chapter 15:

GENETIC DISEASES

OBJECTIVES

After studying this chapter you should be able to:

- outline the major features of the cell cycle;
- explain how genetic traits, including genetic diseases, are inherited;
- describe the general effects of single gene mutations;
- list the ways in which single gene disorders are treated;
- list the types of chromosomal mutations or aberrations;
- outline how genetic diseases are screened *in utero* and in neonates.

15.1 INTRODUCTION

Genes are the fundamental units of heredity and encode specific functional products, such as RNA molecules and polypeptides. They are encoded by sequences of bases in DNA molecules and are found at particular positions in chromosomes in the nucleus and also in the relatively small circular DNA molecules in the mitochondria. Only 37 of the approximately 22 000 human genes occur in mitochondria although mutations of these may become clinically significant as described in *Chapter 16*. The genes constitute the blueprint or the set of instructions which affects hereditary characteristics, for example hair and eye color, height and the susceptibility to certain diseases.

When a cell divides the genetic information needs to be replicated accurately so that these instructions pass on to the daughter cells. When changes occur in the base sequence of DNA, either as a result of incorrect replication or from random changes caused by physical or chemical agents, then the instructions become corrupted. This is a **mutation**, and may eventually lead to disease because the cell is unable to make, for example, a particular enzyme, hormone, transporter or structural protein.

Chromosomes have a complex structure (*Figure 15.1*). Each is comprised of a single double-stranded DNA molecule associated with numerous proteins.

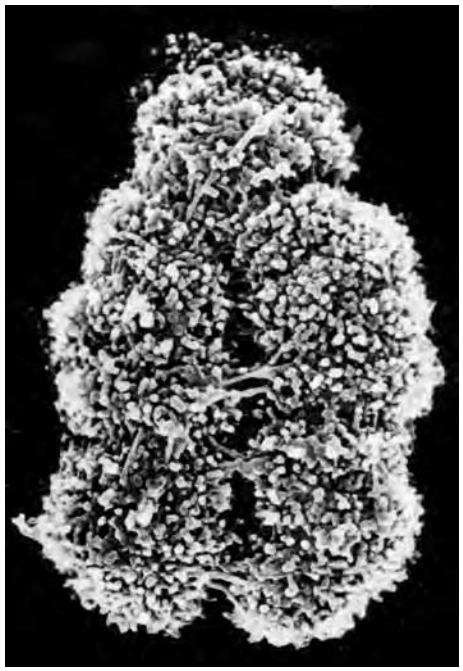


Figure 15.1 Scanning electronmicrograph of a chromosome. Courtesy of Dr C.J. Harrison, Christie Hospital, Manchester, UK.

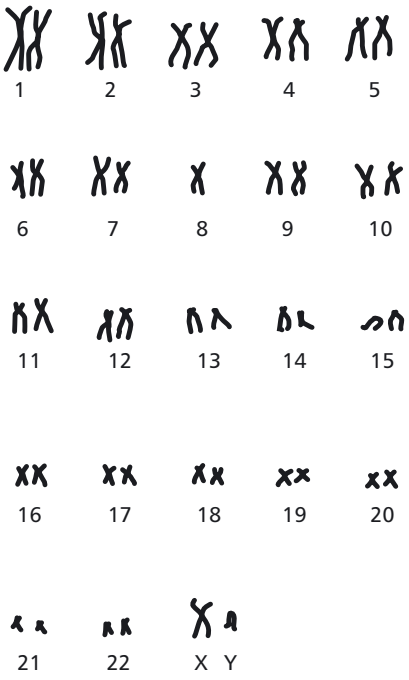


Figure 15.2 The chromosome complement of a normal human male. That of a normal female is shown in *Figure 1.13*.

In general, chromosomes occur in matching or homologous pairs, with each member of a pair containing **alleles** or different forms of the same gene, which are found at the same loci (singular locus) in each member of the pairs. Normal human somatic (body) cells contain 23 pairs of chromosomes and are said to be **diploid** (2N). The 46 chromosomes in diploid cells comprise 22 homologous pairs of **autosomes** (nonsex chromosomes) and one pair of sex chromosomes; XX in females and XY in males (*Figure 15.2*; see also *Figure 1.13*). Oocytes and spermatozoa have half the diploid number and are said to be **haploid** (N); oocytes can only contain an X chromosome but sperm can have an X or a Y chromosome.

15.2 GENETICS AND DNA

Genetics, from the Greek *genno* meaning 'to give birth', is that branch of biology concerned with heredity, genes and DNA (*Figure 15.3*), the genetic material. It is also the scientific study of the variations in inherited characteristics, often called traits, and how these are transmitted from one generation to the next. Inherited characteristics include a number of clinical conditions and diseases that are described in other chapters, for example sickle-cell anemia and hemophilia (*Chapter 13*), the muscular dystrophies and cystic fibrosis (*Chapter 16*). Others, such as phenylketonuria and Down syndrome, will be described in this chapter. Genomics is the study of the full complement of bases in the DNA of an organism.

Genes are the stretches of bases in DNA that carry the code for making RNA or proteins. The code is contained in sequences of the four nucleotide bases, adenine, cytosine, guanine and thymine (A, C, G and T, respectively). DNA normally occurs as the famous double helical molecule (*Figure 15.3 (A)*) that consists of two long polymers of alternating phosphates and deoxyribose sugars, linked together by hydrogen bonds between pairs of complementary bases across the center of the double helix, rather like the steps of a spiral staircase. Adenine always pairs with T and C always pairs with G (*Figure 15.3 (B)*).

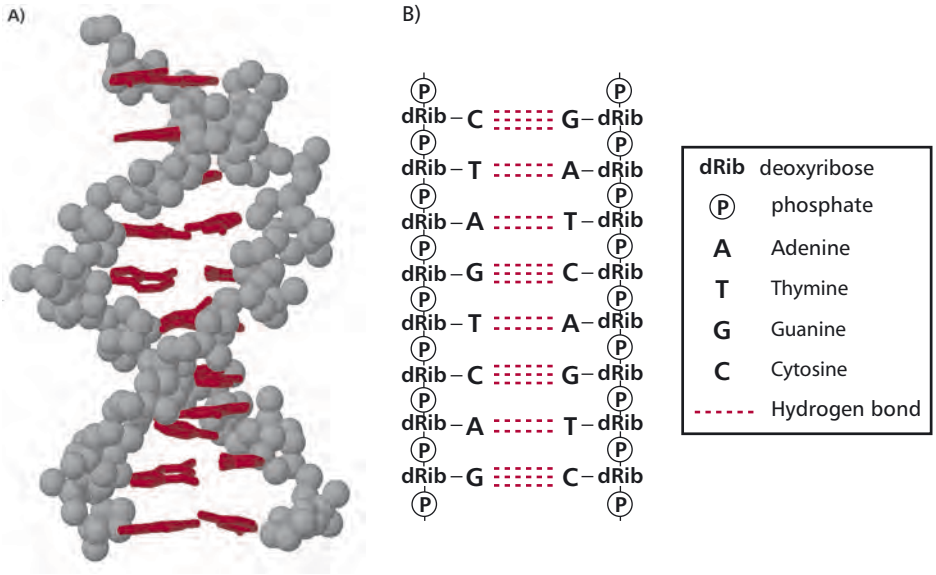


Figure 15.3 (A) Molecular model of DNA, showing the base pairs in red and the sugar-phosphate backbones in gray. PDB file 1ZFM. (B) A schematic to illustrate the structure of DNA.

For a gene to be expressed, the nucleotide base code in a gene in the DNA must be copied or transcribed to form an RNA molecule. The strands of the double helical DNA separate and one of them, 'the gene', acts as a template for the synthesis of a complementary new strand (*Figure 15.4 (A)*). However, the new strand is an RNA molecule not DNA. The base pairing rules are similar to the complementary base pairing in DNA but uridine (U) is used in RNA, not T and the sugar ribose, not deoxyribose. A number of RNA molecules may be transcribed from one gene. In some cases, the formation of an RNA molecule is the major event in gene expression. However, in the vast majority of cases, the expression of a gene results in the formation of a protein (*Figure 15.4 (B)*). In these cases, the RNA formed by transcription is a messenger RNA or mRNA molecule. However, DNA is transcribed in the nucleus but the synthesis of proteins takes place in the cytosol. Thus the mRNA molecules are transported out of the nucleus (*Chapter 16*) and go to the ribosomes in the cytosol where their message is translated into a linear sequence of amino acids to make a protein. Each sequence of three bases in the mRNA codes for the addition of one specific amino acid to the growing polypeptide chain of the protein; for example AUG codes for the amino acid methionine, UUU codes for phenylalanine and so on. Each mRNA molecule may be translated numerous times so that many molecules of protein are produced.

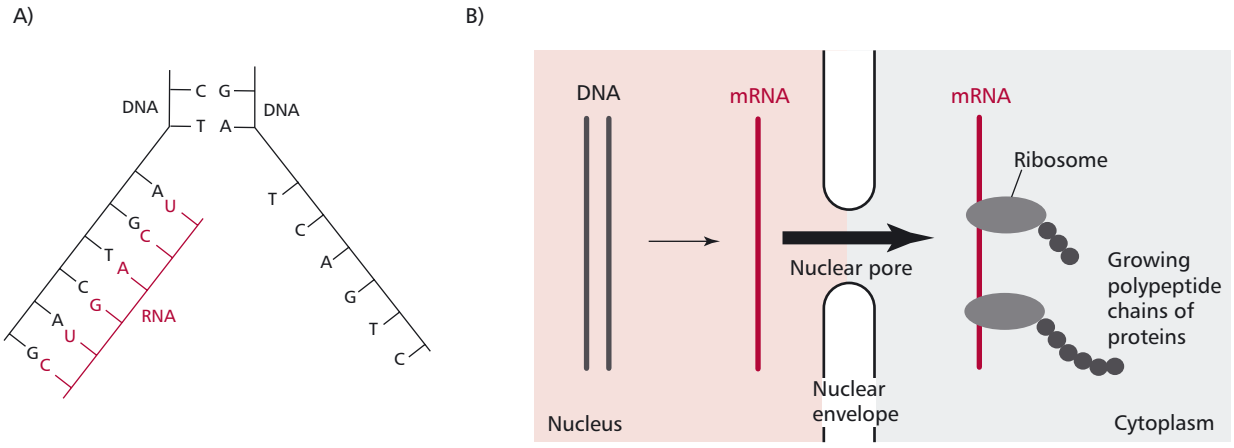


Figure 15.4 (A) A schematic to illustrate the formation of RNA by transcribing a strand of DNA. (B) An overview of protein synthesis as summarized in the main text.

15.3 DNA REPLICATION AND THE CELL CYCLE

When a cell divides the genetic information must be passed on to the two daughter cells. The series of biochemical and morphological events that occur in a population of reproducing cells is called the **cell cycle**. This results in the replication of the genetic material (DNA molecules) and division of the cell into two daughter cells. The replication of DNA involves separating the two DNA strands of the double helix and aligning new bases according to the usual pairing rules; A with T and G with C. The new nucleotides are linked together to form two new strands, each of which is complementary to one of the original (parental) strands. This action forms two new double-stranded DNA molecules, each of which consists of one parental strand and one daughter strand (*Figure 15.5*) and, for this reason, is often called semiconservative replication. This is a very simplified account of an extremely complex process, which is catalyzed by a range of enzymes. This replication is very accurate; it needs to be because the genetic instructions must be retained from generation to generation. Most of the few errors that inevitably occur are corrected by error-detecting enzyme systems in the cell.

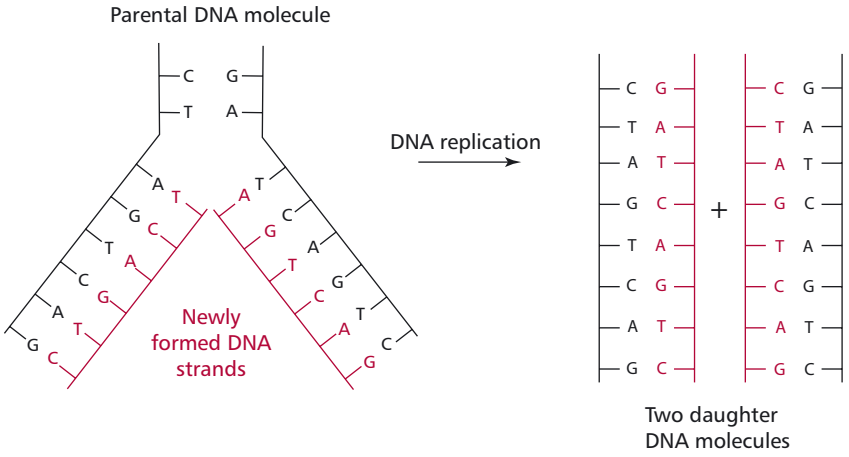
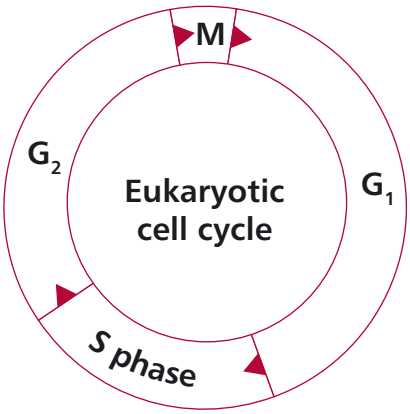


Figure 15.5 A schematic illustration of DNA replication, which emphasizes its semiconservative nature.



M	Mitosis or meiosis
G_1	Gap 1
S phase	DNA sysnthesis
G_2	Gap 2

Figure 15.6 Overview showing the stages of the cell cycle.

Margin Note 15.1 The cell cycle and malignancy

The timed sequence of events in the cell cycle is a highly regulated process controlled by numerous different proteins. Mutations in the genes encoding these proteins can perturb the regulation of the cell cycle and cells can die or their growth can become uncontrolled depending on the nature of mutation. The latter may lead to malignancies (*Chapter 17*). A number of chemotherapeutic drugs act by interfering with the cell cycle. For example, some immunosuppressive drugs, such as aminopterin and cyclophosphamide, disrupt the synthesis of DNA during the S phase. Taxol (*Figure 15.8 (A) and (B)*) is a drug that interferes with mitosis by preventing depolymerization of the microtubules that make up the spindle.

The cell cycle is an orderly sequence of events consisting of **interphase**, the period between cell divisions, and mitosis (or meiosis if gamete producing cells are concerned) when the cell divides. Thus interphase, which lasts about 24 h, prepares the cell for division by building up large energy stores and synthesizing new organelles for the daughter cells; a high metabolic rate is typical of cells about to undergo division. The cell cycle can be divided into four main, but continuous, phases that are often drawn as a circle (*Figure 15.6*). The phases are called G_1, S, G_2 and M. The G_1 (for gap) phase lasts about 8 h during which the cell makes a commitment to divide. It is characterized by the synthesis of RNA and protein. In the S phase, S for synthesis, the DNA is replicated in a process lasting approximately 6 h. The G_2 phase is a relatively quiescent period, which typically lasts 4 h, during which organelles are replicated. Mitosis (or meiosis) occurs in the M phase. Following mitosis, the cells enter interphase, which lasts until the S phase of the next cycle. Cells that divide only rarely, for example neurons, are said to be in a stage called the G_0 phase. It is only when they become committed to divide that they are described as being in the G_1 phase of the cycle. Two different types of cell division are recognized, mitosis and meiosis.

MITOSIS AND MEIOSIS

Mitosis is the type of division that occurs during growth and the renewal of tissues. The daughter cells produced have the same diploid complement of chromosomes as the parental cell. Mitosis is a continuous process that lasts about 1 h. For convenience it is divided into four stages; prophase, metaphase, anaphase and telophase (*Figure 15.7*). In interphase the chromosomes occur as dispersed, thread-like material called chromatin, which cannot be seen with a light microscope. In prophase the chromosomes begin to condense to form distinct chromosomes that are visible with microscopy. Since their DNA has been replicated, each chromosome is present as an identical pair of chromosomes, although at this stage each member of the pair is referred to as a sister **chromatid**, which are joined together by centromeres (*Section 15.7*). The centrioles, normally located just outside the nuclear envelope, undergo replication and migrate to opposite poles of the cell. This leads to the microtubules of the cytoskeleton rearranging to form the spindle, which spans the cell from one end to the other. The ends of the spindle are known as poles whereas its middle region is called an equator. During prophase, the cell's nucleolus disappears and prophase concludes with dissipation of the nuclear envelope. In metaphase, the chromosomes migrate to the center of the cell and are arranged around the equator of the spindle, where the centromere of each chromosome (paired chromatids) becomes attached to spindle fibers. The chromatids are drawn apart at the centromere region towards opposite

poles of the spindle. During anaphase, the chromatids of each chromosome are pulled apart and each chromatid moves towards the poles of the spindles reaching the ends by telophase. In telophase, the cell undergoes division to two daughter cells by the plasma membrane constricting and cutting across the spindle equator. The spindle breaks down and nuclear envelopes form around each separated grouped of chromatids, now called chromosomes. The nucleoli also become apparent in the new nuclei and the chromosomes return to the nonvisible forms typical of cells in interphase. Hence the parental cell has divided to form two daughter cells that are genetically identical to the parent.

