

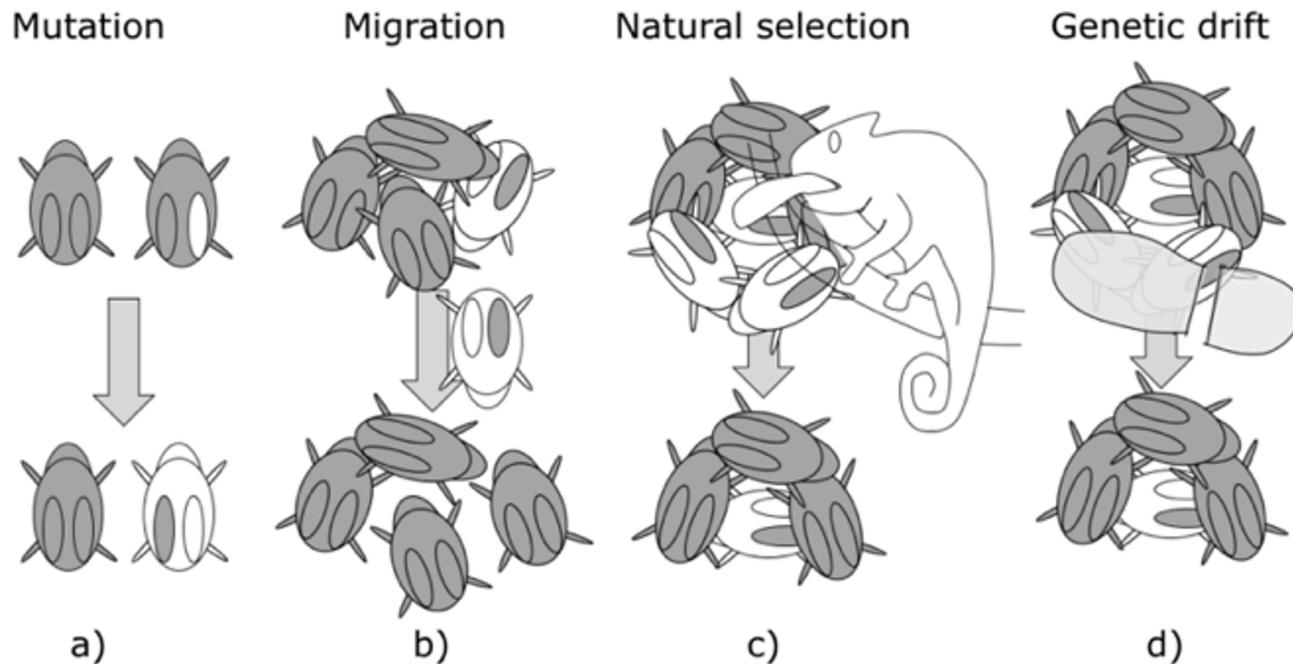
Population Genetics

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$ echo "Data Sciences Institute"
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Population genetics

- A field concerned with genetic variation within and between populations over time and space.
- By looking at genetic variation we can learn about population history, migration patterns, and the impact of natural selection on genetic diversity.

Factors that affect patterns of genetic variation

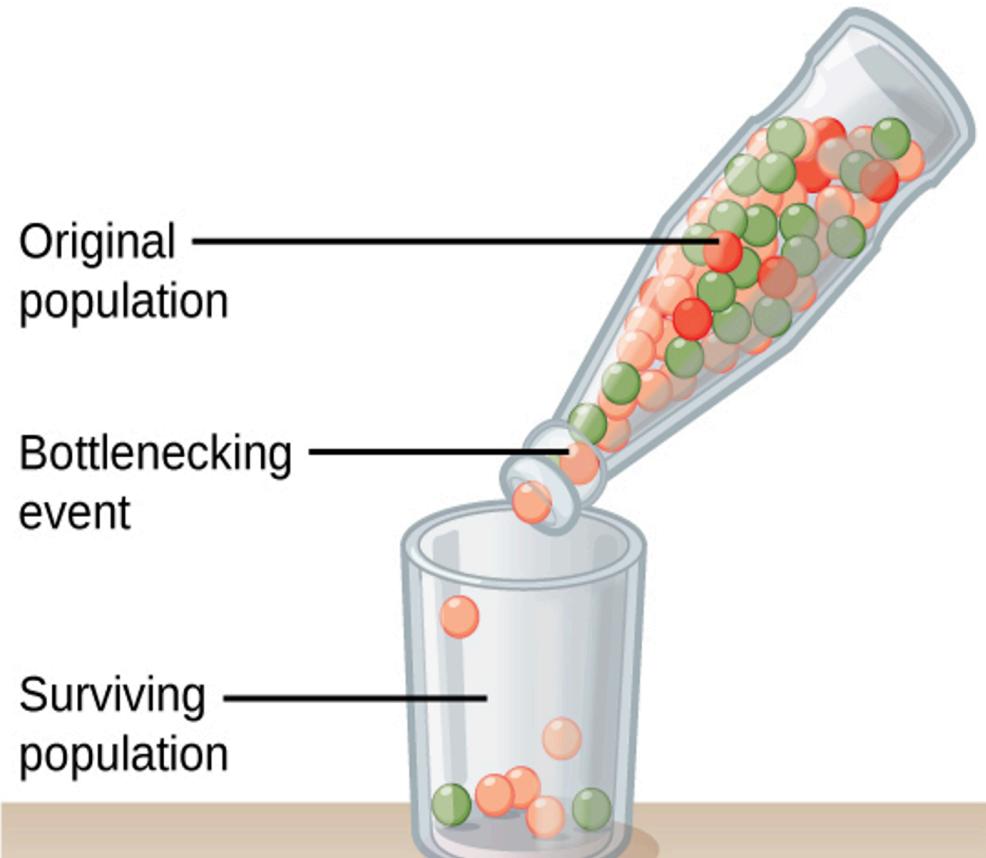


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- By looking at genetic variation we can learn about **population history, migration patterns, and the impact of natural selection on genetic diversity.**

