

What causes genetic disorders?

Genetics is the science of inheritance. It aims to understand the mechanism by which the blueprints for life are passed through generations and how variations in these blueprints are essential for evolution, yet can cause disease. This article aims to define the major types of genetic disorder and provide examples of each.

The GP curriculum and genetic disorders

Statement 6 of the GP curriculum is concerned with genetics in primary care. It requires GPs in training to have a basic knowledge about genetics, and in particular about deoxyribonucleic acid (DNA) as genetic material and how mutations and variants contribute to human disease, and patterns of inheritance.

The basis of human genetic disorders

Genetic diseases can be due to an alteration in one gene, several genes in combination with environmental factors or due to imbalance of many genes. These are the basis of the three main classes of genetic disorders:

- single-gene disorders—mutations in single genes often causing loss of function
- multifactorial conditions—variants in genes interacting with the environment and causing alteration of function
- chromosomal disorders—causing chromosomal imbalance and alteration in gene dosage.

DNA, genes and chromosomes

The clinical effects of human genetic disorders can be explained by understanding how our DNA is organized and copied. Genes are encoded in DNA which is composed of two strands of combinations of four chemical bases, which face in opposite directions and connect pairwise to form a double helix shape—Fig. 1. These chemicals are adenine (A), thymine (T), cytosine (C) and guanine (G). Genetic information exists in the sequence of these nucleotides—genes direct the synthesis of proteins involved in cell structure, metabolism and cell communication (for instance

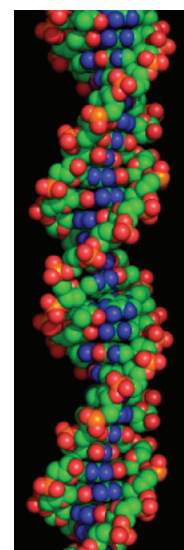


Figure 1. The DNA double helix.

collagen, enzymes and hormones) and special RNA molecules which regulate gene expression.

Different genes are read or ‘expressed’ at different times in different cells in response to requirements. A change to the DNA sequence can change the gene product’s structure and behaviour, and this can have dramatic consequences in the cell and on the individual as a whole.

Each human cell nucleus holds about 2 m of DNA and about 25 000 genes. In order to be able to manage this DNA and pass it from cell to cell, it is organized into smaller units—chromosomes. Each chromosome is made up of a long strand of DNA and contains thousands of genes, arranged in a linear order along the chromosome. Chromosomes also contain histone proteins that are involved in chromosome structure and packing and in gene regulation.

Humans have 23 pairs of chromosomes (Fig. 2), 22 matching pairs with matching genes called the autosomes and one pair of sex chromosomes (XX—female or XY—male). We inherit one of each pair from our mother and one from our father.

gene or block of genes in a family. This can then allow predictions to be made about whether another family member is at risk of being affected or of being a carrier depending on whether or not they have inherited the DNA marker (Fig. 3).

Family members inherit blocks of genes in common with each other. It is possible to use DNA markers to identify a particular

Although chromosomes can be seen down the microscope, genes are too small and so chemical methods have to be used

