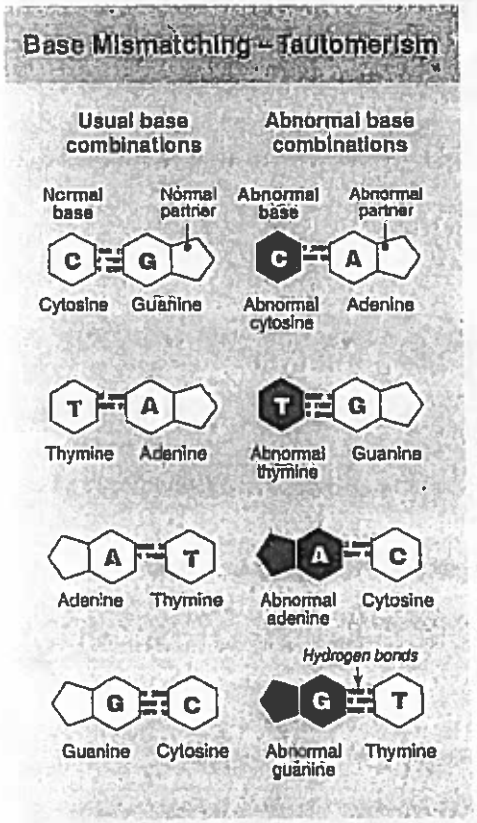
Gene Mutations

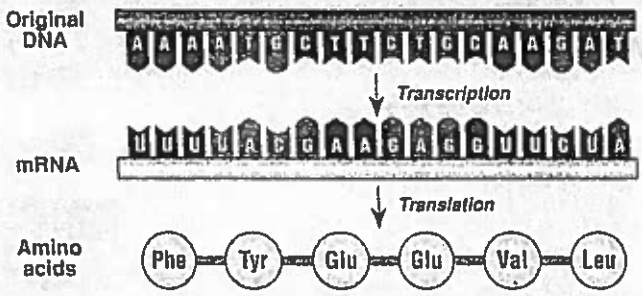
Gene mutations are small, localised changes in the structure of a DNA strand. These mutations may involve change in a single nucleotide (often called **point mutations**), or they may involve changes to a triplet (e.g. deletion or triplet repeat). If one amino acid in a protein is wrong, the biological function of the entire protein can be disrupted. Not all mutations may result in altered proteins. Because of the degeneracy of the genetic code, a substitution of the 3rd base in a codon may code for the same amino acid. The diagrams below and opposite show how various point mutations can occur. These alterations in the DNA are at the **nucleotide** level where individual **codons** are affected. Alteration of the precise nucleotide sequence of a coded gene in turn alters the mRNA transcribed from the mutated DNA and may affect the polypeptide chain that it normally creates.



Base Mismatching

Watson and Crick proposed a theory of how base mismatching could occur. The diagram on the left shows suggested changes in bases and the resulting mismatch of complementary bases. On rare occasions some bases may have altered hydrogen-bond positions. As a result, during DNA replication, such abnormal bases pair with incorrect complementary bases. This gives rise to mutations in DNA molecules, which in turn are expressed as altered forms of mRNA and often altered proteins. NOTE: The abnormal bases on the right hand side of the diagram have a different arrangement of hydrogen bonds than normal.