Bottleneck effects

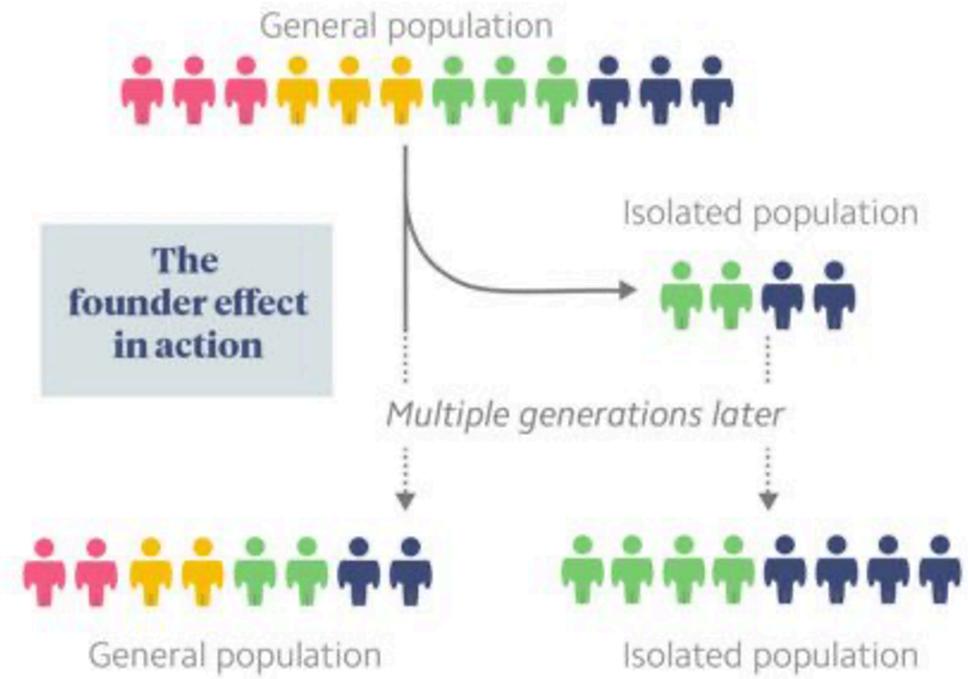
- Natural events like a disaster that kills **at random** a large portion of the population can change the genetic structure of the population.



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Founder population

- A founder effect occurs when a new colony is started by a few members of the original population.
- For example: the Amish community of Pennsylvania. This population is descended from around 200 German immigrants who started their colony.



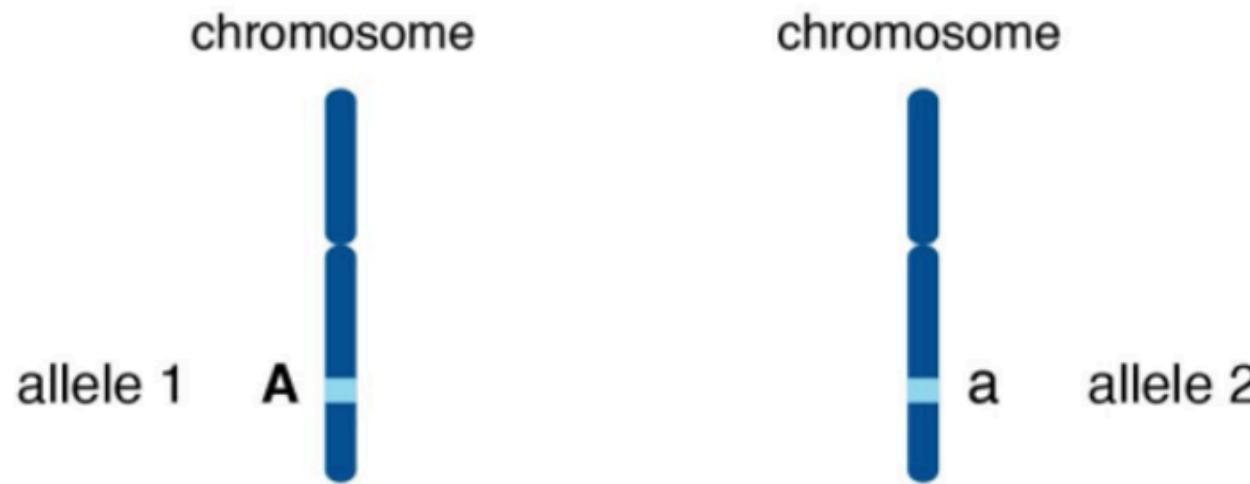
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Important concepts

- Key principles in population genetics that are important in association analysis:
 - Population Substructure
 - Hardy Weinberg Equilibrium
 - Population Substructure leads to Hardy Weinberg Disequilibrium.

Estimation of allele frequency

- An individual has two copies of each autosomal (not sex) chromosomes.



- Goal: estimate the population proportion of a particular allele A (the other allele is a).

