

Genes and Genomes in Populations and Evolution: GWAS Workshop

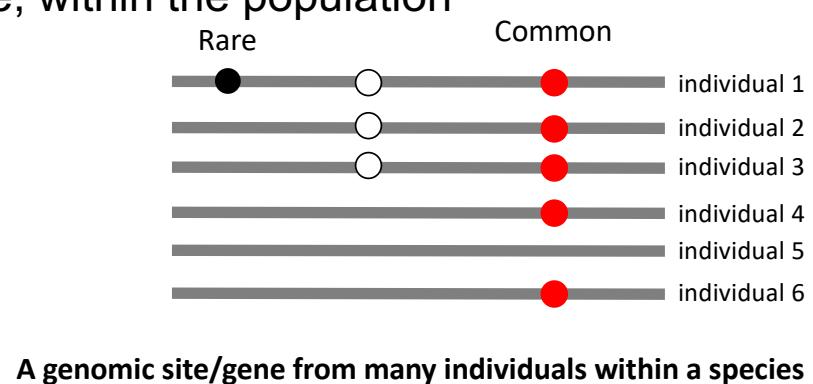
A brief intro: population genomics

- Population **genetics** is the study of genetic variation within species.
- Population **genomics** expands the data to study variation within species using whole genome data.
- **Population genomics:**
 - Is more challenging data to gather, more expensive, more challenging to analyse
 - Genome-scale data produces a more comprehensive picture
- Demography (population size, migration, population structuring)
- Natural selection (purifying, adaptive, balancing)

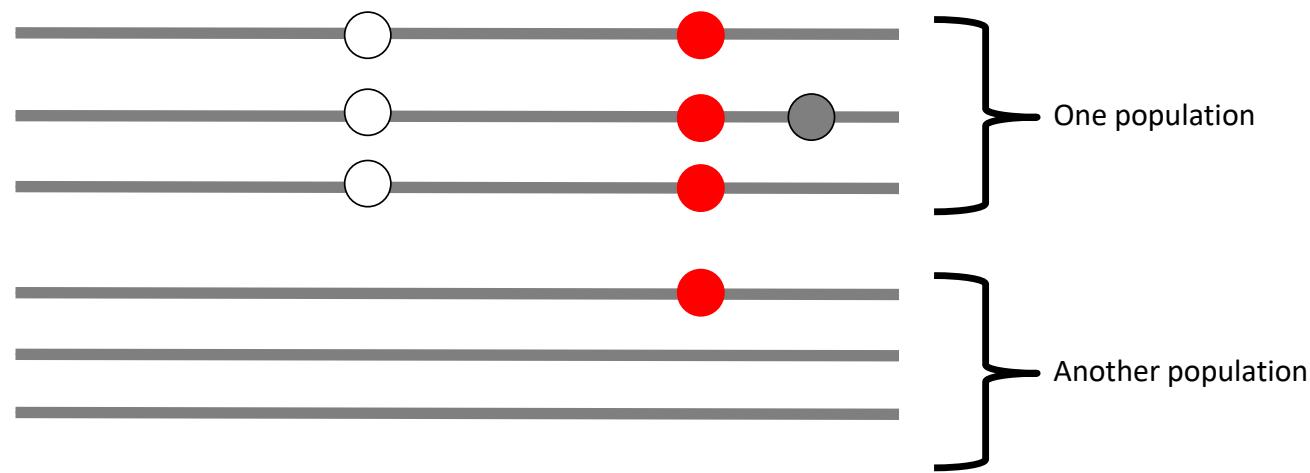
Concept: genetic diversity

- Polymorphisms/alleles/variants: sites in a genome that differ between individuals of a species
 - Single nucleotide polymorphisms (SNPs)
 - Small insertion/deletions (indels)
 - Transposon insertions
 - ‘Structural’ variants: duplications, rearrangements, large insertions/deletions
- Initial origin: a mutation in one individual
 - **All polymorphisms begin their existence in just one individual**
- Polymorphisms then move through space and time, within the population
- Their frequency in the population will change

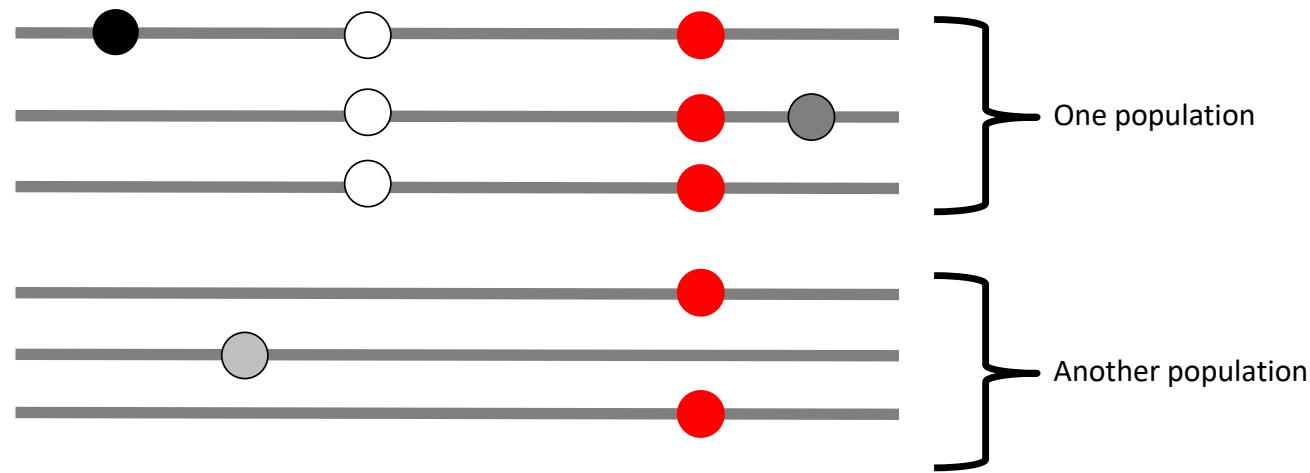
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ATCCG-TAAATTT
AGCCG-TAAATT
AGCCGTAAAATTT



