Genes and chromosomes 4: common genetic conditions

Given that the human genome comprises around 3 billion base pairs of deoxyribonucleic acid (DNA), it is not surprising that errors in the genetic code (genetic mutations) sometimes occur. Many are associated with genetic diseases and pass through generations in a predictable manner. This fourth and final article in our series on genes and chromosomes looks at genetic diseases, from those affecting entire chromosomes (chromosomal disorders) to those affecting single genes (single-gene defects).

Chromosomal disorders
Normal cell division
During cell division (whether mitosis or meiosis), DNA condenses into thin thread-like structures called chromosomes. This allows easier separation of genetic material between mother and daughter cells. With the exception of gametes (spermatozoa and ova), all nucleated human cells contain 23 pairs of chromosomes, giving the diploid number of 46 (see part 2).

With age, cells gradually sustain cumulative damage. To replace old cells, identical daughter cells are produced by mitosis (normal cell division). During this process, the diploid number is rigorously maintained and all daughter cells receive a complement of DNA identical to that of their parent cells (see part 2).

To form new gametes, the germinal cells of the ovaries and testes undergo meiosis, in which the diploid number is halved to the haploid number of 23. Each of the 23 pairs of chromosomes are pulled apart so that each spermatozoon and ovum receives 23 chromosomes. During fertilisation, when a haploid spermatozoon penetrates a haploid ovum, the diploid number is restored. Meiosis also ensures that each offspring receives roughly half their genes from each parent (see part 2).

Nondisjunction and aneuploidy
As the human body ages, the separation of chromosome pairs during meiosis (the process of cell division in germinal cells) becomes less efficient. This can result in spermatozoa or ova receiving extra or

Key points
- An aneuploidy is a deviation from the diploid number – the most well-known is Down’s syndrome
- Trisomies are disorders in which an extra chromosome is present
- People with Klinefelter’s syndrome have an extra X chromosome, but their Y chromosome means they have a male phenotype
- Turner’s syndrome is the only survivable chromosomal disorder in which an entire chromosome is missing
- Single-gene defects can cause inheritable genetic diseases such as cystic fibrosis, albinism and Huntington’s disease
fewer chromosomes – for example, 24 or 22 instead of 23. This faulty separation of chromosomes, known as nondisjunction, can result in various chromosomal diseases (Gottlieb and Tegay, 2018).

During fertilisation, a haploid spermatoozon (bearing 23 chromosomes) fuses with a haploid oocyte (bearing 23 chromosomes), which means the diploid number of 46 is restored in the resulting zygote (fertilised ovum). In nondisjunction, gametes may contain extra or missing chromosomes, so the resulting zygote will not have the diploid number. Any deviation from the diploid number is called aneuploidy – the most well-known is Down’s syndrome.

In Down’s syndrome, nondisjunction usually occurs during oogenesis (ova formation), resulting in some ova having two copies of chromosome 21 instead of one. During fertilisation, the spermatoozon brings its own paternal copy, so the zygote ends up with three copies of chromosome 21 – hence the name trisomy 21 (see part 1).

A variety of other clinically significant aneuploidies occur as a result of nondisjunction. In many of them, embryos are unviable and often spontaneously miscarried early in pregnancy (Jia et al, 2015).

**Trisomies**

Among the survivable aneuploidies, most are trisomies – that is, chromosomal disorders in which an extra chromosome is present. Although it has been estimated that 80-90% of trisomies occur as a result of nondisjunction during oogenesis (particularly in older mothers), there is growing evidence that they can also occur because of nondisjunction during the formation of spermatozoa (Shi and Martin, 2000).

Trisomies result in well-defined syndromes with characteristic physical and psychological features. Patients usually require long-term medical care and interventions from nurses and other specialised health professionals. Two of the more common aneuploidies besides Down’s syndrome are Patau’s syndrome and Edwards’ syndrome.

**Patau’s syndrome.** Patau’s syndrome (trisomy 13) occurs in embryos that have received an extra copy of chromosome 13. It is seen in 1 in 5,000 to 1 in 10,000 live births, and regarded as the most serious survivable trisomy as its clinical features are usually severe. These include:

- Microcephaly (incomplete brain development);
- Missing eyes;
- Displaced nose;
- Cleft palate;
- Ear malformations;
- Polydactyly (extra fingers and/or toes).

Many babies born with Patau syndrome do not survive more than a few days and 90% will die within the first year of life; some rare individuals survive into early adulthood (Bit.ly/NHSPataus).

