- Humans on average differ by 0.1-0.3% (includes CNV, SNP, insertions and deletions)
- Different types of genetic variations:
  - SNP can result in nonsynonymous or synonymous changes
  - Non-coding variations
  - Copy number variations
- Human 1000 genomes project and other related projects increasing our knowledge of genetic variation in different human populations

Terms I

Polymorphism:

- A locus is polymorphic in a population if there are two or more commonly occurring alleles at that locus (each with frequencies greater than 1%)
- e.g. *β* locus in Ghana

Monomorphism:

- One allele has a frequency greater than 99%
- e.g. *β* locus in Europe (where malaria is not and has not been prevalent in recent history

Polytypism

- Differences between populations
- E.g. B locus in humans

Why? Carriage of the sickle cell variant (B^S) is favourable in areas with a high prevalence of malaria

❖ Allele Frequencies

Terminology

Allele: Alternative form of a gene (variant at a locus)
Genotype: Genetic constitution of an individual i.e. inherited genetic matter (alleles)

- Locus is an area on a chromosome – diff forms that can exist on a locus = alleles (the genetic variations)

Phenotype: Trait determined by genotype (+/- environmental pressures)

Homozygote = 2 of the same alleles (BB or bb)
Heterozygote = 2 diff alleles (Bb)

Genotype	AA $\beta^A\beta^A$	AS $\beta^A\beta^S$	SS $\beta^S\beta^S$
Phenotype	*Normal* A	*S. C. trait* AS	*S. C. disease* S

An example - Haemoglobin variation (beta locus)

- A dominant
- S recessive
- Heterozygotes show some sickle cell features but do not have SCA = incomplete dominance
- Heterozygote advantage
- Homo SS = sickle cell anaemia disease
- Freq. of **S** allele highest in populations where malaria is endemic and causes a fitness cost. **S** allele maintained due to heterozygote advantage

Genetic constitutions

The genetic constitution of:
An individual (2 allele system – **A** and **S** at a single locus

- Genotype: AA, AS, SS

A population

- Allele frequency
  - p = f(A) and q = f(S)
  - total number of chromosomes with allele/2n (n=number of individuals)

Genotype frequencies

Genotype	AA	AS	SS	Total
Number	701	135	4	840
Frequency	0.835	0.161	0.005	1

Number of individuals in a population who have a particular genotype

- Divide number of people with genotype by total (e.g. 701/840)
- With 2-allele systems, there are only 3 possible genotypes so their frequencies should always equal to 1

Allele frequency

Genotype	AA	AS	SS	TOTAL
Number	701	135	4	840

- Total number of chromosomes that carry the A allele / total number of chromosomes
- **'AA'** have A allele on both chromosomes, hence (2x701)
- Each individual inherited a copy of chromosome 11 from mother and father – hence 2x840
- In genotype freq. – denominator is number of individuals; in allele freq., the denominator is total no. of chromosomes and therefore it is 2 times the number of individuals
- In 2 allele system, would expect the freq. of S and A to equal 1, i.e. p+q should equal 1

$$f(A) = \frac{\#\ A \text{ alleles}}{\text{total } \#\text{ chromosomes}} = \frac{(2\times 701)+135}{2\times 840} = 0.915 = p$$

$$f(S) = \frac{\#\ S \text{ alleles}}{\text{total } \#\text{ chromosomes}} = \frac{135+(2\times 4)}{2\times 840} = 0.085 = q$$

$$p+q=1$$

- The allele frequency is the basic measure of the genetic constitution of a population
- The allele frequency is also the basic measure of evolutionary change

Summary

- Genetic variation exists within and between organisms and is the catalyst for evolution
- Evolution is a change in the allele frequency over time
- Allele frequency is the basic measure of the genetic constitution of a population and evolutionary change
- Changes in allele frequency can occur due to evolutionary forces

❖ Evolutionary Forces

Mutation

Principles:

- Creates variation
- Makes small changes in allele frequencies
- Is a weak evolutionary force (if it acts alone)
- Mutation alone can change freq. but only over a long period of time. Some changes may have a dramatic impact
- E.g. single nucleotide polymorphisms, copy number variation, and chromosome inversions or duplications etc.