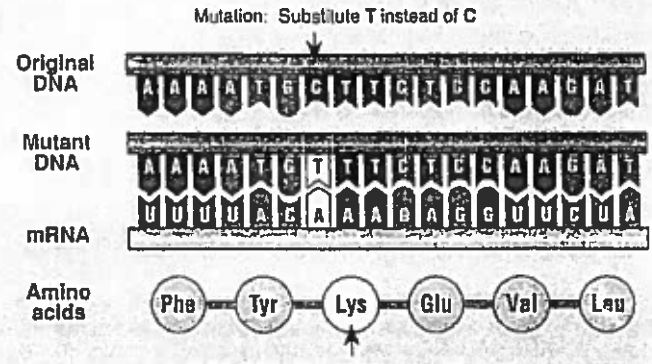
A normal sequence without mutations



Amino acid sequence forms a normal polypeptide chain

Missense substitution

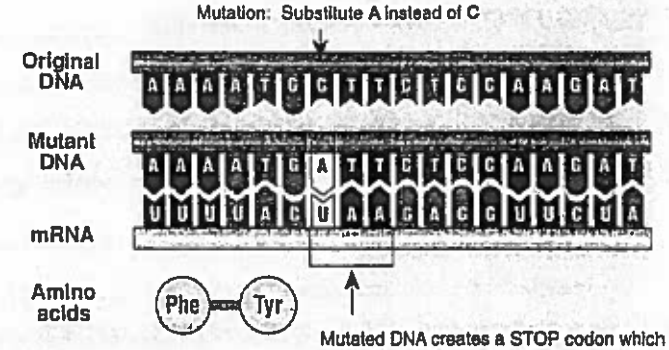
A single base is substituted for another base which may result in a codon that codes for a different amino acid. Some substitutions, however, may still code for the same amino acid, because of the high degree of degeneracy in the genetic code (i.e. many amino acids have 4 or 6 codons coding for them). In the illustrated example, placing a T where a C should have been, results in the amino acid lysine appearing where glutamic acid should be. This could affect how this protein functions.



Polypeptide chain with wrong amino acid

Nonsense substitution

Some amino acids can be coded for by 4 or 6 different codons and are therefore less affected by substitutions. In the example illustrated, a single base substitution in the first nucleotide of the third codon has a dramatic effect on the nature of the polypeptide chain it is coding for. The codon no longer codes for an amino acid, but instead is an instruction for the termination of the translation process of protein synthesis. This results in a very short polypeptide chain that is likely to have little or no function since the **STOP** codon is introduced near the **START** codon.

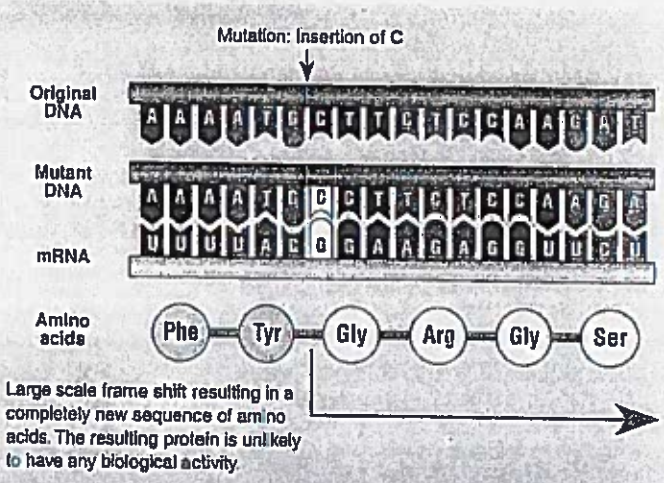


Mutated DNA creates a STOP codon which prematurely ends synthesis of polypeptide chain

Reading frame shift by insertion

A major upset can occur when a single extra base is inserted into the DNA sequence. This has the effect of displacing all the other bases along one position and thereby creating a whole new sequence of codons. Such mutations are almost always likely to lead to a non-functional protein, but this does depend on the distance of the insertion or deletion from the START codon (i.e. the closer the insertion is to the START codon, the more the protein will be affected).

