Overview of current methods for population structure analysis

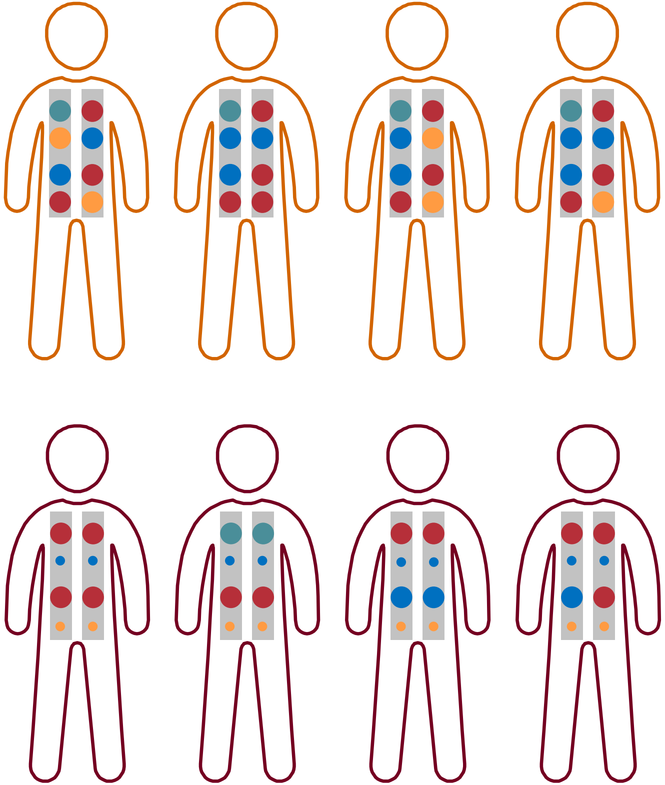
Journal club

Imperial College London

Human genetic diversity

Studying the human genetic diversity

Summarizing the genetic diversity within a population



Summarizing the genetic diversity within a population

- **Watterson estimator**

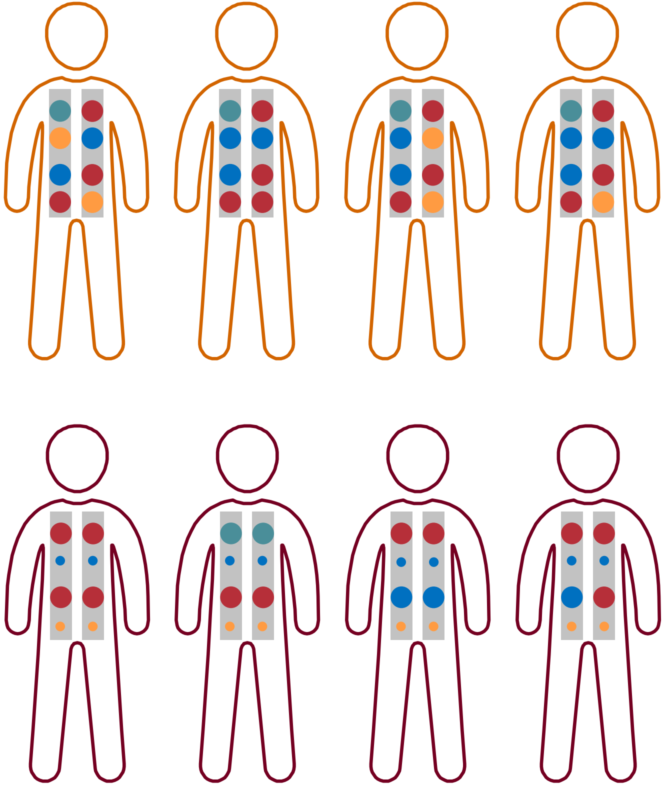
$$\hat{\theta}_W = \frac{S}{\sum_{k=1}^{n-1}\frac{1}{k}}$$

Number of segregating sites

- **Tajima's estimator**

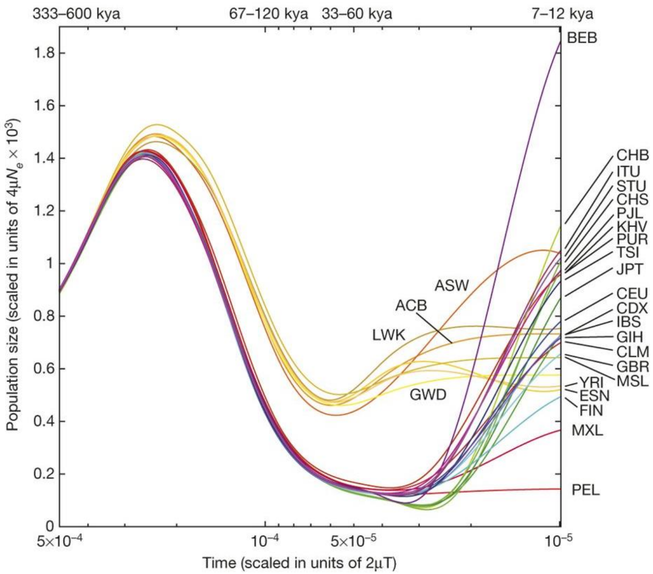
$$\pi = \frac{\sum_{i<j} d_{i,j}}{n(n-1)/2}$$