Estimation of allele frequency

- The allele proportion (frequency) in the population is the proportion of chromosomes carrying that allele.
- Suppose we have a sample of n individuals from a population with a proportion p of A alleles.
- We want to estimate p .
- $q = 1 - p$ is the frequency of the other allele, a.

Estimation of allele frequency

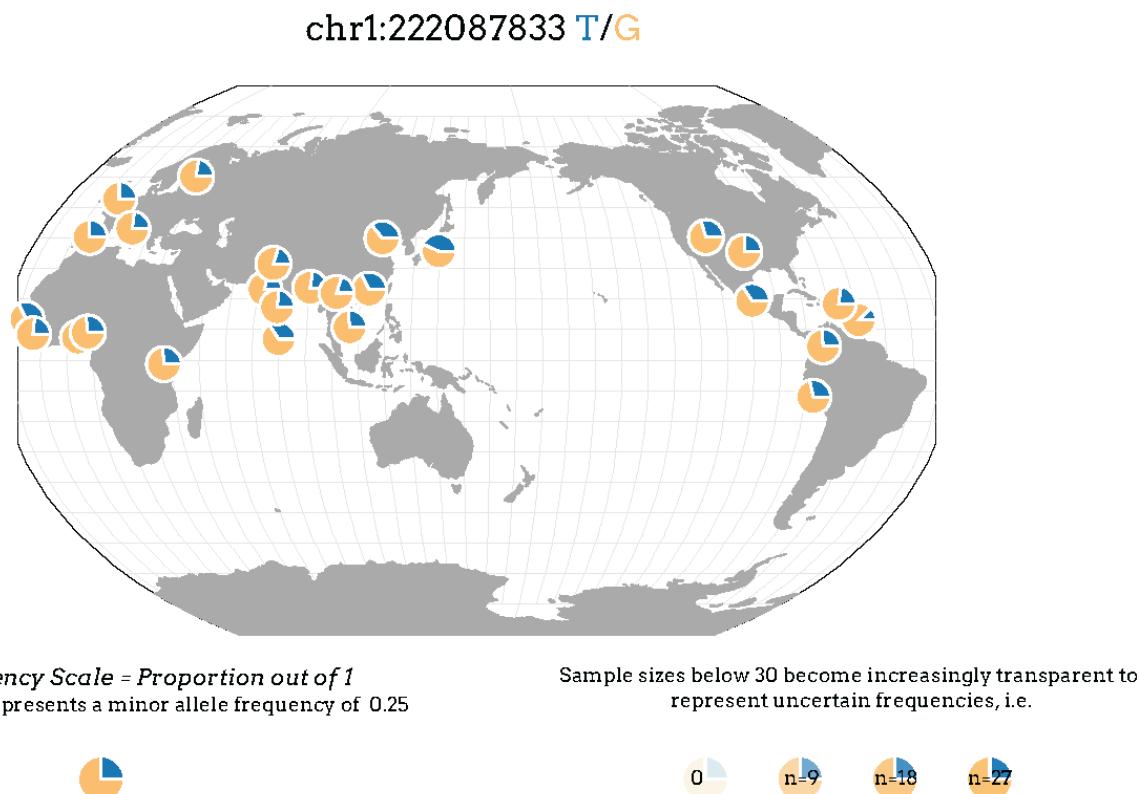
- n_{AA}, n_{Aa}, n_{aa} = number of individuals with genotype AA, Aa, aa.
- $n = n_{AA} + n_{Aa} + n_{aa}$
- $\hat{p} = \frac{2n_{AA} + n_{Aa}}{2n}$
- $\hat{q} = 1 - \hat{p}$
- `plink --bfile your_data --freq --out allele_freq`

Estimation of allele frequency

- \hat{p} is an unbiased estimate of p if **random sample with equal probability sampling** (each individual has the same probability of being included in the sample).
- In practice, this means the probability of selection in the sample does not depend on genotype directly or indirectly through a phenotype related to genotype.
 - e.g., some genotypes might be overrepresented if you only sample people with a disease linked to the allele.
- Standard error for proportion $\sqrt{\hat{p}(1 - \hat{p})/2n}$ assumes independence -- may not hold.
 - e.g., family-based or structured populations

