16 Inherited change

Genetic information is transmitted from generation to generation to maintain the continuity of life. In sexual reproduction, meiosis introduces genetic variation so that offspring resemble their parents but are not identical to them. Genetic crosses reveal how some features are inherited. The phenotype of organisms is determined partly by the genes they have inherited and partly by the effect of the environment. Genes determine how organisms develop and gene control in bacteria gives us a glimpse of this process in action.

16.1 Passage of information from parent to offspring

Diploid organisms contain pairs of homologous chromosomes.

The behaviour of maternal and paternal chromosomes during meiosis generates much variation amongst individuals of the next generation.

By the end of this section you should be able to:

a) explain what is meant by homologous pairs of chromosomes
b) explain the meanings of the terms haploid and diploid and the need for a reduction division (meiosis) prior to fertilisation in sexual reproduction
c) outline the role of meiosis in gametogenesis in humans and in the formation of pollen grains and embryo sacs in flowering plants
d) describe, with the aid of photomicrographs and diagrams, the behaviour of chromosomes in plant and animal cells during meiosis, and the associated behaviour of the nuclear envelope, cell surface membrane and the spindle
e) explain how crossing over and random assortment of homologous chromosomes during meiosis and random fusion of gametes at fertilisation lead to genetic variation including the expression of rare, recessive alleles

Diploid organisms contain homologous pairs of chromosomes

We introduced the structure and features of chromosomes in Topic 5:

- The **number of chromosomes** per **species** is fixed.
- The shape of a chromosome is characteristic; they are of **fixed length** and with a narrow region, called the **centromere**, somewhere along their length.
- The centromere is always in **the same position** on any given chromosome, and this position and the length of the chromosome is how it can be identified in photomicrographs.
- Chromosomes hold the hereditary factors, **genes**. A particular gene always occurs on the same chromosome in the same position.
- The position of a gene is called a **locus**.
- Each gene has two or more forms, called **alleles**.

The **loci** are the positions along the chromosomes where genes occur, so alleles of the same gene occupy the same locus.

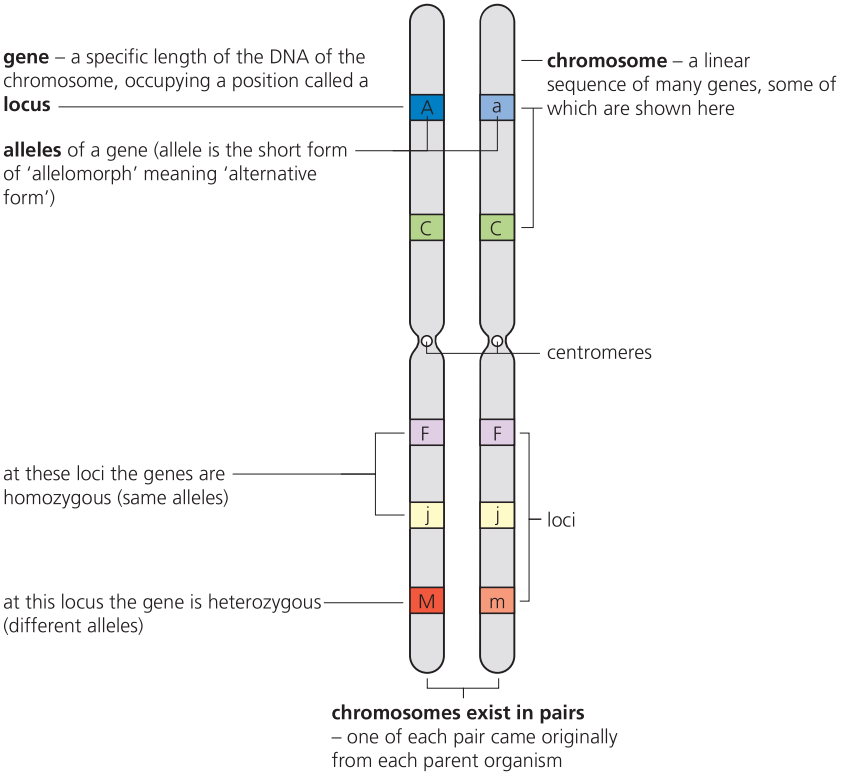


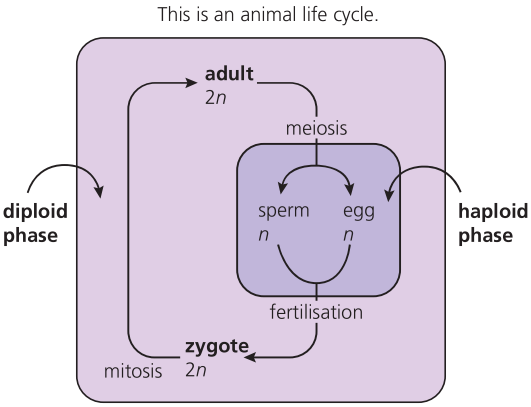
Figure 16.1 The genes and alleles of a homologous pair of chromosomes

We have also seen that the **nuclear division** that occurs during growth, known as **mitosis**, results in the exact duplication of these chromosomes in the daughter nuclei formed.

Examination of the chromosomes at certain stages in mitosis discloses another important feature. Chromosomes occur in pairs. These pairs of chromosomes are known as **homologous pairs** (Figure 16.1). These homologous pairs of chromosomes arise in the first place because one member of the pair has come from the male parent and the other from the female parent. Homologous pairs are then maintained by the exact replication that takes place prior to each mitotic division. A cell with a full set of chromosomes (all homologous pairs) in its nucleus is said to be in the **diploid** condition.

Diploid: a eukaryotic cell or organism containing two complete sets of chromosomes (two copies of each homologous chromosome), shown as *2n*, such as a human body (somatic) cell.

Haploid: a eukaryotic cell or organism containing only one complete set of chromosomes (only one of each homologous pair of chromosomes), shown as *n*, such as a human sperm or secondary oocyte.



Self-fertilisation = sperm + egg from same individual.
Cross-fertilisation = sperm + egg from different individuals.

Figure 16.2 Meiosis and the diploid life cycle

Meiosis – the reductive division

There is a different type of nuclear division that results in daughter nuclei each containing half the number of chromosomes of the parent cell.

In **sexual reproduction**, two sex cells (called **gametes**) fuse; this is **fertilisation**. The resulting cell is called the zygote, and it will grow and develop into a new individual.

Because two nuclei fuse when sexual reproduction occurs, the chromosome number is doubled at that time. For example, human gametes (each egg cell and sperm) have just 23 chromosomes each. When the male and female gametes fuse, the full component of 46 chromosomes is restored.

The doubling of the number chromosome each time sexual reproduction occurs (every generation) is avoided by a nuclear division that halves the chromosome number. This reductive division is called **meiosis**. The sex cells formed following meiosis contain a single set of chromosomes, a condition known as **haploid**. When haploid gametes fuse the resulting cell has the diploid condition again.

Question

1 a Explain why chromosomes occur in homologous pairs in diploid cells.
b How do the products of mitosis and meiosis differ?

The event of meiosis in the formation of gametes (a process known as **gametogenesis**) in humans is shown in Figure 16.3. In the formation of gametes in flowering plants (the pollen grains and embryo sacs) meiosis features similarly. The differences between mitosis and meiosis are summarised in Figure 5.4, page 102.

Note that meiosis features in the maturation stage of garnete formation.

Note that meiosis features in the maturation stage of garnete formation.

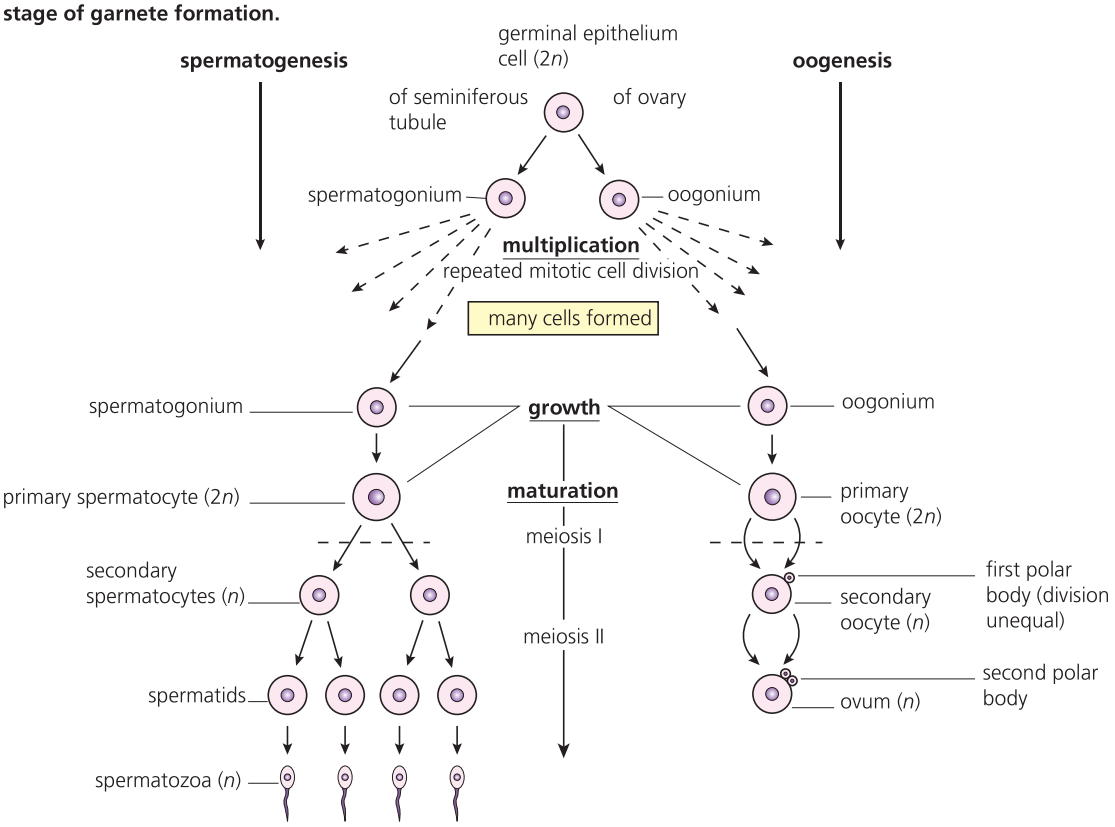


Figure 16.3 Meiosis is gametogenesis in humans

Extension

Asexual reproduction

Organisms reproduce asexually or sexually and many reproduce by both these methods. In **asexual reproduction** a single organism produces new individuals. Asexual means 'non-sexual'; no gametes are formed in asexual reproduction. The cells of the new offspring are produced by **mitosis** (page 102), so the progeny are identical to the parent and to each other. Identical offspring produced by asexual reproduction are known as **clones**.

Mammals reproduce by sexual reproduction only, but many flowering plants reproduce by both asexual and sexual reproduction.

The process of meiosis

Once started, meiosis proceeds steadily as a continuous process of nuclear division. However, the steps of meiosis are explained in four distinct phases (**prophase**, **metaphase**, **anaphase** and **telophase**). This is just for convenience of analysis and description, there are no breaks between the phases in nuclear divisions.

The behaviour of the chromosomes in the phases of meiosis is shown in Figure 16.4. For clarity, the drawings show a cell with a single pair of homologous chromosomes.

Meiosis involves **two divisions of the nucleus**, known as **meiosis I** and **meiosis II**. Both of these divisions *superficially* resemble mitosis. For example, as happens in mitosis, chromosomes are copied, appearing as sister **chromatids** during interphase, before meiosis occurs. However, early in meiosis I, **homologous chromosomes pair up**. By the end of meiosis I, homologous chromosomes have separated again, but the chromatids they consist of do not separate until meiosis II. So, meiosis consists of two nuclear divisions but only one replication of the chromosomes.

Meiosis I

Prophase I

What happens to chromosomes during prophase I is quite complex and difficult to see when you are looking at dividing cells under the microscope. However, you can follow the changes in Figure 16.5.

The chromosomes appear under the light microscope as single threads with many tiny bead-like thickenings along their lengths. These thickenings represent an early stage in the process of shortening and thickening by coiling that continues throughout prophase. In fact, each chromosome has already replicated and consists of two chromatids but the individual chromatids are not visible as yet.

The formation of pairs of homologous chromosomes

As the chromosomes continue to thicken, homologous chromosomes are seen to come together in specific pairs, point by point, all along their length. Remember, in a diploid cell each chromosome has a partner that is the same length and shape and with the same linear sequence of genes.

The homologous chromosomes continue to shorten and thicken. Later in prophase the individual chromosomes can be seen to be double-stranded, as the sister chromatids become visible.

Crossing over

Within the homologous pair, during the coiling and shortening process, breakages of the chromatids occur frequently. Breakages occur in non-sister chromatids at the same points along the length of each. Broken ends rejoin more or less immediately, but where the rejoining is between non-sister chromatids, swapping of pieces of the chromatids has occurred, hence the name 'crossing over'. This results in new combinations of genes on the chromosomes.

Figure 16.4 Photomicrograph of homologous chromosomes held together by chiasmata

The point of the join between different chromatids is called a **chiasma** (*plural*: **chiasmata**). Virtually every pair of homologous chromosomes forms at least one chiasma at this time, and two or more chiasmata in the same homologous pair is very common.

In the later stage of prophase I the attraction and tight pairing of the homologous chromosomes ends, but the attractions between sister chromatids remains for the moment. This attraction of sister chromatids keeps the homologous pairs together. The chromatids are now at their shortest and thickest.

In late prophase I the two centrioles of the centrosome present in animal cells (page 19) duplicate. The two centromeres then start to move apart as a prelude to spindle formation. Plant cells do not have centrioles.

Finally, the disappearance of the nucleoli and **nuclear envelope** marks the end of prophase I.