Nucleotide pairwise differences

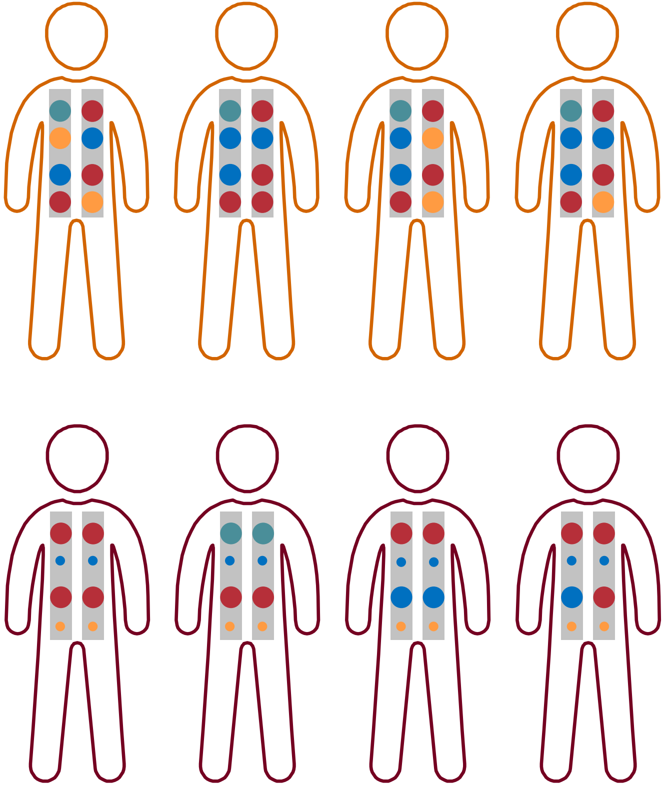


Summarizing the genetic diversity within a population

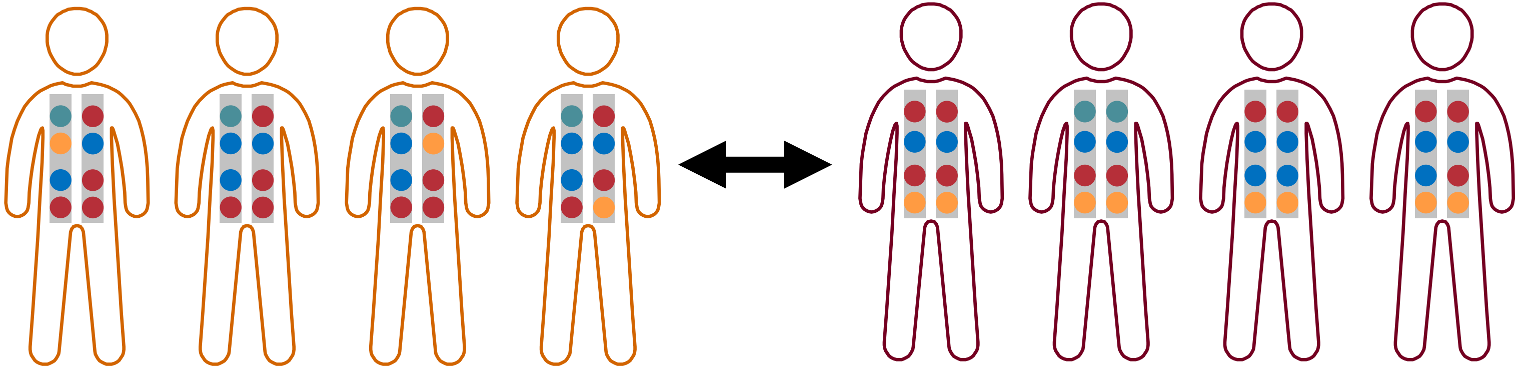
- **Effective population size** (N_e)



The 1000 Genomes Project Consortium. 2015, Nature



Genetic distances between populations

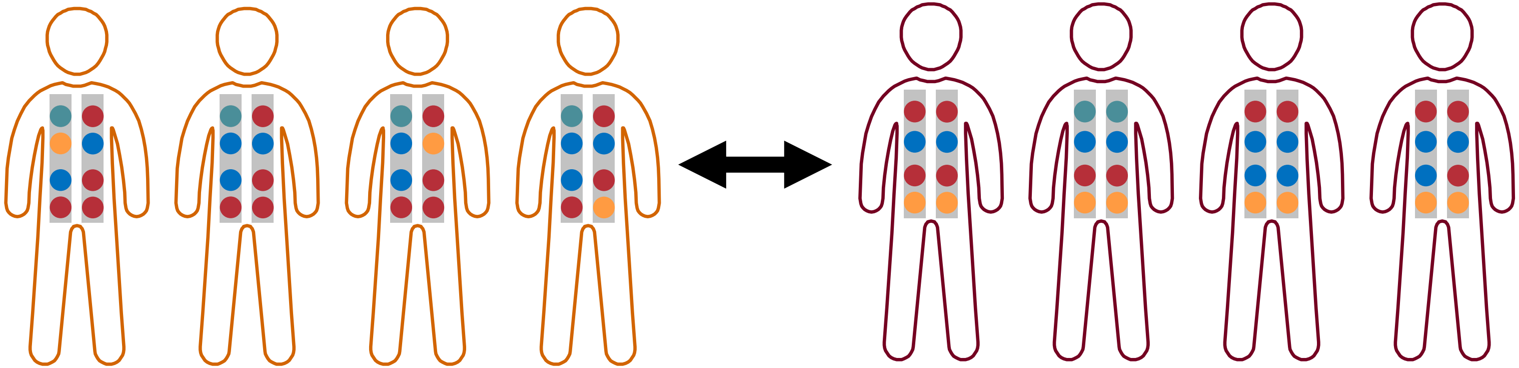


Genetic distances between populations

Allele frequency methods

- **Nei's D** $$D = -\ln\left(\frac{J_{12}}{(\sqrt{J_{11}J_{22}})}\right)$$

- **F_{ST}** $$F_{ST} = \frac{\pi_{\text{Between}} - \pi_{\text{Within}}}{\pi_{\text{Between}}}$$

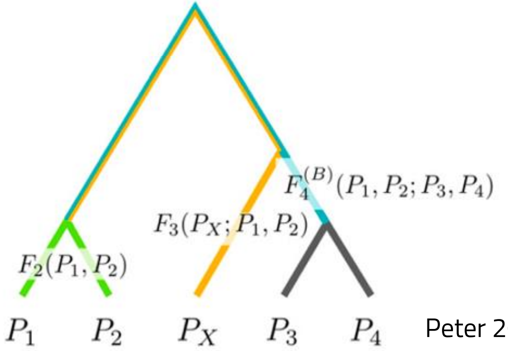


Genetic distances between populations

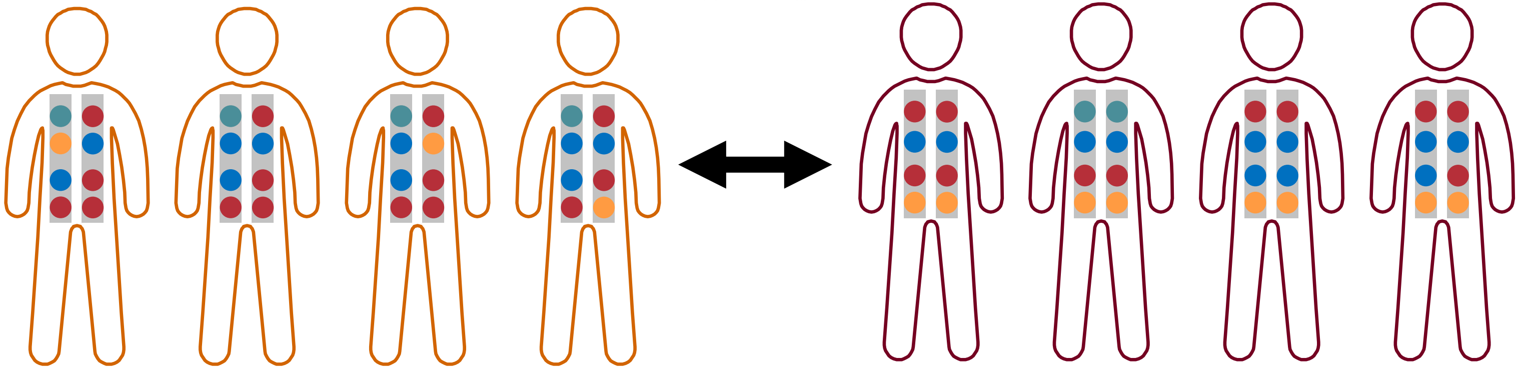
Allele frequency methods

F-statistics (Reich et al. 2009, Nature)