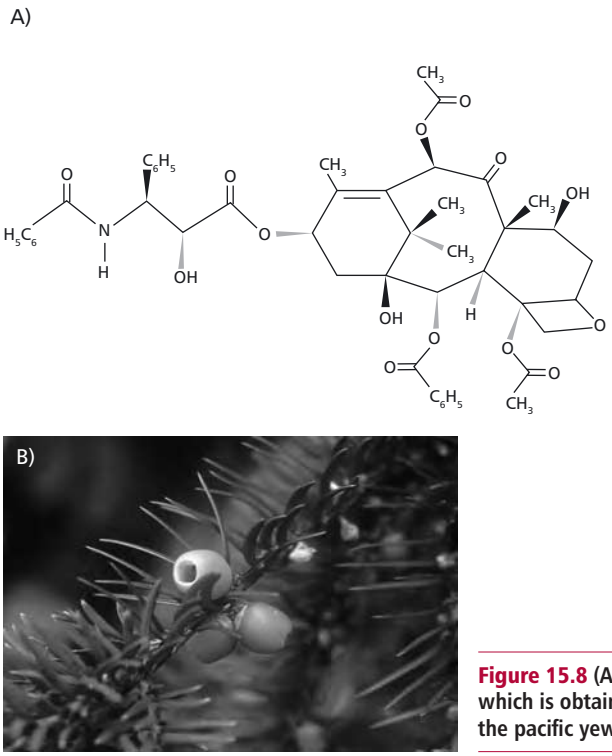


Figure 15.8 (A) The structure of taxol, which is obtained from (B) the leaves of the pacific yew tree (*Taxus brevifolia*).

Meiosis occurs prior to reproduction during the formation of gametes (*Chapter 7*). The parental cell has a diploid number of chromosomes, whereas the daughter cells are now gametes with the corresponding haploid number of chromosomes. During meiosis, the number of chromosomes is halved and the daughter cells receive only one of each type of chromosome and, for this reason, meiosis is sometimes called reduction division.

Meiosis may be thought of as consisting of two separate divisions (*Figure 15.9*). In the first meiotic division (prophase I through to telophase I) the parent cell divides into two cells each of which receives one of each pair of homologous chromosomes. Each of these chromosomes consists of two chromatids. The second meiotic division (prophase II through to telophase II) results in each chromosome being separated into chromatids, with the result that four daughter cells each with a haploid chromosome complement are formed. In prophase I, the chromosomes contract and the nucleolus shrinks in size. Homologous chromosomes lie side by side in pairs, a situation called synapsis. Each member of the pair is bivalent. It is at this stage that genetic recombination or crossing over occurs. While they are paired, the nonsister chromatids, that is one maternal and one paternal chromatid, of a homologous pair are broken at equivalent positions and exchange homologous pieces of material (*Figure 15.9*). The crossed strands of the chromatids formed during recombination are called chiasmata (singular chiasma). Recombination

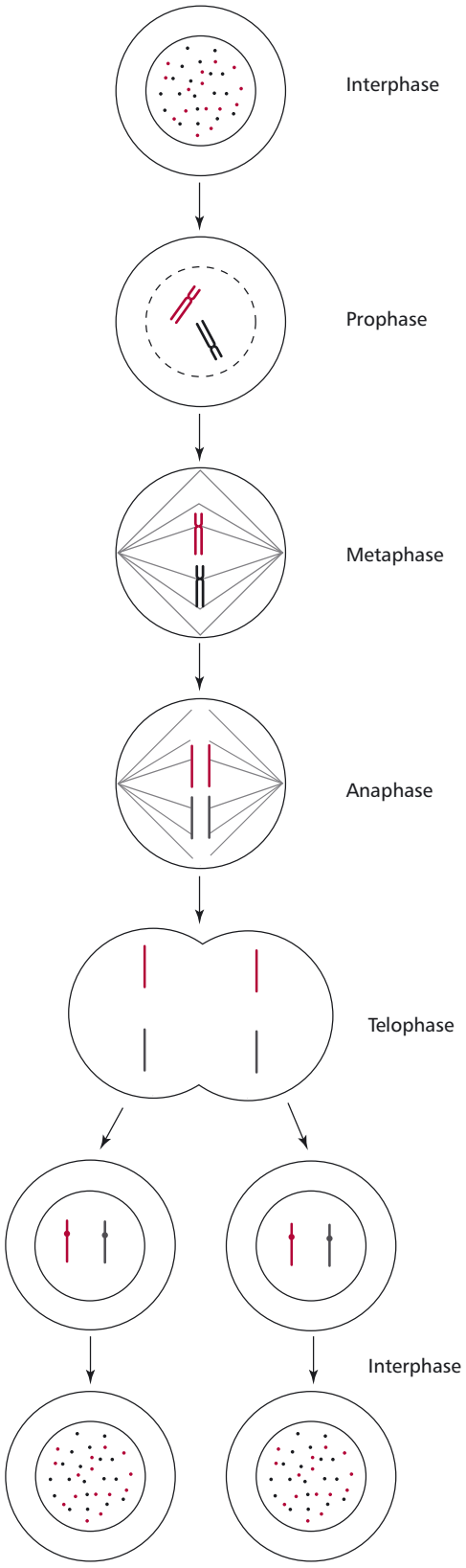


Figure 15.7 An outline of mitosis as described in the main text. For simplicity only two chromosomes, each consisting of two chromatids, are shown.

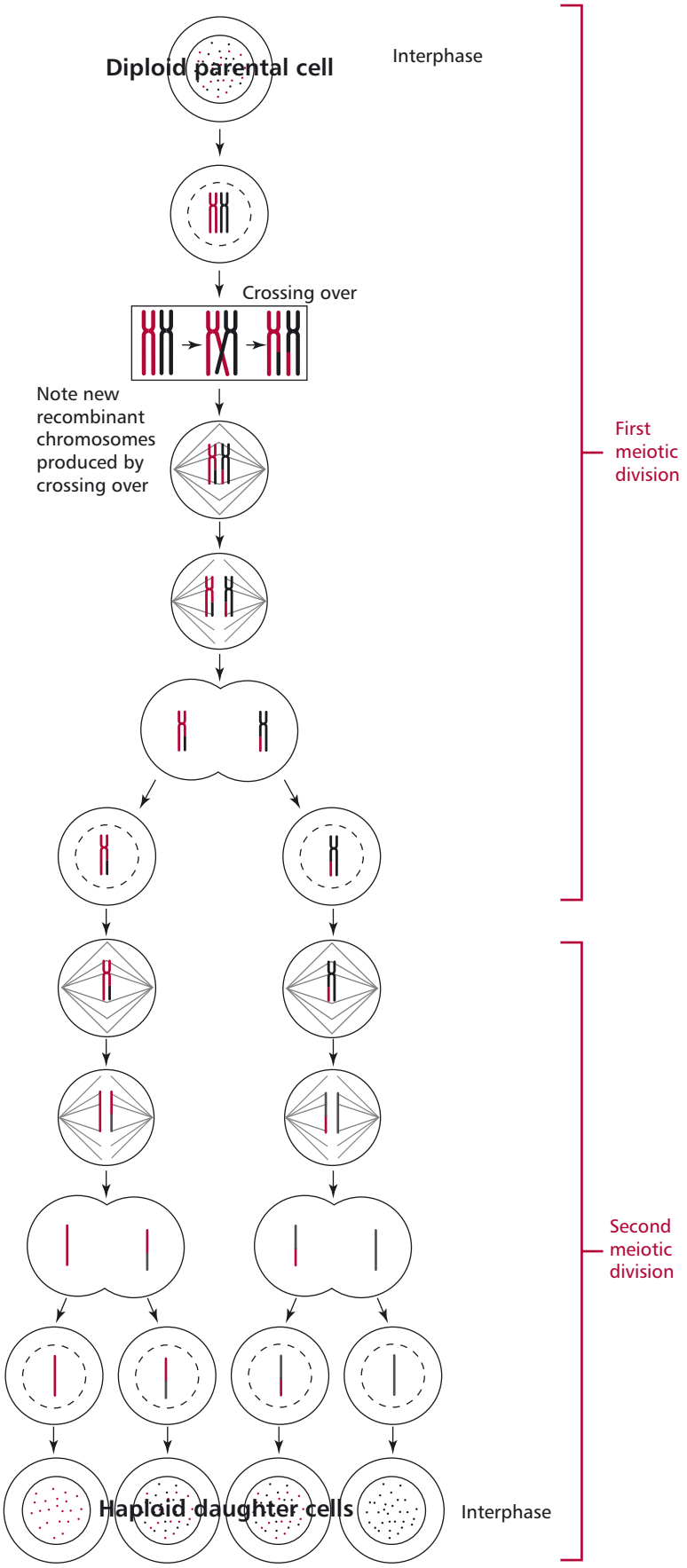


Figure 15.9 An outline of meiosis as described in the main text. For simplicity only a single pair of homologous chromosomes is shown. Each member of the pair consists of two chromatids. The insert illustrates recombination between the two nonsister chromatids.

results in each chromatid acquiring genes or parts of genes from the other and the process leads to the formation of new combinations of genes or parts of genes in chromosomes. Eventually recombinant gametes are formed that differ from their paternal cells in their gene content. Thus crossing over promotes genetic variation.

During metaphase I, the homologous chromosomes or bivalents move to the equator of the spindle. The sister chromatids orientate towards the same pole whereas the homologous chromosomes orientate themselves towards opposite poles. During anaphase I, the homologous chromosomes, each of course consisting of a pair of chromatids, migrate towards opposite poles of the cell. During telophase I, the cell divides as in mitosis to give rise to two daughter cells whose chromosomes each consist of paired chromatids. Following a brief interphase, these cells enter the second meiotic division. In prophase II, the two daughter cells essentially prepare for the second division with formation of a new spindle. In metaphase II, the chromosomes move to the equator of the spindle and the chromatids arrange themselves towards opposite poles and in anaphase II, the chromatids separate from each other and move to opposite poles of the cell. Finally, in telophase II, each cell divides into two daughter cells but these have only the haploid number of chromosomes. Thus the diploid parental cell has produced four haploid daughter cells (sperm or ova (*Chapter 7*)).

Failure of chromosomes to separate at metaphase in mitosis or either of the metaphases in meiosis is called nondisjunction. Nondisjunction can have serious clinical consequences as explained in *Section 15.9*.

15.4 GENOTYPE AND PHENOTYPE

The genetic or hereditary constitution of an individual, which is the whole complement of genes present, forms the **genotype**. The term can also be applied to any particular pair of alleles that an individual possesses at a specific locus on a chromosome. In contrast, the visible or measurable characteristics of an individual constitute the **phenotype**. A phenotype includes biochemical, physiological, morphological and behavioral characteristics or, indeed, any observable biological trait that is apparent throughout life, such as the total physical appearance and constitution of an individual or any specific trait, such as size, weight or eye color and, of course, includes characteristics of clinical importance and the presence of a disease. Some phenotypic traits, for example eye color, are directly observable but others, such as the blood group of a patient (*Chapter 6*), may only become apparent following specific tests. Phenotypic traits do not necessarily occur merely following the expression of the genotype of an individual; some, such as the blood groups, are completely determined by heredity but many others, for example weight and height, result from interactions between the genotype and the environment.

15.5 INHERITANCE AND MUTATIONS

Genes occur as paired alleles. Each corresponding allele is carried by one of a pair of homologous chromosomes. If the two alleles are identical, the individual is **homozygous** for that gene and, if they differ, the individual is said to be **heterozygous**. In the heterozygous state, one allele may be **dominant** over the other which is therefore **recessive**. In this situation, only the characteristic encoded by the dominant trait will be expressed, as would also be the case if the individual was homozygous for both dominant alleles. The recessive trait will only become apparent in a homozygous recessive individual.

Dominant genes are conventionally written as an upper case italic letter, for example *G*, while its recessive counterpart is given the lower case form, *g*. *Figure15.10 (A)* illustrates the normal inheritance pattern first established by Mendel (1822–1884). If one parent is homozygous for an autosomal dominant gene (*GG*) and the other parent is homozygous for the recessive form (*gg*), then all the offspring will be genetically heterozygous (*Gg*) and phenotypically will express the dominant trait. If both parents are heterozygotes (*Figure 15.10 (B)*), then 25% of offspring will be homozygous for the dominant gene (*GG*), 25% homozygous for the recessive gene (*gg*) and the remaining 50% of offspring will be heterozygous (*Gg*).

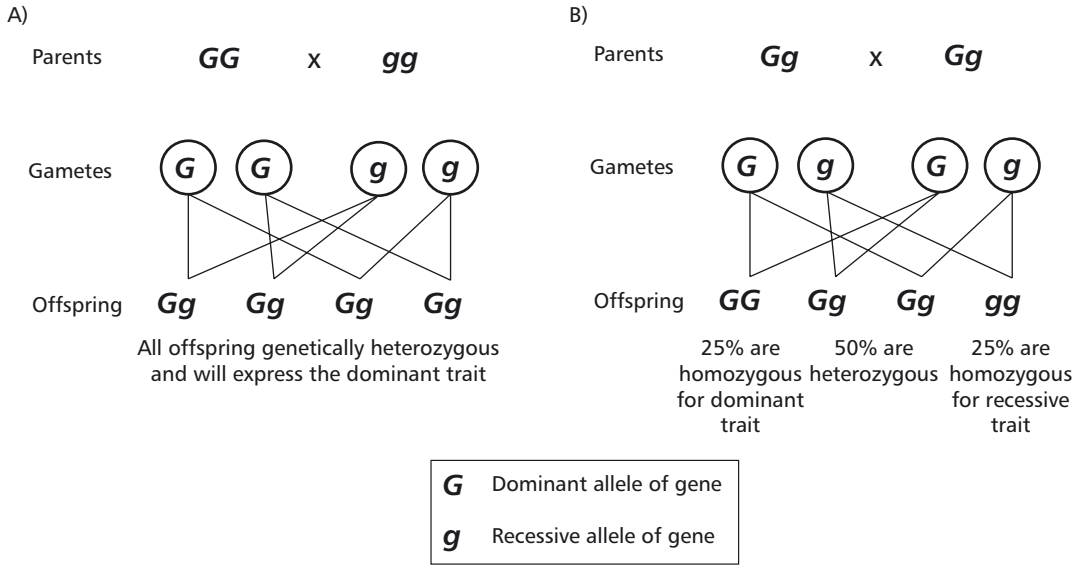


Figure 15.10 **The inheritance patterns shown for a single pair of genes between (A) two contrasting homozygous parents and (B) two heterozygous parents.**

Margin Note 15.2 The human genome

The genome is the complete sequence of bases in the DNA molecules, which is all of the hereditary material possessed by an individual. The human haploid genome contains about 3 000 000 000 pairs of nucleotides. The total length of this DNA is about a meter and is divided into 23 individual molecules; 22 of which are found in the autosomes and one in the sex chromosome. Mitochondrial DNA contains 37 genes.

Mutations are changes that occur in the genome and can give rise to clinical disorders (*Margin Note 15.2*). Mutations include changes within single genes and changes to whole chromosomes. They may be simple substitutions of one nucleotide for another (point mutations), involve the insertion or deletion of one or more nucleotides within the normal sequence of DNA within a chromosome or even alter the structures of individual chromosomes or the number of chromosomes present. When considering the effects of mutations, it is important to distinguish between a genetic change which occurs in somatic cells and one occurring in gametes. Mutations arising in somatic cells will not be transmitted to future generations although they may represent the first step in the development of cancer (*Chapter 17*). In somatic cells, mutations that produce a recessive autosomal allele are unlikely to have clinical consequences because their expression is masked by the corresponding dominant allele. However, somatic mutations that are dominant or X-linked (*see below*) can have a greater impact because they are likely to be expressed. Similarly, their impact is greater if they arise early in development before undifferentiated cells give rise to differentiated tissues or organs. In adult tissues, the activities of many nonmutant cells often mask mutations in a few other cells. Mutations in gametes or gamete forming tissues are part of the germ line (*Chapter 17*) and are of greater clinical concern because as well as affecting that individual, they will also be transmitted to offspring.

