SISG 2023 - Module 2

Introduction to Genetics and Genomics

Population Genetics

Block #8 – Tuesday, July 11

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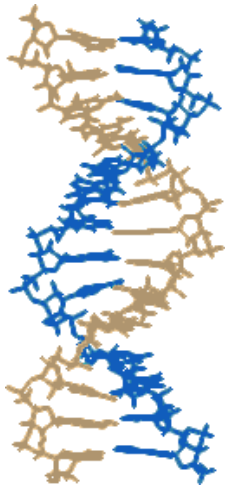
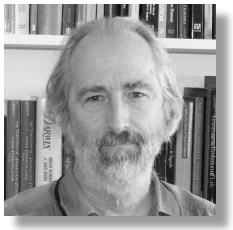


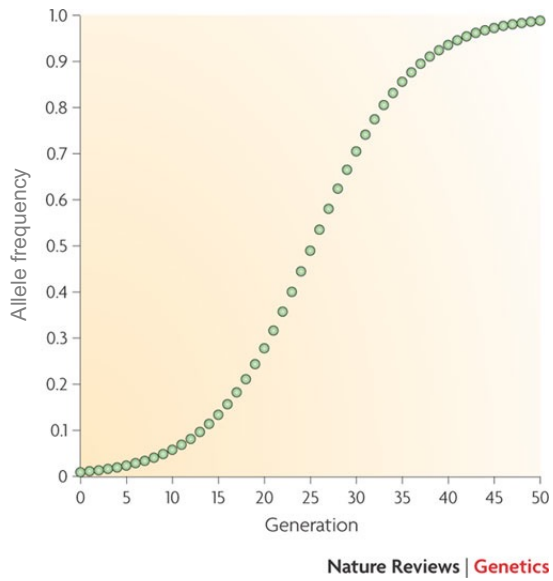
The importance of population genetics

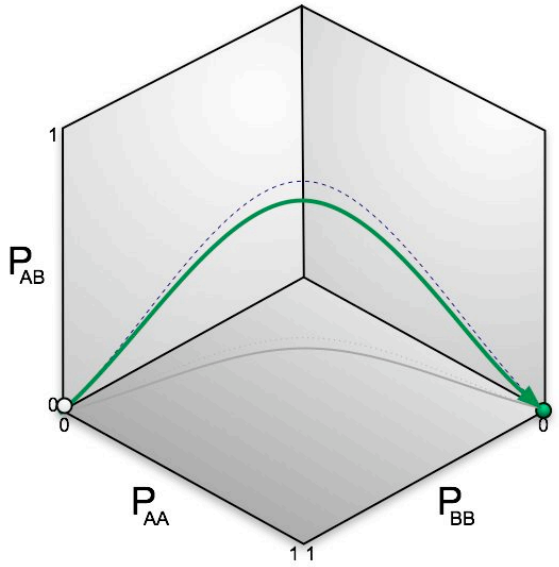
- “Nothing in biology makes sense except in the light of evolution.” T. Dobzhansky

- “Nothing in evolution makes sense except in the light of population genetics." M. Lynch



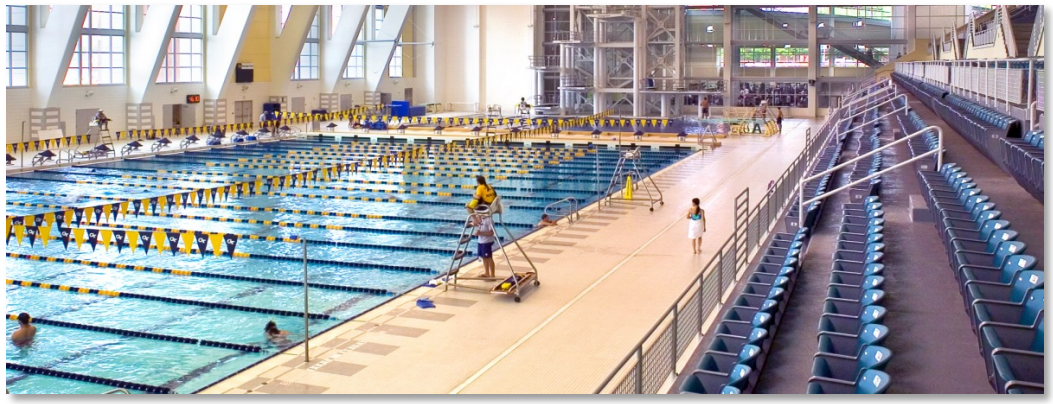
Allele and genotype frequency space





- Allele frequencies (and genotype frequencies) sum to 100%
- A diploid population can be represented by a point in genotype frequency space
- Allele and genotype frequencies can be tracked over time
- When alleles are rare most copies are found in a heterozygous state

Gene pool metaphor



- Gene pool: aggregate total of all the alleles in a population
- Contributions to next generation's gene pool are weighted by fitness
- Genotypes next generation found by binomial sampling (w/ replacement)

Image : Georgia Tech CRC

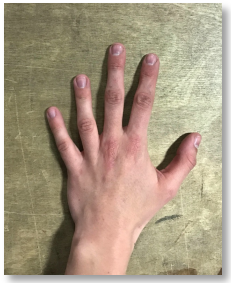
The birth of population genetics (1908)

- The rediscovery of Mendelian genetics in early 20th century was not without some misinterpretations…
  - Brachydactyly is a dominant trait
  - Yule: "75% of people should have short fingers"
  - Punnett: "Something is amiss with that thinking"

- G. H. Hardy correctly inferred the genotype proportions in a randomly mating population, but not without writing:

  "I would have expected the very simple point which I wish to make to have been familiar to biologists"

- Wilhelm Weinberg, a German physician, independently derived the same result as Hardy



Type E Brachydactyly

G. H. Hardy

Wilhelm Weinberg

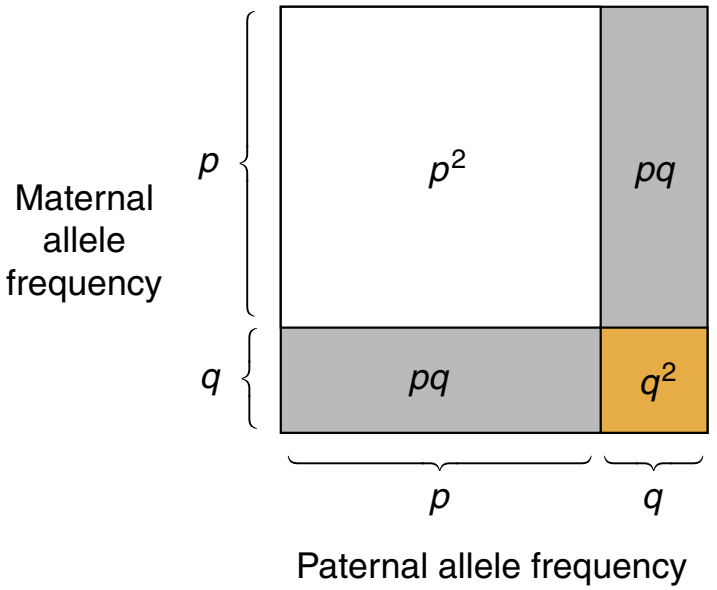
Clearing up some common misconceptions

- Dominant alleles need not be the major (most common) allele
- Higher fitness alleles are not always dominant (and vice versa)
- Higher fitness alleles need not be major alleles

