Chapter 21
Mutations

Unit
2B

Unit content

Inheritance
Changes in DNA (mutations) are caused by a variety of factors. Mutations affect cellular and body functions.

Mutations:

- causes of mutations
- changes in the DNA sequence
- conditions caused by mutations including somatic *e.g. cancer* and germ line *e.g. PKU*
- chromosomal mutations including analysis of karyotypes.

Variation and evolution
The changing environment influences survival of genetic variations.

Variations and the environment:

- new variations due to mutations may be advantageous or disadvantageous to survival
- differential survival of genotypes/ phenotypes *e.g. lethal recessives.*

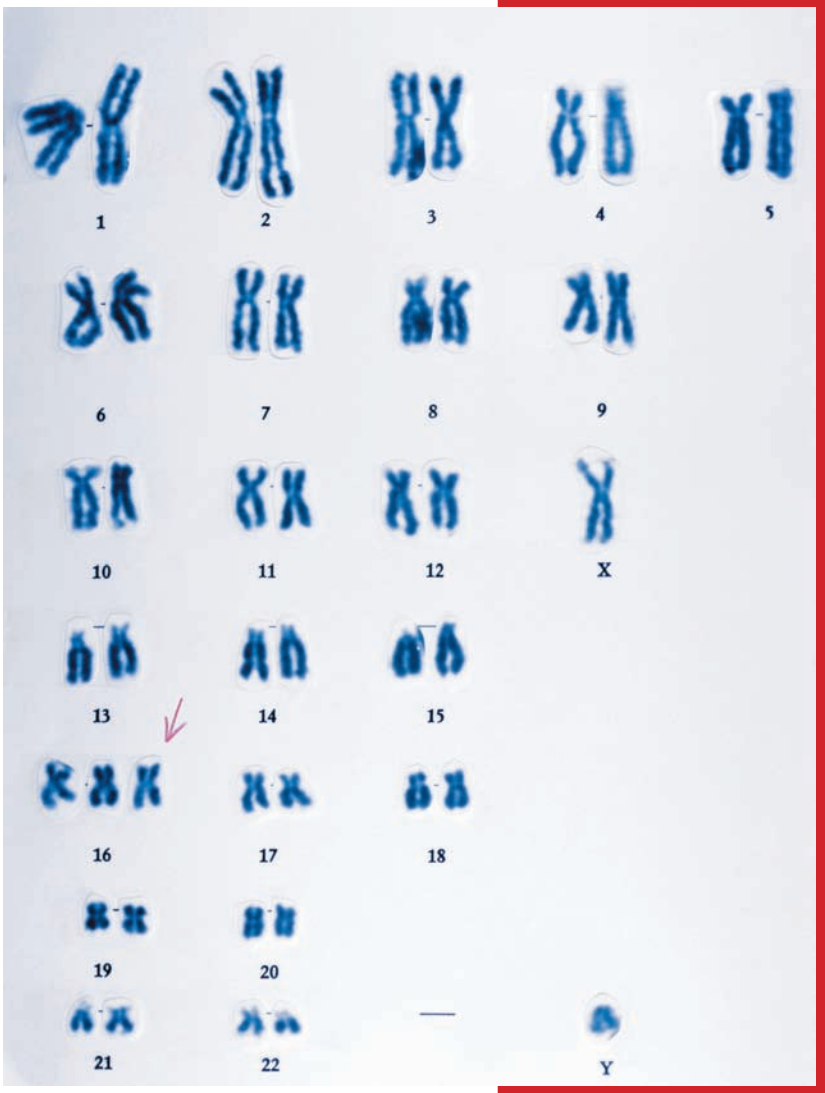


Figure 21.1
A karyotype of trisomy 16. The extra chromosome is indicated by an arrow

Offspring may show variations that do not resemble either parent and have never occurred before in the history of the family. These may occur quite suddenly and purely by chance. Characteristics occurring like this are referred to as **mutations**. Not all mutations are harmful, but many are. An organism with a characteristic resulting from a mutation is called a **mutant**. There are two main types of mutations: **gene mutations**, which are changes in a single gene so that the traits normally produced by that gene are changed or destroyed; and **chromosomal mutations**, in which all or part of a chromosome is affected.

Gene mutations occur during the replication of the DNA molecule before cell division (see Chapter 5). DNA is the molecule in the cells of all living things that contains the genetic information that determines the characteristics of the organism (see Chapter 17). It is a complex molecule and any subtle alteration in the DNA structure can produce changes in the usual characteristics of the species. If a mistake occurs when the DNA molecule is copied, the change may have significant effects on the characteristics of the organism.

When a cell divides, the genetic information is normally passed on correctly. If a mistake has occurred it will be faithfully copied each time the DNA molecule replicates, so the mutation may be passed on from generation to generation.

However, there are relatively few mutations in human populations when the millions of cell divisions that occur are taken into consideration. Those that do occur sometimes result in traits better suited to a particular environment, and so may contribute to human survival.

