Gene Inheritance and Transmission
Extensions of Mendelian genetics

Lecture 5
SLE254 Genetics
Chapter 4 Concepts of Genetics (12th ed)
Pp 98-130

Departures from clear cut Mendelian transmission genetics

- Lethal alleles
- Incomplete dominance
- Codominance
- Multiple alleles
- Epistasis
- Pleiotropy
- Genetic heterogeneity
- Penetrance
- Expressivity
- Anticipation
- Germline mosaicism
- Phenocopies
- Linkage
- Continuous variation

Lethal alleles

- Mutations occur giving rise to new forms of alleles
  - Some of these are **lethal mutations**
- A **dominant lethal** is an allele that causes death of the organism that contains it, whether homozygous or heterozygous for the allele
- A **recessive lethal** is an allele that that causes death when **homozygous**
  - In the heterozygote, a lethal allele is masked by the presence of an allele for 'wild type'.

Lethal alleles – dominant

- Dominant lethal genes are rarely detected due to their rapid elimination from populations

How could they be maintained in populations?

- **Huntington's disease –** a neurological disorder in humans, which reduces life expectancy
- Because the **onset of Huntington's disease is slow**, individuals carrying the allele can pass it on to their offspring

Lethal alleles – recessive

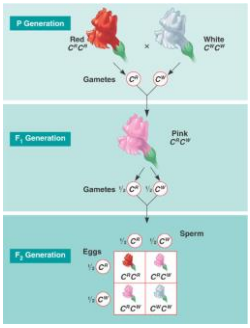
- Manx cats are heterozygous for a dominant mutation that results in no tails
- A cross between two Manx cats produces a 2:1 phenotype ratio (tailless to tailed) instead of the normal 3:1 phenotype ratio
  - The recessive homozygotes do not survive

	T	t
T	TT	Tt
t	Tt	✗

1/4 normal (TT), 1/2 Manx (Tt),
1/4 not born; lethal (tt)

Incomplete (Partial) dominance

- **Both alleles blend their effects**
- The phenotype of the heterozygote lies somewhere between those of the two kinds of homozygotes
- The F_2 generation shows only one pair of alleles determines the phenotype
  - However, phenotype ratio is identical to genotype ratio 2:1:1 and not 3:1 like complete dominance



Incomplete (Partial) dominance

- Neither allele is recessive so different symbols are used
  - Examples include

R^1R^1	R^1R^2	R^2R^2
W^2W^2	W^1W^2	W^1W^1
C^RC^R	C^RC^W	C^WC^W

Codominance

- Both alleles show their effects – **DO NOT blend**
- In codominance, neither allele are dominant; both are expressed. A cross between organisms with two different phenotypes produces offspring with has both phenotypes of the parental traits shown.

White

Red

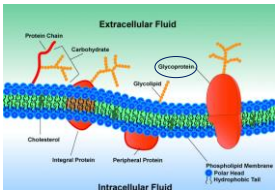
Roan (red and white hairs, NOT pink)

Codominance

- Both alleles show their effects – **DO NOT blend**
- In codominance, neither allele are dominant; both are expressed. A cross between organisms with two different phenotypes produces offspring with has both phenotypes of the parental traits shown.

Codominance

- The MN blood group
  - In humans, **two forms of a glycoprotein** exist on the surface of red blood cells – designated **M and N**
- An individual may exhibit either one or **both** proteins



Genotype	Phenotype
L^ML^M	M
L^ML^N	MN
L^NL^N	N

Multiple alleles

- Many genes have more than two alternative alleles
- This increases the number of different genotypes and phenotypes that exist with respect to the particular gene
- **Multiple alleles can only be studied in populations**
  - An individual diploid organism will only have, at most, two alternative forms of the same gene
  - A population will show all the alternatives

Population

Individual

Only 1-2 colours

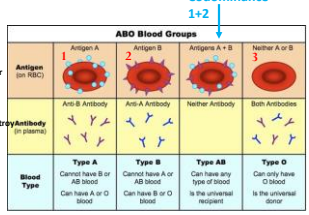
Multiple alleles – ABO blood groups

- **Three alternative alleles** of one gene
- Presence of antigens of the surface of red blood cells
  - Four phenotypes depending on the presence or absence of antigens

Codominance 1+2

Alleles code for presence or absence of cell marker molecules on the erythrocyte surface

Antibodies in the serum which can identify and destroy Antigens on the surface of another blood group