**Edwards’ syndrome.** Edwards’ syndrome (trisomy 18), seen in around 1 in 5,000 live births, occurs in embryos that have inherited an extra copy of chromosome 18. It is the second most common autosomal trisomy after Down’s syndrome. (The concept of autosomal disease is explained later in this article.) A large number of affected embryos are spontaneously miscarried or stillborn (Cereda and...
Carey, 2012).

For babies born with Edward’s syndrome, the outlook is generally poor. Most die shortly after birth and only around 10% survive longer than a year. Sometimes only an extra fragment of chromosome 18 is inherited: these babies tend to have less severe physical abnormalities and can live longer (Bit.ly/NHSEdwards).

All forms of Edwards’ syndrome display a range of clinical features including:
- Low birthweight;
- Exomphalos (born with intestines outside the body);
- Microcephaly (small/abnormally formed head);
- Small mouth and lower jaw;
- Cleft palate;
- Heart defects;
- Kidney disease;
- Severe learning disabilities.

With medical support, some individuals with Edwards’ syndrome survive into early adulthood.

Sex chromosome disorders

Gender is determined by the final 23rd pair of chromosomes (see part 1) and, in most people, sex chromosomes come in one of two combinations:
- XX – female;
- XY – male.

Some chromosomal disorders affect the sex chromosomes. In terms of gender determination, the presence of a Y chromosome is of greatest significance, as anyone with a Y chromosome will physically appear to be male (that is, have a male phenotype), irrespective of the number of X chromosomes they possess.

Klinefelter’s syndrome. Klinefelter’s syndrome (XXY) occurs in between 1 in 500 and 1 in 1,000 male live births as a result of nondisjunction of the sex chromosomes during the formation of either spermatozoa or ova. Some ova of older mothers may have two copies of the X chromosome (XX) instead of only one. If such an ovum is fertilised by a normal Y-bearing spermatozoon, the result is an individual carrying the sex chromosomes XXY. Nondisjunction during spermatogenesis can result in an abnormal spermatozoon that has both an X and a Y chromosome. If such a spermatozoon fertilises a normal X-bearing ovum, the result is, again, an XXY individual.

The presence of a Y chromosome means that all individuals with Klinefelter’s syndrome have a male appearance; however, there is often some feminisation, together with other characteristics of the syndrome (Fig 1a). According to Groth et al (2013), common clinical features of Klinefelter’s syndrome include:
- Hypogonadism (reduced testicular mass);
- Reduced testosterone production;
- Reduced fertility;
- Reduced facial and body hair;
- Weakened muscles;
- Osteoporosis;
- Tall stature;
- Gynecomastia (development of feminine breast tissue);
- Poor language and reading skills.

Most people with Klinefelter’s syndrome lead full, productive lives and can father children, albeit usually with the help of in vitro fertilisation.

Turner’s syndrome. Turner’s syndrome (X) is the only survivable chromosomal disorder in which an entire chromosome is missing. People with Turner’s syndrome have 45 chromosomes instead of 46. As they carry no Y chromosome, they always have a female physical appearance (female phenotype).

As with Klinefelter’s syndrome, Turner’s syndrome arises as a result of nondisjunction during the formation of ova or spermatozoa. If an ovum loses its X chromosome or a spermatozoon loses either its X or Y chromosome, there will only be one X chromosome present after fertilisation.

Turner’s syndrome (Fig 1b) occurs in around 1 in 2,000 female live births and affected individuals display clinical features such as:
- Absence of mature ovaries (rudimentary ovarian tissue);
- Wide shield-like chest with widely spaced nipples;
- Infertility;
- Amenorrhoea (absence of a menstrual cycle);
- Lack of breast tissue;
- Patches of darkened skin (nevii);
- Short stature;
- Small fingernails;
- Heart-valve problems;
- Aortic coarctation (narrowed aorta);
- Risk of aortic aneurysm and aortic dissection;
- Webbing of skin around the neck;
- Attention deficit hyperactivity disorder.

Although women with Turner’s syndrome generally lead healthy normal lives, the lack of ovarian tissue means that most cannot become pregnant or carry a child to term naturally. However, they can become pregnant using either ova that have been harvested from their rudimentary ovaries early in life or donated eggs. Hormonal therapy may be needed during pregnancy to ensure it progresses to term. Women with Turner’s syndrome need to undergo a variety of cardiovascular tests, both before becoming pregnant and during pregnancy, because of their increased risk of aortic dissection (Gravholt et al, 2017).