Image: Affe mit Schädel by Hugo Rheinhold

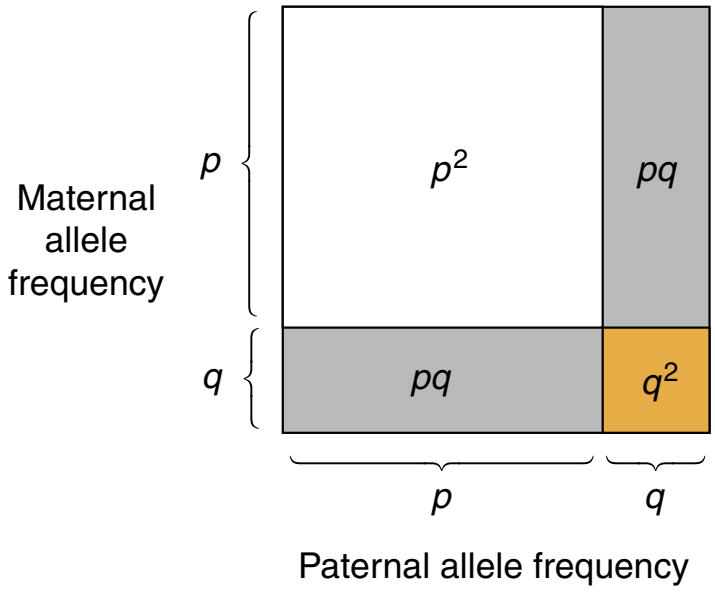
Hardy-Weinberg principle

- Allele frequencies used to calculate genotype frequencies
- Equilibrium reached in a single generation (so long as assumptions hold)
- Allele frequencies
  - Frequency of allele *A*: p
  - Frequency of allele *B*: q
- Genotype frequencies
  - Frequency of *AA* homozygotes: p^2
  - Frequency of *AB* heterozygotes: $2pq$
  - Frequency of *BB* homozygotes: q^2
- $p + q = 1$
- $(p + q)^2 = p^2 + 2pq + q^2 = 1$

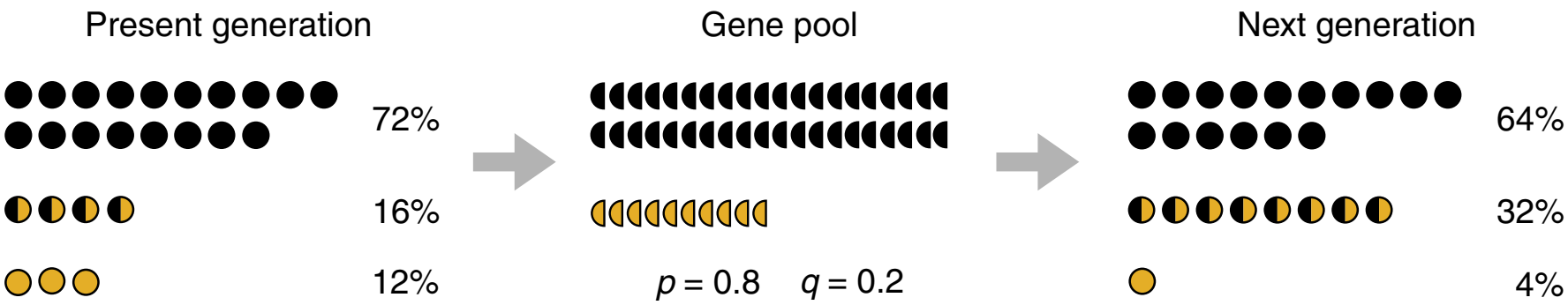


Assumptions of the Hardy-Weinberg principle

- Infinite population size
- No selection
- No mutation
- No migration
- Random mating



Hardy-Weinberg example



- Under Hardy-Weinberg conditions the gene pool remains unchanged
- Subsequent generations will have the same equilibrium genotype frequencies

Testing for departures from HW proportions

- Chi-square test with 1 degree of freedom
- Chi-square (χ^2) > 3.84 indicates statistical significance (p-value < 0.05)
- Example:

Genotype	Observed	Expected	**Chi-square**
AA	145	131.31	1.426
AB	68	95.37	7.854
BB	31	17.32	10.815
Total	**244**	**244**	**20.095**

$$p = \frac{145 + 68/2}{145 + 68 + 31} = 0.7336$$

$$\chi^2 = \sum \frac{(O - E)^2}{E}$$

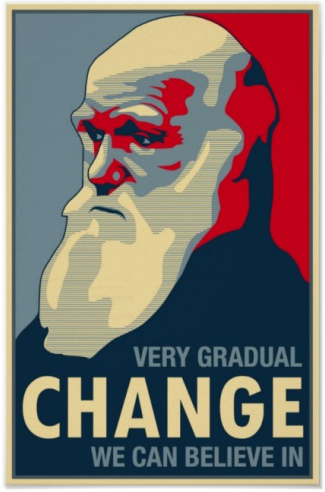
Binomial sampling and beanbag genetics

$$P(x \text{ copies next generation}) = \binom{2N}{x} p^x (1-p)^{2N-x}$$

- How many copies of an allele will be in next generation's gene pool?
- N refers to population size; p refers to current allele frequency

Major processes of population genetics

- Genetic drift
- Natural selection
- Mutation
- Migration (gene-flow)
- Population structure & mating patterns



