Dr Katja Vogt

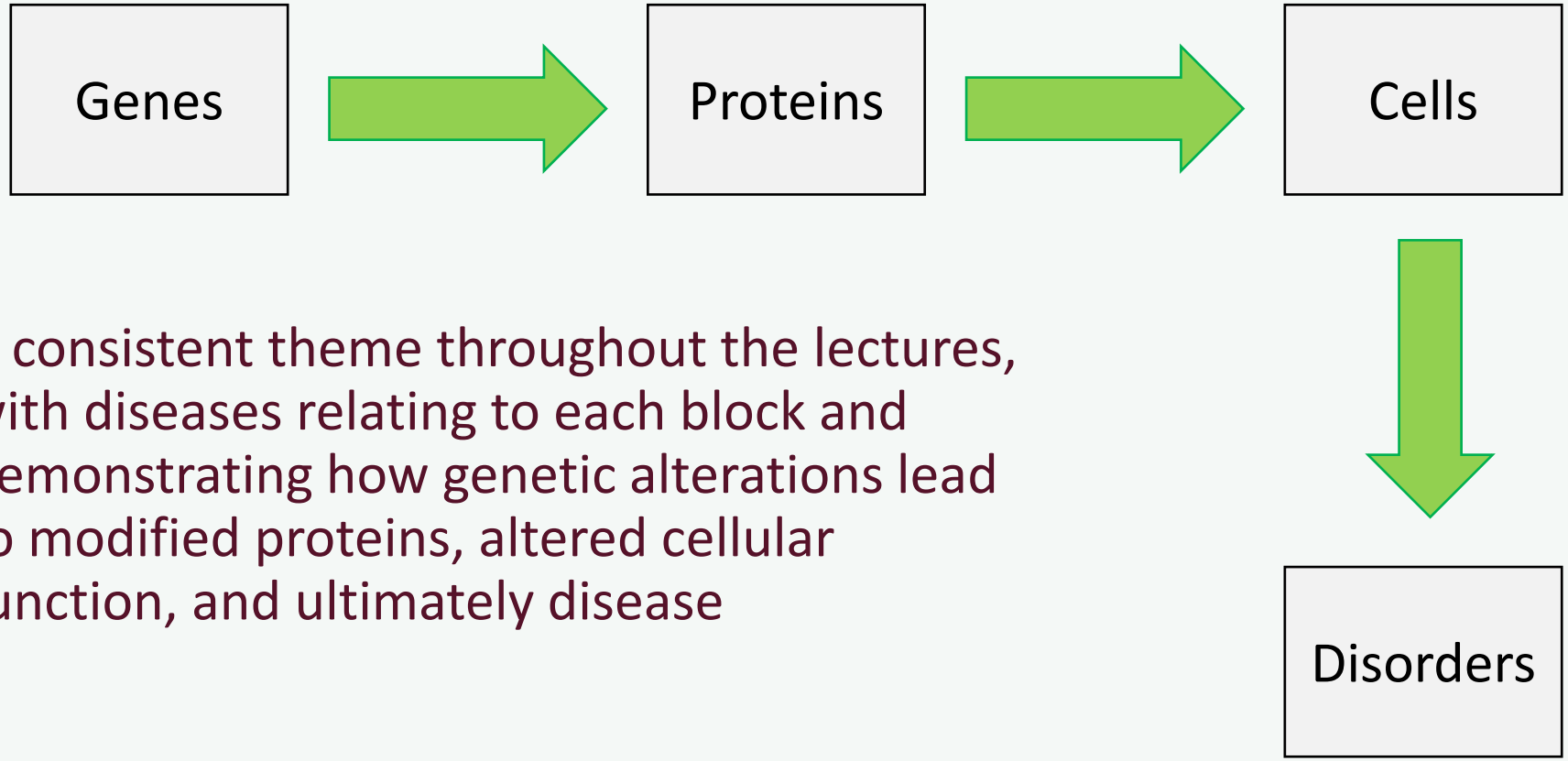
Introduction to Genetics & Pedigree Analysis

Today we are going to…

- … revisit your knowledge on genetics
- … gain an appreciation of the role of genetics in medicine, disease presentation and patient counselling
- … discover the basics of population genetics
- … explore genetic pedigrees and understand consanguinity
- … understand key aspects of genetics such as penetrance and expressivity

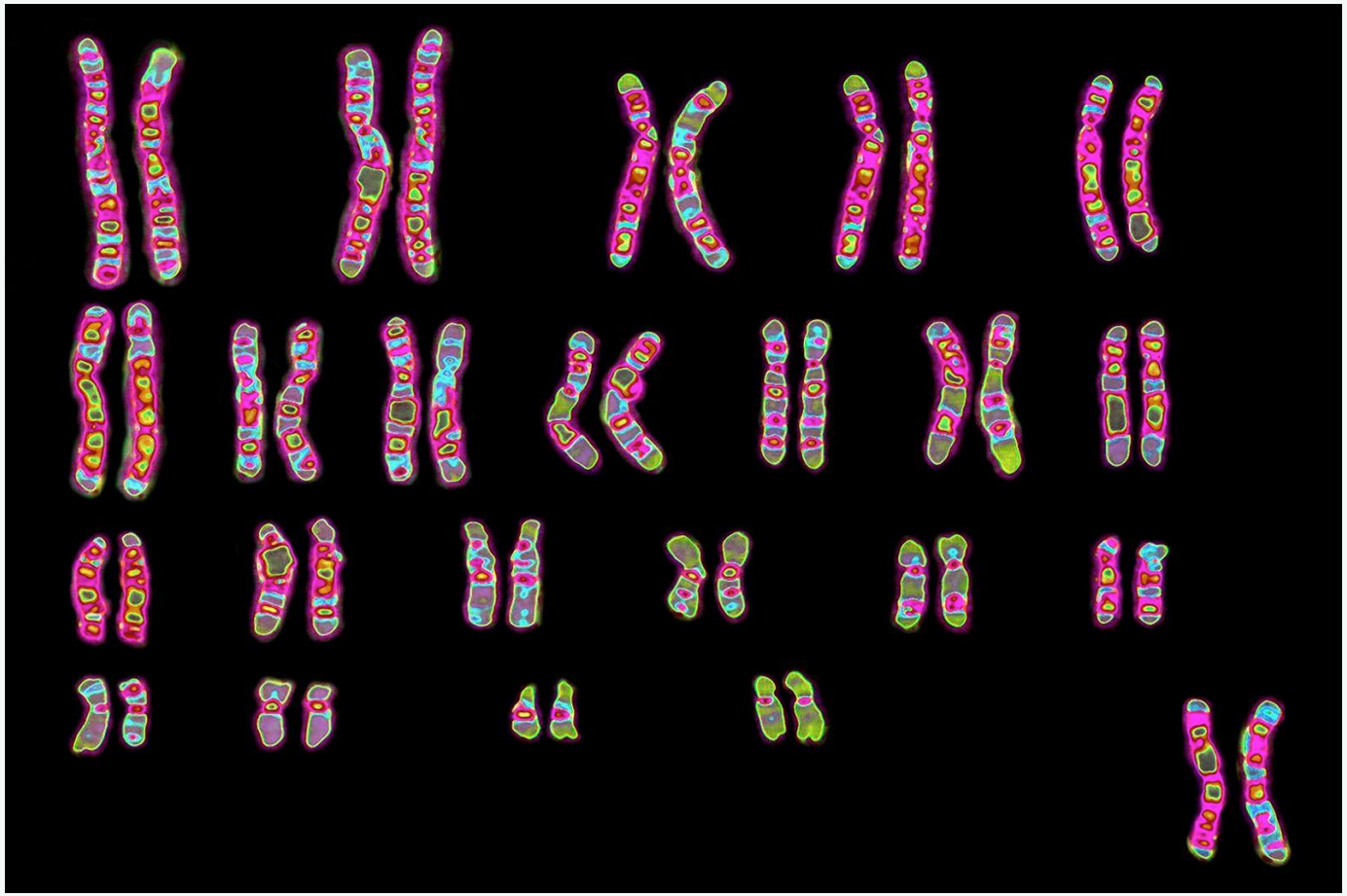
Slides and context are based on Dr Emyr Bakers material

Scope of genetics lectures in UM2010



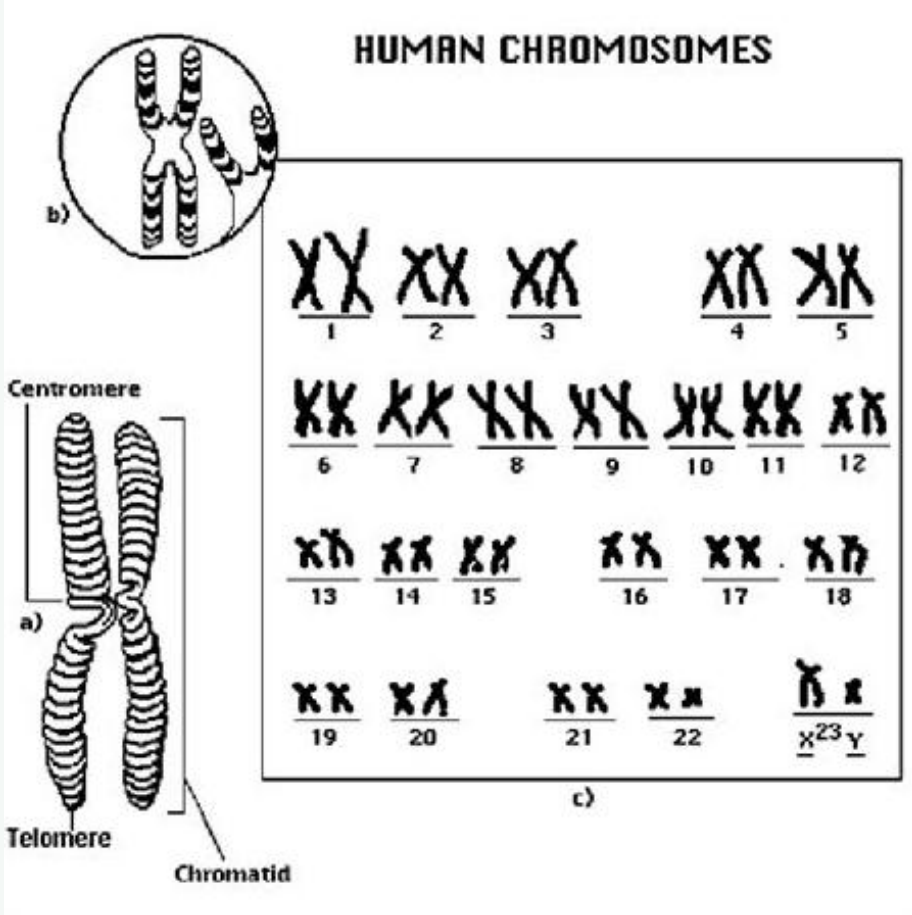
- A consistent theme throughout the lectures, with diseases relating to each block and demonstrating how genetic alterations lead to modified proteins, altered cellular function, and ultimately disease