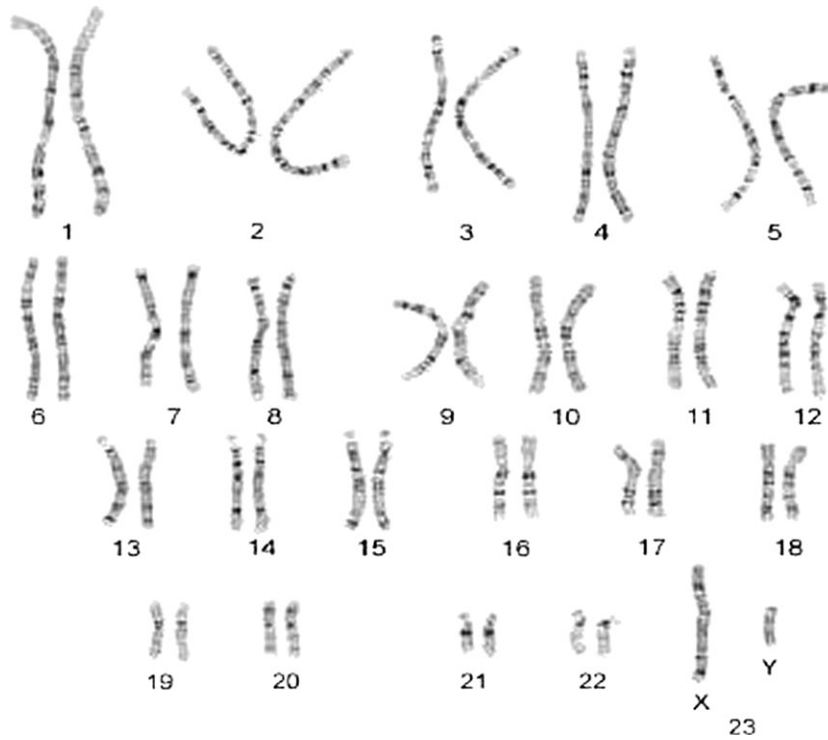


Figure 2. Twenty-three pairs of chromosomes arranged according to size with chromosome 1 being the largest. The final two chromosomes are the sex chromosomes. Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

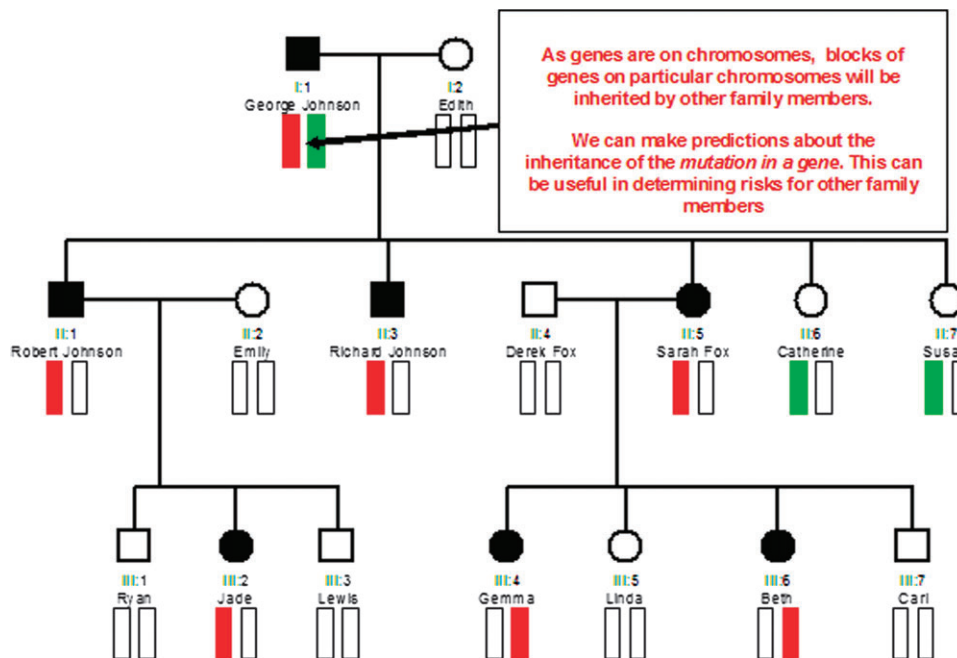


Figure 3. The chromosome theory of inheritance.

to determine the DNA sequence of a gene—usually by a process called sequencing. When a variant in a gene sequence has been identified, it has to be interpreted to see whether the change is likely to be the cause of a disease or is a normal variant. Some changes will cause a medical condition, some predispose to disease, while some have no effect at all.

In addition to the DNA in the nucleus, mitochondria in the cytoplasm also contain DNA which codes for some genes involved in the production of energy in the mitochondria. The DNA in the nucleus and mitochondria is called the ‘human genome’. The Human Genome Project completed decoding the whole human DNA sequence in 2001. However, it is still not known what role all the genes in the human genome play or how they interact with each other.

How common are genetic disorders?

Abnormal function of genes causes genetic disorders. We all carry genes that are potentially hazardous. Some are hidden in recessive form and we may never know that we carry them. Some will only exert their influence through interactions with environmental triggers. Others are manifest from or even before our birth. A working party of the Royal College of Physicians has estimated that 2–3% of births result in babies with either congenital or genetically determined abnormalities. This means that approximately 13 000 births a year in the UK are affected by a genetic disorder. Some conditions may manifest themselves only later in life and 5.5% of the population will have developed a genetic condition by the age of 25 years. Later in life, this figure rises to approximately 60% if conditions in which

genetics plays some role are included. Table 1 summarizes the prevalence of genetic disease in the UK.