- Each of these processes can lead to departures from Hardy-Weinberg proportions

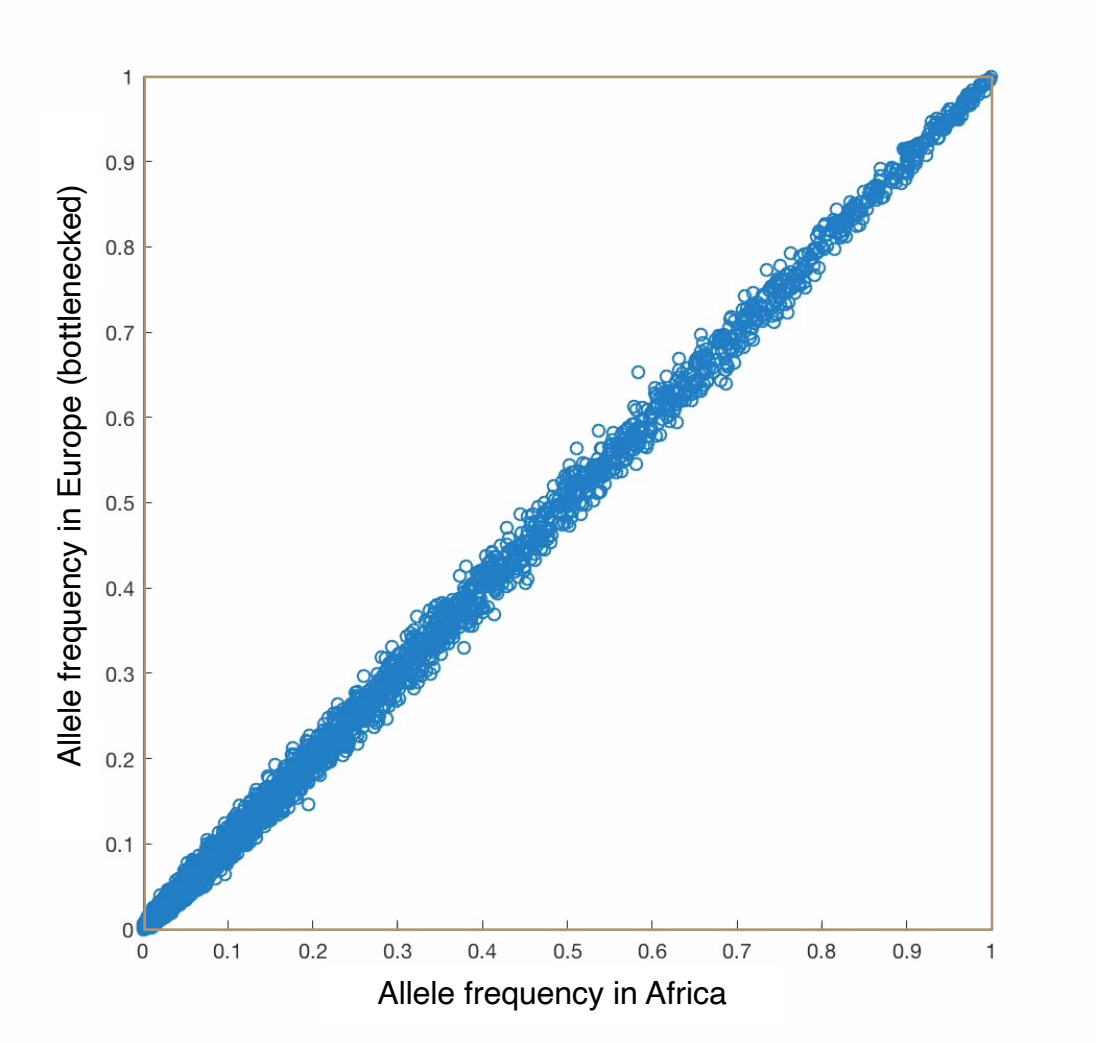
- These processes are mechanisms of evolutionary change

Image source: Zazzle

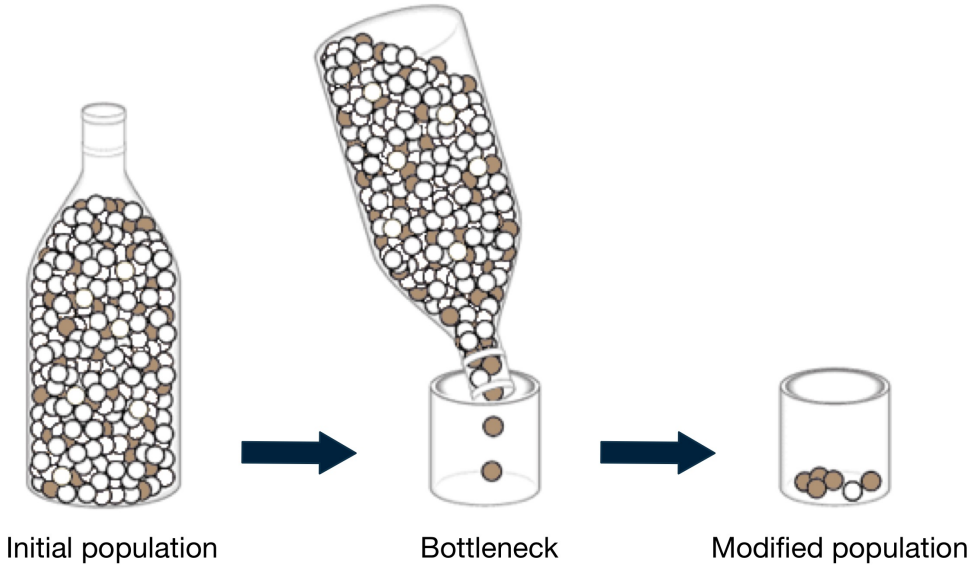
Genetic drift: key points

- Genetic drift is unbiased
- Random fluctuations in allele frequencies are larger in smaller populations
- Drift causes genetic variation to be lost
- Drift causes populations that are initially identical to become different
- An allele can become fixed without the benefit of natural selection