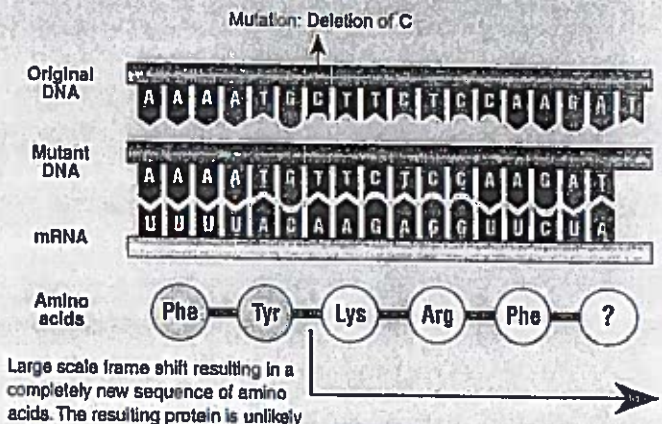
NOTE: could also lead to nonsense



Reading frame shift by deletion

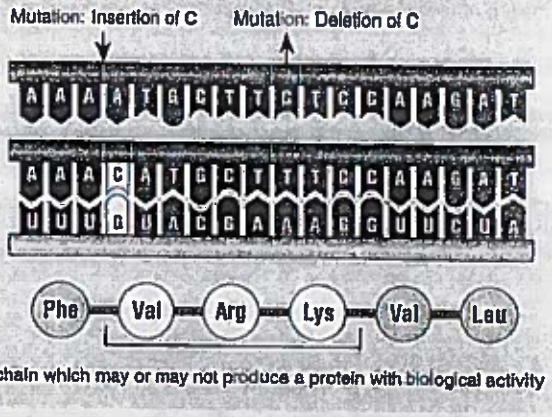
In the same way that an insertion of an extra base into the DNA sequence has a large scale damaging effect, a deletion may also cause a frame shift. Again the result is usually a polypeptide chain of doubtful biological activity.

NOTE: could also lead to nonsense



Partial reading frame shift

Both an insertion and a deletion of bases within a gene can cause a frame shift effect where each codon no longer has the correct triplet of three bases. In this example, three codons have been affected, along with the amino acids they code for. The error is limited to the codons including and between the insertion and deletion. There is no biological activity if the amino acids altered are important to the functioning of the resulting protein.



Mutations involving change in only one nucleotide may have no observable effect on the phenotype of the organism; the subtle changes in the DNA sequence may still produce a chain of identical amino acids in the protein, or at least produce a protein that is unaffected by the change. Because of the degeneracy of the genetic code, many mutations of this type are unlikely to cause any change in the biological activity of the protein (there are exceptions, e.g. sickle cell disease).

1. Explain what is meant by a **reading frame shift**: _____

   _____

2. Not all gene mutations have the same effect on the organism, some are more disruptive than others.

   (a) Identify which type of gene mutations are the most damaging to an organism: _____

   (b) Explain why they are the most disruptive: _____

   _____

3. Explain why **biological activity** of a protein might be affected by a reading frame shift: _____

Point Mutation Problems

In the exercise below, determine from the original DNA, the new mutant DNA, the new mRNA sequence, and the amino acid sequence. Use the examples on the previous pages as a guide and refer to the mRNA amino acid table on the activity *The Genetic Code*. In each case, identify the type of point mutation and describe its effect on the coding for the protein:

1. Substitute the 6th base (G) in the original DNA with a C (cytosine).

   (a) Identify this type of point mutation:

   _____

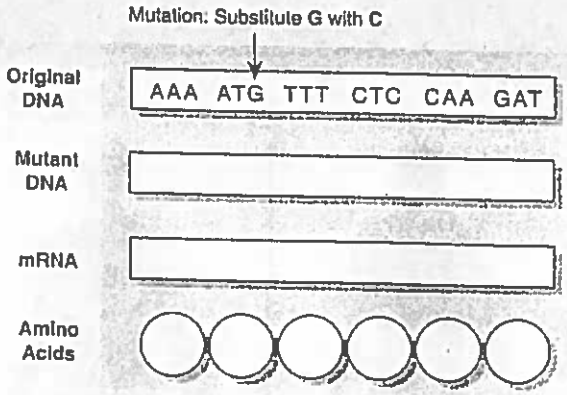
   (b) Describe its effect on the protein produced:

   _____

   _____

   _____

   _____



2. Delete the 14th base (A) in the original DNA, with no replacement.

   (a) Identify this type of point mutation:

   _____

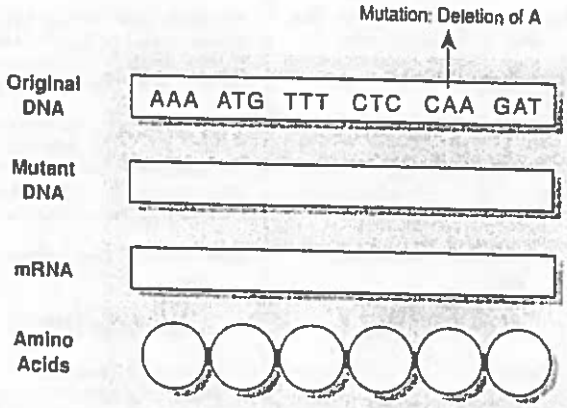
   (b) Describe its effect on the protein produced:

   _____

   _____

   _____

   _____



3. Insert a new base (G) between the 14th and the 15th base, and delete the 6th base (G) in the original DNA.

   (a) Identify this type of point mutation:

   _____

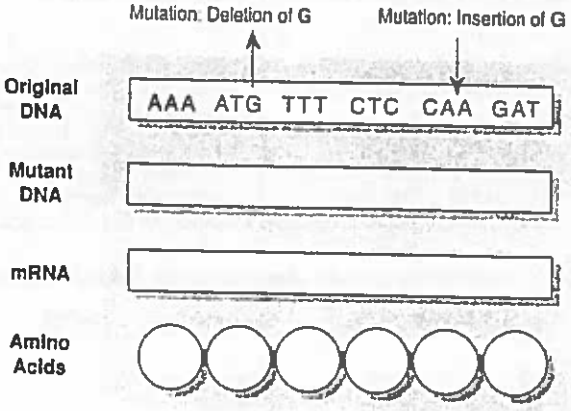
   (b) Describe its effect on the protein produced:

   _____

   _____

   _____

   _____



4. Discuss the difference between a **gene mutation** and a **chromosome mutation**: _____

   _____

   _____

   _____

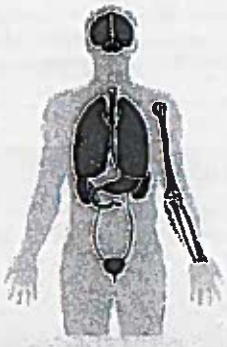
   _____

Examples of Gene Mutations

Humans have more than 6000 physiological diseases attributed to mutations in single genes and over one hundred syndromes known to be caused by chromosomal abnormality. The number of genetic disorders identified increases every year. Rapid progress of the Human Genome Project is enabling the identification of the genetic basis of these disorders. This will facilitate the development of new drug therapies and gene therapies. Four genetic disorders are summarised below.

Sickle Cell Disease

Synonym: Sickle cell anaemia



Incidence: Occurs most commonly in people of African ancestry.
West Africans: 1% (10-45% carriers)
West Indians: 0.5%

Gene type: Autosomal mutation which results in the substitution of a single nucleotide in the HBB gene that codes for the beta haemoglobin chain. The allele is codominant.

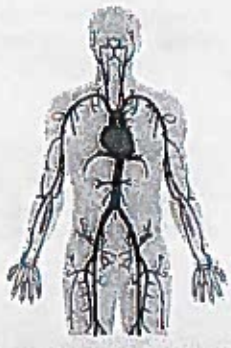
Gene location: Chromosome 11

Symptoms: Include: anaemia; mild to severe pain in the chest, joints, back, or abdomen; jaundice; kidney failure; repeated infections, in particular pneumonia or meningitis; eye problems including blindness; swollen hands and feet; gallstones (at an early age); strokes.

Treatment and outlook: Patients are given folic acid. Acute episodes may require oxygen therapy, intravenous infusions of fluid, and antibiotic drugs. Experimental therapies include bone marrow transplants and gene therapy.

β-Thalassaemia

Synonyms: Cooley anaemia, Mediterranean anaemia



Incidence: Most common type of thalassaemia affecting 1% of some populations. More common in Asia, Middle East and Mediterranean.

Gene type: Autosomal recessive mutation of the HBB gene coding for the haemoglobin beta chain. It may arise through a gene deletion or a nucleotide deletion or insertion.

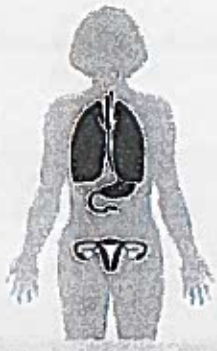
Gene location: Chromosome 11

Symptoms: The result of haemoglobin with few or no beta chains, causes a severe anaemia during the first few years of life. People with this condition are tired and pale because not enough oxygen reaches the cells.