Single-gene defects

Structural genes encode for the synthesis of proteins, while control genes regulate the activity of structural genes (see part 1 and part 3). Mutations to both structural and control genes can result in defective genes. These are classified according to the chromosomes on which they are located – that is, their locus. Single-gene defects cause many of the inheritable genetic conditions; for example, cystic fibrosis, albinism and Huntington’s disease.

![Fig 2. Inheritance of cystic fibrosis](image)

When two carriers of a single recessive cystic fibrosis gene have a child, there is a 1 in 4 risk that the child will inherit the two recessive genes and thus develop the disease

<table>
<thead>
<tr>
<th>Father carrying one dominant and one recessive cystic fibrosis gene</th>
<th>Mother carrying one dominant and one recessive cystic fibrosis gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Cc</td>
<td>Cc</td>
</tr>
<tr>
<td>cc</td>
<td>cc</td>
</tr>
</tbody>
</table>
The first 22 pairs of chromosomes are the same in men and women; these are called the autosomes. The 23rd and last pair determines gender and its chromosomes are called the sex chromosomes (see part 1). As there are 22 pairs of autosomes and only one pair of sex chromosomes, most gene defects appear in the autosomes; they are therefore called autosomal genetic disorders. Disorders affecting the sex chromosomes, called sex-linked genetic disorders, are rarer.

**Autosomal recessive disorders**
Most autosomal gene disorders are called ‘recessive’. In these diseases, two copies of the defective gene are present – the presence of even one of the normal dominant genes would override, and thereby mask, the effects of a single recessive defective gene (in which case the disease would not develop). As most single-gene defects are autosomal and recessive in nature, the resultant genetic diseases are described as ‘autosomal recessive’.

In genetics, dominant genes are represented by capital letters and recessive genes by lower-case letters.

**Cystic fibrosis.** Cystic fibrosis is a single-gene defect particularly common in Northern-European races, where it affects around 1 in 2,000 to 1 in 3,000 newborn babies (Bit.ly/CysticFibrosisStats). The cystic fibrosis gene is located on chromosome 7 (one of the autosomes) and is recessive in nature.

There are three possible combinations of the cystic fibrosis gene (three genotypes):

- **CC** – normal genotype (disease not present, the person carries two dominant genes);
- **Cc** – carrier (the person carries one dominant and one recessive gene, so they do not develop the disease but can pass it on to their children);
- **cc** – disease present (the person carries two recessive genes).

It is estimated that around 1 in 25 people are carriers of the recessive disease-causing gene (Bit.ly/CysticFibrosisCauses). A Punnett square (simple grid used in noughts and crosses) shows that, when two carriers (Cc) have a child, there is a 1 in 4 risk that the child will inherit the two recessive genes, thereby developing the disease (Fig 2). This 3:1 ratio is common in single-gene recessive diseases and is known as a Mendelian ratio (named after Gregor Mendel, who first accurately described inheritance in plants in the 1800s).

People with cystic fibrosis have problems regulating the movement of water and electrolytes in certain tissues. This results in a build-up of thick, sticky mucus in the lungs, pancreatic ducts and gastrointestinal tract. Patients require frequent assessments in hospital, regular physiotherapy and medications to help shift the mucus from inside the lungs. Static mucus in the lungs increases the risk of infection and, over time, irritates lung tissue, which becomes scarred (fibrosis). This makes breathing progressively more difficult.

Lung fibrosis increasingly strains the right side of the heart, so many patients have pulmonary hypertension and cor pulmonale (enlargement of the right side of the heart), which increases their risk of mortality (Hayes et al, 2014). In the gut, blocked pancreatic ducts and thickened mucus can impede digestion (particularly of fats), thereby reducing the absorption of nutrients (Smyth, 2005).

Although the treatment of cystic fibrosis has improved, life expectancy is still relatively low (30-40 years) (Bit.ly/CysticFibrosisLifeExpectancy). Cystic fibrosis is one of the genetic disorders that may be amenable to treatment and even cured by using emerging gene therapies, in which viruses are genetically manipulated to deliver the healthy cystic fibrosis gene into cells, with the aim of restoring normal function.

**Albinism.** Albinism, another autosomal recessive genetic disease, affects 1 in 20,000 people. Albinos have very little or no melanin in their skin and eyes, which gives them a distinctive pale skin and pale blue, violet or pinkish eyes. As with cystic fibrosis, there are three possible genotypes:

- **AA** – normal genotype (disease not present);
- **Aa** – carrier;
- **aa** – condition present.

It is thought that around 1 in 100 people carry the defective recessive gene. When two carriers have children, there is a 1 in 4 risk that the child will have albinism, giving the same classic 3:1 Mendelian ratio as in cystic fibrosis.

