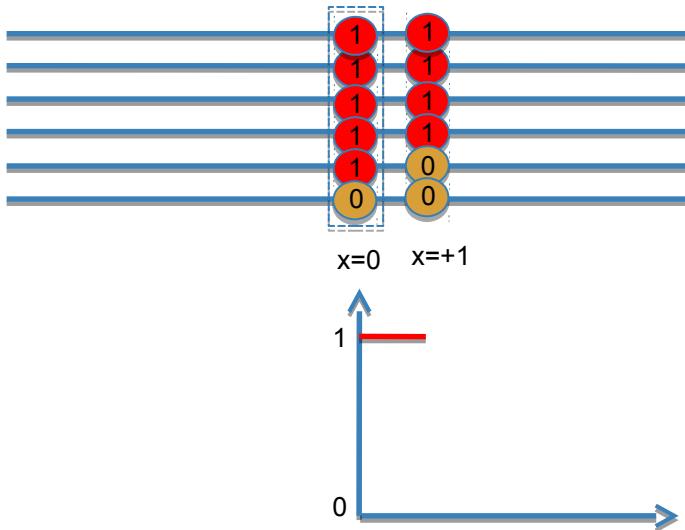
n_h is haplotype frequency of h

n_c is haplotype frequency of the core SNP

Sum across all unique haplotypes carrying the core SNP

$$EHH_c(x_i=0) = \frac{\begin{pmatrix} 5 \\ 2 \end{pmatrix}}{\begin{pmatrix} 5 \\ 2 \end{pmatrix}} = 1$$

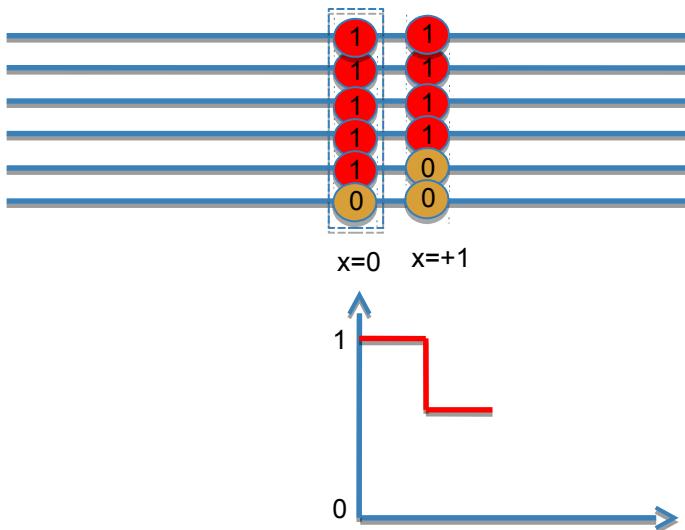
Extended Haplotype Homozygosity



$$EHH_c(x_i = +1) = ?$$

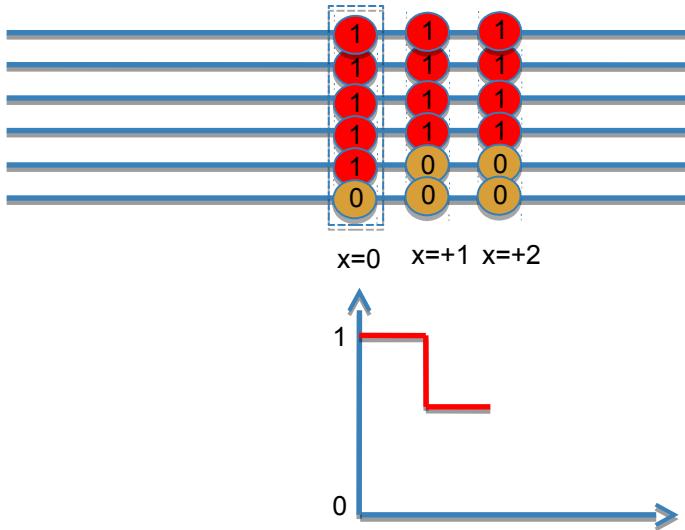
How many unique haplotypes carrying the core SNP?
What is their frequency?