Part 1: Refresher on genetics



Recap on chromosomes

- Most human cells contain 46 chromosomes
- Gametes are haploid (23)
- Mutations such as trisomy may result in more than 46, as can diseases such as cancer
- We have 22 pairs of chromosomes known as autosomes
- And two sex chromosomes (XY)
- We also have mitochondrial DNA, which is typically maternally inherited (see Part 1b)



The C-Value paradox

- The C-Value represents the total amount of DNA in the genome
- Logic would tell you that the more complex an organism is, the more DNA it needs to "run"
- But this is not necessarily the case…
- The discovery of non-coding DNA largely resolved the c-value paradox

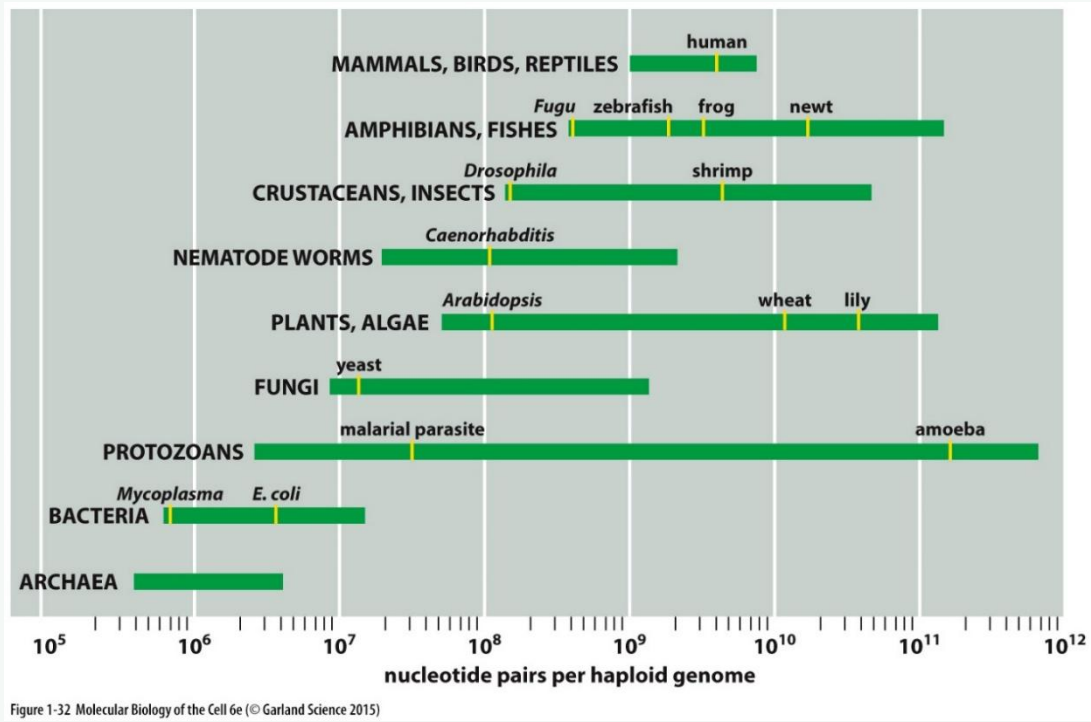
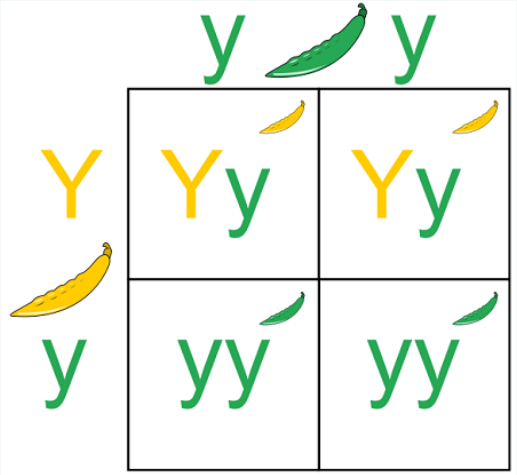
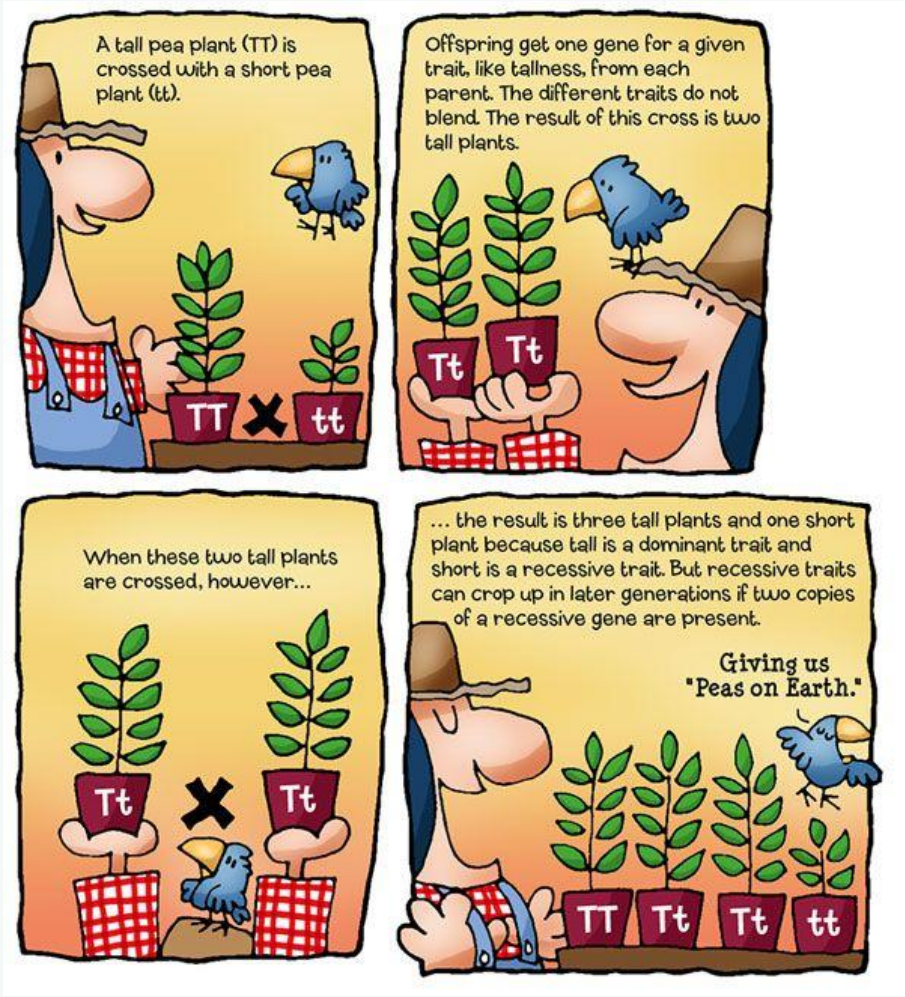


Figure 1-32 Molecular Biology of the Cell 6e (© Garland Science 2015)

Classical Mendelian Genetics

- Mendelian genetics is the classical genetic inheritance you are familiar with – one gene, one phenotype
- Applied to disease, this would typically be mutations in a single gene causes the disease (for instance mutations in CFTR cause cystic fibrosis)
- Mendelian genetics applied to disease can be thought of as **single gene** disorders





Mendel's proposed laws

Dominance: One allele is more dominant than the other. If both alleles are present, then the phenotype reflects the dominant allele.

Independent assortment: Chance decides which factor for a particular trait is inherited, and this is not influenced by other genes

Independent segregation: Only one of the two alleles present in somatic cells will be present (via random selection) in gametes

… but as we will highlight later, this is not enough anymore.

Dominant vs Recessive Alleles

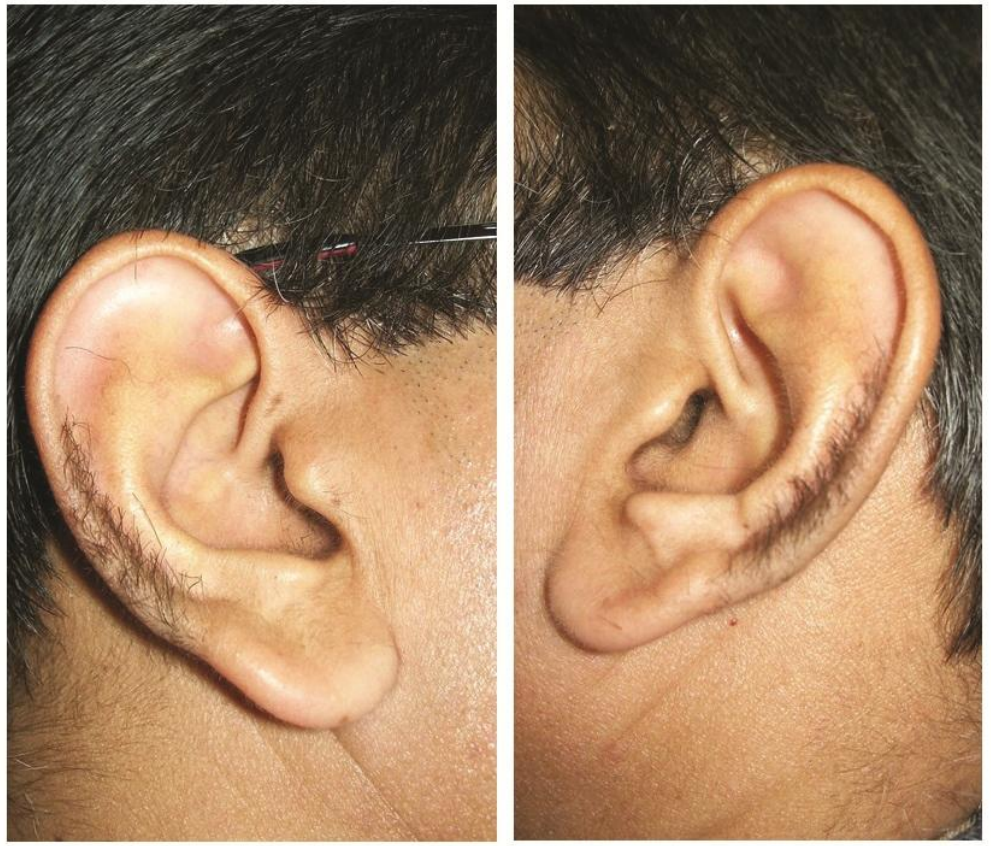
- An **allele** is a particular *version* of a gene, which arises through DNA mutation and hence **differ in sequence** at one or more site

- In typical genetic nomenclature, capital letters are dominant alleles, whilst lower case letters are recessive alleles.

