

## Neurofibromatosis

Neurofibromatosis (NF) is a term used to describe two completely separate genetic conditions – NF1 and NF2. These two types of neurofibromatosis are caused by different faulty genes, which may be inherited or may have spontaneously changed (mutated) at conception. Neurofibromatosis type 1 (NF1 – also called von Recklinghausen’s disease) is the most common type.

### Neurofibromatosis type 1

Neurofibromatosis type 1 is a very common genetic condition. It affects about one in 3,000 to 5,000 people. It was first described in 1882 by a German doctor named Frederick von Recklinghausen. This is why the condition used to be known as von Recklinghausen’s disease.

NF1 is a syndrome. This means it is a condition with a number of features that often occur together. NF1 has a wide range of severity and many people with the condition will only be mildly affected. For most people, NF1 does not significantly affect their health. For a few others, NF1 can cause major health problems at certain stages of their lives.

At present, it is impossible to predict who will remain only mildly affected and who will be more severely affected with NF1. Even different members of the same family can be affected differently.

### NF1 features

The range of features that are characteristic of NF1 (from most to least frequent) include:

- Flat, coffee-coloured ‘birth marks’ on the skin – these are called cafe-au-lait patches, which means ‘milk coffee’ in French. The cafe-au-lait patches are harmless and are due to an increase in the pigment (melanin) in the cells in this area of the skin. They usually appear before a child is two years of age. Most often, six or more are present but the number does not relate to the severity of the condition. People without NF1 can also have two or more café-au-lait patches.
- Freckles – these occur in areas that aren’t usually exposed to sunlight, particularly the armpits and groin region. They are harmless.
- Tiny lumps (Lisch nodules) – these harmless small brown spots develop inside the coloured part of the eye (iris) and can usually only be seen with a special lamp (called a slit lamp). They do not affect vision.
- Neurofibromas – harmless, soft pink, small lumps that can grow on nerves anywhere in the body. They are most visible in the skin. Most commonly, neurofibromas first appear around adolescence but, by age 30, almost all people with NF1 will have several (and some have hundreds). Over time, neurofibromas may slowly grow in size. It is rare for them to cause any problems; however, some people may have concerns about their appearance. These lumps are usually absent or are few in childhood and generally increase in number during puberty or pregnancy.
- Plexiform neurofibromas – localised areas where a tangle of extra nerve tissue sits within normal tissues. They can occur anywhere in the body. About five per cent of plexiform neurofibromas cause a major problem with appearance. They almost always develop before birth and most become obvious by two years of age.
- Learning difficulties – these are particular learning disabilities where a child of normal intellect has specific problems in certain areas of their learning. For example, around half of people with NF1 experience learning difficulties in the areas of reading, mathematics or spelling. Most are usually weak in only one or two areas and can cope in a normal classroom.
- Bone problems – about 15 per cent of children with NF1 develop a noticeable curve in the spine (scoliosis) and a small number require surgery to straighten the spine. Rarely, children are born with a weakness of the shin bone so that it bows or breaks during childhood. These breaks often heal poorly and require specialist treatment.

- Cancer risk – there is a slightly increased risk (10 per cent over the person’s lifetime) that a neurofibroma can become cancerous. Any rapid change in the growth or symptoms of a neurofibroma should be reported to a doctor.

## **NF1 is caused by a faulty gene on chromosome number 17**

Everyone is born with two copies of the NF1 gene that is located on chromosome number 17 in all the cells of their body. People with NF1 are born with a variation in this gene that has made the gene faulty. This variation is called a mutation. Usually, they will have one copy of their NF1 gene that is faulty and the other copy will be working correctly. However, the faulty copy overrides (dominates) the information in the working copy and causes NF1.

Scientists have studied the NF1 gene in detail and have found a number of different mutations in this gene that can cause the problem.

Up to 50 per cent of people who have NF1 are the first in the family to be affected by the condition. In these people, the condition was caused by a variation that occurred in the NF1 gene on chromosome 17 when the egg or sperm was formed during conception. These mutations are called ‘spontaneous mutations’. Spontaneous mutations are not caused by anything the parents have done; they occur by chance. Once a person has NF1, however, they can pass on the faulty gene to their children.

In each pregnancy, an affected parent has a one in two (50 per cent) chance of passing the NF1 faulty gene on to their child, causing the child to be affected. This pattern of inheritance is referred to as autosomal dominant. This is because chromosome number 17 is called an autosome and the faulty gene copy dominates over the working copy.

## **Diagnosis of NF1**

NF1 is diagnosed using a number of tests, including:

- physical examination
- medical history
- x-rays
- computed tomography (CT) scans
- magnetic resonance imaging (MRI)
- biopsy of skin neurofibroma
- eye tests.

## **Genetic testing and counselling for NF1**

Even though NF1 is a genetic condition, genetic testing is not used to diagnose the condition, as it is not widely available and is expensive. Children at risk of having NF1 will have signs of the condition by the age of five. A genetic specialist will be able to accurately make a diagnosis based on the signs and symptoms. Genetic testing can be helpful in some situations, such as during pregnancy, where one parent is affected. Any genetic testing needs to be carried out in association with expert genetic counselling.