Extended Haplotype Homozygosity



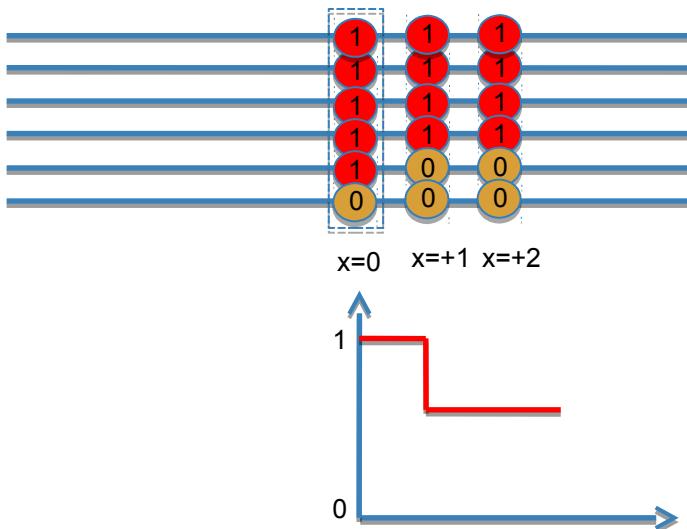
$$EHH_c(x_i = +1) = \frac{\binom{4}{2} + \binom{1}{2}}{\binom{5}{2}} = \frac{6 + 0}{10} = 0.60$$

Extended Haplotype Homozygosity



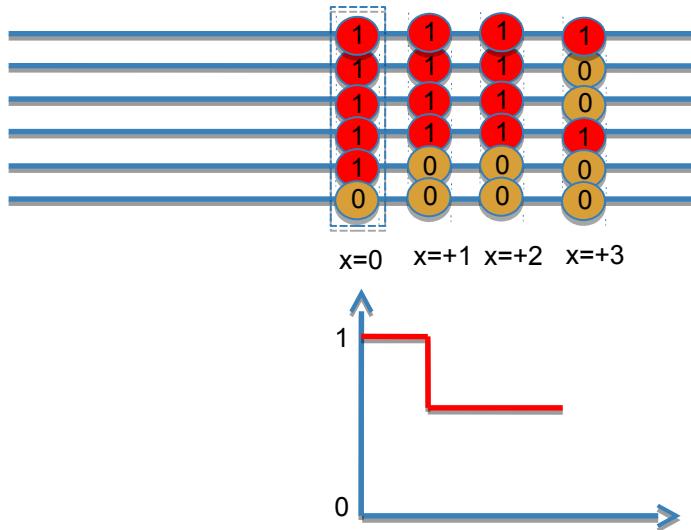
$$EHH_c(x_i = +2) = ?$$

Extended Haplotype Homozygosity



$$EHH_c(x_i = +2) = EHH_c(x_i = +1) = 0.60$$

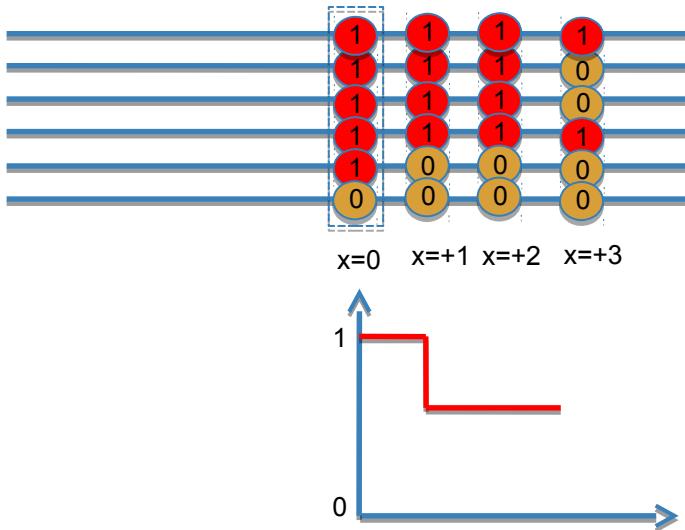
Extended Haplotype Homozygosity



$$EHH_c(x_i) = \sum_{h \in H_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}$$

How many unique haplotypes carrying the core SNP?
What is their frequency?

Extended Haplotype Homozygosity



How many unique haplotypes carrying the core SNP?

What is their frequency?

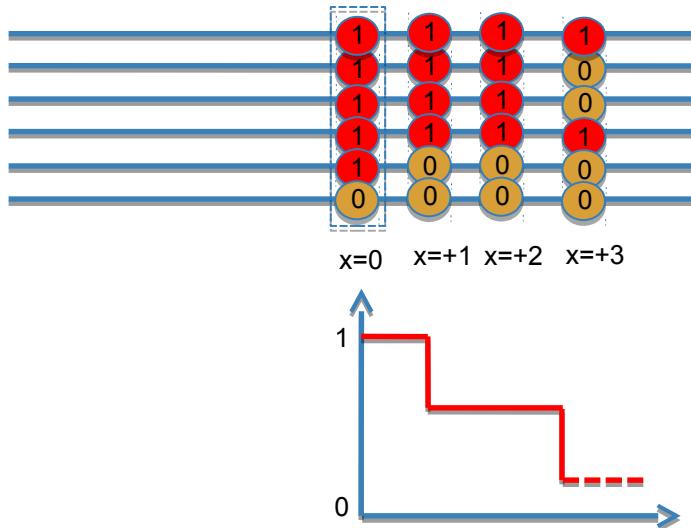
1111 with freq=2

1110 with freq=2

1000 with freq=1

$$EHH_c(x_i = +3) = ?$$

Extended Haplotype Homozygosity



$$EHH_c(x_i) = \sum_{h \in H_c(x_i)} \frac{\binom{n_h}{2}}{\binom{n_c}{2}}$$

How many unique haplotypes carrying the core SNP?