- **Homozygous** means two copies of the same allele (AA for dominant, aa for recessive)

- **Heterozygous** means carrying two different alleles (i.e. Aa).

Mendelian inheritance pathways



- Autosomal dominant; e.g. Huntington's disease. Gain of function. 1 copy from 1 parent is enough (Aa or AA)
- Autosomal recessive; e.g. cystic fibrosis. Loss of function, Affected allele from each parent (aa).
- X-linked; e.g. Haemophilia (blood clotting factor) and colour blindness. Usually affects males.
- X-linked dominant diseases affect males and females at roughly a similar rate, whilst men are more commonly affected by X-linked recessive diseases due to carrying only one X-chromosome.
- Y-linked eg. Hypertrichosis of the Ear (Hairy Ears)

Sources of genetic –based diseases

SNPs

- Single nucleotide polymorphisms represent a single base change and are a common genetic mutation
- Missense – different amino acid
- Nonsense – premature stop codon
- Silent – same amino acid due to genetic code redundancy

Epigenetics

- This can be thought of as reversible modifications to DNA without changing the underlying sequence (such as DNA methylation)

Penetrance and Expressivity

- Penetrance is related to how likely you are to develop the phenotype if you have the mutation
- Expressivity is related to how severely the phenotype manifests
- Anticipation is the idea that a disease can manifest earlier and with higher severity in subsequent generations (see: trinucleotide repeat disorders)

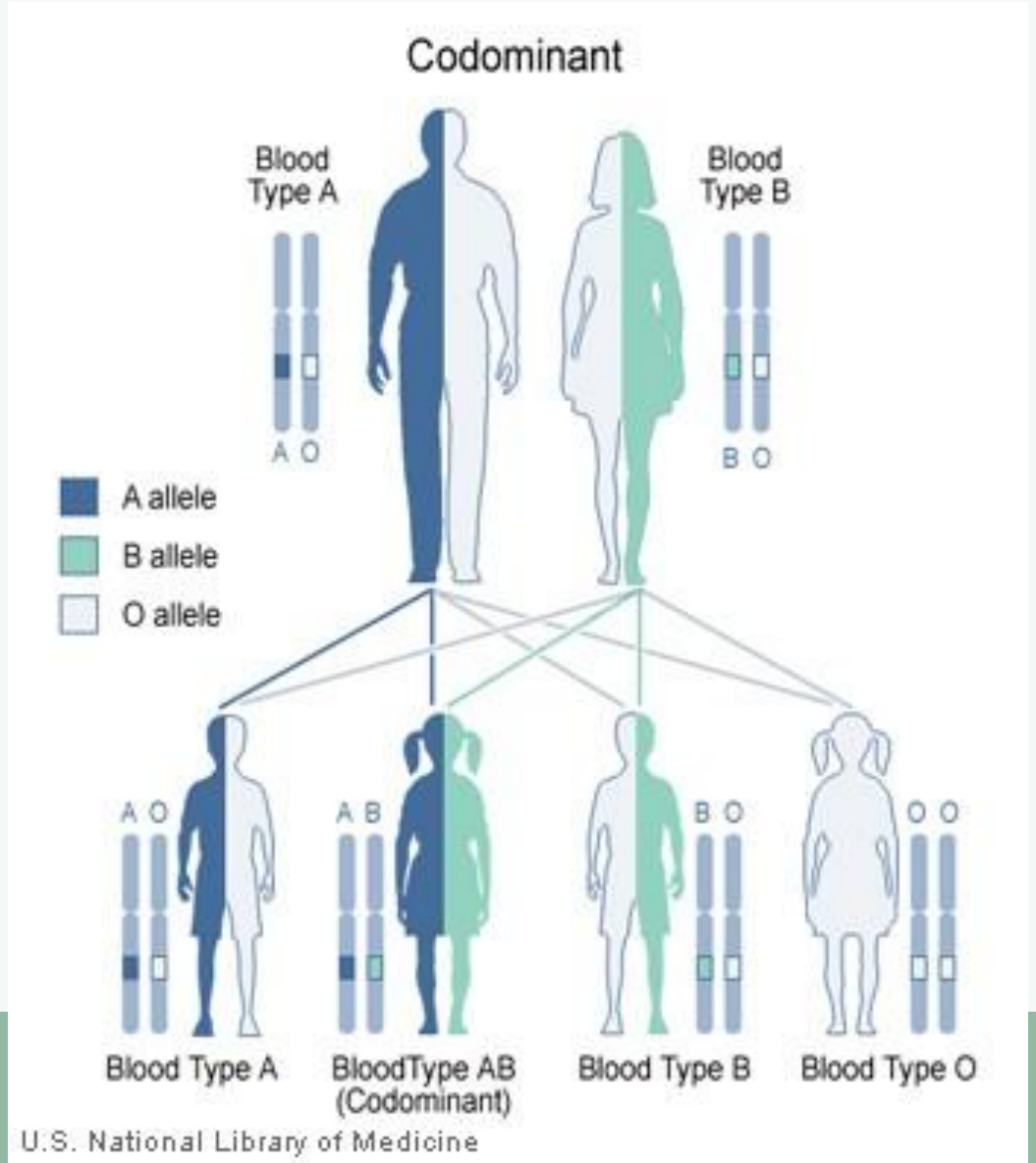
Part1B: Non-Mendelian Genetics

Incomplete Dominance

- Incomplete dominance is a common exception to the Mendelian rules of inheritance
- It is most easily visualised through flower colour, where homozygous dominant allele (double upper case RR) produces a strong red colour. Homozygous recessive allele (double lower case rr) produces white colour. Heterozygous (upper case and lower case Rr) individuals generate an intermediate, as not enough “red enzyme” is produced
- Therefore, in medical genetics, whilst inheritance patterns are important, it is also important to focus on the phenotypic outcome
- Fun fact: people with wavy hair are examples of incomplete dominance, having inherited a “straight hair” gene and a “curly hair” gene!

From Medical Genetics: An Integrated Approach (available on Access Medicine)

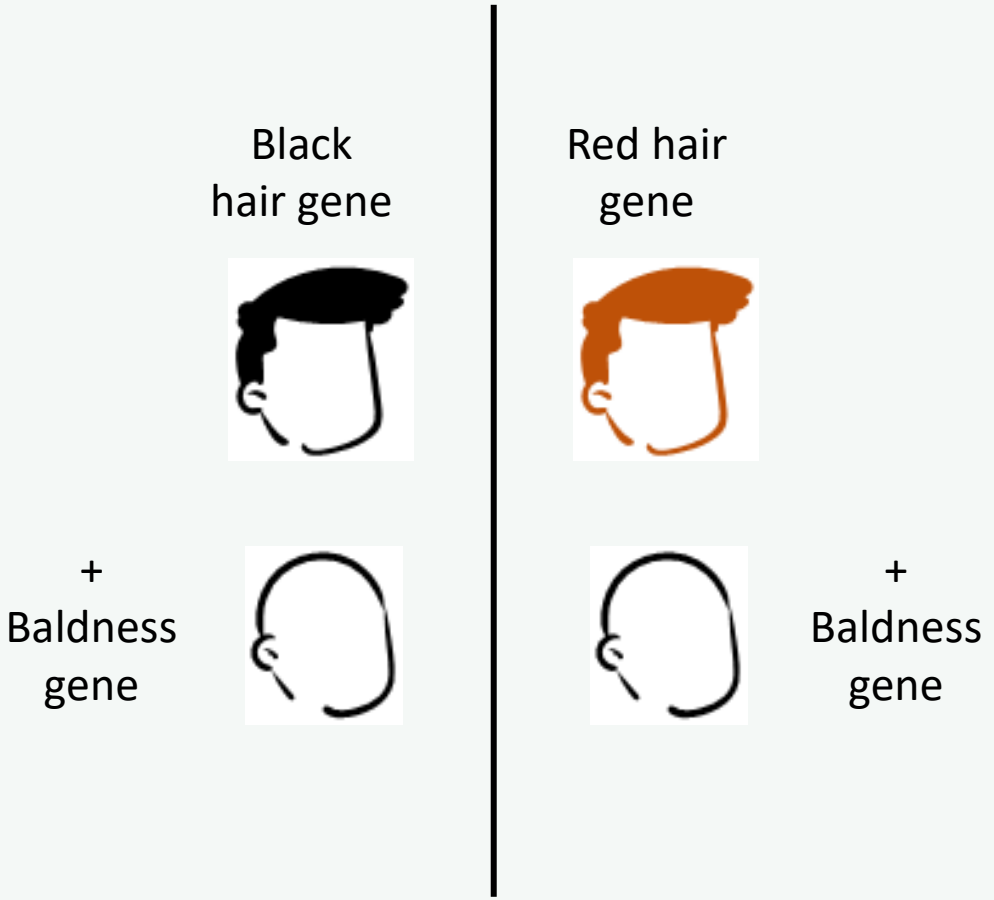
Co-Dominance



- Co-dominance, much as the name implies, is the simultaneous expression of both alleles in a **compound heterozygote**
- Co-dominance is rare in humans
- Though one example of co-dominance in humans is ABO blood typing; A and B are dominant, whilst O is recessive
  - ABO genes are also an example of **multiple alleles**, another example of Non-Mendelian Inheritance. We do not just have one dominant and one recessive allele for our genes!

Epistasis

- Epistasis (literal meaning “to stand above”) describes how gene interactions can affect the phenotype
- You can think of this as one gene masking another
- For example: if you are bald due to genetic factors, then your baldness is epistatic to your hair colour or curliness



Simplified schematic of epistasis

Variations on sex inheritance

Sex-Linkage

- Refers to genes located on the X or Y chromosomes.
- Not strictly defined in genetics.
- Both X and Y chromosomes carry genes not necessarily related to sex differences.