Multiple alleles – ABO blood groups

- **Three alternative alleles** of one gene
- Presence of antigens of the surface of red blood cells
  - Four phenotypes depending on the presence or absence of antigens

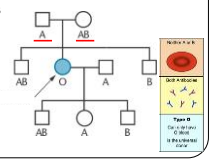
Genotype	Antigen	Phenotype
I^AI^A	A	A
I^AI^O	A	
I^BI^B	B	B
I^BI^O	B	
I^AI^B	A, B	AB
I^OI^O	neither	O

codominance

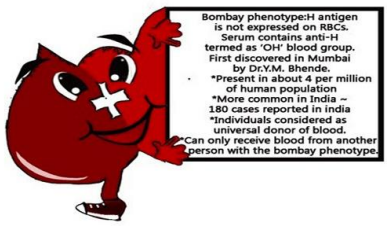
The Bombay phenotype

- The Bombay Phenotype was first reported in 1952 in Bombay, India.
- Bombay cells **can't be** converted to group A or B
  - Mutation in the *FUT1* gene prevents synthesis of H substance, vital for producing functional A and B antigens

So individual may have I^A and/or I^B alleles, but neither antigen is added to the cell surface and they are **functionally type O**



The Bombay phenotype



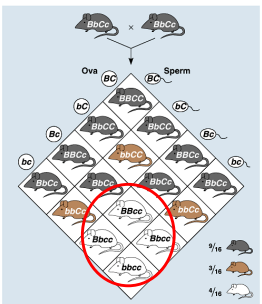
http://www.bloodconnect.org/bombay-bloodtype

Epistasis

- A form of **gene interaction** in which one gene **masks** the phenotypic expression of another
- There are no new phenotypes produced by this type of gene interaction
- The alleles that are masking the effect are called **epistatic alleles**
- The alleles whose effect is being altered or suppressed are called the **hypostatic alleles***

An example of epistasis

- **If individual is cc, then is albino regardless of allele at *b* locus - due to gene interaction**
- Normally two gene (dihybrid) crosses would produce a 9:3:3:1 ratio
- Due to gene interaction, we see a 9:3:4 F_2 ratio. The *c* locus is epistatic to the *b* locus.
- ***cc* masks the *b* locus**



Epistasis

Case	Organism	Character	F_2 Phenotypes 9/16	3/16	3/16	1/16	Modified ratio
1	Mouse	Coat color	agouti	albino	black	albino	9:3:4
2	Squash	Color	white		yellow	green	12:3:1
3	Pea	Flower color	purple	white			9:7
4	Squash	Fruit shape	disc	sphere		long	9:6:1
5	Chicken	Color	white		colored	white	13:3
6	Mouse	Color	white-spotted	white	colored	white-spotted	10:3:3
7	Shepherd's purse	Seed capsule	triangular			ovoid	15:1
8	Flour beetle	Color	6/16 sooty and 3/16 red	black	jet	black	6:3:3:4

Was Mendel just wrong?
No, none of these cases has violated the principles of segregation and independent assortment - just added **complexity**

Epistasis

- Squash fruit colour is controlled by two genes
  - Gene 1 is represented by a W
  - Gene 2 is represented by a G

Which allele is epistatic in squash colour?

The dominant W allele is epistatic

Every time a dominant W allele shows up in a squash genotype, the squash fruit colour is white

- Genotypes and Phenotypes:
  - W-/G- white
  - W-/gg white
  - ww/G- green
  - ww/gg yellow

Cross a green squash (wwGg) with a white squash (Wwgg). What colour are the offspring?

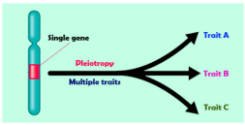
8 : 4 : 4

wwGg x Wwgg

	wG	wG	wg	wg
Wg	WwGg	WwGg	Wwgg	Wwgg
Wg	WwGg	WwGg	Wwgg	Wwgg
wg	wwGg	wwGg	wwgg	wwgg
wg	wwGg	wwGg	wwgg	wwgg

Pleiotropy

- Occurs when one **gene influences multiple phenotypic traits**
- The gene codes for a product that is, for example, used by various cells, or has a signalling function on various targets

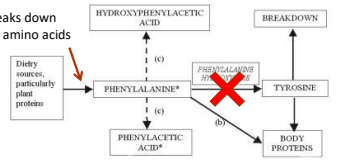


Problem
a mutation in a pleiotropic gene may have an effect on some or all traits simultaneously