Simulating genetic drift

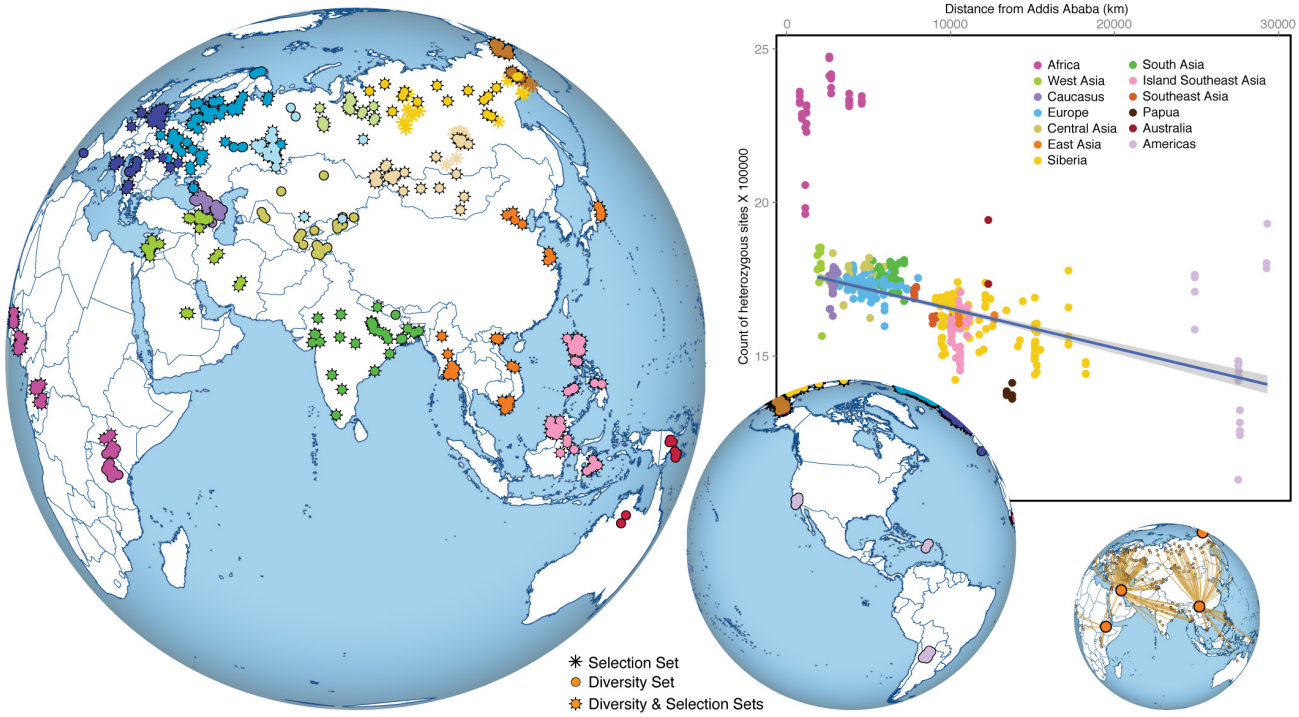


Population bottlenecks and founder effects



- **Population bottleneck**: A sharp reduction in the size of a population
- **Founder effect**: Bottleneck caused by the founding of a new population
- Random chance determines whether an allele increases or decreases in frequency

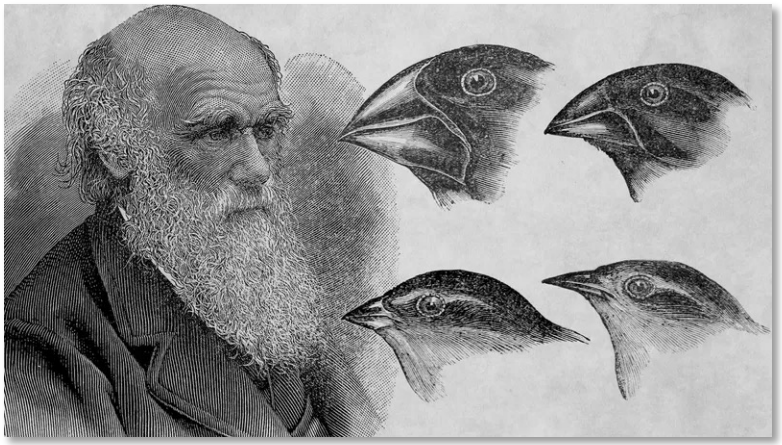
Non-African genomes contain less variation



- Serial founder effects reduce the proportion of sites in an individual's genome that are heterozygous

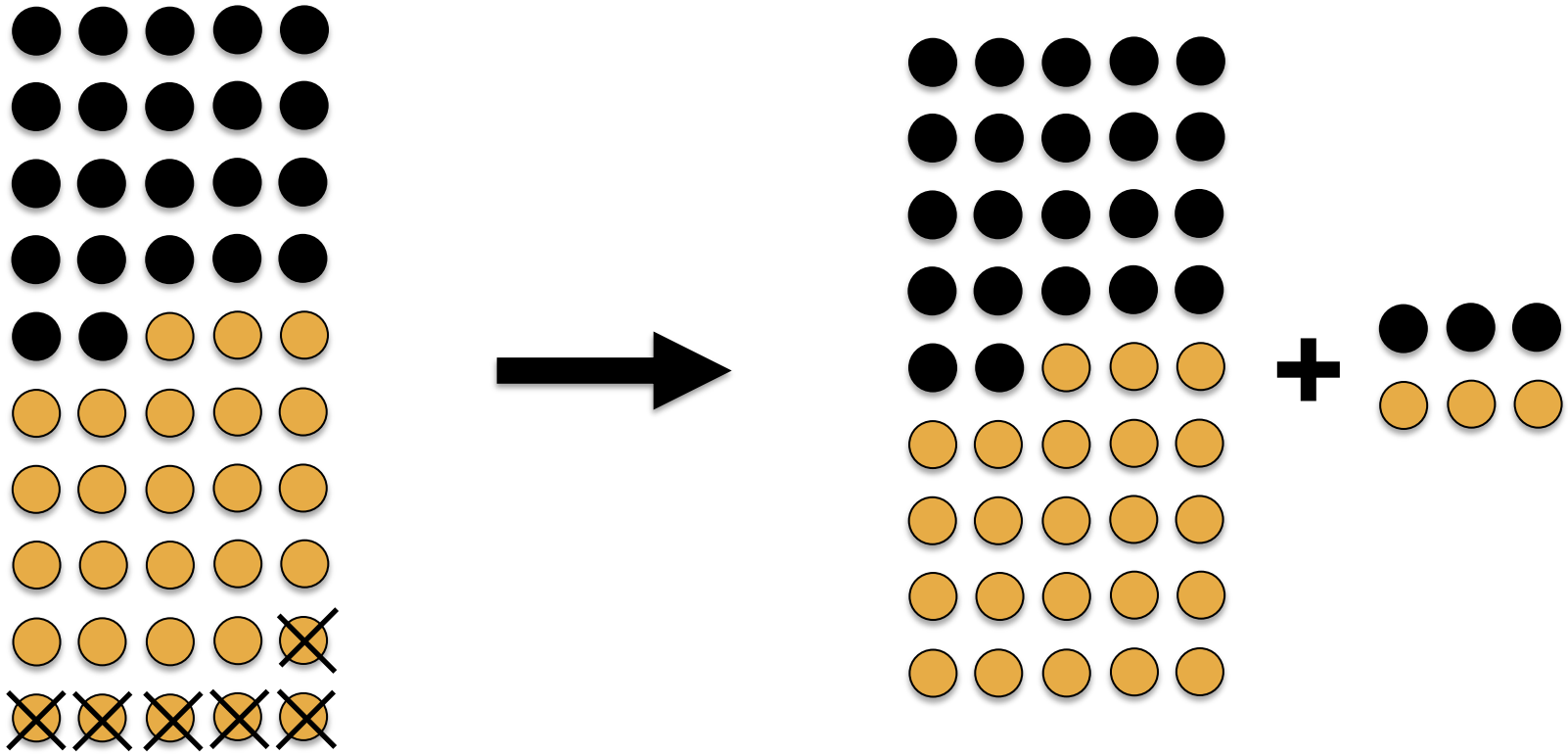
Figure from Pagani et al. (*Nature*, 2016)