## **Neurofibromatosis type 2**

Neurofibromatosis type 2 (NF2) is much less common than NF1. It occurs in about one in 33,000 to 40,000 births. NF2 is a condition with a number of features, which often occur together (syndrome).

## **NF2 often affects ‘hearing’ nerves**

The major feature of NF2 is the development of swellings (non-cancerous tumours) on the nerves that control hearing and balance (the auditory and vestibular nerves). The tumour that develops on the nerves is called a schwannoma.

In the majority of cases, the schwannomas develop on both sides of the body (bilaterally), but not necessarily at the same time. This means the hearing loss may be of different degrees in both ears. In some cases, the schwannomas develop on only one side of the body (unilateral).

## Other nerves may be affected

Different types of tumours in NF2 may affect other nerves in the body. This can impact on the control of:

- swallowing
- speech
- eye movements
- facial sensations.

Tumours may also occur in the central nervous system – the brain and spinal cord.

## NF2 develops later

Signs of NF2 usually develop in late adolescence, but may not be obvious until adult life. Some people do not develop problems until their 40s or 50s.

## NF2 is caused by a faulty gene on chromosome 22

Everyone is born with two copies of the NF2 gene that is located on chromosome number 22 in all the cells of their body. It contains the information for cells to make a protein that has a role in 'tumour protection' in the body.

People with NF2 are born with a variation in this gene that has made the gene faulty. This variation is called a mutation. Usually, they will have one copy of their NF2 gene that is faulty and the other copy will be working correctly. However, the faulty copy overrides (dominates) the information in the working copy and causes NF2.

In people with a faulty NF2 gene, the tumour protection protein does not work as well in stopping the growth of the tumours.

Scientists have studied the NF2 gene in detail and have found a number of different mutations in this gene that can cause the problem.

## NF2 family history

Often there is a family history of NF2 – where other family members have the condition, particularly a parent. An affected parent has one chance in two (or a 50 per cent chance) in every pregnancy of passing the NF2 faulty gene on to their child. This pattern of inheritance is referred to as autosomal dominant. This is because chromosome number 22 is called an autosome and the faulty gene copy dominates over the working copy.

Where there is no family history, the condition results from a variation in the NF2 gene (mutation) that occurred for unknown reasons. This may occur either during the formation of the egg or sperm or during (or shortly after) conception. As in NF1, these are 'spontaneous gene mutations'. The affected person will be the first person in their family to be affected with NF. That person will be able to pass on the faulty NF2 gene to their children, but the chance of that may not always be 50 per cent.

## Inheriting NF2

If the mutation occurred shortly after conception, not all the baby's cells may contain the mutation – the person is said to be 'mosaic' for the faulty NF2 gene. The faulty gene might not be in all their egg or sperm cells, so the chance that their child will inherit the faulty gene is less than 50 per cent.

People who are 'mosaic' for the NF2 faulty gene often have a milder form of the condition and the tumours tend to occur on one side of the body (unilateral rather than bilateral). Nevertheless, if a child of a parent who is mosaic does inherit the faulty NF2 gene, the child will be more severely affected by the condition. This is because the faulty gene will be present in all the cells of their body, unlike their parent. That child has a 50 per cent risk of passing on the faulty gene to his or her children.

## Diagnosis of NF2

Neurofibromatosis type 2 is diagnosed using a number of tests, including:

- physical examination
- medical history
- tests for particular symptoms, such as hearing or balance tests.

## Advice on genetic testing for NF2

Children of a parent with NF2 should be considered to be at 50 per cent risk of having NF2. Screening for tumours can start early in the child's life. Genetic testing to determine if a person has definitely inherited the faulty NF2 gene requires the identification of the mutation in a family member who has NF2.

Once the mutation is identified, family members who have a 50 per cent risk of having inherited the faulty gene, but who do not have any symptoms of the condition, can have 'pre-symptomatic' genetic testing.

Family members who have not inherited the NF2 faulty gene do not have to be screened for symptoms, as they will not develop the condition. However, the identification of the mutation is time consuming and expensive and it may not be found in the gene, even if it is there. In most families with more than one affected member, the genetic test will consider 'markers' in the DNA that are close to the gene and the age of onset of symptoms in the family. This will predict the likelihood that the faulty gene has been inherited.

## Where to get help

- Your doctor
- Genetic counsellor
- Genetic Health Services Victoria, Royal Children's Hospital Tel. (03) 8341 6200

## Things to remember

- There are two different types of neurofibromatosis – NF1 and NF2.
- Neurofibromatosis type 1 (NF1), or von Recklinghausen's disease, is the most common.
- NF2 develops later, is less common and causes non-cancerous tumours to develop.
- NF1 and NF2 are caused by different faulty genes, which may be inherited or may have spontaneously mutated during the development of the egg or sperm.

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