What is their frequency?

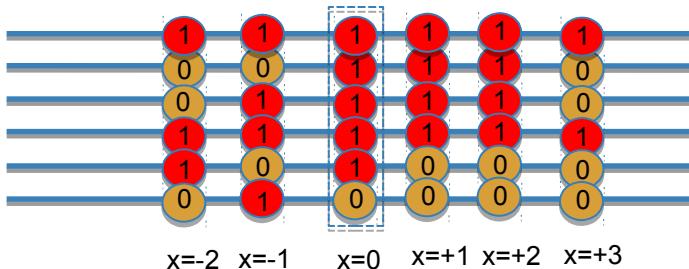
1111 with freq=2

1110 with freq=2

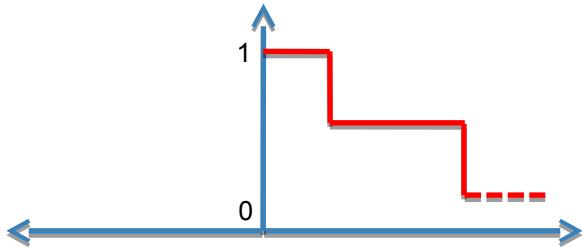
1000 with freq=1

$$EHH_c(x_i = +3) = \frac{\binom{2}{2} + \binom{2}{2} + \binom{1}{2}}{\binom{5}{2}} = \frac{1+1+0}{10} = 0.20$$

Extended Haplotype Homozygosity



n	$n \text{ choose } 2$
1	0
2	1
3	3
4	6
5	10
6	15

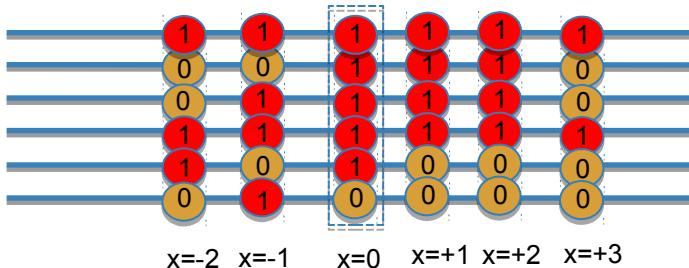


$$EHH_c(x_i = -1) = ?$$

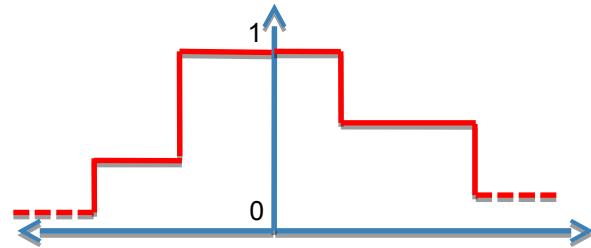
$$EHH_c(x_i = -2) = ?$$

Comment on differences (if any) between $EHH(x=+2)$ and $EHH(x=-2)$.

Extended Haplotype Homozygosity



n	$n \text{ choose } 2$
1	0
2	1
3	3
4	6
5	10
6	15



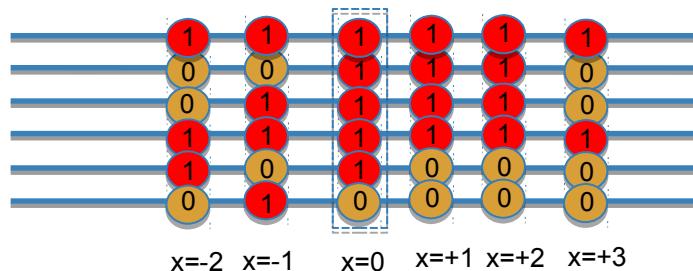
$$EHH_c(x = -1) = \frac{\binom{3}{2} + \binom{2}{2}}{\binom{5}{2}} = \frac{3+1}{10} = 0.4$$

$$EHH_c(x = -2) = \frac{\binom{2}{2} + \binom{1}{2} + \binom{1}{2}}{\binom{5}{2}} = \frac{1+0+0}{10} = 0.1$$

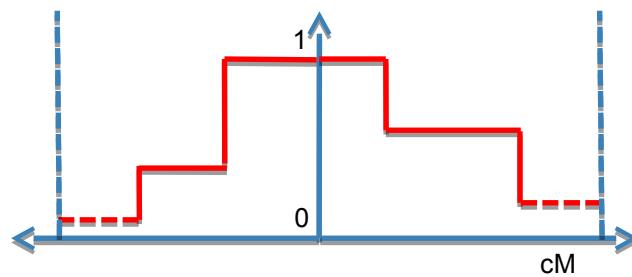
+ (1 choose 2)

Comment on differences (if any) between $EHH(x=+2)$ and $EHH(x=-2)$?