Chromosomal disorders

Anomalies of chromosome number

Both the autosomes and the sex chromosomes may be altered in number. Examples of autosomal duplication are Down’s syndrome caused by an additional chromosome 21 (Fig. 4), Edward’s syndrome due to an additional chromosome

Table 1. Prevalence of genetic disease in the UK

Type of genetic disease	Estimated prevalence per 1000 population
Single gene	
Autosomal dominant	2–10
Autosomal recessive	2
X-linked recessive	1–2
Chromosomal abnormalities	6–7
Common disorders with appreciable genetic component	7–10
Congenital malformations	20
Total	38–51

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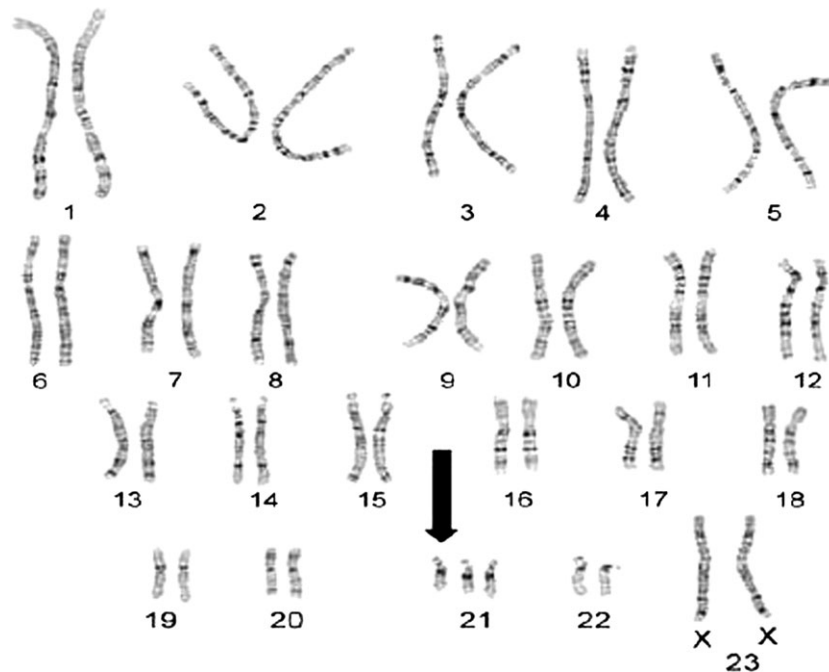


Figure 4. Chromosomes from a girl with Down’s syndrome showing an additional chromosome 21. Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

18 and Patau's syndrome where there is trisomy of chromosome 13. Examples of alterations in the number of sex chromosomes are Turner's syndrome (45, X) in which the second sex chromosome is absent and Klinefelter's syndrome (47, XXY) where there is more than one X chromosome in a male. Table 2 summarizes the most common conditions caused by structural chromosomal abnormalities.

The usual cause of anomalies in chromosome number is 'non-disjunction'. This can occur during gamete formation in meiosis or during mitotic somatic cell division. This accounts for more than 90% of these abnormalities. In meiosis, an error causes both copies of a chromosome to segregate into an egg or sperm (Fig. 5). The incidence of meiotic non-disjunction increases with increasing maternal age.

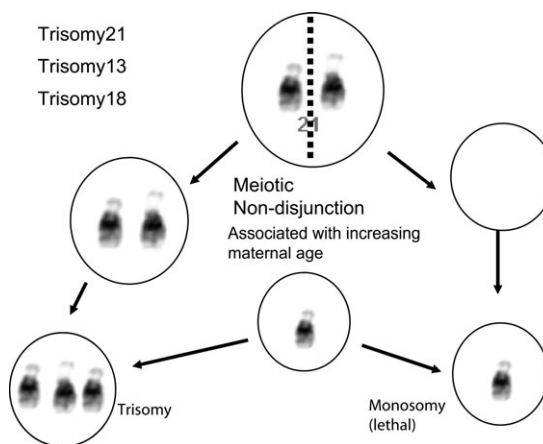


Figure 5. Meiotic non-disjunction.