- **F_2**
- **F_3**
- **F_4**

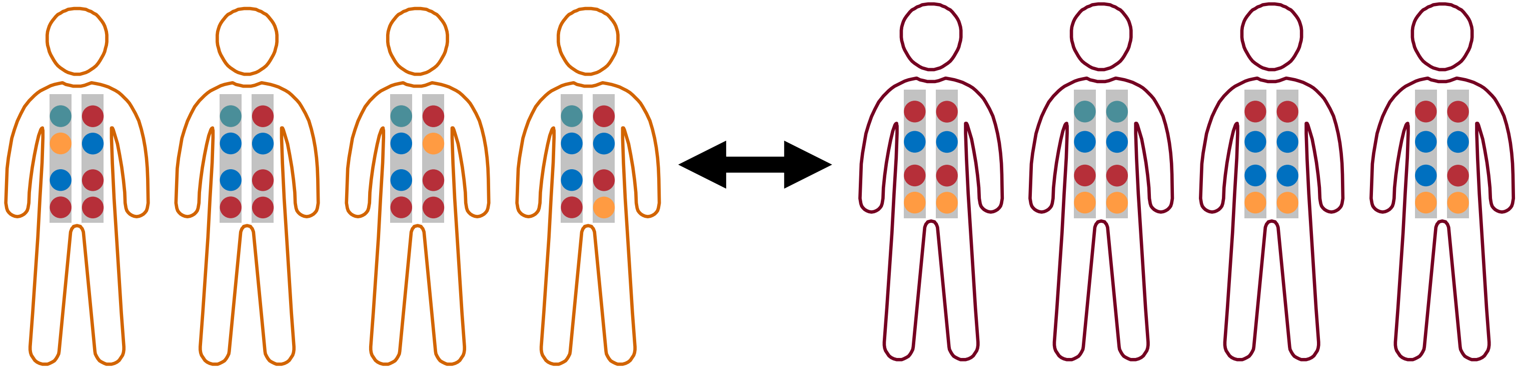


Peter 2016, Genetics



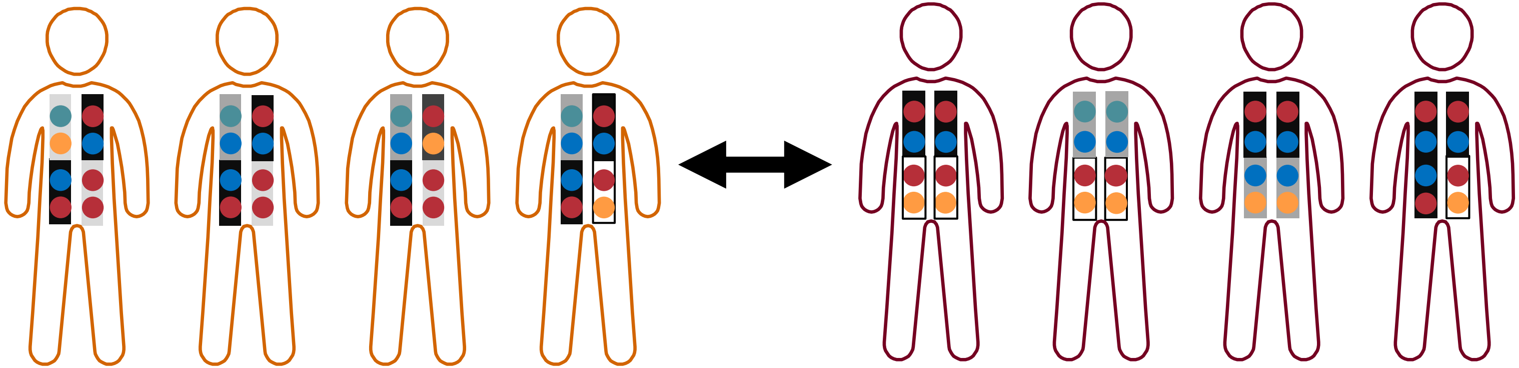
Genetic distances between populations

Haplotype-based methods



Genetic distances between populations

Haplotype-based methods

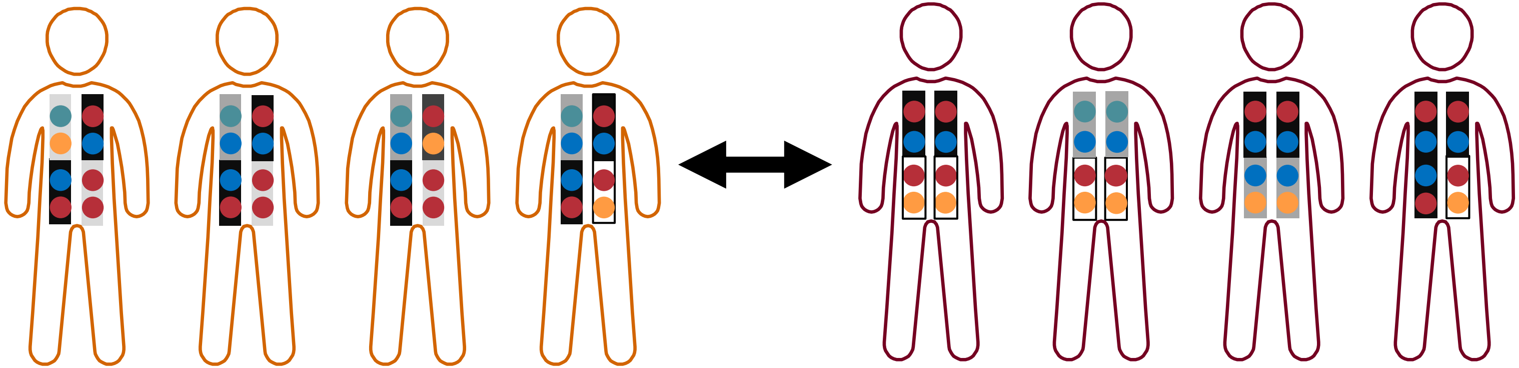


Genetic distances between populations

Haplotype-based methods

- ChromoPainter

  Lawson et al. 2012, PLoS Genet



Genetic distances between populations

Haplotype-based methods

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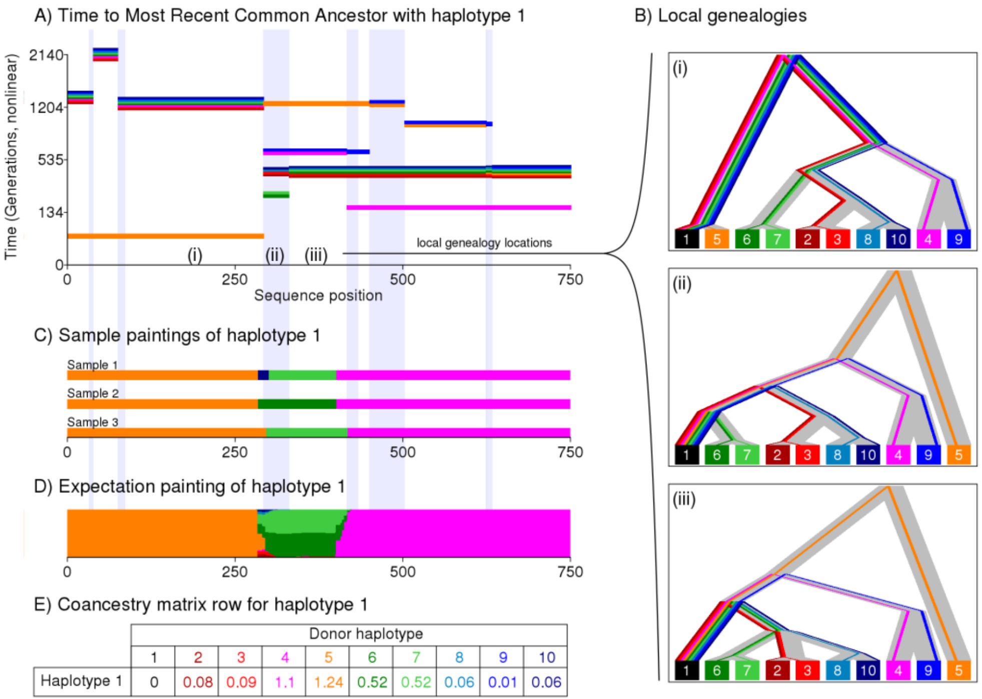
- Search for the most common recent ancestor of each individual haplotype within the haplotypes of the other individuals of the datsaset