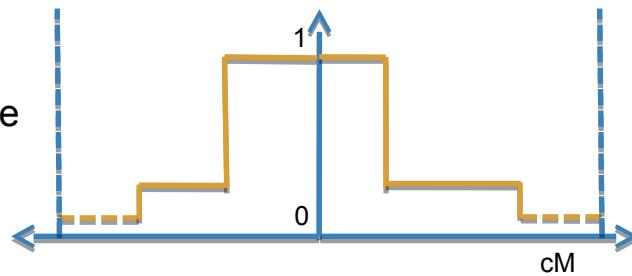
Integrated Haplotype Score



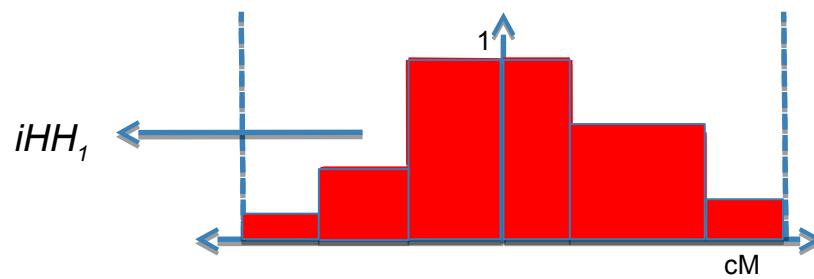
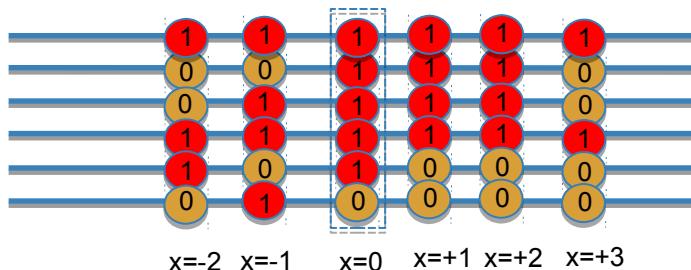
For the derived allele



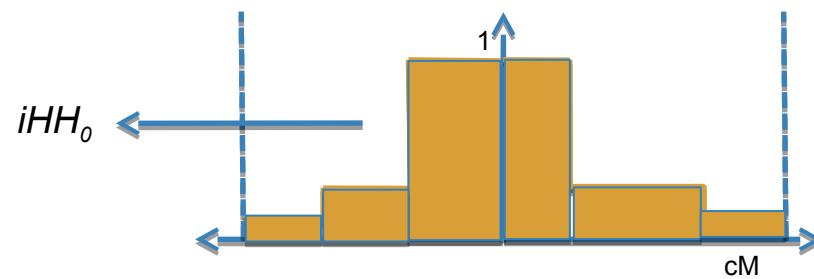
For the ancestral allele



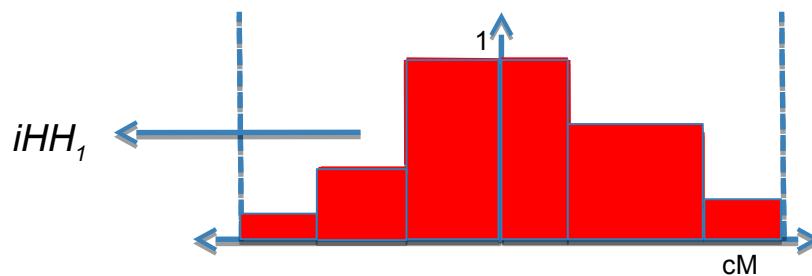
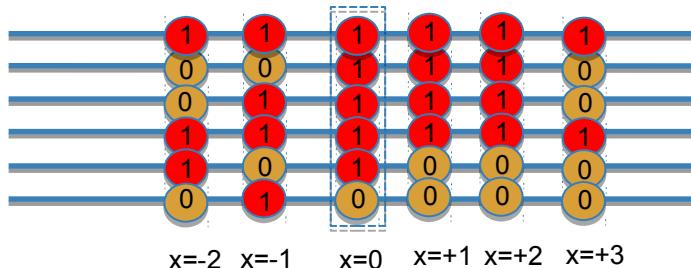
Integrated Haplotype Score