Mutagens

Mutations occur without any known cause but a number of agents are known to increase the rate at which they occur. These are called **mutagenic agents** or **mutagens**. Mutagens are different from teratogenic agents (see Chapter 15) in that they do not necessarily cause defects: they increase the rate at which mutations take place. Some known mutagens are mustard gas, formaldehyde, sulfur dioxide and some antibiotics. Ionising radiation of all kinds—including ultraviolet light, X-rays, cosmic rays, radiation from radioactive waste and the fallout from atomic and nuclear explosions—is also mutagenic. If a woman is treated with large doses of X-rays during the first three months of her pregnancy, the child may be born with mental retardation, skeletal malformations, or a small head in relation to the rest of its body. For this reason, doctors try to avoid using X-rays early in pregnancy.

Somatic and germline mutations

Mutations can occur in the body cells or in the reproductive cells of a person. The first case, where the body cells, or somatic cells, are involved is known as a **somatic mutation**. Only the individual with the somatic mutation is affected. Each time the mutant body cell divides the mutation is passed on to the daughter cells. The reproductive cells are not affected and once the individual dies, the mutation is lost. Somatic mutations are involved in many cancerous growths that may be a result of a mutagenic agent.

If the reproductive cells are affected the mutation can occur in the gametes and may then be passed on to the next and subsequent generations. These are known as **germinal** or **germline mutations**. In this case the individual in whom the mutation occurs is not usually affected. However, that individual produces gametes with changed DNA. If conception occurs involving one of the affected gametes, the embryo is often naturally aborted early in the pregnancy. However, diseases such as **phenylketonuria (PKU)**

can arise through a mutation during the formation of gametes and can be passed on to an offspring (see Chapter 19).

It is also important to realise that not all mutations are harmful. Some may have little effect and some may have definite advantages for the individual.

Effects of mutations

Gene mutations

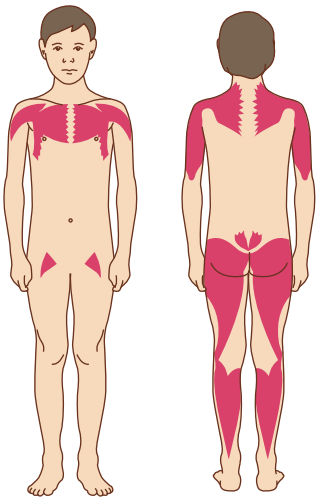
DNA is composed of a double helix, each side of which is a long string of four types of nucleotides (see Fig. 17.4 on page 231). Each nucleotide possesses identical sugar–phosphate groups that contribute to the DNA framework but differs in the base that links the two frameworks. Within genes, the sequence of the bases in the DNA is the code for the amino acids used to build a protein. Each group of three bases is the code for an amino acid.

When it was recognised that the genetic information was contained in the sequence of bases in the DNA, it became possible to understand the chemical nature of gene mutations. A change in just one base, known as a **point mutation**, could alter a protein, have no effect at all, or prevent the protein from being produced. Thus if the DNA of a particular gene is altered, the protein for which it codes may be missing or abnormal. Just one missing or abnormal protein can have an enormous effect on the entire body. Albinism, for instance, is the result of one missing protein. **Albinism** is marked by an absence of pigment from the hair, skin, and eyes (Fig. 21.2). The hair of an albino tends to be whitish blond, the skin extremely pale, and the eyes pinkish.

Another condition that may occur through gene mutation is the **Duchenne form of muscular dystrophy** (Fig. 21.3). This may arise through a mutation in the mother, which can then be inherited by her sons. The mutation may also occur in a male zygote so that the child develops the disease. This disease results in a wasting of the leg muscles and later the arms, shoulders and chest. Duchenne muscular dystrophy usually becomes apparent around the age of 3 to 5 years, when muscle weakness becomes evident. Young boys may stumble easily and have difficulty in climbing. To stand up they frequently have to push their hands down on their legs. As an affected boy gets older muscle tissue is increasingly replaced by fatty substances. By around 12 to 14 years of age the child is unable to walk and later becomes bedridden. Eventually death occurs due to failure of the respiratory muscles. Boys with the Duchenne form of muscular dystrophy are unlikely to live for more than 20 to 25 years.

Figure 21.2 A group of people with albinism

Figure 21.3 The muscles that are affected by Duchenne muscular dystrophy



Cystic fibrosis is another genetically determined disease caused by a mutation. The mutation occurs in a huge gene on chromosome number 7. The gene has the code for 1480 amino acids that make up a protein that regulates the passage of chloride ions across the cell membrane. Without the correct protein the affected person suffers from a variety of symptoms: salty-tasting skin; persistent coughing, wheezing or pneumonia; digestive and other problems. The mutant allele is recessive so to suffer from cystic fibrosis a person must inherit the mutant allele from both parents.