Table 2. Structural chromosome problems seen in general practice	
Genetic problem	Features
<p><i>Down's syndrome</i> Trisomy 21 (92%) Translocation (6%) Mosaicism (2%) Affects 1:600 births</p>	<p><i>Facial abnormalities:</i> flat occiput, oval face (mongoloid facies), low set eyes with prominent epicanthic folds <i>Other abnormalities:</i> single palmar crease, hypotonia, congenital heart disease, developmental delay Life expectancy is reduced but about half live to 60 years</p>
<p><i>Edward's syndrome</i> Trisomy 18 Affects 1:6000 births 5:482:1</p>	<p><i>Facial abnormalities:</i> low-set malformed ears, receding chin, protruding eyes, cleft lip or palate <i>Other abnormalities:</i> short sternum makes the nipples appear too widely separated, fingers cannot be extended and the index finger overlaps the third digit, umbilical/inguinal hernias, rocker-bottom feet, rigid baby with flexion of limbs, developmental delay Life expectancy is about 10 months</p>
<p><i>Patau's syndrome</i> Trisomy 13 Affects 1:7500 births</p>	<p><i>Facial abnormalities:</i> small head and eyes, cleft lip and palate <i>Other abnormalities:</i> skeletal abnormalities e.g. flexion contractures of hands often with polydactyly with narrow fingernails, brain malformation, heart malformation, polycystic kidneys 50% die within a month. Usually fatal in the first year.</p>
<p><i>Cri du chat syndrome</i> Deletion of short arm of chromosome 5 Affects 1:50 000 births</p>	<p><i>Facial abnormalities:</i> microcephaly, marked epicanthic folds, moon-shaped face, alert expression <i>Other abnormalities:</i> abnormal cry (cat like), developmental delay Usually fatal in the first year</p>
<p><i>Turner's syndrome</i> 45,X—deletion of one X chromosome Mosaicism may occur (45,X; 46,XX) Affects 1:2500 births</p>	<p>Female appearance <i>Facial abnormalities:</i> ptosis, nystagmus, webbed neck <i>Other abnormalities:</i> short stature (less than 130 cm), hyperconvex nails, wide carrying angle (cubitus valgus), inverted nipples, broad chest, coarctation of the aorta, left heart defects, lymphoedema of the legs, ovaries rudimentary or absent Lifespan is normal</p>
<p><i>Klinefelter's syndrome</i> 47,XXY polysomy Affects 1:1000 live births</p>	<p>Male appearance Often undetected until presentation with infertility in adult life <i>Clinical features:</i> may present in adolescence with psychopathy, d libido, sparse facial hair, gynaecomastia, small firm testes <i>Associations:</i> hypothyroidism, diabetes mellitus, asthma <i>Specialist management:</i> androgens and plastic surgery may be useful for gynaecomastia</p>

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Non-disjunction occurring in mitosis after formation of the zygote results in 'mosaicism' (Fig. 6). The person has two populations of cells—one with the original normal chromosome complement and an additional population of cells with an aberrant pattern of chromosomes. How the person is affected depends on the number of cells with the altered chromosome pattern and their distribution in the body.

Changes in chromosome structure

During meiosis, the two chromosomes of a particular pair naturally swap genetic material between themselves, by breaking and rejoining, thereby producing different combinations of genes to pass on to offspring. This is part of the process to ensure that (apart from identical twins) we all have different combinations of genes. Sometimes repair of the breaks can be faulty, or unusual pairing of chromosomes can occur. This may result in deletion or duplication of genetic material in the gamete (Fig. 7).

Deletions

A part of a chromosome is lost or deleted (Fig. 8). This can happen to any chromosome. The effects of the deletion depend on the nature and amount of information coded for on the portion of the chromosome lost. An example of a condition caused by deletion of part of a chromosome is Cri du Chat syndrome due to deletion of the short arm of Chromosome 5 (see Table 2).

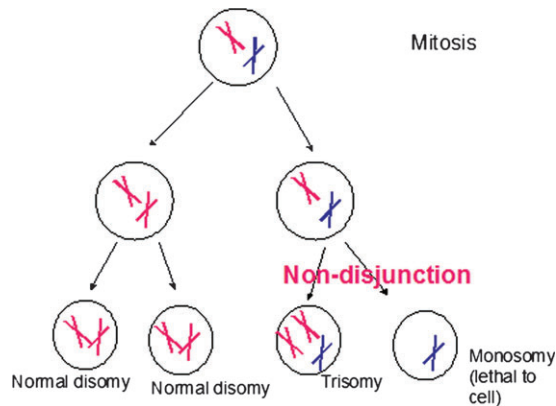


Figure 6. Somatic mosaicism as a result of non-disjunction in mitosis.