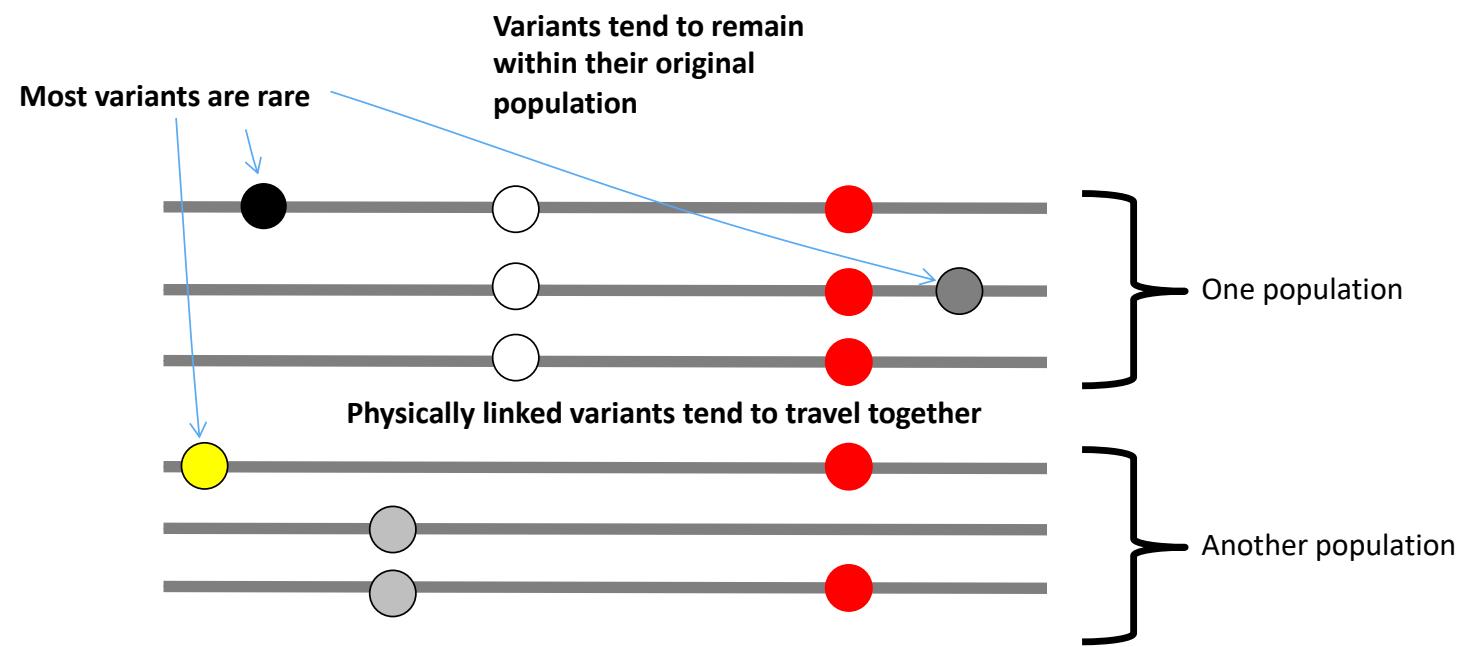
Concept: genetic diversity



Concept: genetic diversity



Concept: genetic diversity



Many signals can be found within polymorphism data.

The patterns of polymorphism data are complex.

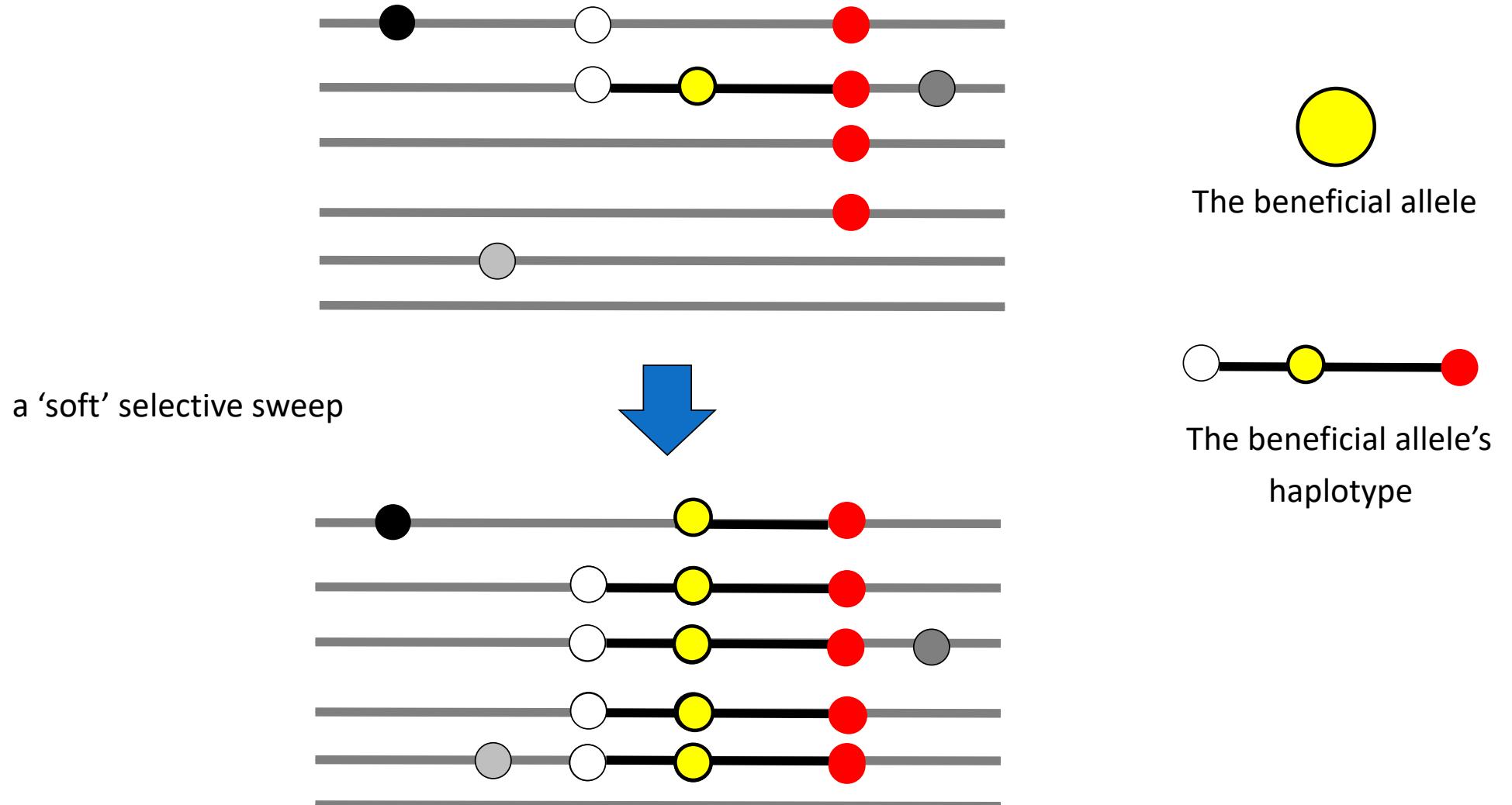
Hence: summary statistics

Concept: Adaptive evolution – expectations and observations

Adaptive evolution is the increase in frequency of an adaptive (helpful) variant

This process will

- Reduce diversity around the beneficial allele
- Increase rare alleles
- Cause negative Tajima's D
- Strong adaptive evolution is expected to be a **rare event**