Dominant autosomal mutations *M* will be expressed phenotypically in both the homozygous and heterozygous condition. However, if the mutation is recessive (*m*) then it is not likely to affect an individual unless both chromosomes carry

the same mutation. The inheritance patterns shown by dominant/recessive alleles that are associated with a clinical condition follow the Mendelian rules explained above. If only a single member of a homologous pair of chromosomes carries the mutation, it can, however, be passed on to the next generation and the parent is described as a carrier (*Figure 15.11 (A)* and *(B)*). If one parent is homozygous for the normal gene (*MM*) and the other parent heterozygous for the mutated allele (*Mm*) then 50% of the offspring will be homozygous for the normal gene (*MM*) and the other 50% heterozygous (*Mm*) and carriers. None of the children will be affected. If both parents are heterozygotes (*Mm*) then 25% of offspring will be dominant homozygotes (*MM*), 50% of offspring will be heterozygotes and carriers (*Mm*) but the remaining 25% will be recessive homozygotes (*mm*) and express the condition (*Figure 15.11 (B)*).

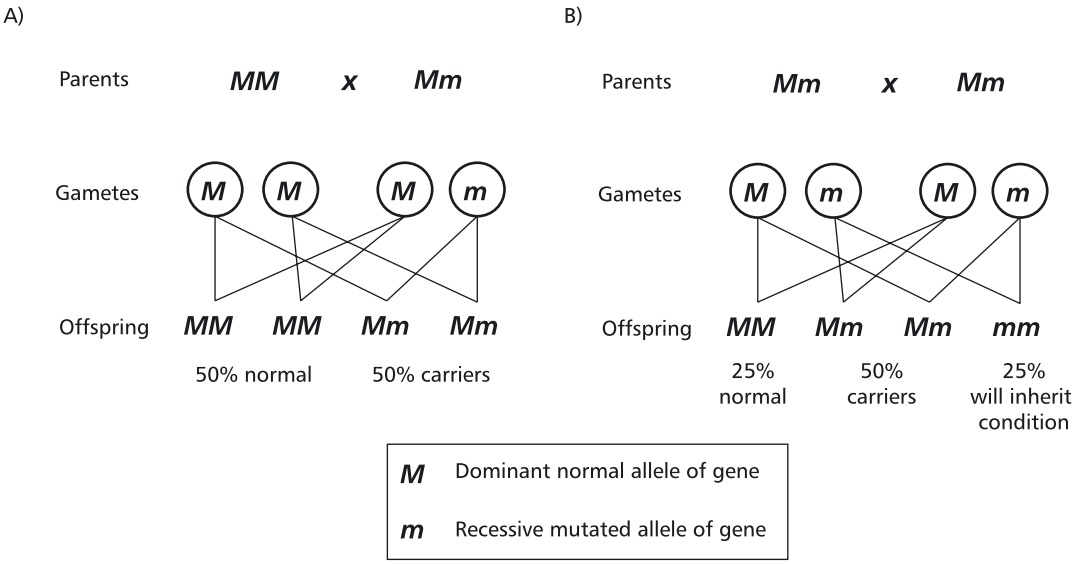


Figure 15.11 **The inheritance patterns shown for a recessive allele of a gene between (A) dominant homozygous and heterozygous parents and (B) two heterozygous parents.**

Heterozygosity means that autosomal recessive mutations, even one resulting in a lethal allele, may go unnoticed and be maintained in the population for many generations, until the resultant allele has become widespread in the population. The new allele will become evident only when a chance mating brings two copies of it together in the homozygous condition.

SEX-LINKED GENETIC DISEASES

A number of genetic diseases are caused by defective alleles of genes of the sex (X and Y) chromosomes. The X chromosome contains many more genes than the Y, although they do have some genes in common, thus any defective (mutated) gene on the X chromosome is likely to be expressed in males (XY) but be masked in females (XX). Genetic diseases associated with the X chromosome are commonest and they are often referred to as X- or sex-linked genetic conditions. X-linked diseases can be recessive or dominant, although the former, for example hemophilia described in *Chapter 13*, are the better known (*Table 15.1*). Given that females have two X chromosomes but males only one together with a Y chromosome, then the expression of sex-linked genes differs between females and males because many genes on the Y chromosome lack a corresponding allele on the X chromosome. Thus X-linked recessive genes are only expressed in females if there are two copies of the gene; one on each of the X chromosomes. However, for males,

Recessive	Dominant
Duchenne and Becker muscular dystrophies (*Chapter 16*)	Coffin-Lowry syndrome
Hemophilia (*Chapter 13*)	incontinentia pigmenti
Red–green color blindness	
Wiskott-Aldrich syndrome (*Chapter 5*)	
X-linked agammaglobulinemia (*Chapter 5*)	

Table 15.1 Examples of X-linked diseases

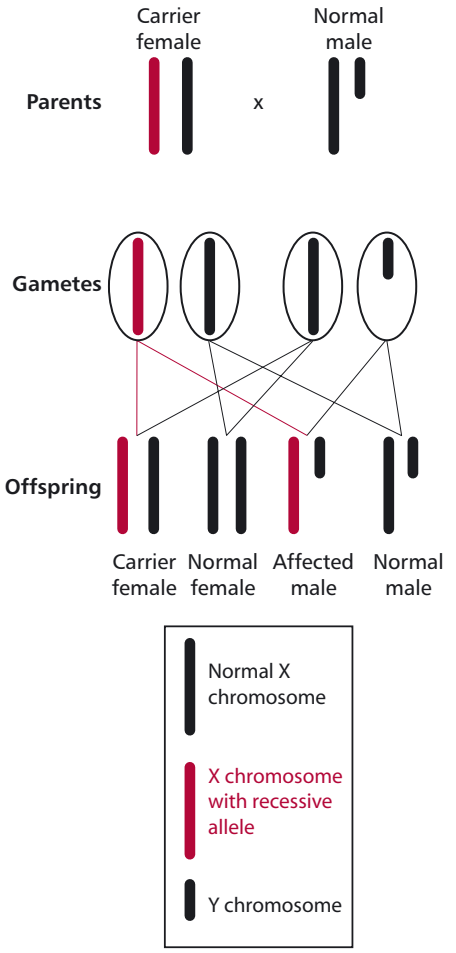


Figure 15.12 The inheritance pattern shown for a recessive allele carried on one of the X chromosomes of the mother with a normal male father.

there only needs to be one copy of a defective (mutated) X-linked recessive gene for the disorder to be expressed. For example, if a woman carried a mutated recessive gene on one of the X chromosomes (*Figure 15.12*) then statistically, 50% of her sons would inherit the defective gene and show the disorder; however, 50% of her sons would not receive the gene and would not express the condition. Similarly, half of her daughters would not receive the gene and therefore would be unable to pass it to future generations. The other half would receive the defective gene and be able to transmit it to the next generation. Like their mother, they are asymptomatic carriers of the disorder.

A common recessive X-linked condition only expressed in males is red–green color blindness. This is an inability to distinguish between red and green colors although visual acuity (keenness of vision) is normal. It is not associated with any serious complications but affected individuals may not be considered for some occupations that involve transport or the armed forces, where the ability to distinguish colors is essential. The defective gene is located on the X chromosome and males are 16 times more likely to be affected than females. Its prevalence in males is about 10%.

15.6 INHERITED GENE DISORDERS

Most inherited diseases are due to mutations in genes in the nuclear chromosomes although they can also occur as a result of mutations in mitochondrial genes as described in *Chapter 16*. The mutation of a single gene may lead to the absence or modification of a specific protein, for example, the abnormal hemoglobin in sickle cell anemia (*Chapter 13*). In some cases, the inherited disorder may result in defective receptor synthesis, such as in familial hypercholesterolemia (*Chapter 14*) where there is a defect in low density lipoprotein (LDL) receptors, or in defective carrier proteins, such as in cystinuria where renal reabsorption of cystine (formed by the oxidation of two cysteines) is impaired. If the defective or absent protein is an enzyme the result is a metabolic disorder. Most inherited metabolic disorders are autosomal recessive diseases, that is, symptoms are only seen in the homozygous condition and heterozygotes are phenotypically normal because sufficient amounts of the protein are produced. Nevertheless a number of these conditions have an autosomal dominant mode of inheritance and consequently heterozygotes are affected. Examples of these include porphyrias (*Chapter 13*) and familial hypercholesterolemia (*Chapter 14*).

CONSEQUENCES OF AN ENZYME DEFICIENCY

In inherited metabolic disorders caused by a complete or partial deficiency of an enzyme that controls a particular reaction in a metabolic pathway, the

BOX 15.1 Spongiform encephalopathies or prion diseases

The spongiform encephalopathies (SEs) or prion diseases (*Table 15.2*) are a rather peculiar group of diseases that can be inherited although this is not their usual method of transmission. It was noted in *Chapter 2* that these are infectious diseases but also have a low sporadic occurrence of about one in a million for CJD. However, they are unusual in that they can also be familial, that is they are also inherited (genetic) diseases. Irrespective of cause, these diseases generally develop slowly over 10 to 20 years in older individuals and are characterized by the presence of holes or plaques in brain tissue that can only be observed postmortem, giving it a spongy appearance (*Figure 15.13*), hence the name spongiform. There are no cures for these diseases and all are fatal. Variant CJD, which first appeared in the UK in the 1980s, differs from 'conventional' CJD in that it occurs in younger people and death occurs relatively rapidly within about 2 years following the first appearance of symptoms.

Name of disease
Atypical dementias
Creutzfeldt-Jacob disease (CJD)
Variant Creutzfeldt-Jacob disease (vCJD)
Fatal familial insomnia (FFI)
Gerstmann-Sträussler-Scheinker disease (GSS)
Kuru

Table 15.2 Examples of human spongiform encephalopathies or prion diseases

Prions are proteins that are normally found in a predominantly α helical conformation, the native form. However, these molecules can change shape to a form with an increased β sheet content that is a pathological conformation (*Figure 15.14*). In a poorly understood manner, the β sheet-rich prion protein somehow induces conformational changes in native α helical-rich molecules to change them to the β type conformation. These newly misfolded molecules can, in turn, stimulate conformational changes in other molecules in a chain reaction that deposits aggregates of prions in the brain leading to the destruction of neurons and finally the lethal spongiform condition. Thus SEs are a subdivision of a group of diseases called protein conformational diseases.

The sporadic forms of these diseases occur in individuals with point mutations in the gene that encodes the prion protein. These mutations alter the sequence of amino acid residues in the prion protein molecules and predispose them to misfold to the β sheet-rich, pathological form. Different mutations in the gene are associated with different SEs (*Table 15.3*). The mutations are, of course, heritable but since the symptoms of the diseases usually only become apparent after reproductive life is over, they can run in families producing the familial forms of the disease.

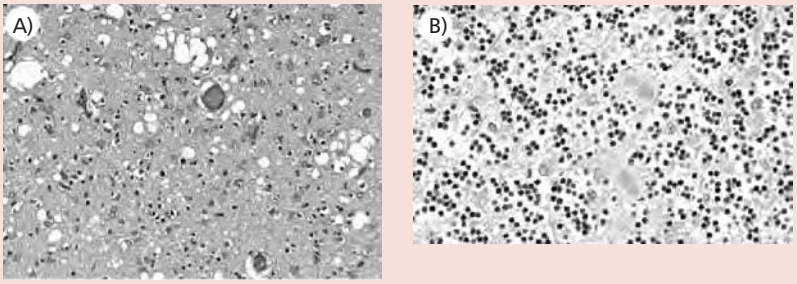


Figure 15.13 (A) The distinctive spongiform appearance of the cortex of the brain associated with CJD and (B) Aggregates of the pathological form of the protein deposited in the cerebellum. Courtesy of National CJD Surveillance Unit, UK.

Mutation	Disease
Pro102Leu	GSS
Pro105Leu	GSS
Ala117Val	GSS
Tyr145Stop	GSS
Asp178Asn	familial CJD, FFI
Val180Ile	GSS
Phe198Ser	GSS
Glu200Lys	familial CJD
Arg208His	CJD
Val210Ile	familial CJD
Gln217Arg	GSS
Met232Arg	GSS(?)
Octarepeat insert	familial CJD

Table 15.3 Some mutations of the human prion protein associated with spongiform encephalopathies

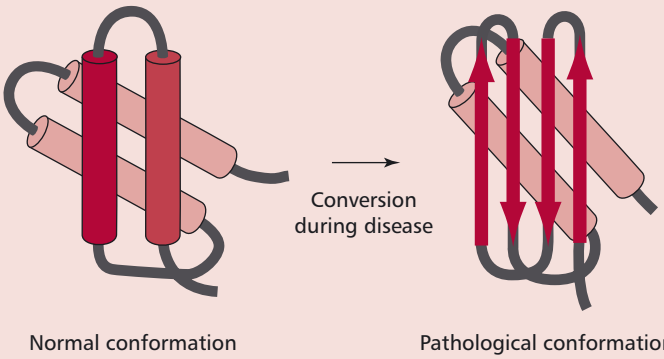


Figure 15.14 Schematic to show the change in conformation of the normal (α helical-rich) prion protein to the pathological (β sheet-rich) conformation.

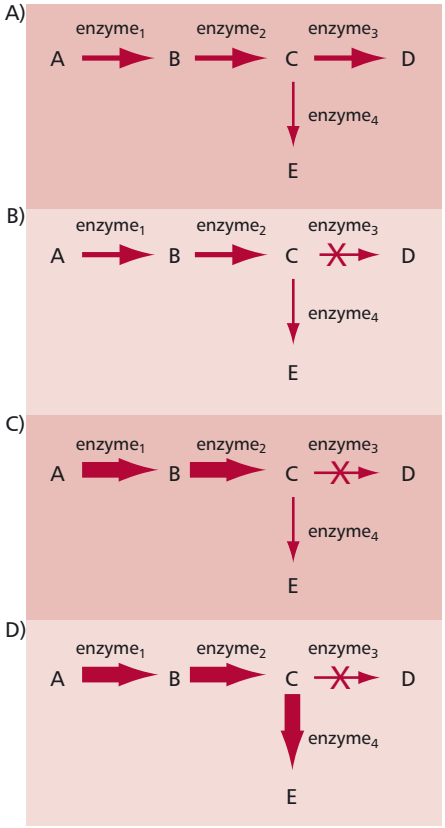


Figure 15.15 Idealized metabolic pathways to show effects of an enzyme deficiency. Metabolites are shown in upper case letters, while the relative rates of the reactions are indicated by the size of the arrows. (A) The metabolic pathway illustrates synthesis of product D from substrate A by a series of reactions catalyzed by enzymes 1, 2 and 3. Product E is derived from a minor pathway by the action of enzyme 4 on substrate C. A deficiency of enzyme 3 has a number of consequences including (B) where conversion of C to D is blocked resulting in a decline in the production of D. In (C) the concentration of B and C increases due to the increased activities of enzymes 1 and 2 because the lack of D means there is no negative feedback on enzyme 1 and possibly 2 and (D) shows the increase in the conversion of C to E by enzyme 4.

clinical features are a consequence of the enzyme deficiency. *Figure 15.15* shows how this may occur. Symptoms arise from a lack of product D if this is an essential substance and alternative pathways for its synthesis do not exist. Moreover, an accumulation of precursor C will occur if the enzyme is absent and may produce clinical features if the substrate is toxic when it accumulates. Intermediates of the pathway may also accumulate especially since there will be no negative feedback effect as the final product of the pathway is absent and cannot inhibit the first enzyme of the pathway. Finally, accumulation of a product of a minor pathway, E, may occur and if this is toxic in excess it may produce clinical features.

The treatment of inherited metabolic disorders aims at trying to prevent the accumulation of precursor(s) and provide the necessary product of the pathway. The removal of toxic products of any minor pathways may also be necessary. Future strategies are aimed at replacing the deficient enzyme or correcting the defective gene by gene therapy. Many inherited metabolic disorders caused by a deficiency of an enzyme are known (*Table 15.4*); one of the most thoroughly documented is phenylketonuria.

Phenylketonuria

Phenylketonuria (PKU) is the commonest disorder of amino acid metabolism. It has an autosomal recessive mode of inheritance, which leads to a deficiency, mostly in the liver, of phenylalanine hydroxylase (*Figure 15.16*), which catalyzes the hydroxylation of phenylalanine to tyrosine (*Figure 15.17*). Tyrosine is required for the synthesis of proteins, the pigment melanin, thyroxine and the catecholamine hormones (*Chapter 7*). However, if the enzyme is absent, then phenylalanine and its metabolites accumulate and are toxic to the developing brain. The manner in which damage occurs is not completely understood but it is believed that hyperphenylalaninemia interferes with brain amino acid metabolism and inhibits the release of neurotransmitters. There is also an increase in the level of phenylpyruvic acid, a phenylketone, which is normally a minor metabolite of phenylalanine (*Figure 15.17*). Excess phenylpyruvic acid is excreted in urine, hence the name phenylketonuria. The incidence of PKU is one in 10 000 in the UK; in other countries it varies from one in 5000 to one in 20 000 births.