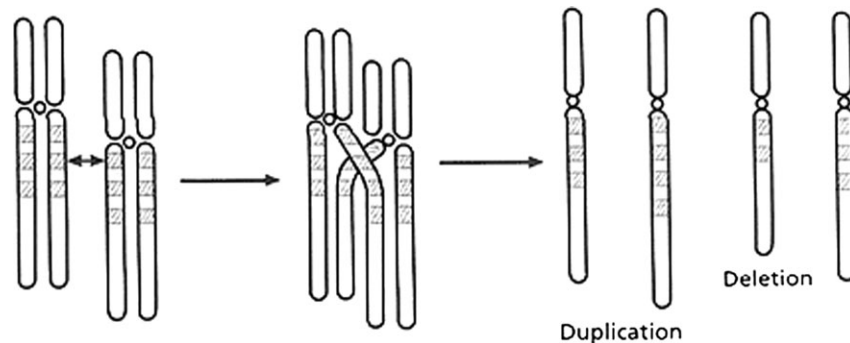


Figure 7. Chromosome deletions and duplications occurring due to unequal crossing over in meiosis following misalignment, often at the sites of repeated sequences.

Duplications

A part of a chromosome is doubled or duplicated (Fig. 9). The effects of the duplication depend on the nature and amount of information coded for but duplications may cause developmental delay and other health effects.

Translocations

Translocations are common and affect around 1 in 500 people though most are unaware that they have them. There are two types of translocations—reciprocal and Robertsonian.



Figure 8. Deletion of part of a chromosome. *w* Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

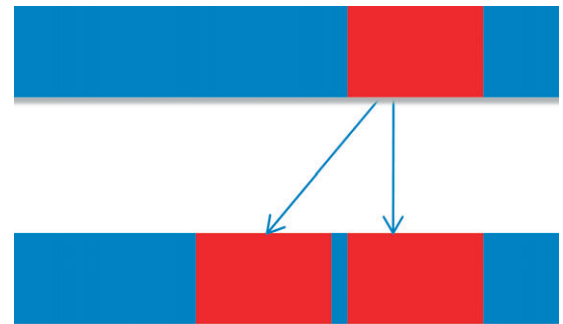


Figure 9. Duplication of part of a chromosome. Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

Most people with a ‘reciprocal translocation’ have inherited it from a parent; occasionally it can occur *de novo*. During the formation of the translocation during meiosis, breaks occur in chromosomes from different pairs with rejoining in an unusual pattern. Chromosomal material normally found on one particular chromosome is now found on another (Fig. 10).

A ‘Robertsonian translocation’ occurs when a whole chromosome from one pair has become attached to the end of a whole chromosome from another pair (Fig. 11). Around 4% of children with Down’s syndrome have an unbalanced Robertsonian translocation involving chromosome 21.

As long as no genetic information is gained or lost, a translocation does not affect the individual and is described as a ‘balanced’ translocation. However, it may affect the offspring of that individual. Children of the affected individual may inherit normal chromosomes, the same balanced translocation as the parent or, if the child inherits an extra piece of one chromosome or a missing piece of another, an ‘unbalanced’ translocation. The effects of this unbalanced translocation depend on the particular genes involved and can result in miscarriage or multiple congenital anomalies and/or development delay.

Single-gene inheritance

At its most fundamental level, inheritance in organisms occurs by means of individual discrete traits or genes. To recognize the contributions of an Augustinian monk, Gregor Mendel, the term ‘Mendelian’ inheritance is applied to patterns of inheritance compatible with the segregation of characteristics apparently under the control of a single gene.

With the exception of some genes on the X chromosome, each individual has two versions of the same gene within their genetic make up. These are called ‘alleles’. Individuals with two versions of the same gene are called ‘homozygotes’ and those with two different alleles are termed ‘heterozygotes’. The set of alleles that an individual has is his or her ‘genotype’. When two individuals breed, their offspring randomly inherit one of the alleles from each parent. Single-gene disorders occur as a result of a single gene (or allele) being altered and may arise due to errors in chromosome replication during formation of the individual (*de novo* mutations) or be inherited from generation to generation and thus run in families. The genotype of the individual is responsible for that individual’s ‘phenotype’ or the outwardly apparent traits that the individual has.