Natural selection



- **Natural selection**: the differential survival and/or reproduction of different genotypes due to unequal fitnesses
- Natural selection is not the same thing as evolution
- Selection operates on short time scales
- Probability of fixation: ~2s
  (where s is the selective advantage of a new mutation

Selection changes gene pools



p = 0.44

p = 0.5

Mathematics of natural selection

- Assumptions: diploid population of infinite size (no genetic drift)
- Frequencies next generation can be found by weighting contributions to the gene pool

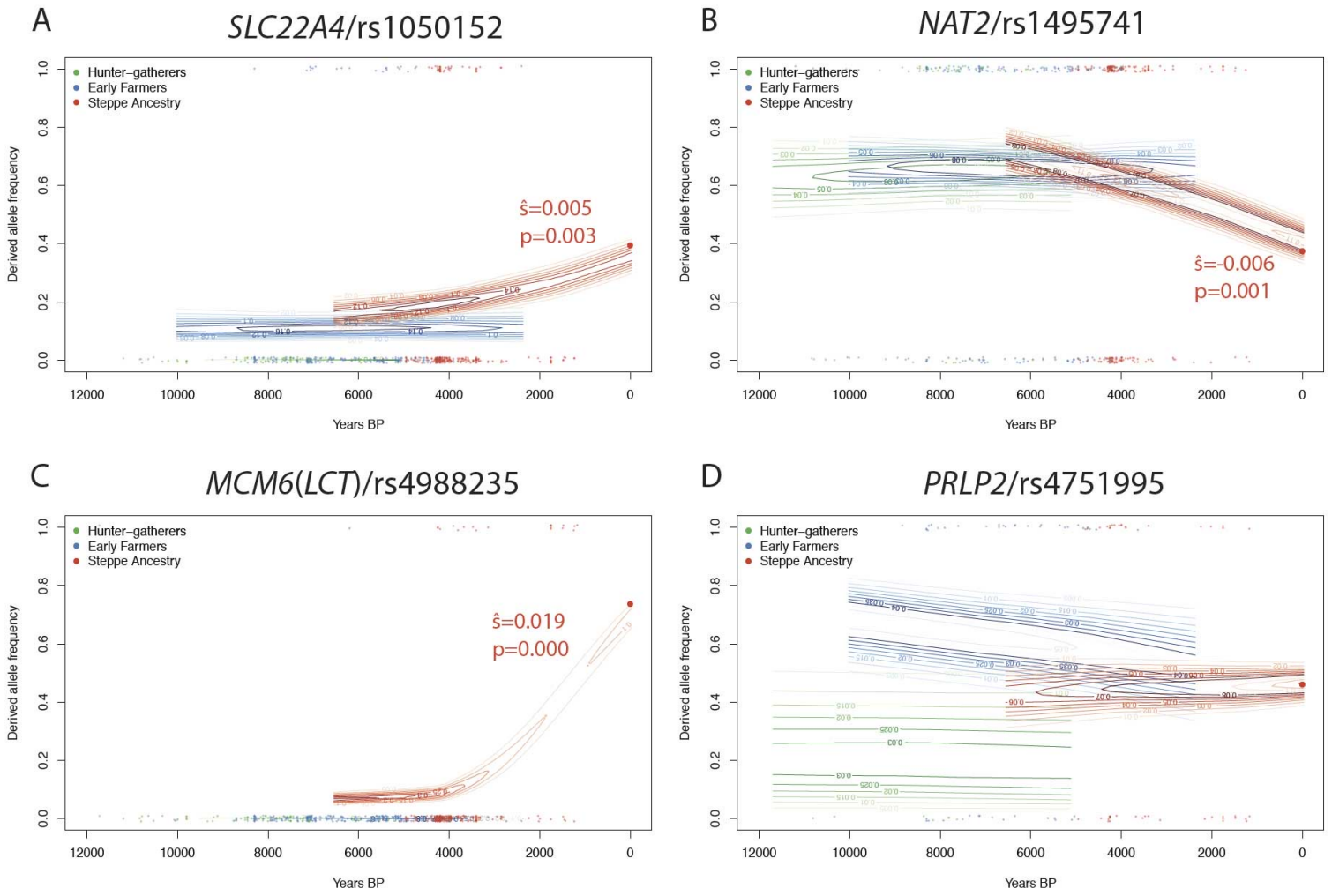
$$P_{AA}{}' = \frac{p^2 w_{AA}}{p^2 w_{AA} + 2pq w_{AB} + q^2 w_{BB}}$$

$$P_{AB}{}' = \frac{2pq w_{AB}}{p^2 w_{AA} + 2pq w_{AB} + q^2 w_{BB}}$$

$$P_{BB}{}' = \frac{q^2 w_{BB}}{p^2 w_{AA} + 2pq w_{AB} + q^2 w_{BB}}$$

$$p' = \frac{p^2 w_{AA} + pq w_{AB}}{p^2 w_{AA} + 2pq w_{AB} + q^2 w_{BB}}$$

Selection: allele frequency trajectories

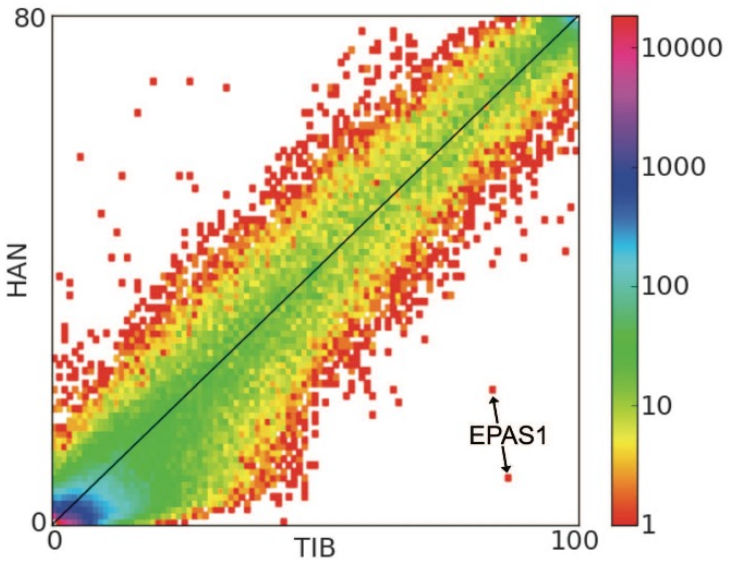


Mathieson and Mathieson (*Molecular Biology and Evolution*, 2018)