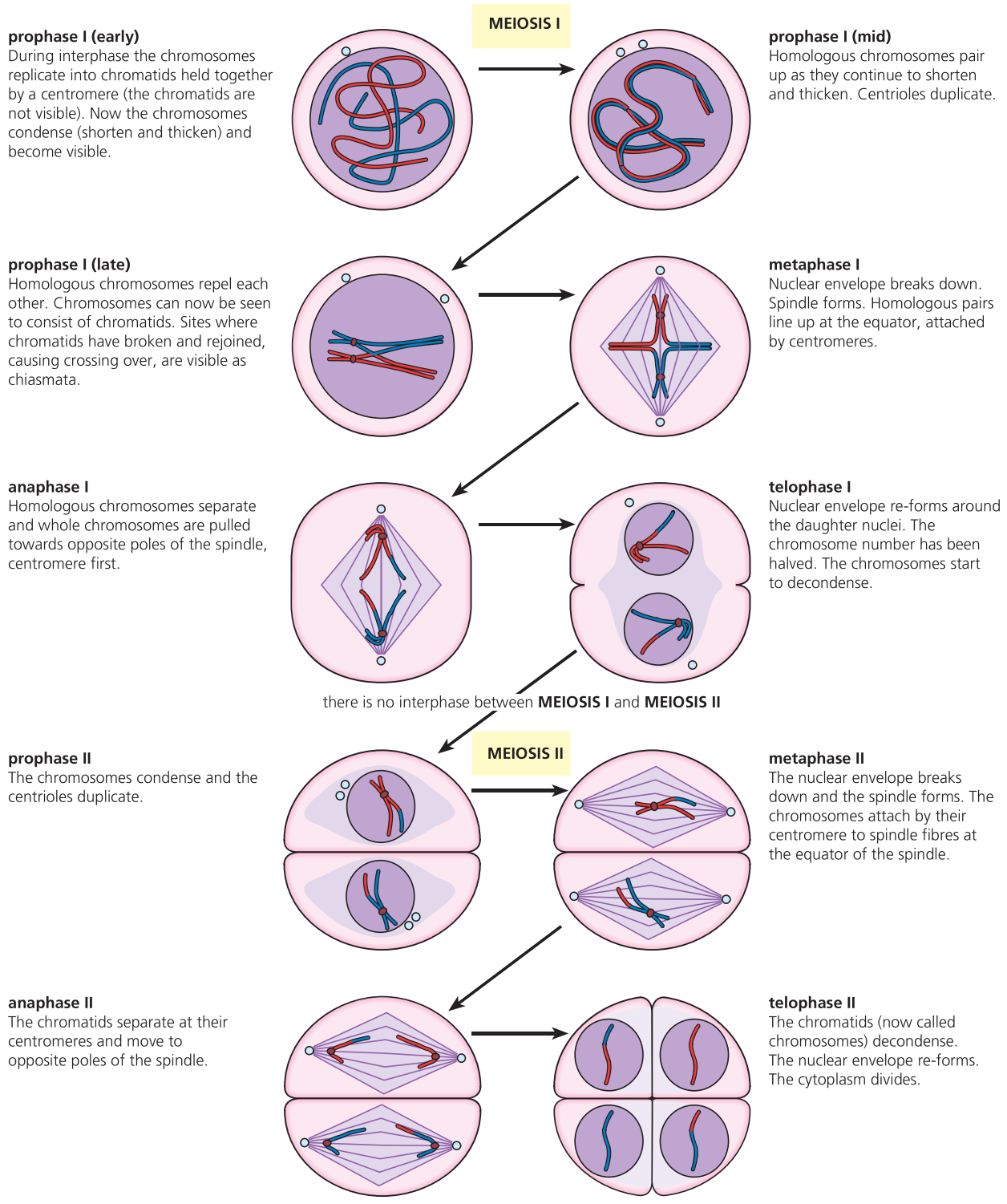


Figure 16.5 The process of meiosis

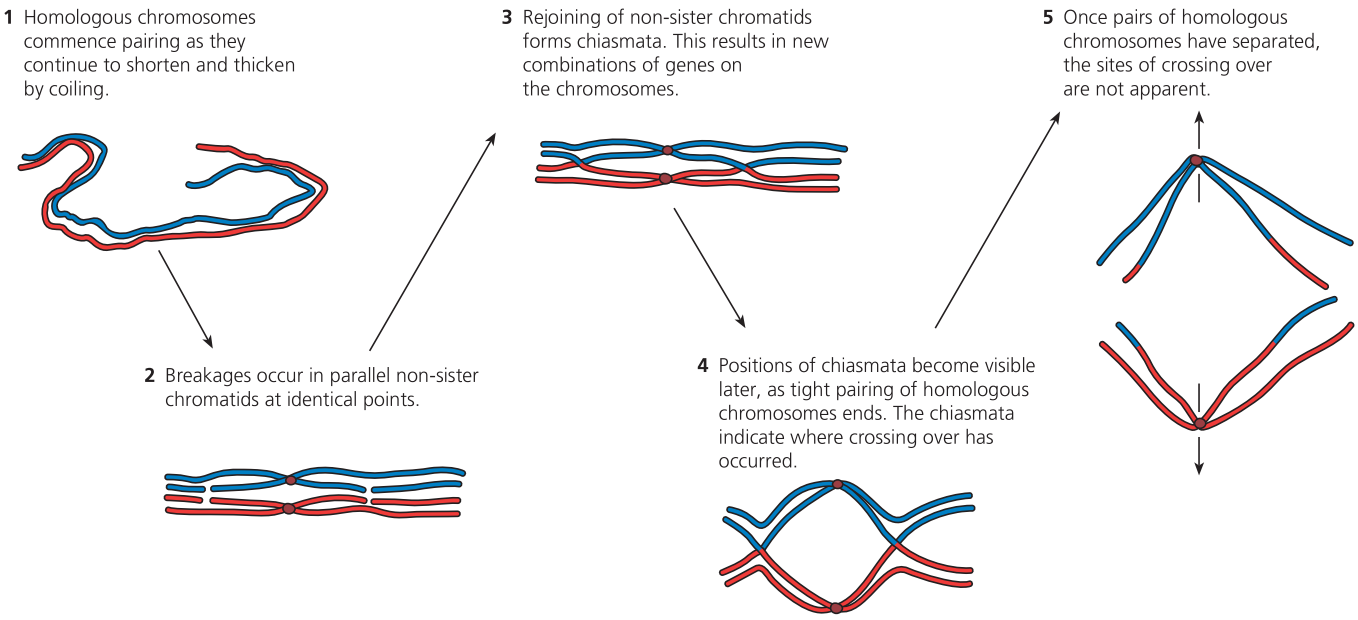


Figure 16.6 The formation of chiasmata

Metaphase I

Next, the spindle forms, and the homologous pairs become attached to individual microtubules of the spindle by their centromeres. The homologous pairs are now arranged at the equatorial plate of the spindle framework – we say that they line up at the centre of the cell. By the end of metaphase I, the members of the homologous pairs start to repel each other and separate. However, at this point they are held together by one or more chiasmata and this gives a temporary but unusual shape to the homologous pair.

Anaphase I

The chromosomes of each homologous pair now move to opposite poles of the spindle, but with the individual chromatids remaining attached by their centromeres. The attraction of sister chromatids has lapsed, and they separate slightly – both are clearly visible. However, they do not separate yet; they go to the same pole. Consequently, meiosis I separates homologous pairs of chromosomes but not the sister chromatids of which each is composed.

Telophase I

The arrival of homologous chromosomes at opposite poles signals the end of meiosis I. The chromosomes tend to uncoil to some extent, and a nuclear envelope re-forms around both nuclei. The spindle breaks down, but these two cells do not go into interphase, rather they continue into meiosis II, which takes place at right angles to meiosis I. There may, however, be a delay between meiosis I and meiosis II, as in oogenesis (page 344).

Question

2 What is the major consequence of there being no interphase between meiosis I and meiosis II?

3 At precisely which points in the process of meiosis (Figure 16.5) do the following events occur?

- **a** the nuclear envelope breaks down and the spindle forms
- **b** homologous chromosomes pair up
- **c** the presence of chiasmata becomes visible
- **d** chromatids separate at their centromeres
- **e** homologous chromosomes separate
- **f** haploid nuclei form

Meiosis II

Meiosis II is remarkably similar to mitosis:

- **Prophase II**
  The nuclear envelopes break down again, and the chromosomes shorten and re-thicken by coiling. Centrioles, if present, duplicate and move to opposite poles of the cell. By the end of prophase II the spindle apparatus has re-formed, but at right angles to the original spindle.
- **Metaphase II**
  The chromosomes line up at the equator of the spindle, attached by their centromeres.
- **Anaphase II**
  The centromeres divide and the chromatids move to opposite poles of the spindle, centromeres first.
- **Telophase II**
  Nuclear envelopes form around the four groups of chromatids, so that four nuclei are formed. Now there are four cells, each with half the chromosome number of the original parent cell. Finally, the chromatids – now recognised as chromosomes, uncoil and become apparently dispersed as **chromatin**. Nucleoli re-form.

  The process of meiosis is now complete, and is followed by division of the cytoplasm (cytokinesis, page 101).

Allele: one of two or more alternative nucleotide sequences at a single gene locus, so alleles are variant forms of a gene. For example, the alleles of the ABO blood group gene are found at a locus on chromosome 9, with the alleles including I^A, I^B and I^O. Diploid body cells contain two copies of each homologous chromosome, so have two copies of chromosome 9, and so have two copies of the gene. These may be the same allele (homozygous), for example $I^A\ I^A$, or $I^B\ I^B$ or $I^O\ I^O$, or they may be different alleles (heterozygous), for example $I^A\ I^B$, or $I^A\ I^O$ or $I^B\ I^O$. The gene for producing the haemoglobin β-polypeptide has a number of alleles. Two of these are the normal allele, Hb^A, and the sickle cell allele, Hb^S, giving $Hb^A\ Hb^A$ and $Hb^S\ Hb^S$ as homozygous genotypes and $Hb^A\ Hb^S$ as a heterozygous genotype.

Meiosis and genetic variation

There are differences in the genetic information carried by different gametes. This variation arises in meiosis and is highly significant for the organism, as we shall see. The reason why the four haploid cells produced by meiosis differ genetically from each other is because of two important features of meiosis. These are:

- **the independent assortment of maternal and paternal homologous chromosomes**. The way the chromosomes of each homologous pair line up at the equator of the spindle in meiosis I is entirely random. Which chromosome of a given pair goes to which pole is unaffected by (independent of) the behaviour of the chromosomes in other pairs. Figure 16.7 shows a parent cell with only four chromosomes, for clarity. Of course, the more homologous pairs there are in the nucleus, the greater the variation that is possible. In humans there are 23 pairs of chromosomes, so the number of possible combinations of chromosomes that can be formed as a result of independent assortment is 2^{23}. This is over 8 million.
- **the crossing over of segments of individual maternal and paternal homologous chromosomes**. This results in new combinations of genes on the chromosomes of the haploid cells produced, as illustrated in Figure 16.8. Crossing over generates the possibility of an almost unimaginable degree of variation. For example, if we were to assume for sake of discussion that there are 30 000 individual genes on the human chromosome complement, all with at least two alternative alleles, and that crossing over is equally likely between all of these genes, then there are $2^{30\,000}$ different combinations! Of course, all these assumptions will be inaccurate to varying extents, but the point that virtually unlimited recombinations are possible is established.

Finally, further genetic variation in the progeny of organisms that reproduce sexually is assured by the **random fusion** of male and female gametes in sexual reproduction.

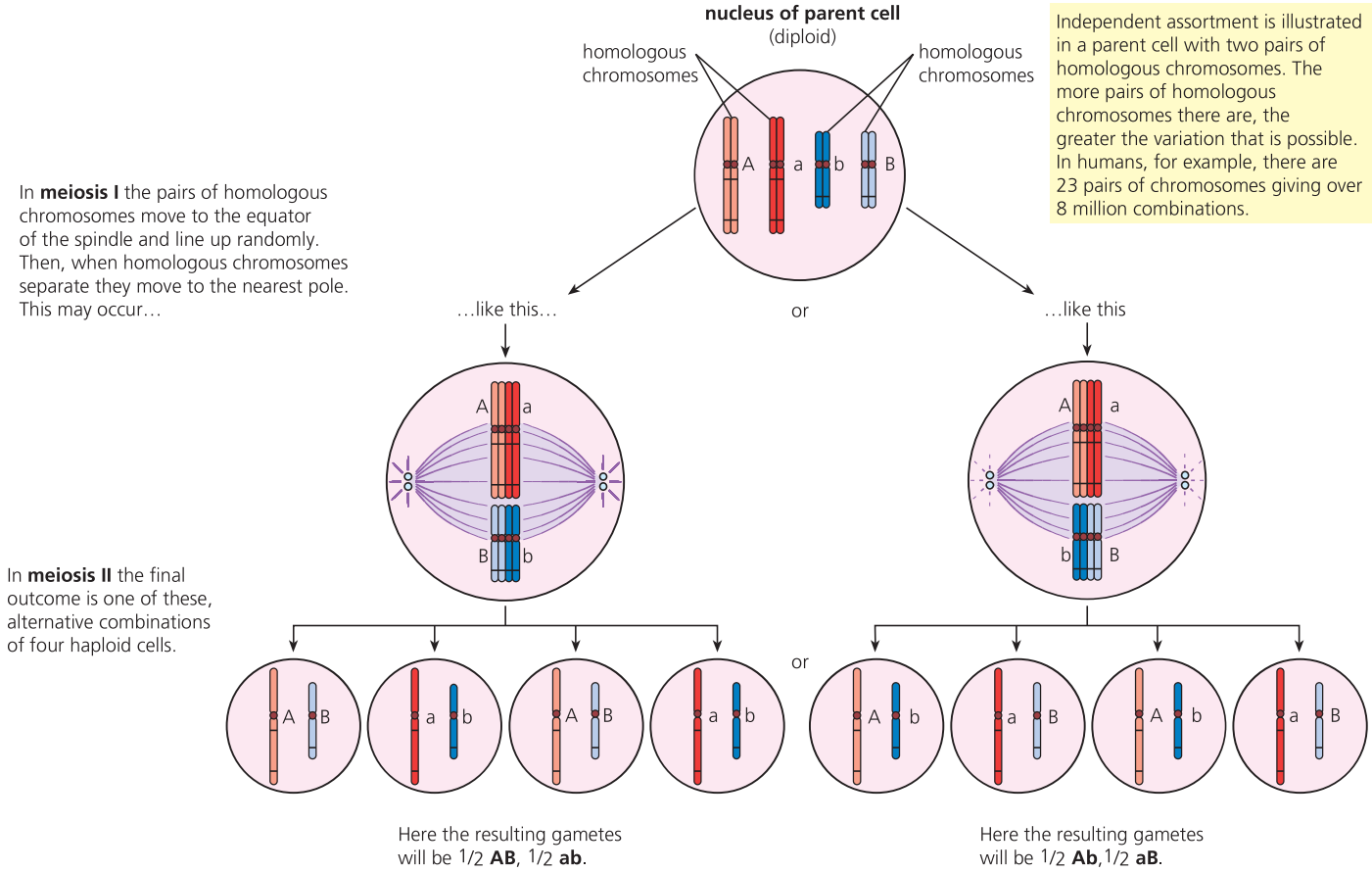
A note on 'recombinants'

Offspring with combinations of characteristics different from those of their parents are called **recombinants**. Recombination in genetics is the re-assortment of alleles or characters into different combinations from those of the parents. We have seen that recombination occurs for genes located on separate chromosomes (unlinked genes) by chromosome assortment in meiosis (Figure 16.7), and for genes on the same chromosomes (linked genes) by crossing over during meiosis (Figure 16.8).

We shall see in the next section, how crossing over, random assortment of homologous chromosomes during meiosis, and random fusion of gametes at fertilisation may also lead to the expression of rare, recessive alleles, such as those that are responsible for albinism, sickle cell anaemia, haemophilia and Huntington's disease.

Question

4 What are the essential differences between mitosis and meiosis?



Independent assortment is illustrated in a parent cell with two pairs of homologous chromosomes. The more pairs of homologous chromosomes there are, the greater the variation that is possible. In humans, for example, there are 23 pairs of chromosomes giving over 8 million combinations.

Figure 16.7 Genetic variation due to independent assortment

The effects of genetic variation are shown in one pair of homologous chromosomes. Typically, two, three or more chiasmata form between the chromatids of each homologous pair at prophase I.

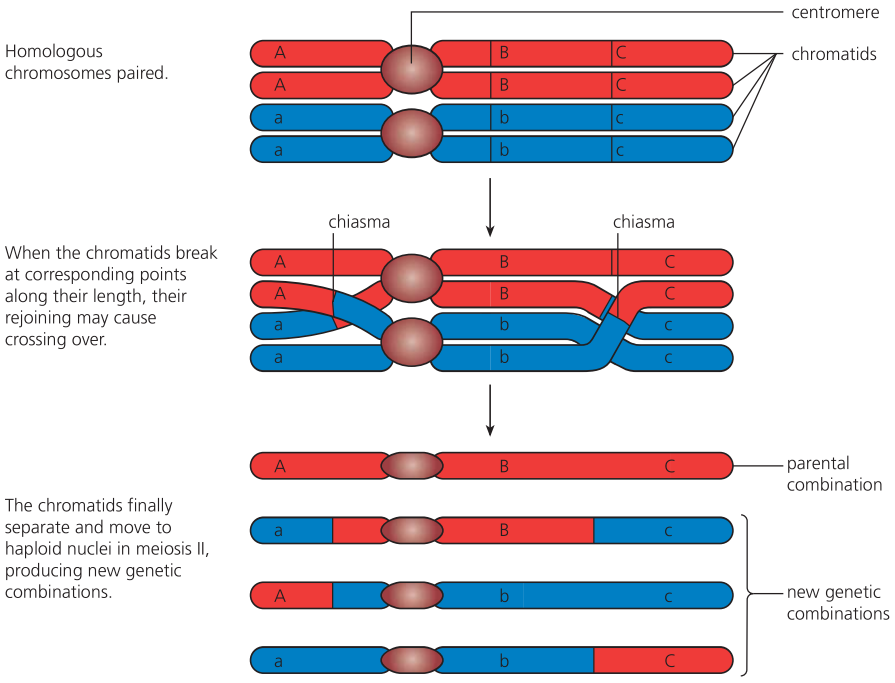


Figure 16.8 Genetic variation due to crossing over between non-sister chromatids

16.2 The roles of genes in determining the phenotype

Patterns of inheritance are explained by using genetic diagrams. The results of genetic crosses are analysed statistically using the chi-squared test.

By the end of this section you should be able to:

a) explain the terms gene, locus, allele, dominant, recessive, codominant, linkage, test cross, F1 and F2, phenotype, genotype, homozygous and heterozygous
b) use genetic diagrams to solve problems involving monohybrid and dihybrid crosses, including those involving autosomal linkage, sex linkage, codominance, multiple alleles and gene interactions
c) use genetic diagrams to solve problems involving test crosses
d) use the chi-squared test to test the significance of differences between observed and expected results

Inheriting genes in sexual reproduction

In sexual reproduction haploid gametes are formed by meiosis. At fertilisation, male and female gametes fuse to form a zygote. As a consequence, the zygote, a diploid cell, has two sets of chromosomes (homologous pairs), one from each parent. Thus there are two alleles of each gene present in the new individual.

Genotype and phenotype

The alleles that an organism carries (present in every cell) make up the **genotype** of that organism. A genotype in which the two alleles of a gene are the same is said to 'breed true' or to be **homozygous** for that gene. In Figure 16.12, the parent pea plants (P generation) were either homozygous tall or homozygous dwarf. Alternatively, if the alleles are different the organism is **heterozygous** for that gene. In Figure 16.12, the F_1 generation were all heterozygous tall.

So the genotype is the genetic constitution of an organism. Alleles interact in various ways (and with environmental factors, as we shall see later). The outcome is the phenotype. The **phenotype** is the way in which the genotype of the organism is expressed. It is the appearance of the organism. Here the dwarfness and tallness of the plants were the phenotypes observed.

The monohybrid cross

The mechanism of inheritance was successfully investigated *before* chromosomes had been observed or genes were known about. It was **Gregor Mendel** who made the first important discoveries about heredity (Figure 16.9).

An investigation of the inheritance of a single contrasting characteristic is known as a **monohybrid cross**. It had been noticed that the garden pea plant was either tall or dwarf. How this contrasting characteristic is controlled is made clear by analysing the monohybrid cross.