EXTENSION

Recombinant DNA technology is used to take genes from one organism and place them into the chromosomes of another. It could be used for the benefit of patients suffering from cystic fibrosis, rheumatoid arthritis and certain cancers. The same technology can be used to identify mutations and to determine whether people are affected by, or are carriers for, hereditary diseases.

Find out:

- the genetic disorders that recombinant DNA technology can be used to detect
- the procedure used in such diagnosis
- how a segment of DNA can be isolated from one organism and transferred to another.

Lethal recessives

Most gene mutations produce a recessive allele because they prevent the gene from producing a protein that will be able to function in the body. A person could therefore have large numbers of mutations in the genes and be totally unaware of them. If the person reproduced with a partner who had the same recessive mutation the recessive condition could appear in their offspring. This is what happens when couples unexpectedly have a child with cystic fibrosis.

Some recessive mutations are lethal if they are not masked by a dominant normal allele. These **lethal recessives** cause the death of the embryo or foetus (a miscarriage or spontaneous abortion) or the early death of the child.

In Chapter 18 **Tay-Sachs disease (TSD)** was described. TSD is a disorder of lipid metabolism that is inherited in an autosomal recessive pattern. It occurs most frequently in individuals of Jewish descent from eastern Europe (the Ashkenazi Jewish population). This is a lethal recessive condition as the missing enzyme results in the accumulation of a fatty substance in the nervous system. A baby with two recessive alleles for TSD develops normally for the first few months, and then deterioration causing mental and physical disabilities begins. Death usually occurs in early childhood.

Chromosomal mutations

Chromosomal mutations involve all or part of a chromosome and therefore affect not just one but a number of genes. Types of chromosomal mutations are:

- deletions—the loss of part of a chromosome
- duplications—where a section of chromosome occurs twice. This may happen if part of a chromatid breaks off and joins on to the wrong chromatid

- inversions—where breaks occur in a chromosome and the broken piece joins back in, but the wrong way around. This changes the order of genes on the chromosome and it may disrupt the pairing of homologous chromosomes during meiosis
- translocations—where part of a chromosome breaks off and is re-joined to the wrong chromosome
- non-disjunctions—where, during meiosis, a chromosome pair does not separate so that one daughter cell has an extra chromosome and one daughter cell has one less than the normal number (see also Chapter 20). These are sometimes not referred to as mutations but as **aneuploidy**—a change in the chromosome number.

Chromosomal mutations cause abnormalities so severe that miscarriage often occurs early in the pregnancy.

A chromosomal mutation that occurs relatively frequently, especially in children of older mothers, is **Down syndrome**, or **trisomy 21** (see Figs 20.5 and 20.6 on page 273).

Trisomy is a result of non-disjunction occurring during the formation of an egg or sperm cell resulting in it having an extra chromosome. In the case of Down syndrome, the affected gamete will have an extra chromosome 21. When this gamete contributes the extra chromosome 21 to the embryo, trisomy 21 results.

Many of the symptoms of Down syndrome can also occur when part of an extra copy of chromosome 21 is attached to one of the other chromosomes. This is called partial trisomy and was discussed in Chapter 20.

Trisomy also occurs with other human chromosomes. **Patau syndrome** is when an extra chromosome 13 produces individuals with mental retardation, a small head, an extra finger on each hand, a cleft palate and/or cleft lip, and malformations of the ears and eyes. The extra chromosome 13 can come from either the mother's egg cell or the father's sperm cell. The features of trisomy 13 result from having this extra chromosome in each of the body's cells. Trisomy 13 occurs in about 1 out of every 5000 live births. However, more than 80% of children with trisomy 13 die within a month of birth.

Trisomy 16 (see Figure 21.1) is the most common trisomy in humans, occurring in more than 1% of pregnancies.