EPAS1 and adaptation to high-altitude

- Reduced [O_2] is a strong selective pressure
- Allele frequencies compared between Tibetans (TIB) and Han Chinese from Beijing (HAN)
- Outlier SNPs are located near *EPAS1*, a hypoxia-induced transcription factor
- The Tibetan EPAS1 haplotype comes from Denisovans (Huerta-Sanchez et al. 2014)**!!!**
- Positively selected *EPAS1* haplotype contains a deletion that occurred 12kya (Lou et al. 2015)

Image rights: EasyTourChina



Yi et al. (Science, 2010)

Mutation

- Human mutation rates
  - $\mu = 2.5 \times 10^{-8} bp^{-1} gen^{-1}$ from comparative genomics (phylogenetic approach)
  - $\mu = 1.2 \times 10^{-8} bp^{-1} gen^{-1}$ from direct sequencing of families

- A “Goldilocks” scenario:
  - Too low a mutation rate and a population will lack genetic diversity
  - Too high of a mutation rate and a population will be unable to purge mutations via natural selection (mutational meltdown, Muller’s rachet)

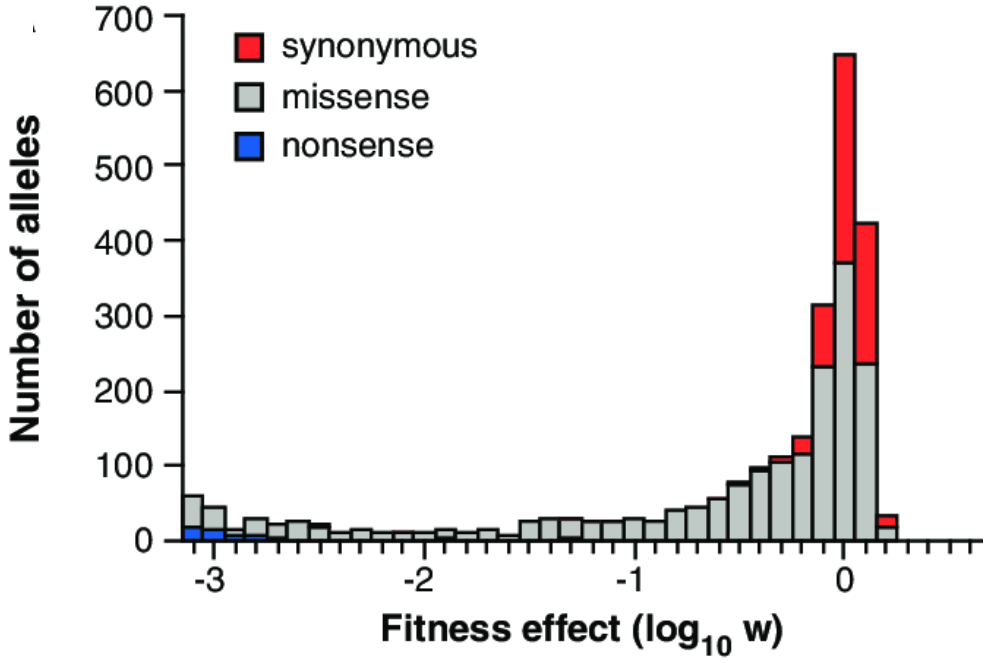
- Mutation does not lead to large allele frequency changes in of itself

Mutation example: super-cows?!

- Double-muscling caused by a mutation in the *myostatin* (*GDF8*) gene
- Recurrent mutation in Belgian Blue cattle

Image source: imgur.com

Distribution of fitness effects (DFE)

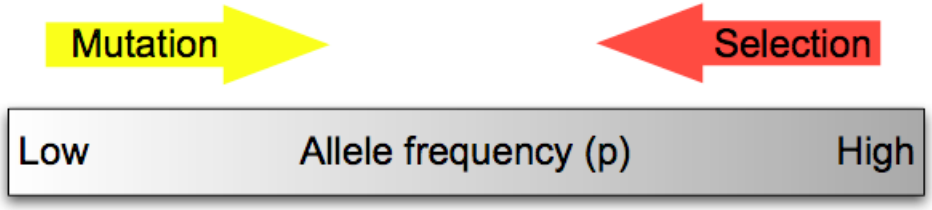


Gene*: TEM-1*
Species: *E. coli*

- Most mutations are deleterious or neutral (they do not increase fitness)
- Mutations of large phenotypic effect are more likely reduce fitness
- The DFE is different for coding mutations (i.e., mutations in exons)

Firnberg et al. (MBE, 2014)

Mutation-selection balance



- Deleterious alleles are maintained due to a balance between mutation and selection
- Equilibrium allele frequencies:

$$\hat{p} \approx \sqrt{\frac{\mu}{s}}$$ (recessive)

$$\hat{p} \approx \frac{\mu}{sh}$$ (non-recessive)

- Implications:
  - Recessive disease alleles can segregate at moderate frequencies
  - Strongly selected disease alleles tend to be rare

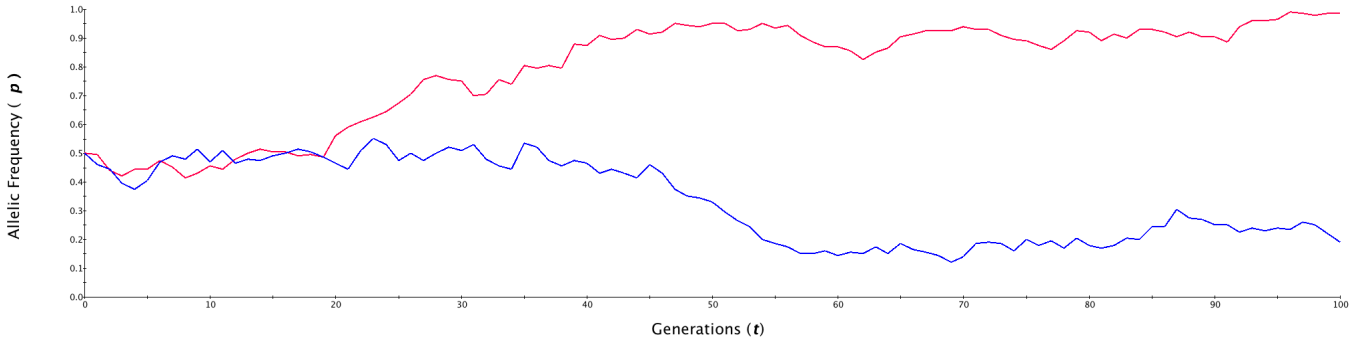
Migration

- When population geneticists refer to migration, they mean ***gene flow***
- The parameter m equals the proportion of alleles in a population that are from immigrants
- Gene flow homogenizes populations
- Local differentiation occurs when there is < 1 migrant per generation (Nm < 1)

