

Inherited diseases

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Each of us is the product of our genes, inherited from our parents, interacting with our environment. This environment is not just the physical one but also the social one, of our interactions with other people. How can the unique set of chromosomes and genes inherited from our parents cause problems?

Before considering the inherited diseases described in Boxes 1–3 overleaf, let's look at the basics of genetics. Inheritance can be considered either at the chromosome level or at the level of the DNA in the chromosomes, from which genes are made. Most people have 46 chromosomes, in 22 pairs plus either a pair of X chromosomes or a single X chromosome and a single Y chromosome.

Cell division

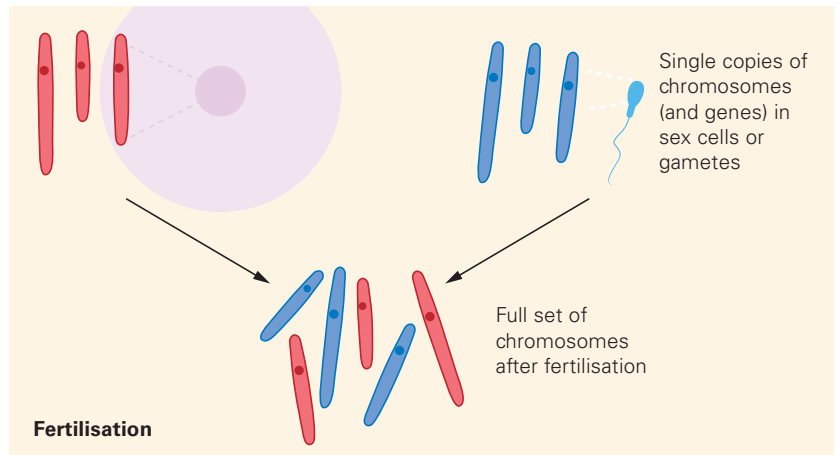
Throughout our lives these chromosomes are copied each time a cell divides to repair damage or add growth. Each new cell ends up with the full 46 chromosomes. This type of cell division is called **mitosis**.

Another type of cell division, called **meiosis**, occurs when sex cells are formed. In this type of cell division, occurring inside the ovaries or testes, the pairs of chromosomes split up and go separate ways into the sex cells produced. The pairs separate at random (Figure 1), so each sex cell contains a unique set of chromosomes and genes — a mixture of those the person originally received from each of their parents. Particular genes are positioned on particular chromosomes, and for convenience we number the chromosomes 1–22.

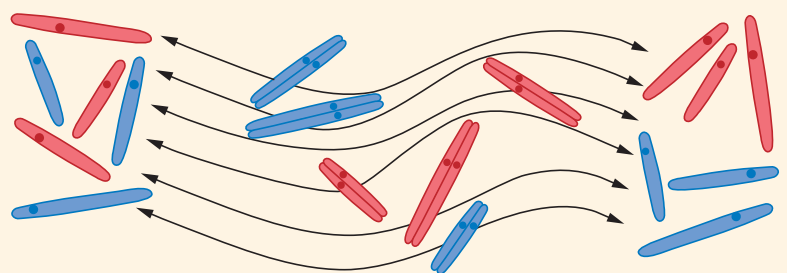
Things can go wrong during cell division. This may happen because of some fault in the genes carried on chromosomes, because of faulty copying, or it may be a chance event as chromosomes move around during cell division. Fortunately we have repair enzymes that can correct many faults. Other faults may occur when bits of genes (or sections of whole chromosomes) get broken off and attach themselves to other chromosomes. Sometimes pairs of chromosomes don't separate so we get cells with three copies of a chromosome or missing chromosomes.

The molecular level

Genes are made from DNA, which contains coded instructions for making proteins. Proteins are made out of long chains of amino acids, in some cases more than 100. Each protein contains a particular selection of amino acids from the 20 or so commonly available,



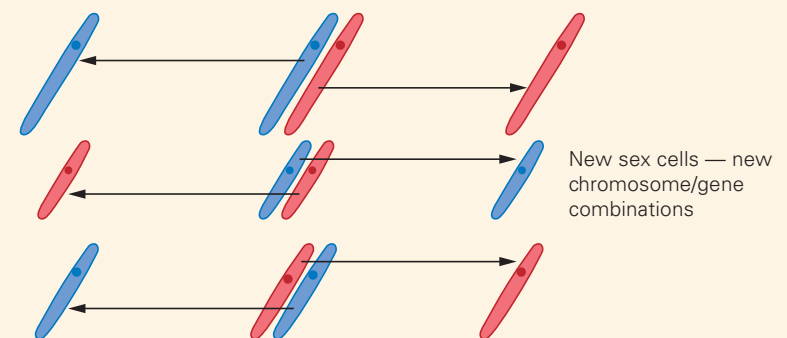
Cell division: mitosis



Between one cell division and the next, chromosomes and the DNA in them are copied or duplicated. Chromosomes start the next division as double structures which split in two and separate. In this way both new cells end up with a full set of chromosomes