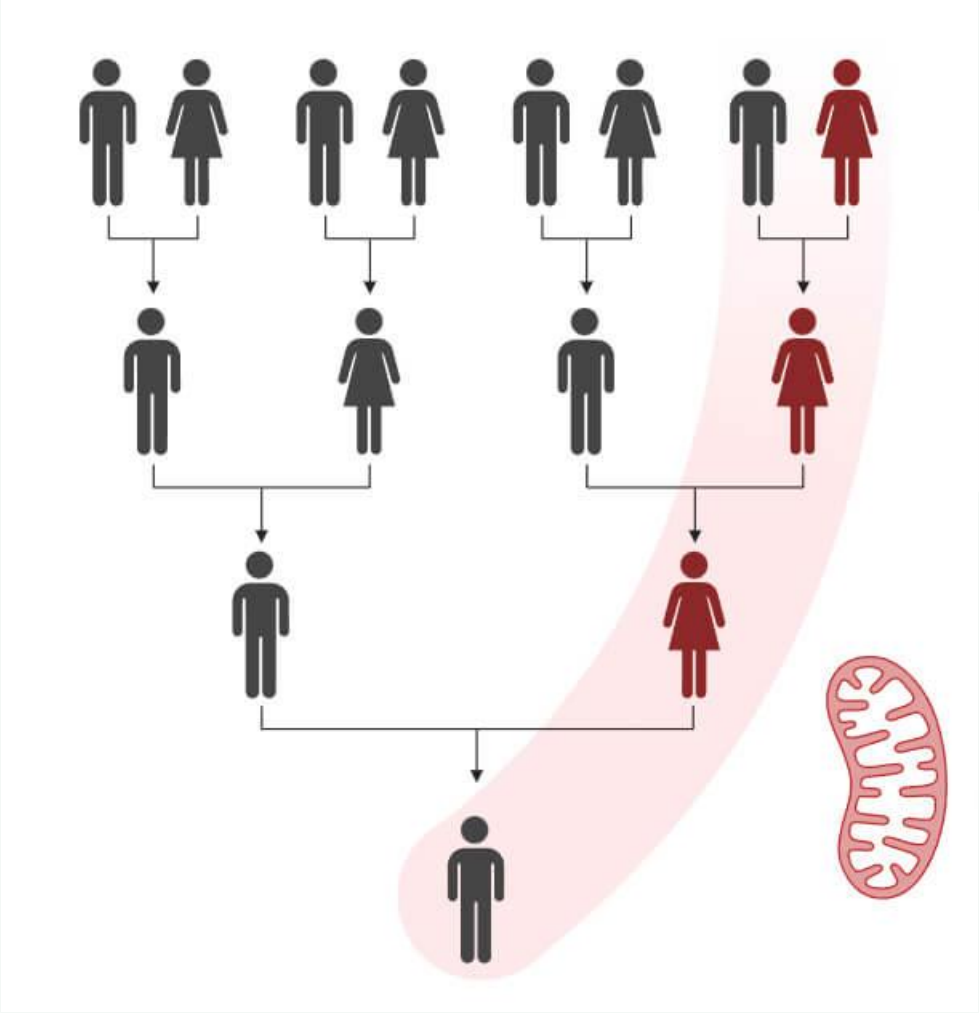
Sex-Limited Traits

- Traits that are expressed only in one sex.
- Example: Sperm formation occurs only in males.
- These traits are genetically determined but limited by sex-specific physiology.

Sex-Influenced Traits

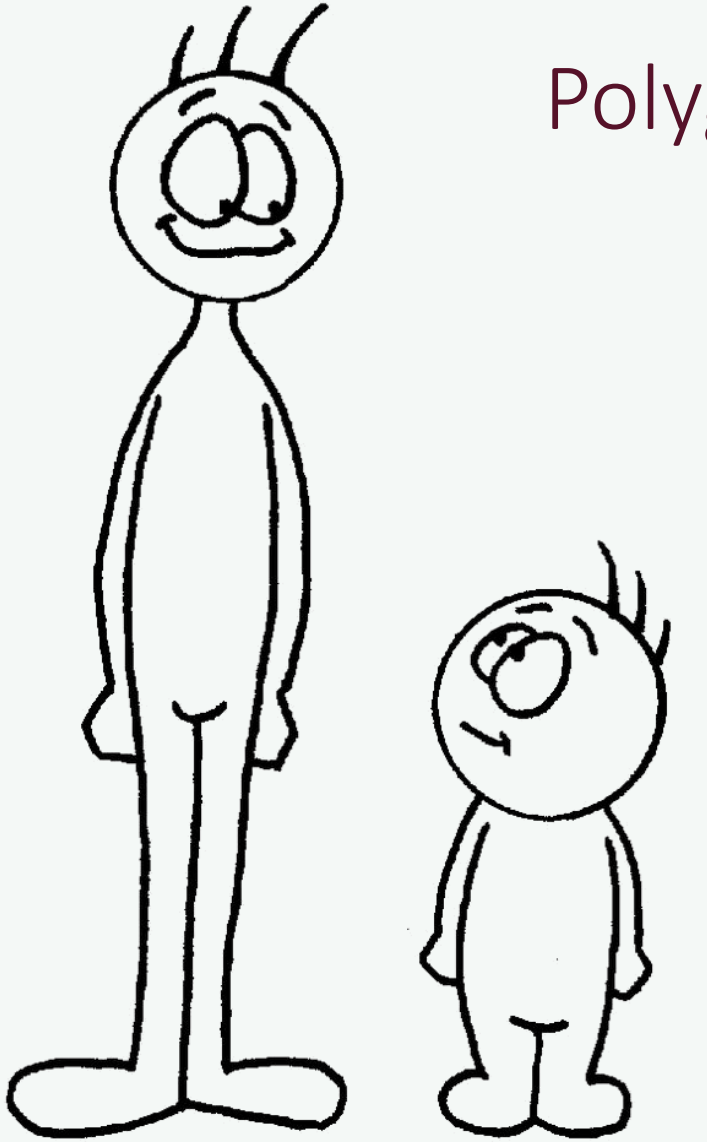
- Traits that are more likely to appear in one sex than the other.
- Example: Breast cancer is more common in women than in men.
- Expression is influenced by hormonal or physiological differences between sexes.

Extranuclear inheritance



- Mitochondrial inheritance, which in almost all cases is maternally inherited*
- The maternal inheritance of mitochondria leads to importance for the analysis of mitochondrial disease—not just tracking it, but also the ethics of preventing it

*rare cases of paternal transmission have been observed

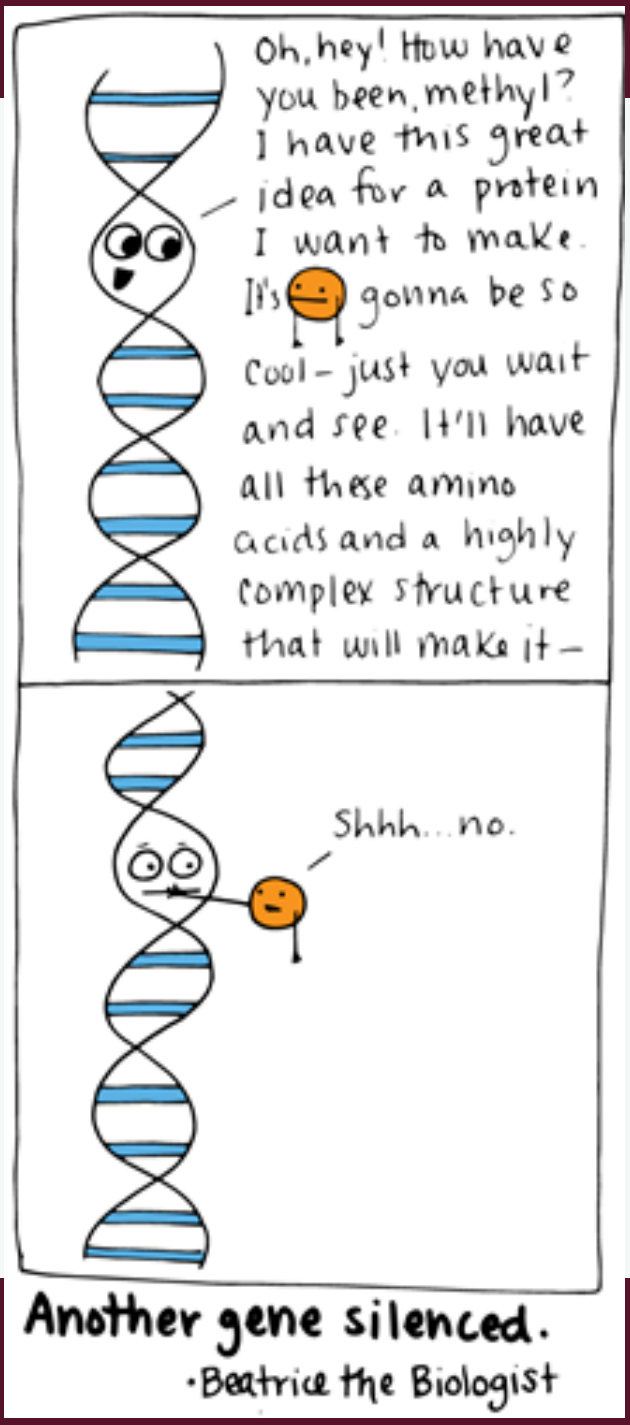


Polygenic traits

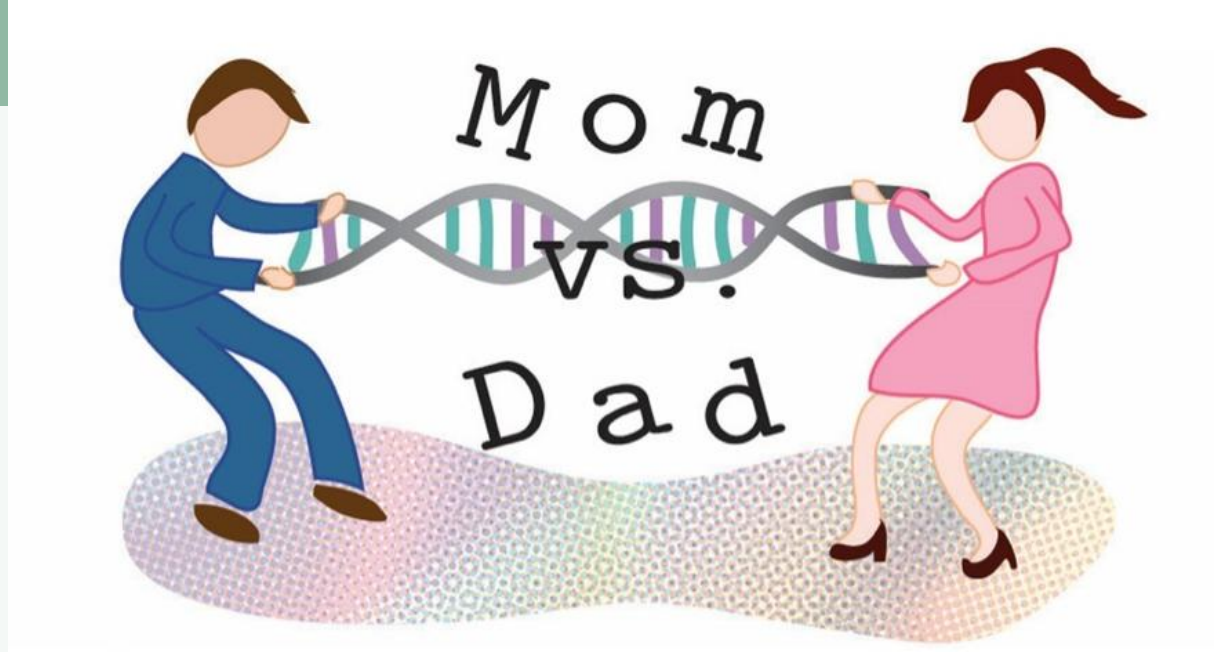
- A polygenic trait is one where it is influenced by several genes
- This includes height, skin colour, and eye colour, for example
- Many polygenic traits are also influenced by the environment and hence are **multifactorial**
- For instance: You have genes that would make you tall, but experienced malnutrition as a child/adolescent, then you will not be as tall as you “could have” been