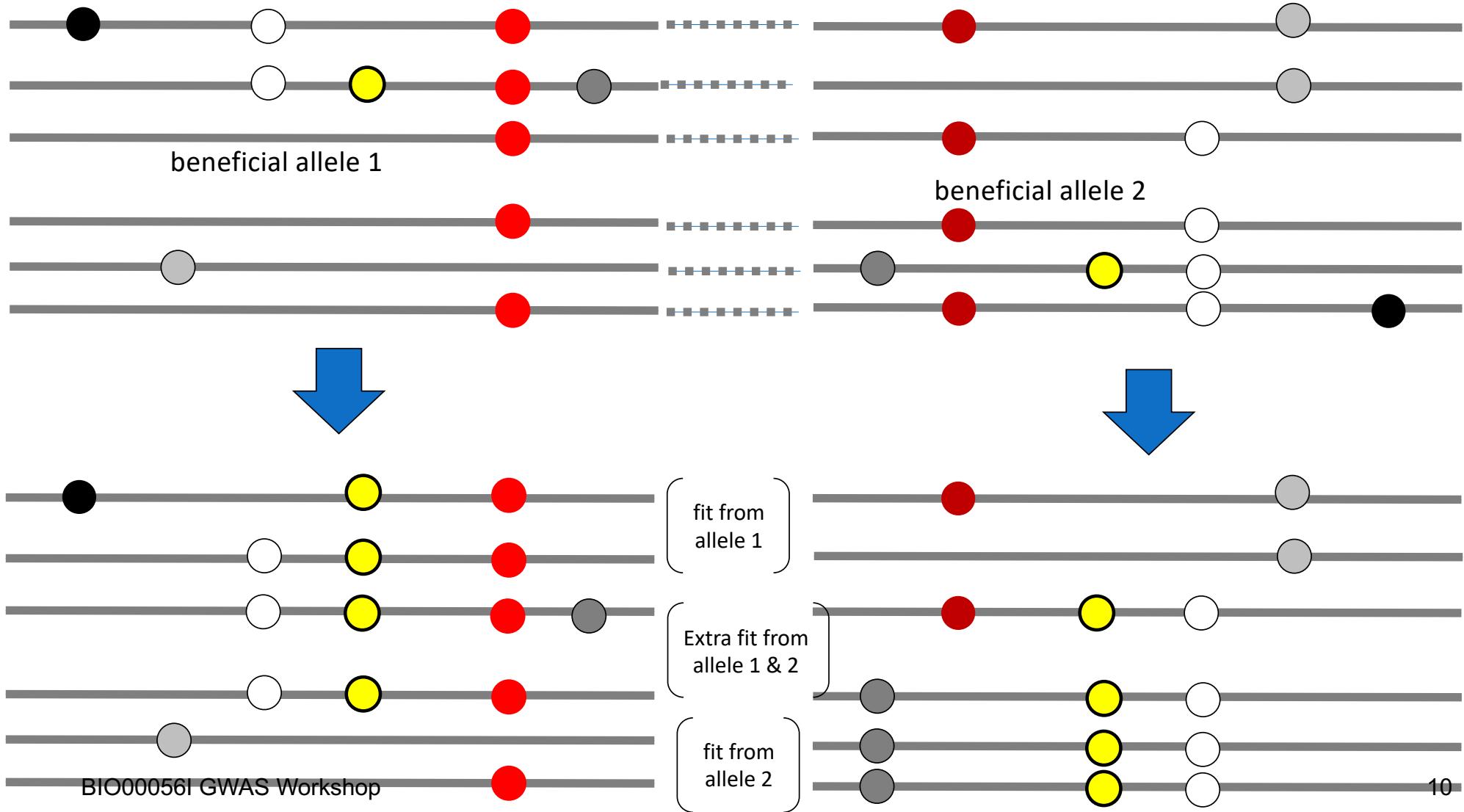


Concept: Polygenic selection and genome-scale data

- GWAS shows that most traits are determined by multiple genes
 - (multiple alleles within the genes)
- Called ‘complex traits’
- Selection **acts on all the alleles at once**
- This may be why **strong selective sweeps are rare events**

Somewhere in the genome

At another location in the genome



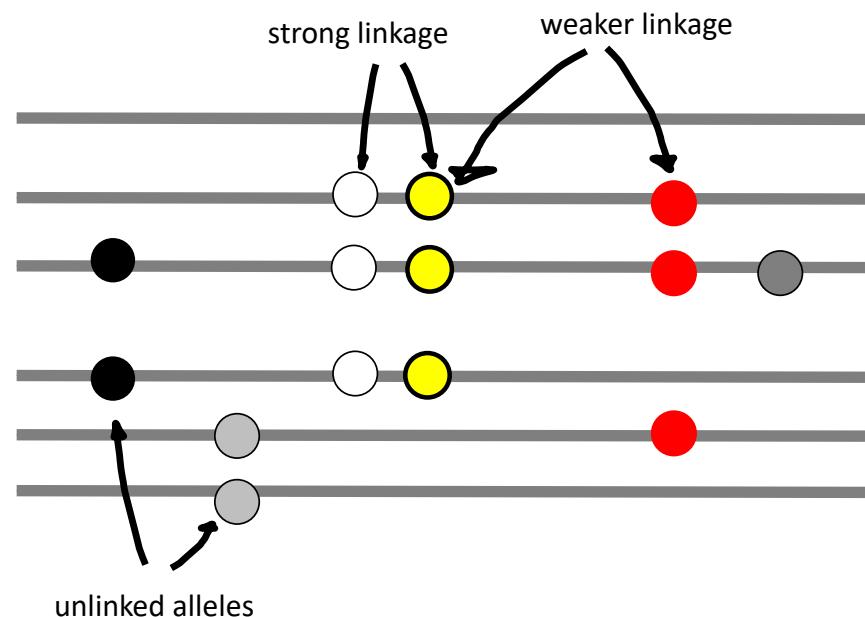
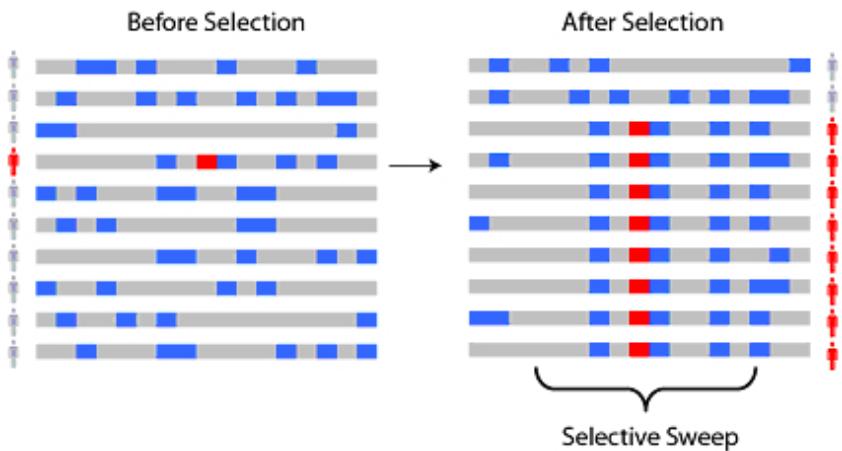
Concept: Linkage of alleles on chromosomes

When a strongly beneficial allele arises it will 'sweep' through the population.

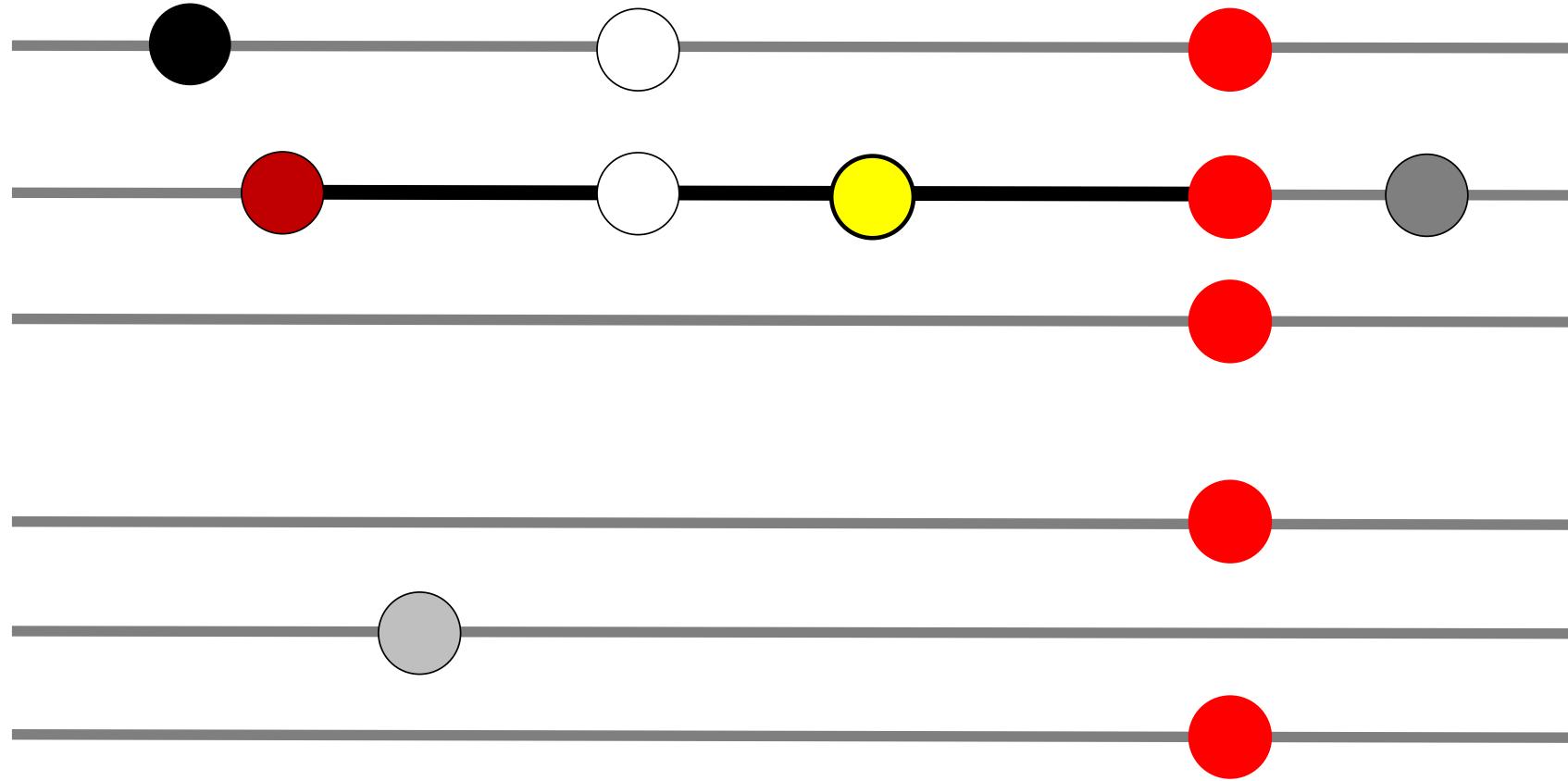
This will cause strong genetic signatures in the genome:

- loss of diversity around the sweep (asses by looking at π)
- increase in linkage (look at linkage)

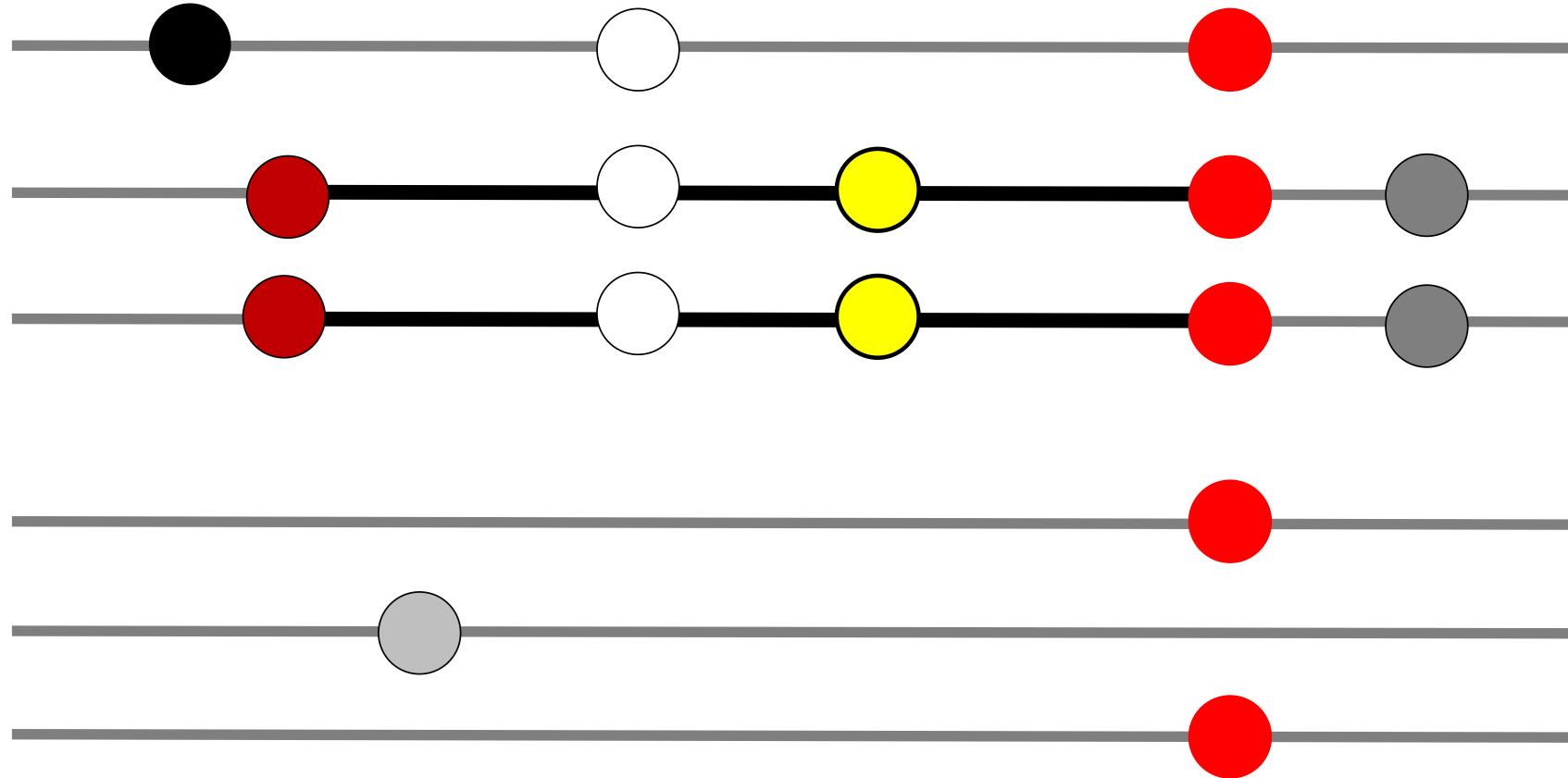
Alleles are referred to as 'linked' when they are often found together
linkage is strongest for alleles that sit close on the same chromosome



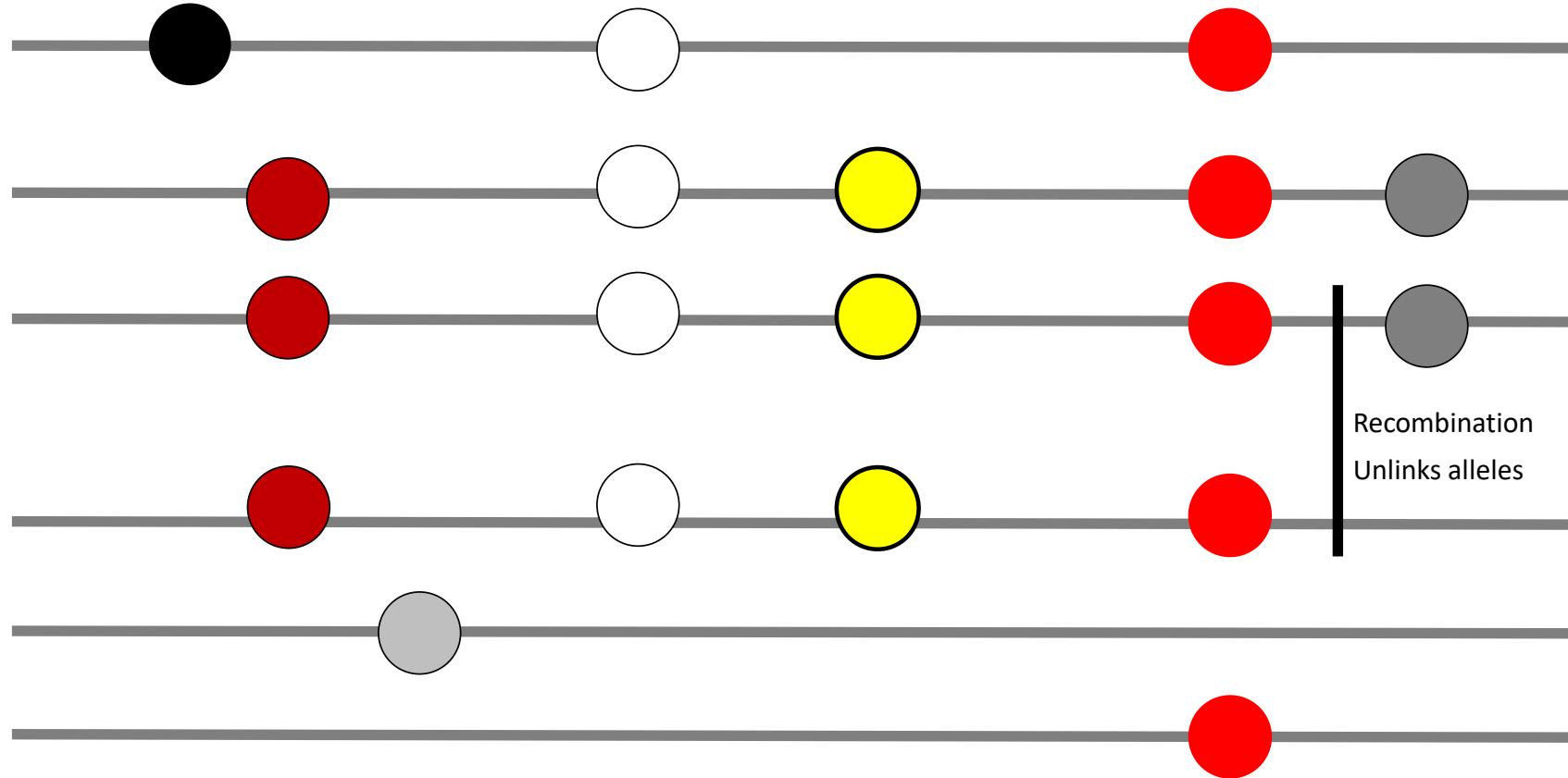
See: https://BIO00056I/GWAS/Workshop/selective_sweep