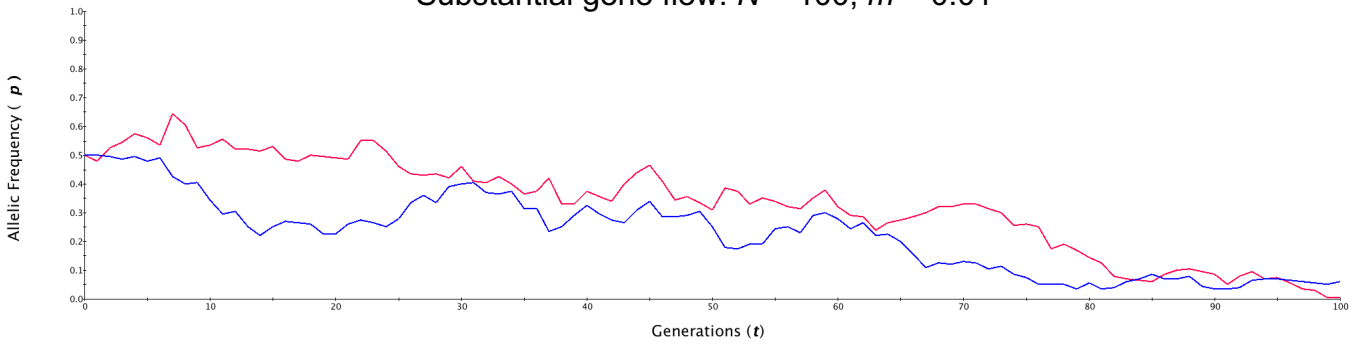
Image source: Sam Falconer/New Scientist

Simulations of migration (and genetic drift)

No gene flow*: N*=100, *m* =0



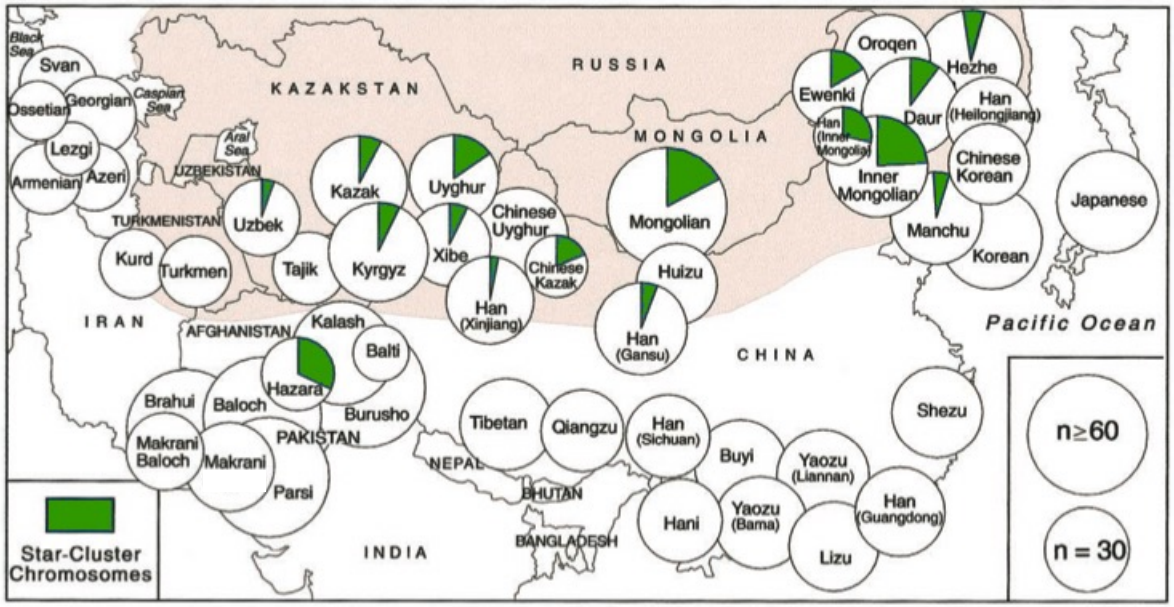
Substantial gene flow: *N* = 100, *m* = 0.01



Allele frequency trajectories generated using *Populus*

Migration example

- Geographic proximity results in genetic similarity



- The Y-chromosome legacy of Ghengis Khan
  (Zerjal et al. 2003, American Journal of Human Genetics)

Assortative mating

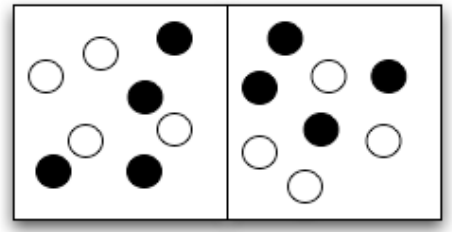
- Positive assortative mating
  - Phenotypically similar individuals prefer to mate with each other
  - Can result in the maintenance of different phenotypes

- Negative assortative mating
  - Phenotypically different individuals prefer to mate with each other
  - Maintains genetic variation despite loss of phenotypic variation