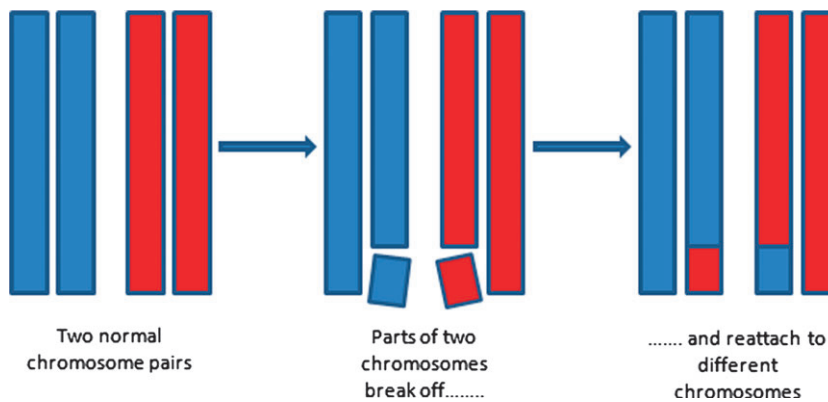


Figure 10. The formation of a reciprocal translocation. Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

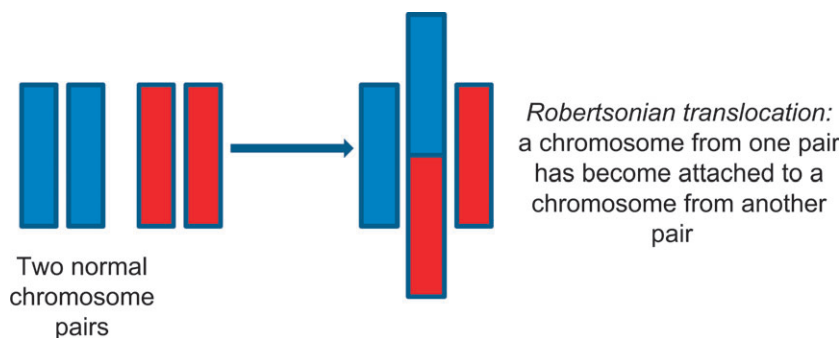


Figure 11. The formation of a Robertsonian translocation. Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

A trait or condition expressed in an individual who is heterozygous is called 'dominant' as its qualities 'dominate' the phenotype of the individual. A 'recessive' trait or condition is one which is expressed only in homozygotes. Note that these terms describe the phenotype and the pattern of inheritance, not how the gene products cause their effects.

Table 3. Approximate frequency of the most common Mendelian disorders in the UK population

Disorder	Frequency (per 1000 births)
Autosomal dominant inheritance	
Familial combined hyperlipidaemia	5.0
Familial hypercholesterolaemia	2.0
Dominant otosclerosis	1.0
Adult polycystic kidney disease	0.8
Multiple exostoses	0.5
Huntington's disease	0.5
Neurofibromatosis	0.4
Myotonic dystrophy	0.2
Congenital spherocytosis	0.2
Polyposis coli	0.1
Autosomal recessive inheritance	
Cystic fibrosis	0.4
Alpha1-antitrypsin deficiency	0.2
Phenylketonuria	0.1
Congenital adrenal hyperplasia	0.1
Spinal muscular atrophy	0.1
Sickle cell anaemia	0.1
Beta thalassaemia	0.05
X-linked recessive inheritance	
Fragile X syndrome	0.5
Duchenne muscular dystrophy	0.3
X-linked ichthyosis	0.1
Haemophilia A	0.1
Becker muscular dystrophy	0.05
Haemophilia B	0.03

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Autosomal dominant inheritance

Autosomal dominant disorders result from the inheritance of a single copy of an altered gene found on a non-sex chromosome. Usually, these conditions affect male and female offspring equally. Over a thousand diseases are known to be inherited this way but individually they are rare accounting for less than 1% of all disease (Table 3). The single altered copy is sufficient to cause the phenotype.

A person with an autosomal dominant disorder will pass on either the normal or altered gene and so each child has a one in two probability of inheriting the gene (Fig. 12). Autosomal dominant diseases include many of the serious and more common genetic disorders of adult life, such as polycystic kidney disease and Huntington's disease. A particular characteristic of some autosomal dominant disorders (for instance, myotonic dystrophy and neurofibromatosis type 1) is that they can be very variable in their manifestations between different members of the same family, so it is important to examine a relative before assuming that they are unaffected.

Autosomal recessive inheritance

Autosomal recessive disorders are the result of inheriting a copy of an altered gene found on a non-sex chromosome from each parent. These diseases usually affect male and female offspring equally. Over 700 autosomal recessive diseases are recognized and some of the most common are listed in Table 3. If just a single copy of the altered gene is inherited, the single functional copy is sufficient for normal function. The individual is not affected by the disorder, but is termed a genetic 'carrier' of the condition. On average, each of us carries about six autosomal recessive diseases unknowingly.