	Donor haplotype									
	1	2	3	4	5	6	7	8	9	10
Haplotype 1	0	0.08	0.09	1.1	1.24	0.52	0.52	0.06	0.01	0.06

Genetic distances between populations

Haplotype-based methods

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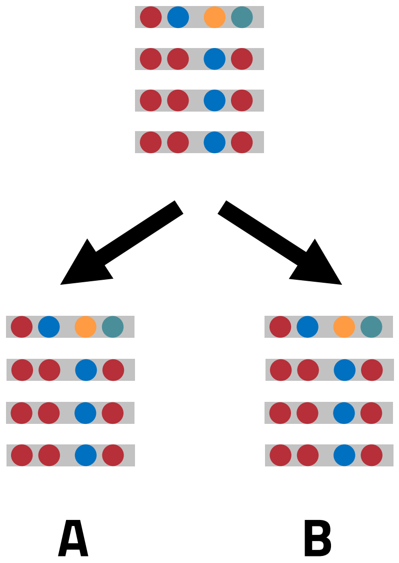

Genetic distances between populations

Haplotype-based methods

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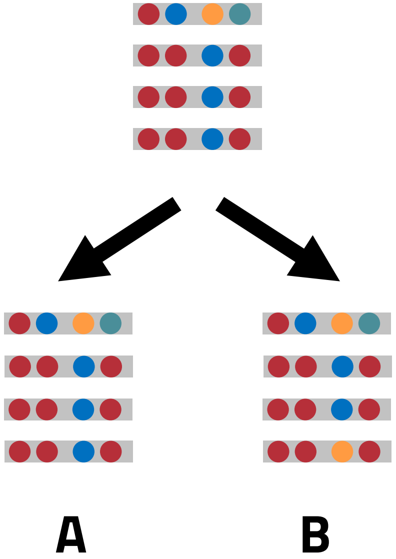

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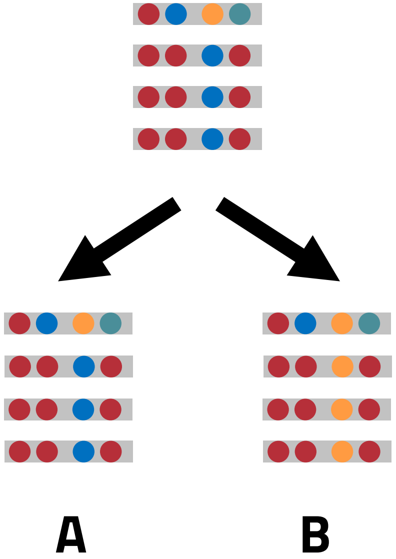

Genetic distances between populations

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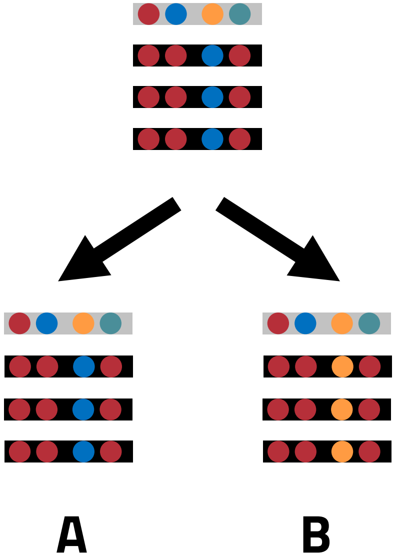

Analyzing the context of the snps, **the haplotypes**, we can smooth the weight of increased allele frequencies after genetic drift and **relate the populations trough shared haplotypes**

Genetic distances between populations

Haplotype-based methods

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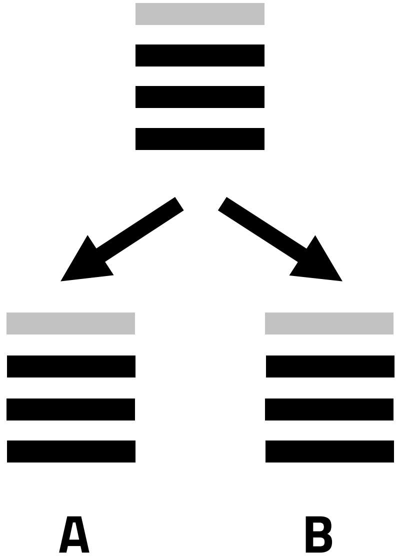


Analyzing the context of the snps, **the haplotypes**, we can smooth the weight of increased allele frequencies after genetic drift and **relate the populations trough shared haplotypes**

Genetic distances between populations

Population structure through clustering methods

Genetic distances between populations

Population structure through clustering methods

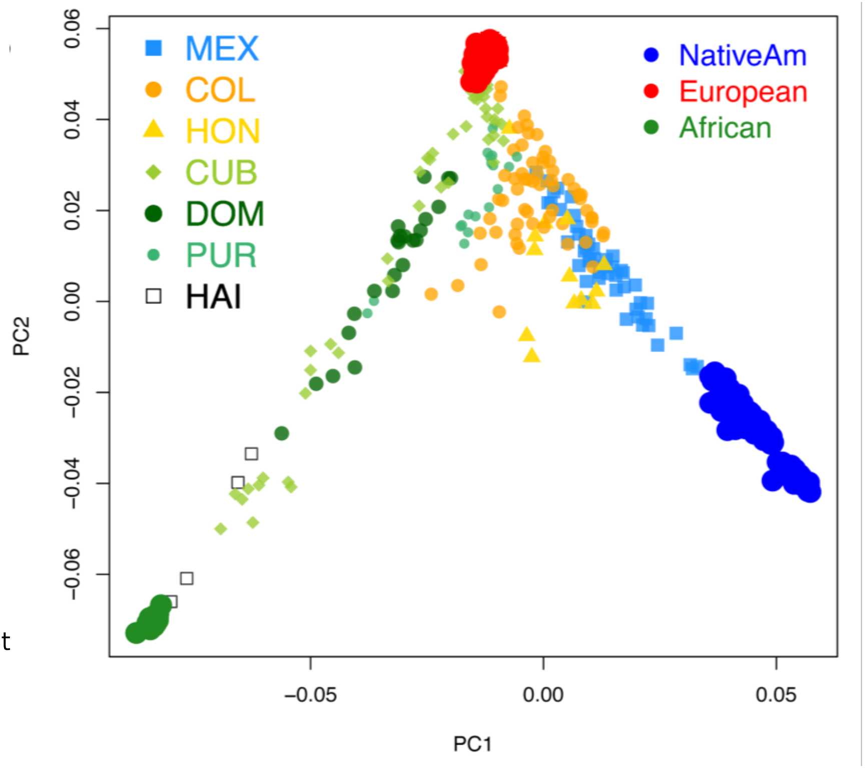
From allele frequencies

Genetic distances between populations

Population structure through clustering methods

From allele frequencies

- **Principal Component Analysis**
  - Transforms allele frequencies to a set of linearly uncorrelated variables called principal components.
  - The visualization of the indivudals as points of two principal component coordinates clusters them based on their genetic distances.