Cells produced in this way are genetically identical — they are part of a clone

Meiosis: sex cell production



In meiosis, pairs of chromosomes (one originally from dad/one from mum) pair up and then pairs separate at random

New sex cells — new chromosome/gene combinations

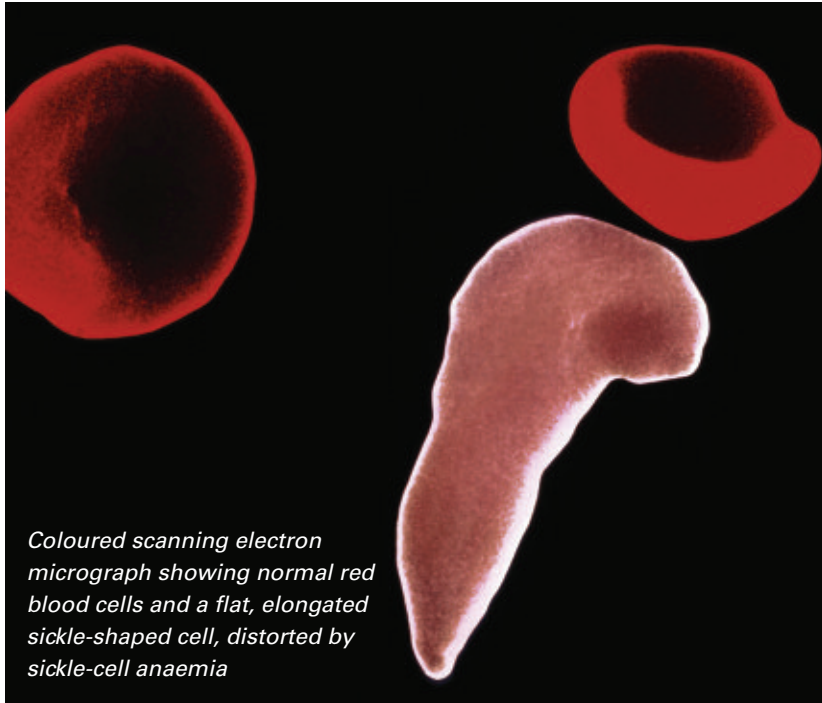
Figure 1 Fertilisation, mitosis, meiosis and parental chromosomes

Table 1 Frequency of various inherited conditions

Condition	Frequency per 10 000 births
Sickle-cell anaemia	1
Cystic fibrosis	4
Huntington's disease	5

GCSE key words

DNA
Chromosome
Sickle-cell anaemia
Mitosis
Meiosis
Cystic fibrosis



Coloured scanning electron micrograph showing normal red blood cells and a flat, elongated sickle-shaped cell, distorted by sickle-cell anaemia

Dr Gopal Murti/SPL

Box 1 Sickle-cell anaemia

People with sickle-cell anaemia have sickle haemoglobin (HbS) which is different from normal haemoglobin (HbA). Normal red blood cells can bend and flex easily. When sickle haemoglobin gives up its oxygen to the tissues (CATALYST Vol. 15, No. 1, page 9) the haemoglobin sticks together to form long rods inside the red blood cells. This makes the cells rigid and sickle-shaped. Because of their shape, sickled red blood cells can't squeeze through small blood capillaries. As a result the capillaries get blocked. This stops the oxygen from getting through to where it is needed and can lead to severe pain and damage to organs.

The mutation causing sickle-cell anaemia involves a change in one base in a triplet in a gene. As a result the amino acid valine is built into a β chain, instead of glutamic acid.

You can find out more about sickle cell at <http://www.sicklecellsociety.org> or at <http://www.bbc.co.uk/health/awareness/sickle.shtml>

arranged in a specific sequence. DNA contains a linear code for putting the right amino acids together in the right sequence. The unique sequence of amino acids in a protein helps to determine how the protein wraps itself up into a particular working shape – perhaps as an enzyme or a hormone, or perhaps a contractile muscle protein or the tough protein in fingernails.