Treatment and outlook: Patients require frequent blood transfusions. This causes iron build-up in the organs, which is treated with drugs. Bone marrow transplants and gene therapy hold promise and are probable future treatments.

Cystic Fibrosis

Synonyms: Mucoviscidosis, CF



Incidence: Varies with populations:
United States: 1 in 1,000 (0.1%)
Asians in England: 1 in 10,000
Caucasians: 1 in 20-26 are carriers

Gene type: Autosomal recessive. Over 500 different recessive mutations (deletions, missense, nonsense, terminator codon) of the CFTR gene have been identified.

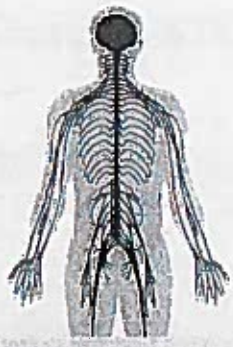
Gene location: Chromosome 7

Symptoms: Disruption of glands: the *pancreas*, *intestinal glands*, *biliary tree* (biliary cirrhosis), *bronchial glands* (chronic lung infections), and *sweat glands* (high salt content of which becomes depleted in a hot environment). *Infertility* occurs in males/females.

Treatment and outlook: Conventional: chest physiotherapy, a modified diet, and the use of TOBI antibiotic to control lung infections. Outlook: Gene transfer therapy inserting normal CFTR gene using adenovirus vectors and liposomes.

Huntington Disease

Synonyms: Huntington's chorea, HD (abbreviated)



Incidence: An uncommon genetic disease present in 1 in 20 000.

Gene type: An autosomal dominant mutation of the HD gene (IT15) caused by an increase in the length (36-125) of a CAG repeat region (normal range is 11-30 repeats).

Gene location: Chromosome 4

Symptoms: Mutant gene forms defective protein: huntingtin. Progressive, selective *nerve cell death* associated with chorea (jerky, involuntary movements), *psychiatric disorders*, and *dementia* (memory loss, disorientation, impaired ability to reason, and personality changes).

Treatment and outlook: Surgical treatment may be possible. Research is underway to discover drugs that interfere with *huntingtin* protein. Genetic counselling coupled with genetic screening of embryos may be developed in the future.

1. For each of the genetic disorder below, indicate the following:

   (a) Sickle cell disease: Gene name: HBB Chromosome: 11 Mutation type: Substitution

   (b) β-thalassaemia: Gene name: _____ Chromosome: _____ Mutation type: _____

   (c) Cystic fibrosis: Gene name: _____ Chromosome: _____ Mutation type: _____

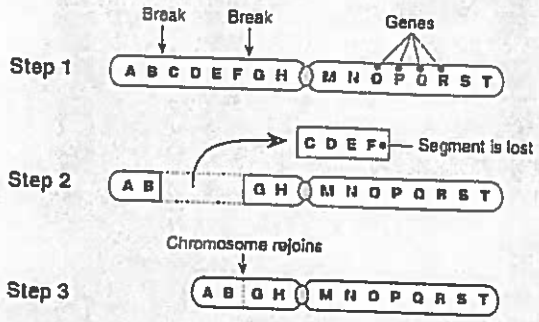
   (d) Huntington disease: Gene name: _____ Chromosome: _____ Mutation type: _____

2. Explain the cause of the symptoms for people suffering from β-thalassaemia: _____

3. Suggest a reason for the differences in the country-specific incidence rates for some genetic disorders:

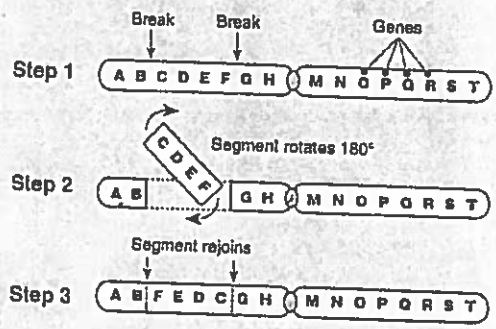
Chromosome Mutations

The diagrams below show the different types of chromosome mutation that can occur only during **meiosis**. These mutations (sometimes also called block mutations) involve the rearrangement of whole blocks of genes, rather than individual bases within a gene. Each type of mutation results in an alteration in the number and/or sequence of whole sets of genes (represented by letters) on the chromosome. In humans, **translocations** occur with varying frequency (several rare types of Down syndrome occur in this way). Individuals with a **balanced translocation** have the correct amount of genetic material and appear phenotypically normal but have an increased chance of producing faulty gametes. Translocation may sometimes involve the fusion of whole chromosomes, thereby reducing the chromosome number of an organism. This is thought to be an important mechanism by which **instant speciation** can occur.