Epigenetics

- Epigenetics are a heritable changes to DNA, that are modifications, not alterations.
- They are reversible.
- Reversible modification to DNA or to histones without changing the underlying genetic sequence
- Put crudely, DNA can be “open” or “closed” (helping the gene to be ON or OFF) and epigenetic modulation such as methylation helps to control this



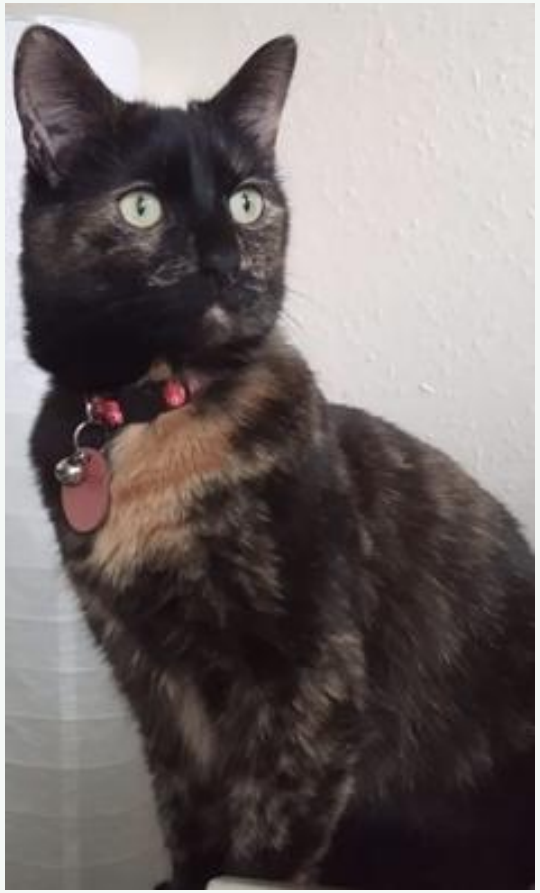
Genomic imprinting



- Only a small proportion of human genes (~1%)
- In most cases, you inherit a copy of a gene from both your father and mother. Both are typically active.
- In the case of genomic imprinting, one of the parent's allele's are switched off through epigenetic mechanisms (DNA or histone methylation).
- This does not change the DNA sequence itself, but the epigenetic alteration "stamps" the DNA at the germline level and subsequently maintained through mitotic division

Mocaicism

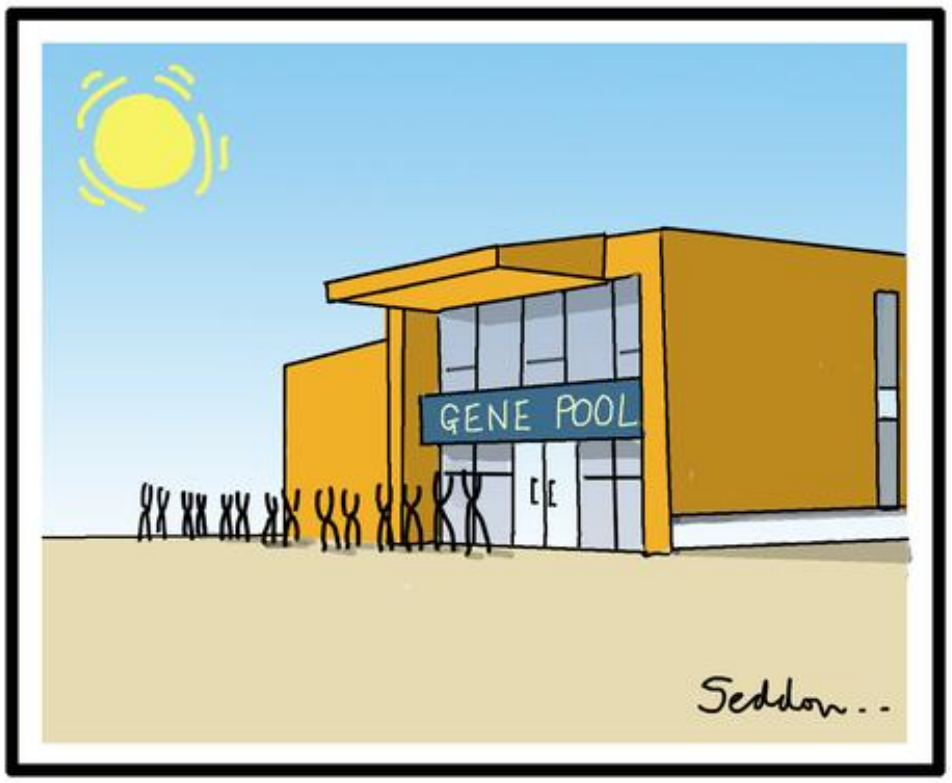
- Mosaicism means an individual's cells are not genetically identical.
- Caused by mutation events that alter the genome in some cells.
- Earlier mutations in development affect more cells, increasing the chance of visible traits.
- X-inactivation in females is a form of mosaicism:
- One X chromosome is randomly inactivated in each cell.
- Prevents double dosage of X-linked genes.
- A classic visual example: tortoiseshell cats, where X-linked coat colour genes are expressed differently across patches.



PART 2: BASICS OF POPULATION GENETICS

Population genetics

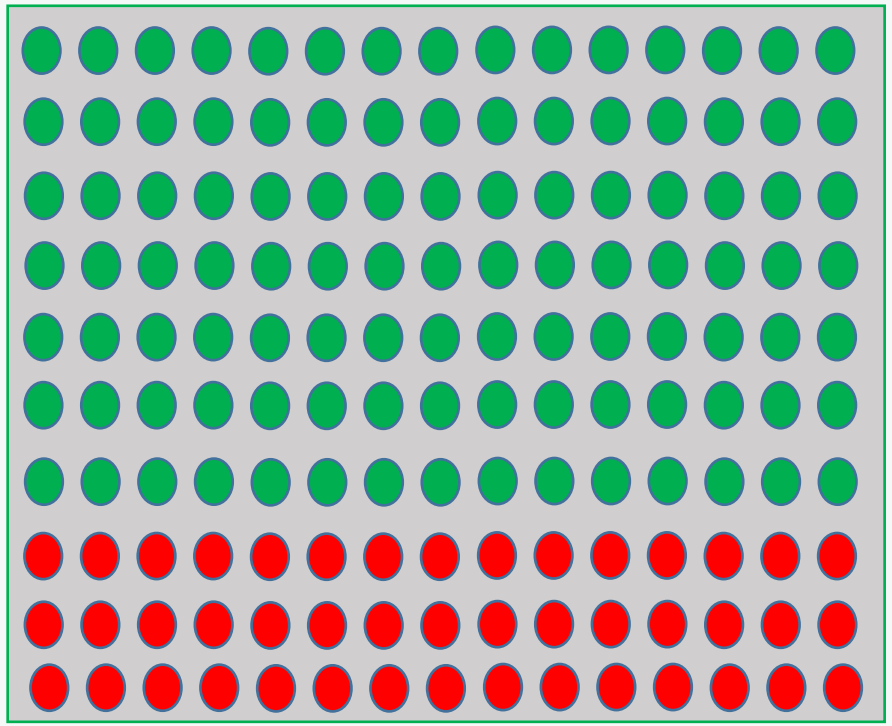
- Population Genetics studies how the genetic makeup of populations changes between generations.
- Population geneticists study how genes/traits are maintained or lost from a population's gene pool.
- **Gene pool** is defined as all the genes at all the loci in all members of the population



Leisure time for chromosomes.

The Founder Effect

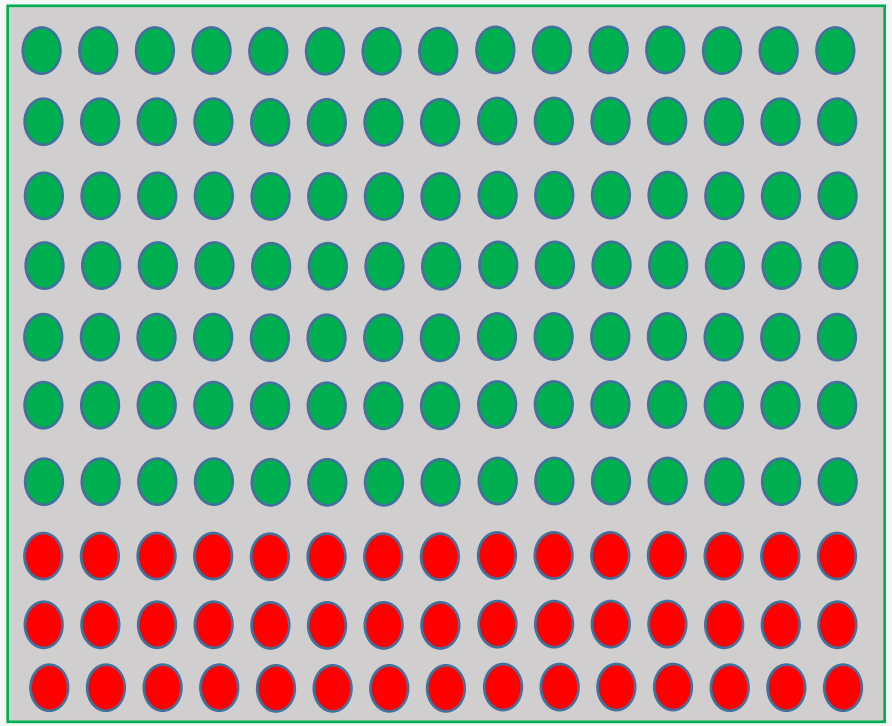
Population



Mainland
(Primary Location)