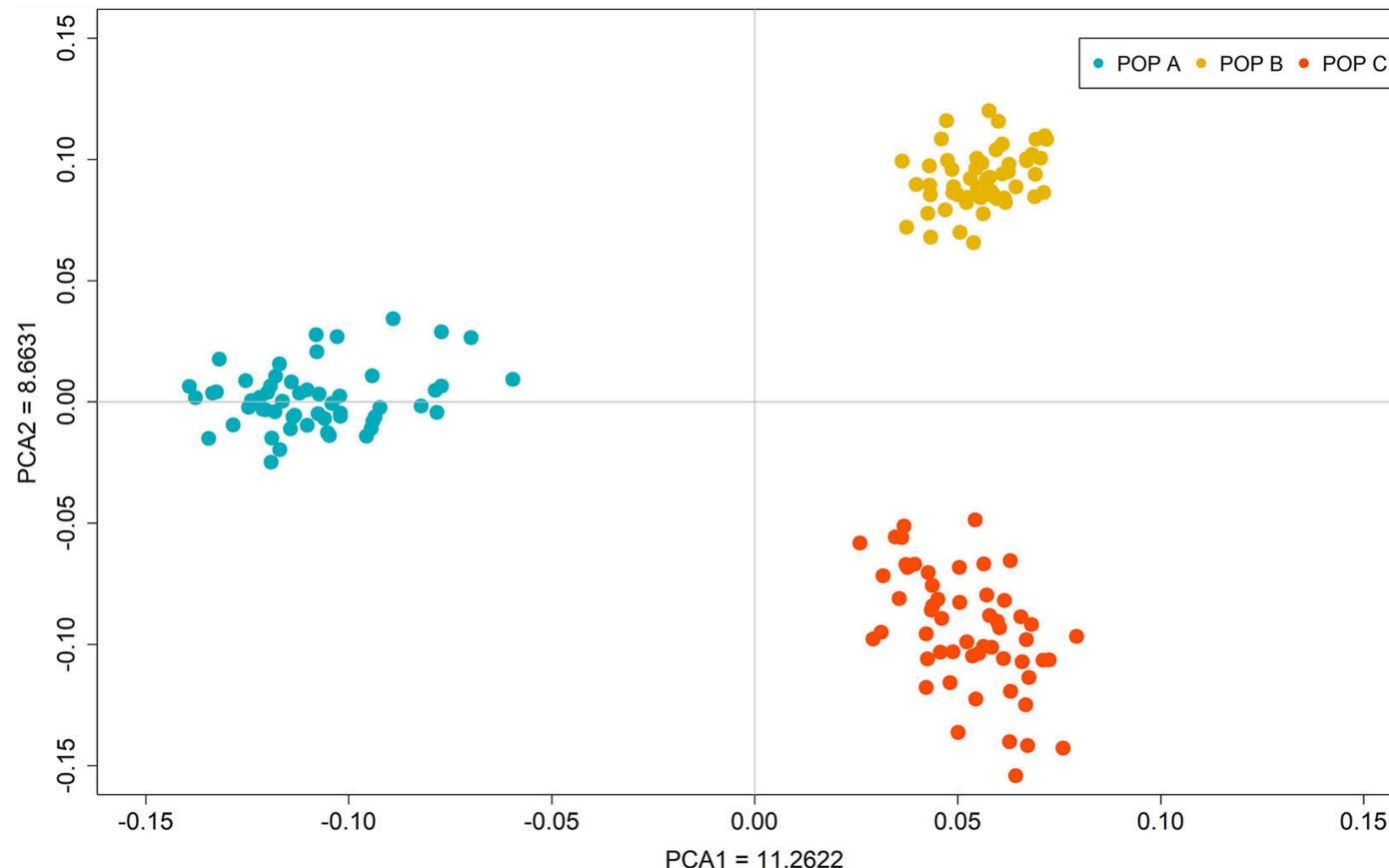
Visualizing the geography of genetic variants

- <http://popgen.uchicago.edu/ggv/>



Population Substructure

- Different subgroups present within your population



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Population substructure

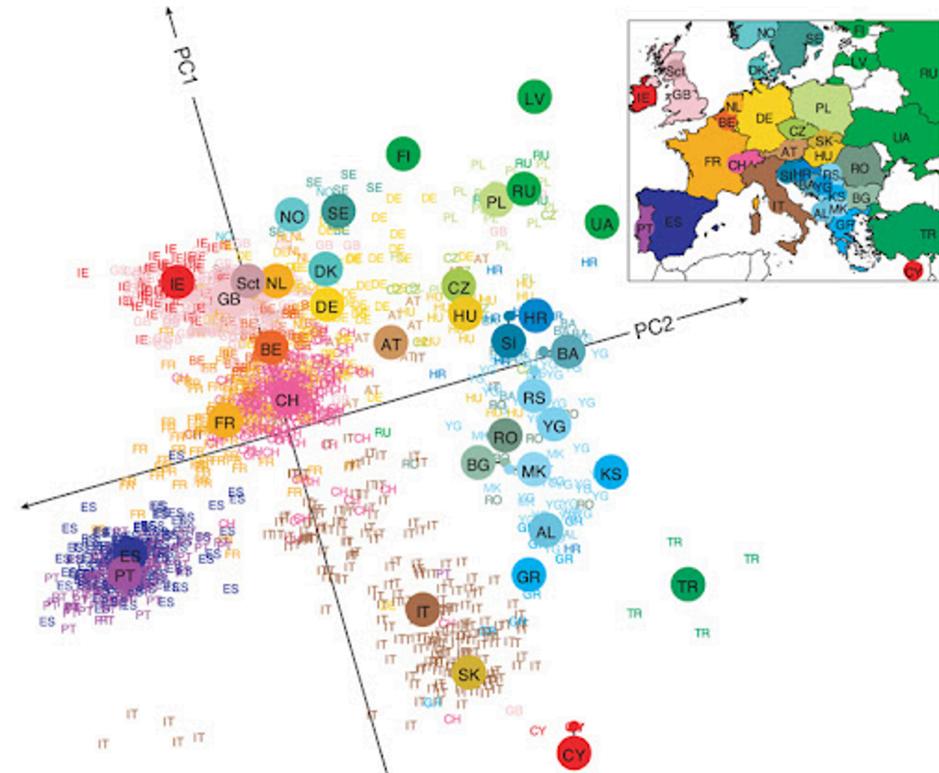
Three common types of population substructure

- Population Stratification
- Population admixture
- Population inbreeding

Population Stratification

- Simplest form of population substructure.
- Individuals in a population can be divided into disjoint strata.
- Strata: ethnic, racial, geographic group.
- Allele frequency can vary among strata.