The coded instructions in DNA involve four **bases** – A, G, C and T for short. These bases are strung along the DNA backbone in groups of three. Each group of three bases – or **triplet** – codes for a particular amino acid. AGC is the code for one called serine, CGT for alanine, GCA for a third called arginine and so on. Using four letters, in groups of three, in any order, provides 64 possible triplet combinations. With only 20 common amino acids to code for that is more than enough.

The bases in DNA are:

A = adenine
C = cytosine
G = guanine
T = thymine

Box 2 Cystic fibrosis

Cystic fibrosis (CF) is the UK's most common life-threatening inherited disease and affects more than 7500 babies, children and young adults. One in 25 people in the UK carry the CF gene, usually without knowing it. People with CF have a build-up of mucus that is much thicker than normal, mainly in the lungs and digestive tract. As a result they suffer from a constant cough, an excessive appetite but failure to gain weight, bowel problems and repeated lung infections.

Some of these symptoms can be treated. Regular physiotherapy – tapping the chest – helps to loosen the mucus from the lungs. Enzymes taken with meals help with food digestion and antibiotics can protect against infections. At present there is no cure for CF, but the gene involved has been identified and doctors and scientists are working to find ways of repairing or replacing faulty alleles.

The gene codes for an important protein found in the cell membrane that affects the movement of salt into and out of cells. If too much salt is inside cells, water is pulled back from the mucus by osmosis, making the mucus more sticky. A genetic test can identify family members who may be unaffected carriers of the condition.

You can find out more about cystic fibrosis at <http://www.cftrust.org.uk/index.jsp> Click on *Living with cystic fibrosis*.

To look at an example, altogether there are 574 triplets which code for the 574 amino acids needed to make the complex protein haemoglobin. Each haemoglobin molecule contains two types of amino acid chains – α and β . The particular gene for making the α chain (146 amino acids) is on chromosome 11 and that for the β chain (141 amino acids) is on chromosome 16.

Mutation

Mutation involves a change in the inherited material. It applies to changes in both chromosomes and DNA.

Chromosome mutation

Some babies end up with an extra copy of a whole chromosome when chromosomes move during meiosis. This might be an extra chromosome 21, in which case the baby will show Down's syndrome. If it is an extra X chromosome the person will be XXY which means that they have Klinefelter's syndrome.

Sometimes different changes in the same chromosome have much the same effect. Where a small section of chromosome 15 is lost, or there is an extra chromosome 15, or bits of chromosome 15 have been switched and found on other chromosomes, the result is a condition known as Prader-Willi syndrome. Another condition, called cri-du-chat, involves loss of part of chromosome 5.

Box 3 Huntington's disease

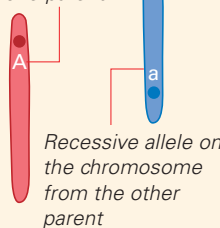
In this disease the mutation has occurred in a gene on chromosome 4. This gene produces a protein called **huntingtin**. In some way — which is not yet understood — the faulty version of the huntingtin protein leads to nerve-cell damage in areas of the brain. This causes gradual physical, mental and emotional changes, which become more acute as time goes on. The actual cause of death is usually a secondary illness, such as pneumonia.

The symptoms of Huntington's disease tend to develop when people are between 30 and 50 years old, although they can start much earlier or much later.

You can find out more about Huntington's disease at <http://www.hda.org.uk> Click on *What is Huntington's disease* at the top of the page.

Genes come in different versions or **alleles**. **Dominant** alleles always result in a characteristic appearing while **recessive** alleles do not have an effect unless there is also recessive allele on the other chromosome (i.e. the trait is inherited from both parents).

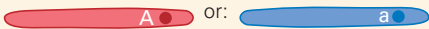
Dominant allele on the chromosome from one parent



Recessive allele on the chromosome from the other parent

A recessive disease

During meiosis the pairs of chromosomes separate into two sex cells, which then include either:



If two people are both carrying a recessive allele on one chromosome (e.g. the allele for cystic fibrosis or sickle-cell anaemia) the probability of what their offspring will inherit can be worked out using a simple table:

		Sperm	
		A	a
Egg	A	AA Normal	Aa Carrier for CF or sickle-cell
	a	Aa Carrier for CF or sickle-cell	aa Suffers CF or sickle-cell

• Draw a similar diagram for someone who is a carrier having children with someone who is not a carrier.