The clinical features of PKU are absent at birth but develop within a few days if the newborn is untreated. These signs include a characteristic mousy odor, irritability, poor feeding, vomiting, eczema, mental retardation, as well as a pale skin, fair hair and blue eyes due to decreased melanin synthesis. The most serious of these features is irreversible mental retardation which develops within three to six months following birth. A diagnosis of PKU is made on the

Disorder	Enzyme deficiency
Phenylketonuria	phenylalanine hydroxylase
Porphyria cutanea tarda	uroporphyrinogen decarboxylase
Gaucher's disease	glucocerebrosidase
Forbe's disease	α,1,6-glucosidase
Fabry disease	α galactosidase
Glycogen storage diseases	deficiency of one of several enzymes involved in interconverting glycogen and glucose
G6PD deficiency	glucose 6-phosphate dehydrogenase

Table 15.4 Inherited enzyme deficiencies

demonstration of a concentration of phenylalanine in the serum in excess of 0.7 mmol dm^{-3}, compared with the reference range value of less than 0.1 mmol dm^{-3}. Clinical determinations are performed a few days following birth since it is vital to begin any treatments as soon as possible. The management of PKU involves restricting the dietary intake of phenylalanine so that the serum phenylalanine concentration does not exceed the limits shown in *Table 15.5*.

In the early stages of life, when the brain is developing rapidly, strict control of phenylalanine concentrations must be imposed to prevent brain damage. Commercially prepared diets with a low phenylalanine content are available. The concentration of this amino acid is low but cannot be zero since phenylalanine is an essential amino acid (*Chapter 10*) and some must be provided in the diet to support protein synthesis. Tyrosine is not an essential amino acid unless phenylalanine intake is limited. Therefore adequate quantities of tyrosine must also be provided in the diet of PKU patients. Regular monitoring of treatment is advisable. Blood is collected as a dried spot or as liquid plasma for laboratory analysis. The diet can become somewhat less rigorous after the age of 10, although many clinicians now believe that dietary restriction should be continued throughout life.

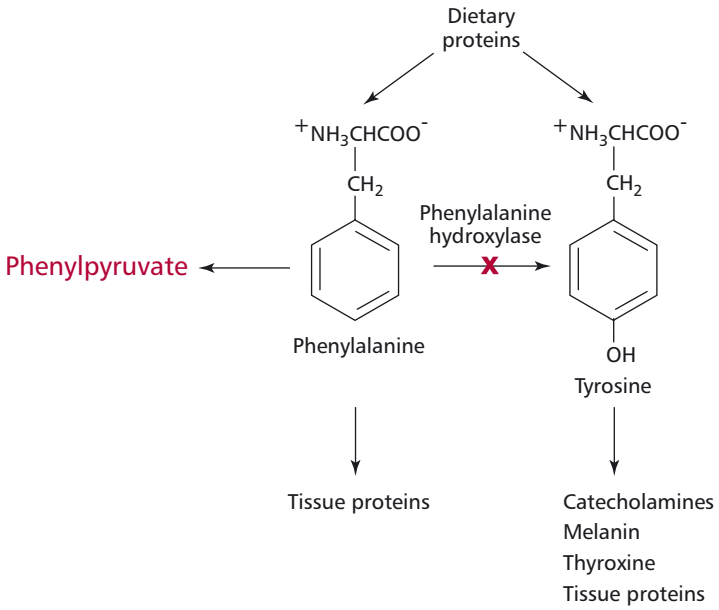


Figure 15.17 The metabolism of phenylalanine. The red cross indicates the step blocked in PKU.

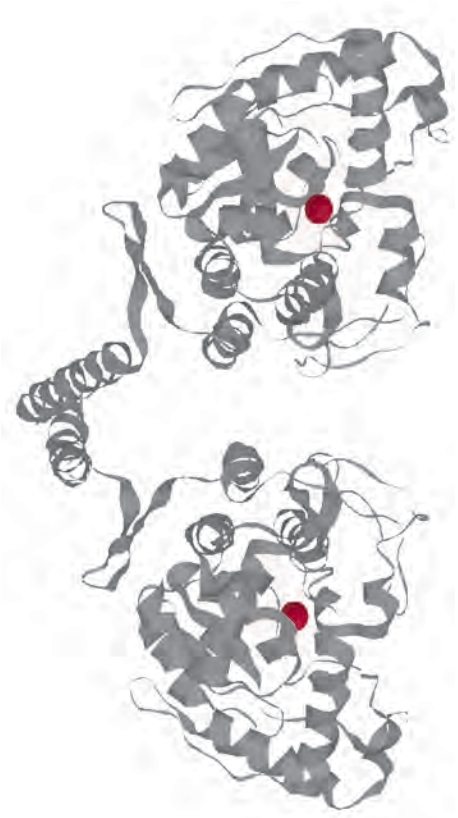


Figure 15.16 Molecular model of a phenylalanine hydroxylase molecule. The colored spheres represent Fe atoms. PDB file 2PAH.

Age/years	[Phenylalanine]/mmol dm^{-3}
0–5	<0.36
5–10	<0.48
10+	<0.70

Patients should be tested regularly to check that they are adhering to their diets.

Table 15.5 Recommended limits of serum phenylalanine in PKU patients

Children who have been diagnosed shortly after birth and properly treated by dietary management develop normally. Early treatment is crucial because the IQ of an affected individual rarely exceeds 70 and brain damage caused by untreated PKU is irreversible. Strict dietary control is also necessary in pregnant women who have PKU, since maternal hyperphenylalaninemia can affect the fetus *in utero*, even if the fetus itself does not have PKU. Mental retardation and congenital abnormalities can occur in a large proportion of these infants.

NATIONAL SCREENING PROGRAMS FOR INHERITED DISEASES

A number of factors need to be considered before a screening program (*Chapter 1*) for any inherited disease is instituted. These include:

- does the disease have a relatively high incidence;
- can the disease be detected within days of birth;
- can the disease be identified by a biochemical marker that is easily measured;
- will there be a failure in diagnosing the disease early and would this cause irreversible damage to the baby;
- can the disease be treated and will the result of any screening test be available before irreversible damage to the baby occurs?

Thus, for example, neonatal screening programs for PKU are well established in practically all the countries of the developed world, including the UK. Any screening program has to be cost effective. Screening for PKU involves collecting a specimen of capillary blood from the baby at 6 to 10 days after birth, which allows for sufficient time for feeding and protein intake to become established. The test involves determining the concentration of phenylalanine in the plasma. If the result is indicative of PKU, further definitive tests are performed. The plasma phenylalanine concentration used to be determined by the Guthrie test, which involves determining the ability of plasma to support the growth of the bacterium *Bacillus subtilis*, which can only grow if phenylalanine is present in the medium. Nowadays, however, most laboratories use chromatographic, fluorimetric or mass spectrometric methods for the estimation of phenylalanine.

15.7 CHROMOSOMES AND THE HUMAN KARYOTYPE

Interphase chromosomes are present as extended structures and cannot be seen with the light microscope. At the onset of cell division, both mitotic and meiotic, the chromosomes condense to form compact structures, referred to as mitotic figures. All chromosomes have a narrowed region called the centromere that divides the chromosome into two portions and allows them to be classified as metacentric, submetacentric, acrocentric or telocentric as shown in *Figure 15.18*. When the chromosome is divided into two unequal lengths, the shorter is called the *p* arm and the longer the *q* arm. When stained with Giemsa stain (*Figure 15.19*), most arms are divided into two or more regions by prominent bands and each region is further subdivided into subbands that can be numbered unambiguously. For example, band Xp21.2 is to be found on the *p* arm of the X chromosome in region 2, band 1, subband 2.

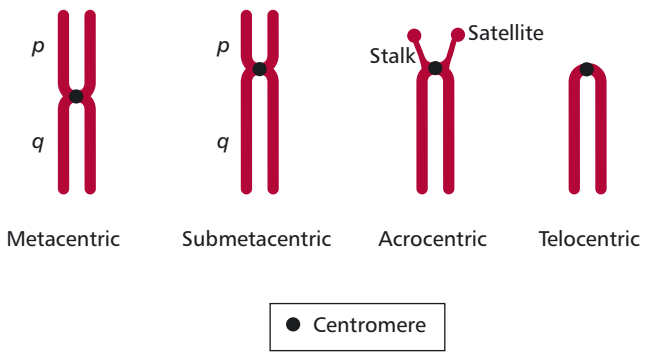


Figure 15.18 A classification of chromosomes into metacentric, submetacentric, acrocentric and telocentric types based on the position of the centromere.

A **karyotype** is the characteristic number, size and shape of chromosomes of a species. A **karyogram** is a photographic representation of these chromosomes stained and arranged in order, as for example in *Figures 15.2* and *15.20*. An **idiogram** is a diagrammatic representation or interpretive drawing of the chromosomes based on the physical features seen in the karyogram. The karyotype of normal humans is 46. Human autosomal chromosomes are divided into seven groups (*Table 15.6*) on the basis of their sizes and the positions of their centromeres.

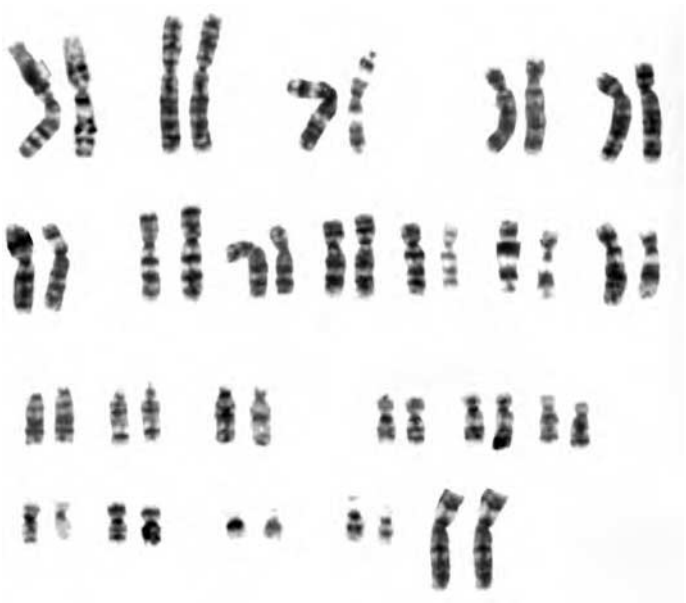


Figure 15.20 Karyogram of a normal human female showing G banding. Courtesy of J.S. Haslam and K.P. O'Craft, Tameside General Hospital, Ashton under Lyne, UK.

Figure 15.19 A single human A2 (*Table 15.6*) chromosome showing G banding. Courtesy of J.S. Haslam and K.P. O'Craft, Tameside General Hospital, Ashton under Lyne, UK.

Chromosome group	Chromosome numbers	Structures
A	1 to 3	
B	4 to 5	
C	6 to 12, X	
D	13 to 15	
E	16 to 18	
F	19 to 20	
G	21 to 22, Y	

Table 15.6 The seven groups of human chromosomes

Cytogenetics is the microscopic study of chromosomes. Small lymphocytes isolated from a blood sample or cells obtained by amniocentesis or chorionic villus sampling (*Section 15.10*) are stimulated to divide by treatment with the plant lectin, phytohemagglutinin (PHA) and mitosis is then arrested at metaphase by an inhibitor such as colchicine. Metaphase chromosomes are visible by microscopy when stained in one of several different ways to allow their accurate identification when examined by microscopy. For routine karyotyping, Giemsa (G) staining is usually the preferred procedure since this produces a pattern of alternating dark and light bands characteristic for each pair of chromosomes. These patterns reflect differences in the detailed

structure of each chromosome. Karyotyping can be performed on white cells from whole blood as described above or from amniotic fluid, which contains cells from the developing fetus. When a patient's chromosomes are examined using a microscope, it is possible to identify aberrations in chromosome number and structure.

The phenotype of a patient with a chromosomal disorder depends on the nature of their chromosomal defect. The first human chromosomal disorder was discovered in 1959 when three copies of chromosome 21 were found to be associated with Down syndrome (*Section 15.9*). The development of chromosomal banding in 1970 has markedly increased the ability to resolve small chromosomal aberrations.

FRAGILE SITES

When human cells are grown in culture, some of the chromosomes in cells derived from certain individuals fail to stain in particular regions, giving the appearance of a gap. These sites are known as **fragile sites**, since they are susceptible to breakage when the cells are cultured in the absence of certain chemicals such as folic acid, which is normally present in the culture medium. More than 80 such sites have been identified since they were first discovered in 1965. The cause of the fragility at these sites is not known with certainty but they may represent regions where the DNA has been incompletely replicated.

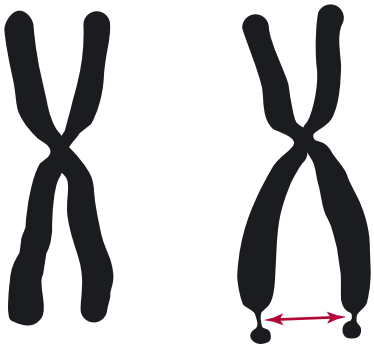


Figure 15.21 Schematic of a human X chromosome with a fragile site (arrowed).

Almost all studies on fragile sites have been carried out *in vitro* on cells halted in mitosis. Initially they were not considered to be clinically relevant and, indeed, most fragile sites do not appear to be associated with any clinical syndrome. However, a strong association has been shown to exist between a form of mental retardation called fragile X or Martin-Bell syndrome and a fragile site on the X chromosome at position Xq27.3 (*Figure 15.21*) associated with the *FMR1* gene. It is a dominant trait but fortunately fails to be fully expressed (incomplete penetrance) in many individuals. However, it is the commonest cause of mental retardation and has been estimated to affect one in about 4100 males in the UK. Most suffer mental retardation to the point that they are unable to live an independent life, and have a distinct physical appearance, including long, narrow faces with protruding chins, enlarged ears, and increased testicular size particularly after puberty. The syndrome also affects about one in 8000 females, who tend to suffer milder forms of retardation. Most humans carry a stable version of *FMR1* which has about 30 CGG repeats (*Box 15.2*). Individuals who have genes with about 45 to about 55 CGG repeats are in a gray zone; they do not have fragile X syndrome and, while they are likely to pass on a stable gene to their children, they have an increased chance of having children with a larger number of CGG repeats. People with about 55 to about 200 are said to have a *premutation* since although they generally have few or lack symptoms of fragile X syndrome, they can have children with more than 200 CGG repeats. This is the full mutation that initiates inappropriate methylation of cytosine bases and unfortunately can lead to the full blown syndrome.

The *FMR1* gene is carried on the X chromosome and shows Mendelian patterns of inheritance for X-linked disorders (*Figure 15.12*), although if it reaches the premutation stage it has a high probability of mutating (by repeat amplification) from one generation to the next. However, amplification of the CGG repeats can only occur in females, not males. Thus although there may be no family history of fragile X syndrome, it can suddenly appear in a number of offspring. The patterns of inheritance of fragile X syndrome are also somewhat complicated compared with a disorder like phenylketonuria, described in *Section 15.6*. Given that *FMR1* is on the X chromosome, a father cannot pass on any form of it to male offspring. However, daughters generally

BOX 15.2 Dynamic mutations and DNA methylation

In the early 1990s types of mutation called dynamic or expansion mutations were identified that were associated with a number of genetic disorders that increased in severity, or had an earlier onset over several generations. These disorders are referred to as trinucleotide repeat disorders. Repeating combinations of three nucleotides occur commonly in DNA molecules. All combinations of triplets, such as CGG, CAG, AGG and ACC, are found but the first two are commonest. Such sequences seem to be a normal part of the DNA and are thought to have regulatory roles in gene expression. However, if the number of repeats becomes too large, clinical problems that result in an identifiable disease are triggered. Fragile X syndrome is one such disease and is associated with an increase in the number of CGG repeats that are normally found in the *FMR1* (fragile X mental retardation 1) gene at the Xq27.3 fragile site. One consequence of the expansion in the number of CGG repeats is that methylation of the regulatory region of the gene occurs and prevents the cell from expressing *FMR1* and synthesizing fragile X mental retardation protein (fmrp), an RNA binding protein that is expressed in the brain. The lack of fmrp leads to fragile X syndrome. Methylation of DNA is the addition of methyl ($-CH_3$) groups (*Chapter 10*) to some of its bases from the donor molecule, *S*-adenosylmethionine (SAM). Only a few percent of A and C nucleotides are methylated and in vertebrate eukaryotic cells only the formation of 5-methylcytosine (Me^5C) occurs (*Figure 15.22*). Methylation at particular CpG sequences may inhibit transcription and have a role in gene regulation by switching off the expression of that gene, although the mechanism by which this occurs is unclear. However, the methyl group is known to project into the DNA molecule and interfere with the attachment of DNA binding proteins. The patterns of methylation are inherited, that is they are repeated from generation to generation. In general, *FMR1* is copied by the DNA polymerase during DNA replication with high fidelity and this stable version is almost always inherited. However, in some circumstances amplification occurs that increases the number of CGG repeats in the daughter chromosome. This is possible because repeats containing G and C nucleotides can base pair with themselves to form hairpin structures (*Figure 15.23*), which increases the risk of slipped mispairing occurring during DNA replication leading to an increase in the number of triplet repeats. The number of CGG repeats in the *FMR1* is the major factor that determines the presence or absence of fragile X syndrome. In fragile X syndrome, the mutant *FMR1* gene is nonmethylated in asymptomatic males, methylated in the inactive X chromosome of females and totally methylated in most fragile X males, which prevents its expression.