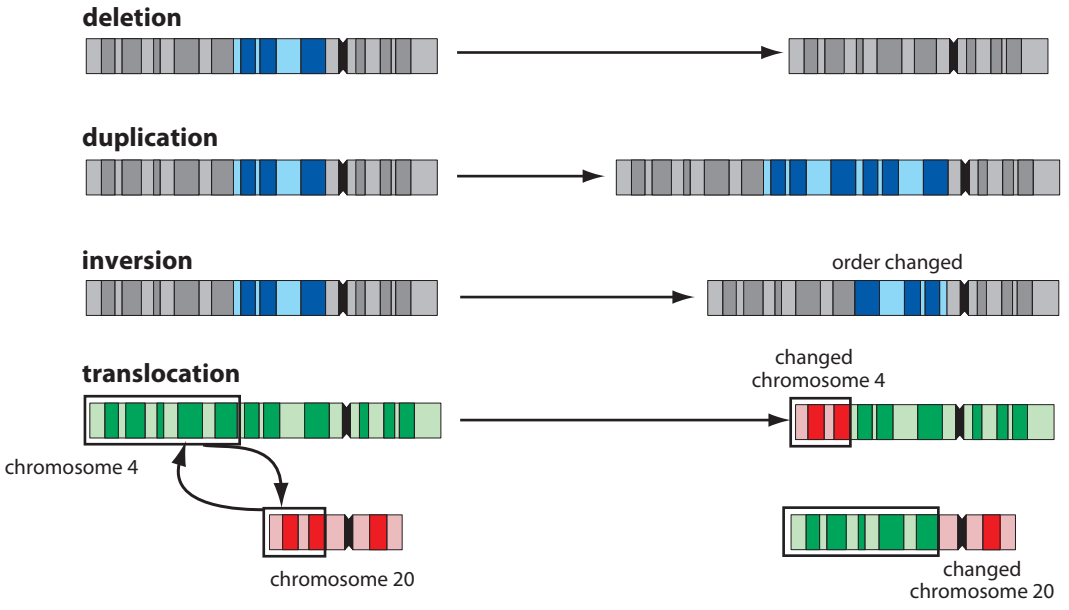


Figure 21.4 Types of chromosome mutation

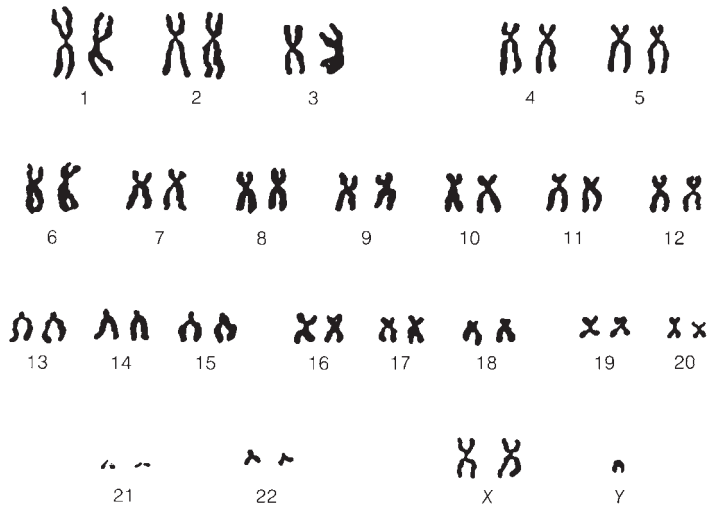


Figure 21.5 Karyotype for Klinefelter's syndrome

This condition also usually results in spontaneous miscarriage in the first three months of pregnancy.

Trisomy can also occur with the sex chromosomes. In males, non-disjunction may occur during either the first or the second meiotic division, producing individuals with either an extra *X* chromosome (*XXY*) or an extra *Y* chromosome (*XYY*). Individuals with trisomy *XXY* are normal as boys but develop **Klinefelter's syndrome** as adults (Fig. 21.5). They have small testes that do not produce sperm, the breasts are enlarged and body hair is sparse. Occasionally, the individual is mentally retarded.

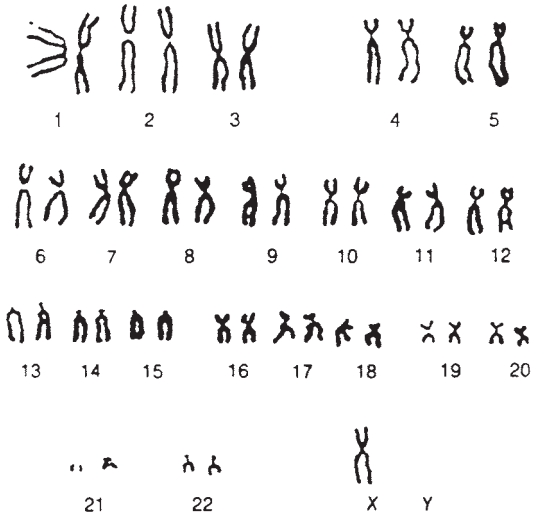
EXTENSION

Western Australia has been a world leader in the application of carrier detection to reduce the incidence of Duchenne muscular dystrophy.

Find out:

- what carrier detection involves
- what takes place following the detection of a carrier
- what is preventing the complete elimination of Duchenne muscular dystrophy.

Figure 21.6 Karyotype for Turner's syndrome



Monosomy is where an individual is missing a chromosome—they have only one copy instead of the normal two. If an autosome is completely missing, monosomy usually results in severe malformations and miscarriage. If only part of a chromosome is missing it is referred to as **partial monosomy**. Part of the chromosome has two copies, but part has only one copy. An example of partial monosomy is **Cri du chat syndrome** (from the French for 'cry of the cat'), a rare genetic disorder due to a missing portion of chromosome 5. The syndrome gets its name from the characteristic cry of infants born with the disorder. The infant sounds just like a meowing kitten, due to problems with the larynx and nervous system. This cry identifies the syndrome. About one third of children lose the cry by age 2. Other symptoms of cri-du-chat syndrome may include feeding problems because of difficulty swallowing and sucking, low birth weight and poor growth, and unusual facial features which may change over time.