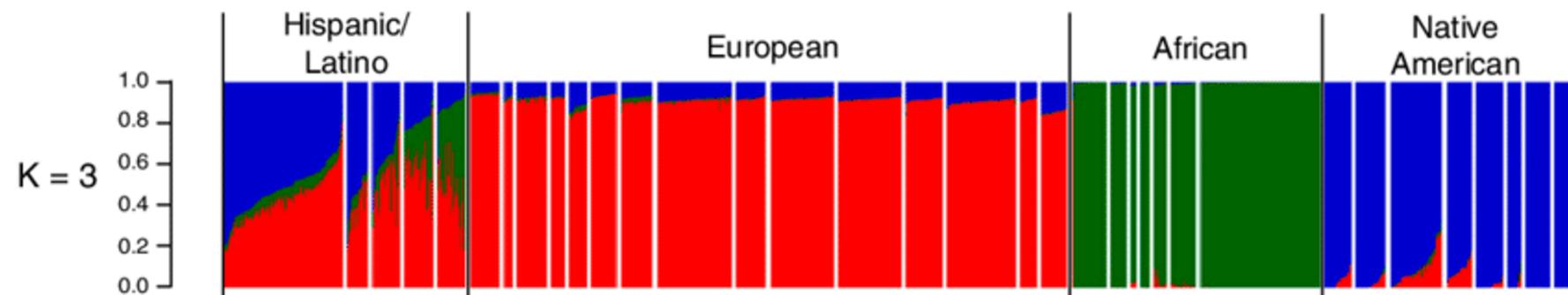
Population Structure in Europe



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Population Admixture

- Individuals in a population have a mixture of different genetic ancestries due to mixing of two or more populations in the past.
- E.g. Hispanic populations:



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Population Admixture

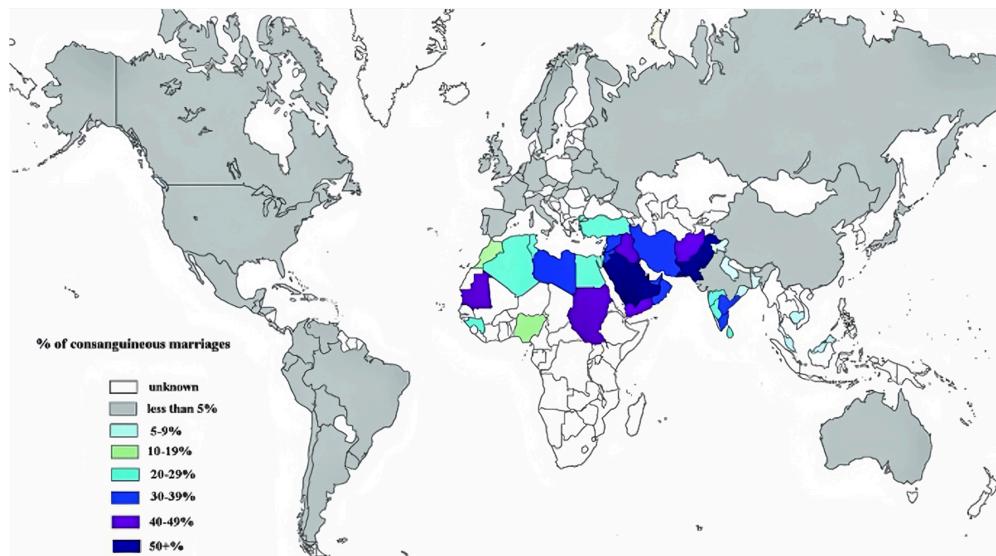
- If allele frequency differs between these populations, then the probability that an individual carries an allele depends on the mixture of that individual ancestry.
- If different disease rates across populations, you can have **SPURIOUS ASSOCIATIONS**.
 - Example: Allele frequencies and the percentage with diabetes for Native Americans, stratified by the number of great grandparents with Indian heritage:

Indian Heritage	Gm3;5;13;14%	% Diabetes
0	65.8%	18.5%
4	42.1%	28.6%
8	1.6%	39.2%

Population Inbreeding

- Preference of mating among relatives in a population or because of geographic isolation restricts mating choices.