Random Genetic Drift

- A mechanism for evolutionary change resulting from random fluctuations in allele frequencies from one generation to the next, or from any form of random sampling of the larger gene pool (i.e. as in founder effect)
- Allele frequencies change due to chance – sampling variation
- Variation lost: One allele lost, one allele "fixed"
- Affects all populations and makes isolated populations genetically different
- Magnitude is inversely proportional to N (population size). Has greatest impact in small populations
- Because it is due to chance, the direction in which allele freq. will change is unpredictable

Founder – special case of drift

- Small number of individuals migrate from original population and start a new population (founders). Mating gives rise to new generations
- Allele freq. in generations that arise from the founder population may be different to the original population purely by chance (due to sampling error)

Example of founder effect: Ellis van-Creveld syndrome in Amish

- Autosomal recessive; extra digit on hand
- Worldwide $p < 0.001$
- All cases trace to 1 couple
- In founders $p \approx 0.01$
- Now $p \approx 0.07$

Drift outcomes

- Reduces genetic variability within populations
- Makes populations different from one another: Two isolated populations: allele A could be lost in population 1 and become fixed in population 2
- Very important in human evolution
  - Effective population size (Ne) ≈ 10,000 (for species)
  - Populations much smaller

Gene flow (migration)

Keeps population similar

- Counteracts genetic drift by:
- Increases genetic variability (drift makes pops. more diff. but GF makes them more genetically similar)
- Increases effective population size
- E.g. one pop. that migrates and has gene flow with another pop. = mixture of two types of alleles OR Gene flow between 2 pops. which both acquire new alleles

Increases genetic variability

Natural Selection

- Process: Some genotypes leave more offspring than others, so the frequency of alleles change
- Measure: Fitness (reproductive success)
- Result: Alleles with higher fitness increase in frequency
- The only adaptive force

Measure of NS

Fitness components:

- Viability (survival, mortality)
- Fertility

Example of NS:

- Imagine a population is exposed to a virus which is pathogenic for some individuals and not others.
- B1 allele has selective advantage over B2. Therefore, its freq. will increase over time as those with the B2 allele are more likely to die due to the virus

NS and adaptation

Natural selection acts in two basic ways

1. Changing allele frequencies
   - a) directional
2. Maintaining allele frequencies
   - a) stabilising
   - b) balancing selection

Changing allele frequencies

- evolutionary change
- Directional selection = an extreme phenotype is favoured over other phenotypes, causing the allele frequency to shift over time in the direction of that phenotype
- Over generations - a shift in freq. of favoured genotype and corresponding allele frequencies, giving rise to a particular phenotype
- Due to fitness advantage for this particular genotype
- Speed at which it moves depends on
  - Starting allele freq.: Takes longer to increase if at initially at a low allele freq. prior to selective pressure
  - Expression: **1)** recessive (needs two copies) = only the alternate homozygous has a selective advantage. Allele frequency is slower to increase
  - **2)** Dominant: Homozygotes and heterozygotes have a selective advantage. Increases in allele freq. is therefore more rapid

Maintaining allele frequencies

Stabilising selection

- Extreme phenotypes are disadvantageous (have lower fitness and therefore selected against (their freq. decrease)
- Favours average phenotypes
- e.g. mean birthweight: Mortality increases for babies who are highly overweight or underweight

Balancing selection: Heterozygote advantage

e.g. Haemoglobin variation

- In areas where malaria is prevalent, the genotype with greatest fitness is heterozygous (B^A B^S)
- Homozygous normal – likely to die from malaria. Homozygous recessive – likely to die from sickle cell disease = both have low fitness
- Carriers have some protection against malaria because of their slightly different RBC shape
- So, in populations where malaria is prevalent the S allele is maintained even though if malaria was not present, the S allele is rare because it should be removed from the population (by NS)