Monosomy can also occur with the sex chromosomes. Individuals with a chromosome set with only one *X* chromosome (**monosomy *X***) suffer from **Turner's syndrome** (Fig. 21.6). These females are short in stature, lack secondary sexual characteristics and are infertile. Sometimes there are other physical features such as low-set ears, low

hairline, webbed neck, and puffy hands and feet. However, the intellect of Turner's syndrome individuals is within the range of that for the normal population. With appropriate medical treatment these women are able to lead normal lives.

The chromosomal abnormalities described above can frequently be diagnosed before birth by analysing cells in the amniotic fluid or from the placenta. A chromosome analysis, whether performed on a blood sample, cells from the amniotic fluid, or placenta, would provide the parents with information about the karyotype of the foetus (see Chapter 15). If a serious abnormality were indicated the parents would then be in a position to decide whether to go ahead with the pregnancy or to terminate.

New variations and survival

In Chapter 18, the relatively rare blood disorder haemophilia was discussed. The mutant allele resulting in haemophilia is recessive to that controlling normal clotting of the blood and is carried on the *X* chromosome. Males, therefore, can be either normal or haemophiliacs, as they have only one *X* chromosome, whereas females can be homozygous normal; or heterozygous and, therefore, carriers of the condition; or haemophiliacs.

An interesting article on how haemophilia affected the royal families of Europe can be found at http://www.englishmonarchs.co.uk/haemophilia.html

The most famous family pedigree for haemophilia is that of the European royal families descended from Queen Victoria (see Fig. 21.7). She was a carrier of the mutant allele and passed it on to her daughters Alice and Beatrice. Her son Leopold was a haemophiliac. He was one of the rare male haemophiliacs of that time to survive to adulthood and have children. None of Queen Victoria's ancestors showed the trait, and so it is believed that a mutation occurred in an *X* chromosome during the formation of the gametes in one of her parents. This single mutation had a huge influence on the royal families of Europe.

Another recessive condition described in Chapter 18 that arises through mutation is **sickle-cell anaemia**. Sickle shaped red blood cells are formed because of a mutation of the gene responsible for the production of normal haemoglobin. Haemoglobin is the pigment found in red blood cells and is essentially a protein that contains iron. The mutant allele responsible for the sickle shape of the affected red blood cells causes the substitution of one amino acid (valine) for another (glutamic acid) during the formation of the haemoglobin protein. The mutation affects only one of the 287 amino acids in the haemoglobin molecule, but this change is enough to affect the functioning

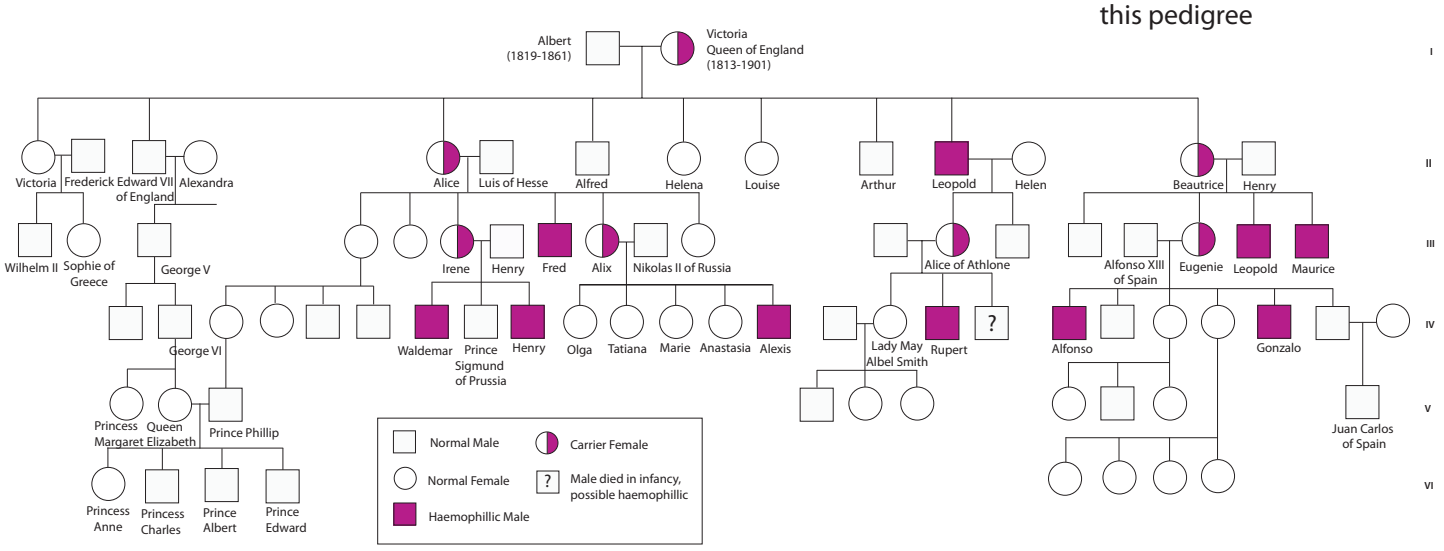


Figure 21.7 Pedigree for haemophilia in the royal families of Europe. Carriers, shown half shaded, have been determined by the pattern of inheritance in this pedigree

of the red blood cell. It results in the red blood cells being a crescent-like, or sickle, shape (see Fig. 18.8 on page 251).

