In summary

- Neurofibromatosis type 1 (NF1) involves a number of areas of the body with characteristic skin changes and formation of mostly benign tumours.
- Mutations (changes) in the *NF1* gene result in loss of tumour suppressor function, allowing cells to grow in an uncontrolled manner.
- In around 50% of affected individuals NF1 has been inherited from a parent (mother or father) who also has the condition.
- In the other 50% of individuals with NF1 the disorder has arisen in that person for the first time in the family.
- The diagnosis of NF1 is usually made by clinical examination by a doctor experienced in the condition. Genetic testing is available in certain circumstances but is not routinely performed.

WHAT IS NEUROFIBROMATOSIS TYPE 1?

Neurofibromatosis type 1 (NF1) is a genetic condition characterised by skin changes and the risk of benign (non-cancerous) and malignant (cancerous) tumours. It is a relatively common genetic disease, affecting around 1 in 5,000 people. A range of body systems can be involved in individuals with NF1, with some individuals being mildly affected and others more severely. We do not fully understand what influences the severity of NF1 in different individuals, with a large degree of variation seen even within the same family. Features of NF1 are summarised below:

**Skin Features**

‘Birth marks’ and freckling of the skin are characteristic of NF1. Flat, coffee-coloured ‘birth marks’ known as *cafe-au-lait patches* (‘milk coffee’ in French) are common in the general population, however more than 6 and often many more are seen in individuals with NF1. These are harmless and the number of *café-au-lait* patches does not relate to the severity of the condition.

Freckling is present in skinfold areas that are not usually exposed to sunlight, including the armpits, groin region and under the breasts in women. Again, these are harmless.

**Neurofibromas** are benign soft pea-sized lumps that can grow on nerves anywhere in the body. Neurofibromas are most visible on the skin. They are usually absent in childhood, begin to appear around puberty and continue to grow throughout adulthood. Their growth is variable and unpredictable. Some individuals with NF1 have very few and others have thousands. Over time, some neurofibromas may grow in size. They rarely cause any medical problems however some people may have concerns over their cosmetic appearance. They may increase in number during pregnancy in some women.

**Plexiform neurofibromas** are benign tumours where a tangle of extra nerve tissue sits within normal tissues and can occur anywhere in the body but most often in the arms, legs and trunk. Rarely they may grow on the face in early childhood but if not present by around the age of two will not develop after this time. Some plexiforms may be deep in the body and not visible from the outside. While these do not always cause problems they may sometimes cause pain, grow to large sizes and can be disfiguring. They almost always develop before birth. Rarely, plexiforms can become malignant.

Some other lumps and bumps on the skin are more common in individuals with NF1 including *juvenile xanthogranuloma*, small tan or orange pimple-like lumps that don’t resolve, and *nevus anemicus*, an area of pale skin discolouration that doesn’t change colour with the surrounding skin when rubbed.
Eye Features

**Lisch nodules** are harmless small brown spots on the iris (the coloured part of the eye). These are not visible, except to an eye specialist looking with a special examination microscope called a slit lamp. They do not affect vision. **Optic pathway glioma** (OPG) is a non-cancerous growth of the optic nerve that connects each eye to the brain. OPGs occur in around 15% of children usually by the age of around 7 years. They do not always cause symptoms but where they do may impair vision. OPGs that cause symptoms are rare at older ages.

**Neurological (Brain) Features**

Most individuals with NF1 have normal intelligence, but mild learning disabilities and difficulties in attention, memory, and organisational tasks are common. There are specific problems in certain areas of learning such as reading, mathematics or spelling. Most are usually weak in only one or two areas and can cope in a normal classroom but may underperform academically. Autistic type behaviours and other behavioural issues are also seen more frequently in individuals with NF1. Children may seem socially immature compared to their peers. They may favour playing with younger children and may seem less able to read social cues.

Seizures are more common in people with NF1 than in the general population and can occur at any age. Sleep disturbances, headaches and migraines, and pain associated with benign tumours are all also features of NF1.

**Muscular and Skeletal Features**

About 15% of children with NF1 develop a noticeable curve in the spine known as **scoliosis** and a small number require surgery to straighten the spine. Rarely, children are born with a weakness of the long bones of the leg, called a **pseudarthrosis** that is at risk of bowing or breaking during childhood. These breaks often heal poorly and require specialist treatment. Bones may also be generally weaker overall, known as **osteopenia**.

Children with NF1 may have low muscle tone, making them weaker than average, they may have difficulties with coordination and find sports difficult at school.

**Cardiovascular Features**

Hypertension is common in individuals with NF1. Abnormalities of the heart may also occur including narrowing of the valve that allows blood to flow from the heart to the lungs, known as **pulmonary valve stenosis**, which slows down blood flow.

**Tumour Features**

Most tumours found in individuals with NF1 are benign, however there is a slightly increased risk of cancerous tumours compared with the general population. The most common cancers associated with NF1 are **gliomas (brain tumours)** and **malignant peripheral nerve sheath tumours (MPNST)** which arise from the protective layer (sheath) around nerves in the periphery (outside of the brain and spinal cord). Individuals with NF1 are at 10% risk of developing MPNST over their lifetime. Other benign and cancerous tumors associated with NF1 include pheochromocytoma (tumours of the adrenal gland), leukemia in children and gastrointestinal tumours known as GIST tumours (in adults). Women with NF1 are at moderately increased risk of developing breast cancer over their lifetime and should begin breast screening from age 40 years which is earlier than women in the general population.