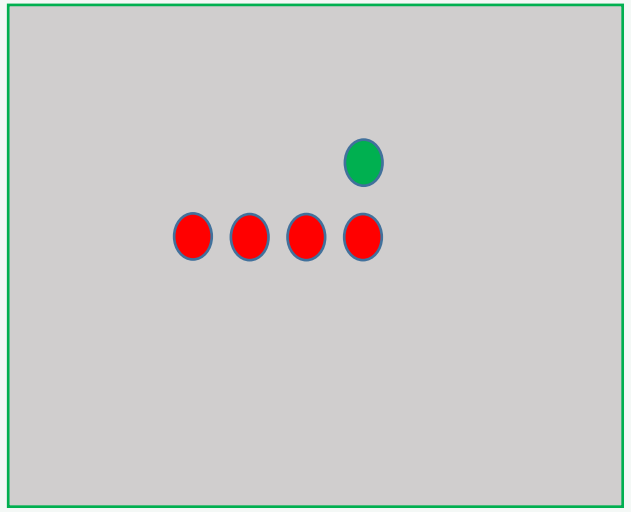
Island
(Secondary
Location)

The Founder Effect II



Mainland
(Primary Location)

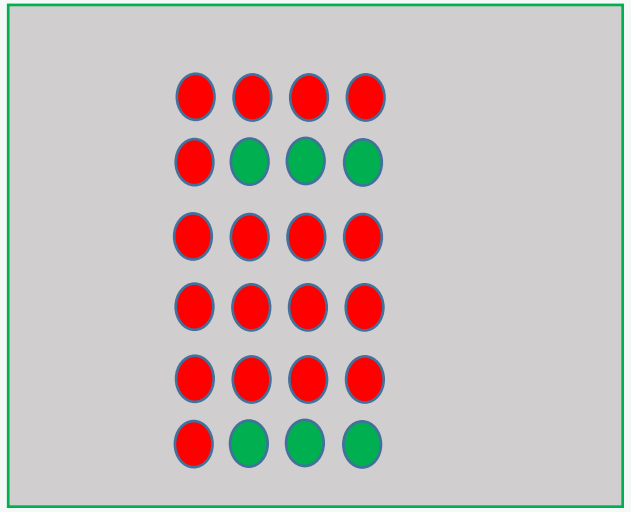
A few individuals from the original population colonise a new isolated secondary location…



Island
(Secondary Location)

The Founder Effect III

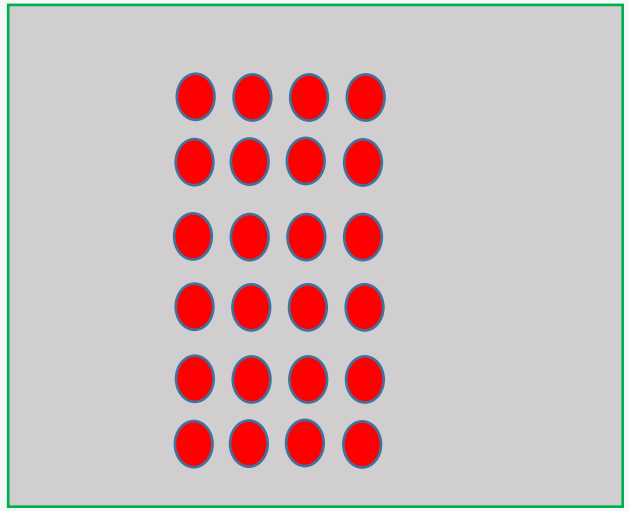
Over time, the island's population will grow…



Island (Secondary Location)

The Founder Effect IV

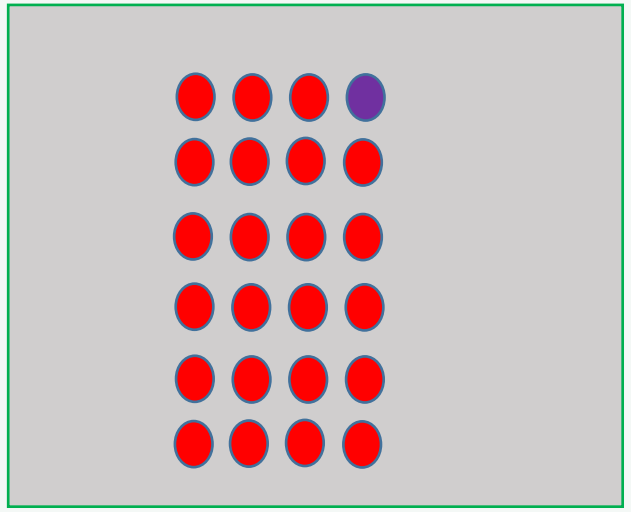
And after several generations, the green allele may be lost from this population… if the people carrying it fail to produce offspring



Island (Secondary Location)

The Founder effect V

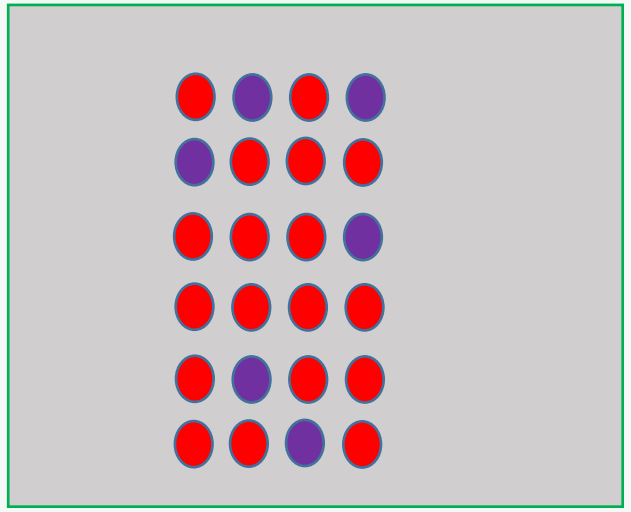
New mutations could occur, creating new alleles (purple)



Island (Secondary Location)

The Founder Effect VI

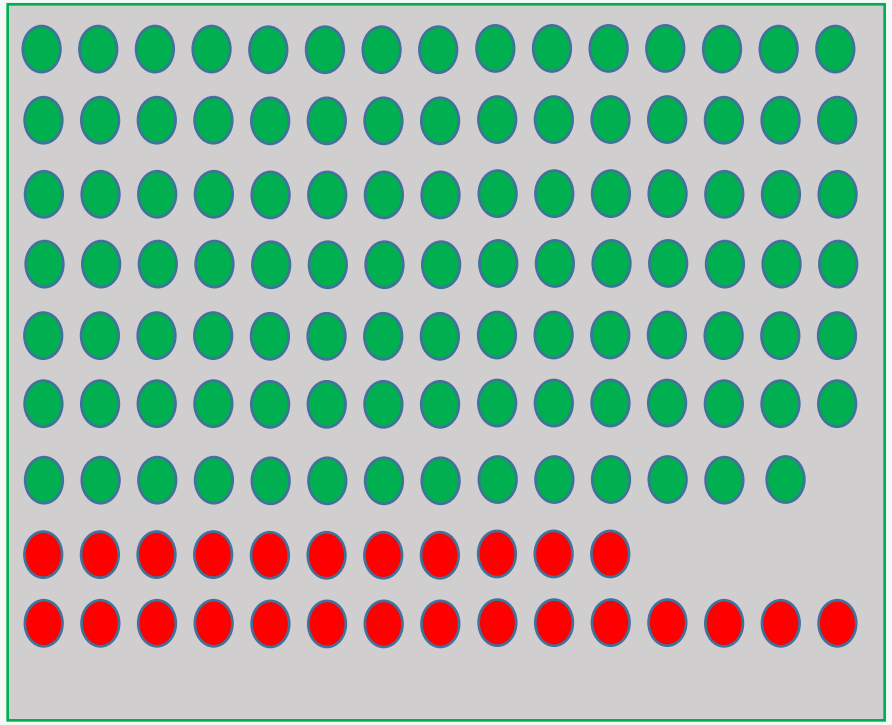
And after a few more generations, perhaps this new allele is quite common

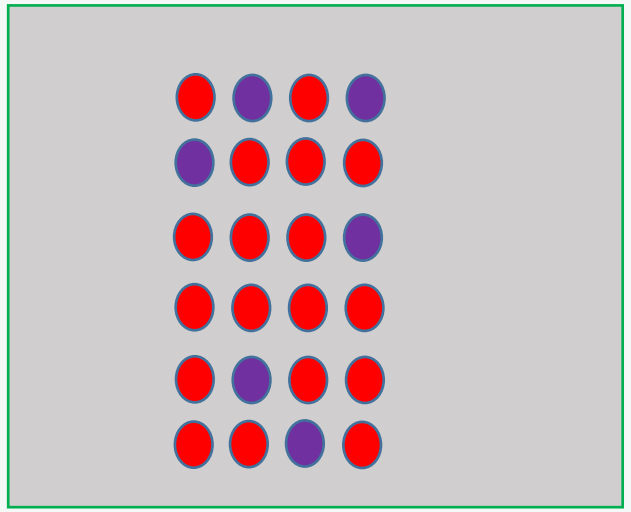


Island (Secondary Location)

The Founder Effect VII

And now the two populations look very different





Island (Secondary Location)

The Founder Effect - Summary

- Small groups of individuals may become isolated from the original population
- This ‘founding’ population of a small number of individuals is susceptible to inbreeding issues if they are all closely related
- Often a non-representative sample of the original population
- The population at the secondary location could evolve quite differently from the original population
- Genetic diversity could be lost due to missing alleles or other alleles could become overrepresented