A person who has just one of the mutant alleles has **sickle cell trait**, a condition that is not fatal but the red blood cells become sickle shaped when oxygen concentration is low. Sickle cell anaemia occurs when a person inherits the recessive allele from both parents. It is usually fatal because the sickle shaped cells do not carry as much oxygen as normal red blood cells. They also stick together and block small blood vessels.

If a person with sickle-cell anaemia dies before reproducing, the allele that causes the disease would obviously not be passed on to the next generation. Therefore it would be expected that over many generations the frequency of the sickle-cell allele would decline until it was eliminated from the population. However, if the rate of mutation of normal alleles to sickle cell alleles was great enough, it could cancel out the loss of alleles through the death of affected individuals. Investigations have shown this is *not* the case; in fact, the rate of alleles being lost from the population is about one hundred times greater than the average rate of mutation at any point along a human chromosome. There must be some other reason why sickle cells are maintained in the population. Figure 21.8 shows places in the world where the sickle-cell gene occurs in the population. Compare this with Figure 21.9 which shows the world distribution of malaria. What do you notice? The sickle-cell allele occurs only in areas where malaria is prevalent.

One of the first to notice this relationship was A. C. Allison, who reported his observations in the *British Medical Journal* in 1954. He noted that the sickling allele tended to have its highest frequency in areas where the risk from malarial parasites was greatest. He concluded that the heterozygotes, those with the sickle-cell trait, were more resistant to malaria than those individuals with normal haemoglobin in their red

Figure 21.8 Distribution of sickle-cell anaemia

blood cells. This conclusion was based on Allison's observations that malarial patients who were also 'sicklers' had fewer malarial parasites than did malarial patients who were 'non-sicklers'. Allison conducted experiments to gain further support for these observations. He inoculated both 'sicklers' and 'non-sicklers' with malaria and then treated those individuals in whom the disease developed. This experiment showed, once again, that heterozygotes were less susceptible to malarial infection than those who were homozygous for normal haemoglobin. Since Allison's time, further studies have supported his findings. Today, it is generally accepted that individuals with the sickle-cell trait are less susceptible to malaria and, therefore, have a survival advantage in areas where malaria is prevalent.

You can find out more about sickle cell anaemia at http://www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_Causes.html

The sickle-cell example illustrates a **selectively advantageous** mutation. Possession of the sickle-cell trait gives a survival advantage in high-risk malarial areas over both of the homozygous alternatives. Homozygous recessives, those with sickle-cell anaemia, often die, and those who are homozygous dominant, with normal haemoglobin, are more susceptible to malaria. The heterozygotes, therefore, have a survival advantage in areas where malaria occurs. Situations like this, where the environment is such that one genotype is favoured over another, are called **natural selection**.

Natural selection tends to favour characteristics that help the individual to survive and reproduce. Individuals with characteristics that hinder survival, and/or reproduction, tend to die before their unfavourable characteristics can be passed on to offspring.

The theory of evolution through natural selection was put forward independently by Charles Darwin and Alfred Russel Wallace in 1858. However, it is Charles Darwin's name that is usually associated with this theory because of the massive amount of supporting evidence he collected.