Moreno-Estrada et al. 2013, PLoS Genet

Genetic distances between populations

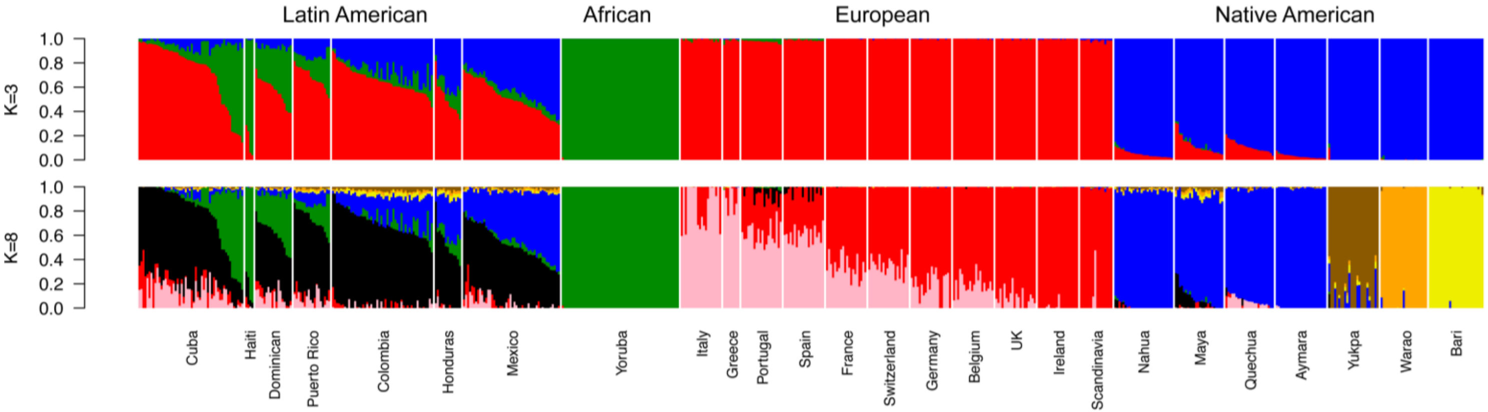
Population structure through clustering methods

From allele frequencies

- **Admixture**

  Alexander et al. 2019, Genome Res

Moreno et al. 2013, PLoS Genet



  - analyses differences in the distribution of allele frequencies amongst individuals with a Bayesian iterative algorithm by placing samples into groups whose members share similar patterns of variation

Genetic distances between populations

Population structure through clustering methods

From haplotype-based methods

Genetic distances between populations

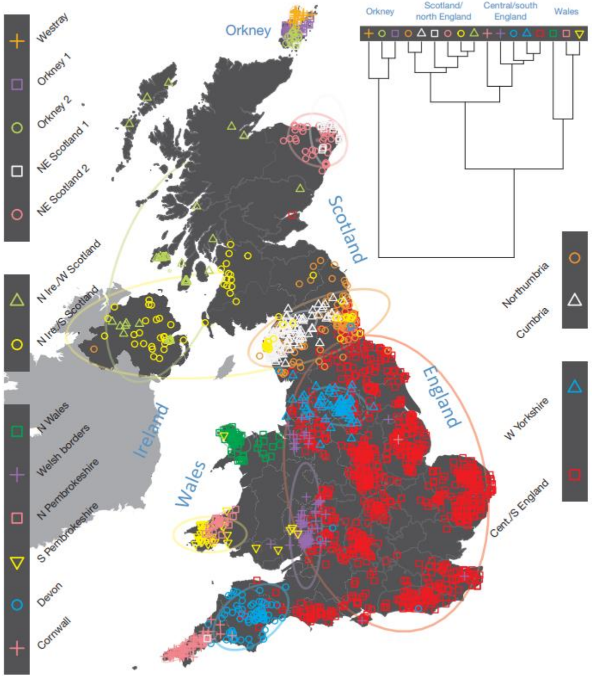
Population structure through clustering methods

From haplotype-based methods

- **FineStructure**

  Lawson et al. 2012, PLoS Genet

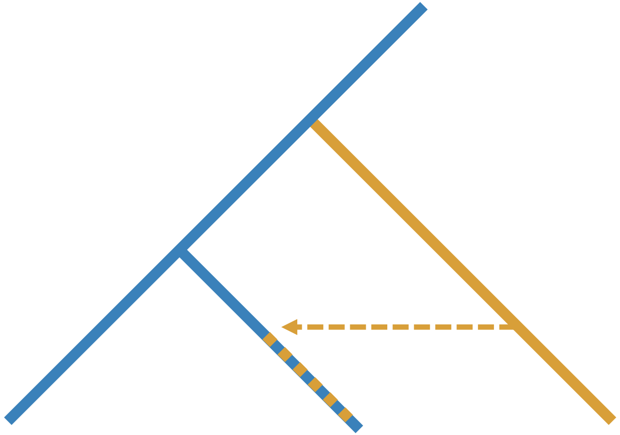
  - Clusters the individuals based on their **haplotypic similatiries** computed in the ChromoPainnter coancestry matrix