Global consanguinity

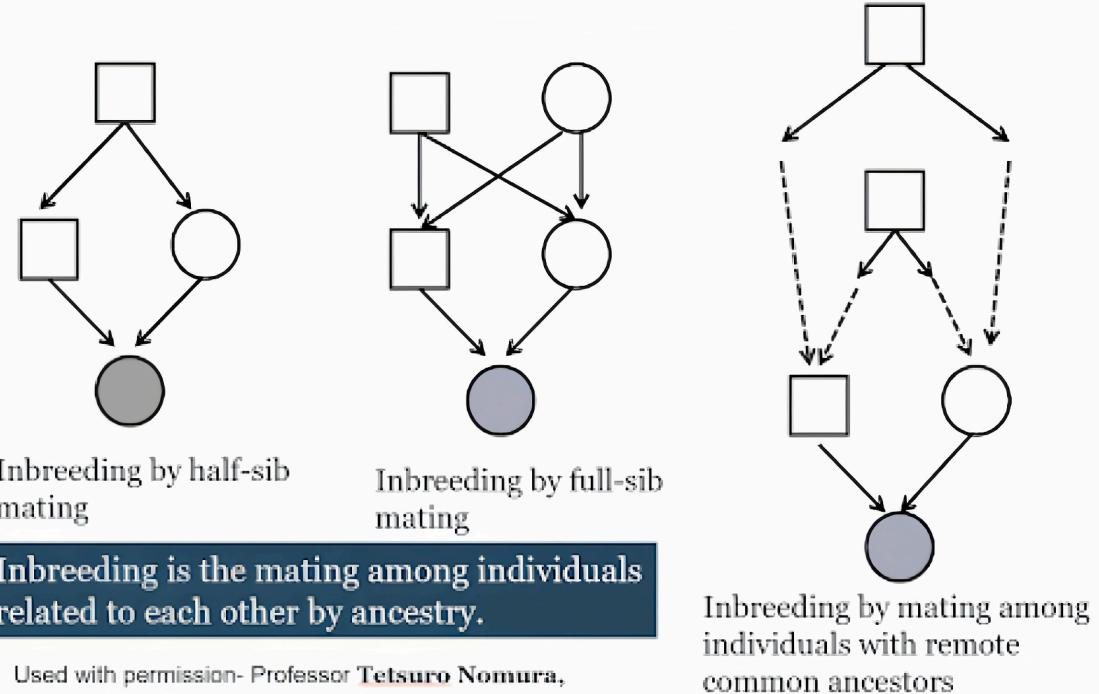


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Inbreeding coefficient

- The inbreeding coefficient:
 F = probability that a random individual in a population inherits two copies of the same allele from a common ancestor.
- In large, random mating populations $F=0$.

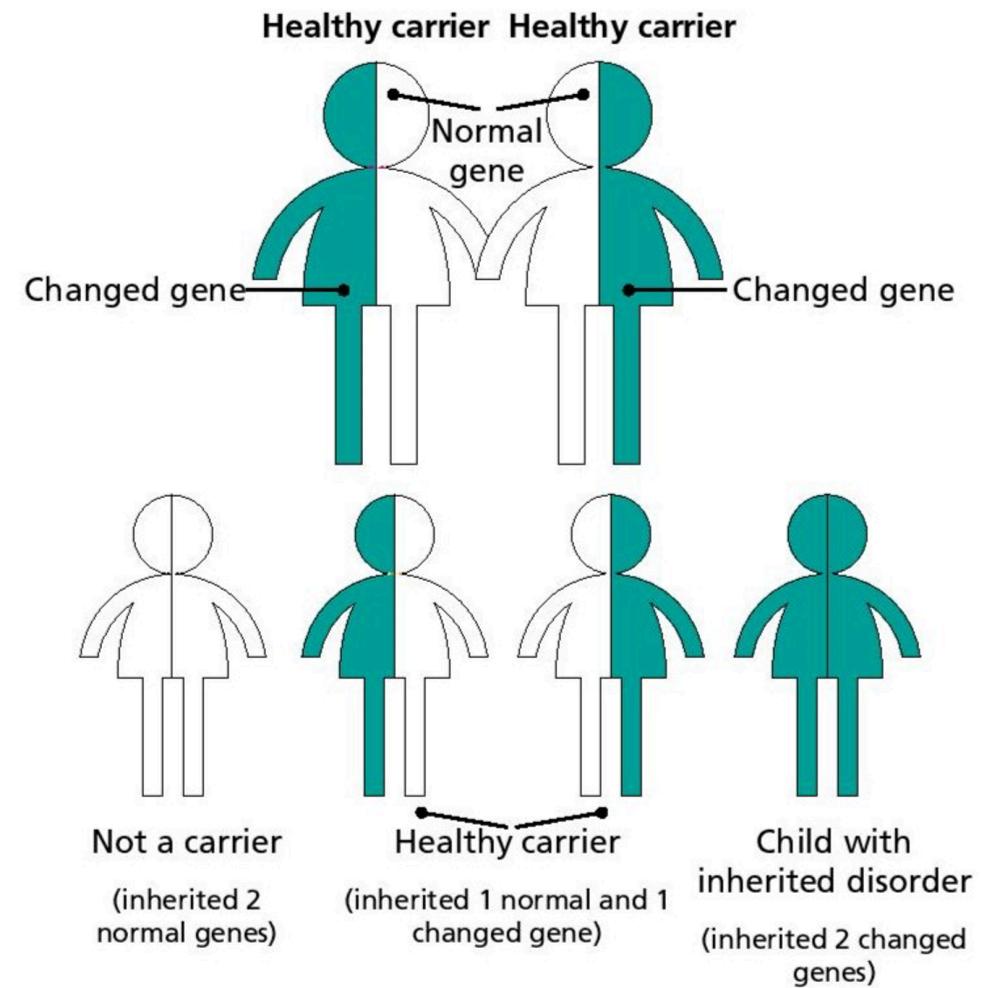
Inbreeding: What is inbreeding ?



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Inbreeding coefficient

- Inbreeding tends to **increase the number of homozygous** in a population, and so inbred populations tend to have **higher than expected frequency of rare recessive disorders**.