Pleiotropy - example

- Phenylketonuria (PKU)
- Symptoms include intellectual impairment, reduced hair and skin pigmentation, microcephalic, eczema, musty smell.
  - **Caused by any of over 400 mutations in a single gene** that codes for the enzyme **phenylalanine hydroxylase**, which converts the amino acid phenylalanine to tyrosine

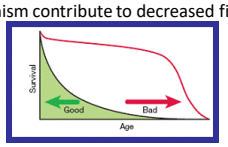
Digestion breaks down proteins into amino acids



Melanin – skin colour
Dopamine-neurotransmission

Antagonistic pleiotropy

- The expression of a gene resulting in multiple competing effects, some beneficial but others detrimental to the organism
- Theory of aging (G. C. Williams, 1957)
  - Some genes responsible for increased fitness in the younger, fertile organism contribute to decreased fitness later in life



  - E.g. BRCA2 gene, women with mutations are more fertile but **after reproduction** the gene causes cancer

Genetic Heterogeneity

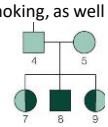
- A phenomenon in which a single phenotype or genetic disorder may be caused by any one of a multiple number of alleles or non-allele (locus) mutations
  - **Allelic heterogeneity** – different mutations within a **single gene locus** (forming multiple alleles of that gene) cause the same phenotypic expression
    - E.g. 1000 known mutant alleles of the CFTR gene that cause cystic fibrosis
  - **Locus heterogeneity** – variations in completely **unrelated gene loci** cause a single disorder
    - E.g. has Ehler's Danlos syndrome

autosomal dominant, autosomal recessive, and X-linked origins

Penetrance

- The probability of a gene or genetic trait being expressed.
  - Complete penetrance – the gene or genes for a trait are expressed in all the population who have the genes
  - Incomplete penetrance – the genetic trait is expressed in only part of the population
- Penetrance can be difficult to determine reliably
  - E.g. in disease, the onset of symptoms could be age related, or affected by environmental codeterminants such as nutrition and smoking, as well as genetic cofactors

Camptodactyly

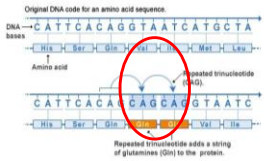


Expressivity

- Refers to **variations in a phenotype among individuals carrying a particular genotype**
  - *E.g. Drosophila* flies homozygous for recessive mutant gene *eyeless* exhibit range of phenotypes from normal eyes to complete absence of one or both eyes
- Other genes or environmental factors such as nutrition and temperature may be influencing or modifying the phenotype- severity ranges with developmental temperature

Anticipation

- A phenomenon whereby the symptoms of a genetic disorder exhibit an earlier age of onset and are more severe **as it is passed on to the next generation**
  - E.g. Huntington's disease – trinucleotide repeat disease



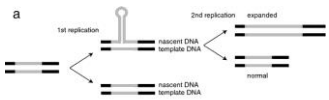
Repeat count	Classification	Disease status
<28	Normal	Unaffected
28–35	Intermediate	Unaffected
36–40	Reduced Penetrance	+/- Affected
>40	Full Penetrance	Affected

Why do Triplet repeat mutations get worse over generations*??

1. Slippage of the two complementary DNA strands during **replication**
2. Homologous recombination- **every meiosis event**
3. **DNA repair**

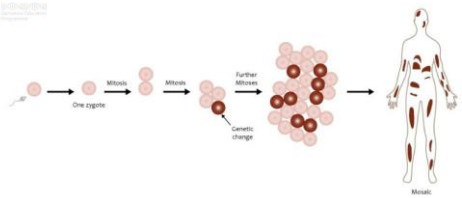
Mutation caused by denaturation and misplacement of the strands
-Mispairing of the complimentary strands
In high sequence repeat regions

Replication slippage



Germline mosaicism

- **Mosaicism** – the presence of two or more populations of cells with different genotypes in one individual who has developed from a single fertilized egg

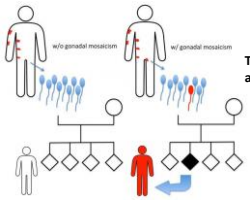


https://www.flickr.com/photos/genomicseducation/13080775333

Germline mosaicism

Germline mosaicism – a special form of mosaicism, where **some gametes (sperm or oocytes) carry a mutation**, but the rest are normal