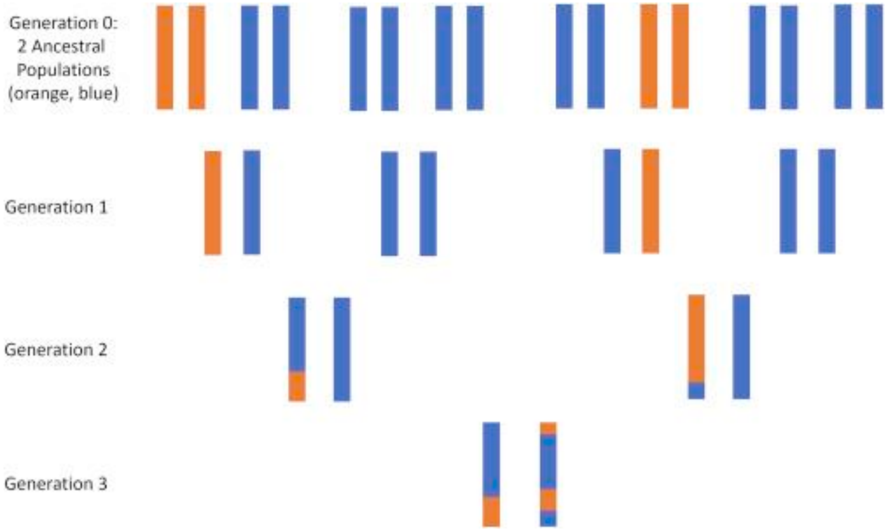
Leslie et al. 2015, Nature

Inference of admixture between populations

Inference of admixture between populations



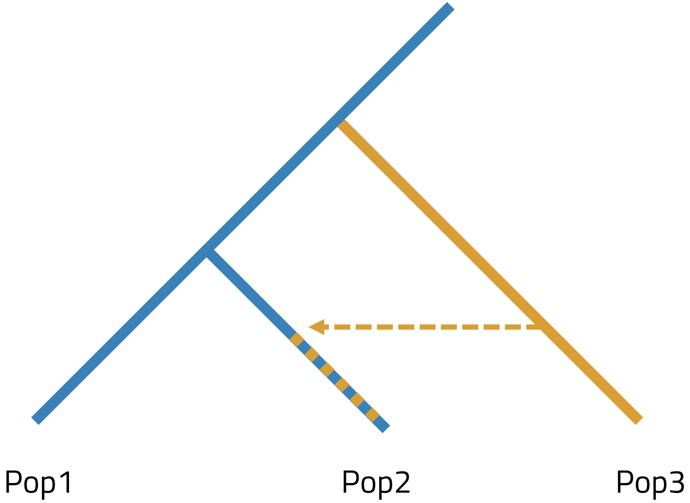
Grinde et al. 2014, AJHG



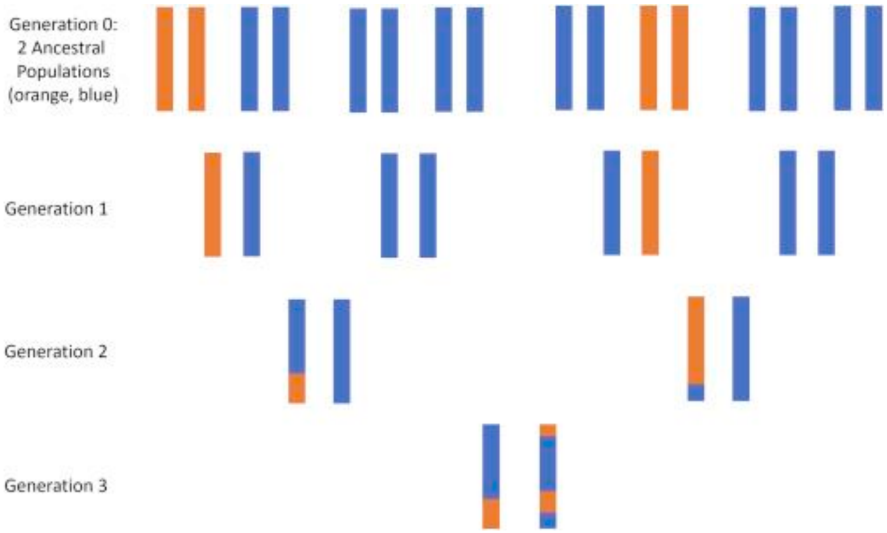
Inference of admixture between populations