When two people who are carriers of an autosomal recessive condition come to have children, each passes on either the

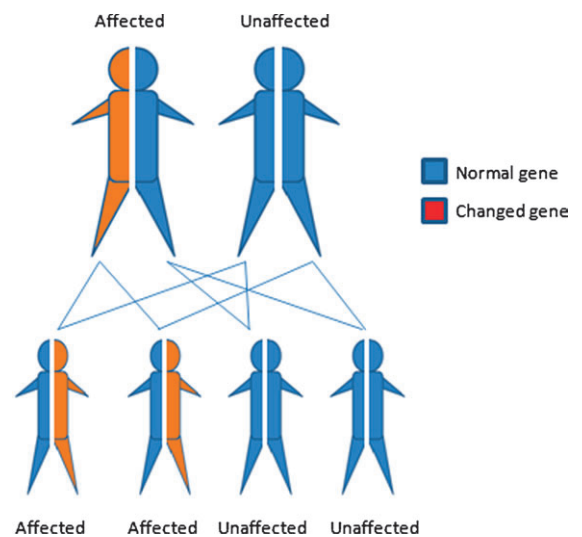


Figure 12. Autosomal dominant inheritance.
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normal or the altered gene. At conception, each child has a 1 in 4 probability of being affected, a 2 in 4 probability of being a healthy carrier and a 1 in 4 probability of not having inherited the altered gene (Fig. 13).

Although individuals affected with an autosomal recessive condition will pass on the altered gene to all their offspring, it is unusual for their children to be affected because it would be unlikely for their partner to be a heterozygote for the same condition.

High frequencies of recessive disorders in particular populations are thought to lie in the relative benefits conferred by the carrier state in certain circumstances. For example, the highest frequency of sickle cell anaemia is found in populations with a mid-African background as a single copy of the sickle-cell gene grants some protection against malaria, while cystic fibrosis is most common among North Europeans and their descendants because a single copy of the cystic fibrosis gene is believed to have offered some protection against chloride-losing diarrhoea, such as cholera.

Sex-linked inheritance

Sex-linked disorders are those in which the altered gene lies on, and is inherited with, the X chromosome. Around 100 sex-linked conditions have been described and the most common are listed in Table 3. X-linked recessive conditions are normally seen only in males because males have only one X chromosome and therefore (unlike carrier females) do not have a normal allele to counterbalance its effects. Usually, the condition is inherited from a mother who is a carrier but who is asymptomatic (because she has a normal allele on the second X chromosome) but some males with an X-linked recessive disorder are the first person to be affected in the family as a result of a new mutation occurring.

Each offspring of a woman heterozygous for an X-linked recessive allele has a 1 in 2 chance of inheriting the allele. If

the child is male, he has a 1 in 2 chance of being affected, and if the child is female, a 1 in 2 chance of being a carrier (Fig. 14).

Female carriers do not usually show symptoms of X-linked recessive disorders, but occasionally they can. Although females have two X chromosomes, in each cell one is inactivated at random (this ensures that males and females have equal amounts of gene products from the X chromosome). Sometimes the inactivation is not random, so that by chance more of her cells have the X chromosome with the disease gene active than the normal gene. As a daughter of a male with an X-linked recessive disease must have inherited his X chromosome, she must be an obligate carrier of her father's condition.

Multifactorial inheritance

Some families have a pattern of affected people which cannot be explained by the rules of Mendelian inheritance. Common examples are diabetes mellitus, cleft lip and palate and neural tube defects. It is thought that these—called multifactorial conditions—are due to particular combinations of several genes inherited from both parents (polygenic inheritance) acting together with environmental factors. It is this group of conditions which give the greatest contribution to morbidity and mortality. Studies in identical (or monozygotic) twins and non-identical (or dizygotic) twins can help to determine if there is a large genetic component in a particular condition (Table 4).

However, detecting the genes responsible and how these interplay with each other, and environmental factors, is much more difficult. This is being addressed through large population studies, where the genetic patterns of

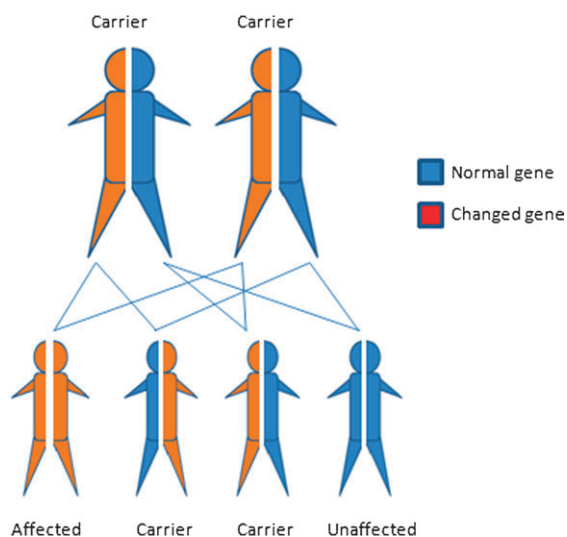


Figure 13. Autosomal recessive inheritance. Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