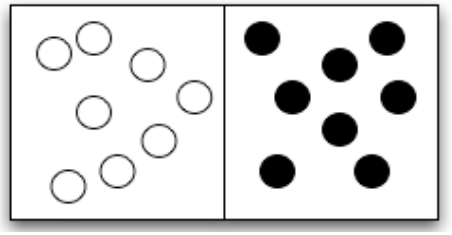
Images: ECNS and Getty Images

Population structure: F_{ST}

$$F_{ST} = \frac{Var(p)}{\bar{p}(1-\bar{p})}$$



F_{ST} = 0

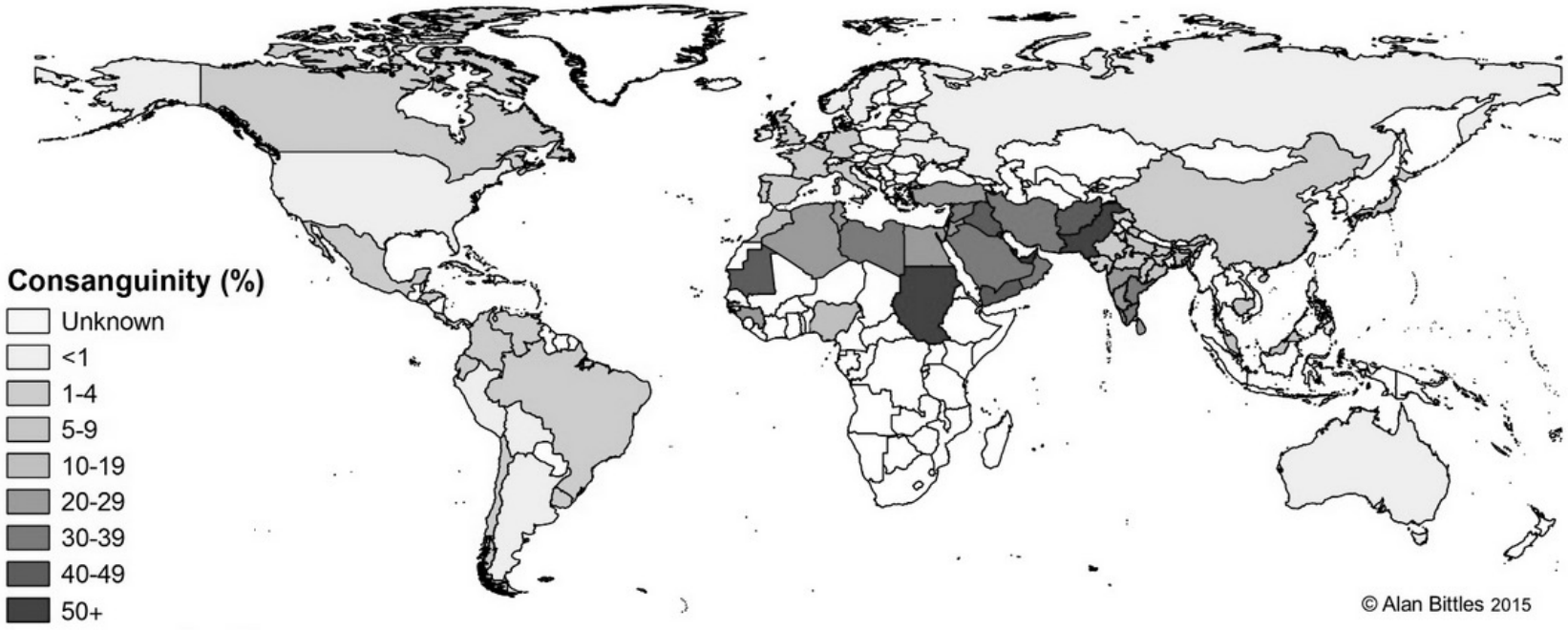


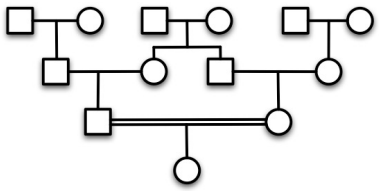
F_{ST} = 1

- F_{ST} measures how much genetic variation can be explained by sub-populations within the total population

- F_{ST} between divergent populations increases over time $F_{ST} = 1 - \left(1 - \frac{1}{2N}\right)^t$

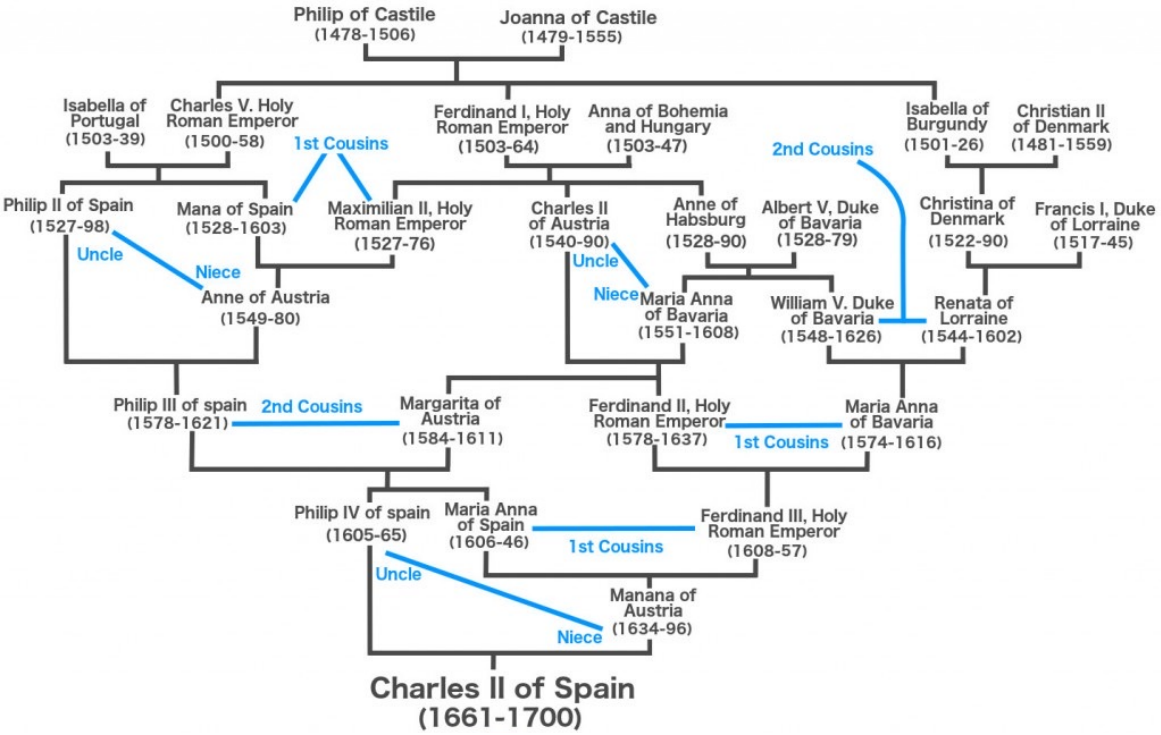
Inbreeding is widespread





- **Inbreeding**: preferential mating between relatives
- Inbreeding coefficients quantify excess amounts of homozygosity

Effects of inbreeding



- Inbreeding can have negative consequences if disease alleles are recessive

Painting by Juan Carreño de Miranda

Effects of each major process

	Genetic Drift	Natural Selection	Mutation	Migration	Mating Structure
Time-scale	Medium	Fast	Slow	Medium	Fast
Effect on variation	Reduced	"It depends"	Increased	Homogenized	"It depends"