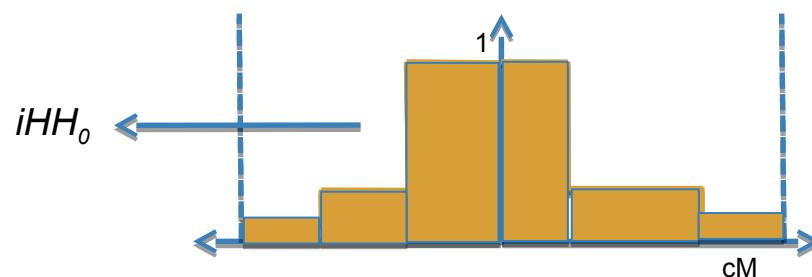
Integrated haplotype homozygosity (iHH)



Integrated Haplotype Score



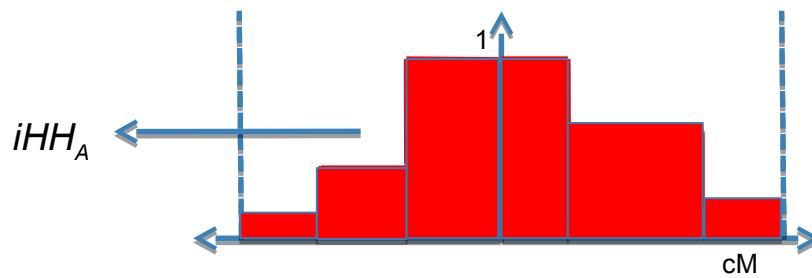
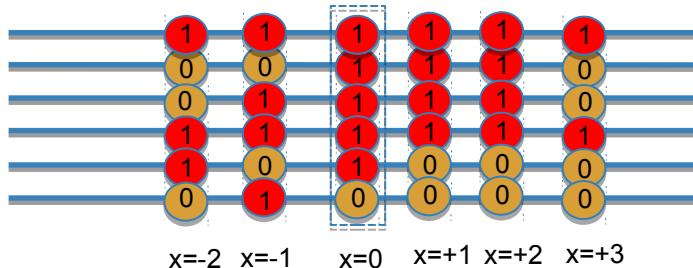
Integrated haplotype homozygosity (iHH)



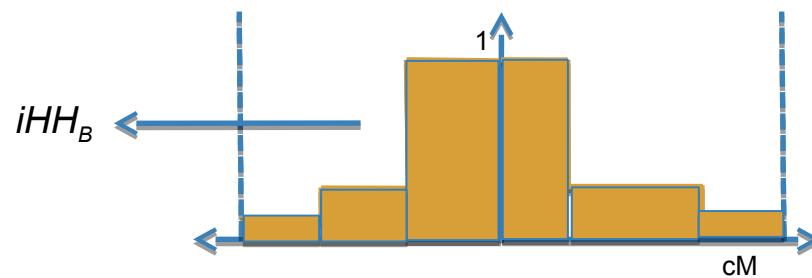
Integrated haplotype score:
 $iHs = \ln(iHH_1/iHH_0)$

Genome-wide normalization in frequency bins
(to mean=0 and sd=1)