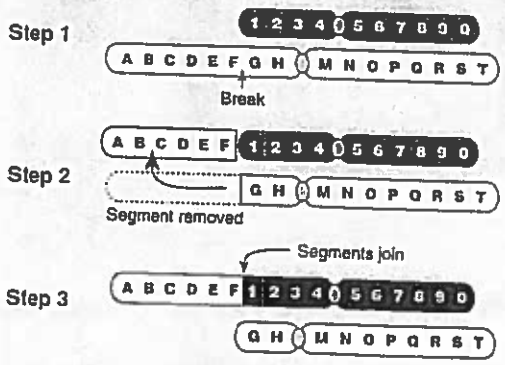
Deletion

A break may occur at two points on the chromosome and the middle piece of the chromosome falls out. The two ends then rejoin to form a chromosome deficient in some genes. Alternatively, the end of a chromosome may break off and is lost.



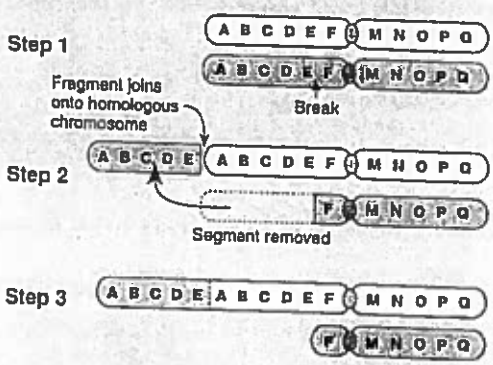
Inversion

The middle piece of the chromosome falls out and rotates through 180° and then rejoins. There is no loss of genetic material. The genes will be in a reverse order for this segment of the chromosome.



Translocation

Translocation involves the movement of a group of genes between different chromosomes. The large chromosome (white) and the small chromosome (black) are not homologous. A piece of one chromosome breaks off and joins onto another chromosome. This will cause major problems when the chromosomes are passed to gametes. Some will receive extra genes, while some will be deficient.



Duplication

A segment is lost from one chromosome and is added to its homologue. In this diagram, the darker chromosome on the bottom is the 'donor' of the duplicated piece of chromosome. The chromosome with the segment removed is deficient in genes. Some gametes will receive double the genes while others will have no genes for the affected segment.

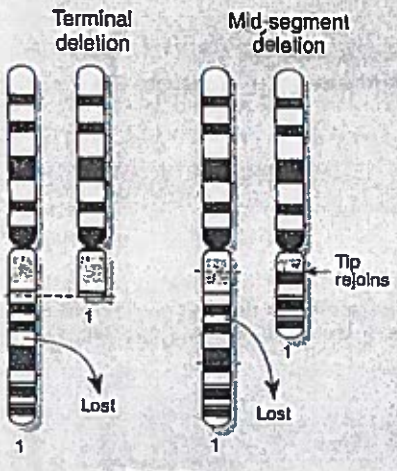
Mutations

1. For each of the chromosome (block) mutations illustrated above, write the original gene sequence and the new gene sequence after the mutation has occurred (the first one has been done for you):

	Original sequence(s)	Mutated sequence(s)
(a) Deletion:	A B C D E F G H M N O P Q R S T	A B G H M N O P Q R S T
(b) Inversion:		
(c) Translocation:		
(d) Duplication:		