In Figure 16.11 the steps of this investigation into the inheritance of height in the pea plants is summarised. Note that the experiment began with plants that always '**bred true**', that is the tall plants produced progeny that were all tall and the dwarf plants produced progeny that were all dwarf, when each was allowed to self-fertilise. Self-fertilisation is the normal condition in the garden pea plant.

Extension

Gregor Mendel – the founder of modern genetics

Gregor Mendel was born in eastern Europe in 1822, the son of a peasant farmer. As a young boy he worked to support himself through schooling, but at the age of 21 he was offered a place in the monastery at Bruno (now in the Czech Republic). The monastery was a centre of research in natural sciences and agriculture, as well as in the humanities. Mendel was successful there. Later, he became Abbot.

Figure 16.9 Gregor Mendel

Mendel discovered the principles of heredity by studying **the inheritance of seven contrasting characteristics of the garden pea plant**. These did not 'blend' on crossing, but retained their identities, and were inherited in fixed mathematical ratios.

He concluded that hereditary factors (we now call them genes) determine these characteristics, that these factors occur in duplicate in parents, and that the two copies of the factors segregate from each other in the formation of gametes.

Today we often refer to Mendel's laws of heredity, but Mendel's results were **not presented as laws** – which may help to explain the difficulty others had in seeing the significance of his work *at the time*.

Mendel was successful because:

- his experiments were carefully planned, and used large samples
- he carefully recorded the numbers of plants of each type but expressed his results as ratios
- in the pea, contrasting characteristics are easily recognised
- by chance, each of these characteristics was controlled by a single factor (gene)* rather than by many genes, as most human characteristics are
- pairs of contrasting characters that he worked on were controlled by factors (genes) on separate chromosomes*
- in interpreting results, Mendel made use of the mathematics he had learnt.

*Genes and chromosomes were not known then.

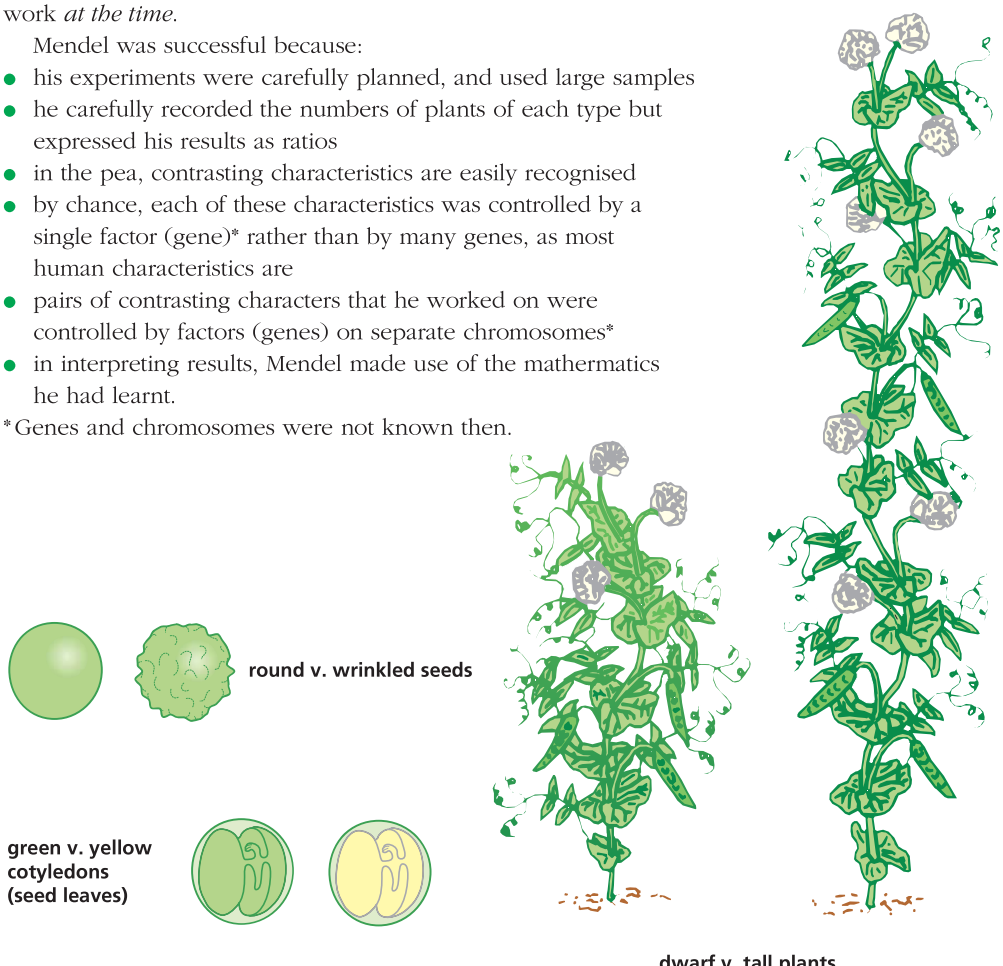


Figure 16.10 Features of the garden pea

Question

5 At the time of Mendel's experiments it was thought that the characteristics of parents 'blended' in their offspring. What features of Mendel's methods enabled him to avoid this error?

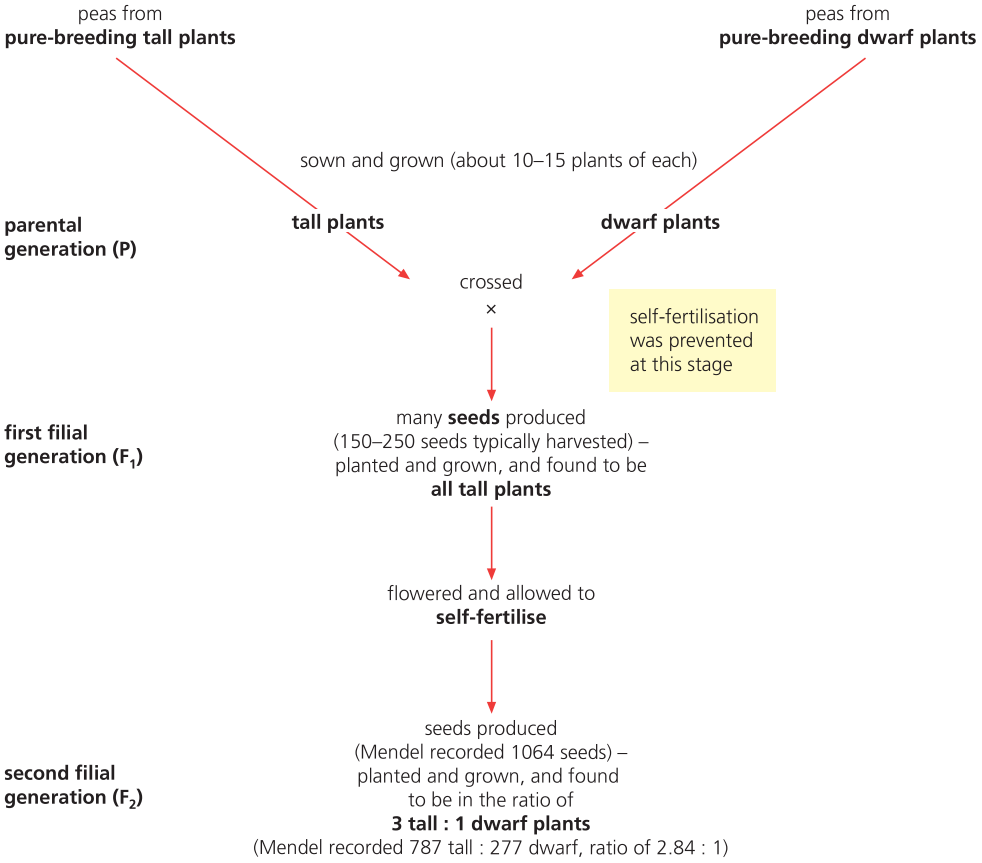


Figure 16.11 The steps of the monohybrid cross

Dominant: an allele with a phenotype that is expressed even when present with an allele that is recessive to it. For example, in the ABO blood group gene, I^A is dominant to I^O. Therefore a person with the genotype $I^A I^O$ has blood group A because only the dominant allele is expressed.

Recessive: an allele with a phenotype that is not expressed when an allele that is dominant to it is present. For example, I^O is recessive to I^A, so a person with the genotype $I^A I^O$ has blood group A, and a person can only be blood group O if they are homozygous recessive, $I^O I^O$.

In the monohybrid cross it appears that the 'dwarf' characteristic disappeared in the first generation (F_1 generation) but then reappeared in the F_2 generation. We can explain what is going on if there is a factor controlling 'dwarfness'. This 'factor' remained intact from one generation to another. However, it does not have any effect (we say it does not 'express itself') in the presence of a similar factor for 'tall'. In other words, 'tall' is a **dominant** characteristic and 'dwarf' is a **recessive** characteristic. So there must be two independent factors for height, one from one parent and the other factor from the other parent. A sex cell (gamete) must contain only one of these factors.

Today we see that these 'factors' are **alleles** of the gene for height in the pea plant. When the tall plants of the F_1 generation were allowed to self-fertilise, the resulting members of the F_2 generation were in the ratio of 3 tall plants to 1 dwarf plant. The genetic diagram in Figure 16.12 is the way we explain what is going on.

From the monohybrid cross we see that:

- within an organism are genes (called 'factors' when first discovered) controlling characteristics such as 'tall' and 'dwarf'
- there are two alleles of the gene in each cell
- one allele has come from each parent
- each allele has an equal chance of being passed on to an offspring
- the allele for tall is an alternative form of the allele for dwarf
- the allele for tall is dominant over the allele for dwarf.

We call this the **Law of Segregation**.

> During meiosis, pairs of alleles separate so that each cell has one allele of a pair. Allele pairs separate independently during the formation of gametes.

Phenotype: the physical, detectable expression of the particular alleles of a gene or genes present in an individual. It may be possible to see the phenotype (e.g. human eye colour) or tests may be required (e.g. ABO blood group). When the phenotype is controlled by a small number of alleles of a particular gene, it may be genetically determined (e.g. human eye colour), giving rise to **discontinuous variation**. When the phenotype is controlled by the additive effects of many genes (polygenic), it may be affected by the environment as well as genes (e.g. human height), giving rise to **continuous variation**.

Genotype: the particular alleles of a gene at the appropriate locus on both copies of the homologous chromosomes of its cells (for example, $I^A I^B$). It is sometimes described as the genetic constitution of an organism with respect to a gene or genes.

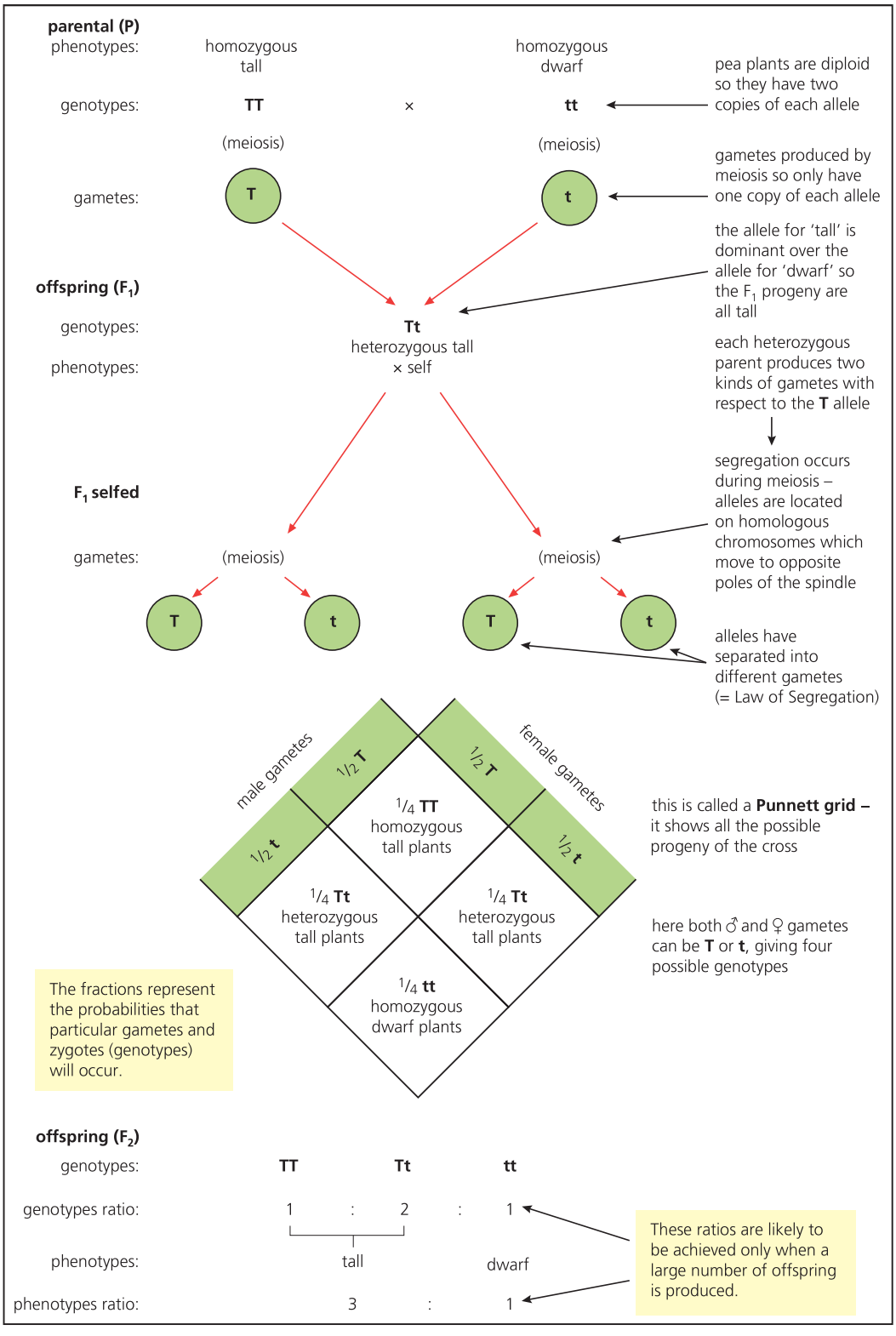


Figure 16.12 Genetic diagram showing the behaviour of alleles in the monohybrid cross

Question

6 From the Punnett grid in Figure 16.12, a ratio of 3 tall to 1 dwarf pea plants was predicted. In fact, a ratio of 2.84 : 1 occurred (Figure 16.11). Suggest what chance events may influence the actual ratios of offspring obtained in breeding experiments like these.

The test cross

If an organism shows a recessive characteristic in its phenotype (for example, it is a dwarf pea plant) it must have a homozygous genotype (**tt**). However, if it shows the dominant characteristic (for example, it is a tall pea plant) then it may be either homozygous for the dominant allele (**TT**) or heterozygous for the dominant allele (**Tt**). In other words, **TT** and **Tt** look alike. They have the same phenotype but different genotypes.

You can tell plants like these apart only by the offspring they produce in a particular cross. When tall heterozygous plants (**Tt**) are crossed with homozygous recessive plants (**tt**), the cross yields 50 per cent tall and 50 per cent dwarf plants (Figure 16.13). This type of cross has become known as a **test cross**. If the offspring produced were all tall this would show that the tall parent plants were homozygous plants (**TT**). Of course, sufficient plants have to be used to obtain these distinctive ratios.

Homozygous: a term describing a diploid organism that has the same allele of a gene at the gene's locus on both copies of the homologous chromosomes in its cells (e.g. Hb^A Hb^A) and therefore produces gametes with identical genotypes (all Hb^A). A homozygote is an organism that is homozygous.

Heterozygous: a term describing a diploid organism that has different alleles of a gene at the gene's locus on each of the homologous chromosomes in its cells (e.g. Hb^A Hb^S) and therefore produces gametes with two different genotypes (½ Hb^A and ½ Hb^S). A heterozygote is an organism that is heterozygous.