Cross-population Extended Haplotype Homozygosity



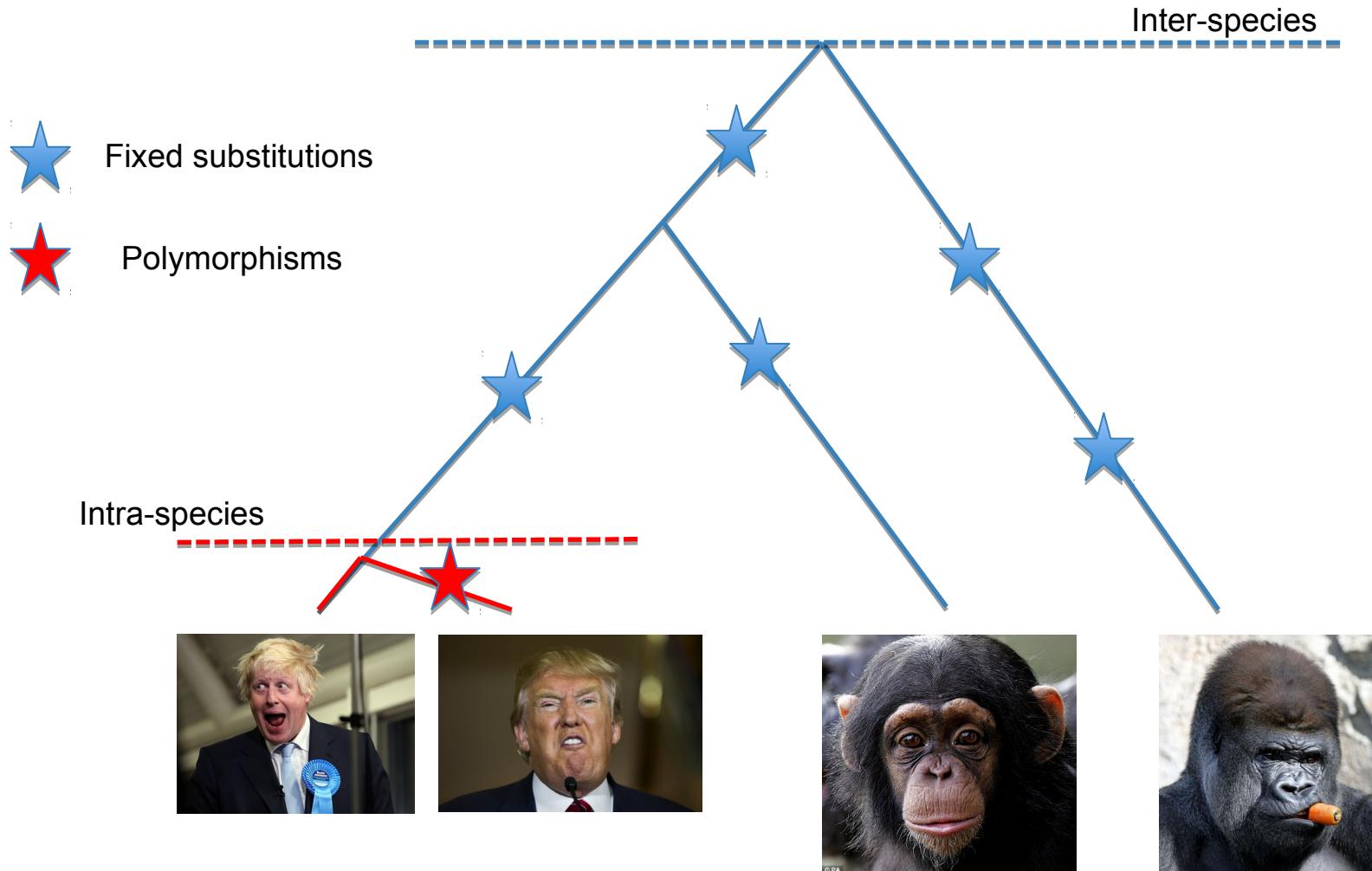
Integrated haplotype homozygosity (iHH)
for **populations A and B**



Integrated haplotype score:
 $XP-EHH = \ln(iHH_A/iHH_B)$

Genome-wide normalization in frequency bins
(to mean=0 and sd=1)

Inferring inter-species selection



State-of-the-art methods to detect natural selection

1. Composite scores (Grossman et al. 2013)

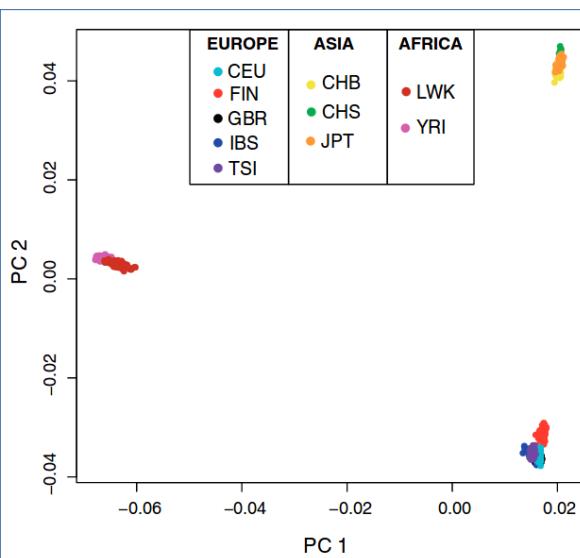
$$BF_t = \frac{P(v_t \in bin_{t,k} | selected)}{P(v_t \in bin_{t,k} | unselected)}$$

and defined the composite score as the product of the Bayes factor of each test:

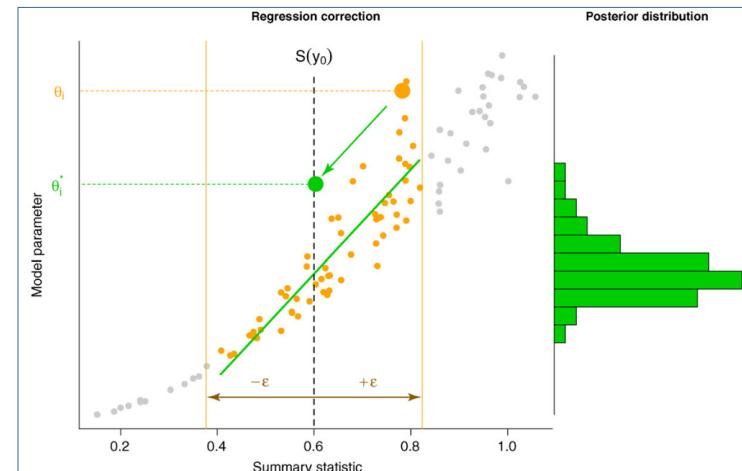
$$CMS_{GW} = \prod_{t \in tests} BF_t$$

3. Unsupervised machine learning

(PCA, Duforet-Frebourg et al. 2016)



2. Simulations-based (rejection, ABC)

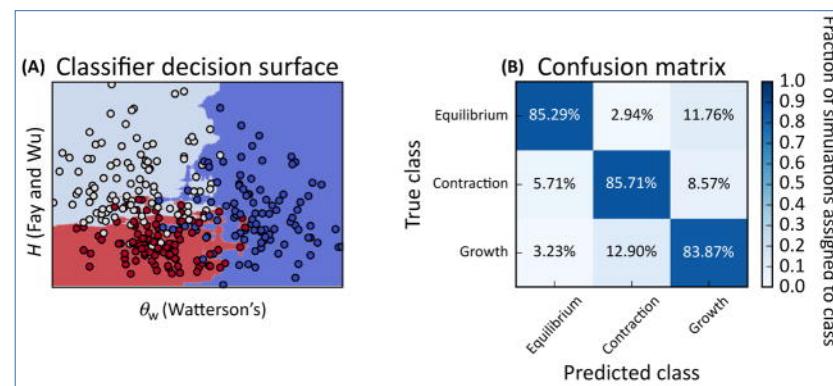


3. Unsupervised machine learning

(PCA, Duforet-Frebourg et al. 2016)

4. Supervised machine learning

(SVM, Schrider & Kern 2018)

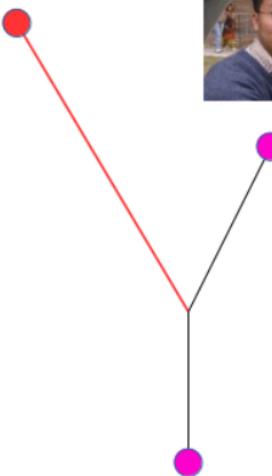
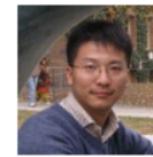