**Other Physical Features**

Some individuals with NF1 may have a large head. They may also appear shorter than average when compared to other relatives.

NF1 is caused by mutations in the **NF1 gene**, which produces a protein called **neurofibromin**. This protein is important in many cell types, in particular nerve cells and also specialised cells that form the fatty coverings that insulate and protect nerve cells. Neurofibromin acts as a **tumour suppressor protein**, preventing cells from growing and dividing too rapidly or in an uncontrolled way.
Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

**HOw Is Neurofibromatosis Type 1 Inherited?**

Everyone has two copies of each of our genes, one inherited from our mother and the other from our father. In individuals with NF1, they have one working copy and one faulty copy of their NF1 gene. This faulty gene can be passed on to future generations in a pattern known as **autosomal dominant inheritance** (see figure 1).

For every pregnancy in this situation there is:

- 50% chance that a child, either male or female, will inherit only working copies of a gene from their parents and be healthy
- 50% chance that they will inherit one copy of the faulty gene, and one working copy and be affected with NF1
- A mother or a father can pass on an autosomal dominant condition and both male and female children may be affected.

In about 50% of individuals with NF1, the faulty gene was inherited from an affected parent as shown above. However in the other 50% of individuals they are the first person in their family to be affected. In these individuals, NF1 occurred due to a mutation in one copy of the NF1 gene that arose during formation of the egg or sperm, during conception or shortly after. These changes that make one of the NF1 gene copies faulty are called **spontaneous mutations**.

![Figure 45.1](image_url)  
**Figure 45.1** Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by ‘D’; the working copy of the gene by ‘d’.

If the NF1 gene became faulty shortly after conception, not all of the baby’s cells may contain the mutation and this individual is said to be **mosaic** for the faulty NF1 gene. They may experience milder symptoms because the faulty gene may not be present in all of the organs usually affected in NF1. The faulty gene might also not be in all the egg or sperm cells of an individual with mosaic NF1 and therefore their chance of passing on the faulty gene is less than 50% but difficult to estimate accurately.
If a child of a parent who is mosaic for NF1 inherits the faulty NF1 gene copy, they may be more severely affected by NF1 than their parent. This is because the child has the faulty gene in all the cells of their body, while their parent only has the faulty gene in some cells. That child also has a 50% chance of passing on the faulty gene copy to his or her children.

Because of the possibility that an unaffected parent of a child with NF1 is mosaic for the faulty NF1 gene only in their egg and sperm cells, the chance of having another child affected by NF1 is estimated to be between 1% and 2%. The chance that a spontaneous mutation in the NF1 gene would happen again in further pregnancies is low. NF1 does not ‘skip generations’ although sometimes the features of the condition are so mild that individuals may never come to medical attention. An assessment by a skin specialist (dermatologist), eye doctor (ophthalmologist) and genetics doctor (clinical geneticist) may be useful in either confirming or ruling out whether someone is affected by NF1.

**IS THERE ANY TESTING OR TREATMENT AVAILABLE FOR NEUROFIBROMATOSIS TYPE 1?**

NF1 is a highly variable genetic condition that is usually diagnosed in childhood and affects the skin, bones and nervous system. It cannot be cured but the symptoms of NF1 can be treated and/or managed.

Usually, a diagnosis is made by examination of the skin by a doctor experienced in NF1 such as a clinical geneticist or dermatologist. An individual must have 2 or more signs of the condition for a diagnosis of NF1 to be made.

This can help determine if an individual has NF1 however it is not possible to predict how mildly or severely a child or adult may be affected throughout life.

**Genetic Testing**

Often, genetic testing may not be helpful because NF1 can be diagnosed from the clinical signs and whether other close family members have the condition. Genetic testing is may be available for some individuals or families and is best discussed in a genetic counselling setting where the risks, limitations and benefits of testing can all be considered prior to going ahead.

**Prenatal testing and PGD**

For couples where the familial mutation is identified testing may be available during a pregnancy to determine whether or not the baby has inherited the NF1 gene. It may also be possible to undergo pre-implantation genetic diagnosis (PGD) on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, in order to ensure all possible risks, benefits and outcomes are explored.

**Management of NF1**

This involves monitoring for NF1 associated complications in children and adults, and ensuring that families are aware of symptoms of NF1 that need medical attention.

All individuals with NF1 should have an annual check of their health including blood pressure. Regular scans such as MRI brain scans are not recommended as a screening measure where a person does not have symptoms.

Children with NF1 should be monitored for growth, development and complications of NF1. This can be done by a general paediatrician or specialist neurofibromatosis centre. The doctor will look for symptoms of NF1 such as scoliosis and any medical complications of NF1. Children should attend an eye doctor (ophthalmologist) once a year to ensure the back of the eye is healthy. Where children have difficulties with learning parents may wish to inform the school about the way NF1 can affect schooling.

Adults should attend their GP once a year for a general health check and to have their blood pressure monitored. Adults with more complex NF1 may be referred to a range of specialists to manage their particular set of symptoms. In the case of a cancerous tumour, treatment is determined on the basis of type and location as with other cancers in the general population.

Adults may be concerned about the cosmetic appearance of neurofibromas on the skin. Neurofibromas can be removed surgically or by laser.