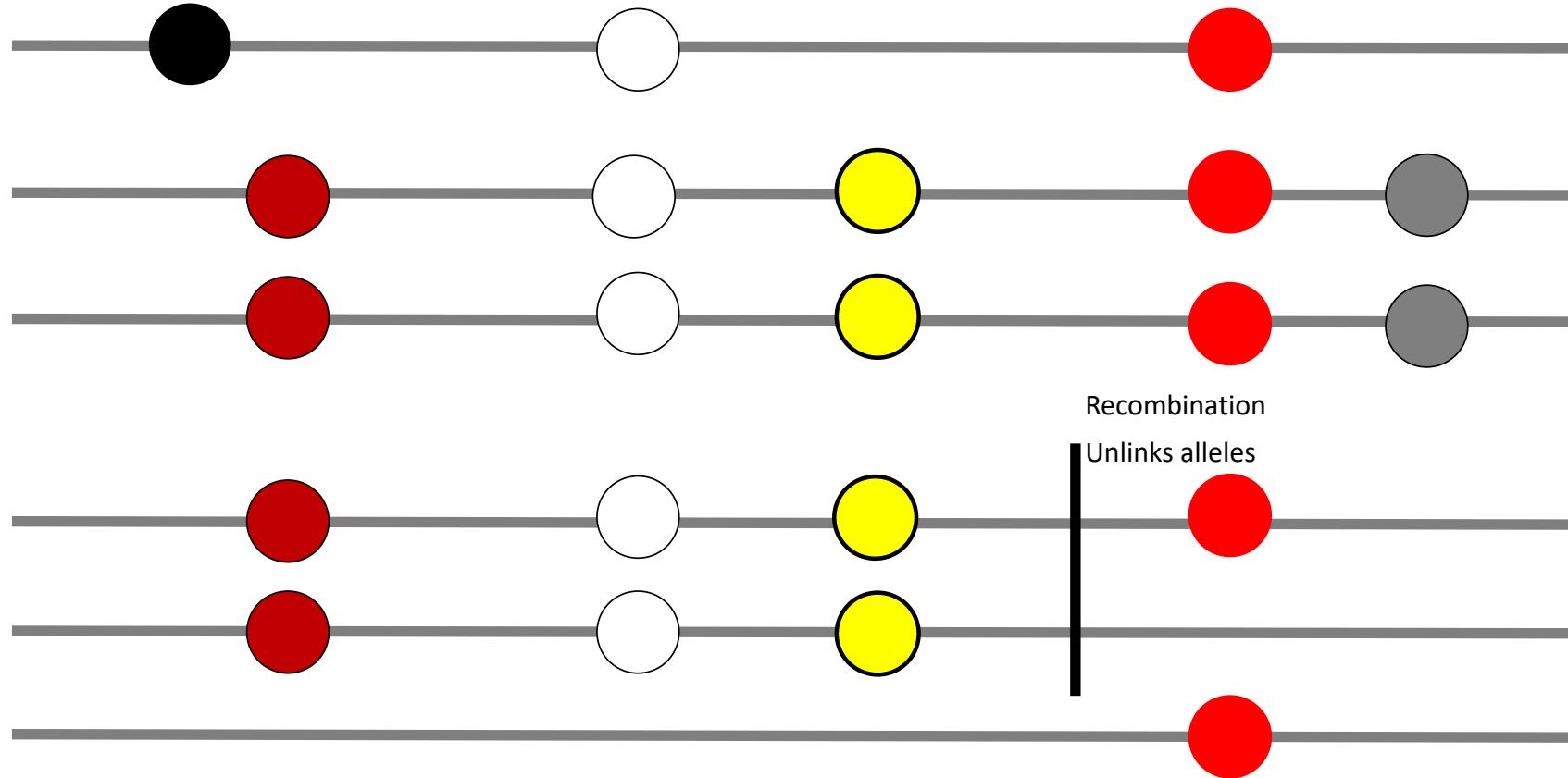
Affect of linkage in a sweep



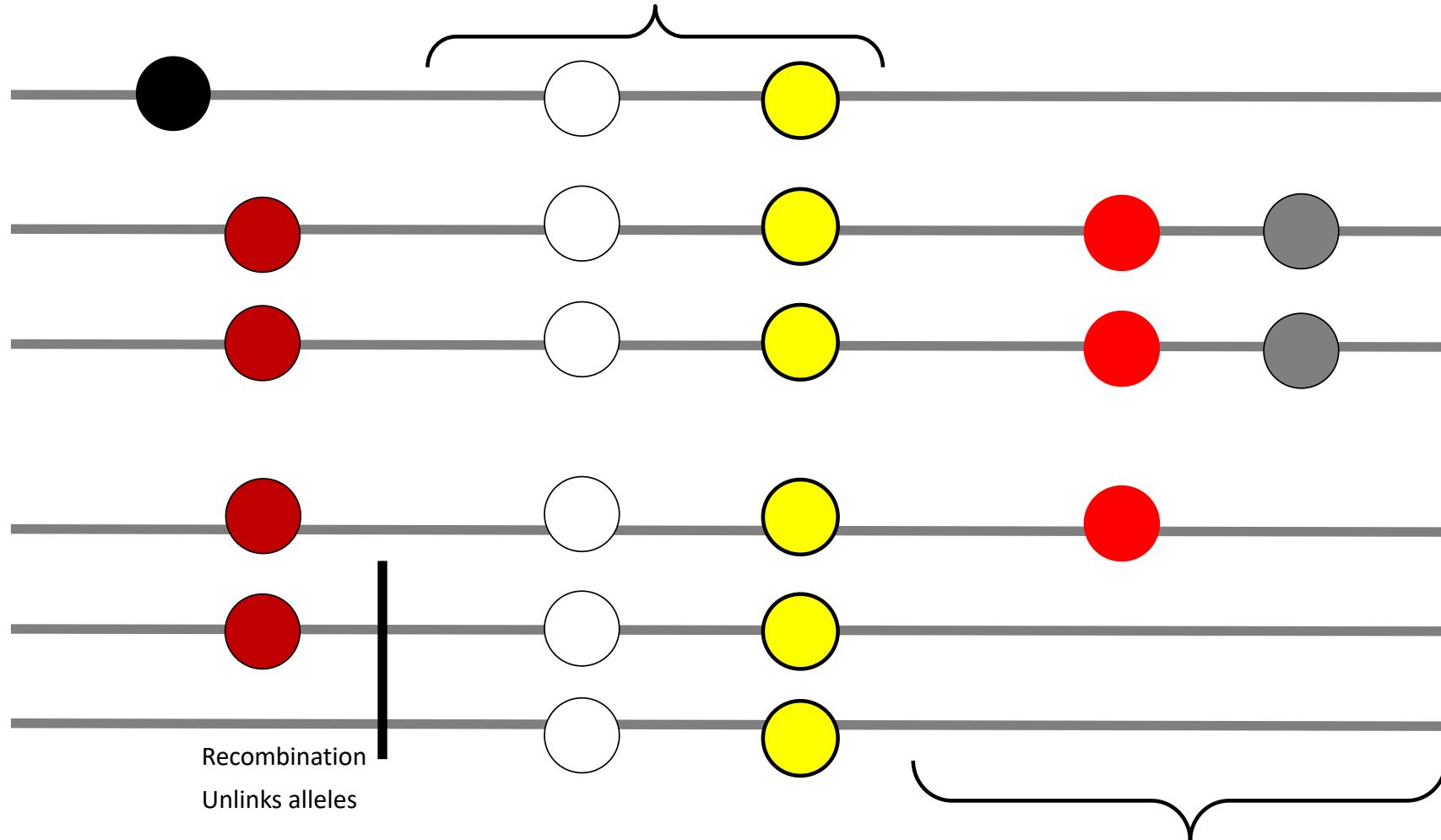
Affect of linkage in a sweep



Affect of linkage in a sweep



Very close to advantageous allele: very low diversity (none), all alleles linked



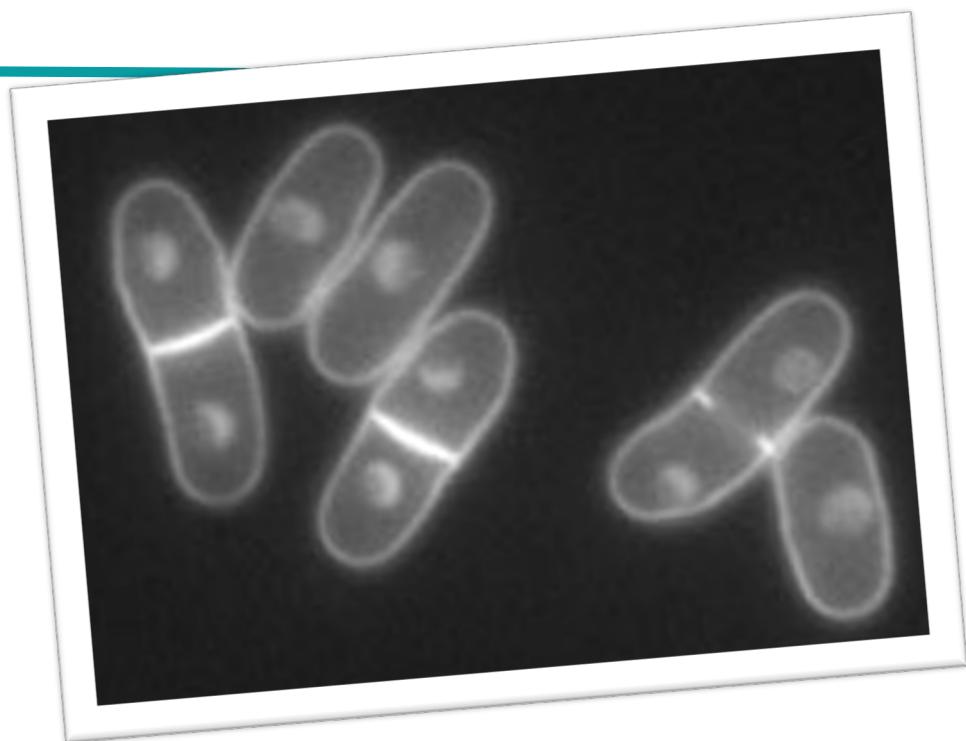
Affect of linkage in a sweep

Near to advantageous allele:
some loss of diversity, increased linkage

Fission yeast introduction:

The *S. pombe* model:

- ✓ Excellent annotation
- ✓ Genetically tractable
- ✓ Genome-wide data:
 - ✓ gene expression studies
 - ✓ knockout library
 - ✓ overexpression library
 - ✓ genetic interaction screens
- ✓ **Genetic diversity data (by me)**



Genome facts

12 Mb genome

~5,000 protein coding genes

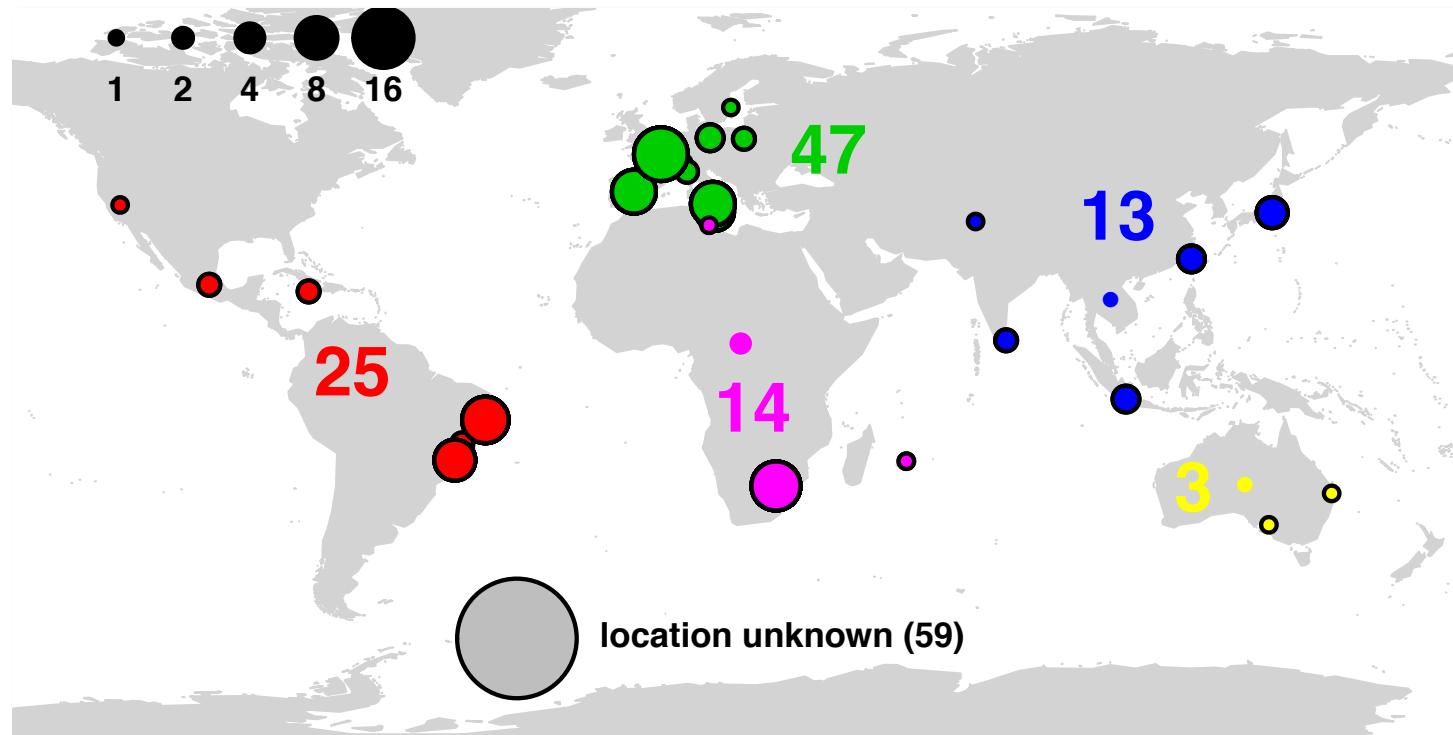
~1500 non-coding RNAs

Haploid

Excellent model

Fission yeast population genomics:

- We sequenced the genomes of all the wild *Schizosaccharomyces pombe* strains that we could get (n=161).
- We also measured quantitative traits for all strains in various labs.