Adaptation and population genetic differentiation

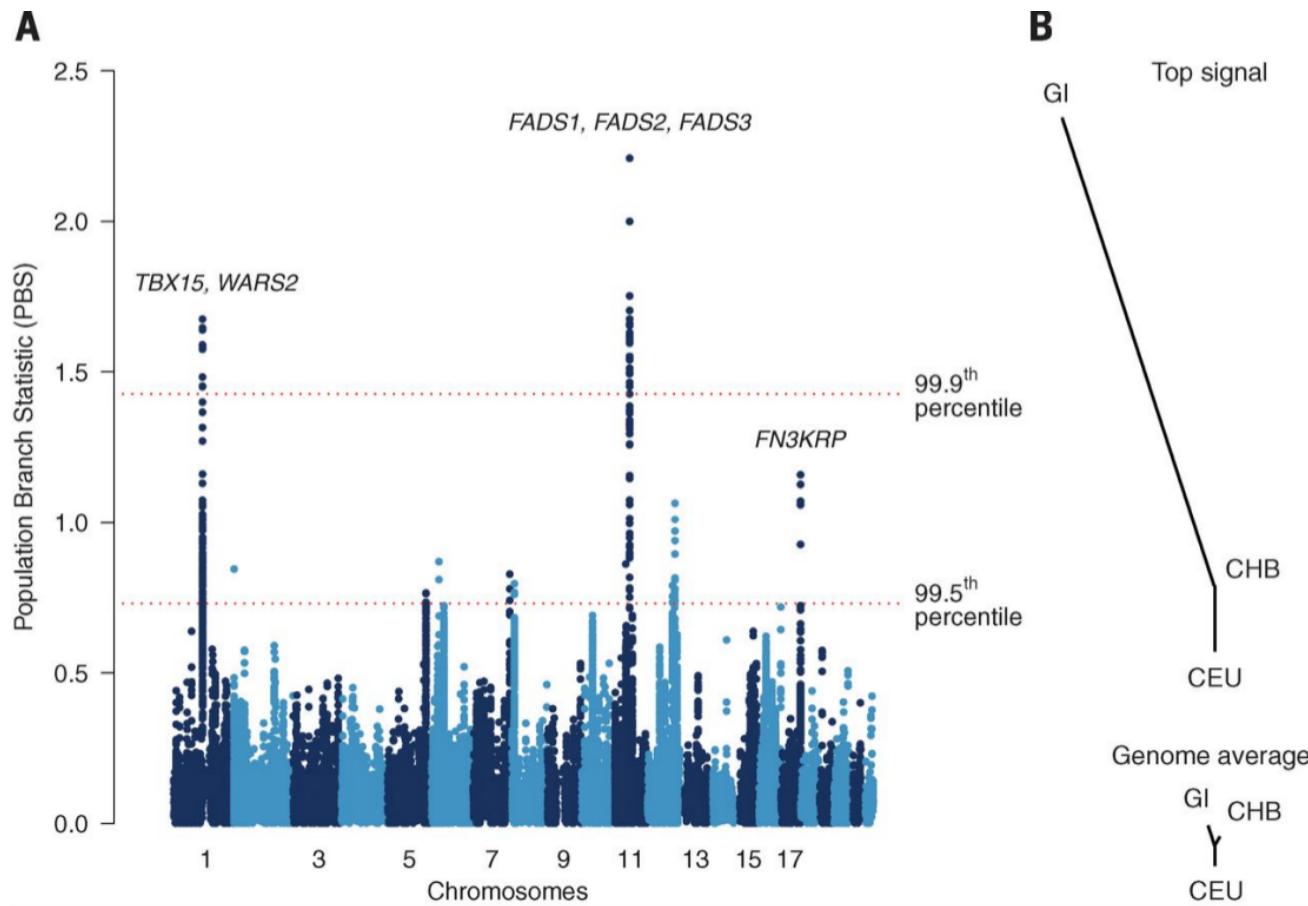
Neutral evolution



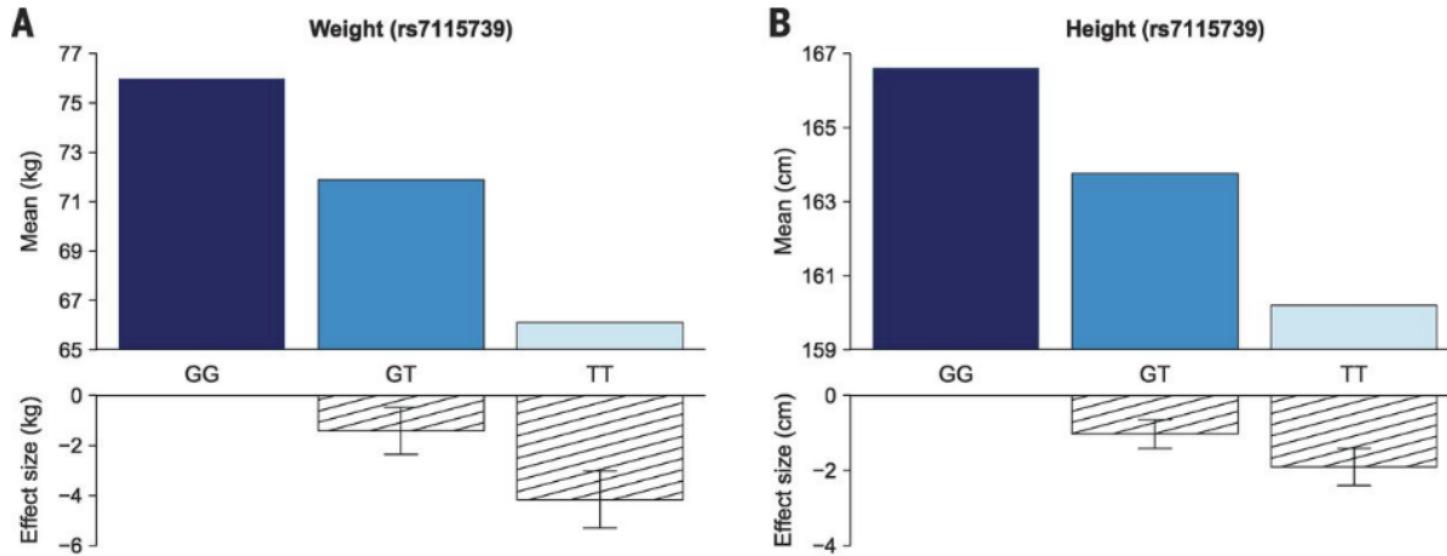
Adaptive evolution



Adaptation and population genetic differentiation



Effect on anthropometric phenotypes



1. Large effect sizes (4kg and 2cm)
2. Association with height replicated in European cohorts

→ Sites targeted by natural selection are likely to be **functional**; population **histories** affect the frequency of functional alleles

Population and medical genetics