Cause is usually a mutation that occurred in an early stem cell that gave rise to the gonadal tissue



This can cause only some offspring to be affected, even for a dominant disease

Phenocopies

- A phenocopy is an individual whose phenotype under a particular environmental condition, is identical to the one of another individual whose phenotype is determined by the genotype
  - The phenocopy environmental condition mimics the phenotype produced by a gene (i.e. black coat)

Himalayan rabbit standard coat
Raised 20deg

Mutation in Tyrosinase (Gene C) active between 15-25 degrees

Himalayan rabbit 'copying' black rabbit
Raised in cold <15deg

Raised 20deg

Raised in cold <15deg

Raised in heat 30deg

20-25°C = standard coat: melanin mostly supressed
<20°C = black coat: melanin expressed
>25°C = white coat: melanin fully suppressed

Think about this one for prac 1!

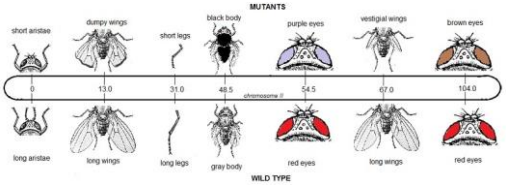
https://www.nature.com/scitable/topicpage/environmental-influences-on-gene-expression-536/#

Genomic imprinting

- Normally there is no difference of expression of the paternal and maternal alleles
- Genomic imprinting causes **selective** expression of a gene or genes inherited from one parent
- Not a mutation or permanent change
- Plays a role in several genetic disorders
  - E.g. **The same region of chromosome 15 mutated but causes a different disease if inherited from mother or father**
  - Prader-Willi syndrome: Paternal copy
  - Angelman syndrome: Maternal copy

Linkage

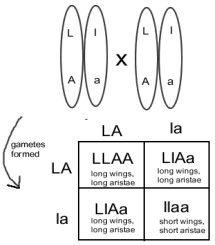
- **Two or more genes located on the same chromosome that do not show independent assortment and tend to be inherited together**



- In a given cross, the outcome depends on the proximity of genes on a chromosome

Linkage – two gene example

- A fly that is heterozygous for long wings (Ll) and heterozygous for long aristae (Aa) is crossed with another fly of the same type. AaLl x AaLl. **In both cases the dominant alleles are located on the same chromosome.**

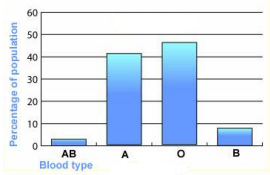


3/4 long wings, long aristae
1/4 short wings, short aristae

What ratio of offspring phenotypes would you expect?

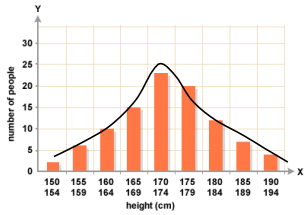
Different definitions of variation

- Some traits are controlled by **two** or **more genes**
- Phenotypes can be discontinuous or continuous
- **Discontinuous variation** shows distinct (discrete) phenotypes
  - E.g. Pea plant colour, ABO blood group



Continuous variation

- Continuous variation shows a series of overlapping phenotypic classes
  - E.g. Height, weight, hand span, shoe size, milk yield in cows

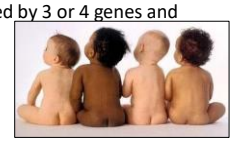


How are traits defined?

- Polygenic traits
  - Traits controlled by **two or more genes**
  - Patterns of inheritance that can be measured quantitatively
    - Example: human eye colour
- Multifactorial traits
  - Polygenic traits resulting from interactions of **two or more genes** and **one or more environmental factors**
    - Example: skin colour

A multifactorial trait: skin colour

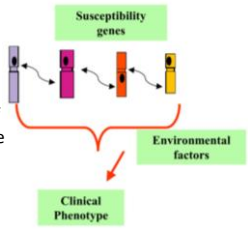
- Skin colour is controlled by 3 or 4 genes and environmental factors



- We're all born with a skin colour based on our genes but the environment can alter this

How are traits defined?

- Complex traits
  - Traits controlled by multiple genes and the interaction of environmental factors where the contributions of genes and environment are undefined
    - Example: hypertension, obesity, cardiovascular disease, depression, autism



Many human diseases are controlled by the action of several genes