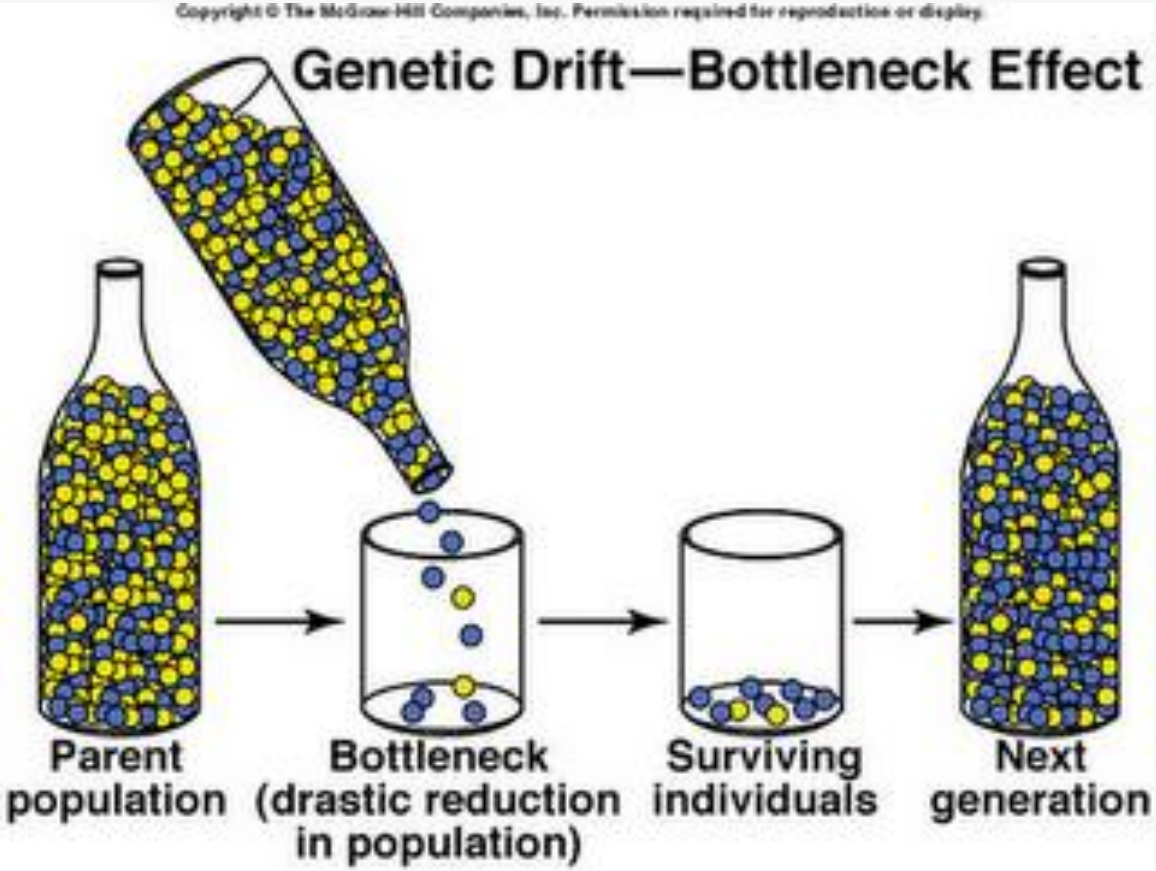
⭐ refers to the reduction in genomic variability that occurs when a small group of individuals becomes separated from a larger population.

Genetic Drift

A mechanism of evolution characterised by random fluctuations in the frequency of a particular version of a gene (allele) in a population.

- The smaller the population, the less genetic variety it has.
- In a very small population, alleles can be lost from one generation to the next, simply by random chance.
- When a population evolves only because of this type of **random sampling error**, **GENETIC DRIFT** is taking place.

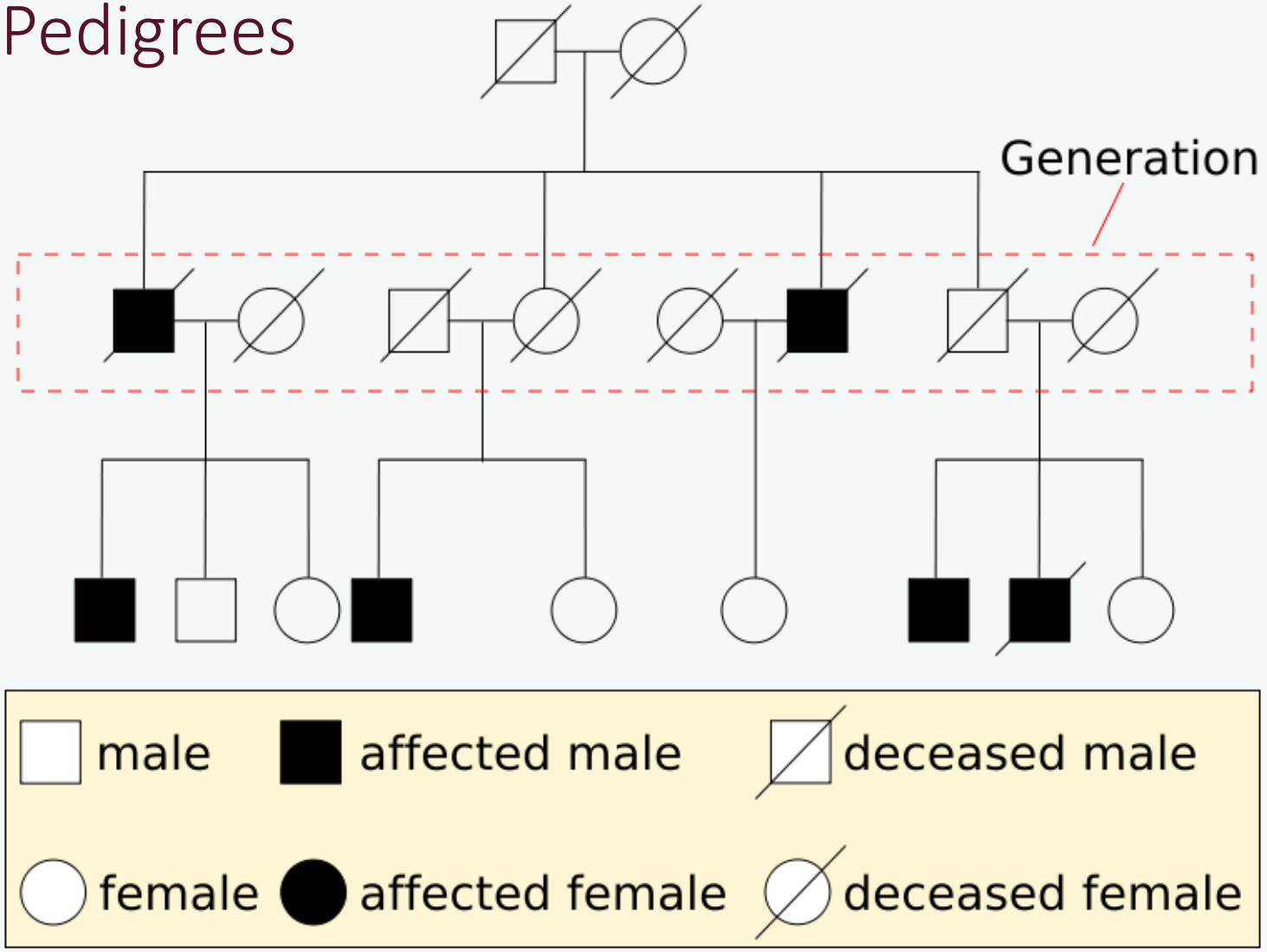
Loss of genetic diversity – population bottlenecks



- Ecological events such as earthquakes, fires, or floods may dramatically reduce population sizes. These are unselective disasters.
- The small surviving population is not likely to be representative of the original population.
- As a result, alleles may be eliminated completely or overrepresented, just by chance

PART 3: GENETIC PEDIGREES

Genetic Pedigrees



Genetic Pedigrees – Problem #1

A woman's brother died from Tay Sach's Disease (autosomal recessive, lethal), but she is unaffected. What are the chances that she is a carrier of the disease?

1 2/3 (66.6%)

2 1/2 (50%)

3 1/4 (25%)

4 1/6 (17%)

5 1/8 (12.5%)

Genetic Pedigrees – Problem #1 - solution

1 2/3 (66.6%)

2 1/2 (50%)

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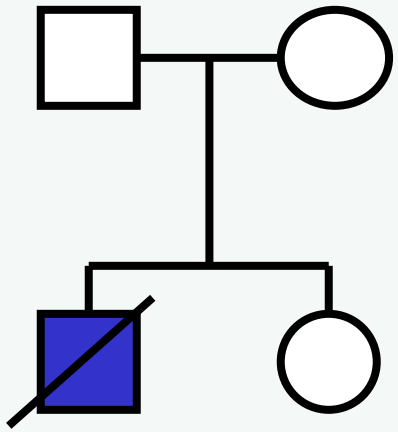
A woman's brother died from Tay Sach's Disease (autosomal recessive, lethal), but she is unaffected. What are the chances that she is a carrier of the disease?



	D	d
D	DD	Dd
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Genetic Pedigrees – Problem #2

A patient's grandfather is a carrier (heterozygote) of a rare recessive disease allele. What's the chance that the patient is also a carrier?

1 2/3 (66.6%)

2 1/2 (50%)

3 1/4 (25%)

4 1/6 (17%)

5 1/8 (12.5%)

Genetic Pedigrees – Problem #2 - solution

A patient's grandfather is a carrier (heterozygote) of a rare recessive disease allele. What's the chance that the patient is also a carrier?

1 2/3 (66.6%)

2 1/2 (50%)

3 1/4 (25%)

4 1/6 (17%)

5 1/8 (12.5%)

Genetic pedigrees – problem #3

A patient comes to the genetic counselling clinic and discloses that their grandfather's sister had cystic fibrosis (autosomal recessive). She was the only case in the family. What is the likelihood that your patient is a carrier?

1 2/3 (66.6%)

2 1/2 (50%)

3 1/4 (25%)

4 1/6 (17%)

5 1/8 (12.5%)

Genetic pedigrees – problem #3 - solution

A patient comes to the genetic counselling clinic and discloses that their grandfather's sister had cystic fibrosis (autosomal recessive). She was the only case in the family. What is the likelihood that your patient is a carrier?

1 2/3 (66.6%)

2 1/2 (50%)

3 1/4 (25%)

4 1/6 (17%)

5 1/8 (12.5%)

PART 4: CONSANGUINITY

Genetics and Consanguinity

⭐ Union between two individual who are related as second cousins (6th degree relatives or closer

- One billion of the current global population live in communities with a preference for consanguineous union