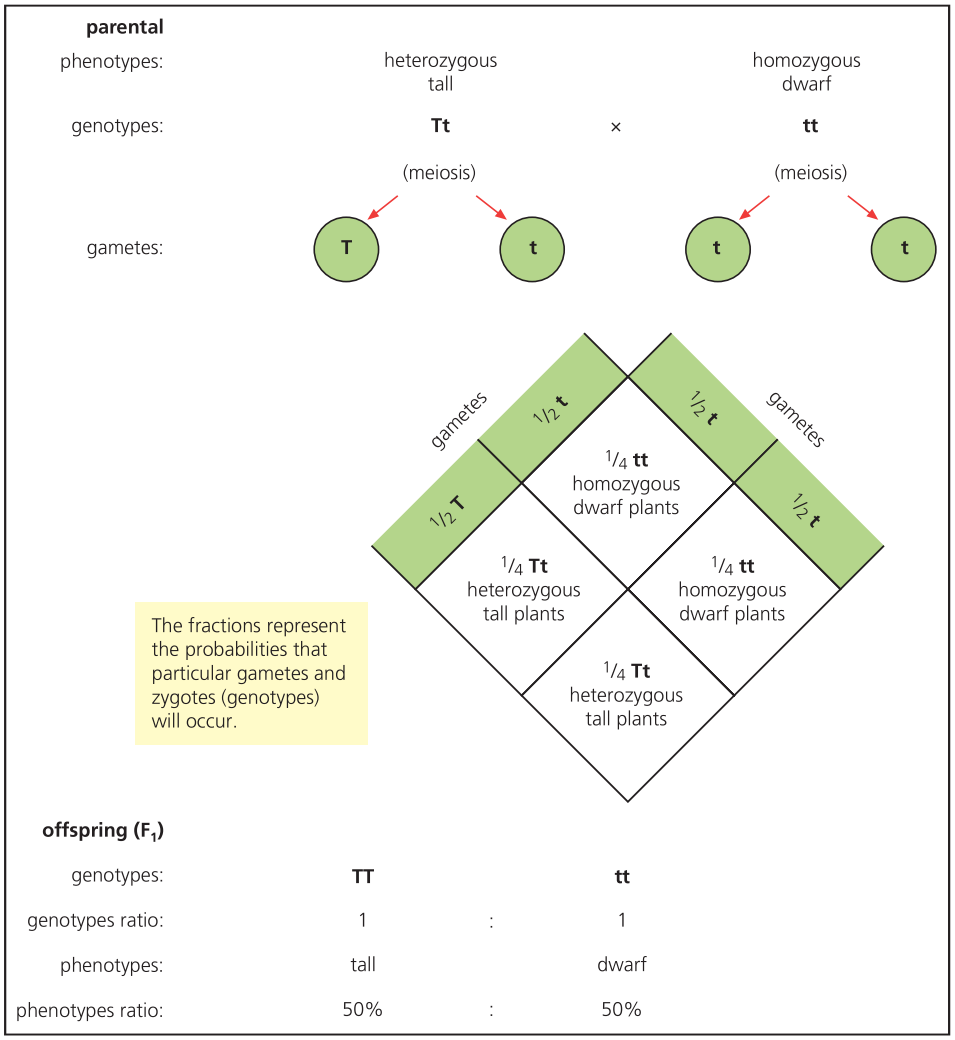


Figure 16.13 Genetic diagram showing the behaviour of alleles in the monohybrid test cross

Codominant: alleles that are both expressed if they are present together in a heterozygous organism. For example, alleles I^A and I^B of the ABO blood group gene are codominant. Therefore, in a heterozygous person, I^A I^B, both alleles are expressed and the blood group is AB. In the case of the haemoglobin α-polypeptide gene, codominance means that the phenotype of a person who has Hb^A Hb^A is unaffected by sickle cell disorder, the phenotype of a person who has Hb^A Hb^S is the less severe sickle cell trait and the phenotype of a person who has Hb^S Hb^S is the more severe sickle cell anaemia.

Modification of the 3:1 ratio

In certain types of monohybrid cross the 3:1 ratio is not obtained. Two of these situations are now illustrated.

Codominance – when both alleles are expressed

In the case of some genes, both alleles may be expressed, rather than one being dominant and the other recessive in the phenotype, as has been the case up to now. When both alleles are expressed codominantly we know that both are transcribed into messenger RNA.

An example of **codominance** is the case of the haemoglobin β-polypeptide gene, where the phenotype of a person who has the genotype Hb^A Hb^A is unaffected by sickle cell disorder, the phenotype of a person who has the genotype Hb^A Hb^S is the less severe sickle cell trait and the phenotype of a person who has the genotype Hb^S Hb^S is the more severe sickle cell anaemia. You can see that, in a cross between parents both of whom have the sickle cell trait, the probability that any offspring will have sickle cell anaemia is one in four (Figure 16.14).

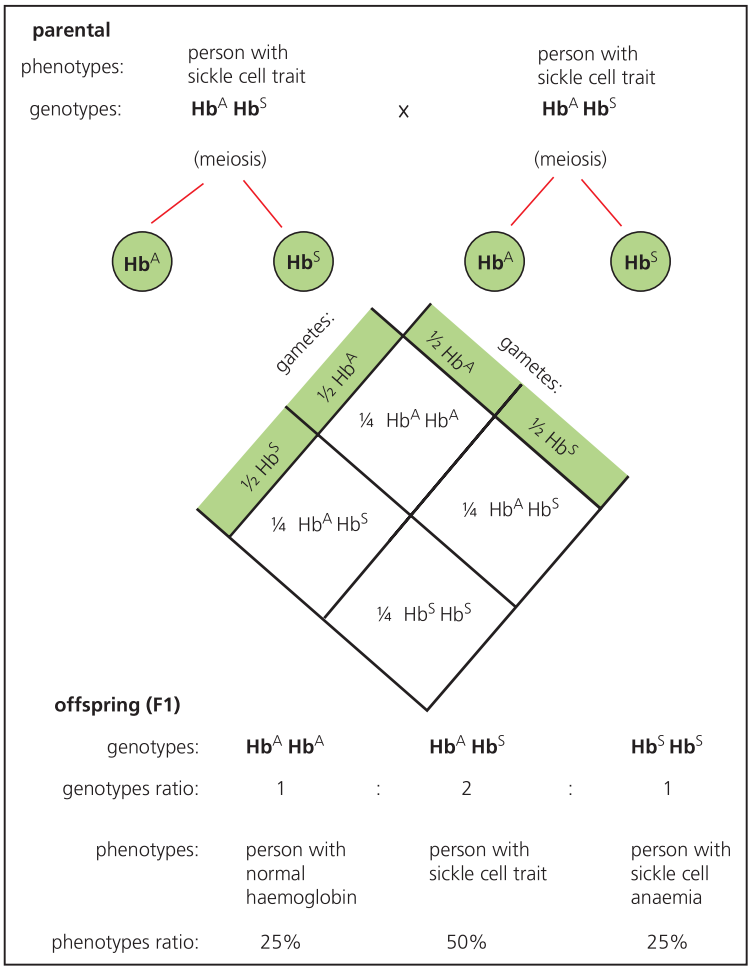


Figure 16.14 Genetic diagram showing the inheritance of sickle cell haemoglobin – an example of codominance

Question

7 Construct for yourself (using pencil and paper) a monohybrid cross between cattle of a variety with a gene for coat colour with codominant alleles, 'red' and 'white' coat. Homozygous parents produce 'roan' offspring (red and white hairs together). Predict what offspring you expect and in what proportions when a sibling cross (equivalent to 'selfing' in plants) occurs between roan offspring.

Locus: the position of a gene or other specific piece of DNA (such as a marker) on a chromosome. The same gene is always found at the same locus of the same chromosome (unless there has been a mutation). The locus is designated by the chromosome number, its arm, and its place. For example, the gene associated with ABO blood groups is at locus 9q34, meaning the gene is found on chromosome 9, on the long arm (q) at region 34. The gene associated with sickle cell anaemia is at locus 11p15.5, meaning chromosome 11, short arm (p), region 15.5.

More than two alleles exist for a particular locus

To begin this discussion we considered the inheritance of a gene for which there are just two forms (two alleles), like the 'height' gene of the garden pea, which has tall and dwarf alleles. We represented this situation in a genetic diagram using a single letter (**T** or **t**) according to whether we were representing the dominant or the recessive allele. However, we now know that not all genes are like this. In fact, most genes have more than two alleles, and these are cases of **multiple alleles**.

With multiple alleles, we choose a single capital letter to represent the locus at which the alleles may occur and represent the individual alleles by a single capital letter in a superscript position (Table 16.1) – as with codominant alleles.

An excellent example of multiple alleles is those controlling the ABO blood group system of humans. Our blood belongs to one of either A, B, AB or O group. Table 16.1 lists the possible phenotypes and the genotypes that may be responsible for each.

So, the ABO blood group system is determined by various combinations of alternative alleles. In each individual only two of these three alleles exist, but they are inherited as if they were alternative alleles of a pair. Alleles I^A and I^B are dominant to I^O which is recessive. Alleles I^A and I^B are **codominant alleles**. Figure 16.15 shows one possible cross between parents with different blood groups.

Table 16.1 The ABO blood groups – phenotypes and genotypes

Phenotype	Genotypes
A	I^AI^A or I^AI^O
B	I^BI^B or I^BI^O
AB	I^AI^B
O	I^OI^O

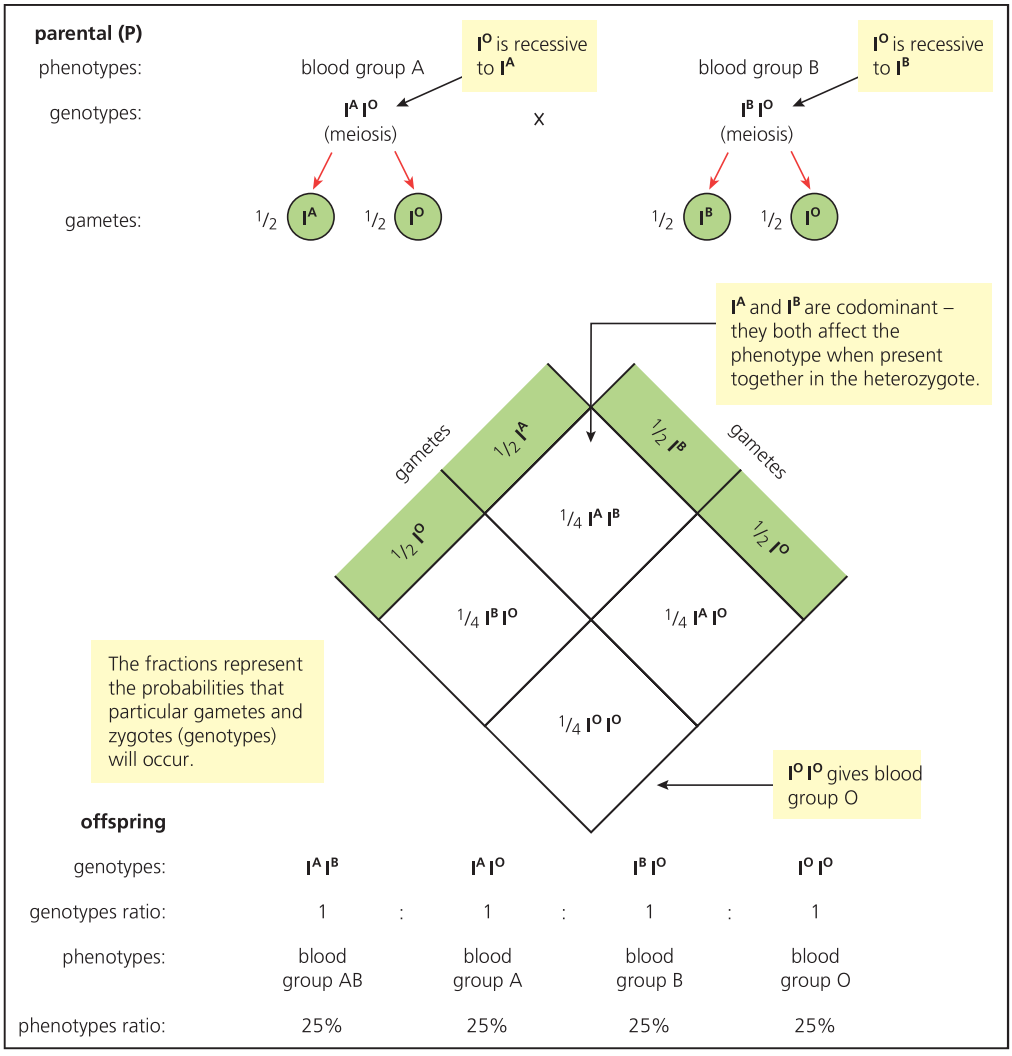


Figure 16.15 Genetic diagram showing the inheritance of human blood ABO group alleles

Question

8 One busy night in an understaffed maternity unit, four children were born about the same time. Then the babies were muddled up by mistake; it was not certain which child belonged to which family. Fortunately the children had different blood groups: A, B, AB and O.
The parents' blood groups were also known:

- Mr and Mrs Jones A and B
- Mr and Mrs Lee B and O
- Mr and Mrs Gerber O and O
- Mr and Mrs Santiago AB and O

Staff were able to decide which child belonged to which family. How was this done?

Reviewing the genetic terms learnt so far

Table 16.2 lists the essential genetic terms and defines each, succinctly.

Cover the right hand column with a piece of paper, temporarily, and see if you can define each correctly, in your own words.

Table 16.2 Essential genetic terms

Haploid	a eukaryotic cell or organism containing only one complete set of chromosomes (only one of each homologous chromosome)
Diploid	a eukaryotic cell or organism containing two complete sets of chromosomes (two copies of each homologous chromosome)
Gene	a length of DNA that codes for a particular polypeptide or protein
Allele	one of two or more alternative nucleotide sequences at a single gene locus; alleles are variant forms of genes
Locus	the position on the chromosome where a gene occurs; alleles of the same gene occupy the same locus
Genotype	the genetic constitution of an organism with respect to a gene or genes
Phenotype	the physical, detectable expression of the particular alleles of a gene or genes present in an individual
Homozygous	a term describing a diploid organism that has the same allele of a gene at the gene's locus on both copies of the homologous chromosomes in its cell
Heterozygous	a term describing a diploid organism that has different alleles of a gene at the gene's locus on both copies of the homologous chromosomes in its cell
Dominant allele	an allele that affects the phenotype of the organism whether present in the heterozygous or homozygous condition
Recessive allele	an allele that affects the phenotype of the organism only when the dominant allele is absent (i.e. the individual is homozygous recessive)
Codominant alleles	alleles that are both expressed if they are present together in a heterozygous person
Test cross	testing a suspected heterozygote by crossing it with a known homozygous recessive

Sex chromosomes

In humans, inheritance of sex is controlled by specific chromosomes known as the sex chromosomes. Each of us has one pair of **sex chromosomes** (either XX or XY chromosomes) along with the 22 other pairs. (These others are known as **autosomal chromosomes**.)

Female gametes produced by meiosis all carry an X chromosome, but half of male gametes carry an X chromosome and half carry a Y chromosome. At fertilisation, a female gamete may fuse with a male gamete carrying an X chromosome, which results in a female offspring. Alternatively, the female gamete may fuse with a male gamete carrying a Y chromosome, which results in a male offspring.

So, the sex of offspring in humans (and all mammals) is decided by which type of male gamete fuses with the female gamete – that is, by the male.

Note also that we would expect equal numbers of male and female offspring to be produced by a breeding population over time.

How human X and Y chromosomes control sex

Both male and female embryos develop identically in the uterus, initially. At the seventh week of pregnancy, however, if a Y chromosome is present in the embryonic cells a cascade of developmental events is triggered, leading to the growth of male sex organs.

On the Y chromosome is the prime male-determining gene. This gene codes for a protein – the **testis determining factor** (**TDF**). TDF functions as a molecular switch; on reaching the embryonic gonad tissues, TDF initiates the production of a relatively low level of testosterone. The effect of

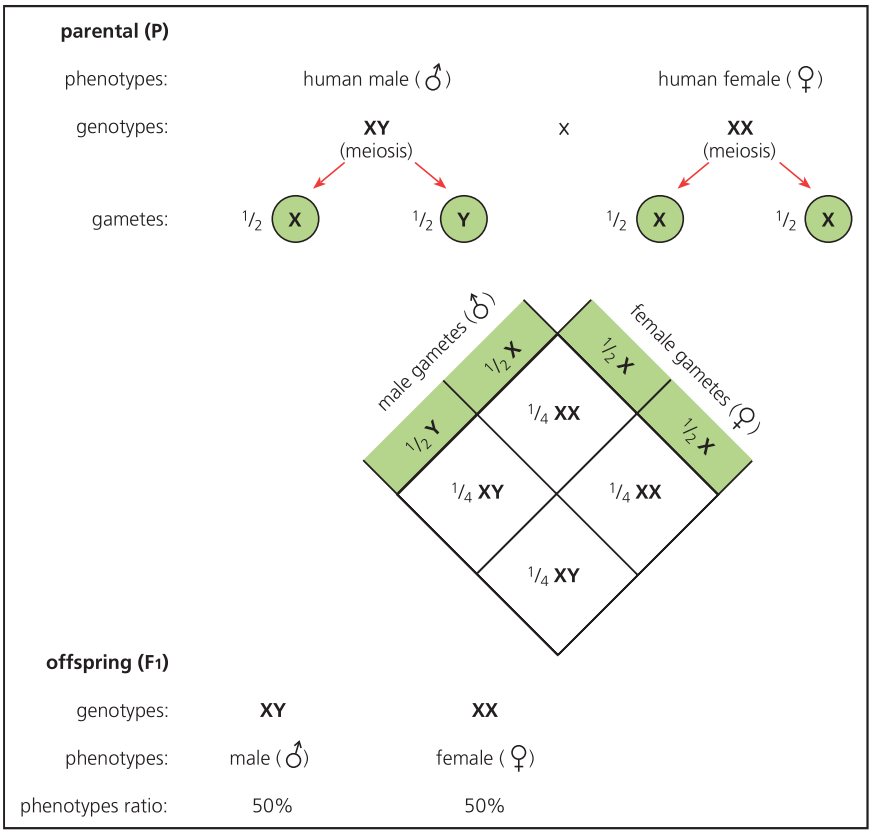


Figure 16.16 X and Y chromosomes and the determination of sex

this hormone at this stage is to inhibit the development of female sex organs and to cause the formation of the testes, scrotum and penis. In the absence of a Y chromosome an ovary develops. Then, partly under the influence of hormones from the ovary, the female reproductive structures develop.