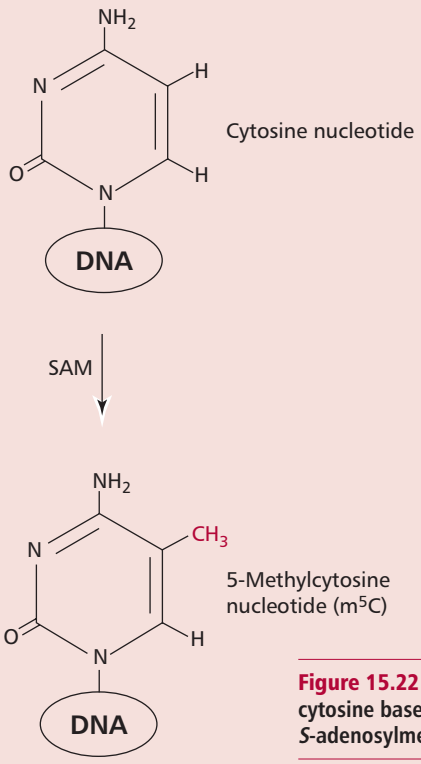


Figure 15.22 Schematic illustrating the methylation of a cytosine base in DNA to 5-methylcytosine. SAM, *S*-adenosylmethionine.

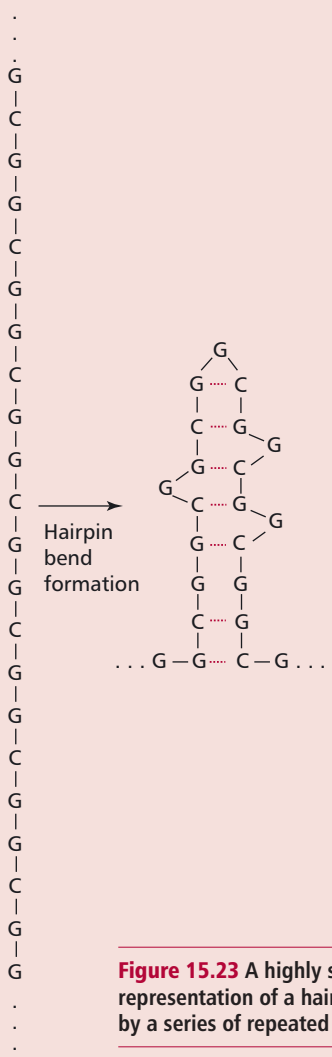


Figure 15.23 A highly schematic representation of a hairpin bend formed by a series of repeated CGG trinucleotides.

receive the paternal type. For example, almost all males with the stable version generally have daughters with the stable version. However, males with premutations, who are generally phenotypically normal and called normal transmitting males, have premutation type daughters. This inheritance can have severe consequences for any male grandchild as explained below. Most full mutation males do not have children. Those few who do would give the full mutated version to their daughters but surprisingly the daughters only express the premutation. Hence the father is passing on a reduced number of CGG repeats presumably because there are protected cells in the testes that never expand to the full mutation or a reduction in the repeat number occurs in some male reproductive cells. This means that all females who do have the full mutation must have received it from their mothers since they cannot receive it from their fathers.

Females have two X chromosomes and every child, male or female, has an equal, random chance of receiving one or the other of them. A female who has a copy of the premutation from her normal transmitting father can pass it on to her children. Most daughters who receive the premutation will show an increase in repeat number compared with their mother and, while most will show only the premutation, others will express the full mutation. Sons who inherit an X chromosome from a mother carrying a premutation are the principal group affected by fragile X syndrome since they are much more likely than females to have amplification to the full mutation. The probability of the full mutation is dependent upon the mother; those at the lower end of the premutation range, about 56–70 repeats, are less likely to have a son with the full mutation than those at the higher end with more than 100 repeats.

All males with the full mutation will experience significant symptoms. Some females with the full mutation will have symptoms of fragile X but, in general, the severity is less. Finally, there are individuals who cannot be assigned to these categories but have cells that vary regarding repeat size or the extent of methylation (*Box 15.2*). The severity of their symptoms depends on the proportion of cells affected and the tissues involved.

The phenomenon of trinucleotide repeats is seen in several other human disorders. For example, a fragile site on chromosome 3 containing the gene *FHIT* (fragile histidine triad) is often altered in cells from tumors of patients with lung cancer (*Chapter 17*). Huntington disease, myotonic dystrophy and spinobulbar muscular atrophy or Kennedy disease are also associated with trinucleotide amplifications, although they differ from fragile X syndrome in that the amplification can occur in both sexes at each generation and is not associated with chromosome fragility. However, they are similar in that a threshold number of triplet repeats must be exceeded before symptoms of the disease appear.

15.8 CHROMOSOMAL MUTATIONS OR ABERRATIONS

Chromosomal mutations include structural changes within a single chromosome or changes in the number of chromosomes present. Structural mutations occur when chromosomes break and, although in general repair mechanisms rejoin the two ends to restore rapidly the original structure, if more than one break occurs, the repair mechanisms are unable to distinguish between the broken ends and portions of different chromosomes may be joined together. This can lead to one of four major types of chromosomal structural aberration or mutation. In deletions, a section of the DNA is lost; in duplications, one or more extra copies of a segment of DNA occur in a chromosome; in inversions, there is a reversal of direction of a portion of the DNA in the chromosome and in **translocations**, segments of the DNA are

moved to a different chromosome. Deletions and duplications change the amount of DNA in a chromosome. Inversions and translocations change the arrangement of bases in a length of DNA but do not change the amount of DNA present in the chromosome.

If the exchange of chromosomal material during a translocation and inversion does not involve breaks within a gene or alter the amount of DNA, then the individual will be clinically normal and is said to have a balanced translocation. However, if the structural alteration occurs in the gonads, even a balanced translocation has clinical significance for future generations since it may lead to offspring who are chromosomally unbalanced, that is, who have lost DNA (*Figure 15.24*). Since most fetuses with unbalanced translocations tend to be spontaneously aborted, people with balanced translocations may only attract clinical attention if they and their partner are investigated because of a history of miscarriages. Infants with unbalanced translocations that do survive are mentally retarded and show multiple **dysmorphic** features, that is alterations (abnormalities) to the accepted appearance. Specific disorders can also occur when discrete genes are damaged at the translocation fractures, the resulting disorder being dependent on which genes are damaged.

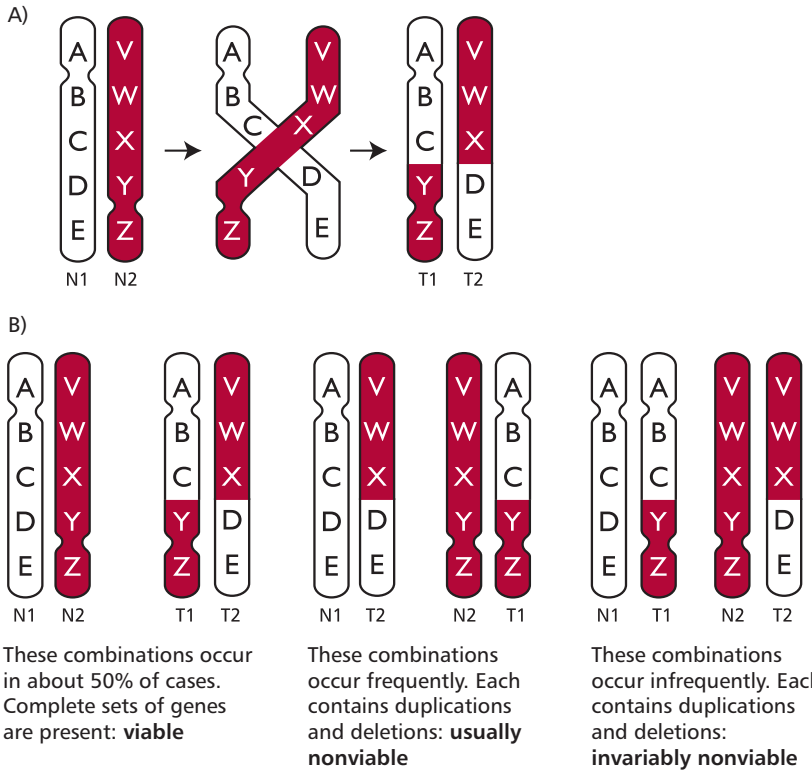


Figure 15.24 (A) Schematic showing a possible balanced translocation between two chromosomes. (B) Illustrates the types of gametes, both normal and genetically deficient that could result from translocations shown in (A). For simplicity, it has been assumed that recombination did not occur during meiosis. See text for details.

DELETIONS

Deletion of part of a chromosome can arise between two breakpoints as a result of unequal crossing over during meiosis (*Section 15.3*) or as a result of a parental translocation. Several clinical disorders are caused by deletions. In many cases, the abnormalities only occur in individuals who are heterozygous since the homozygous condition is lethal, especially if the deleted portion of the chromosome is large. However, any chromosomal deletion that can

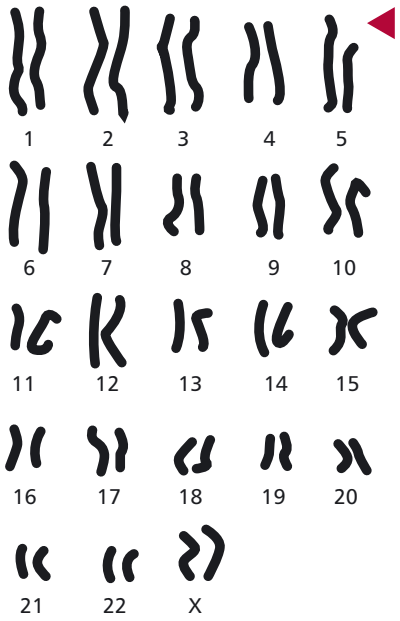


Figure 15.25 Deletion of part of one chromosome 5 (arrowed) in a karyogram of a child showing cri-du-chat syndrome.

be observed microscopically almost invariably produces a phenotype with multiple abnormal features and mental retardation because of the absence of expression of the deleted genes. For example, cri-du-chat syndrome is a heterozygous condition that occurs in about one in 50 000 births. Infants with this syndrome show anatomical malformations including gastrointestinal and cardiac complications and are often mentally retarded. The glottis and larynx also develop abnormally giving the characteristic cry, similar to the meowing of a cat, which names the syndrome. Cri-du-chat syndrome is caused by a deletion of part of the short arm of chromosome 5 (46,5p-, *Figure 15.25*). The length of the deleted portion varies; the longer the deletion the more defective the syndrome in surviving children. The effects of the syndrome are severe, although individuals who receive good home care and early special schooling can walk and communicate verbally and develop self-care skills.

Prader-Willi syndrome (frequency one in 10 000 to 25 000) and Angelman syndrome (exact frequency unknown) both result from the 'microdeletion' of the band 15q11–13 although they have different phenotypes depending upon the parental origin of the deletion. In Prader-Willi syndrome the deletion occurs invariably on the chromosome 15 inherited from the father whereas in Angelman syndrome the deletion occurs almost exclusively on the chromosome 15 from the mother. Hence inheritance of paternal and maternal copies of this region of chromosome 15 is important for normal development, a phenomenon known as **genetic imprinting**. People with Prader-Willi syndrome are mentally retarded, have small external genitalia and characteristic facial features. Babies with Prader-Willi syndrome have a poor sucking reflex hence feeding is difficult and results in weakness and stunted growth. Strangely, children with Prader-Willi syndrome become compulsive eaters at five to six years of age and suffer obesity and its related health problems (*Chapter 10*). If untreated, afflicted individuals may feed themselves to death.

Angelman syndrome is characterized by developmental delay, absence of speech, jerky movements, paroxysms of inappropriate laughter and characteristic facial features which differ from those of Prader-Willi syndrome.

Many other portions of the genome are also subject to genetic imprinting although the precise mechanisms controlling whether the paternal or maternal copies of a gene are expressed are not fully understood.

DUPLICATIONS

Chromosomal mutations that result in the doubling of a part of a chromosome are called duplications. The size of the duplicated segment varies enormously and duplicated segments may occur in a tandem configuration, that is, adjacent to each other or in different locations in the genome (*Figure 15.26*). Duplications can result in gene redundancy and may produce phenotypic variation, since there are now two copies of the gene and one copy may mutate independently of the other. This is thought to be a significant source of genetic variability during evolution. For example, gene duplications have been essential in the evolution of multigene families. These are groups of several genes whose products are similar in structure or functions. The genes for globins are a particularly well studied multigene family. Hemoglobins are tetrameric proteins consisting of two pairs of differing polypeptides each with an attached heme group able to bind and release a dioxygen molecule. Human individuals produce different hemoglobins at different stages during their lives as described in *Chapter 13*. Each of the globin polypeptides has slightly different primary structures, but consist of the α types that are found as a cluster on chromosome 16 and the β types clustered on chromosome 11. It is thought that each group of genes evolved from one original ancestral gene that underwent duplications and subsequent sequence divergence.

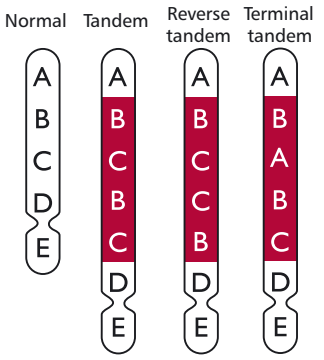


Figure 15.26 Schematic to illustrate some possible types of chromosomal duplications.

INVERSIONS

Figure 15.27 illustrates how inversions might arise. A chromosomal loop forms before fractures occur at two places on the chromosome. The insertion of the inverted segment at the newly created sticky ends and their subsequent joining within the chromosome completes the inversion. There are two types of inversions: paracentric inversions do not include the centromeres whereas pericentric inversions do. Genetic material is not lost during inversions although there can be clinical problems when fractures occur within genes or within regions that control gene expression. The meiotic consequences of a chromosomal inversion depend on the type of inversion encountered and the resulting gametes may be nonviable leading to reduced fertility.

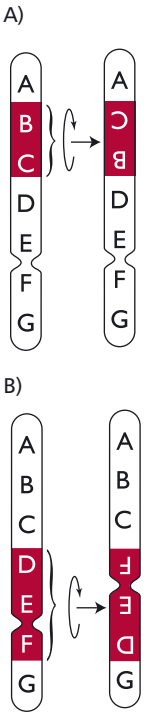


Figure 15.27 Schematics to show (A) a paracentric and (B) a pericentric inversion.

TRANSLOCATIONS

Numerous translocations occur in the human population. The simplest kinds are intrachromosomal translocations that move part of a chromosome to a different position within the same chromosome. Interchromosomal translocations transfer part of a chromosome to a nonhomologous chromosome (*Figure 15.28* and *Box 15.3*). Reciprocal translocation involves an interchromosomal translocation between two nonhomologous chromosomes. The least complex way for this event to occur is for two nonhomologous chromosome arms to come close to each other so that an exchange is facilitated.

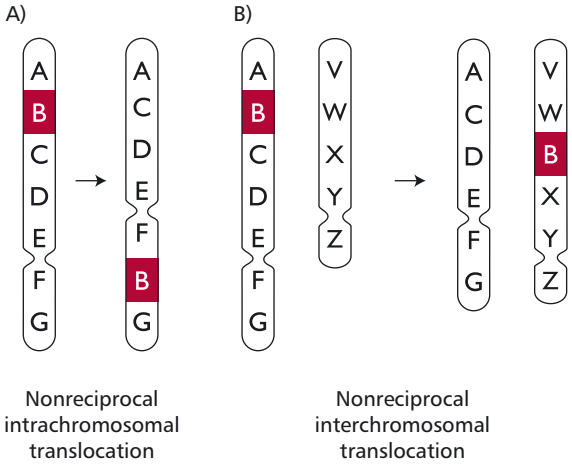


Figure 15.28 (A) Intrachromosomal and (B) interchromosomal translocations.

Homologues that are heterozygous for a reciprocal translocation undergo unorthodox synapsis during meiosis and pairing results in mitotic figures with a cross-like configuration. These chromosomes produce genetically unbalanced gametes and often result in reduced fertility. As few as 50% of the progeny of parents that are heterozygous for a reciprocal translocation survive, a condition known as semisterility. In humans, translocation can result in variations from the normal diploid number of chromosomes leading to a variety of birth defects. Translocations may transfer a gene to a region of a chromosome that is more transcriptionally active. This can lead to the development of some forms of cancer (*Chapter 17*).

A common type of translocation involves breaks at the extreme ends of the short arms of two nonhomologous acrocentric chromosomes (*Figures 15.29* and *15.34*). The small fragments produced are lost but the larger ones fuse together at their centromeric regions. This type of translocation produces a new, large submetacentric or metacentric chromosome and is often called a Robertsonian translocation.

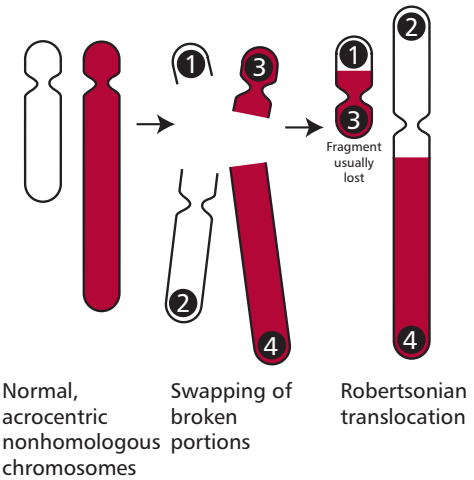


Figure 15.29 The formation of a Robertsonian translocation following breaks in two acrocentric chromosomes.

BOX 15.3 Acute promyelocytic leukemia

The biological functions of vitamin A are varied. In its aldehyde form, retinal, it participates in vision and, as the acid, retinoic acid, it controls embryonic development and the development of skin and other organs, by regulating cell proliferation and differentiation. The naturally occurring and many synthetic forms of vitamin A produced by pharmaceutical companies are called **retinoids**. The main natural retinoids are all-*trans*-retinoic acid (ATRA) and its isomer, 9-*cis*-retinoic acid. They act in similar ways to steroid hormones (*Chapter 7*). Retinoids penetrate the plasma membrane of target cells and interact with intracellular receptor proteins. The retinoid–receptor complexes are translocated to the nucleus where they interact with specific sections of DNA, leading to changes in gene expression, in other words, genes are turned on or off (*Figure 15.30 (A) and (B)*). There are two types of intracellular receptors for retinoids. One is called RAR, for retinoic acid receptor, and interacts with ATRA. The other receptor is called RXR because originally the retinoid which it recognized was unknown. However, it was subsequently found to interact with the 9-*cis* isomer. These receptors must be present in the cytosol of the cell if retinoids are to exert their influence on gene transcription.

Leukemia is a tumor that originates in the bone marrow and results in the overproduction of immature leukocytes (*Chapter 17*). Several types of leukemia have been linked with chromosomal disorders, including acute promyelocytic leukemia (APL). In APL there are abnormal hypergranular promyelocytes or immature granulocytes (*Chapter 13*) and the bleeding disorder called disseminated intravascular coagulation (DIC), which is thought to be linked to procoagulant phospholipids present in the leukemic cells. Patients may present with severe bleeding and this tends to worsen when treatment is started as the leukemic cells break down and consume large amounts of clotting factors and platelets. Eventually it was discovered that the defect in APL was a chromosomal translocation between parts of the long arms of chromosomes 15 and 17. The translocation is balanced and reciprocal and results is one abnormally long chromosome 15 (15q+) and one abnormally short chromosome 17 (17q–). This is clinically significant because of effects on the *PML* gene located on chromosome 15 that encodes the so-called PML protein and the *RAR* gene located on chromosome 17. The net result of the translocation is that a PML-RAR fusion protein is formed. This protein interferes with the normal function of PML as a growth suppressor and with that of RAR which is involved in myeloid differentiation to produce different types of blood cells from progenitor cells in the bone marrow.

In the early 1990s it was found that ATRA treatment was beneficial to patients with APL, although at the time the reason for this was not understood. It is now known that ATRA influences the genes affected by the chromosomal translocation involving chromosomes 15 and 17 as described above. Treatment with ATRA produces remission of the leukemia by promoting the conversion of leukemic blast cells into mature leukocytes. Unfortunately the remission does not usually last and normally needs to be consolidated with conventional chemotherapy.

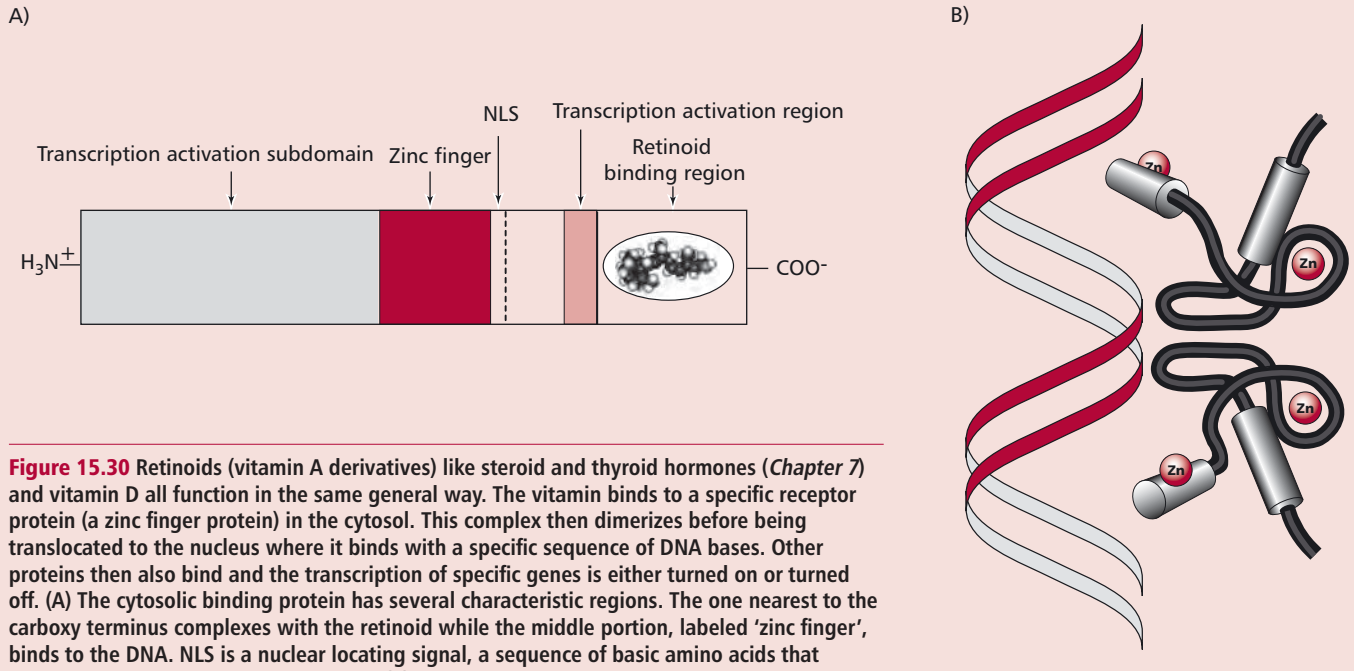


Figure 15.30 Retinoids (vitamin A derivatives) like steroid and thyroid hormones (*Chapter 7*) and vitamin D all function in the same general way. The vitamin binds to a specific receptor protein (a zinc finger protein) in the cytosol. This complex then dimerizes before being translocated to the nucleus where it binds with a specific sequence of DNA bases. Other proteins then also bind and the transcription of specific genes is either turned on or turned off. (A) The cytosolic binding protein has several characteristic regions. The one nearest to the carboxy terminus complexes with the retinoid while the middle portion, labeled 'zinc finger', binds to the DNA. NLS is a nuclear locating signal, a sequence of basic amino acids that ensures the complex enters the nucleus. (B) Schematic showing the DNA double helix binding to the dimeric form of the zinc finger protein.

15.9 VARIATIONS IN CHROMOSOME NUMBERS

Eukaryotic organisms are normally diploid and produce haploid gametes (*Section 15.3*). However, chromosomal mutations with numerical aberrations in the number of chromosomes present occur. These can be divided into two major types. **Aneuploidy** occurs when the number of chromosomes differs in having more or fewer than an exact multiple of the haploid number of chromosomes. *Table 15.7* lists a number of human aneuploid abnormalities of autosomes and sex chromosomes. In contrast, **euploidy** is the presence of an exact multiple of the haploid number of chromosomes.

Chromosomes	Syndrome
Autosomes	
Trisomy 13	Patau syndrome
Trisomy 18	Edward syndrome
Trisomy 21	Down syndrome
Sex chromosomes, female	
X0	Turner syndrome
XXX	triple X syndrome (trisomy X)
XXXX	tetrasomy
Sex chromosomes, male	
Y0	nonviable
XYY	XYY syndrome
XXY	Klinefelter syndrome
XXXY	Klinefelter syndrome
XXYY	Klinefelter syndrome

Table 15.7 Aneuploid abnormalities of human chromosomes

ANEUPLOIDY

Aneuploidy is usually caused by the nondisjunction of paired chromosomes at meiosis I or of sister chromatids at meiosis II or by delayed movement of a chromosome at anaphase. Nondisjunction is caused by the failure of pairs of homologues to separate or disjoin during segregation. *Figure 15.31 (A)* and *(B)* illustrates the consequences of nondisjunction during first meiosis and second meiosis for a single chromosome. Thus gametes are formed that either lack the chromosome or contain two copies of it. If these are fertilized by a normal haploid gamete, then zygotes are produced with one or three chromosomes. Thus nondisjunction can lead to a variety of aneuploid conditions.

The loss of a single chromosome from an otherwise diploid genome is called monosomy (2N – 1). Nullisomy results from the loss of one pair of homologous chromosomes (2N – 2). The gain of one chromosome results in trisomy (2N + 1). Tetrasomy describes the presence of four copies of a specific chromosome rather than the normal two (2N + 2). Aneuploidy can also involve the loss or the addition of more than one particular chromosome or pair of chromosomes. Thus a double monosomy involves the loss of two separate nonhomologous chromosomes (2N – 1 – 1), while a double tetrasomy would describe the presence of four copies of two chromosomes (2N + 2 + 2). Both

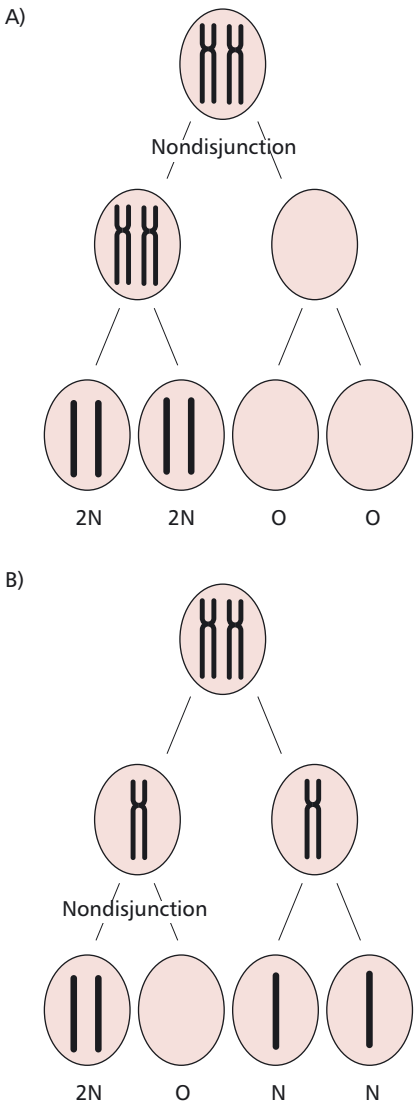


Figure 15.31 The consequences of nondisjunction of a single chromosome at (A) meiosis I and (B) meiosis II.

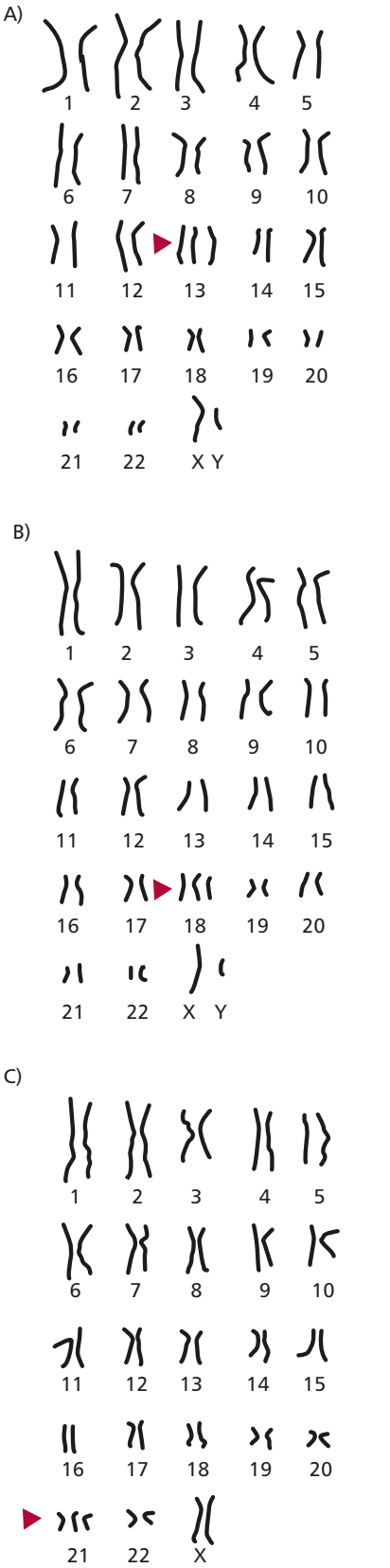


Figure 15.32 Karyotypes showing (A) trisomy-13, Patau syndrome, (B) trisomy-18, Edward syndrome and (C) trisomy-21, Down syndrome.

these cases involved meiotic nondisjunction in two different chromosomes prior to gamete formation.

Monosomy results in two types of haploid gametes, N and N – 1. Also, the single unpaired chromosome in the 2N – 1 cell is easily lost during meiosis resulting in the formation of two gametes with N – 1 chromosomes. Other types of aneuploidy also have serious, often lethal consequences in humans. Approximately 90% of all chromosomal aberrations lead to a termination of pregnancy in a spontaneous abortion.

Autosomal monosomy is rare since monosomic embryos do not develop significantly and are usually lost early in pregnancy although the abnormalities can be detected in aborted fetuses. The extra chromosome in trisomy produces individuals who are likely to have more chance of being viable provided that the chromosome involved is relatively small. The addition of a large autosomal chromosome has severe effects and is usually lethal during development. Autosomal trisomies are found in about half of the chromosomal abnormalities that lead to fetal death.

Trisomy-13 (47,13+) produces Patau syndrome (*Figure 15.32 (A)*) and affects about one in 5000 live births. The syndrome is characterized by many abnormalities including mental and physical retardation, cardiac anomalies, **polydactyly**, that is extra fingers or toes, cleft lip and palate and small eyes. Most such babies die before they are three months old.

Trisomy-18 (47,18+) is associated with Edwards syndrome (*Figure 15.32 (B)*) and occurs in about one in 4000 live births. About 80% of cases of Edwards syndrome are female. Sufferers are small at birth and have multiple congenital malformations that affect almost all body systems. Among the many abnormalities associated with the syndrome are mental and developmental retardation, elongated skull, low-set malformed ears and clenched fists. Ninety percent of infants with trisomy-18 die within six months, often from cardiac problems.

Trisomy-21 (*Figure 15.32 (C)*) leads to Down syndrome, the only human autosomal trisomy in which significant numbers of individuals survive more than a year following birth. It was named after its 'discoverer', a doctor called (Langdon) Down (1828–1896), in 1866. Affected individuals have common physical features and affectionate, loving natures. They generally have flat faces with epicanthic folds over the eyes, round heads with a protruding furrowed tongue that causes the mouth to remain partially open. They are below average height and have short, broad hands. Their physical and mental development is retarded and muscle tone and motor skills are poor. Down patients are prone to respiratory disease, 50% of them have heart problems and their incidence of leukemia is approximately 15 times higher than that of the normal population. Not surprisingly, life expectancy is reduced and few survive to 50 years of age. Many die of Alzheimer's disease (*Chapter 18*).

Down syndrome affects, on average, one in every 700 live births. However, the incidence increases with the age of the mother but not that of the father. *Figure 15.33* illustrates the relationship between the incidence of Down syndrome and maternal age, although in terms of gross numbers, most affected children are born to women under 35 years old since the majority of pregnancies occur below this age.