As melanin plays an essential role in protecting the skin and eyes from harmful ultraviolet (UV) light (see part 3), albinos are at greater risk of UV-induced skin and eye damage and skin malignancies such as malignant melanoma (Yasumizu et al, 2015). They need to limit their exposure to direct sunlight and protect their eyes with glasses or contact lenses that block the entry of UV light.

**Autosomal dominant disorders:**

**Huntington’s disease**
Not all single-gene defects are recessive in nature. Huntington’s disease, also known as Huntington’s chorea, is an autosomal dominant genetic disease. In autosomal dominant genetic disorders, one inherited copy of the defective gene is enough for the disease to develop.

In Huntington’s disease, three gene combinations are possible:

- **HH** – disease present (in a person possessing two dominant defective genes);
- **Hh** – disease present (in a person possessing one dominant defective gene);
- **hh** – normal genotype, disease not present (no defective genes present).

### Fig 3. Inheritance of Huntington’s disease (autosomal dominant disorder)

<table>
<thead>
<tr>
<th>Person who carries one dominant defective gene (HH) and therefore has Huntington’s disease</th>
<th>Person who carries the normal genotype (hh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>h</td>
</tr>
<tr>
<td>Hh</td>
<td>hh</td>
</tr>
<tr>
<td>Hh</td>
<td>Hh</td>
</tr>
<tr>
<td>Hh</td>
<td>Hh</td>
</tr>
</tbody>
</table>

Risk that the child will have Huntington’s disease:

- **HH** – 100% chance
- **Hh** – 50% chance
- **hh** – 0% chance

### References


If a person who carries a single copy of the defective gene (Hh) has a child with a person who carries the normal genotype (hh), there is a 50% chance that the child will inherit the defective gene and therefore have Huntington’s disease (Fig 3).

Huntington’s disease is a neurodegenerative disease that usually manifests between the ages of 30 and 50 years; the defective gene is located on chromosome 4. It results in the production of an abnormal form of a protein called huntingtin, which progressively damages neural tissue – however, the exact mechanisms remain poorly understood (Sari, 2011). Patients present with a range of neurological issues including:

- Poor coordination;
- Jerky, spasmodic and uncontrollable movements (chorea) similar to those seen in Parkinson’s disease;
- Problems chewing and swallowing food;
- Gradual change in cognition with progression to dementia.

In the UK, Huntington’s disease affects around 6.68 in 100,000 people (Rawlins et al, 2016). On average, following the onset of symptoms, life expectancy is around 20 years. During that time, patients will require increasing medical care from nurses and other health professionals. Although there is currently no cure, there are many medications that can help relieve the symptoms of Huntington’s disease.

Sex-linked genetic disorders

When faulty genes are located on either of the sex chromosomes (X or Y), the ensuing genetic disorders are described as ‘sex-linked’. Most sex-linked genetic diseases are associated with the X chromosome. As females have two copies (XX) and males only one (XY), males are more likely to be affected: unlike females, they have no chance of having a healthy gene that could compensate for the defective one. For that reason, all X-linked genetic disorders – such as red-green colour blindness and haemophilia – disproportionately affect males (VanPutte et al, 2017).

More than 200 genes are known to be located on the Y chromosome and are therefore, described as ‘Y-linked’. Many are associated with male reproductive function – for example, TSPY, a gene that encodes for testes-specific protein. Daughters can never inherit any gene that is Y-linked as, by definition, females cannot possess a Y chromosome.

Gene mutations and breast cancer

As well as risk factors such as age, obesity, certain forms of hormone-replacement therapy, alcohol consumption and smoking, several gene mutations also increase the risk of breast cancer. Two of the best understood are the BRCA1 and BRCA2 mutations.

The normal forms of BRCA1 and BRCA2 genes encode for proteins that play an important role in repairing DNA damage. Mutations in these genes result in the synthesis of abnormal proteins, which are unable to effectively repair DNA. This increases the risk of breast cancer (Friedenson, 2007). BRCA1 and BRCA2 mutations are estimated to affect between 1 in 400 and 1 in 800 people in the general population (NHS England, 2015).

Like Huntington’s disease, BRCA1 and BRCA2 mutations are dominant in nature, so a single inherited copy of the defective gene is enough to significantly increase the risk of breast cancer (Fig 4). The inheritance of defective BRCA1 or BRCA2 genes is also associated with an increased risk of other malignancies, including ovarian cancer and some forms of lymphoma and leukaemia (Friedenson, 2007).

References