Sex linkage

It is obvious that any gene present on the sex chromosomes is likely to be inherited with the sex of the individual. These genes are said to determine **sex-linked characteristics**. However, the inheritance of these sex-linked genes is different from the inheritance of genes on the other chromosomes present. This is because the X chromosome is much longer than the Y chromosome, so many of the genes on the X chromosome are absent from the Y chromosome. In a male (XY), an allele present on the X chromosome is most likely to be on its own and will be apparent in the phenotype **even if it is a recessive allele**.

Meanwhile, in a female, a single recessive gene is often masked by a dominant allele on the other X chromosome, and in these cases the recessive allele is not expressed. A human female can be homozygous or heterozygous with respect to sex-linked characteristics, whereas males will have only one allele.

'Carriers'

In a heterozygous individual with one dominant allele and one recessive allele of a gene, the recessive allele will not have an effect on their phenotype. The individual is known as a **carrier**. They 'carry' the allele but it is not expressed. It is masked by the presence of the dominant allele.

Consequently, female carriers are heterozygous for sex-linked recessive characteristics. In the case of a male (XY), the unpaired alleles of the X chromosome are all expressed. The alleles on the short Y chromosome are mostly concerned with male structures and male functions.

However, there are some recessive genetically-inherited conditions caused by recessive alleles on the X chromosome. Examples of these are Duchene muscular dystrophy, red–green colour blindness and haemophilia. Notice that these examples are **genetically-inherited conditions**.

The consequence of the presence of one of these alleles may be quite different for males and females. This is because, if a single recessive allele is present in a male human, the allele will be expressed. Meanwhile, a female must be homozygous recessive for a sex-linked characteristic for the allele to be expressed. A female who is heterozygous for one of these will be a 'carrier'. We can illustrate this point by looking at the inheritance of the conditions of red–green colour blindness and of haemophilia.

Red–green colour blindness

A person who is red–green colour blind sees the colours green, yellow, orange and red all as the same colour. The condition affects about 8 per cent of males, but only 0.4 per cent of females in the human population. This is because a female may be homozygous, with both alleles for normal development of cones in the retina ($X^B X^B$), or she may be heterozygous, with an allele for normal colour vision and a mutant allele for abnormal development of these cones ($X^B X^b$). For a female to be red–green colour blind, she must be homozygous recessive for this allele ($X^b X^b$) and this occurs extremely rarely. On the other hand a male with a single recessive allele for red–green colour blindness ($X^b Y$) will be affected.

The inheritance of red–green colour blindness is illustrated in Figure 16.17. It is helpful for those who are red–green colour blind to recognise their inherited condition. Red–green colour blindness is detected by the use of multicoloured test cards.

Question

9 **a** How is the genetic constitution of a female who is red–green colour blind represented?
b Explain why it is impossible to be a 'carrier' male.

Colour blindness is detected by multicoloured test cards. A mosaic of dots is arranged on the cards so that those with normal colour vision see a pattern that is not visible to those with colour blindness.

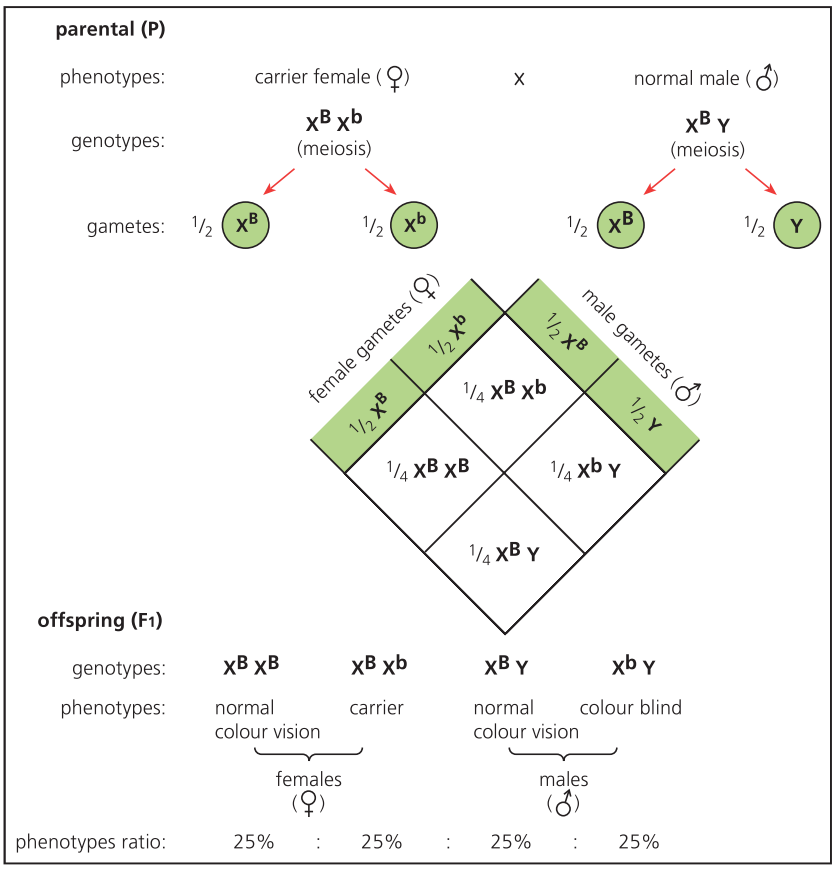


Figure 16.17 The detection and inheritance of red-green colour blindness

The dihybrid cross

Another early investigation by Mendel into the inheritance of variation involved **two pairs of contrasting characters**, again using the garden pea plant. This is now referred to as a **dihybrid cross**.

For example, pure-breeding pea plants from **round seeds** with **yellow cotyledons** (seed leaves) were crossed with pure-breeding plants from **wrinkled seeds** with **green cotyledons** (P generation). All the progeny (F_1 generation) had **round seeds with yellow cotyledons**.

When plants grown from these seeds were allowed to self-fertilise the following season, the resulting seeds (F_2 generation) – of which there were more than 500 to be classified and counted – were of four phenotypes and were present in the ratio shown in Table 16.3 and in Figure 16.18.

Table 16.3 Expected ratio of offspring from a dihybrid cross

Phenotype	round seed / yellow cotyledons	round seed / green cotyledons	wrinkled seed / yellow cotyledons	wrinkled seed / green cotyledons
Ratio	9	3	3	1

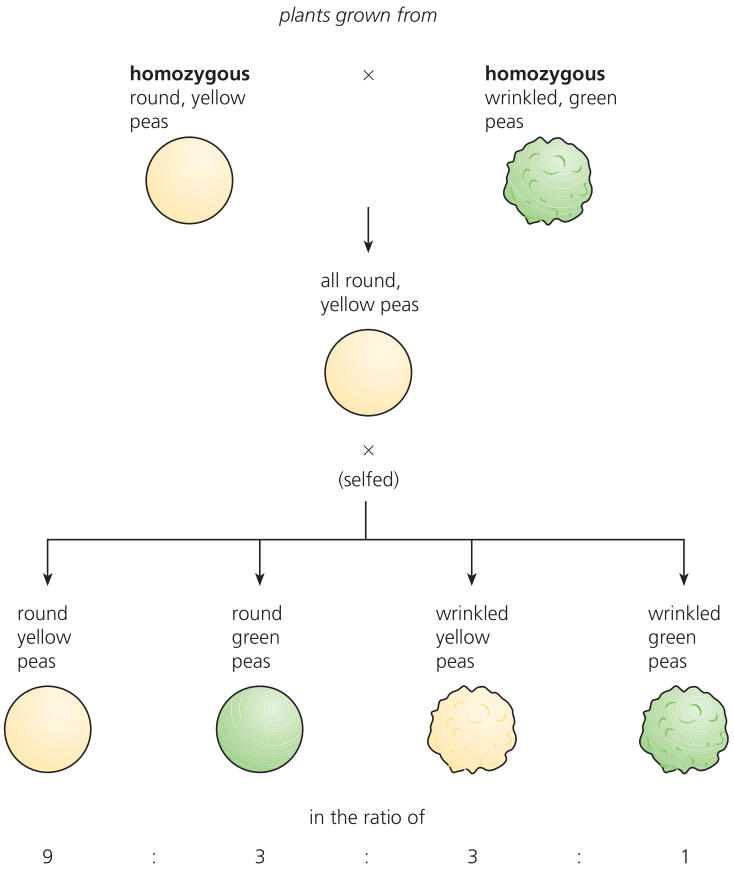


Figure 16.18 A dihybrid cross

It was noticed that two new combinations (**recombinations**), not represented in the parents, appeared in the progeny: either 'round' or 'wrinkled' seeds can occur with either 'green' or 'yellow' cotyledons.

Thus the two pairs of factors were inherited independently. That means either one of a pair of contrasting characters could be passed to the next generation. This tells us that a heterozygous plant must produce four types of gametes in equal numbers. This is explained in Figure 16.19.

From the dihybrid cross we can conclude a **Law of Independent Assortment**:

> During meiosis the separation of one pair of alleles is independent of the separation of another pair of alleles.

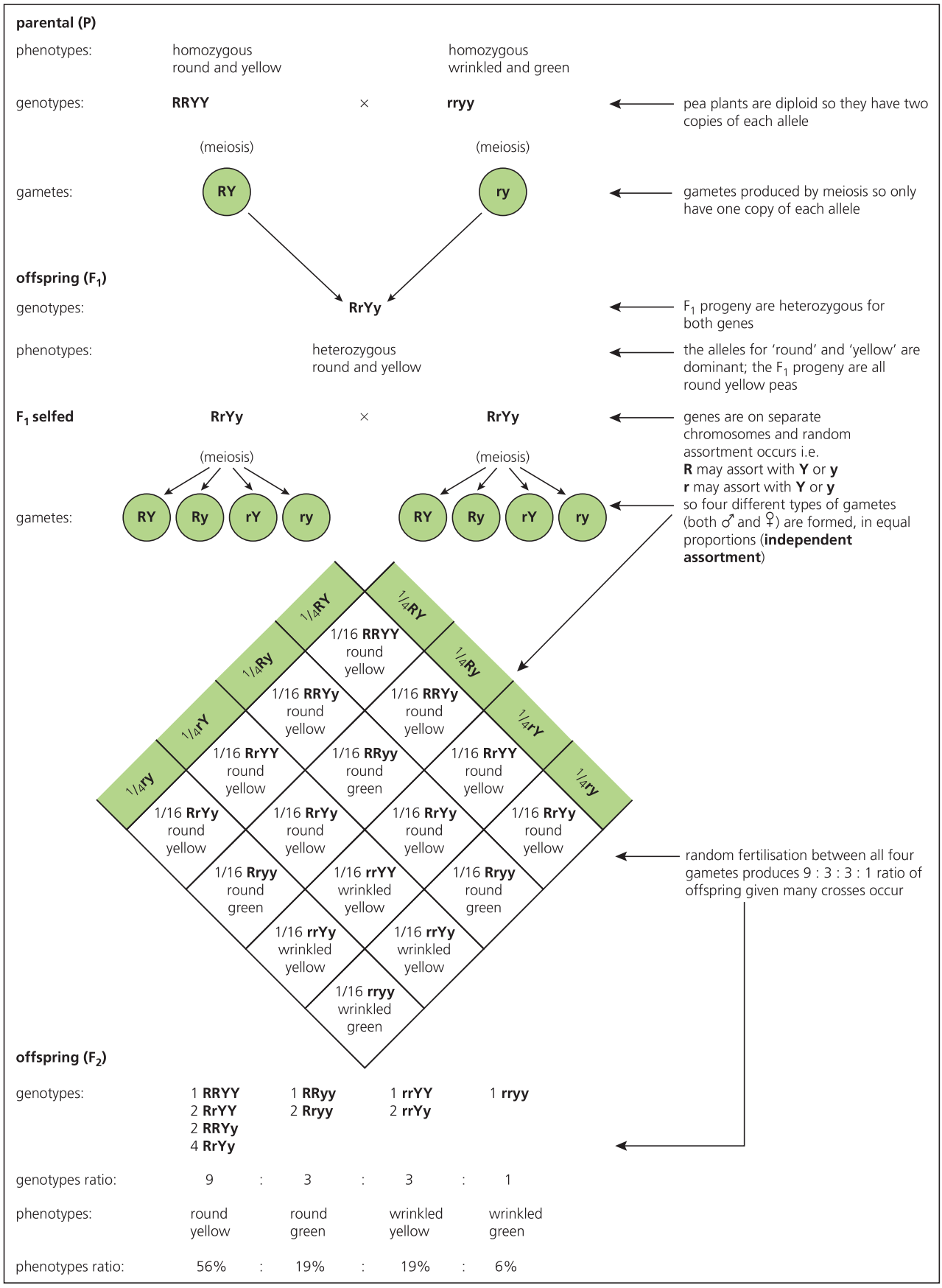


Figure 16.19 Genetic diagram showing the behaviour of alleles in the dihybrid cross

Questions

10 In Figure 16.19, identify the progeny that are recombinants.

11 When a tall, cut-leaved tomato plant and a dwarf, potato-leaved tomato plant were crossed all their progeny were tall and cut-leaved. These were subsequently crossed and the progeny of this second generation were in the ratio:

- tall and cut-leaved 9
- tall and potato-leaved 3
- dwarf and cut-leaved 3
- dwarf and potato-leaved 1

Draw a fully annotated genetic diagram to show genotypes of the parents and progeny.

12 In a breed of cocker spaniel black coat (**B** allele) is dominant to red coat (**b** allele) and solid pattern (**S** allele) is dominant to spotted pattern (**s** allele).

a What are the possible genotypes of a spaniel with a solid-patterned black coat?

b How could you find out the genotype of this animal?

The dihybrid test cross

Look back to page 350 to remind yourself of the issue the monohybrid test cross sorts out.

Why is a test cross sometimes necessary?

In the case of dihybrid inheritance, too, whilst homozygous recessive genotypes such as wrinkled green peas (**rryy**) can be recognised in the phenotype, homozygous round yellow peas (**RRYY**) and heterozygous round yellow peas (**RrYy**) look exactly the same (Figure 16.18). They can only be distinguished by the progeny they produce, as illustrated in a dihybrid test cross (Figure 16.20).

Unlike the monohybrid test cross where the outcome is a ratio of 1 : 1, in the dihybrid test cross the outcome is a ratio of 1 : 1 : 1 : 1.

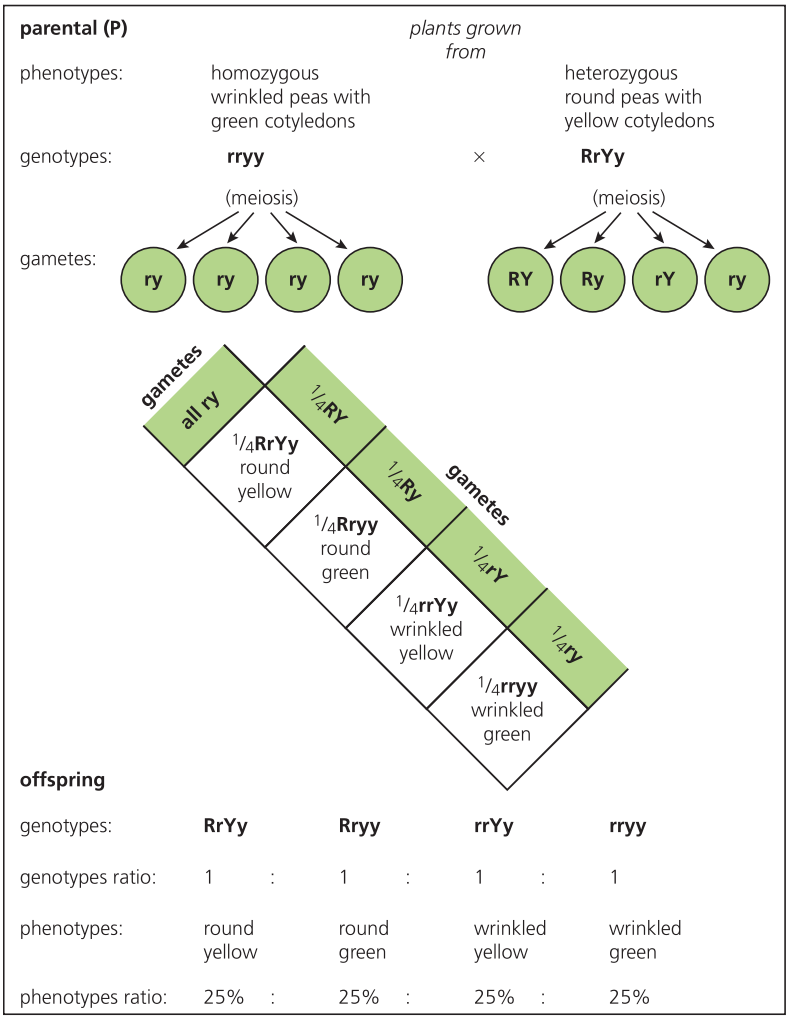


Figure 16.20 Genetic diagram showing the behaviour of alleles in the dihybrid test cross

Introducing *Drosophila*

The fruit fly (*Drosophila)* commonly occurs around rotting vegetable material. The most common form is often called the 'wild type', to differentiate it from the various naturally occurring mutant forms.