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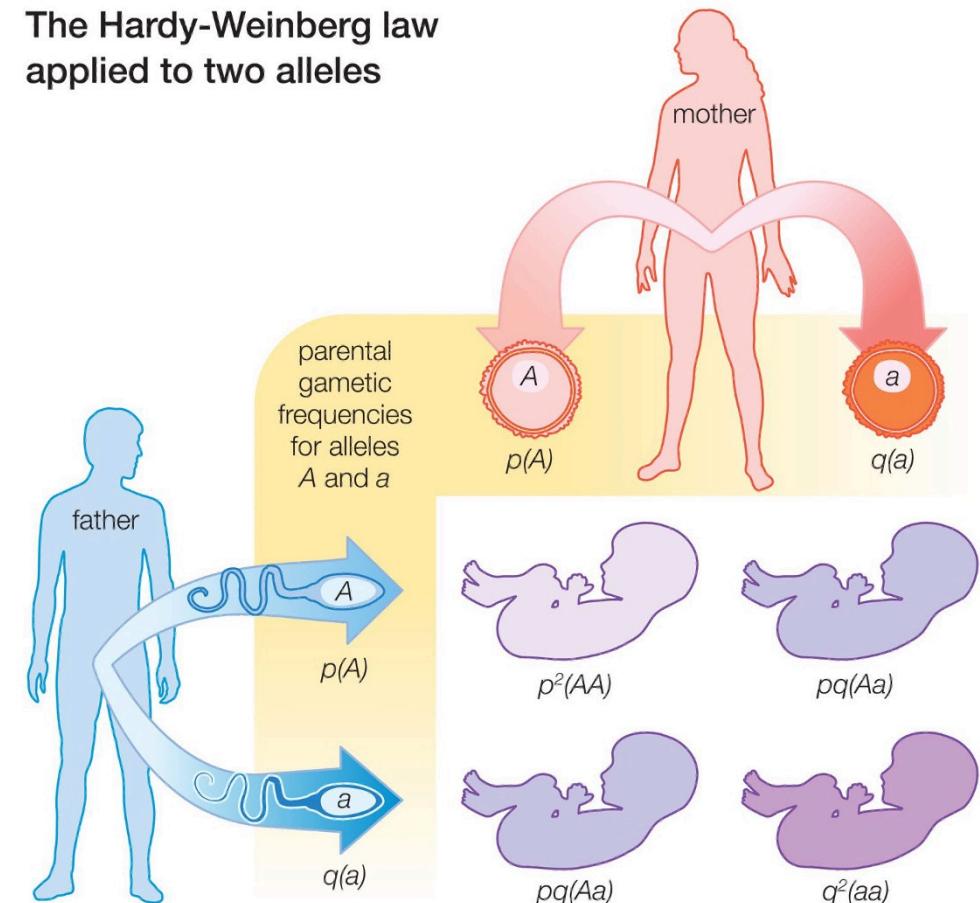
Hardy Weinberg Equilibrium (HWE)

- In 1908, Hardy and Weinberg independently derived a formula relating the genotype frequencies in offspring to allele frequencies in parents.
- The genotype distribution at a locus is defined by the allele frequencies.
- Assumptions: random mating, no inbreeding, no selection, no mutation, no migration, infinite population size.
- HWE simplifies statistical theory and is often assumed.

Hardy Weinberg Equilibrium

- Let p be the frequency of A allele.
- After one generation of random mating:
$$P(AA) = p^2, P(Aa) = 2pq, P(aa) = q^2$$
- Thus, with random mating, the number of A alleles in the offspring generation
 $\sim \text{Bin}(2, p)$.

The Hardy-Weinberg law applied to two alleles



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Testing for HWE

- Common first step in any genetic analysis.
- H_0 : HWE holds. Vs H_1 : HWE does not hold.
- Compare the observed genotype frequencies with those expected under HWE (under H_0).

Testing for HWE

- The Pearson Goodness of Fit Test for HWE:
- H_0 : HWE holds. Vs H_1 : HWE does not hold.
- Given a sample size n from the population:

- | | AA | Aa | aa | |
|----------|--------------|--------------------|--------------|-----|
| Observed | n_{AA} | n_{Aa} | n_{aa} | n |
| Expected | $n\bar{p}^2$ | $2n\bar{p}\bar{q}$ | $n\bar{q}^2$ | n |

- $\bar{p} = (2n_{AA} + n_{Aa})/(2n)$
- $T = \sum_{i=1}^3 \frac{(O_i - E_i)^2}{E_i}; T \sim \chi^2_{(1)}$ under H_0 .

Exercise

- Assume you observe that the proportion of a population affected with sickle cell anemia is 0.01. Assuming an autosomal recessive disease model and HWE, estimate the frequency of the sickle cell mutation at the hemoglobin locus in this population.

Exercise

- **Autosomal recessive disorder** → affected = homozygous recessive (aa)
- Under HWE, q^2 = Frequency of affected individuals = 0.01 → $q = \sqrt{0.01} = 0.1$.
- Frequency of normal allele (A) = $p = 1 - q = 0.9$
- Genotype distribution under HWE:
 - Homozygous normal (AA): $p^2 = 0.81$
 - Heterozygous carriers (Aa): $2pq = 2 \times 0.9 \times 0.1 = 0.18$
 - Homozygous sickle cell (aa): $q^2 = 0.01$

Exercise - Testing HWE

- | Genotypes | AA | Aa /aA | aa | Total |
|-----------------|------|--------|------|-------|
| Observed counts | 189 | 89 | 9 | 287 |
| Expected counts | | | | 287 |
| Expected freq. | 0.81 | 0.18 | 0.01 | 1 |

- $$T = \sum_{i=1}^3 \frac{(O_i - E_i)^2}{E_i} \sim \chi^2_{(1)} \text{ under } H_0.$$

Exercise - Testing HWE

- | Genotypes | AA | Aa /aA | aa | Total |
|-----------------|---------------------------------|--------------------------------|--------------------------------|-------|
| Observed counts | 189 | 89 | 9 | 287 |
| Expected counts | $0.81 \times 287 \approx 232.5$ | $0.18 \times 287 \approx 51.7$ | $0.01 \approx 287 \approx 2.9$ | 287 |
| Expected freq. | 0.81 | 0.18 | 0.01 | 1 |

- $$T = \sum_{i=1}^3 \frac{(O_i - E_i)^2}{E_i} = \frac{(189 - 232.5)^2}{232.5} + \frac{(89 - 51.7)^2}{51.7} + \frac{(9 - 2.9)^2}{2.9} = 47.88.$$
- P-value = 4.53×10^{-12} ; reject HWE.