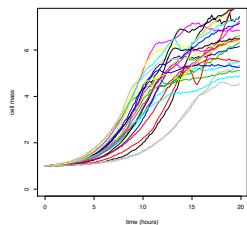


Why did we do this?

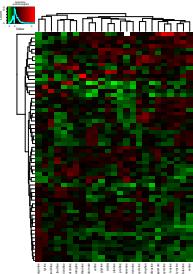
Jeffares et. al. Nature Genetics 2015
Jeffares et. al. Nature Communications 2016

Fission yeast quantitative traits :

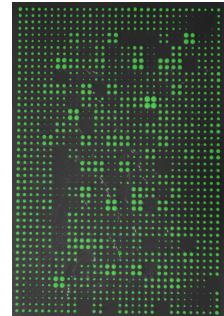
We measured more than 100 quantitative traits for each strain.
With pre-existing data we collected >220 traits.



growth in liquid media (n=14)



free amino acids concentrations (n=19)
(LC-MS/MS)



colony size in different solid media (n=42)



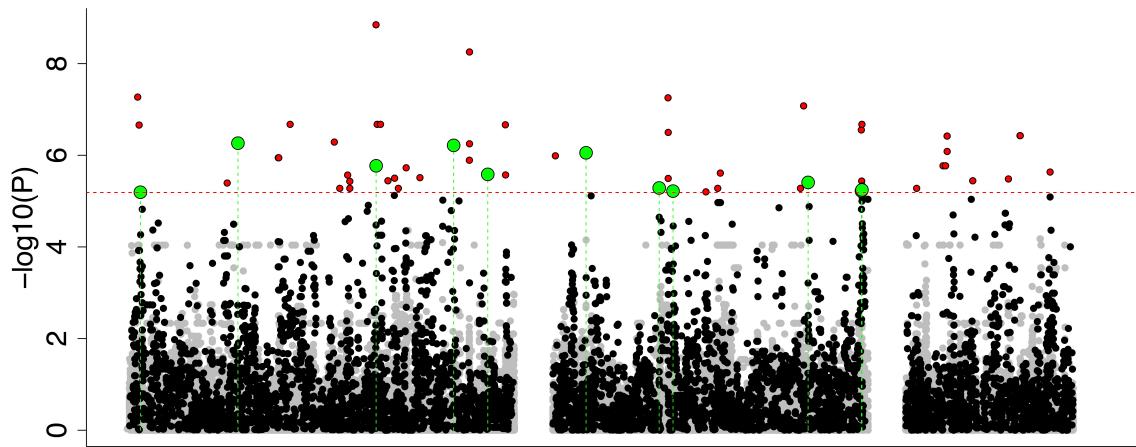
cell shape parameters (n=24)

Fission yeast quantitative traits :

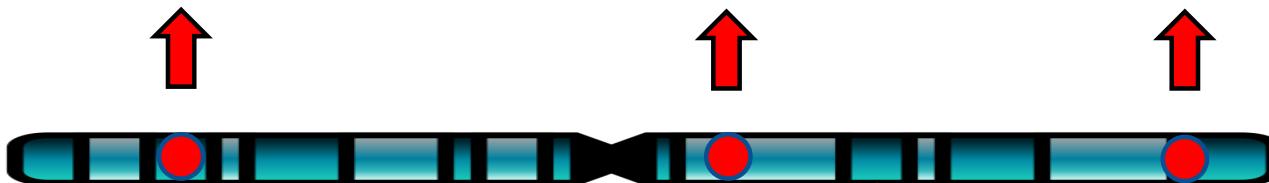
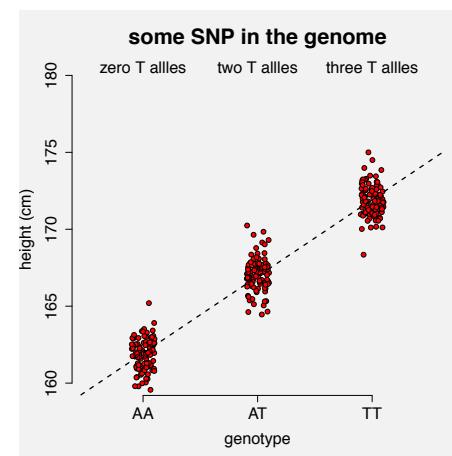
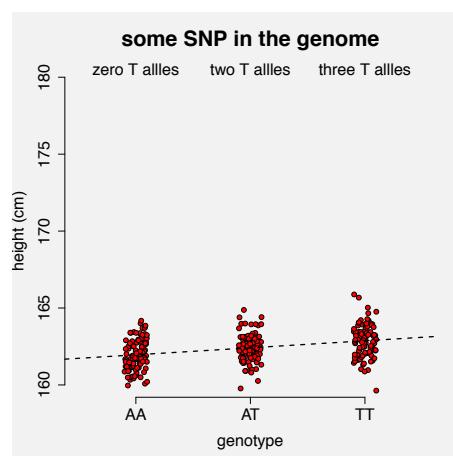
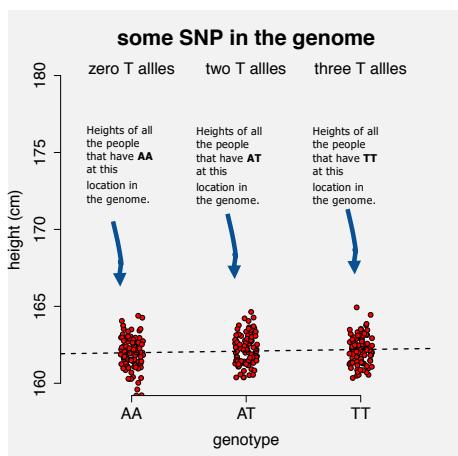
- We conducted the 223 GWAS with yeast
- GWAS was feasible because:
 - trait measures are accurate
 - environments controlled
 - genomes are small
 - genotyping is accurate

GWAS: genome-wide association study

A method to identify alleles in a population that associate with (and therefore probably influence) a trait.



GWAS: how its done



Bingo!
Looks like this SNP affects height

Some of your traits that are influenced by genetics*:

Your height

Your weight

Personality (Extraversion, Openness, Agreeableness, and Conscientiousness)

How you sleep

Risk of alcoholism

Age-related macular degeneration (loss of vision with age)

Autism

Risk of breast cancer, lung cancer and many others.

Risk of Parkinson's disease

Risk of depression

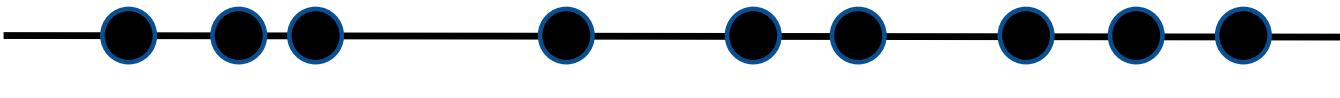
Risk of Alzheimer's Disease

Musical ability (or lack thereof!)

*Most of these traits are influenced by both genetics and environment. e.g. smoking increases your risk of lung cancer, caffeine influences sleep.