Drosophila has become a useful experimental animal in the study of genetics because:

- *Drosophila* has four pairs of chromosomes (Figure 16.21)
- from mating to emergence of adult flies (generation time) only takes about 14 weeks
- one female produces hundreds of offspring
- fruit flies are relatively easily handled, cultured on sterilised artificial medium in glass bottles and they can be temporarily anaesthetised for setting up cultures and sorting progeny.

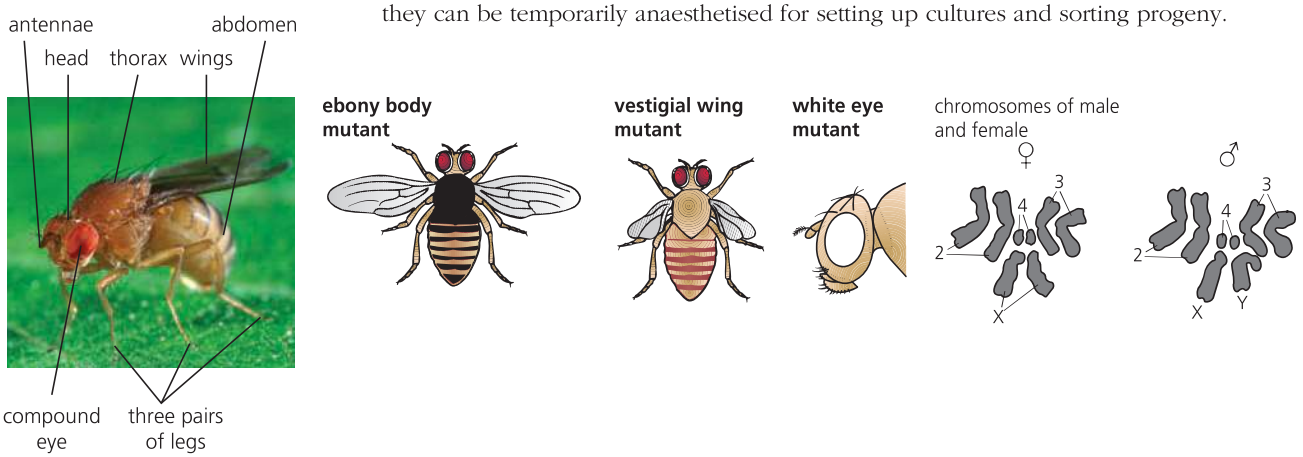


Figure 16.21 Wild type *Drosophila* and some common mutants

A dihybrid cross can be shown in *Drosophila,* for example by crossing normal flies (wild type) with flies homozygous for vestigial wings and ebony body (Figure 16.22). These characteristics are controlled by genes that are not on the sex chromosomes. The genes concerned in this *Drosophila* cross are on different autosomal chromosomes.

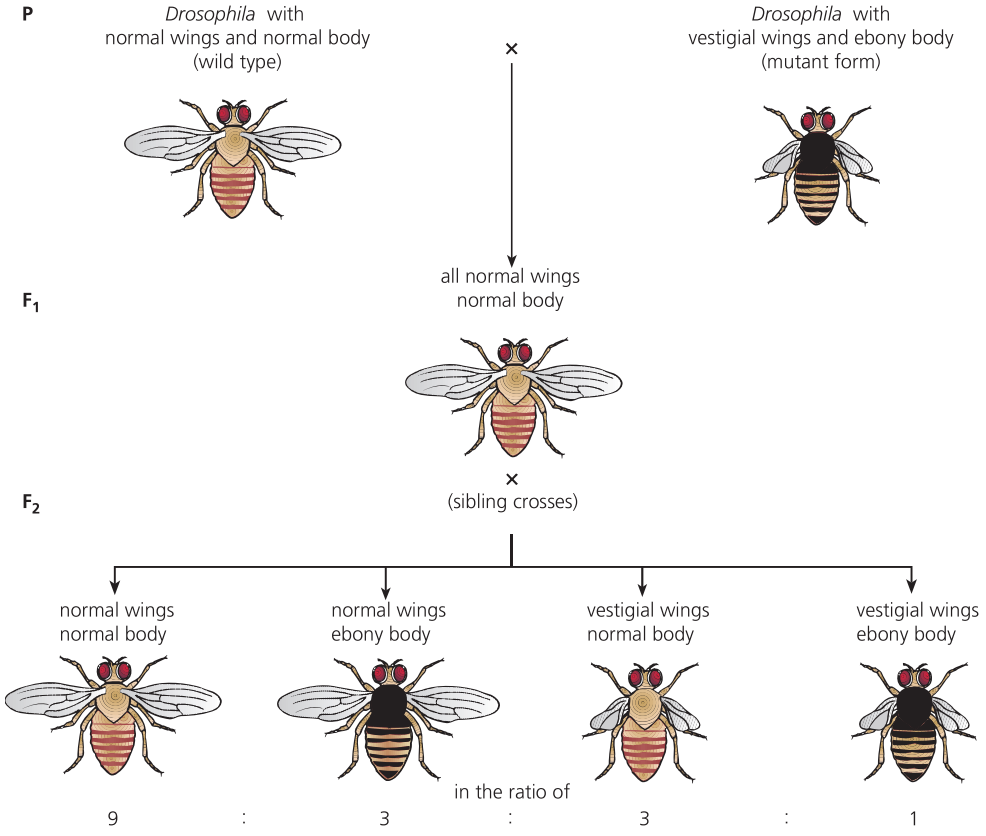


Figure 16.22 A dihybrid cross in *Drosophila*

Questions

13 Define what is meant by the term mutant organism (or cell).

14 **a** Construct a genetic diagram for the dihybrid cross shown in Figure 16.22, using the layout given in Figure 16.19.

b Determine the genotypes of the offspring of the F_2 generation.

c Identify which of these are recombinants.

Extension

Drosophila and the dihybrid cross

Mendel had died in 1884 – in relative obscurity, at least as far as the scientific community was concerned. Few seemed to know of his scientific work and those who were aware did not appear to understand his results. But his papers were rediscovered in 1900, as a result of careful literature searches by people keen to advance our understanding of inheritance. Mendel's results came to be confirmed and then extended by many others, using a range of species.

Drosophila melanogaster (the fruit fly) was first selected by an American geneticist called **Thomas Morgan** in 1908 as an experimental organism for the investigation of genetics in an animal. Morgan was awarded a Nobel Prize in 1933 because by his experiments he had:

- shown that Mendel's 'factors' are linear sequences of genes on chromosomes (what is now called the **Chromosome Theory of Inheritance**)
- discovered sex chromosomes and sex linkage
- demonstrated crossing over and the exchange of alleles between chromosomes resulting from chiasmata formed during meiosis.

Probability and chance in genetic crosses

We can see that there is an expected ratio of offspring of 9:3:3:1 when the dihybrid cross is carried out. Actually, the offspring produced in many dihybrid cross experiment do not *exactly* agree with the expected ratio. This is illustrated by the results of an experiment with mutant forms of *Drosophila* in Table 16.4.

Table 16.4 Observed and expected numbers of offspring from a dihybrid cross

Phenotypes in F_2 generation	normal wings, normal body	normal wings, ebony body	vestigial wings, normal body	vestigial wings, ebony body	Total numbers
Predicted ratio	9	3	3	1	
Expected numbers of offspring	313	104	104	35	556
Actual numbers of offspring	315	108	101	32	556

Clearly, these results are fairly close to the ratio of 9:3:3:1, but they are not exactly in the predicted ratio, precisely. *What, if anything, went 'wrong'?*

Well, we can expect this ratio among the progeny only if three conditions are met:

- fertilisation is entirely random
- there are equal opportunities for survival among the offspring
- very large numbers of offspring are produced.

In this experiment with *Drosophila*, the exact ratio may not have been obtained because, for example:

- more male flies of one type may have succeed in fertilising females than of the other type
- more females of one type may have died before reaching egg-laying condition than of the other type
- fewer eggs of one type may have completed their development than of the other types.

Similarly, in breeding experiments with plants such as the pea plant, exact ratios may not be obtained because of parasite damage or by the action of browsing predators on the anthers or ovaries in some flowers or because some pollen types fail to be transported by pollinating insects as successfully as others, perhaps.

The chi-squared test

Experimental geneticists are often in the situation of asking 'Do the observed values differ significantly from the expected outcome?' – for example, for the sort of reasons discussed above.

This question is resolved by a simple statistical test, known as the **chi-squared (χ^2) test**. This is used to estimate the probability that any difference between the observed results and the expected results is due to chance. If it is not due to chance, then there may be an entirely different explanation and the phenomenon would need further investigation.

The chi-squared statistic is calculated using this formula:

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

where:

O = observed result
E = expected result
(Σ means 'the sum of').

The chi-squared test applied

We can test whether the observed values obtained from the dihybrid cross between wild type (normal) *Drosophila* flies and flies homozygous for vestigial wings and ebony body (Table 16.5) differ significantly from the expected outcome.

First we calculate χ^2 (In this example, χ^2 is 0.47).

Table 16.5 χ^2 calculation

Category	Predicted ratio	Observed number, *O*	Expected number, *E*	$O - E$	$(O - E)^2$	$\chi^2 = \frac{\Sigma(O-E)^2}{E}$
normal wings, normal body	9	315	312.75	2.25	5.0625	0.016
normal wings, ebony body	3	108	104.25	3.75	14.0625	0.135
vestigial wings, normal body	3	101	104.25	−3.25	10.5625	0.101
vestigial wings, ebony body	1	32	34.75	−2.75	7.5625	0.218
Total		**556**	**556**			**0.470**

We now consult a table of the **distribution of χ^2** to find the **probability** of obtaining a deviation by chance alone as large as (or larger than) the one we have.

The table takes account of the number of independent comparisons involved in our test. Here there were four categories and therefore there were three comparisons made – we call this 'three **degrees of freedom (d.f.)**'.

Table 16.6 Table of χ^2 distribution

Degrees of freedom	Probability greater than:						
	0.99	**0.95**	**0.90**	**0.10**	**0.05**	**0.01**	**0.001**
d.f. = 1	0.0001	0.0039	0.0158	2.706	3.841	6.635	10.83
d.f. = 2	0.0201	0.103	0.211	4.605	5.991	9.210	13.82
d.f. = 3	0.115	0.352	0.584	6.251	**7.815**	11.345	16.27

Question

15 In the dihybrid test cross between homozygous dwarf pea plants with terminal flowers (ttaa) and heterozygous tall pea plants with axial flowers (TtAa), the progeny were:

- tall with axial flowers: 55
- tall with terminal flowers: 51
- dwarf with axial flowers: 49
- dwarf with terminal flowers: 53

Use the χ^2 test to determine whether or not the difference between these observed results and the expected results is significant.

The probability given by the table suggests that the differences between the results we expected and the outcome we observed is due to chance.

- If the value of χ^2 is **bigger** than the critical value highlighted (a probability of 0.05) then we can be at least 95 per cent confident that the difference between the observed and expected results is significant.
- If the value of χ^2 is **smaller** than the critical value highlighted (a probability of 0.05) then we can be confident that the differences between the observed and expected results are due to chance.

In biological experiments we take a **probability of 0.05 or larger** to indicate that the differences between observed (*O*) and expected (*E*) results are **not significant**. We can say they are due to chance.

In this example, the value (0.47) lies between a probability of 0.95 and 0.90. This means that a deviation of this size can be expected 90–95 per cent of the times the experiment is carried out. There is clearly no significant deviation between the observed (*O*) and the expected (*E*) results.

The chi-squared test is similarly applicable to the results of test crosses and monohybrid crosses. However, in any chi-squared test that does not confirm that the results conform to the anticipated result (i.e. if it gives us a value for χ^2 that is **bigger** than the critical value meaning that the **probability** of getting that result is **smaller** than 0.05), then we must reconsider our explanation of what is occurring. In this outcome, the statistical test gives no clue as to the actual position or behavior of the alleles concerned. Further genetic investigations are required.

Extension

How environment may affect the phenotype

If plants of a tall variety of pea are deprived of nutrients (nitrates and phosphates, for example) in the growing phase of development, full size may not be reached. A 'tall' plant may *appear* dwarf. The same occurs in humans who have been seriously and continuously underfed and malnourished as growing children.

Many characteristics of organisms are affected by both the environment and their genotype. In fact the **phenotype** is the product of **genotype and influences of the environment**.

A striking example of this occurs in the honey bee (*Apis mellifera*). In a colony of honey bees there are three phenotypes (**workers**, **drones** and **queen** – Figure 16.23), but only two genotypes. The drones are the community's males and they develop from unfertilised eggs (their genotype is haploid). The queen and the workers develop from fertilised eggs and have identical genotypes. The queen, who is a much larger organism, differs from her workers only by the diet she is fed in the larval stage (an environmental factor). Her protein-rich food is not given to the larvae that will be workers. This makes a significant difference in their phenotypes.

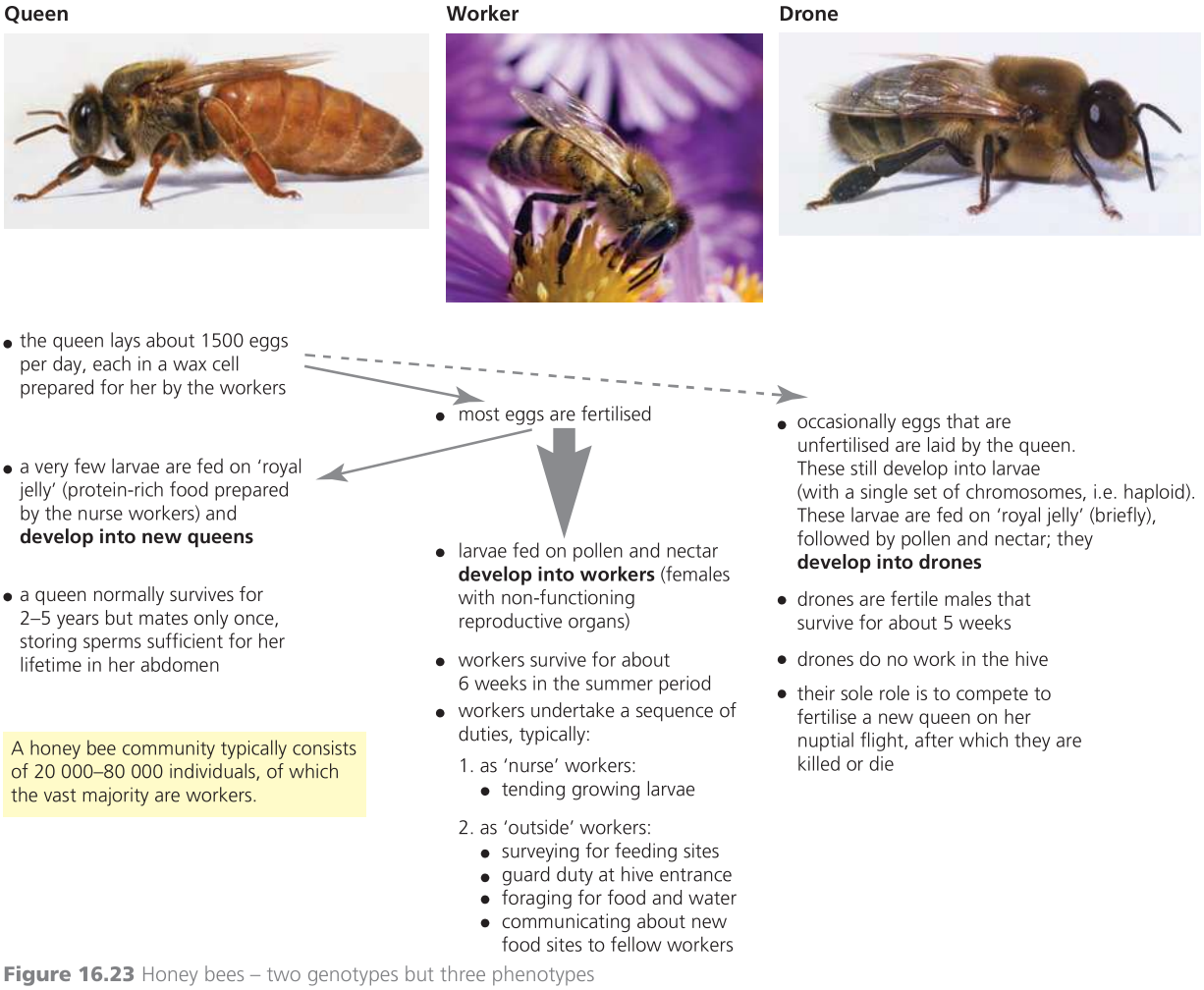


Figure 16.23 Honey bees – two genotypes but three phenotypes

16.2 *continued*... How mutations may affect the phenotype – studies in human genetics

Studies of human genetic conditions have revealed the links between genes, enzymes and the phenotype.