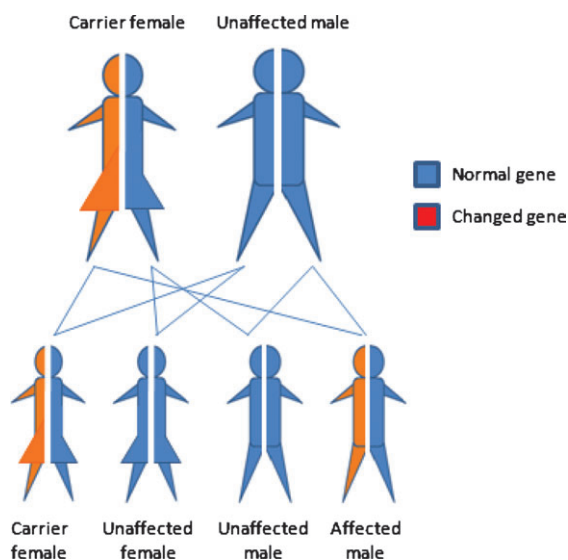


Figure 14. X-linked recessive inheritance from a female carrier. Reproduced with permission from the Genetic Interest Group www.gig.org.uk.

Table 4. Twin concordance for common disorders with a multifactorial inheritance pattern

Trait	Concordance (%)	
	Monozygotic twins	Dizygotic twins
Congenital malformations		
Cleft lip and palate	35	5
Club foot	30	2
Congenital hip dislocation	40	3
Pyloric stenosis	20	2
Spina bifida	6	3
Adult diseases		
Diabetes mellitus (type 2)	50	10
Hypertension	30	10
Bipolar affective disorder	80	10
Multiple sclerosis	20	5
Schizophrenia	40	10
Alzheimer's disease	40	10

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people with a particular condition are compared with the patterns of unaffected people. One study used 14 000 cases of seven conditions, including bipolar disorder, rheumatoid arthritis, diabetes mellitus, Crohn's disease and coronary artery disease, and 3000 controls and found areas of the genome which appear to be associated with a predisposition to the conditions. The search is now on to identify the responsible genes and variants within these regions. When they have been found, the next step will be to assess the clinical utility and validity for combinations of gene variants in various conditions—some may identify people at higher risk of developing a condition, who are more likely to have a particular clinical outcome or who respond best to a particular management strategy.

Later changes in genetic make up

Once the human body is formed, there is a constant process of cell replication to repair tissues and replenish stocks of cells needed for specific functions. During each cell

replication, the genetic information from that cell is cloned to form the genetic information of the daughter cells. Many factors can result in small changes or 'mutations' occurring in the genetic make up of cells during this process. Exposure to radiation, drug effects or viral infection are examples. Small point changes (or mutations), for instance, are thought to be involved in the ageing process.

Genetic mutations may also be responsible for many cancers. Cancer genes or 'oncogenes' are usually mutated forms of normal cellular genes or 'proto-oncogenes'. Proto-oncogenes code for proteins that help to regulate cell growth and differentiation. Oncogenes cause the process of cell growth or differentiation to be altered and are found in the oncogenically activated state in transformed cancer cells and in their normal proto-oncogenic state in non-transformed cells. Oncogenes were discovered in the 1970s and since that time dozens have been implicated in human cancers. Study of these genes is now beginning to yield new cancer treatments.

Key points

- Genetics is a rapidly evolving field
- The blueprint for a given individual is coded on genes contained within that individual's DNA
- A copy of each gene is inherited from the individual's mother and another copy from the individual's father
- The copy of the gene that is expressed and thus affect the way that the individual turns out depends on whether the genes inherited are dominant, co-dominant or recessive
- Genes are packages onto chromosomes. Humans have 22 pairs of autosomal chromosomes and one pair of sex chromosomes
- Genetic abnormalities may result from abnormalities in the number or structure of the chromosomes or defective genes
- Genetic abnormalities may arise within the individual or be inherited from one or both of the parents
- It is estimated that up to 60% of conditions affecting humans have a genetic element.

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