Concept: haplotypes

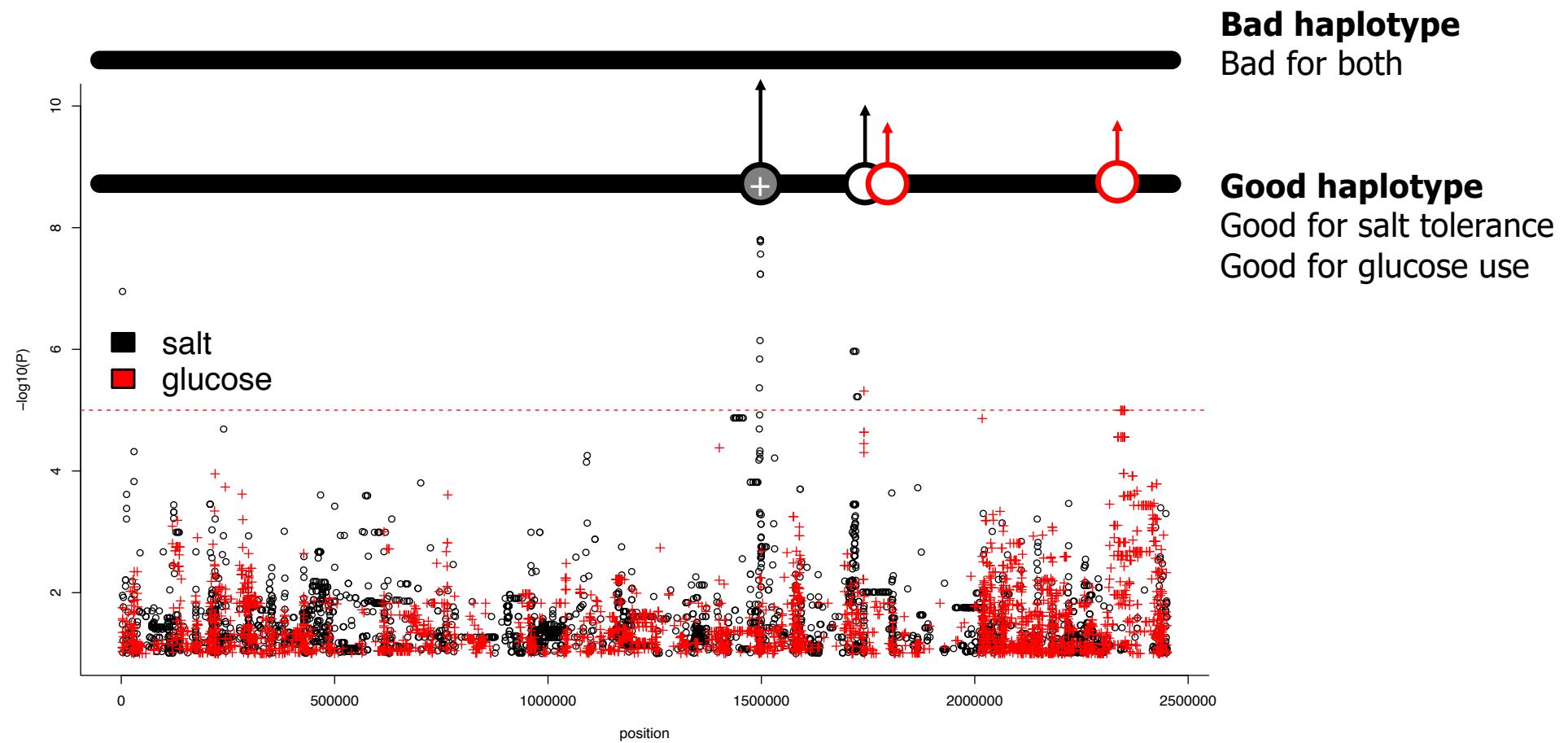
the **red** haplotype — 

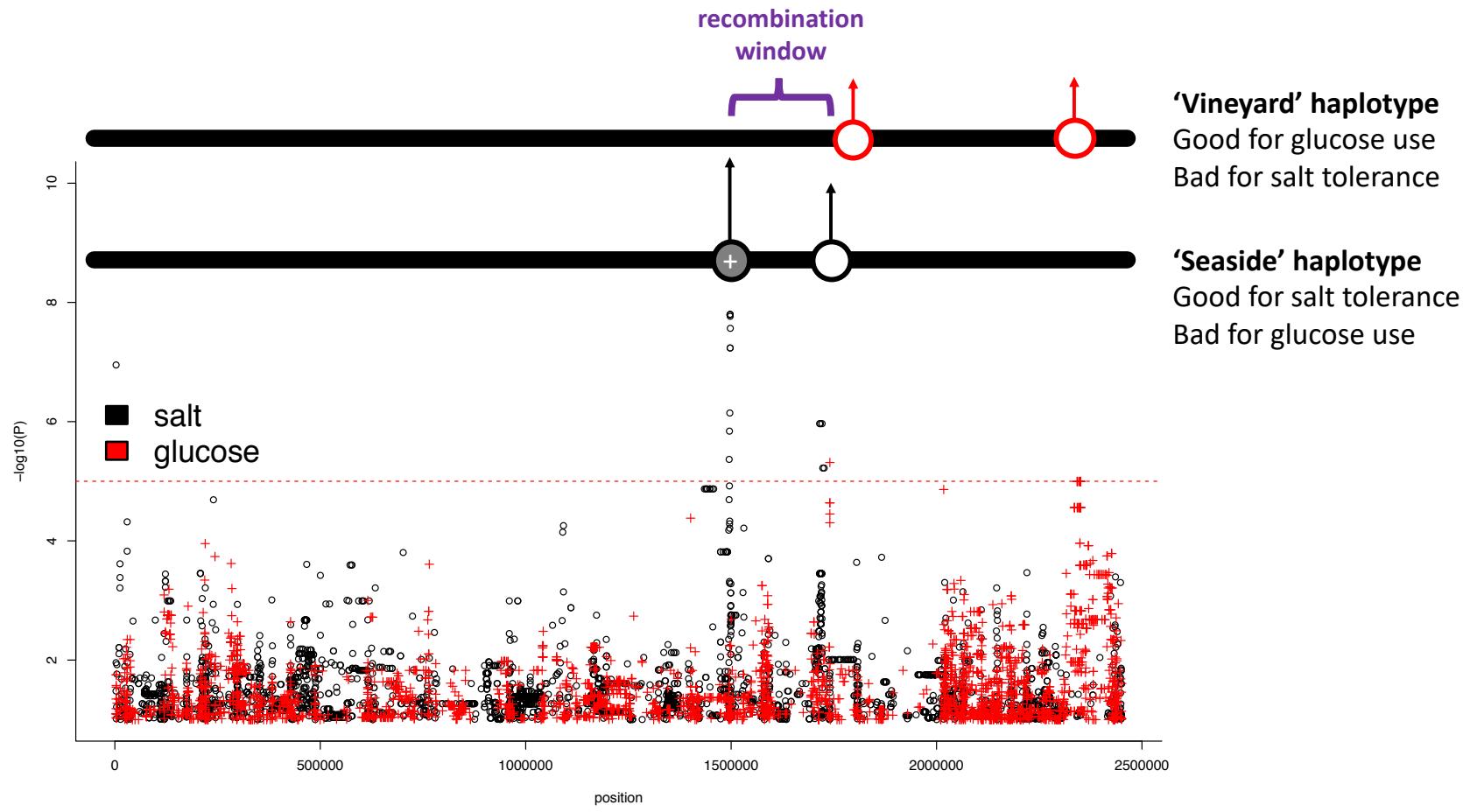
the **black** haplotype — 

a **recombinant** haplotype — 

Physically a haplotype is: a length of DNA on one chromosome, that carry's some genetic variants

Conceptually a haplotype is : is a number of alleles that travel through time and space, carrying linked genetic variants.





Workshop material:

<https://www-users.york.ac.uk/~dj757/BIO00056I/evolution-gwas.html>

Or via the VLE

Or via www-users.york.ac.uk/~dj757

Read more:

- Jeffares et al (2015). The Genomic and Phenotypic Diversity of *Schizosaccharomyces pombe*. *Nature Genetics* 47(3):235-241. doi: 10.1038/ng.3215.
- Jeffares et al. (2016). Transient structural variations have strong effects on quantitative traits and reproductive isolation in fission yeast. *Nature Communications* 8:14061. doi:10.1038/ncomms14061.
- Tusso et al. (2019). Ancestral admixture and structural mutation define global biodiversity in fission yeast. *Molecular Biology and Evolution*. doi:10.1093/molbev/msz126

Get the pdfs here: <https://jeffareslab.org/publications/>