By the end of this section you should be able to:

e) explain that gene mutation occurs by substitution, deletion and insertion of base pairs in DNA and outline how such mutations may affect the phenotype
f) outline the effects of mutant alleles on the phenotype in the following human conditions: albinism, sickle cell anaemia, haemophilia and Huntington's disease
g) explain the relationship between genes, enzymes and phenotype with respect to the gene for tyrosinase that is involved with the production of melanin

How mutations may affect the phenotype

DNA can change. An abrupt change in the structure, arrangement or amount of DNA of chromosomes may result in a change in the characteristics of an organism (its phenotype) or of an individual cell. This is because the change, called a **mutation**, may result in the alteration or non-production of a cell protein (because of a change in the **messenger RNA** which codes for it, pages 124–5). This issue was introduced in Topic 6.

Gene mutations can occur spontaneously as a result of errors in normal cell processes such as DNA replication *but this is rare*. Alternatively, gene mutations can be caused by environmental agents we call **mutagens**. These can include ionising radiation in the form of X-rays, cosmic rays, and radiation from radioactive isotopes (alpha particles, beta particles and gamma rays). Any of these can cause breakage of the DNA molecule. Non-ionising mutagens include UV light and various chemicals, including carcinogens in tobacco smoke (tar compounds). These act by modifying the chemistry of the base pairs of DNA. The different ways this may happen are shown in Table 16.7.

Table 16.7 Different ways the base sequence in a gene may be altered

Change within the gene	Likely impact or effect
Base addition: one or more bases are **added** to a sequence e.g. GAG CCT GAG → GAG **T**CC TGA G	These bring about '**frame shifts**' in the code. (Look up which amino acids this sequence coded for originally in Figure 6.10, page 119. What does it code for now?) Often, the effect is to change the properties of the protein, particularly its tertiary structure (page 47) – or to cause no protein to be coded for at all.
Base deletion: one or more bases are **lost** from a sequence e.g. GAG **C**CT GAG → GAG CTG AG	
Base substitution: one or more bases are **substituted**: e.g. CCT G**A**G CCT → CCT G**T**G CCT	Many of the amino acids have two or more triplet codes, so a substitution may have no effect. Alternatively, a substitution may cause an alternative amino acid to be built into a protein, changing its tertiary structure and properties, as is the case in the sickle cell mutation in haemoglobin – see below.

Base substitution mutation and sickle cell anaemia

The smallest form of gene mutation occurs when one base is replaced by another – a **base substitution**. An example of this type of gene mutation is the cause of the human condition known as **sickle cell anaemia**. This was illustrated in Figure 6.17 (page 125). The gene that codes for the amino acid sequence of the beta chain of haemoglobin occurs on chromosome 11 and is prone to a substitution of the base adenine (A) by thymine (T) in a codon for the amino acid glutamic acid. As a consequence, the amino acid valine appears at that point, instead.

Turn back to pages 125–6 now and note the consequence of this substitution at the transcription and translation stages.

The effects on the properties of the haemoglobin molecule of this simple change of one amino acid residue for another within the whole haemoglobin molecule are dramatic. The molecules with this unusual haemoglobin (known as **haemoglobin Hb^s**) tend to clump together and form long fibres that distort the red blood cells into sickle shapes. In this condition they transport little oxygen and the sickle cells may even block smaller vessels. People who are heterozygous for the mutated allele (**Hb Hb^s**) have less than 50 per cent of the sickle-shaped red blood cells. The person is said to have **sickle cell trait** and they are only mildly anaemic. However, people who are homozygous for sickle-cell haemoglobin (**Hb^s Hb^s**) have a serious problem and are described as having **sickle cell anaemia**. Problems with the heart and kidneys are common in people affected with sickle cell anaemia.

We have already noted the potential advantage in having the sickle cell trait. Malaria is the most important of all insect-borne diseases (see Figure 10.7, page 197). The malarial pathogen *Plasmodium* completes its lifecycle in red blood cells, but it cannot do so in red blood cells containing the abnormal form of haemoglobin (**Hb^s**). People with sickle cell trait are protected to a significant extent. Where malaria is endemic in Africa, possession of one mutant allele (i.e. having sickle cell trait but *not sickle cell anaemia*) is advantageous.

Turn back to Figure 10.9 (page 199) now and note the correlations between the distributions of the sickle cell allele and of the distribution of malaria in Africa.

Question

16 Explain how the cause of sickle cell trait and sickle cell anaemia supports the concept of a gene as a linear sequence of bases.

The nucleotide sequence in DNA, the amino acid sequence in proteins and phenotype

We recognise that a person with sickle cell trait has a different phenotype from that of a person with normal haemoglobin. For example, the former has an improved chance of surviving malaria in regions where this disease is endemic.

We have just seen that sickle cell anaemia is due to the substitution of a single nucleotide in one codon of the gene for the protein in the beta chain of haemoglobin. So sickle cell anaemia is a case of a chance change in the nucleotide sequence in DNA affecting the amino acid sequence in a protein and the phenotype of the organism.

Investigating human genetics

Studying human inheritance by experimental crosses (by selecting parents, sibling crosses, and the production of large numbers of progeny) is out of the question. Instead we may investigate the pattern of inheritance of a particular characteristic by researching a family pedigree, where appropriate records of the ancestors exist. A human pedigree chart uses a set of rules. These are identified in Figure 16.24.

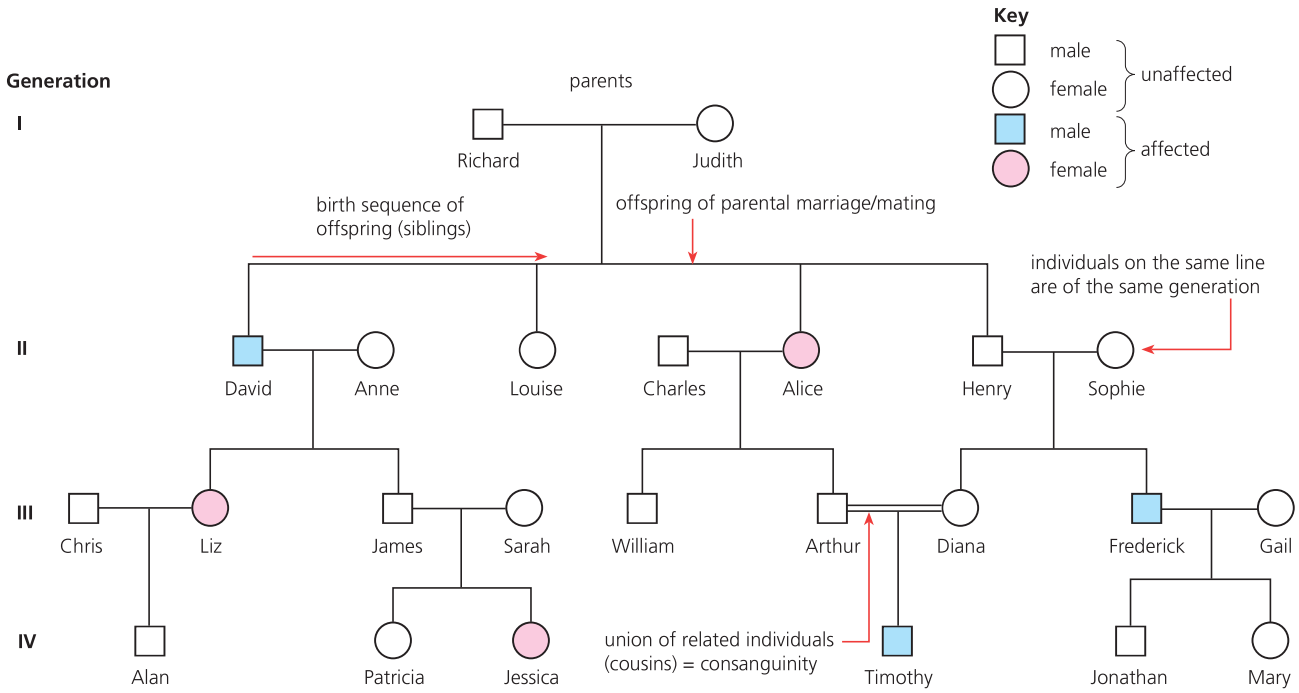


Figure 16.24 An example of a human pedigree chart

Questions

17 In the human pedigree chart in Figure 16.24:
- **a** who are the female grandchildren of Richard and Judith
- **b** who are Alan's
  - **i** grandparents
  - **ii** uncles
- **c** how many people in the chart have parents unknown to us
- **d** what are the names of two offspring who are cousins?

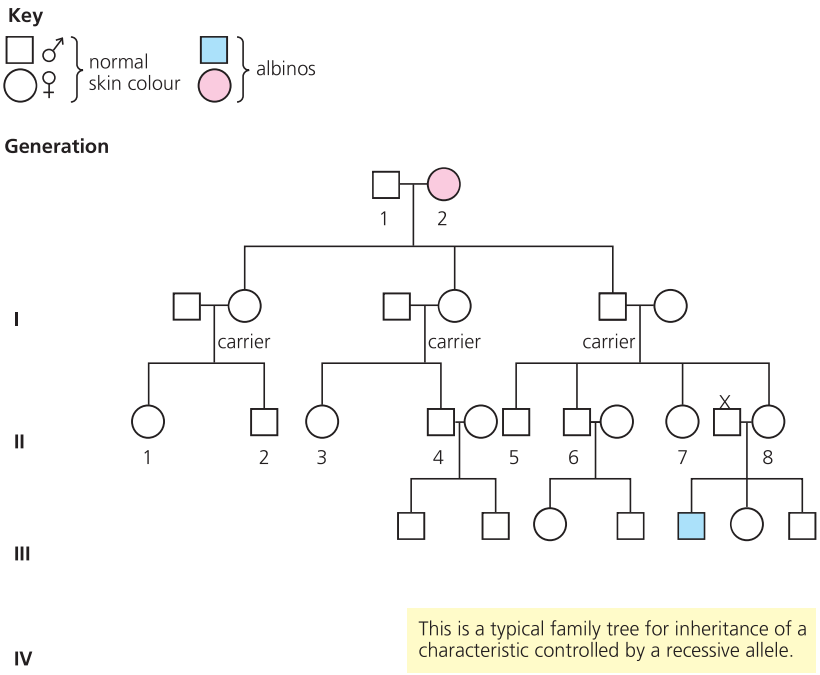
18 Explain why conditions controlled by a mutant, dominant allele are likely to appear in every subsequent generation, but characteristics due to a single recessive allele are likely to appear infrequently in the family pedigree chart.

We can use a pedigree chart to detect conditions likely to be due to dominant and recessive alleles. In the case of a characteristic due to a **dominant** allele, the characteristic tends to occur in one or more members of the family in every generation. On the other hand, a **recessive** characteristic is seen infrequently, often skipping many generations.

Albinism

Albinism is a rare inherited condition of humans (and other mammals) in which the individual has a block in the biochemical pathway by which the pigment melanin is formed. Albinos have white hair, very light coloured skin and pink eyes. Albinism shows a pattern of recessive monohybrid inheritance in humans (Figure 16.25). In the chart shown of a family with albino members, albinism occurs infrequently, skipping two generations altogether.

Albino people must be homozygous for the recessive allele (**pp**). People with normal skin pigmentation may be homozygous normal (**PP**) or carriers (**Pp**).



This is a typical family tree for inheritance of a characteristic controlled by a recessive allele.

Figure 16.25 Pedigree chart of a family with albino members

Biochemical basis of albinism – the relationship between gene, enzyme and phenotype

A mutation in the gene for the enzyme tyrosinase, in which glutamine is substituted for arginine at a particular locus, results in a defective gene that fails to code for the tyrosinase protein. As a consequence, active tyosinase and the pigment melanin are absent from pigment-forming cells in the body. This has evident impacts on the phenotype. The mutated allele is recessive, so the albino people are homozygous for the mutant allele.

Huntington's disease

Huntington's disease (HD) is due to an autosomal **dominant** allele on chromosome 4. The mutation takes the form of repeats of three nucleotides (CAG) between 36 and 120 times at a particular locus in the gene. The function of the gene, or rather of the protein it codes for, is unclear, but it appears to be active in the brain.

The disease is extremely rare (1 case per 20 000 live births). Affected individuals are almost certainly heterozygous for the mutant (defective) gene. Appearance of the symptoms is usually delayed until the age of 40–50 years, by which time the affected person – unaware of the presence of the disease – may have passed a copy of the dominant allele to one or more of his or her children. Any child of an affected person has a 50 per cent chance of inheriting the condition.

The disease takes the form of progressive mental deterioration, which is accompanied by involuntary muscle movements (twisting, grimacing and staring in 'fear'). A person with HD then loses all control of his or her mental and physical abilities, and death occurs within 10 years. The disease is named after the American doctor who first investigated the condition. There is no known treatment.

Haemophilia

In the circulatory system of a mammal, if an injury occurs there is a risk of uncontrolled bleeding. This is normally overcome by the **blood clotting mechanism** that causes any gap in a blood vessel to be plugged. Haemophilia is a rare genetically-determined condition in which the blood does not clot normally. The result is frequent, excessive bleeding.

There are two forms of haemophilia, known as haemophilia A and haemophilia B. They are due to a failure to produce adequate amounts of particular blood proteins essential to the complex blood clotting mechanism. Today, haemophilia is effectively treated by the administration of the clotting factor the patient lacks.

Haemophilia is a sex-linked condition because the genes controlling the production of the blood proteins concerned are located on the X chromosome. Haemophilia is caused by a recessive allele. As a result, haemophilia is largely a condition of the male, since in him a single X chromosome carrying the defective allele (X^hY) will result in disease. For a female to have haemophilia, she must be homozygous for the recessive gene (X^hX^h), but this condition is usually fatal *in utero*. It may result in a natural abortion.

A female with one X chromosome with the recessive allele and one with the dominant allele (X^HX^h) is a carrier. She has normal blood clotting but for any daughters she has with a normal male, there is a 50 per cent chance of them being carriers; for any sons there is a 50 per cent chance of them being haemophiliac (Figure 16.26).

Question

19 Haemophilia is sex-linked condition that results from the inheritance of an allele carried on the X chromosome. Explain why haemophilia is more common in males.

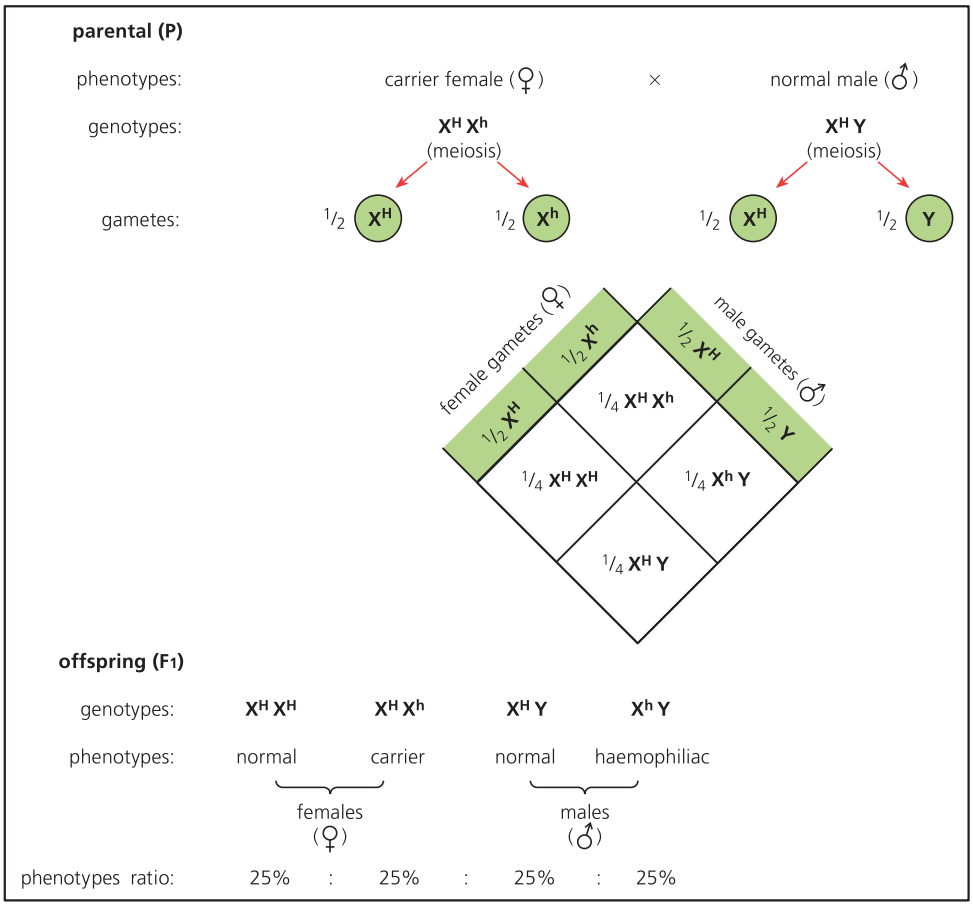


Figure 16.26 Genetic diagram showing the inheritance of haemophilia

16.3 Gene control

Some genes are transcribed all the time to produce constitutive proteins; others are only 'switched on' when their protein products are required.

By the end of this section you should be able to:

a) distinguish between structural and regulatory genes and between repressible and inducible enzymes
b) explain genetic control of protein production in a prokaryote using the lac operon
c) explain the function of transcription factors in gene expression in eukaryotes
d) explain how gibberellin activates genes by causing the breakdown of DELLA protein repressors, which normally inhibit factors that promote transcription

Regulation of gene expression

We have seen that chromosomes are effectively a linear series of genes. We define a gene as a specific region of a chromosome that is capable of determining or influencing the development of a specific characteristic of an organism. It is a specific length of the DNA double helix, hundreds or (more typically) thousands of base pairs long. Remember, every living cell carries a full complement of genes; this genetic complement constitutes the **genome** of the cell or organism.