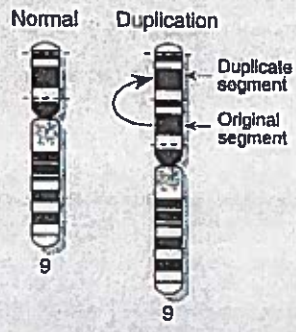
2. State which of the above types of block mutation is likely to be the least damaging to the organism, giving a reason:

Examples of Chromosome Mutations in Humans



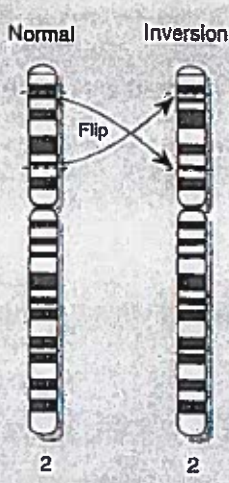
Deletion

Two types of deletion are known to occur on chromosome 1: a *'terminal deletion'* on the left removes a portion at the end, while an *'interstitial deletion'* on the right removes a central block of a chromosome.



Duplication

In the duplication mutation for chromosome 9, the extra segment of chromosome could be produced by an unequal exchange of chromatids during crossing over with its homologous chromosome 9.

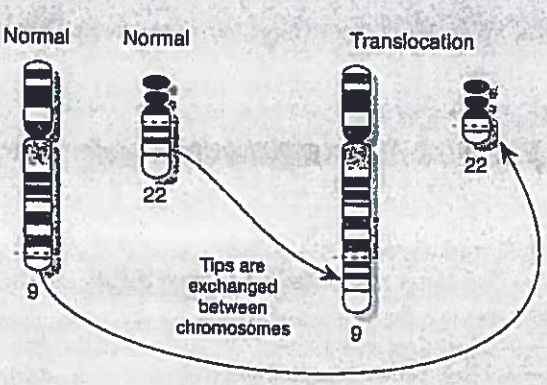


Inversion

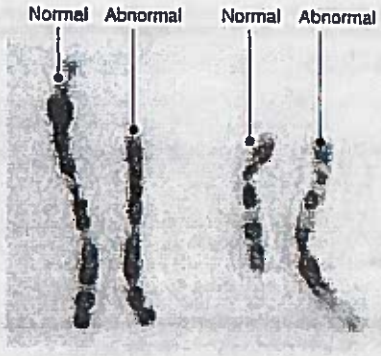
The diagram above shows an inversion on chromosome 2. No change in the content of the chromosome has occurred, it has simply been rearranged. However, it has important implications during crossing over.

Translocation

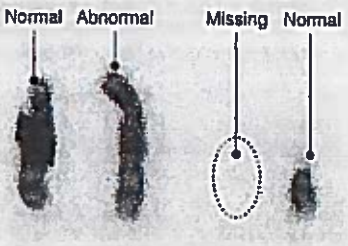
The chromosome rearrangement on the right shows a two-way **translocation** where the tips of chromosomes 9 and 22 are *exchanged*. This specific translocation is found associated with **chronic myeloid leukaemia** and is a vivid demonstration that if the stability of the chromosome structure is upset too greatly, the resulting phenotype may have impaired fitness (reduced ability to survive and reproduce). This example did not even involve the loss of genetic material, just a movement of genes from one chromosome to another. It may be that a specific gene at the point of the break was affected to cause the illness.



Chromosome 15



Chromosome 1 Chromosome 10



Chromosome 14 Chromosome 21

Offspring inheriting 2 normal chromosome 21s as well as the abnormal chromosome 14 have a rare type of Down syndrome (they have three copies of the genes on chromosome 21).

The examples above illustrate block mutations in human chromosomes. Individuals with these karyotypes could produce faulty gametes leading to recognisable genetic disorders in the offspring. Individuals with translocated chromosomes could produce normal gametes but also gametes either missing or with extra genetic material. *Photos & information: Cytogenetics Department, Waikato Hospital, Hamilton, NZ.*

3. The photographs above were taken by the cytogenetics department at a hospital. Using the diagram explanations on this page as a guide, draw arrows to show the movement of chromosome segments on the photographs.

4. Identify the kind of chromosome rearrangement shown in each photo involving:

   (a) Chromosome 15: _____

   (b) Chromosome 1 and 10: _____

   (c) Chromosome 14 and 21: