CHAPTER 03 Genetics: how cells divide and introduce variation

Learning points for this chapter

After working through this chapter, you should be able to:

• Understand the relevance and importance of genomics
• Detail the key steps in DNA replication and gene expression
• Describe the processes of cell division and provide examples of how genetic variation may occur
• Discuss, with specific examples, the implications of genetic knowledge for the practice of healthcare

3.1 Introduction and clinical relevance

The interaction of genetic and environmental factors is responsible for the development of the majority of disease, and in some cases the probability of developing a disease is known because the genetic factors can be traced through generations of families. In other cases, the exact contribution of genetic and environmental factors is less clear. Each of the patients introduced in this chapter has a clinical condition strongly influenced by genetic factors. It is worth bearing in mind as you read this chapter that recent scientific and technological advances are rapidly altering our understanding of health and disease, and this is beginning to transform healthcare practice.

As discussed in Chapter 2, Sheila has been told that she is a possible candidate for a form of cancer therapy with a compound that blocks the action of the HER2 receptor. She will continue to receive other recommended forms of treatment as necessary, including surgery, chemotherapy and radiotherapy. It is also expected that the addition of this form of ‘targeted’ therapy should significantly reduce the risk of the cancer reoccurring in the future.
Sarah, who is now 17 years old, was diagnosed at the age of 1 year with cystic fibrosis, a life-threatening inherited disease that clogs the lungs and digestive system with thick sticky mucus, making it hard for her to breathe and digest food. The fact that Sarah has cystic fibrosis was a surprise for her parents because no other family members were known to have the condition, although this is often the case with autosomal recessive conditions and especially when family histories are not well recorded.

Sarah leads as full a life as possible, enjoys dancing and skiing, and plans to go to university. Assisted by her mother, Sarah completes a daily series of physiotherapy exercises to clear her lungs of the viscous mucus secretions. Sarah has experienced very frequent admissions to hospital for exacerbation of her breathing problems due to the development of recurrent chest infections.

Alexei is a 14-year-old boy with Down syndrome as a result of being born with an extra chromosome 21. He currently attends a mainstream school and has until recently enjoyed this. He has made firm friends and, with dedicated educational support, has made good progress. Recently, however, the teachers say his progress has plateaued and Alexei has been described as a bit withdrawn and occasionally disruptive. At home, Alexei’s parents notice a change in Alexei’s mood and that he is reluctant to engage in homework and attend school. Alexei really looks forward to a half round of golf with his friends and has surprised everyone with how good he is. However, for some weeks, he has not completed the round with his friends, preferring instead to catch his breath and rest for a few minutes with a drink and some chocolate.

Alexei’s mother, Adelia, was 36 years old when she became pregnant with Alexei. The risk of Down syndrome increases with maternal age, and so her family doctor suggested she consider prenatal diagnosis. This would involve taking a sample of fetal cells from the fluid surrounding the developing fetus by a procedure known as amniocentesis. The procedure carries a small increase in the risk of miscarriage, but Adelia refused the procedure as she felt the information would not change her mind about her pregnancy. She preferred instead to provide a blood sample, which can estimate the extent of her increased risk, and underwent an ultrasound assessment of her developing baby (Alexei), which can also provide an estimate of the risk of Down syndrome.
The structure and function of our body, with its trillions of cells, complex physiological processes and varied form, rely on the inheritance and expression of the genetic material (nucleic acids) present within the nucleus of all our body cells. This hereditary material represents the physical link between generations and populations of people, helping to explain how people are similar and yet also different. When considered together with our adaptive physiological responses to the environment, this hereditary material, present within all of our cells, helps us to understand how we develop from a single cell into a fully formed human. Knowledge of genetics is therefore fundamental to understanding the basis of health and disease. Indeed, much of modern healthcare is being informed by a rapid explosion in genetic knowledge. This carries significant implications for the individual, families and society. In this chapter, we will explore the nature of this genetic material and how it functions to affect our lives and our health.

3.2 What you need to know – essential anatomy and physiology

3.2.1 The genome

The biological information required to make and maintain a living organism is present in all cells, encoded in the form of deoxyribonucleic acid (DNA). This, in its entirety within the nucleus of a cell, is termed the genome. During periods of cell division, the DNA can be seen under a microscope, organized within structures called chromosomes.

The genome represents the hereditary information in the form of genes, which provide the organism with a mechanism to function and to reproduce. A gene contains the information for the cell to make molecules called ribonucleic acid (RNA) and, through a type of RNA called messenger RNA (mRNA), to make the
proteins required by the body (see Figure 3.1 and Table 3.1). It is estimated that in humans there are approximately 20,000–25,000 genes that code for proteins, although these genes represent only a small fraction of our genome. The remaining DNA does not directly code for proteins via the manufacture of mRNA. Instead, much of it is used to form a variety of non-coding RNA molecules that function as regulators, essential to the process of protein manufacture. Many thousands of proteins are required by the body and its cells. It is important that the amount of protein produced by individual and by different cells is carefully regulated by non-coding RNA. Protein turnover, affected by synthesis, protein stability and rates of degradation, is a crucial element for cell function.

**Figure 3.1 – The hierarchy of the genome.**
The human genome contains all of the genetic information and is found in every cell, stored in the nucleus in the form of chromosomes. The chromosomes are tightly coiled DNA molecules, which contain genes that are transcribed to produce RNA, which is then translated to produce proteins.

**Table 3.1 – Organization of the genome**

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body</td>
<td>Made up of trillions of cells.</td>
</tr>
<tr>
<td>Cells</td>
<td>Every cell has a nucleus.</td>
</tr>
<tr>
<td>Nucleus</td>
<td>The nucleus contains chromosomes.</td>
</tr>
<tr>
<td>Chromosomes</td>
<td>There are 46 chromosomes in human somatic (body) cells and 23 in sex cells (sperm/ovum); they are made up of a complex of proteins and DNA.</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid (DNA) is the molecule that carries the 'genetic code'. The code is structured into individual genes.</td>
</tr>
<tr>
<td>Gene</td>
<td>A unit of inheritance (there are approximately 20,000 within each body cell), which is a specific segment of DNA that codes for the making of a polypeptide or a functional RNA molecule.</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid (RNA) carries hereditary information transcribed from DNA. There are a variety of forms of RNA (including ribosomal RNA and transfer RNA), but it is messenger RNA (mRNA) that is used directly within the cytoplasm for making proteins.</td>
</tr>
</tbody>
</table>
Structure of the genome

The genome comprises all of the genetic information and is contained within 46 chromosomes in the nucleus of a somatic (body) cell; a small amount of (circular) DNA also exists within mitochondria, but this has a specialized role that is beyond the scope of this book. The chromosomes themselves are highly organized structures composed of DNA wrapped around histone proteins to form a coiled structure called chromatin. Chromosomes are normally only visible during cell division when the chromatin becomes tightly folded; throughout the rest of the cell cycle, chromatin remains in a more extended relaxed state.

DNA is synthesized from building blocks called nucleotides. There are three parts to a nucleotide used for making DNA (called a deoxynucleotide): a sugar molecule (2’-deoxyribose), a phosphate molecule and a molecule called a DNA base. There are four types of DNA base: adenine (A), thymine (T), guanine (G) and cytosine (C) (see Figure 3.2a).

To synthesize DNA from nucleotides, the sugar molecule of one nucleotide is joined to the phosphate molecule of another nucleotide by a phosphodiester bond to form a linear chain (see Figure 3.2b), which is several million nucleotides long. In all, there are approximately 6 billion DNA nucleotides within the genomic DNA of a human somatic cell. A DNA molecule in the nucleus of a human cell is double-stranded and forms a helical structure (see Figure 3.2a) – called the DNA double helix – with the DNA bases on one strand hydrogen bonded to the DNA bases on the other strand. This base pairing only occurs in two configurations:

- adenine (A) can bind to thymine (T)
- guanine (G) can bind to cytosine (C).

Thus, there are only two possible pairings (A–T and C–G) to bind the two strands of DNA; these are referred to as DNA base pairs. The weak hydrogen bonds holding together DNA base pairs are shown as dotted lines in Figure 3.2b; there

Figure 3.2 – The structure of a DNA molecule.  
(a) Pairing of complementary base pairs. [b] The structure of the DNA double helix.
are two hydrogen bonds between A and T and three hydrogen bonds between G and C. When a gene is expressed, specific enzymes separate the two DNA strands to allow mRNA to be made from the correct strand. The order of DNA bases along the entire length of the DNA molecule is crucially important, because it is the order of the bases that represents the ‘genetic code’ that is read during protein synthesis (see Box 3.2, later).

**Function of the genome**

The genetic material, in the form of DNA, must be able to:

- be repeatedly and accurately replicated, in order to create new and viable cells
- code for the development and function of cells as they grow and contribute to the maintenance of homeostasis
- change (a process called mutation), producing variations between individuals in a population so that the species can adapt for survival in its environment.

A specific sequence of DNA bases containing the information required to make a protein is called a gene. All the genes present in an individual's cells, responsible for coding for all the proteins to be made, are collectively referred to as the genotype. The phenotype of an individual is the observable characteristics, such as physical appearance, behaviour and biochemical activity, that arise as a consequence of protein synthesis following the reading of all the code in the genotype. The type and amounts of protein required by a living organism are dynamic and can change within minutes. Proteins govern and regulate cellular metabolism and so it is important that the amounts and types of protein available are tightly regulated. It is important to understand that the range and amounts of proteins synthesized (called the proteome) are highly dynamic, while the inherited genome remains static (except for the occasional mutation).

Modern technology is able to map and identify the genes held within a human cell and so is able to establish the genes that are expressed and translated into proteins. The aim of the Human Genome Project was to map and record the sequence of all of the 3 billion DNA base pairs within the haploid human genome (the term haploid will be explained later in this chapter). This was completed with an estimated accuracy of 99.9% in 2003 and is important for a number of reasons:

- It will enable an increased understanding of how genes interact and are involved with causing disease.
- It will help to identify who is susceptible to diseases and how they can be protected from them. This is especially pertinent to chronic diseases that exert a high burden and economic cost to patients and society.
- It will also enable a better understanding of how the expression of the genome is influenced by the environment. This will be important for populations and carries implications for public health programmes, including the development of strategies aimed at offering healthier lifestyle choices to people to limit or even prevent the development of disease.
- It will increase the potential for the development of gene therapies.
- It will stimulate the design of personalized therapies through the development
of drugs that act selectively on particular genetic variants (some of these are already available: see Sheila, Patient 2.3, with breast cancer).

• It will help improve the development of new diagnostic methods.

All organisms possess a genome, and efforts are under way to characterize the genome of a wide variety of species. Knowledge that emerges from these other genome projects can be extremely useful for humans; for example:

• Genes conserved among distantly related species can be indicative of important functions conserved through evolutionary time, suggesting how these particular genes may function in humans.
• Knowledge of plant genomics can be applied to the optimization of nutrition, food quality and supply.
• An improved understanding of microbial genomics can be applied to the clean-up of polluted environments, energy generation and the capturing of carbon released from human activity. Indeed, one application of

**BOX 3.1**

**Genomic technology used to control outbreaks of infection in a hospital**

Meticillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of community- and hospital-acquired infection worldwide (MRSA was discussed in *Chapter 1*) (Figure 3.3). It is resistant to many antibiotics, is very difficult to eradicate and causes potentially lethal infection. The control of MRSA and healthcare-acquired infection is a patient safety issue and a public health priority.

Patients admitted to hospital are routinely screened for colonization with MRSA (see Francine, Patient 1.3) so that they can be treated before it causes infection in themselves or other people, especially vulnerable patients such as the young, the elderly and immunocompromised patients.

Researchers and clinicians from the Wellcome Trust Sanger Institute and the University of Cambridge and Cambridge University Hospitals in the UK used advanced DNA sequencing technology to identify specific strains of MRSA responsible for an outbreak of infection on a special care baby unit in real time. This allowed the researchers to identify whether an actual outbreak of MRSA infection was taking place. An unsuspected carrier of the bacterial strain linked to the outbreak was also identified and successfully treated. The study also revealed that the strain of MRSA responsible for the outbreak was being carried by, or was causing infection in, more people than previously recognized, having spread into the wider community; this conclusion could not be reached with traditional methods.

The DNA sequencing project was key in bringing the outbreak to an early end, possibly saving the hospital money and making patients safer.

Sir Mark Walport, then Director of the Wellcome Trust, was quoted as saying 'This is a dramatic demonstration that medical genomics is no longer a technology of the future – it is a technology of the here and now. By collaborating with NHS doctors, geneticists have shown that sequencing can have extremely important applications in healthcare today, halting an outbreak of a potentially deadly disease' (http://www.sanger.ac.uk/news/view/2012-06-13-tracking-mrsa-in-real-time).
microbial genomics has recently been used to successfully control outbreaks of infection within hospitals (see Box 3.1).

- Knowledge of virus genomes and their infection strategies has also created the opportunity to vaccinate against specific forms of cancer caused by viruses, such as cervical cancer (see Jess, Patient 14.1).

It is clear that genomic technologies are likely to play an increasingly important part in our lives and not just in the healthcare environment.

**Gene expression: using the genetic code to make proteins**

The information stored in the form of a sequence of DNA bases in a gene has to be expressed in a physical form, which is that of the encoded protein. In humans, the DNA sequence representing the code for a particular protein is not stored in a continuous stretch of DNA bases in the gene. The gene actually comprises a number of protein-coding regions called *exons* (representing expressed sequences) interspersed with non-coding regions called *introns* (representing intervening sequences). A large amount of the human genome is composed of these non-coding introns, which have been shown to have a role in controlling gene expression.

There are several sequential steps involved in making a protein, and these are summarized quite simply by the so-called ‘central dogma’ of molecular biology (see Box 3.2).

**Transcription: DNA makes RNA**

Transcription involves copying one strand of double-stranded DNA into a single strand of RNA. Three main processes are required to make an RNA molecule: initiation, elongation and termination of an RNA chain (illustrated in Figure 3.4).

**The central dogma of molecular biology**

The central dogma of molecular biology represents a one-way sequential process whereby genetic information in the form of DNA is used to make RNA (in the form of mRNA for protein-coding genes), which is used to direct the synthesis of its corresponding protein.

However, we now know that in some limited biological circumstances the process can be reversed; that is, RNA can be used to synthesize DNA. For example, some viruses such as human immunodeficiency virus (HIV) contain RNA, rather than DNA, together with an enzyme called reverse transcriptase. When HIV infects a cell (as has happened to Jerry, Patient 11.2), its reverse transcriptase is used to make viral DNA from its RNA (the reverse of the central dogma of molecular biology). This viral DNA can then be integrated into the host genome.
**Initiation**
Regulatory proteins called transcription factors interact with chromatin (as described earlier, a complex of DNA and histone proteins) to unwind the DNA helix and reveal specific nucleotide sequences of DNA to which an enzyme called RNA polymerase can bind. These DNA sequences are located at a site called the promoter region, which is close to the gene to be transcribed. This region often contains a DNA sequence known as a TATA box, comprising the DNA nucleotide bases thymine (T) and adenine (A), marking the start of transcription. Once bound to the DNA, and assisted by a number of protein transcription factors, RNA polymerase begins to unwind and separate the two strands of DNA. The exposed DNA bases on a separated single strand of DNA (A, T, G and C) then become available for copying. The strand of DNA that is actually used to make an RNA copy is known as the template or anti-sense strand. The RNA produced has the same sequence as the non-template strand of DNA, called the sense strand or coding strand (except that the RNA contains U instead of T; discussed in the following paragraph).

**Elongation**
RNA polymerase travels along the template strand of DNA, interacting with the exposed DNA bases. As it does so, RNA polymerase catalyses the formation of a long polynucleotide chain from RNA nucleotides. The order of the growing chain of RNA nucleotides is matched according to the order of A, T, G and C present on the DNA: if guanine is present on the DNA, then the complementary nucleotide in the RNA will be cytosine; if it is thymine, then adenine is added. However, the RNA molecule is slightly different chemically from DNA, in that RNA contains the base uracil (U) instead of thymine, and so when the RNA polymerase finds adenine on the DNA template, it adds uracil to the growing polynucleotide chain. The replacement of thymine by uracil does not change the order of nucleotide bases and so the encoded information remains the same (see Figure 3.5).
Termination

As the RNA polymerase travels along the DNA, copying it, the growing strand of RNA detaches from the DNA, which reforms as a double-stranded molecule. The newly synthesized RNA molecule is usually modified in a variety of ways; for example, each end of the RNA molecule is chemically modified. Most importantly, non-coding intron sequences from the gene are removed by post-transcriptional processing mechanisms called RNA splicing, which cut the RNA molecule at the exon–intron junctions and then join together the RNA coding for exon sequences. The RNA transcript then contains a continuous stretch of nucleotides coding for the corresponding protein with all intron sequences removed; at this stage, it is referred to as messenger RNA (mRNA). The mRNA molecules then leave the nucleus through pores in the nuclear membrane and enter the cytoplasmic compartment of the cell, where they attach to ribosomes and are translated into protein. Ribosomes can be found free within the cytoplasm, but are most frequently found within the extensive mesh-like network of the rough endoplasmic reticulum (see Chapter 2). Other forms of RNA, for example ribosomal RNA (rRNA) and transfer RNA (tRNA), play important roles in the process of translation, although they do not code for proteins.

Translation: RNA makes protein

The process of reading an mRNA and using the coding information to synthesize a functional protein is called translation.

Proteins are macromolecules made of amino acids. In order to make a functional protein, the correct amino acids have to be covalently bound together in the correct order. The order of amino acids is crucial because this ultimately determines the protein's physical and chemical properties. Translation occurs in the cytoplasm using ribosomes (discussed in Chapter 2), tRNA molecules and amino acids; it also requires the presence of specific proteins called translation factors.

Three nucleotide bases in mRNA are required to specify a particular amino acid; this triplet of bases is known as a codon. Four different nucleotide bases are used to make up mRNA, and so 64 different codon combinations are possible \((4 \times 4 \times 4 = 64)\). There are only 20 amino acids in total and so there are more than enough codons to represent all the amino acids. In fact, 61 codons represent the amino acids and the remaining three act as stop signals to terminate protein synthesis. The relationship between the codons and the amino acids they represent is called the genetic code (see Box 3.3).

Transfer RNA (tRNA) plays an important role in the process of translation, although it does not code for proteins. At one end of any given tRNA molecule is a site for the binding of just one of the 20 amino acids; after it forms a covalent bond with that amino acid, it is called aminoacyl-tRNA. The tRNA also contains a nucleotide sequence of three bases called an anticodon, which matches a complementary codon on mRNA and is able to hydrogen bond to it. This is the basis of how the genetic code is translated: a tRNA molecule recognizes a specific codon, has the correct amino acid already bound to it and so is ready to be incorporated into the protein to be synthesized. The process of protein synthesis also requires a ribosome that associates with the aminoacyl-tRNAs and the mRNA molecule.

Protein synthesis can be summarized as three main phases (see Figure 3.6).
The genetic code

The genetic code can be interpreted by reference to a codon table (see Table 3.2). Each triplet of RNA nucleotides is a codon and the order of codons on a strand of mRNA specifies which amino acids will be added to a polypeptide chain during protein synthesis.

**Table 3.2 – A codon table**

<table>
<thead>
<tr>
<th>1st base in codon</th>
<th>2nd base in codon</th>
<th>3rd base in codon</th>
<th>3rd base in codon</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>C</td>
<td>A</td>
<td>G</td>
</tr>
<tr>
<td>U</td>
<td>Phe</td>
<td>Ser</td>
<td>Tyr</td>
</tr>
<tr>
<td>U</td>
<td>Phe</td>
<td>Ser</td>
<td>Tyr</td>
</tr>
<tr>
<td>Leu</td>
<td>Ser</td>
<td>STOP</td>
<td>STOP</td>
</tr>
<tr>
<td>Leu</td>
<td>Ser</td>
<td>STOP</td>
<td>STOP</td>
</tr>
<tr>
<td>C</td>
<td>Leu</td>
<td>Pro</td>
<td>His</td>
</tr>
<tr>
<td>Leu</td>
<td>Pro</td>
<td>His</td>
<td>Arg</td>
</tr>
<tr>
<td>Leu</td>
<td>Pro</td>
<td>Gln</td>
<td>Arg</td>
</tr>
<tr>
<td>Leu</td>
<td>Pro</td>
<td>Gln</td>
<td>Arg</td>
</tr>
<tr>
<td>A</td>
<td>Ile</td>
<td>Thr</td>
<td>Asn</td>
</tr>
<tr>
<td>Ile</td>
<td>Thr</td>
<td>Asn</td>
<td>Ser</td>
</tr>
<tr>
<td>Ile</td>
<td>Thr</td>
<td>Lys</td>
<td>Arg</td>
</tr>
<tr>
<td>Met</td>
<td>Thr</td>
<td>Lys</td>
<td>Arg</td>
</tr>
<tr>
<td>G</td>
<td>Val</td>
<td>Ala</td>
<td>Asp</td>
</tr>
<tr>
<td>Val</td>
<td>Ala</td>
<td>Asp</td>
<td>Gly</td>
</tr>
<tr>
<td>Val</td>
<td>Ala</td>
<td>Glu</td>
<td>Gly</td>
</tr>
<tr>
<td>Val</td>
<td>Ala</td>
<td>Glu</td>
<td>Gly</td>
</tr>
</tbody>
</table>

Some amino acids such as serine and arginine have multiple codons, whereas tryptophan and methionine have only one each. AUG doubles as the start codon and as the codon for internal methionines. Note the three stop codons.

**Abbreviations**

<table>
<thead>
<tr>
<th>Ala</th>
<th>Alanine</th>
<th>Leu</th>
<th>Leucine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg</td>
<td>Arginine</td>
<td>Lys</td>
<td>Lysine</td>
</tr>
<tr>
<td>Asn</td>
<td>Asparagine</td>
<td>Met</td>
<td>Methionine</td>
</tr>
<tr>
<td>Asp</td>
<td>Aspartic acid</td>
<td>Phe</td>
<td>Phenylalanine</td>
</tr>
<tr>
<td>Cys</td>
<td>Cysteine</td>
<td>Pro</td>
<td>Proline</td>
</tr>
<tr>
<td>Glu</td>
<td>Glutamic acid</td>
<td>Ser</td>
<td>Serine</td>
</tr>
<tr>
<td>Gln</td>
<td>Glutamine</td>
<td>Thr</td>
<td>Threonine</td>
</tr>
<tr>
<td>Gly</td>
<td>Glycine</td>
<td>Trp</td>
<td>Tryptophan</td>
</tr>
<tr>
<td>His</td>
<td>Histidine</td>
<td>Try</td>
<td>Tyrosine</td>
</tr>
<tr>
<td>Ile</td>
<td>Isoleucine</td>
<td>Val</td>
<td>Valine</td>
</tr>
</tbody>
</table>

The codon AUG specifies the amino acid methionine. This codon also acts as the start codon, and so all polypeptides start with the amino acid methionine. Protein synthesis ends when one of the three stop codons (also called termination codons: UAA, UAG and UGA) is presented to the ribosome. The stop codons do not specify amino acids; instead, when the ribosome encounters a stop codon, a protein called a release factor binds and causes translation to end.
**Initiation**

Initiation of protein synthesis requires a start codon (AUG) in the mRNA, which encodes the amino acid methionine (see Table 3.2). The corresponding aminoacyl-tRNA molecule (with methionine attached and an anticodon (UAC) complementary to the start codon) binds to the start codon and a ribosome also binds to form an initiation complex.

**Elongation**

Another aminoacyl-tRNA molecule, together with its complementary anticodon, binds to the next codon on the mRNA. With the help of the ribosome and a variety of enzymes, the two amino acids become joined together with a peptide bond. This process occurs repeatedly along the length of the mRNA molecule to form a growing polypeptide chain of amino acids that correspond to the codons in the mRNA. Many ribosomes can simultaneously interact with an mRNA molecule along its length forming a structure known as a polysome, to produce more than one copy of the protein at a time, ensuring that protein synthesis can occur rapidly and efficiently.

**Termination**

This occurs when a stop codon is reached. The polypeptide chain then leaves the mRNA and the ribosome. After translation, many proteins need to be chemically modified (in a wide variety of ways called ‘post-translational modification’) before they can become fully functional.

The genetic code – continued

Note that the genetic code is degenerate, i.e. there are more codons than necessary for the 20 amino acids so there are often multiple codons coding for the same amino acid. Therefore, although a single nucleotide change in a DNA sequence (a mutation), and hence to the corresponding mRNA sequence, will change the codon to a different codon, this may still encode the same amino acid. In this case, therefore, the mutation will not alter the amino acid sequence of the final protein.

Each of the 20 amino acids has its own standard abbreviation, making it easier to compile a list of the amino acid sequence that makes a protein (see Table 3.2). This is useful for understanding how alterations in the genetic code or the amino acid sequence of a protein affect function and thereby influence health and disease (see Sarah, Patient 3.1, and Yasmeen, Patient 3.4). In the case of Sarah with cystic fibrosis, the genetic code is frequently altered by deletion of three DNA nucleotides in just one specific gene. This changes the amino acid sequence of a particular protein, which causes cystic fibrosis (discussed later in this chapter). In the case of Yasmeen with sickle cell disease, just one DNA nucleotide in the β-globin (pronounced beta-globin) gene changes from adenine to thymine (A to T), altering the polypeptide chain by just one amino acid, resulting in glutamic acid being substituted by valine (see Chapter 7) to cause sickle cell disease.

The amino acids highlighted in red in Table 3.2 are essential amino acids that cannot be synthesized in the body and so they must be obtained from food (see Chapter 7).
What influences gene expression and what are the consequences?

It is tempting to think that, because all cells contain the same genomic DNA, they are all the same type of cell. In fact, there are over 200 different types of body cells that give rise to our organs, grouped into the four main types of tissue (discussed in Chapter 2). The differentiation of cells into the different types is determined by which genes are expressed and when they are expressed. It is important to recognize that cells and tissues are responsive to their local
environment and this will influence the expression of genes, which then make the proteins necessary for cellular processes. Gene expression, therefore, determines in what way a cell becomes specialized; for example, many of the cells lining the gastrointestinal tract possess the ability to absorb nutrients, whereas others are able to secrete mucus.

Differentiated cells generally have a limited lifespan; for example, gastrointestinal epithelial cells and skin keratinocytes are replaced every few days, erythrocytes remain functional for a few months, while neurones and memory T-lymphocytes persist for decades. A few types of differentiated cells, such as neurones, which comprise the brain, and muscle cells, which form skeletal and cardiac muscle, are no longer capable of cell division. These cells, produced during embryonic development, then differentiate, and are retained throughout the life of the organism as post-mitotic cells. When injured, they are capable of limited repair and regeneration, but if lost, they are not replaced. An example of this would be the death of cardiac muscle cells due to a myocardial infarction (heart attack).

In contrast, cells of other tissues, especially those with a rapid cell turnover such as skin, smooth muscle, fibroblasts, endothelial cells of blood vessels and the epithelial cells of most internal organs are able to proliferate as needed throughout life to maintain the homeodynamic state of tissues and organs. For example, keratinocytes and fibroblasts proliferate rapidly to repair tissues after injury, participating in the process of wound repair, while liver cells (hepatocytes), which in adults do not normally divide, can be induced to proliferate when large numbers of the liver cells are removed (for example, by surgical removal of part of the liver). Human liver transplants can be successful with only a part of a donated liver transplanted. This ability of hepatocytes to divide and regenerate to form a fully functioning liver makes liver transplants from living donors a realistic therapeutic option. However, it requires major surgery, with a high risk of morbidity and a small risk of death to the healthy donor, and so the procedure is restricted to specialist centres.

Stem cells – cells that are able to self-renew and remain undifferentiated while producing progeny that do differentiate (introduced in Chapter 2) – are of great interest in scientific and clinical research because they retain the potential for manipulation of gene expression, particularly in those genes involved in cell division and differentiation. The process of differentiation involves several stages as cells become increasingly specialized; this is influenced by external signals such as molecules in the local microenvironment, which influence which sets of genes are expressed, appropriate for the tissue they arise within. Stem cells hold great promise for the treatment of diseases that might best respond to the replacement and transplantation of cells or tissue; this represents the field of regenerative medicine.

Genetic factors mean that some people may be more or less susceptible or resistant to the development of specific diseases, such as cardiovascular disease or infection. However, the extent of their risk of developing the disease can be modified by environmental and lifestyle factors. For example, the risk of experiencing a heart attack – a blockage of a blood vessel in the heart causing heart muscle to die (discussed further in Chapter 9, see Robert, Patient 9.1) – is known to
be influenced by inherited variations within genes on chromosome 9. However, recent findings from a large study of these genetic variations and lifestyle factors revealed that consuming a diet rich in raw fruit and vegetables reduced the risk of a heart attack. Cardiovascular diseases represent the leading cause of death in Western societies and have complex causes influenced by smoking, activity levels and diet. It is important to recognize that genetic inheritance may predispose a person to an increased risk of development of disease, but does not necessarily determine future health, as lifestyle and environmental factors play an important part in this. Globally, the most common chronic diseases are caused by four well-known and modifiable risk factors:

- tobacco use
- physical inactivity
- unhealthy diet
- being overweight.

Therefore, avoiding exposure to tobacco, participating in regular exercise and eating a healthy diet to maintain a healthy weight are simple but effective measures for improving population health, regardless of genetic inheritance. Promoting health through education and support is an important element of healthcare professional practice. To illustrate this, Robert (Patient 9.1), introduced in Chapter 9, will reduce his risk of further complications and possibly avoid an early death from heart disease if he is able to adjust his lifestyle.

In addition, people sometimes respond differently to therapeutic drugs depending on their genetics. The new discipline of ‘pharmacogenetics’ aims to understand individual responses to drugs based on an individual genotype. It is anticipated that personalized pharmacological therapy will increase as knowledge from the Human Genome Project is exploited.

The control of gene expression is influenced by many factors and by mechanisms that are still not fully understood, but it involves both transcription and translation. For example, the close interaction of histone proteins (a part of chromatin) with DNA affects the accessibility of DNA sequences available for transcription. Chromatin also controls the availability of regulatory proteins such as transcription factors to DNA, thereby regulating transcription. Given that a large number of protein-coding genes are estimated to be present in the genome, there is a requirement for the majority of these to be inactive until needed, and therefore tight control of gene expression is essential.

The availability of transcription factors to influence gene expression is often under the influence of external and internal environmental factors. The external environmental factors include stressors acting on the cell, such as heat, injury and light, while the internal environmental factors include changes in the local chemical environment such as the presence of reactive oxygen species and pro-inflammatory cytokines (see Chapter 11). The latter also includes the actions of hormones; for example, the hormone oestrogen produced in the ovaries binds onto oestrogen receptors present on cells within the uterus or breast. The receptor itself is a protein and, as such, is a product of gene expression. Activated oestrogen receptors bind to

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DNA and influence the expression of many genes, some of which are required for the proliferation of uterine or breast cells, regulation of the menstrual cycle and the development of female secondary sexual characteristics (see Chapter 5).

Direct modification of DNA itself also influences gene expression, such as the addition of methyl groups (hypermethylation) to cytosine nucleotides within regulatory sequences of DNA, or the modification of histone proteins associated with DNA. The hypermethylation of DNA does not involve changing the order of DNA bases (A, T, C or G), but it does influence transcription, determining which proteins can be synthesized. This is an example of an epigenetic change (a change to the phenotype that is not caused by a change in the DNA sequence) that often results in suppression of gene expression. For example, if hypermethylation of DNA occurs within genes that regulate cell division, then rates of cell proliferation might change. Among many triggers, methylation of DNA is now recognized to occur in response to changes in the diet and exposure to environmental chemicals over the lifespan. Maternal nutrition is observed to influence the health of her offspring, not only at birth but also much later in life, affecting the risk of heart disease and obesity. The exact mechanism is not fully understood, but evidence is emerging indicating that epigenetic modification of DNA is involved. Epigenetic changes are now recognized to be a feature in a wide variety of clinical disorders, including cancer, type 2 diabetes mellitus, rheumatoid arthritis, Alzheimer’s disease and neurodevelopmental disorders.

Understanding and mapping epigenetic changes is of great interest today because it represents chemical features of the genome that are important to gene expression and are therefore important in gaining a fuller understanding of the processes involved in health and disease. Where epigenetic changes occur in germ cells, these can be inherited and will be reflected in the phenotype of offspring. Studies of identical (monozygotic) twins show that although they share a common genotype, making them ‘genetically identical’, they are observed to develop clinical conditions such as rheumatoid arthritis or schizophrenia at different rates. Some of these differences can be accounted for by epigenetic changes that occur as identical (monozygotic) twins gradually age, live different lifestyles and begin to live apart as adults. Indeed, studies of twins over time provide very important information about the role of genetics and epigenetics in health and disease. A multinational project, similar to the Human Genome Project, is currently under way to map the human ‘epigenome’. This project is likely to increase our understanding of how genes are regulated and involved in the development of disorders as diverse as cancer and neurodevelopmental disorders such as autism.

### 3.2.2 Chromosomes

**Sources of genetic variation: ‘We are all different, aren’t we?’**

Each somatic cell in humans is known as a diploid cell because it has two copies of each chromosome, that is, 46 chromosomes organized into two sets of 23 pairs. Twenty-two of these pairs of chromosomes are called autosomes and the remaining pair is referred to as the sex chromosomes (X and Y) because they carry genes that determine the sex of the individual. Germ cells that produce the gametes (sperm and ovum) undergo meiosis, a form of cell division that reduces
the number of chromosomes by half, so that each gamete contains only one copy of each chromosome and the gametes are described as haploid cells. Fertilization of an ovum with a sperm cell to produce a zygote restores the chromosome complement to a diploid state, that is, a full set of 46 chromosomes. Mitosis (a type of cell division that maintains the diploid state of reproduced cells) creates all future somatic cells that will develop into a full human being.

The 23 pairs of chromosomes found in every somatic cell are termed homologous chromosomes. The two chromosomes in a pair are similar in that they carry the same set of genes and can be recognized to form a pair with each other during the process of cell division. It is important to recognize that the genes are also inherited in pairs, but that these two genes are not identical. There are different forms of genes, called alleles, which usually provide a range of phenotypes; for example, there are three main alleles that determine the major blood groups (discussed in Chapter 9). The importance of alleles to heredity will be discussed later in this chapter.

During fertilization, when the haploid sperm and ovum join, one of each of the 23 pairs of chromosomes is inherited from the father and the other from the mother. We therefore inherit two copies of each gene. The sex chromosomes are an exception because they are not the same and are termed X and Y chromosomes. A human that inherits two X chromosomes will become a woman, whereas a man possesses one X chromosome and one Y chromosome (XY). Expression of genes located on the Y chromosome causes the formation and development of sexual and other organs that provide a male phenotype (see Figure 3.7).

The transfer of genetic information from DNA starts with the making of RNA – transcription of a gene. The chromosomes present within a cell can be observed under a microscope during a phase of cell division called metaphase. When stained with dyes and placed in order, the characteristic structure, number and staining pattern of chromosomes is revealed; this is called a karyotype (see Figure 3.8a). Any abnormality observed in a karyotype represents gross alterations to the genome and may indicate serious consequences for an individual's phenotype (an abnormal karyotype containing...
Figure 3.8 – (a) Normal female karyotype and (b) karyotype of an individual with Down syndrome.

[a] Note that the autosomes are grouped in similar pairs, with a single pair of sex chromosomes – in this case, the karyotype is described as 46,XX, meaning 23 pairs of chromosomes with two of them being X chromosomes.

[b] This karyotype is described as 47,XX,+21 and is characteristic of an individual with Down syndrome – there is an extra copy (known as trisomy) of chromosome 21. Reproduced from Binns, V. and Hsu, N. (2001) Prenatal Diagnosis, eLS, © 2001 John Wiley & Sons, Ltd.

an extra chromosome representing Down syndrome is shown in Figure 3.8b and Alexei (Patient 3.2) has Down syndrome. Chromosomal abnormalities usually occur during the cell division process of meiosis, which occurs exclusively within germ cells, or during mitosis within somatic cells. The karyotype is a useful tool for the clinical geneticist in the diagnosis of genetic disorders and birth defects. Chromosomal abnormalities are sometimes, but not always, lethal to the individual.

3.2.3 Cell division

Mitosis

Dividing somatic cells form a population or ‘clone’ of genetically identical cells. This is because the process of somatic cell division (called mitosis) results in two genetically identical ‘daughter’ cells. Mitosis can be thought of as a cycle with a series of distinct phases (see Figure 3.9). When a cell is formed after mitosis, it may either enter a resting state or begin to enter another round of cell division. The stages of the cell cycle are as follows.

Resting

- $G_0$: this is the gap 0 or resting stage and represents the stage in which most of our body cells can be found as they metabolize, express genes and function normally. In this phase, the tightly coiled chromosomes relax and are not visible under a light microscope. In $G_0$, the cell may have temporarily or permanently left the cell cycle.

Interphase

A cell preparing to divide enters a period of growth and metabolism called interphase. Within interphase are three discrete phases called $G_1$, $S$ and $G_2$:

- $G_1$: during this first gap phase, the cell grows and prepares to express proteins necessary for DNA synthesis; from here, the cell can continue round the cycle or can enter the resting phase, $G_0$. 
Figure 3.9 – The cell cycle.
Cell division represents a brief period in the cell cycle and is subdivided into five short phases. When cells escape the cell cycle, they enter G0 until division is required again. Alternatively, they may become terminally differentiated or may die through a process known as apoptosis.

- **S phase**: during this synthesis phase, replication of DNA occurs to produce two identical copies of DNA (as 92 chromosomes)
- **G2**: during the second gap phase, the cell organizes the structures required for the separation of the replicated DNA (in chromosomes) between the two daughter cells.

As the cell moves from one part of interphase to another, it passes through various checkpoints. The boundaries between the G1 and S phase and between the G2 and S phase are known as the G1/S and G2/S checkpoints, respectively. These checkpoints are sensitive to conditions of stress, allowing a cell to halt cell division and undergo repair; that is, they check that conditions are favourable for replication and allow DNA repair processes to occur if necessary. If the cellular stress is too great, the cell can undergo a self-destruct process called apoptosis. The molecular processes involved within these checkpoints are of great interest because they are informative about clinical conditions involving altered processes of cell division, such as occurs in cancer.
Mitosis

The actual act of division, the M or mitosis phase (Figure 3.10), represents only a relatively short period in the life of the cell, but it contains four main phases, culminating in the final act of cell division known as cytokinesis.

• **Prophase:** within the nucleus, replicated chromatin becomes highly organized and tightly coiled to form condensed chromosomes. Each of the original 46 chromosomes is paired with its duplicated copy and held close together at the centromere as sister chromatids. During prophase, two centrioles within the cell initiate the organization of cytoskeletal microtubular proteins into a complex called a spindle. The nuclear membrane then breaks down and the centrioles migrate to each end of the cell; the sister chromatids attach to the spindle at the centromere.

• **Metaphase:** chromatid pairs can be seen to be pulled by the spindle through the cytoplasm towards the middle of the cell where they become aligned.

• **Anaphase:** contraction in the spindle apparatus attached to the sister chromatids causes the centrosome holding the chromatid pairs to break down and the sister chromatids begin to separate (each forming a separate chromosome) and move towards opposite ends of the cell, pulling apart the replicated chromosomes so that one complete set (23 pairs of chromosomes) can be found at either end of the cell.

• **Telophase:** the spindle apparatus disintegrates, a new nuclear membrane forms around each set of chromosomes and these begin to uncoil.

Finally, the process of cytokinesis occurs. The plasma membrane invaginates, separating the two newly formed nuclei and forming two new genetically identical cells, which can then separate. During the process, organelles such as the Golgi apparatus and endoplasmic reticulum become fragmented, but others such as mitochondria are preserved and become distributed between the newly formed cells.

Meiosis

This form of cell division is reserved for the production of the gametes, the sperm and ovum (a process known as gametogenesis). Gametes are haploid, containing half the number of chromosomes (23) of our diploid body (somatic) cells. There are some important differences in the process of division between mitosis and meiosis (see Figure 3.11):

- meiosis generates haploid cells
- each haploid gamete produced by meiosis will contain just one chromosome obtained from each of the 23 pairs of chromosomes
- meiosis consists of two consecutive divisions of the nucleus to produce daughter cells
- each gamete cell produced through meiosis is genetically unique – this is the basis of genetic diversity.
Meiosis I
During prophase of the first division (meiosis I), each pair of replicated chromosomes align together to form four chromatids known as a ‘tetrad’. During this event, the chromosomes become very tightly bundled together, and this close association allows segments of DNA from homologous chromatids to be exchanged; this crossing-over of DNA between paternal and maternal arms of homologous chromosomes is known as recombination and it is this process that generates DNA sequence variation (described below). When chromatid pairs align across the middle of the cell during metaphase, they do so regardless of whether the chromosome was maternally or paternally inherited. When anaphase occurs, the centromeres remain intact so that the chromosomes do not separate, but remain as a pair of chromatids pulled towards each end of the cell. This gives rise to another source of genetic variation called independent assortment (sources of genetic variation are discussed below). As anaphase ends, the cytoplasm organizes into two parts and a nuclear membrane forms around the chromosomes.

Meiosis II
The second phase of meiosis is very much like mitosis, except that there is no S phase; that is, chromosomes are not replicated but the previously duplicated copies are instead separated further to make a total of four daughter cells. Each new cell is haploid and contains half of the total genetic material; importantly, these cells are no longer genetically identical and contain a mixture of maternal and paternal chromosomes.

Genetic variation
Meiosis is used to generate genetic diversity and it achieves this in two ways: the random distribution of maternal and paternal chromosomes between daughter cells (independent assortment), and the exchange of DNA between maternal and paternal chromosomes (recombination).

Independent assortment
During the process of making the sperm and ovum by meiosis, the gametes will end up with only one chromosome from each chromosome pair (one chromosome no. 1, one chromosome no. 2, etc.). Depending on the alignment of the homologous chromosomes at the middle of the cell during anaphase, the chromosome could be either maternal or paternal (Figure 3.12). This process of separation is called independent assortment because the process is thought to be a random or independent event. The sperm and ovum will contain a combination of maternal or paternal chromosomes; the number of possible combinations is huge – because there are 23 chromosome pairs, there are $2^{23} (2 \times 2 \times 2 \ldots 23 \text{ times} \approx 8$ million) possible combinations of maternal/paternal chromosomes that could be distributed to each gamete. This helps to explain why closely related members of a family with the same parents, although genetically similar, are also different.

*Figure 3.11 – The stages of meiosis.*
Note that in meiosis II, chromosomes are not replicated, but are separated into newly formed haploid sex cells [sperm and ovum]. Compare this with mitosis [Figure 3.10] where the end result is diploid somatic [body] cells.
Recombination

During prophase in meiosis I, before independent assortment occurs, homologous chromosomes become closely aligned together in a process called synapsis. Sometimes, a segment of DNA on one chromosome crosses over onto another closely aligned chromosome and DNA is physically exchanged (see Figure 3.13). This event generates new sequences of DNA and the reorganization of maternal and paternal alleles. It is a complex process that occurs frequently on certain chromosomes and less frequently on others. It is an important source of variation in the human genome responsible for variety in the types of genes (alleles) that exist.

Recombination can also occur within somatic cells. It occurs frequently among chromosomes containing genes involved with immunity to infection. For example, the diversity of alleles present within the human population that code for the major histocompatibility complex (MHC) (discussed in Chapter 11) has been used to explain why people appear to have different individual susceptibilities to infectious diseases.

Mutations

Mutations represent a change in the DNA sequence (see Figure 3.14) and they are either inherited from a parent or acquired during a person’s lifetime. If a mutation occurs in a differentiated somatic cell, it is unlikely to have a significant effect on the observable phenotype, because it is the overall population of cells present within an organ that exerts an overwhelming effect on an organ’s physiological function. However, if mutations occur within somatic stem cells (cells that are capable of cell division), then the mutation can be passed on to daughter cells, as occurs in the development of some cancers.

Mutations that occur within germ cells are arguably the most important because (following fertilization) these can be passed on to the cells of future generations. The consequences depend on whether the mutation (altered genotype) actually has an effect on the phenotype and, if it does have an effect, whether this is beneficial or deleterious. There are many different types of mutations, including deletion of DNA bases or the addition and insertion of new sequences, but a more detailed examination of these is beyond the scope of this book.

Mutations can be induced by physical or chemical agents (known as mutagens), which increase the frequency of mutations above the spontaneous mutation rate. Common mutagens include the radiation from X-rays or radioactive decay, ultraviolet light, and chemicals such as those in tobacco smoke or alcohol, or those that occur as a result of human industrial activity. In addition, the highly reactive free radicals generated by mitochondria (discussed in Chapter 11) may also act as mutagens. Mutations can also occur through errors in the DNA replication process itself, although these are rare events.
It is important to recognize that the mutations that occur within germ cells represent a driving force behind evolution. Mutations sometimes cause disease, but they can also lead to advantageous changes. The generation of new genotypes containing beneficial mutations increases the probability of successful survival and reproduction, and such mutations are essential for the survival and evolution of all species, including humans.

Over evolutionary time, an accumulation of mutations within the genome can give rise to many genetic variants within genes. Gene variants occurring in gametes that represent single nucleotide changes detectable within at least 1% of the population are referred to as single nucleotide polymorphisms (SNPs). These SNPs are useful in healthcare because they can act as markers for the location of genes associated with disease, indicating an individual’s susceptibility to disease. Knowledge about SNPs is likely to inform future healthcare by influencing strategies for improving public health and personalized healthcare.

3.2.4 Application of genetics to healthcare

The importance of pedigree

An accurate record of a family history (drawn out as a pedigree diagram) is important in clinical genetics because it provides valuable clues for clinicians about a likely genetic diagnosis. It also provides background information to guide further exploration and counselling for family members affected by clinical disorders arising out of chromosomal abnormalities or genetic disease.

There are about 4000 known genetic disorders caused by mutations in single genes. These are classified as ‘Mendelian’ or single-gene disorders because a predictable pattern of inheritance of these disorders can be traced through generations within families. They are observed to follow the general principles of inheritance first elucidated by Gregor Mendel in the 19th century. Mendelian disorders arising from mutations in a single gene can be seen relatively easily in a pedigree chart, and the probability of them occurring in future generations can be quantified.
A pedigree diagram (see Figure 3.15) shows family relationships using symbols and connected lines (parents by a vertical line and siblings by a horizontal line). Those affected by a genetic condition are usually recorded as a ‘filled-in’ symbol. If possible, three generations are recorded, including all grandparents, parents and siblings of affected members. An internationally agreed set of symbols and instructions are used to create the pedigree. The information is interpreted according to Mendelian principles, to reveal whether the phenotypic trait was inherited and, if it was, the pattern of inheritance.

**Patterns of inheritance**

As described above, genes are inherited in pairs, but each gene can be inherited as one of a variety of forms called alleles. Different alleles may cause different phenotypes, sometimes called traits or characteristics. If both genes of a pair are identical, an individual is said to be *homozygous* for the gene. If the pair of alleles is not identical, then the individual is *heterozygous* for the gene. When an individual is heterozygous for a gene, it is the ‘dominant’ characteristic that is expressed – note that it is the characteristic or phenotype that is dominant and not the gene or allele. A ‘recessive’ characteristic will only be expressed when an individual is homozygous for the gene that produces that characteristic. Thus, an individual can exhibit dominant or recessive traits, depending on whether they are homozygous or heterozygous for the particular gene. Two important points to recognize are as follows:

- Individuals expressing dominant traits (perhaps a feature of a specific disease) will also have an affected parent (this will be evident from a pedigree chart), because the parent will have passed this allele on to their children (see Figure 3.15a).
- Individuals who possess recessive traits might have parents and grandparents who are not affected (see Figure 3.15b), but both of their parents would be carriers of the recessive allele. The offspring of two affected parents will all express the trait, because in order to express the condition, both parents will be homozygous for the recessive allele.

![Figure 3.15](image.png)

*Figure 3.15 – Examples of pedigree charts.*

[a] Typical autosomal dominant inheritance; note that the condition occurs in every generation. (b) Typical autosomal recessive inheritance; note that the condition can be observed to ‘skip’ generations – the allele for the recessive condition may be present, but it is the allele for the dominant condition that is expressed to provide an observable phenotype.
The pedigree is a useful tool, but interpretation of it is not always clear-cut. Some traits are not completely dominant, giving rise to a variable expression, and sometimes a number of genes may interact to modify the expression of alleles. The extent of an allele's effect on a specific trait, both within an individual and within the population, can in part be measured and explained by the concepts of penetrance and expressivity; although these concepts are beyond the scope of this book, suggestions for further reading are provided at the end of the chapter.

Not all disorders caused by alterations to DNA are inherited; for example, when genetic abnormalities occur only in somatic cells and not in germ cells, they will not be passed on to the next generation. Some disorders are caused by new mutations not previously present within a family, and so a pedigree chart will be uninformative. Chromosomal disorders can be inherited, but often they are not, because they are frequently caused by a problem in the process of cell division involving meiosis in germ cells, or mitosis in a developing embryo.

**A chromosomal disorder: Down syndrome**

An abnormal number of chromosomes in a cell is termed aneuploidy. This represents a gross abnormality and tends to have significant effects on phenotype. Down syndrome is caused by trisomy of all or part of chromosome 21 (see Alexei, Patient 3.2). The extra chromosome can be observed (see karyotype in Figure 3.8b) free or fused onto another chromosome. Chromosome 21 contains at least 300 genes; some of these code for several proteins that affect how cells function and influence development – the function of the remainder is not yet known. A wide range of phenotypic consequences of this chromosomal abnormality are observed, including altered neurological development, altered development of morphology and intelligence, earlier development of Alzheimer's disease, decreased muscle tone and increased risk of congenital heart disease.

There can be a great deal of phenotypic variation in people affected by Down syndrome and this can sometimes be explained by the concept of mosaicism. Mosaicism (illustrated in Figure 3.16) represents a mixture of genetically
abnormal and normal cells present in an organism. If the event that causes an extra chromosome 21 occurs during an early stage of development of an embryo and not during meiosis, then a child will be born with some normal and some abnormal cells within the tissues, causing the expression of a range of phenotypes. This might involve more or less intellectual impairment or degrees of impairment in organ function. There is no known treatment for Down syndrome, but sequencing of chromosome 21 was an early and important goal of the Human Genome Project, in the hope that the molecular basis for Down syndrome could be better understood.

**An autosomal recessive single-gene disorder: cystic fibrosis**

In cystic fibrosis (see Sarah, Patient 3.1), the disease is the result of a mutation in a single gene on an autosome and not on a sex chromosome. As a single-gene disorder, the clinical condition is caused by only one faulty gene and is not reliant on the interaction of other genes. Cystic fibrosis is a recessive condition and so the disease is only expressed in individuals homozygous for the affected allele; in other words, two copies of the mutated gene must be present.

Cystic fibrosis is one of the most common inherited life-threatening conditions, affecting approximately 5% of the general population. It is caused by a mutation in the gene that codes for the ‘cystic fibrosis transmembrane conductance transporter’ (CFTR) protein. This protein is particularly expressed on intestinal and airway epithelial cells, but also in other tissues. It provides a channel for the transport of chloride ions across the plasma membrane. In patients with cystic fibrosis, the CFTR protein is not expressed and patients usually present with intestinal and breathing problems; for example, viscous mucus accumulates in the lungs and reduces lung function, causing breathing difficulties and respiratory tract infections. Digestive glands also become blocked, interfering with digestion and the absorption of nutrients (see Sarah, Patient 3.1). Cystic fibrosis is a lethal disorder, but improved clinical management of the condition has resulted in patient survival now commonly over 30 years of age.

For a lethal condition, the frequency of carriers with the affected CFTR allele within the population is relatively high. This suggests that the mutated gene might have some benefits in certain environments; this is called ‘heterozygote advantage’. Individuals heterozygous for the mutated CFTR gene might have reduced functioning of the gene, but this is insufficient to cause clinically recognizable disease. It has been hypothesized that reduced efficiency of chloride transport across the epithelial wall of the gastrointestinal tract, as occurs in cystic fibrosis, might provide a survival advantage against diarrhoeal diseases such as cholera. Thus, mutations can be beneficial depending on environmental conditions. It is important to consider phenotype as a product of the genotype interacting within an environmental context.

**A change to a single DNA base: sickle cell disease**

Sickle cell disease is the most common genetic condition in the UK, estimated to affect 12 500 people. Approximately, 240 000 people are estimated to be carriers
of the condition and about 300 babies per year are born with the condition in the UK. It occurs most frequently in people with a black African or Afro-Caribbean ancestry. Symptoms can be mild, highly variable and episodic, the most common symptom being pain, especially in the bones (see Yasmeen, Patient 3.4). However, complications can be life-threatening and include stroke (bleeding into the brain), damage to the spleen and acute lung syndrome. Sickle cell disease is caused by the formation of abnormal haemoglobin, which causes erythrocytes (red blood cells) to become sickle-shaped, fragile and unable to carry oxygen efficiently; their altered shape means that they can also become stuck within small blood vessels, further reducing the amount of oxygen that can reach tissues.

Sickle cell disease is another example of an autosomal recessive condition. However, although heterozygotes usually do not experience significant clinical symptoms, they can be affected. Heterozygotes produce a mixture of normal and abnormal haemoglobin because they possess one normal and one abnormal allele; as both alleles are expressed this is an example of codominance.

The haemoglobin protein used to carry oxygen and carbon dioxide within erythrocytes (discussed in Chapter 10) contains a polypeptide chain called β-globin consisting of 146 amino acids. In normal haemoglobin, the sixth codon on mRNA coding for the β-globin chain codes for the amino acid glutamic acid. A single change to a nucleotide within the codon for glutamic acid can alter the codon to represent instead the amino acid valine (see Figure 3.17) and it is this single amino acid change that is responsible for altering the function of the haemoglobin protein to the sickle condition.

An autosomal dominant disorder: hypertrophic cardiomyopathy

With dominant disorders, an affected gene will always be expressed, even if the individual is heterozygous and also carries a ‘normal’ gene. A general feature of autosomal dominant disorders is that if a parent possesses the mutated gene they will have the condition and any children will have a 50% chance of inheriting the mutated gene.

Figure 3.17 – Sickle cell disease.
(a) In this example of a mutation, a single nucleotide change has caused a change in the code for an amino acid (from glutamine to valine), altering the structure and function of the protein and resulting in sickle cell disease. (b) Photomicrograph of normal and sickle erythrocytes. Wellcome Images.
Hypertrophic cardiomyopathy (HCM; see Katherine, Patient 3.3) is the most common inherited cardiac condition, affecting approximately 1:500 of the general population. It is caused by a large variety of mutations in several genes encoding sarcomere proteins, which are normally expressed in cardiac muscle cells. The mutations cause the cardiac muscle to become enlarged and disorganized, and so patients with this disease may experience a variety of symptoms, including chest pain, sudden loss of consciousness and heart failure. HCM is recognized as the primary common cause of heart-related sudden death in young people, and secondary to the primary disease is an increased risk of abnormal heart rhythms and stroke.

Clinical presentation of HCM is very variable, with little consistent presentation of symptoms by patients, even within affected families. Some patients may not have any obvious disease, while other affected family members experience severe symptoms. Many factors probably act together to influence the disease, but much of this variability can be explained by the variability of mutations involved in several genes. In addition, polymorphisms in hormones that directly or indirectly influence the circulatory system (so-called ‘modifier genes’), diet, exercise and blood pressure may also act together to influence development and progression of the disease.

Diagnosis often follows the sudden unexplained death of a relative, followed by examination of family histories and the construction of a pedigree. Management can involve medication, cardiac ablation, implantable cardiac devices and heart transplantation. Careful history taking, counselling, screening and surveillance of at-risk family members are important considerations that carry significant implications for those affected.

\[A\text{ sex-linked recessive disease disorder: haemophilia}\]

Haemophilia is an X-linked inherited bleeding disorder, in which a protein required for blood clotting is reduced or missing, and so patients bleed for longer than normal. Small cuts or bruises do not cause significant problems, but larger cuts and traumatic injuries can be life-threatening.

The X chromosome is much longer than the Y chromosome and contains many more genes (most of which have nothing to do with sex determination). When alleles on the X chromosome are expressed to produce a trait or a disease, they are said to be X-linked. The majority of X-linked conditions are recessive, which means that a woman (who has two X chromosomes) will not usually develop the condition because she will also be carrying the dominant allele (from her other X chromosome), which will ensure normal function. However, if a male child inherits the recessive allele on the X chromosome, he will develop the condition because all genes on his single X chromosome will be expressed (he inherits a Y chromosome from his father). Two general patterns of X-linked inheritance can be observed:

- a non-affected father paired with a mother carrying the affected gene have a 50% probability of producing a son with the disease (see Figure 3.18)
- a non-affected father paired with a mother carrying the affected gene have a 50% chance of producing a daughter who carries the affected gene but does not have the disease (see Figure 3.18).
Blood clotting involves the interaction of blood cells and a variety of clotting proteins present in plasma in an extensive ‘clotting cascade’ to stop bleeding (haemostasis). Mutations in the genes coding for the clotting proteins reduce the efficiency of the blood clotting cascade. Haemophilia type A is the commonest type of haemophilia and is caused by a deficiency in a blood clotting protein known as factor VIII. The gene coding for factor VIII is found on the X chromosome and so the disease is usually found in the sons of female carriers of the mutated gene. The mutation responsible for haemophilia can occur spontaneously within germ cells in a family that does not have a previous history of haemophilia, but the mechanism by which this occurs is not known.

Four of the five clinical examples described earlier (the exception is HCM) refer to single-gene mutations that cause patterns of inheritance that are relatively easy to observe through successive generations. Clinical geneticists and genetic counsellors, by taking a family history and constructing a pedigree, are able to glean useful information for the management of affected and potentially affected relatives. This information is important for patients for decision making, such as whether or not to have children, and what lifestyle choices to make.

**Genes and cancer**

When mutations in somatic cells occur, they can sometimes provide cells with an abnormal ability to survive independently of normal regulatory mechanisms and to invade other tissues. When these abnormal cells accumulate, they form malignant **tumours**, commonly called cancers. A full discussion of the process of carcinogenesis is a complex subject beyond the scope of this text. However, it is worth understanding some of the key features that represent the ‘hallmarks of cancer’ (as proposed by Hanahan and Weinberg in 2000); they proposed the six hallmarks of cancer cells to be their ability to:

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**Figure 3.18 – Patterns of X-linked inheritance.**
The affected allele (d) is present on the X chromosome, in this example carried by the mother. Note the expected frequencies of unaffected, carrier and affected children.
1. divide independently of positive regulatory controls
2. divide independently of negative regulatory controls
3. divide indefinitely, without growing old
4. avoid apoptosis (signals to self-destruct)
5. form a life-sustaining circulation (angiogenesis)
6. grow into other tissues and establish growth into distant tissues (invasion and metastasis).

More recently, in 2011, Hanahan and Weinberg proposed four additional hallmarks, as follows:
7. deregulated metabolism, for example, the use of abnormal cellular respiratory mechanisms to obtain energy
8. ability to evade normal regulatory controls of the immune system
9. ability to become genetically unstable
10. association with inflammation.

Mutations can assist with gaining these hallmarks in two main ways.

- Increased growth and survival advantage: if a mutation allows a cell to divide faster or more frequently and survive, then any abnormality will be retained by all mutated future cells. Cancer occurring in solid organs will form a larger mass of cells, recognizable as a lump or tumour.
- Increased genetic instability: if dividing cells accumulate mutations over successive generations, then the likelihood of generating abnormal cells that contribute to development of the hallmarks of cancer will be increased. When examined, cancer cells are observed to contain many more mutations and even gross chromosomal abnormalities in comparison with normal cells.

**Colon cancer**

Only 10% of colon cancers are inherited, with the majority of cases being due to the accumulation of genetic alterations over time in colonic epithelial cells (this occurs in approximately 1 in 20 people in the UK population).

Genetic abnormalities that accumulate within the epithelial cells of the colon occur in a multistage, stepwise manner, and so observation of the state of these cells can be used to gauge how far tissue in the colon has developed towards cancer (see Figure 3.19). One of the most commonly mutated genes found in colon cancer is the adenomatous polyposis coli (APC) gene. This normally functions as a tumour suppressor; that is, the protein encoded by the APC gene normally functions to suppress cell division by repressing the activity of a number of proteins that normally promote cell division (see ‘hallmarks of cancer’ discussed above). When the APC gene becomes mutated, it often codes for a protein that is shorter than the normal protein. Any somatic cell in the colon producing a shortened APC protein will no longer be able to suppress cell division and so growth of these cells continues unchecked; the overgrowths of the colonic mucosae that develop are called polyps. The polyps have gained a growth advantage and will have taken a first step towards the development of cancer. When mutation in the APC gene occurs in a stem cell, this will affect all future cells, which will all express abnormal APC protein. The affected cells are predominantly mucosal epithelial cells of the large intestine, and polyps develop along the whole of the large intestine (see Figure 3.19).
A rare inherited disorder called familial adenomatous polyposis (FAP) causes colon cancer at a relatively young age in all individuals with a mutated APC (adenomatous polyposis coli) gene. A more common form of inherited colon cancer, affecting approximately 10% of all cases, is referred to as hereditary non-polyposis colon cancer (HNPCC). With HNPCC, the cancer tends to develop at a young age and polyps are also produced, not because of a mutated APC gene but because of the involvement of a number of other mutated genes. These are frequently genes that encode proteins involved in the repair of mistakes that occur during the replication of DNA – so-called DNA repair proteins. When mistakes are not repaired, genetic instability tends to increase in the affected cells and the risk of cancer consequently increases.

The treatment options for inherited colon cancer are limited, and most commonly prophylactic colectomy (removal of the colon) at a relatively young age is used to prevent the cancer becoming invasive and harder to eradicate; a colectomy significantly reduces the risk of cancer developing in affected individuals. A screening programme to identify people in the early stages of developing colon cancer is currently being implemented by the NHS and is being offered to anyone over the age of 60 years (see www.cancerscreening.nhs.uk/bowel/). The basis of this screening programme is examination of a small amount of faeces for the presence of ‘occult blood’ (blood present in tiny amounts not visible to the eye). If blood is detected, then patients are referred for endoscopic examination of their bowel (called a colonoscopy). If polyps are detected, these can usually be removed and examined for the presence of abnormal cells suggestive of cancer. This screening programme is expected to save thousands of lives in the UK annually.
Breast cancer

One in nine women in the UK is likely to develop breast cancer (making it the most common cancer affecting women), and it has become the leading cause of death in women between the ages of 34 and 54 years. It can also occur in men, but much less frequently. As with colon cancer, the majority of cases of breast cancer are sporadic (non-hereditary), but approximately 3% of cases are related to a known inherited breast cancer gene. Sheila (Patient 2.3) does not have a known family history of breast cancer. In the development of Sheila’s cancer, her breast (somatic) cells have at some point in her life gained a mutation in the human epidermal growth factor receptor 2 (HER2) gene.

Unlike colon cancer, the development of breast cancer does not appear to follow a stepwise progression. The genetic abnormalities appear to accumulate in a more heterogeneous fashion, and a variety of histological types of cancer can develop within the breast. Multiple risk factors have been identified, including ethnicity, diet, exposure to alcohol and smoking. Reproductive factors are important, such as early onset of the menarche, late onset of menopause, giving birth to a first child after the age of 30 and possibly administration of oestrogenic contraceptives. The breast is sensitive to the effects of hormones, in particular oestrogen, progesterone and prolactin, and over-expression of oestrogen receptor genes is a common feature of breast cancer. Therefore, selective oestrogen receptor modulators, such as tamoxifen (a drug that blocks the oestrogen receptor), are used to treat breast cancer and also to prevent its development in women identified as being at high genetic risk for developing breast cancer.

Among others, two specific genes named breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2) have been identified as being important in the development of breast cancer – they are tumour suppressor genes involved in DNA repair, helping to maintain genomic stability and suppress uncontrolled growth of cells. Mutations in BRCA1/2 inactivate their normal function of repairing damaged DNA and so increase the risk of developing breast cancer (they also may increase the risk of developing ovarian cancer) such that up to 80% of women with specific mutations in these genes will develop breast cancer in their lifetime. However, it is important to note that not all inherited mutations in these genes increase the risk of developing breast cancer. Also, even in families possessing a mutated BRCA1/2 gene, these mutations will not necessarily be inherited by the daughters. Moreover, not every woman with harmful forms of the gene will go on to develop breast cancer. Although a family history of breast cancer doubles the risk of developing it, approximately 80% of women with a close family member with breast cancer will never develop it themselves.

Other altered genes are also known to influence the risk of developing breast cancer, and genetic tests to identify mutations in BRCA1/2 and these other genes allow clinicians to estimate the cancer risk for an individual. These tests are generally only offered to individuals with a strong family history at specialist genetic clinics where genetic counselling can be offered to help patients make informed decisions and be supported with the consequences of the information provided to them.
As with many other forms of cancer treatment, treatment for breast cancer usually involves surgery and is often followed by radiotherapy and/or chemotherapy. Sometimes, hormones and biological treatments (as with Sheila, Patient 2.3) are also offered. Prophylactic mastectomy is sometimes considered for women at high risk, for example, those who have a strong family history and are positive for BRCA1/2 mutations or other mutations.

Diseases involving more than one gene

So far, we have discussed the role of mutations occurring in a specific gene, or a few closely related genes, that have a major effect in causing clinically recognizable disease. These single-gene disorders are convenient to discuss because they provide relatively simple but stark examples of the role of genetics in health and disease. However, single-gene disorders are rare, affecting perhaps just 2% of the population. The majority of genetic disorders involve multiple genes and these are known as polygenic disorders.

Polygenic traits represent phenotypes produced by multiple genes, each exerting a small effect on the overall phenotype. Most human traits including eye colour, skin colour, height and weight are in fact polygenic traits. Some traits such as height and weight may also be affected by environmental factors and as such can be thought of as multifactorial traits. This interaction between multiple genes and environmental factors can make it very difficult to identify the alleles involved and the patterns of inheritance occurring within families. Each gene in combination with environmental factors confers a degree of risk or susceptibility towards a particular phenotype. Examples of polygenic and multifactorial diseases include coronary heart disease, diabetes, obesity, Alzheimer's disease and psychoses. Sometimes different combinations of genes produce related ‘co-morbid’ conditions; for example, a family history of rheumatoid arthritis is also associated with other autoimmune diseases such as systemic lupus erythematosus and multiple sclerosis. The variety of possible genetic alterations that might occur within genes, combined with the probability of inheriting specific combinations of genes, means that studying the effects of individual genes within polygenic disorders becomes complicated and problematic. Data from the Human Genome Project and population studies, integrated with advances in biotechnology and bioinformatics, should help to clarify the genetic contribution to disease.

Gene testing and issues for the individual and society

Currently, genetic testing is able to identify families at high risk of developing diseases such as specific types of cancer, for example colon or breast cancer. This allows affected family members to receive advice and recommended surveillance, and to make treatment and lifestyle choices, in order to minimize the risk of development of the disease.

Genetic alterations that occur in malignant tumours can also be investigated for the presence of specific gene mutations, and appropriate chemotherapeutic agents can then be targeted to the tumours. For example, some patients with advanced colon cancer can be treated effectively with a monoclonal antibody
called cetuximab, but only if a gene in their tumour called KRAS is not mutated (the KRAS protein is a regulator of cell division); cetuximab therapy will not work in patients with a mutated KRAS gene in their tumours. Cetuximab therapy, often administered in combination with chemotherapy or radiotherapy, can prolong life and can even eradicate cancer from the body in patients with a specific cancer genotype.

For inherited conditions, identifying genes responsible for disease or those genes that indicate susceptibility can become useful markers of risk and can also be used for diagnosis. However, to date this knowledge has led to just a few limited examples of improved treatment.

Results from the Human Genome Project and the availability of genetic testing have stimulated a number of issues for society to consider including the following:

- Should a patient be screened to confirm the diagnosis of a disease that cannot be treated and does it matter how old the patient is?
- What will the impact of a diagnosis be on an affected person?
- Will a genetic diagnosis influence reproductive choices, or the ability to find work or obtain life insurance?
- Will a genetic diagnosis result in stigmatization and social exclusion?
- Does disability resulting from genetic variation represent disease, or simply difference between people?
- If an inherited condition is diagnosed in an individual, do the family members have a right to the information about it?
- If genetic susceptibility for a condition such as heart disease or obesity can be calculated and modified by a change in lifestyle, can this change be demanded, or even enforced?
- Can genetic information do harm?

Many more questions could be asked and, as our knowledge of the human genome increases, society will be required to respond to them. Clearly, genetic knowledge holds many ethical, legal and societal implications, and our legal system, social institutions and professional bodies are already struggling to keep pace with the rapid advances in genetics and biotechnology. The implications for healthcare practice are huge. The references at the end of this chapter will provide you with a starting point to consider these implications further.

### 3.3 Clinical application

As we have seen, genes can play an important part in the development of certain diseases. Understanding how genetics can result in particular diseases is important in healthcare in order that suitable explanations can be given to patients and appropriate treatment planned. The patients described in this chapter have covered a range of different genetic problems:

- **Sheila (Patient 2.3)** has developed breast cancer as a result of a somatic mutation that resulted in the over-expression of HER2 protein on the plasma membrane; it should therefore be possible to treat her cancer by...
selectively blocking the HER2 receptor and reducing cell division.

- **Sarah (Patient 3.1)** has cystic fibrosis, which has occurred as a result of her inheriting two faulty copies of the *CFTR* gene (remember, cystic fibrosis is an autosomal recessive disorder) and, as a result, Sarah requires daily physiotherapy to keep her lungs clear of viscous mucus, to aid her breathing and to reduce the risk of chest infection.

- **Alexei (Patient 3.2)** has Down syndrome as a result of a chromosomal abnormality (trisomy of chromosome 21). Alexei and his family will require ongoing support for a wide variety of social, psychological and physiological needs, with regular coordinated review of his care to enable Alexei to fully maximize his potential.

- **Katherine (Patient 3.3)** has hypertrophic cardiomyopathy, which is an autosomal dominant condition, and so it is important that Katherine and the rest of her family understand the implications of this for themselves and also for any future children.

- **Yasmeen (Patient 3.4)** has sickle cell anaemia, another autosomal recessive condition, and although she is managing her condition well, she

Breast cancer cells that express too much HER2 receptor are often described as aggressive, because the cells grow very rapidly, become poorly differentiated and stimulate angiogenesis (see the earlier discussion of the ‘hallmarks of cancer’). Over-expression of the HER2 protein is usually caused by multiple copies of the gene formed during the carcinogenic process (called gene amplification). A monoclonal antibody (antibodies are discussed fully in Chapter 11) called trastuzumab, when administered to patients, binds specifically to the over-expressed HER2 receptor, preventing it from exerting its effects on cells, reducing the rate of cell division and limiting the growth of new blood vessels (so the carcinogenic effects of HER2 will be reduced). Patients receiving trastuzumab therapy have been observed to demonstrate a significant decrease in the risk of breast cancer reoccurrence when compared with control patients in randomized clinical trials. The therapy is only effective on cancers caused by over-expression of the HER2 receptor, but, in combination with chemotherapy agents, trastuzumab has been shown to improve survival in patients with breast cancer. This is an example of personalized medicine that uses genetic information about the individual to tailor treatment. In consultation with her doctor and breast care nurse, Sheila chose to accept the addition of trastuzumab to the chemotherapy plan for her breast cancer (further discussion of Sheila’s care is expanded in Chapters 2, 9 and 14). She experienced some minor side-effects, including flu-like symptoms, nausea and fatigue; these only lasted a couple of days and, with the support of her family and the multidisciplinary cancer support team, Sheila is looking forward to an improved prognosis, confirmed by the oncologist looking after her, and she has begun training for a 10K ‘fun-run’ in aid of cancer research.
A sweat test that detects the elevation of salt in sweat was performed on Sarah when she was a baby in order to confirm a diagnosis of cystic fibrosis – remember that the lack of CFTR protein in cystic fibrosis disrupts chloride ion (Cl⁻) transport across membranes and so excess salt (NaCl) is found in the sweat. This is a quick and painless procedure involving stimulation of a small patch of skin with the drug pilocarpine to promote sweating. Sweat is simply collected onto an absorbent card and the concentration of sodium chloride measured. Together with a clinical history, this is generally sufficient for a positive diagnosis to be made. In Sarah’s case, genetic testing was also performed, and this provided useful information for advising Sarah’s family members about their carrier status and will also be useful for Sarah when she starts to make future reproductive choices.

Today, screening for cystic fibrosis is routinely performed as part of the NHS newborn screening programme (https://www.gov.uk/topic/population-screening-programmes/newborn-blood-spot). Midwives generally take a small sample of blood from a newborn baby about 1 week after birth and place some spots of the blood onto a card, which is then sent for analysis. In addition to cystic fibrosis, a variety of other inherited conditions can be detected from this small blood sample, including congenital hypothyroidism, sickle cell disease and two enzyme deficiencies: phenylketonuria and medium-chain acyl-CoA dehydrogenase deficiency.

The carrier status of the relatives of a family member with cystic fibrosis can be discovered by taking a small blood sample or a swab of easily removed cheek cells from the inside of the mouth. This checking of the genetic status of family members is called cascade screening and helps to identify who might be at higher risk of being a carrier or of having a child with cystic fibrosis.

Alexei lives a full and busy life, but recently, as he develops into a young adult, a variety of challenges have begun to present to him. Socially and educationally, Alexei probably will not develop at a comparable rate to his peers; as a result, he will be less able to keep up with his friends at school, and recently he has frequently been left out of activities. Alexei’s real passion is for golf, but bouts of breathlessness have begun to interfere with this. Alexei is at risk of a wide variety of physiological challenges due to the altered expression of genes located on chromosome 21. He is due to receive a hospital appointment soon to assess his health status. This will include hearing and dietary assessments, X-rays to assess his skeletal development, a variety of blood tests including a measurement of haemoglobin concentration, and a cardiology assessment. His recent bouts of breathlessness while playing golf are worrying his mother, Adelia, who knows heart defects are common in children with Down syndrome.
Katherine has been prescribed the anticoagulant drug warfarin to reduce her risk of stroke, and anti-arrhythmic drugs to improve the altered heart rhythm and function of her heart. She has also been advised to have regular reviews with the specialist cardiology team.

Katherine was also referred to a clinical geneticist, and this consultation revealed a family history suggestive of heart disease inherited in an autosomal dominant manner. This led to the extended family getting together and discussing the history of health and early death in the family: one of Katherine’s uncles on her father’s side underwent a heart and lung transplant some years ago, and one of her cousins died suddenly at 17 years of age. DNA was collected from the family for a research project and Katherine was offered a gene test, but none of the commonly affected genes was identified. However, the clinical geneticist informed Katherine that this is not unusual because the condition is caused by the interaction of several genes, and not all genes implicated in causing the condition have so far been identified.

Katherine has two daughters aged 19 and 22 years; one has agreed to undergo annual electrocardiography and echocardiography to screen for HCM. Her other daughter has declined the offer of annual surveillance, saying, ‘If I’ve got it and you can’t cure it, I might as well forget it.’ Her sister, on the other hand, is considering getting married and wants to know what the implications might be for her future children. The genetic nurse counsellor informs her that there is a 50% possibility that she has HCM, and if she does have it, there is a 50% chance that any of her future children will have it, but currently it is not possible to predict how unwell she or her future children might be, because the effects of the condition can be very variable, even within families. She provides her contact details to Katherine and her daughter so that they can arrange to discuss any issues that may arise in the future.

Yasmeen’s family have heard that a bone marrow transplant can cure some people of certain genetic disorders, including sickle cell disease. They are also aware that most of the people around the world who have received a bone marrow transplant for sickle cell disease have survived disease-free. However, their family doctor said that it is a costly and potentially high-risk procedure that has been performed on only a few hundred people worldwide so far. He also cautioned that this would only be suitable if a close genetic match could be found from within the family. Yasmeen’s mother told the doctor that she was planning to have another baby and so she wondered whether a new baby could be a suitable match for a bone marrow transplant to cure Yasmeen of sickle cell disease. The family doctor advised them that using unaffected family members to help cure an affected member raises a number of complex ethical and psychological issues for all those involved, including the unborn child. Yasmeen and her family agreed to accept a referral to a clinical geneticist so that they can explore and understand the implications further.
is interested to discuss possible options for treatment.

Knowledge of genetics is essential in order to understand biochemistry, cell biology and physiology, and the rapid expansion of the disciplines of genetics and genomics is already beginning to change the practice of medicine and healthcare. All health professionals need to be informed of these developments and be able to use their knowledge of genetics appropriately in their practice. Gene therapy might not yet be a realistic option, but personalized therapies, screening for genetic disorders and the use of reproductive technologies are a reality. Patients need informed professionals to help them make sense of this fast-moving discipline, and their explanations can help patients make decisions that are right for them and their families.

3.4 Summary

- All organisms possess a genome. This is the entire DNA content of a cell and represents the hereditary information. Knowledge about the human genome and also the genomes of other organisms is immensely valuable. Genomic and genetic knowledge, driven by the development of associated technologies, provides many ethical, legal and societal implications for individuals, families and populations.
- The human genome is located physically within the nucleus (although some DNA also exists within mitochondria). The human genomic DNA must be accurately copied and reproduced in every cell of the organism.
- DNA contains four types of DNA nucleotide with four types of base. It is the sequence of bases in DNA that carries the genetic information (see Figure 3.2). DNA is transcribed within the nucleus to produce mRNA, which is translated into proteins by ribosomes (see Figures 3.4 and 3.6).
- A gene codes for functional RNA or protein molecules. RNA molecules are important in the process of protein synthesis and in regulating gene expression. The activity of cells is mostly determined by the activity of proteins.
- Genetic variation is an important feature of life and occurs via independent assortment of chromosomes, recombination and mutation, which are crucial events in the processes of meiosis and sexual reproduction.
- Genetic traits can be observed within multiple generations of families. It is possible to construct a pedigree chart to record the transmission of relatively simple Mendelian traits.
- However, the majority of chronic diseases and long-term conditions can be described as polygenic (involving many genes) and multifactorial (involving interaction with environmental factors).

3.5 Further reading

Additional information to help you construct a pedigree can be found at:
https://heartuk.org.uk/FHToolkit/ – click on Section 5 and download the pdf document 5C.

More information about the Human Genome Project and its ethical and societal implications can be found at:
www.ornl.gov/sci/techresources/Human_Genome/home.shtml
www.genome.gov/10001772

The following book gives further details of some of the topics covered in this chapter:

3.6 Self-assessment questions

Answers can be found at www.scionpublishing.com/AandP

(3.1) Mechanisms of genetic variation include which one of the following?
(a) Independent assortment and mutation
(b) Somatic cross-over
(c) Recombinant protein
(d) Independent recombination
(e) Short interfering RNA

(3.2) A mother has inherited an autosomal dominant genetic condition from her father, but her husband does not have the gene for the condition. Select the most appropriate statement that identifies how likely it is that one of their offspring will inherit the disease.
(a) There is a 1 in 2 probability of one of the children having the disease
(b) There is a 1 in 3 probability of one of the children having the disease
(c) There is a 1 in 4 probability of one of the children having the disease
(d) None of the children will inherit the disease
(e) All children will inherit the disease

(3.3) During mitosis, metaphase represents which one of the following phases?
(a) Condensation of chromosomes
(b) Formation of two new cells
(c) Separation of homologous chromosomes
(d) Disappearance of the nuclear membrane
(e) Alignment of homologous chromosomes around the middle of the cell

(3.4) Epigenetic changes include which of the following? More than one answer is possible.
(a) Chemical modification of mRNA
(b) Change in the sequence of DNA nucleotides
(c) Non-heritable changes to DNA
(d) Methylation of DNA
(e) Acetylation of anticodons

(3.5) Mary smokes 20 cigarettes a day. She thinks that because her mother smoked and did not develop lung cancer, she is unlikely to develop it. Is this true or not true? Give reasons for your answer.

(3.6) Ian is only 24 years old and tells you he has seen blood in his stools after going to the toilet. He is worried he might have colon cancer. He thinks his father died of cancer when Ian was only 4 years old. What advice would you offer him?

(3.7) Complete the table to work out the sequence of amino acids coded by the DNA sequence below.

<table>
<thead>
<tr>
<th>DNA</th>
<th>CAT</th>
<th>GGC</th>
<th>TTA</th>
<th>AAC</th>
<th>GCC</th>
<th>CGA</th>
<th>TAT</th>
<th>GTA</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amino acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(3.8) Name three types of RNA and state their role and location in the cell.