From allele frequencies

- **F3**



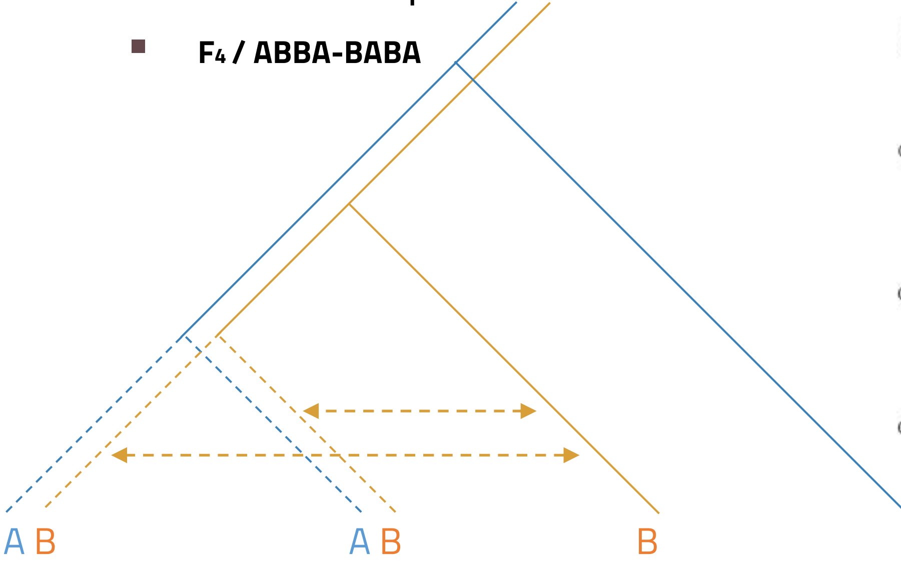
F_3 (Pop2;Pop1,Pop3) < 0

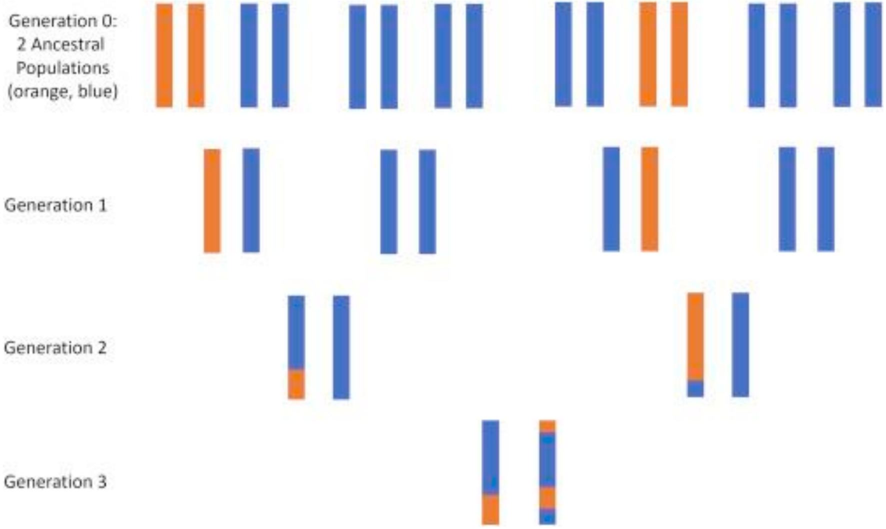


Inference of admixture between populations

From allele frequencies

- **F₄ / ABBA-BABA**





Alleles for a given SNP

Population

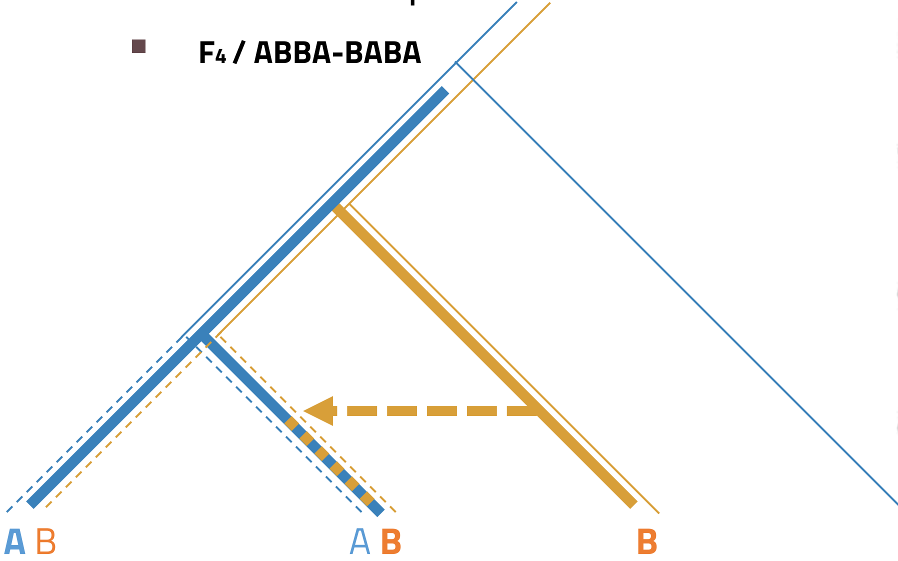
$F_4 > 0$: Admixture in Pop2

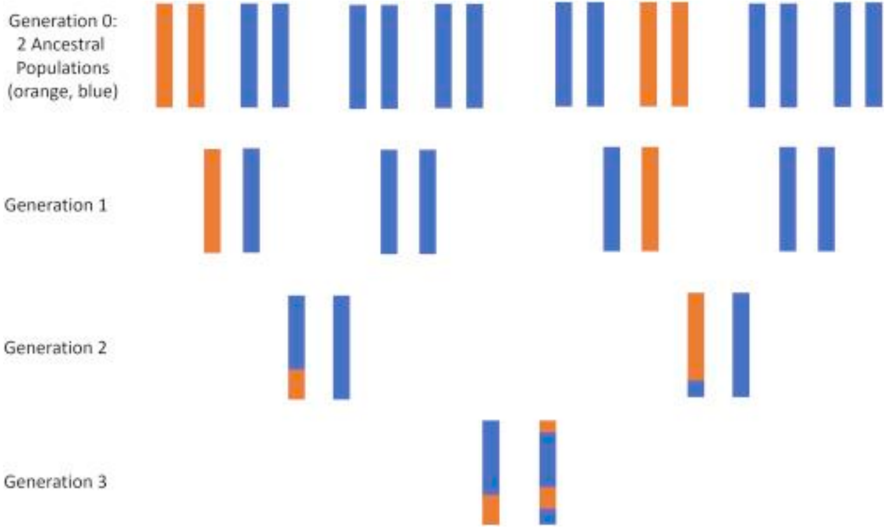
$F_4 < 0$: Admixture in Pop1

Inference of admixture between populations

From allele frequencies

- **F_4 / ABBA-BABA**





Alleles for a given SNP

Population

$F_4 > 0$: Admixture in Pop2

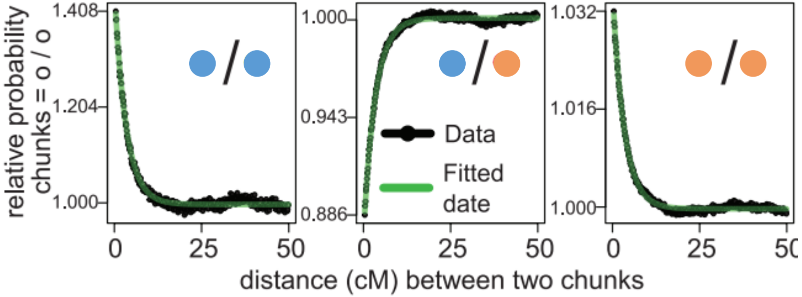
$F_4 < 0$: Admixture in Pop1

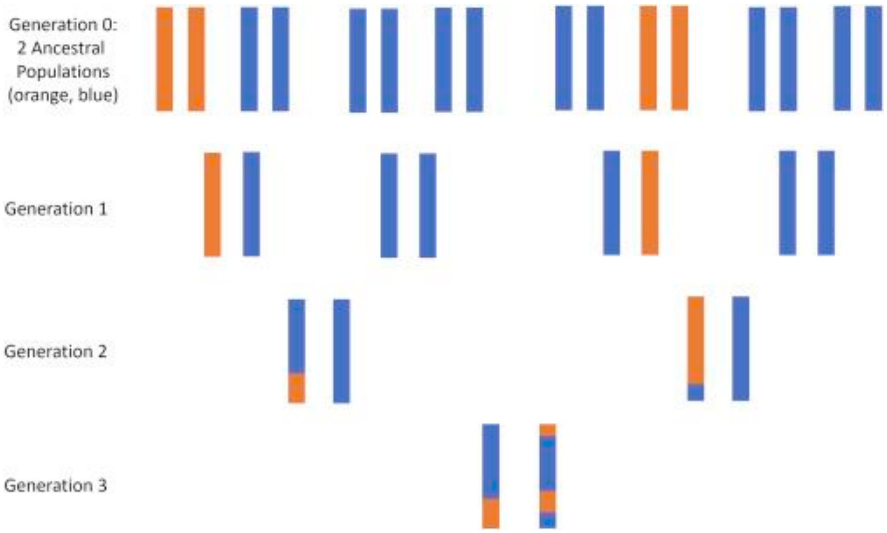
Inference of admixture between populations

From haplotype-based methods

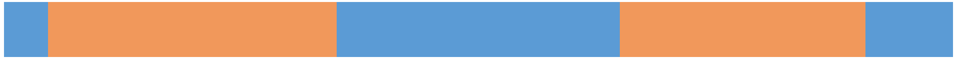
- **Globetrotter**

  Hellenthal et al. 2014, Science

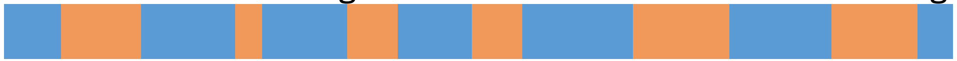




Generation 4 Longer fragments, longer distance between fragments

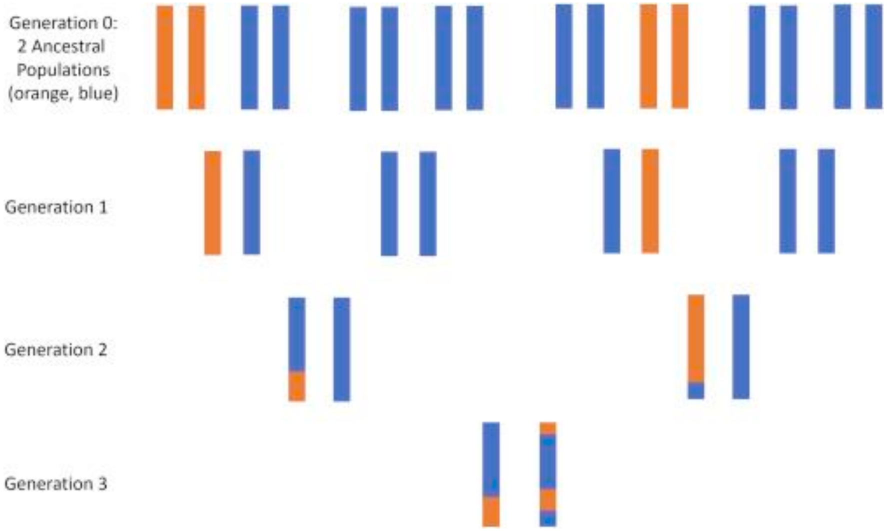


Generation 8 Shorter fragments, shorter distance between fragments



Inference of admixture between populations

- **Other methods using similar approaches**
  - Tracts
    - Gravel et al. 2012, Genetics
  - ALDER
    - Loh et al. 2013, Genetics



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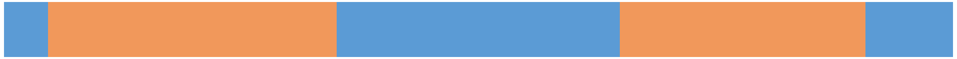