Consequently, cells and organisms must regulate the particular genes that they express at any given time or stage of development. Unicellular organisms and multicellular organisms may continually switch on and switch off genes in response to signals from their external and internal environments. Whilst some genes are actively transcribed throughout the life of the cell, others are activated (we say they are '**expressed**') only at a particular stage in the life of the cell, or when the substance they act on (their substrate molecule) is present, for example. Very many of our genes have to be deliberately activated, as required. In a multicellular organism, every nucleus contains the coded information relating to the development and maintenance of all mature tissues and organs. For example, the genes concerned with development of the organism from the zygote are some of the first to be expressed, but most probably for a limited period only. So, both during development and later in the life of the organism, this genetic information is used selectively. Typically, less than 25 per cent of the protein-coding genes in human cells are expressed at any time. The expression of genes is related to when and where the proteins they code for are needed (Table 16.8).

Table 16.8 Gene regulation – some examples

When and why genes are expressed	
Expressed all the time	genes responsible for routine, continuous metabolic functions (for example, respiration), common to all cells, continuous throughout life
Expressed at a selected stage in cell or tissue development	as cells derived from stem cells are developing into muscle fibres or neurones, for example
Expressed only in the mature cell	genes responsible for antibody production in a mature plasma cell, after these have been cloned
Expressed on receipt of an internal or external signal	when a particular hormone signal, metabolic signal, or nerve impulse is received by the cell, such as the gene for insulin production in β cells in the islets of Langerhans

How is this regulation brought about?

Regulation of gene action is partly regulated by the genes themselves. Whilst the role of many genes is to code for specific enzymes or proteins required by working cells at some stage, others are different – their role is to regulate other genes. Consequently, we can recognise two categories of gene:

- **Structural genes** code for a structural protein, or an enzyme, or an RNA molecule not involved in regulation. They are required by cells to create or maintain the structure, or enable the functioning, of the cell or organism. They are transcribed into proteins.
- **Regulatory genes** are involved in controlling the expression of one or more genes. They may code for a protein or for an RNA molecule.

Genes are also regulated by 'signals' from the environment – typically from within the cell. These act on the enzymes or on the genes that code for them. Consequently, we can recognise two categories of enzymes:

- **Inducible enzymes** are produced under specific conditions, such as the presence of a particular substrate. This substance controls the expression of one or more genes, structural genes, involved in the metabolism of that substance. In the absence of the substrate, gene action is switched off.
- **Repressible enzymes** are generally produced continuously, but their production can be halted. They are formed unless a signal, such as an excess of product, turns their production off.

Case studies in gene regulation

1 Genetic control of protein production in a prokaryote, using the *lac* operon

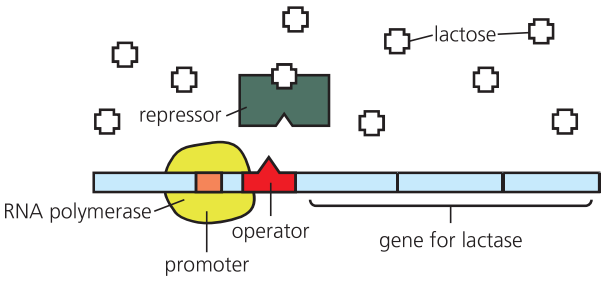
The *lac* operon (lactose operon) is a mechanism that ensures that the enzymes required for the metabolism of lactose are produced only in the presence of lactose. It has been observed in bacteria, such as ***E. coli***.

This mechanism involves a **repressor molecule** (coded for by a regulator gene), an **operator gene** situated close to the gene that is being regulated (a **structural gene**, in this case coding for the lactose metabolising enzyme), and a **promoter gene**. In the absence of lactose, the repressor binds to the operator and prevents transcription of the structural gene. However, if lactose is present, for example, when it becomes available in the medium in which the bacteria is growing, then the lactose molecule reacts with the regulator protein, preventing its binding with the operator gene. As a result, the lactose-metabolising gene is transcribed, and lactose is metabolised. Once all the lactose has been used up, the repressor molecule blocks transcription again. The mechanism is illustrated in Figure 16.27.

This type of mechanism occurs in prokaryotes (bacteria and cyanobacteria) only. In eukaryotes the regulator-gene mechanisms are more complicated

Figure 16.27 The lac operon and gene regulation

In the presence of the substrate lactose:



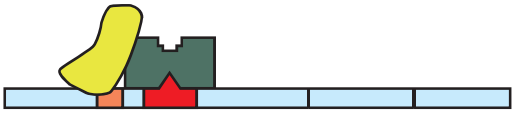
The gene is turned on.

1 Lactose has combined with the repressor and inhibited its action.

2 RNA polymerase has bound to the promoter and is about to express the structural gene for lactase. mRNA for lactase synthesis will be transcribed, and pass straight to ribosomes in the surrounding cytoplasm, where lactase is synthesised.

3 Eventually, all the lactose will have been metabolised, and the repressor will be free to bind to the operator again.

In the absence of the substrate lactose:



The gene is turned off.

1 There is no lactose to combine with the repressor.

2 The repressor binds with the operator.

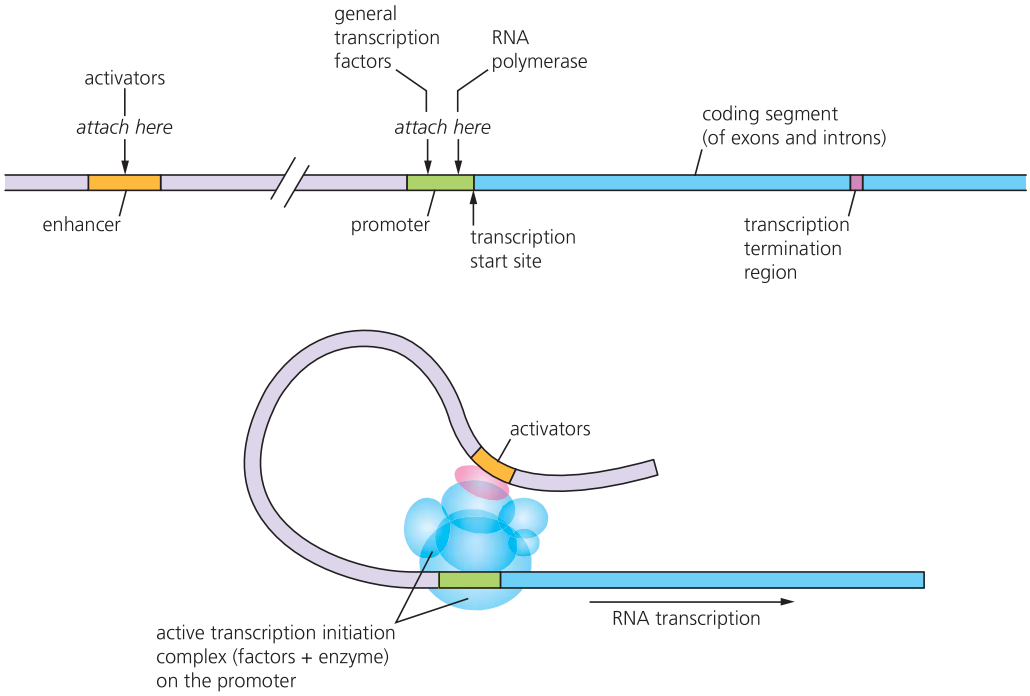
3 The RNA polymerase is obstructed from binding to the promoter.

2 Regulation in eukaryotes by enhancers and transcription factors

In eukaryotes, before mRNA can be transcribed by the enzyme RNA polymerase it first binds together with a small group of proteins called **general transcription factors** at a sequence of bases known as the **promoter**. Promoter regions occur on DNA strands just before the start of a gene's sequence of bases. (The promoter is an example of a length of non-coding DNA with a special function.) Only when this transcription complex of proteins (enzyme + factors) has been assembled can transcription of the template strand of the gene begin. Once transcription has been initiated, the RNA polymerase moves along the DNA, untwisting the helix as it goes, and exposing the DNA nucleotides so that RNA nucleotides can pair, and the messenger RNA strand be formed and peel way.

The rate of transcription may be increased (or decreased) by the binding of specific transition factors on the enhancer site for the gene. The position of an enhancer site of a gene is shown in Figure 16.28. This is at some distance 'upstream' of the promoter and gene sequence. However, when **activator** proteins bind to this enhancer site a new complex is formed and makes contact with the polymerase–transcription factor complex. Then the rate of gene expression is increased.

Regulator transcription factors, activators and RNA polymerase are all proteins, and are coded for by other genes. It is clear that protein-protein interactions play a key part in the initiation of transcription in eukaryotes.



The lower part of the figure shows a portion of the upper DNA molecule with the activator (orange) region, promotor (green) region and coding (blue) region. The DNA is looped so that it comes into contact with different parts of the transcription initiation complex. The complex consists of several proteins and other factors hence the multiple overlapping spheres (blue). The activator (pink) is also part of the complex. These spheres have been drawn transparent so that contact with the DNA molecule can be shown.

Figure 16.28 Control sites and the initiation of transcription

How gibberellin activates genes

Gibberellin (GA) regulates and promotes many aspects of plant growth and development (page 336). *Remind yourself of some of the roles of GA now.*

It is now known that a significant cause of restraint on many aspects of plant growth and development is the presence of a group of nucleus-based proteins called DELLA proteins. These proteins are coded for by specific regulatory genes, and they function in the nucleus itself as powerful transcription factors. How these proteins regulate transcription is poorly understood, but it has been shown that, when GA levels rise in a plant, DELLA proteins are deactivated and the plant grows. For example, GA has this effect as it triggers expression of genes coding for hydrolytic enzymes that convert starch stores to glucose in germinating seeds such as maize and barley (Figure 15.26, page 339).

The way that GA controls the levels of growth-repressing DELLA proteins is apparently by labelling them with a molecule known as ubiquitin. With this marker attached, a DELLA protein is identified and promptly destroyed by a nucleus-based complex, which has the role of degrading unneeded or damaged proteins present in the nucleus.

Summary

- Genetics is the study of **inheritance**. Many characteristics of organisms are controlled by the **genes** which occur as a linear series along **chromosomes**. **Diploid organisms** contain two copies of each gene in each of their cells. Alternative forms of a gene are called **alleles**. In sexual reproduction, **gametes** are formed containing one copy of each gene. Offspring formed from the **zygote** resulting from **fertilisation** receive two copies of each gene (two alleles), one from each parent.
- Meiosis is the reductive nuclear division in which, after cell division, the nucleus present in each of the four daughter cells formed has half the chromosome number of the parent cell, typically one of each type. Meiosis is associated with sexual reproduction and the production of gametes.
- Alleles may be **dominant** or **recessive** or show **codominance**. An organism with two identical alleles of a gene is **homozygous** for that gene; an organism with different alleles of a gene is **heterozygous**. The genetic constitution of an organism is its genotype. The resulting appearance of the organism, its visible and measurable features, is called its **phenotype**.
- In a **monohybrid cross** the inheritance of a contrasting characteristic controlled by a single gene (such as tall and dwarf height in garden pea plants) is investigated. When parents homozygous for a contrasting characteristic are crossed, the first generation (F_1) will be heterozygous The characteristic they show, such as 'tall' in the pea, will establish that the allele for 'tall' is **dominant** over the allele for 'dwarf', which is **recessive**. When the F_1 generation self-fertilise (or sibling crosses are made in animals), a recessive characteristic re-emerges in a minority of the offspring, in the ration of 3 : 1 (provided many offspring are produced). This shows that only one allele of a gene is carried in a single gamete.
- Since the genotype of an organism showing dominant characteristics may be homozygous or heterozygous for the gene concerned, the genotype of this organism must be determined by a **test cross** with an organism that is homozygous recessive for the characteristic. In the monohybrid test cross the outcome is a ratio of 1 : 1 and in the dihybrid test cross the outcome is a ratio of 1 : 1 : 1 : 1.
- Sex is determined in humans by the **sex chromosomes**: XX in the female and XY in the male. The X chromosome is longer than the Y and has genes not present on the Y chromosome. In the male, recessive alleles on the single X chromosome cannot be masked as they often are by dominant alleles in the female. Consequently, a number of rare **recessive conditions** are sex-linked and occur more frequently in males. These include red–green colour blindness, haemophilia and Duchenne muscular dystrophy.
- Exceptions to the monohybrid ratio arise from alleles which are **codominant** (rather than there being one dominant and one recessive allele). In addition, the existence of more than two alleles for a gene, known as **multiple alleles**, complicates inheritance. The human ABO blood group is an example of the latter. It is determined by two of three possible alleles which gives four possible phenotypes, blood groups A, B, AB and O.
- A **dihybrid cross** concerns the inheritance of two pairs of contrasting characteristics located on different chromosomes. The results confirm that each allele of a gene is equally likely to be inherited with each allele of another gene, a reflection of the **independent assortment** of chromosomes that occurs in meiosis.
- The **environmental conditions** experienced by an organism may also influence the expression of alleles. A genetically tall organism deprived of sufficient nutrients and so develops a phenotype that is short is an obvious example. Characteristics influenced by the environment may show a degree of continuous variation.
- **Mutations** may also affect the phenotype. When the nucleotide sequence in the DNA of a chromosome is changed it may lead to alteration in the amino acid sequence of proteins formed in the cell. The consequence may be a different phenotype.
- Some genes are transcribed all the time, whilst others are only switched on when their products are required. **Regulatory genes** control the timing of the expression of other genes whose roles are to create and maintain the structure or functions of the cell or organism.

Examination style questions

1 Colour blindness is a condition characterised by the inability of the brain to perceive certain colours accurately.

- The most common form is termed red–green colour blindness (RGC).
- RGC results from a recessive allele.
- 0.6% of females worldwide have RGC.
- 8.0% of males worldwide have RGC.

Fig. 1.1 shows the occurrence of RGC in one family.

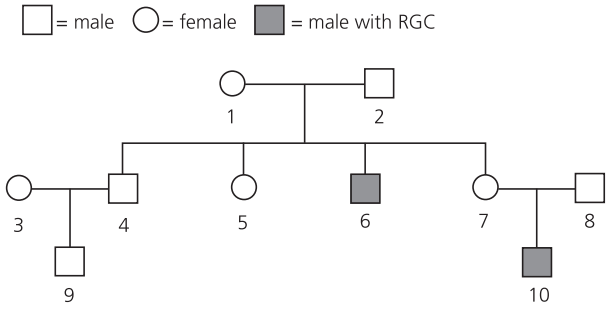


Fig. 1.1

a) Explain the meaning of the terms *allele* and *recessive*. [2]

b) Explain why females are less likely than males to have RGC. [2]

c) With reference to Fig. 6.1, and using the symbols **R** for the dominant allele and **r** for the recessive allele, state the genotypes of the individuals **1**, **4**, **6** and **7**. [4]

[Total: 8]

(Cambridge International AS and A Level Biology 9700, Paper 04 Q6 June 2008)

2 In mice there are several alleles of the gene that controls the intensity of pigmentation of the fur.

The alleles are listed below in order of dominance with **C** as the most dominant.

C = full colour

C^{ch} = chinchilla

Ch = himalayan

C^{p} = platinum

C^{a} = albino

The gene for eye colour has two alleles. The allele for black eyes, **B**, is dominant, while the allele for red eyes, **b**, is recessive.

A mouse with full colour and black eyes was crossed with a himalayan mouse with black eyes. One of the offspring was albino with red eyes.

Using the symbols above, draw a genetic diagram to show the genotypes and phenotypes of the offspring of this cross.

[Total: 6]

(Cambridge International AS and A Level Biology 9700, Paper 04 Q8 November 2008)

3 **a)** Explain what is meant by a gene mutation due to base substitution. [4]

b) In the inheritance of sickle cell anaemia, the normal allele is represented by **Hb** and the sickle cell allele by $\mathbf{Hb^S}$. Draw and complete a genetic diagram to explain the genotypes and phenotypes and the proportions of each resulting from a cross between two individuals of genotype **Hb** $\mathbf{Hb^S}$. [8]

c) A study of a local population in a central African country found that in a sample of 12 5000 people:

9449 were homozygous for normal haemoglobin (**Hb Hb**)

3020 had sickle cell trait (**Hb** $\mathbf{Hb^S}$)

31 had sickle cell anaemia ($\mathbf{Hb^S}$ $\mathbf{Hb^S}$)

Comment on the distribution of the sickle cell allele within this population, and on any environmental factors that may influence it. [8]

[Total: 20]

4 **a)** List four differences between the processes of mitosis and meiosis, and state briefly the significance of each. [8]

b) Where would you expect (i) mitosis and (ii) meiosis to occur in a fully grown flowering plant? [2]

c) For a cell with two chromosomes draw diagrams to show:

i) metaphase of mitosis

ii) metaphase I of meiosis

iii) prophase II of meiosis

iv) metaphase II of meiosis [4]

d) Define the term 'phenotype' and explain with reference to an example, how the environment may affect phenotype. [4]

[Total: 18]