Degrees of relation

LegacyTree Genealogists

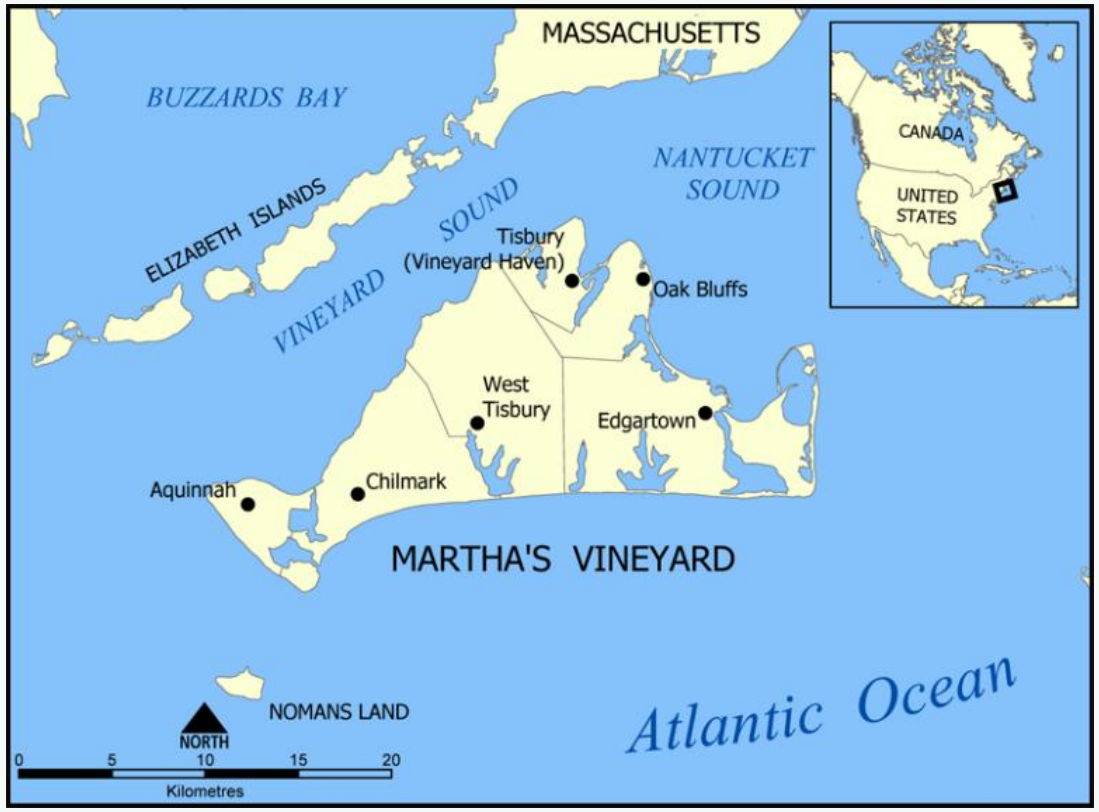
Degree of Consanguinity

5° = 5 degrees of separation

							Gr (X5) grand-parent 7°
						Gr (X4) grand-parent 6°	Gr (X4) grand-uncles/ aunts 8°
					Gr (X3) grand-parent 5°	Gr (X3) grand-uncles/ aunts 7°	1st cousin 5x removed 9°
				Great-great-grand-parent 4°	Gr-gr-grand-uncles/ aunts 6°	1st cousin 4x removed 8°	2nd cousin 4x removed 10°
			Great-grand-parent 3°	Gr-grand-uncles/ aunts 5°	1st cousin 3x removed 7°	2nd cousin 3x removed 9°	3rd cousin 3x removed 11°
		Grandparent 2°	Grand-uncles/ aunts 4°	1st cousin twice removed 6°	2nd cousin twice removed 8°	3rd cousin twice removed 10°	4th cousin twice removed 12°
	Parent 1°	Aunts & Uncles 3°	1st cousin once removed 5°	2nd cousin once removed 7°	3rd cousin once removed 9°	4th cousin once removed 11°	5th cousin once removed 13°
You 0°	Siblings 2°	1st cousin 4°	2nd cousin 6°	3rd cousin 8°	4th cousin 10°	5th cousin 12°	6th cousin 14°
Children 1°	Nephews/ nieces 3°	1st cousin once removed 5°	2nd cousin once removed 7°	3rd cousin once removed 9°	4th cousin once removed 11°	5th cousin once removed 13°	6th cousin once removed 15°
Grandchildren 2°	grand-nephews/ nieces 4°	1st cousin twice removed 6°	2nd cousin twice removed 8°	3rd cousin twice removed 10°	4th cousin twice removed 12°	5th cousin twice removed 14°	6th cousin twice removed 16°
Great-grand-children 3°	great-grand-nephew/ niece 5°	1st cousin 3x removed 7°	2nd cousin 3x removed 9°	3rd cousin 3x removed 11°	4th cousin 3x removed 13°	5th cousin 3x removed 15°	6th cousin 3x removed 17°

Consanguinity and Martha's Vineyard

- A famous example of consanguinity can be seen in Martha's Vineyard
- From 1690 to mid-twentieth century, there was a high rate of genetic deafness – up to 1 in 4 at Martha's Vineyard, but 1/5700 in the rest of the US
- High rates of deafness due to consanguineous marriages



Case study I

- You have a new patient to your practice, 32yo woman in good health
- She is a recent immigrant from Northern Africa and lives with her husband and their two sons ages 6 and 4, all are in good health
- She is about 9 weeks pregnant

- You are discussing conventional prenatal screening options (e.g. integrated prenatal screening) with her and she reveals that she and her husband are related by blood and asks if there are any tests available to better assess the couple's chance of having a child with health concerns

Genetic Counselling

The first step and best tool for counselling a couple with consanguinity involves taking a detailed **family history**.

- Offspring, siblings, parents, grandparents, aunts, uncles, nieces, nephews, and first cousins of your patient, as appropriate
- Ethnicity of all grandparents
- Congenital anomalies
- Intellectual disability, learning disability, developmental delay or regression

- Inherited disorders (e.g. thalassemia)
- Early hearing and/or vision impairment
- Failure to thrive
- Unexplained neonatal or infant death
- Seizure disorder
- Undiagnosed severe conditions

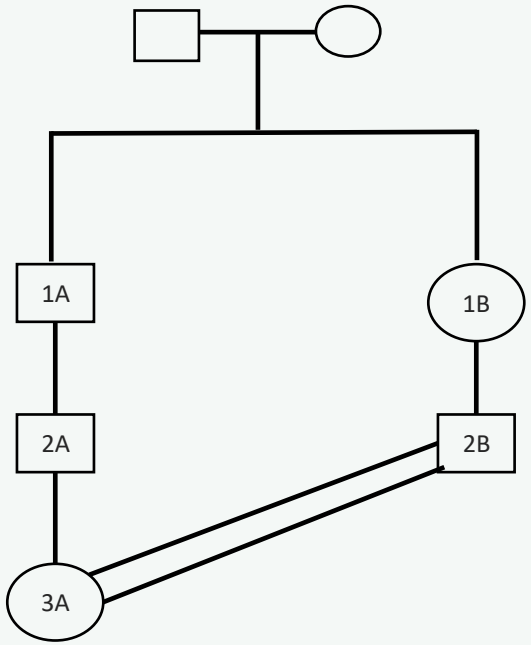
What is the risk of consanguinity?

- The chance for adverse outcome in the offspring of a consanguineous union is not an absolute number but rather an estimate based on:
  - Family history
  - Degree of consanguinity
  - Background population risk

> When there is no known genetic diagnosis in the family, first cousin unions are at a **1.7-2.8% additional risk above the general population risk of 2-3%** to have offspring with a congenital anomaly (e.g. congenital heart defect)

- The risk for a more closely related union is higher and for a more distantly related union is lower

Case study II



- Your patient and her husband are first cousins once removed
- You take a detailed family history and there are no reported significant health or developmental issues
- You normalize for your patient that, in the absence of a genetic diagnosis in the family, all couples have a 2-3% risk of to have offspring with a congenital anomaly (e.g. congenital heart defect)
- For consanguineous couples, there is a small additional risk above the general population risk
  - less than 2x for first cousins once removed as they are more distantly related that first cousins where the additional risk is 1.7-2.8% above the general population

Consanguineous Unions

- 20-50% of all unions in North Africa, Middle and West Asia, and South India (and immigrants from these communities) are consanguineous
- First cousin unions account for about 1/3 of all marriages
- Preference for a consanguineous union:
  - Cultural continuity
  - Family solidarity
  - Reduction of uncertainty associated with health and financial issues

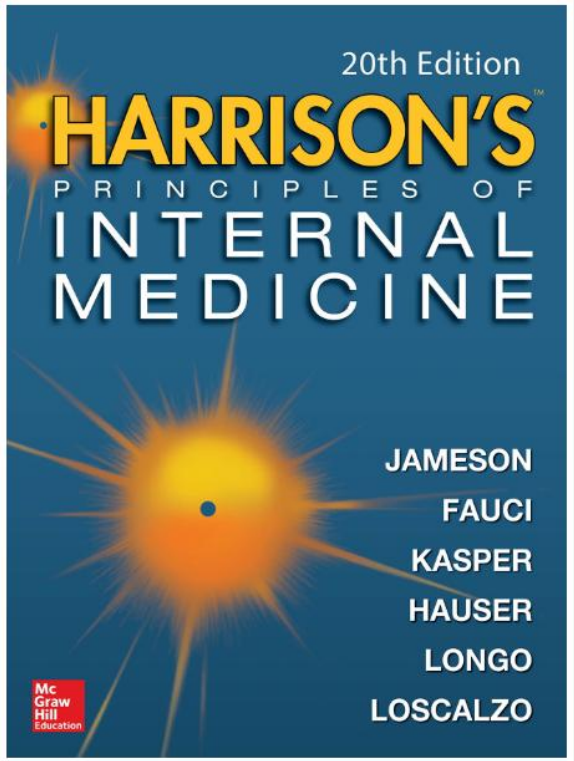
Can you…

- … remember your genetics knowledge from Y1?
- … have an appreciation of the role of genetics in medicine, disease presentation and patient counselling?
- … uncover the basics of population genetics?
- … explain genetic pedigrees and understand consanguinity?
- … understand key aspects of genetics such as penetrance and expressivity?

MBBS learning outcomes

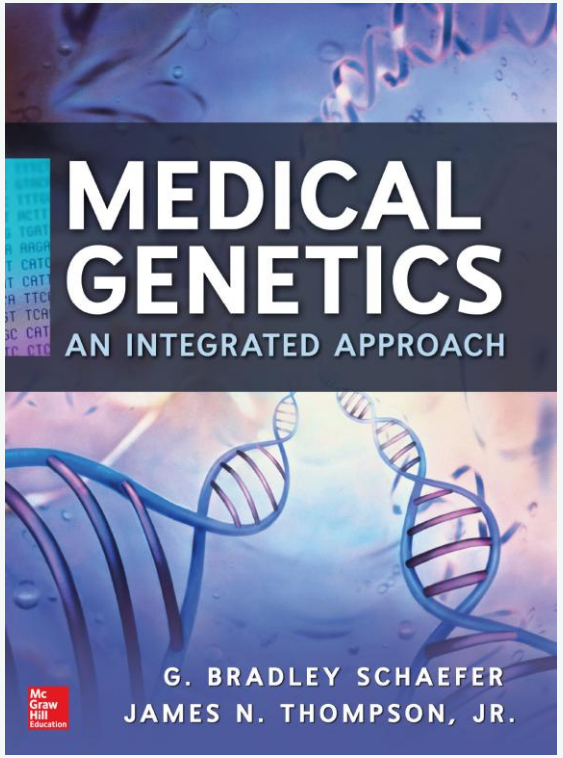
- Outline the molecular genetics of common diseases
- Summarise the principles of genetic inheritance and pedigree analysis

Supplementary reading material



•Harrison's Principles of Internal Medicine 20/e, Chapter 456: Principles of Human Genetics

•Freely available on Access Medicine



•Comprehensive textbook covering the application of genetics to medicine. Includes the science of genetics, how it applies to medicine, and case study examples to provide a clinical tilt to the work.

•Freely available on Access Medicine