Why does HWE fail?

- Rejecting the HWE provides some evidence that HWE does not hold – **Hardy Weinberg Disequilibrium (HWD)**.
- Many reasons for HWD: population substructure, selection, genotyping error, association with trait in case-control design.
- At a disease locus we usually have HWD in cases: if a minor allele homozygous confers greater risk to disease, selecting individuals with disease results in more homozygous and less heterozygous than expected.
- With population substructure or inbreeding, heterozygous individuals tends to be underrepresented relative to HWE.
- In GWAS we use HWE test in controls only to identify variants which might be problematic.

Recap

- Key principles in population genetics that are important in genome-wide association studies (GWAS):
 - Population Substructure
 - Hardy-Weinberg equilibrium (HWE)
 - Population Substructure leads to deviations from HWE => increased false positive rates

What's next

- Not accounting for population stratification leads to wrong variance for the association test statistic → FALSE POSITIVE ASSOCIATIONS.
- We will later learn how to adjust for this confounder – using principal component analysis (PCA) or linear mixed effect models.

Genetic association studies

- Part 1: Given a trait, should we perform genetic studies and under what conditions?
- Part 2: Association tests

How do we know a trait is genetic?

- Most researchers would not undertake a genetic analysis without enough evidence.

Association testing

- **Objective:** establish association between a trait of interest and a genetic marker.
- Study designs: case-control, case-cohort, population-based design.
- Unrelated subjects or **population-based designs:** easy to collect so possible to achieve large sample sizes as in GWAS.
- **Family-based designs:** robust to population stratification, more difficult to collect.
Also hard to collect for late-onset diseases.

Types of tests

- SNP: categorical variable with three genotypes
- Possible tests:
 - 2-DF tests that compare all three genotypes.
 - 1-DF tests : some assumption (e.g. monotonicity) about disease and genotype.
- We assume a case-control design: r cases, s controls, $n=r+s$ total sample size.

Association Testing (2-DF test)

- Y : binary phenotype ($Y = 1$: case).
 - $H_0 : P(Y = 1 | AA) = P(Y = 1 | Aa) = P(Y = 1 | aa)$
 - H_A : At least one inequality holds

	aa	Aa	AA	Total
Cases	r_0	r_1	r_2	r
Controls	s_0	s_1	s_2	s
Total	n_0	n_1	n_2	n

- **Two df Pearson test of independence:** $\chi^2 = \sum(O - E)^2/E$.
 - Sum is over all six entries.
 - e.g. $E [\text{Case} \& \text{aa}] = r * (n_0/n); E [\text{Controls} \& \text{AA}] = s * (n_2/n)$.

Association Testing (2-DF test)

- Most general test: assume nothing about the relationship between disease and genotype.
 - $H_0 : P(Y = 1 | AA) = P(Y = 1 | Aa) = P(Y = 1 | aa)$
 - H_A : At least one inequality holds
- Let G be the genotype of the Disease Susceptibility Locus.
- $f_0 = P(Y = 1 | G = aa), f_1 = P(Y = 1 | G = Aa), f_2 = P(Y = 1 | G = AA)$
•

Penetrance and mode of Inheritance

- Let G be the genotype of the Disease Susceptibility Locus
- **Penetrance function:** $P(Y = 1 \mid G)$
- **Incomplete penetrance:** $0 < P(Y = 1 \mid G) < 1.$
- **Recessive Model:**
 - $P(Y = 1 \mid G = aa) = 0, P(Y = 1 \mid G = Aa) = 0,$
 $P(Y = 1 \mid G = AA) = 1.$
- **Dominance model:**
 - $P(Y = 1 \mid G = aa) = 0, P(Y = 1 \mid G = Aa) = 1,$
 $P(Y = 1 \mid G = AA) = 1.$
- **Incomplete penetrance:** $0 < P(Y = 1 \mid G) < 1.$

General Mode of Inheritance

- **Recessive model:**
 - $f_0 = P(Y = 1 \mid G = aa) = P(Y = 1 \mid G = Aa) = f_1$
 - Simple Mendelian recessive disease further assumes $f_1 = f_0 = 0$ and $f_2 = 1$.
- **Dominant model:**
 - $f_1 = P(Y = 1 \mid G = Aa) = P(Y = 1 \mid G = AA) = f_2$
- **Co-dominant model:**
 - f_1 is somewhere between f_0 and f_2 .

General Mode of Inheritance

- **Additive model** is a special case of co-dominant model: f_1 is average of f_0 and f_2 .
 - Linear scale: $f_1 = \frac{f_0 + f_2}{2}$.
 - Log (or multiplicative scale) $f_1 = \sqrt{f_0 \times f_2}$
- Heterozygote advantage model (or disadvantage model):
 - $f_1 <$ both f_0 and f_2 (or $>$ both).

Dominant Tests

- Dominant model:
 - $H_0 : P(Y = 1 | AA) = P(Y = 1 | Aa) = P(Y = 1 | aa)$
 - $H_A : P(Y = 1 | AA \text{ or } Aa) \neq P(Y = 1 | aa)$
- 1 df chi-square test: Optimal when the true disease model is dominant but not for recessive:
 - $H_A : P(Y = 1 | AA) \neq P(Y = 1 | Aa \text{ or } aa)$

What questions do you have about anything from today?