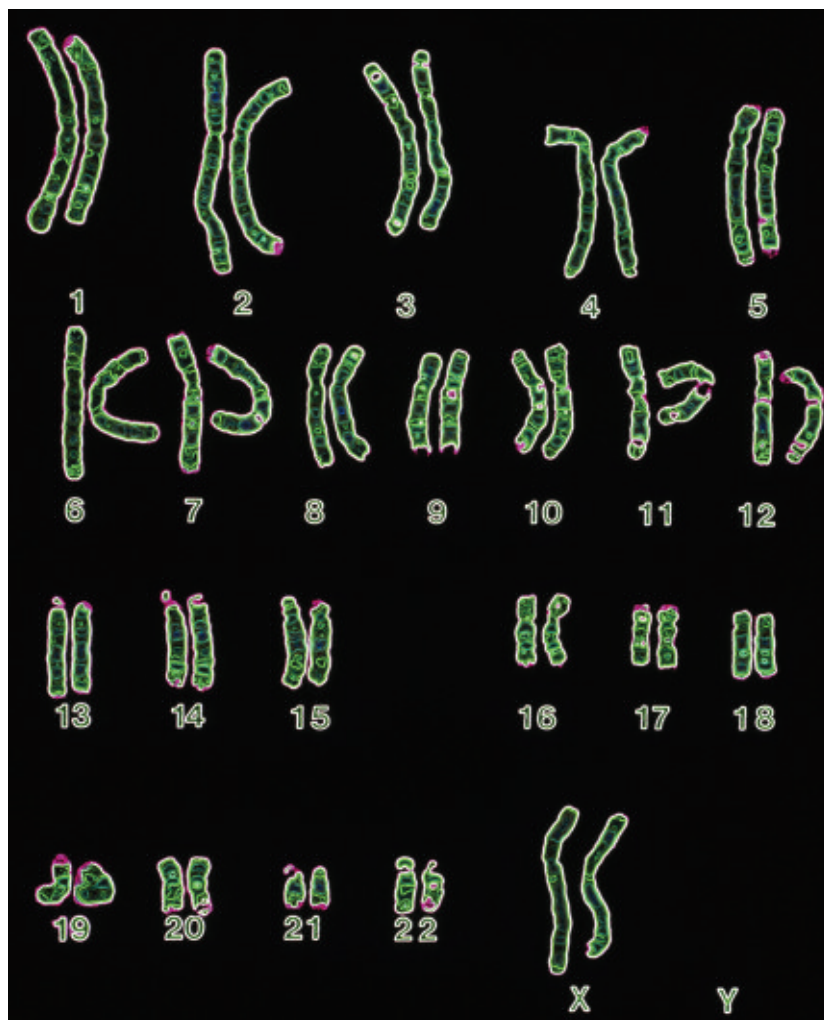
A dominant disease

If the disease is carried on a dominant allele, e.g. Huntington's disease, it is possible to be either AA or Aa and still suffer from it. If a person is Aa and the other parent is aa what is the chance of a child having the disease?

Figure 2 How diseases are inherited

DNA mutation

A mistake in the sequence of bases in DNA — a change in the **coding sequence** — will often lead to a protein being assembled incorrectly. The wrong amino acid may be added to the protein at one point or an amino acid might be missed out. For example, a single base change in the gene for haemoglobin,



An enhanced light micrograph of a normal human female karyotype — the full complement of chromosomes in a woman

involving one change to the triplet coding for one particular amino acid, leads to a different amino acid being incorporated instead. As a result the mutant haemoglobin cannot wrap itself up into the proper working shape. This causes the condition sickle-cell anaemia (Box 1).

Inheritance of disease

Some features of an organism involve many genes, as well as complex interactions with the environment. However, a few characteristics, including some inherited diseases, are controlled by a single gene. Let's consider sickle-cell anaemia first. It turns out that the mutated version of the gene — the mutated allele — is **recessive**. In other words a person needs to inherit this particular allele from *both* parents if the disease is to show up (see Figure 2). Cystic fibrosis is another condition that is caused by the action of a single gene (Box 2).

Another inherited disease that you may be aware of is Huntington's disease (Box 3). In contrast to sickle-cell anaemia and cystic fibrosis, the faulty allele leading to this disease is **dominant**.

• You can find out about genetic disorders at the website of the Genetic Interest Group: <http://www.gig.org.uk> Click on *Education* for general information or on *membership of over 130 charities* in the text for links to other websites.

• Find out about Prader-Willi syndrome or cri-du-chat using the Genetic Interest Group website.