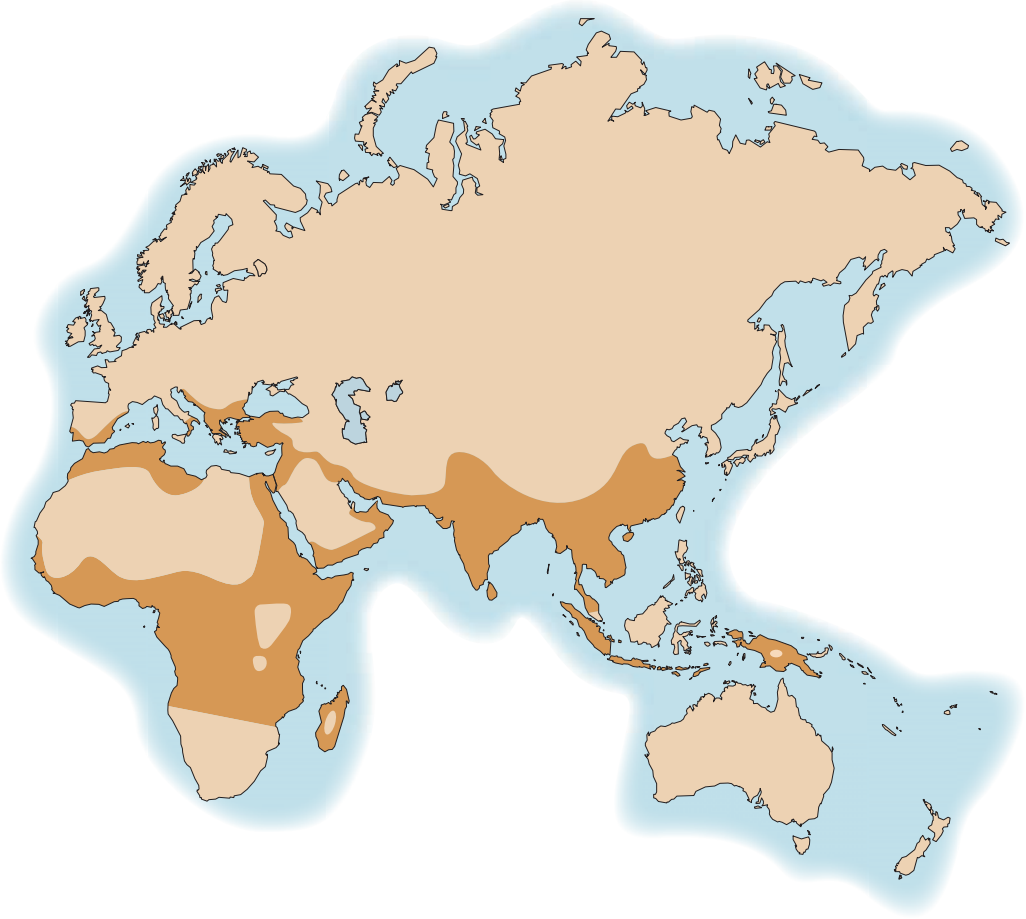


Figure 21.9 Distribution of malaria

Working scientifically

Activity 21.1 The incidence of cancer in Australia

Many cancers arise through mutations that occur in somatic cells. Use references to find out:

- the incidence of different cancers in Australia
- whether there is any relationship between type of cancer and locality in Australia
- what groups of Australians are exposed to mutagens that can cause cancer
- what is being done to limit exposure of Australians to cancer-causing mutagens
- the age groups at which particular cancers are more common in Australia
- whether there are any upward or downward trends in the incidence of particular cancers in Australia.

There are many websites with information about cancer, such as:

- The Cancer Council Australia: http://www.cancer.org.au
- The Cancer Council Western Australia: http://www.cancerwa.asn.au
- The Cancer Council New South Wales: http://www.nswcc.org.au
- The Cancer Council Victoria: http://www.cancervic.org.au.

There are also websites for organisations that deal with specific types of cancer.

As with any information that you use from the Internet, make sure that it has come from a reliable source.

Activity 21.2 Venusians

Venusians are an imaginary group of people from the planet Venus. Because of the intense heat, their skin is a jet-black colour and all individuals are homozygous for skin colour. If a mutation occurs resulting in a Venusian of a lighter skin colour, the individual usually dies before being able to reproduce. However, one such mutation occurred creating a brown skinned individual who did survive and reproduced, passing the new allele to some of his children. The skin of the individuals affected by this mutant allele was extremely thick providing them with an added resistance to a lethal biting insect.

As time went by, the number of Venusians with the mutant allele increased. However, when two of these individuals produced children, homozygotes with the mutant allele died in infancy.

In this activity we will investigate how the mutant allele becomes distributed through the population over time. To simplify our activity, we will start with heterozygotes, and assume that all those who are homozygous for the mutant allele die before they can reproduce. We will also assume that one out of every three Venusians who are homozygous for the normal allele dies from a lethal insect bite.

You will need (for each pair)

Two containers—2 L ice-cream containers work well; 20 black beads or counters to simulate the black skin allele (*B*) in each gamete; 20 white beads or counters to simulate the brown skin allele (*b*) in each gamete; felt pen; tally sheet; pencil

What to do

1. Label one container 'Male Parent' and the other 'Female Parent'.
2. Place 10 of the black beads in each container, then 10 of the white beads in each.
3. Prepare a tally sheet similar to the one below using the symbol *B* for the black skin allele and *b* for the brown-skin allele.

	Genotypes in the Venusian offspring			
	BB	***Bb***	***bB***	***bb***
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

4. Simulate reproduction by shaking the containers well and drawing out one bead (gamete) from each. Place a tick in the relevant box on the tally sheet, then replace the beads.
5. When you have completed 10 draws, place the beads back into the containers. Your partner should repeat steps 1 to 4 above. Together you should have two completed tally sheets.

Studying your data

1. Because the first column contains individuals that are homozygous for black skin (*BB*) only two out of every three survive to adulthood. Tally the number of offspring that will survive to produce the next generation.
2. Individuals with the genotype *bb* will all die in the first year. If you eliminate these individuals how many surviving offspring do you now have?
3. What is the ratio of black skins to brown skins that survive to adulthood?
4. Combine your data with the other groups in the class to obtain a bigger sample. What is the ratio now?