The relationship between the age of the mother and the incidence of Down syndrome is explainable in terms of the production of oocytes (*Chapter 7*). Females have a full complement of primary oocytes that developed in the ovary of the developing female fetus. These oocytes have commenced meiosis but are arrested at the prophase I before birth. In an adult fertile female, the nucleus of a secondary oocyte begins the second meiotic division at each monthly ovulation but progresses only to metaphase II, when division again

stops. The second meiotic division is not completed unless a sperm penetrates the secondary oocyte. Thus the succeeding ovum has been arrested in meiosis for about a month longer than the preceding one. Thus older ovulating women produce ova that are significantly older and have been arrested in meiosis longer than those of younger women. It is possible that the probability of nondisjunction increases with the length of time the primary oocyte spends in the ovary but whether ovum age is the specific cause of the increased nondisjunction leading to Down syndrome is not yet known.

Over 95% of all cases of Down syndrome are caused by trisomy 21 (*Figure 15.32 (C)*) following a nondisjunction event during meiosis in one parent, nearly always the mother. Thus, most people with Down syndrome have 47 chromosomes in all their cells. Approximately 3–4 % have the normal number (46) but have a type of Down syndrome that runs in families called familial Down syndrome, which is the result of a Robertsonian translocation (*Section 15.8*) that produces three copies of the long arm of chromosome 21 by joining the long arm of chromosome 21 with the long arm of chromosome 14 or sometimes 15 (*Figure 15.34*). The heterozygous carrier is normal because there are two copies of all major chromosome arms and hence two copies of all essential genes (*Figure 15.34*). However, meiosis will result in a 25% of the gametes formed having two copies of chromosome 21; one normal chromosome 21 and a copy attached to chromosome 14. When this gamete is fertilized by a normal haploid gamete, it forms a zygote with the normal 46 chromosomes but with three copies of chromosome 21 (*Figure 15.34*). These individuals exhibit Down syndrome.

Some individuals with Down syndrome must be institutionalized but most can be cared for at home and benefit greatly from special education programs. Advances in several areas of medical treatment have resulted in a greater life expectancy for modern day Down syndrome children.

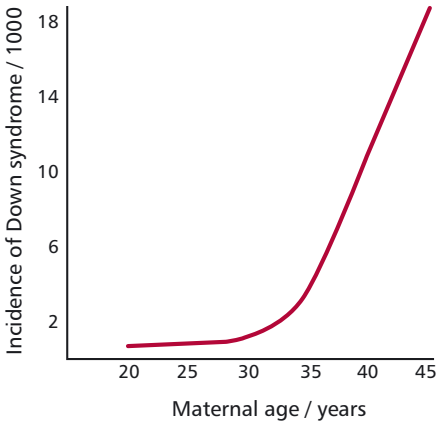


Figure 15.33 **The effect of increasing maternal age on the incidence of Down syndrome babies.**

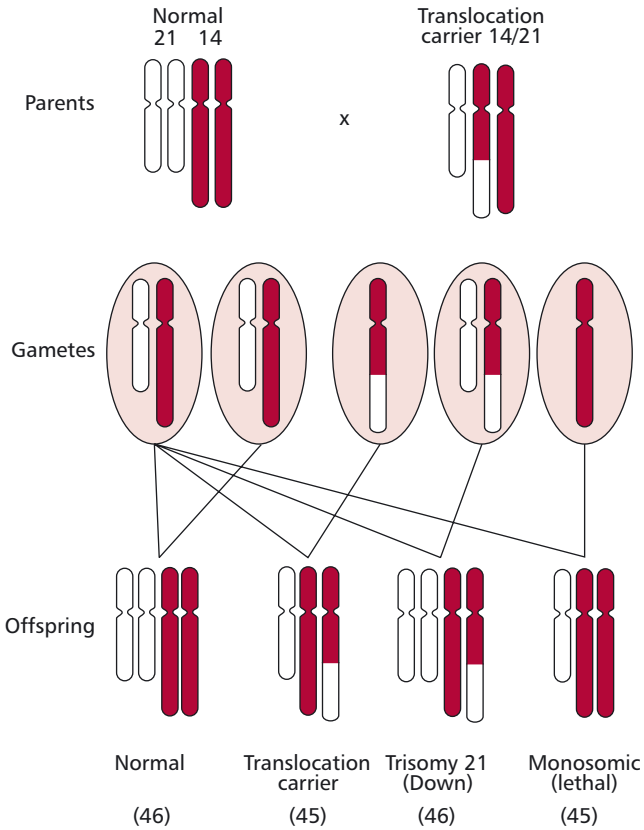


Figure 15.34 **A Robertsonian translocation involving chromosomes 14 and 21 resulting in trisomy-21, Down syndrome.** See text for details.

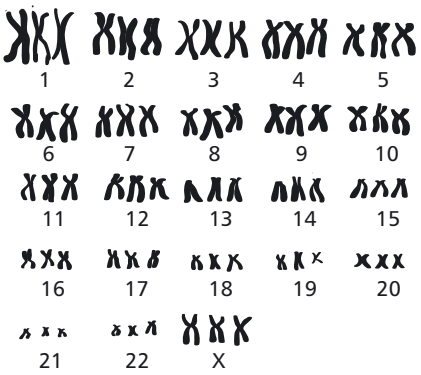


Figure 15.35 A triploid karyotype. Courtesy of J.S. Haslam and K.P. O'Craft, Tameside General Hospital, Ashton under Lyne, UK.

Aneuploidy involving sex chromosomes

Aneuploidy involving sex chromosomes gives rise to a number of well defined syndromes. These include Turner, Klinefelter and XYY syndromes. A female born with a single X chromosome (45X0) shows Turner syndrome (*Table 15.7*). The incidence is one per 5000 female births although the vast majority of 45X0 aneuploids are spontaneously aborted. The condition may arise from nondisjunction in either parent but in 75% of cases of Turner syndrome only the maternal X chromosome is present, implying that the problem originates in spermatogenesis in the father. Females with Turner syndrome are short in stature and rarely undergo secondary sexual development and so are mostly infertile, although their intelligence and life span are normal. A male born with one or more extra X chromosomes (*Table 15.7*) exhibits Klinefelter syndrome. The incidence of 47XXY is one for every 1000 boys born although the risk increases with an increase in the age of the mother. The extra chromosome is donated from the mother in 60% and from the father in 40% of cases and arises by nondisjunction during both maternal and paternal meiotic division. Affected males have underdeveloped testes and are infertile, are often above average height and have mild mental retardation. Approximately one in 1000 male children exhibit XYY syndrome, which arises from a nondisjunction of the Y chromosome. Males with XYY syndrome are above average in height and may be less fertile.

EUPLOIDY

In **monoploidy** only a single set of chromosomes (23 in humans) is present, rather than the normal diploid two (46). Monoploid fetuses do not reach full term presumably because the recessive lethal mutations, which are usually counteracted by dominant alleles in heterozygous individuals, are expressed.

In **polyploidy**, the chromosome number is an exact multiple of the haploid number but exceeds the diploid number. Organisms with three sets of chromosomes are triploid (*Figure 15.35*), those with four sets are tetraploid and so on. Polyploidy usually arises from fertilization of the egg by two spermatozoa, which increases the total number of chromosomes to 69, or from a failure at one of the maturation divisions of the egg or spermatozoon so that a diploid gamete is produced. Thus if nondisjunction occurs at meiosis I, 50% of the gametes lack chromosomes and the other 50% have two sets of chromosomes (*Figure 15.36*). If nondisjunction occurs at meiosis II, 50% of the gametes possess the normal single set of chromosomes, 25% have two sets of chromosomes and 25% lack chromosomes (*Figure 15.36*). Fusion of a gamete with two chromosome sets with a normal gamete produces a zygote with a triploid set of chromosomes (3N). Similarly, fusion of two gametes, each with two chromosome sets, produces a tetraploid (4N) zygote. Polyploidy of somatic cells can also occur following the mitotic nondisjunction of complete chromosome sets.

Polyploidy normally causes an early spontaneous abortion and survival of the fetus to full term is rare. The commonest type of polyploidy in humans is triploidy. However, polyploids with an odd number of chromosome sets always possess an unpaired chromosome for each type, hence the probability of producing a balanced gamete is low. Indeed, triploidy in humans is always lethal and is seen in 15–20% of spontaneous abortions and in only about one in 10 000 births, where death invariably occurs within a month. Triploid babies show many abnormalities, including a characteristically enlarged head. Polyploids with even numbers of sets of chromosomes generally have a better chance of being at least partially fertile because there is the potential for homologous chromosomes to be segregated equally during meiosis. However, tetraploidy is also always lethal in humans and is seen in approximately 5% of spontaneous abortions. Very rarely, tetraploid humans are born although they only survive for a short time.

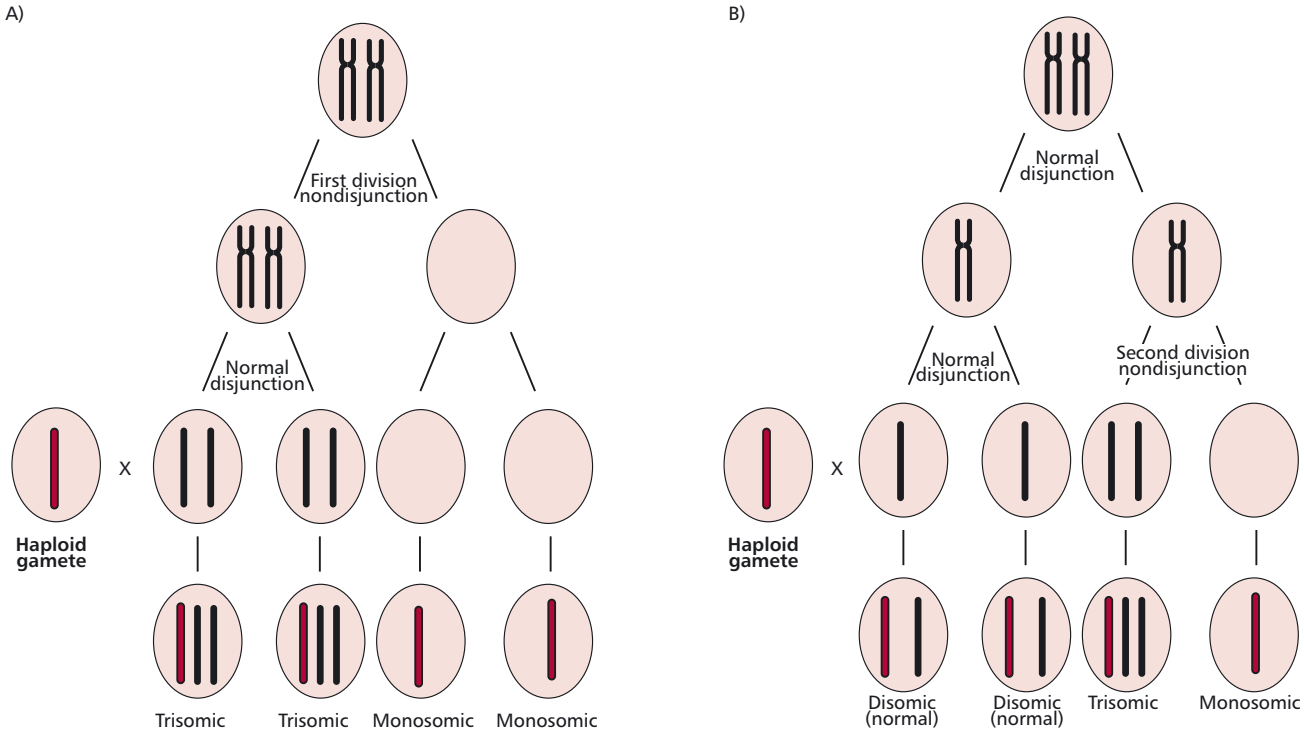


Figure 15.36 Schematic to show the production of abnormal gametes following nondisjunction at (A) at meiosis I and (B) meiosis II resulting in trisomic zygotes following fertilization with a normal haploid gamete.

15.10 DETECTING, DIAGNOSING AND SCREENING HUMAN GENETIC DISEASES

Identifying the genetic basis for a human disorder usually requires an analysis of the family history as far back as possible. If this shows that the trait is inherited, it is possible to predict whether the mutant allele is dominant or recessive and whether it is X- or autosomal-linked. Obviously, dominant mutations are the simplest to detect. If they are X-linked, then affected fathers will pass the trait to all their daughters. However, if autosomal, then dominant mutations would be expected to occur in approximately 50% of the children of an affected heterozygous individual.

In many cases, the diagnosis of a genetic disease can be made prenatally. The most widely used methods for this are amniocentesis and chorionic villus sampling (CVS). In the former, a needle is used to withdraw amniotic fluid (*Figure 15.37 (A)*) containing cells genetically identical to those of the fetus. In CVS, a catheter is inserted into the uterus and a small tissue sample of the fetal chorion removed (*Figure 15.37 (B)*). In both cases, a variety of cytogenetic and biochemical tests can then be performed on the cells and tissue to identify any single gene disorders or chromosomal abnormalities.

People in whom a genetic defect has been detected will be advised to seek genetic counseling, especially if they wish to have children. The advice they are given is based on analyses of the risks that they may produce a child with a genetic abnormality or that they themselves may develop a late onset genetic disease. A broad range of information is required and genetic counselors require training to provide this information with appropriate consideration.

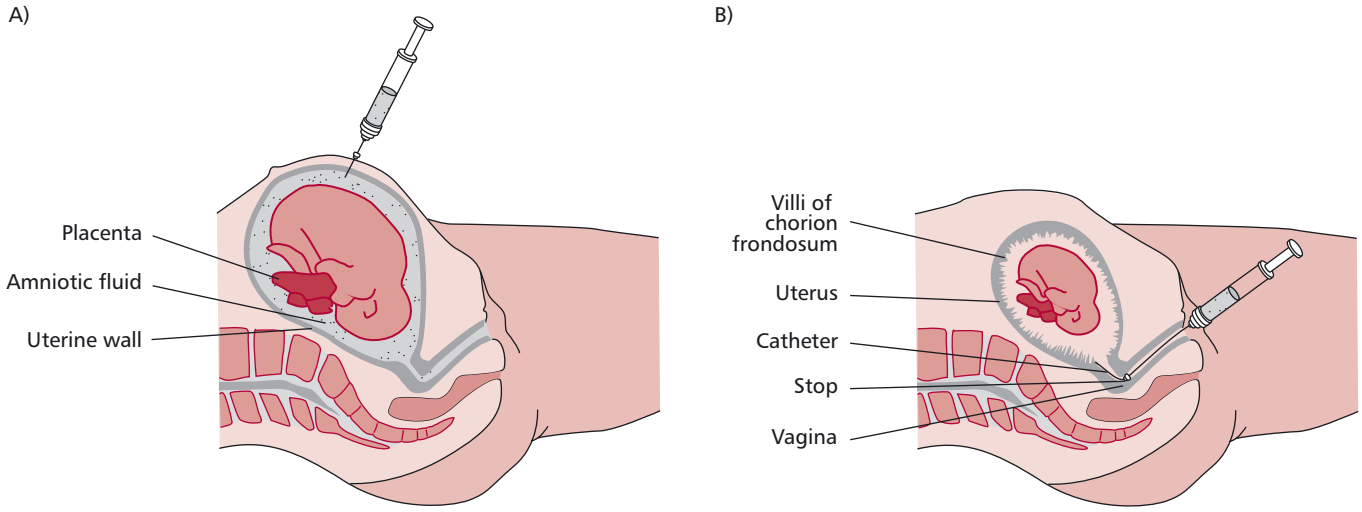


Figure 15.37 Outlines of (A) amniocentesis and (B) chorionic villus sampling to obtain specimens for genetic analysis of the fetus.

DETECTION OF HEREDITARY DISEASES

Tests based on recombinant DNA technology have increased in recent years because of their high sensitivity and accuracy in detecting genetic disorders at the prenatal stage. The detection of hereditary diseases in a given genome was traditionally a long and laborious task. However, modern techniques of chromosome and DNA analyses have resulted in a dramatic increase in the number of tests for genetic diseases with a considerable improvement in the time required for analysis. For example, using PCR, polymerase chain reaction (*Chapter 3*), virtually any portion of a gene or even whole genes can be amplified for analysis by electrophoretic techniques or sequenced to detect mutations. This not only allows for diagnosing patients with inherited disorders but also the detection of mutations in carriers, even though they do not express any symptom of the disorder. It is also a direct way of distinguishing different mutations within a single gene, each of which can lead to disorders, for example muscular dystrophies which are described in *Chapter 16*. It is hoped that eventually predictive tests for disorders that have only some genetic component, such as heart disease and cancers, will eventually be developed. Indeed, PCR analysis of cells lost in feces has demonstrated premalignant changes in the gastrointestinal tract and allowed patients at risk of developing colon cancer to be identified. This is of clinical importance since the earlier treatments of malignant conditions are started, the more favorable the prognosis.