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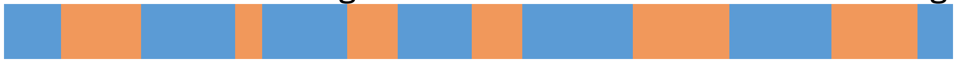
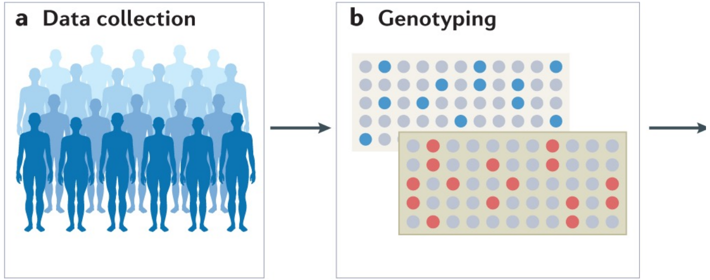


Genome wide association studies (GWAS)



Phenotype of interest (Y)

Genotype (X_s)

→

Linear Regression

$$Y \sim X_s \beta + W\alpha + e$$

→

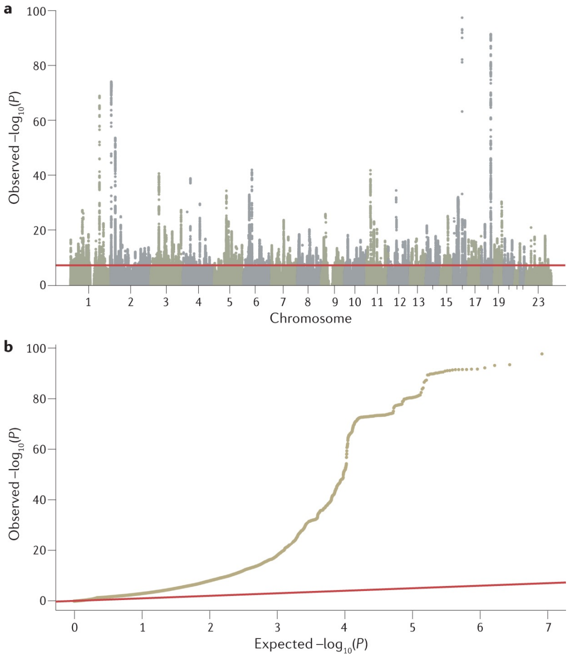
Results

1) β SNP effect size

2) P-value

Genome wide association studies (GWAS)

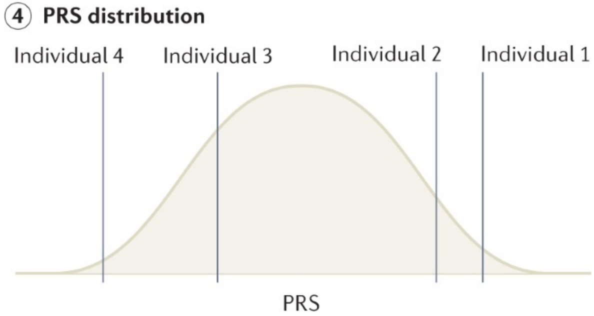
1) P-value → identification of associated loci



2) β **SNP effect size** → **Polygenic Risk Score**

PRS= $\sum_{i=1}^{l} \beta_i$ along the genome, per individual

Express how likely an individual will present a phenotype



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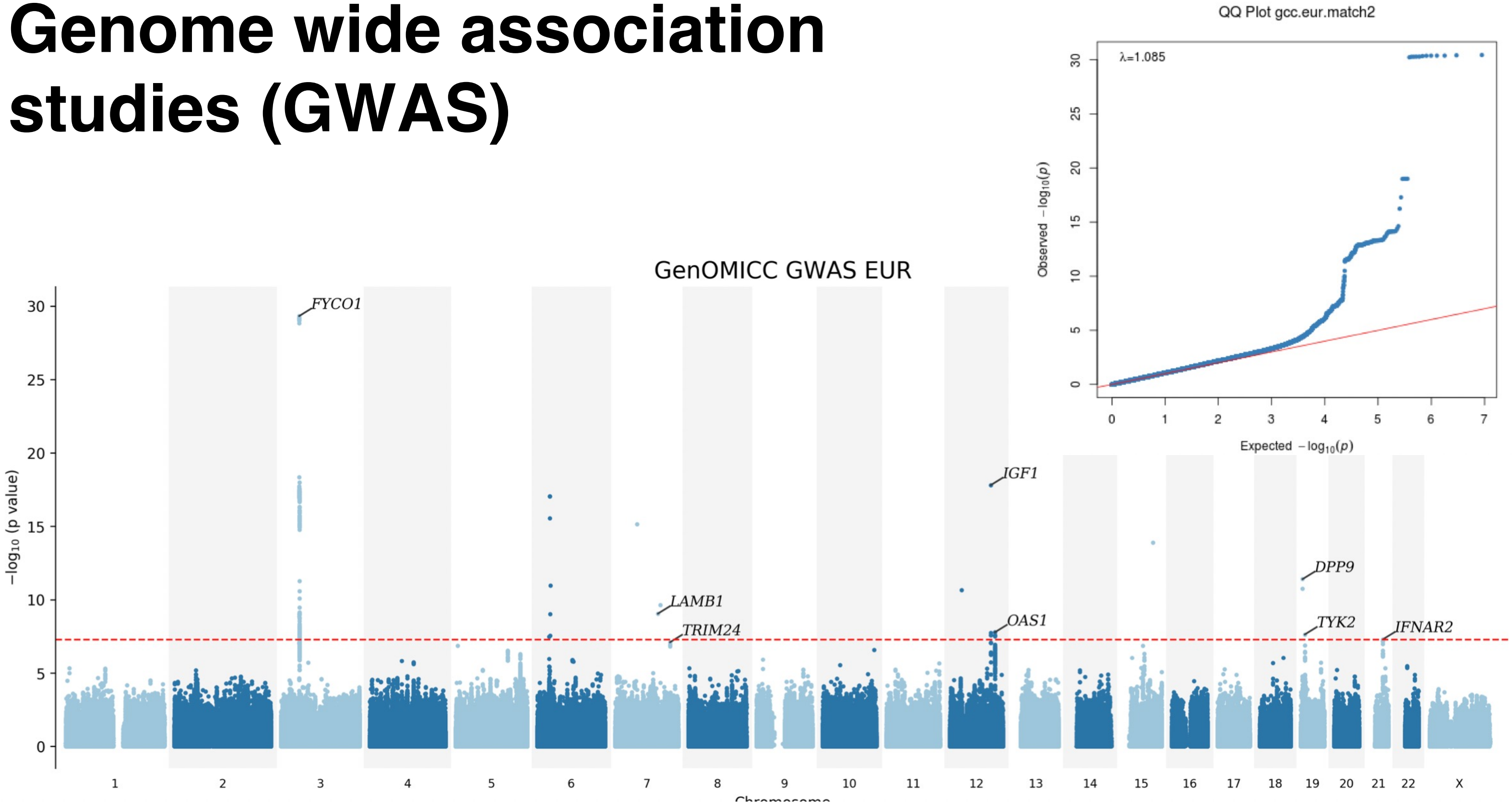

Pairo-Castineira, E., Clohisey, S., Klaric, L. *et al.* **Genetic mechanisms of critical illness in COVID-19**. *Nature* **591,** 92–98 (2021). https://doi.org/10.1038/s41586-020-03065-y

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