Interpreting your data

1. How has this activity shown that selectively advantageous mutations can affect the proportions of particular characteristics in a population?
2. What has happened to the proportion of the allele *b* in the population? Has it been entirely eliminated? Do you think it ever will be?
3. Summarise how this chance mutation has been selectively advantageous to survival of the Venusian population.

REVIEW QUESTIONS

1. **(a)** Define what is meant by the term 'mutation'.
   (b) Explain the difference between somatic and germline mutations.
2. **(a)** Distinguish between gene mutations and chromosomal mutations.
   (b) Give an example of a congenital disorder that can be caused by a gene mutation and one that can be caused by a chromosomal mutation.
3. Describe four different types of chromosomal mutations.
4. **(a)** What are mutagens (or mutagenic agents)?
   (b) List five examples of mutagenic agents.
   (c) Why does special care need to be taken when pregnant women require X-rays?
5. What is meant by a lethal recessive?
6. Summarise the pattern of inheritance that occurs in genetic disorders such as haemophilia and Duchenne muscular dystrophy. When there is no history of such disorders in a family, how are they thought to arise?
7. **(a)** Distinguish between trisomy and monosomy.
   (b) Give an example of each condition.
8. Explain how Klinefelter's syndrome and Turner's syndrome come about.
9. List the advantages and disadvantages of having the sickle-cell trait in an area where malaria is prevalent.
10. Describe what is meant by a selectively advantageous mutation.

APPLY YOUR KNOWLEDGE

1. Discuss why mutations occurring in the reproductive cells are considered more important than those occurring in the body cells. In your discussion, describe the possible long-term effects of the two situations.
2. A large number of mutagenic agents can be found in the environment. Consider those that could possibly affect you in your lifetime and discuss steps that you can take to minimise any risks from exposure to those agents.
3. The more often cells divide the greater the risk of errors and mutations. For this reason, scientists have hypothesized that when a baby is born with a congenital disorder caused by an error in cell division, the father is the parent more likely to have contributed the gene with the mutation. Compare the number of eggs produced by a female with the number of sperm produced by a male and explain why scientists have proposed this hypothesis.
4. Some naturally occurring viruses are considered mutagenic, since they can insert themselves into host DNA. Explain why this ability would make them mutagenic.
5. What is the sex of the individual whose karyotype is shown in Figure 21.1?
6. The risk of a having a baby with Down syndrome increases as the mother gets older. Table 21.1 shows the relationship between Down syndrome and maternal age.

Table 21.1 Mother's age and risk of having a baby with Down syndrome

Age (years) of mother	Risk of Down syndrome
20	1 in 1667
23	1 in 1429
26	1 in 1176
29	1 in 1000
32	1 in 769
37	1 in 227
40	1 in 106
43	1 in 50
46	1 in 23
48	1 in 14
49	1 in 11

Source: University of New South Wales Embryology, http://embryology.med.unsw.edu.au/Defect/page21.htm#Data, viewed 9 February 2008

(a) Draw an appropriate graph to display the data in Table 21.1.
(b) The risk of a baby having any chromosome abnormality increases dramatically with increasing maternal age. Suggest reasons why this should be so.

7. A team of American scientists has been trying to develop a vaccine to give permanent immunity against malaria. If this vaccine is effective, the incidence of malaria will be gradually reduced. What do you think will happen to the frequency of the sickle-cell gene within a population if this occurs? Your answer should contain an explanation in terms of the survival value of the various genotypes.

8. Figure 21.10 shows the sequence of the genes A to M on a chromosome. What type of chromosomal mutation is represented by each of (a), (b) and (c)?

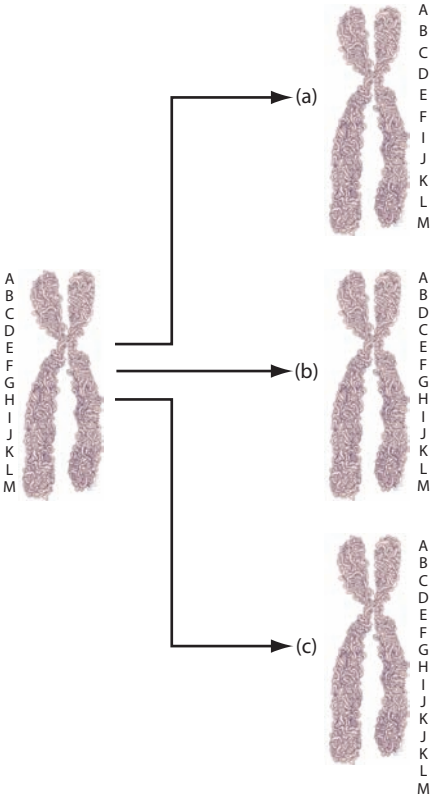


Figure 21.10 Some types of chromosomal mutations