Cloned DNA sequences have expanded the range of prenatal testing because they allow the fetal genotype to be examined directly, rather than relying on secondary tests for the products of the normal or mutant genes. Thus, mutations in DNA can be detected in those cases where an aberrant product cannot be detected prior to birth, even though a test is available. A test for sickle cell anemia using a restriction enzyme has been described in *Chapter 13*. However, RFLP analysis requires that the mutation in the gene alters the restriction sites recognized by restriction endonucleases and this is not always the case. In contrast, allele-specific oligonucleotides (ASOs) are synthetic nucleotide probes, which bind only to their complementary DNA. They will not hybridize to other sequences and, in appropriate highly stringent conditions, differentially bind to and distinguish between alleles that differ by as little as one nucleotide. They can thus distinguish between the native and mutant forms of a gene with excellent resolution and potential versatility.

BOX 15.4 Prenatal diagnosis for Down syndrome

The Quadruple Test for Down syndrome calculates the risk of having a Down fetus taking into account the maternal age at term and four markers, α-fetoprotein (AFP), unconjugated estriol, total human chorionic gonadotropin, hCG (or more usually its free β subunit) and inhibin-A at 14–22 weeks, in the maternal serum. There have been several variations on this test. In Down syndrome, the α-fetoprotein tends to be low compared with the normal (while in neural tube defects, for example spina bifida, it is high). However, concentrations of hCG are increased. A screening protocol was proposed in 1998 that combined maternal serum AFP, the urinary β-core fragment of hCG (a breakdown product of hCG) and total urine estradiol. This test is said to be superior to the 75% sensitivity at the 5% false-positive rate compared with when β-core/estradiol and maternal age alone are used.

Maternal age is important since birth prevalence of Down syndrome increases 100-fold between the maternal ages of 15 and 50 years. Statistics that relate the risk of bearing a Down syndrome child to the age of the mother (*Figure 15.33*) raise serious issues for women who become pregnant later in life. Genetic counseling may also be useful in informing the parents about the probability that their child will be affected and in educating them about Down syndrome. It is important that older pregnant women consider tests to determine whether the fetus has a normal complement of chromosomes. Amniocentesis or chorionic villus sampling and the culture of fetal cells will allow its karyotype to be determined.

The definitive test for Down syndrome is prenatal cytogenetic screening, that is karyotyping (*Section 15.7*), and in the developed countries this is routinely offered to pregnant women. It requires either amniocentesis or chorionic villus sampling. Karyotyping detects a range of numerical and structural abnormalities in the chromosomes in addition to Down and other common autosomal trisomies. However, the cells obtained from amniocentesis or chorionic villus sampling must be cultured to provided sufficient biological material and so full cytogenetic analysis involves a delay of 14 days or longer before a result can be given. Obviously the earlier a definitive positive result is obtained, the sooner the prospective parents can make clinically relevant decisions. Therefore 'molecular methods' have been investigated since these have the potential to give a result much more rapidly. Fluorescence *in situ* hybridization (FISH) is a technique in which fluorescently-labeled DNA probes that will hybridize to relevant regions of the chromosomes are applied to cell preparations (*Chapter 6*). When the preparations are examined with a fluorescent microscope the presence or absence of the target regions are revealed. Alternatively, PCR (*Chapter 3*) can be used to amplify these regions and the results can be seen on electrophoresis gels. Both methods can potentially give a result in 24–48 h. These molecular methods have been shown to be accurate since they would have failed to detect an abnormal karyotype in only about one in 100 amniocentesis samples. Obviously such tests will only give information about regions of the chromosomes for which DNA probes are applied. Many laboratories in the UK now offer FISH or PCR along with karyotyping, mostly to target pregnancies which are considered to be at high risk after screening by the Quadruple test. If the fetus is diagnosed as having Down syndrome, a therapeutic abortion is an option the parents may consider.

Tests based on ASOs are now available to screen for mutations associated with cystic fibrosis (*Chapter 16*) and glaucoma.

Allele-specific oligonucleotides are being increasingly combined with DNA microarrays, or chips. These are small glass slides or nylon membranes divided into squares, called fields, each of which contains a specific probe about 20 oligonucleotides long bound to the slide. DNA microarrays can be produced containing thousands of probes and can thus be used to analyze many different genes simultaneously. DNA is extracted from the cells and digested with one or more restriction endonucleases to produce small sized fragments that are labeled with a fluorescent dye. These are heated to separate the DNA into single strands which are then added to the microarray. Fragments whose sequence is complementary to a probe will hybridize with it and bind to the microarray; others will be washed off even if their complementary sequence differs from the probe by as little as one base. A laser based device is used to scan the array and determine where the binding has occurred to identify specific mutations (*Figure 15.38*). DNA chips are in development that will contain probes for all of the approximately 22 000 human genes to allow the simultaneous analysis of the DNA from a single person for hundreds of genetic diseases or genetic predispositions. The generation of such data has profound social, ethical and legal implications.

Potential parents in whom a genetic defect is detected must be advised to have genetic counseling. The advice they are given is based on analyses of the risks of them having a child with a genetic abnormality or that they may develop a late onset genetic disease. Information drawn from a wide range of sources is required in such circumstances and genetic counselors must provide such information with tact and sensitivity.

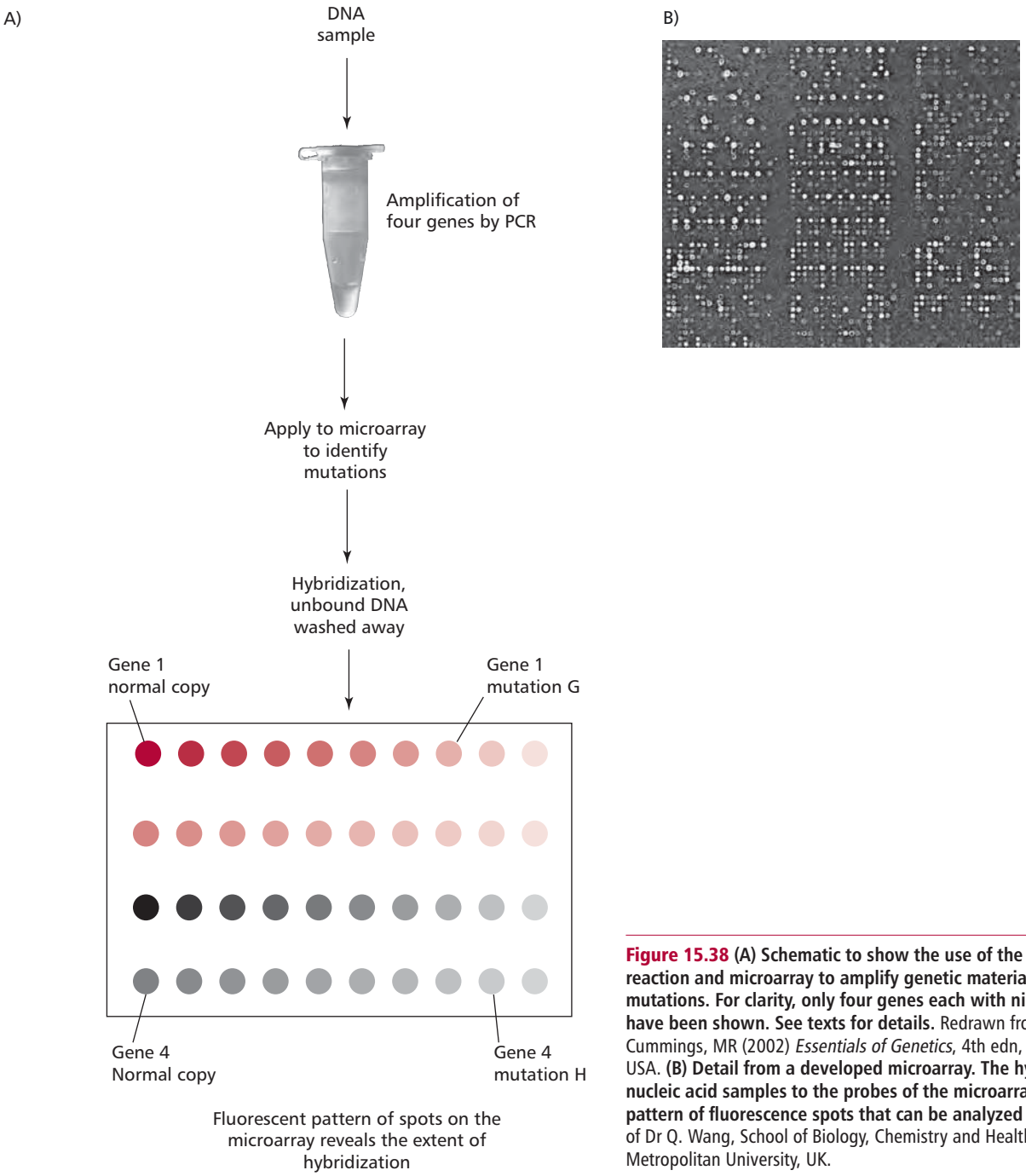


Figure 15.38 **(A) Schematic to show the use of the polymerase chain reaction and microarray to amplify genetic material and detect specific mutations. For clarity, only four genes each with nine (A–I) mutations have been shown. See texts for details.** Redrawn from Klug, WS and Cummings, MR (2002) *Essentials of Genetics*, 4th edn, Prentice Hall, NJ, USA. **(B) Detail from a developed microarray. The hybridization of nucleic acid samples to the probes of the microarray determines the pattern of fluorescence spots that can be analyzed by a laser.** Courtesy of Dr Q. Wang, School of Biology, Chemistry and Health Science, Manchester Metropolitan University, UK.

CASE STUDY 15.1

Christine was born after a normal pregnancy. For the first few days she was healthy but then started to vomit frequently. Her mother noted that her urine had a peculiar mousy smell. About a month after birth, Christine was admitted to hospital for the frequent vomiting where it was realized that the genetic screening test after her birth had been deficient. Her blood was analysed for phenylalanine as shown (reference value in parentheses).

Plasma [phenylalanine]	1.6 mmol dm^{-3}	(<0.1 mmol dm^{-3})

Questions

(a) What is the diagnosis for Christine?

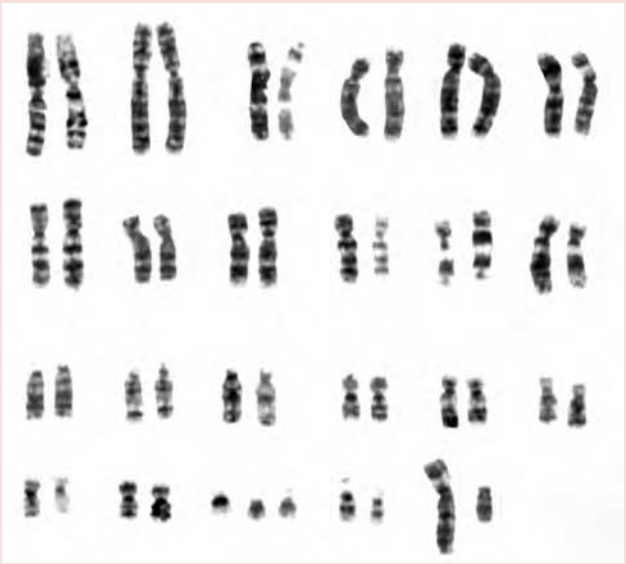
(b) How should Christine be treated?

(c) Why does Christine's urine have a characteristic mousy odor?

(d) What would happen to Christine if she were not treated?

CASE STUDY 15.2

Jane is a 39-year-old healthy woman who has just given birth to her first child, a son, Peter. She had wanted the pregnancy in her words 'to be completely natural' and had refused an amniocentesis. Unfortunately, Peter shows the very obvious physical characteristics of Down syndrome. Below is Peter's karyogram.



Questions

(a) Examine the karyogram. What is the cause of Down syndrome in this case?

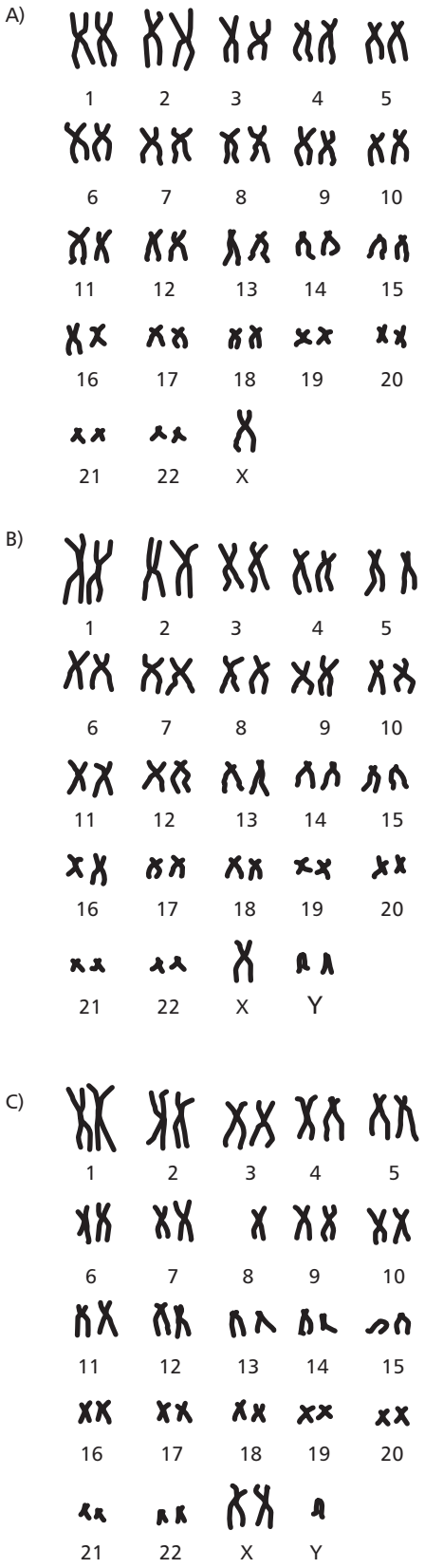
(b) Given that a clinical diagnosis of Down syndrome is nonproblematical, why is it necessary to obtain a karyotype?

(c) What advice would you give Jane?

15.11 SUMMARY

The sequence of nucleotides of the genes in the DNA forms the genetic blueprint of cells, controlling all the cell's activities. This DNA sequence is transmitted to offspring in the gametes. Alterations in the sequence of nucleotides or to the chromosomal content of cells, that is, mutations, can lead to disease and/or death. Mutations may result in absence or abnormality of a protein, perhaps an enzyme. Chromosomal aberrations involve structural changes to individual chromosomes, such as deletions,

duplications, inversions and translocations. Changes to the chromosomal complement include aneuploidy and euploidy. Down syndrome is the commonest aneuploid condition and is characterized by trisomy of the whole, or part of, chromosome 21. Genetic disease can be diagnosed using molecular techniques, including the use of the polymerase chain reaction and DNA probes in microarrays. Once a genetic defect has been diagnosed, genetic counseling can be offered to affected individuals as part of the treatment process.



QUESTIONS

1. Which **ONE** of the following statements about phenylketonuria is **INCORRECT**?
   a) PKU sufferers should be placed on a diet low in phenylalanine.
   b) PKU has an autosomal dominant mode of inheritance.
   c) Individuals with untreated PKU may suffer from mental retardation.
   d) PKU has an incidence of around 1:10 000 in the UK.
   e) PKU sufferers have insufficient melanin in their skin and hair.

2. Which of the following has an aneuploid karyotype?
   a) A male with a balanced Robertsonian translocation involving chromosomes 13 and 21.
   b) A male sufferer of phenylketonuria.
   c) A female sufferer of fatal familial insomnia.
   d) A female with a balanced translocation involving chromosome arms 11q and 22q.
   e) A male with Klinefelter's syndrome.

3. Duchenne muscular dystrophy is an X-linked recessive trait. On average, what proportion of the children of a normal father and carrier mother would be affected?

4. A female is heterozygous for fragile X syndrome. Describe the inheritance pattern you would expect to see in her children, given the father is a normal male.

5. Autosomal dominant and X-linked dominant diseases can both be passed on to children. Suggest characteristics that would help identify whether a particular syndrome was inherited in an autosomal or X-linked fashion.

6. Examine the three accompanying karyotypes (A)–(C). In each case, name the syndrome caused by these karyotypes.

FURTHER READING

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Interesting web sites:

http://www.cjd.ed.ac.uk/

www.doh.gov.uk/cjd

www.orpha.net/consor/cgi-bin/home.php?Lng=GB

The Online Mendelian Inheritance in Man (OMIM™) website. Address: http://www.ncbi.nlm.nih.gov/omim/