

Important points

- Neurofibromatosis type 2 (NF2) is a separate genetic condition from neurofibromatosis type 1 (NF1), and has a different genetic basis
- NF2 is characterised by the development of swellings (non-cancerous tumours called schwannomas) on the nerves that control hearing and balance (*auditory and vestibular nerves*). The tumours usually develop in late adolescence but some people do not develop problems until their 40s and 50s
- In people with NF2, an important protein (NF2) that normally stops tumour growth is faulty so that the 'tumour protection' role in the body does not work properly
- People with NF2, or those who will develop NF2, are born with a faulty copy of the *NF2* gene and a working *NF2* gene copy
- The pattern of inheritance of the faulty gene causing NF2 in families is described as **autosomal dominant inheritance**
- When one of the parents has the faulty *NF2* gene copy ie. has NF2 or will develop NF2, they have 1 chance in 2 (or 50% chance) **in every pregnancy** of having a child who will develop NF2
- In about 50% of cases of NF2, however, the person affected is the first person in the family to have the faulty *NF2* gene copy. This a 'spontaneous' mutation which occurs for unknown reasons. They now have 1 chance in 2 in every pregnancy of passing the faulty gene on to their children
- If the spontaneous mutation in the *NF2* gene copy occurred shortly after conception, not all their cells may contain the mutation: the person is said to be 'mosaic' for the faulty *NF2* gene and may typically have a milder form of the condition where the tumours tend to occur on only one side of the body. The chance for a parent who is mosaic for NF2 to have an affected child is less than 50%
- The *NF2* gene normally has a 'tumour protection' role in the cells
- Children of an individual with NF2 have a 50% risk of having NF2 and developing NF2 related tumours. Screening for tumours may start early in a child's life
- Genetic testing to determine if a person has definitely inherited the faulty *NF2* gene requires the identification of the change in the gene in a family member who has NF2. This testing is complex, time consuming and expensive and the change may not be found in the gene even if it is present
- Once the gene change is identified, family members who are at up to 50% risk of having inherited the faulty gene, but who do not have any symptoms of the condition, may have 'presymptomatic' genetic testing. It is strongly recommended that the advantages and disadvantages of having the presymptomatic test need to be considered **before** having testing
- Genetic testing for changes in the *NF2* gene can be helpful in some situations such as determining who should have screening. It can also be used for testing a baby in pregnancy or an embryo before pregnancy (see Genetics Fact Sheets 17C & 18). It is advisable that considerations of such testing be carried out in the context of genetic counselling (see Genetics Fact Sheet 3)

Neurofibromatosis

The two types of neurofibromatosis are called

- Neurofibromatosis type 1 (NF1)
- Neurofibromatosis type 2 (NF2)

The two types are completely separate genetic conditions, with a different genetic basis, even though they share the same name. NF1 is discussed in more detail in Genetics Fact Sheet 37.

This Fact Sheet describes neurofibromatosis type 2 (NF2) which is much less common than NF1.

NF2 affects about 1 in 33,000-40,000 people.

Features of neurofibromatosis type 2 (NF2)

NF2 is characterised by the development of growths (non-cancerous tumours called *schwannomas*) on the nerves that control hearing and balance (*auditory and vestibular nerves*). The tumours usually develop in late adolescence but some people do not develop problems until their 40's and 50's. In the majority of cases, the schwannomas develop on both sides (*bilateral*) but not necessarily at the same time, so that there may be hearing loss of different degrees in both ears. In some cases, schwannomas develop on only one side (*unilateral*) and other nerves may be affected by different types of tumours that impact on the control of swallowing, speech, eye movements and facial sensations. Tumours may also occur in the central nervous system: the brain and spinal cord.

What causes NF2?

The cells of the body contain information, in the form of genes, for the body to make all the necessary structural components and chemicals to ensure normal function.

A gene that contains a variation in the information that stops it working properly is described as faulty. The variation that makes the gene faulty is called a *mutation*. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

- Everyone has two copies of a gene located on chromosome 22 that contains the information for a protein (NF2) which has a role in 'tumour protection' in the body by stopping tumour growth
- People with NF2 have one faulty *NF2* gene and the other copy on the partner chromosome is working.

What is the pattern of inheritance of NF2 in families?

Often neurofibromatosis type 2 is inherited from an affected parent. Two factors influence the pattern of inheritance of the faulty *NF2* gene in these families.

1. The *NF2* gene is located on chromosome 22, an autosome (one of the numbered chromosomes)
2. The effect of the variation in the *NF2* gene is 'dominant' over the information in the working copy of the gene on the partner chromosome 22 (see Genetics Fact Sheets 1, 4 & 5).

The pattern of inheritance of the faulty gene causing NF2 in families is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In *Figure 52.1*, where the faulty *NF2* gene copy causing NF2 is represented by 'D'; the working copy by 'd', when one of the parents has NF2 due to the faulty *NF2* gene copy, there are four possible combinations of the genetic information that is passed on by the parents.

This means that, **in every pregnancy**, there is

- A 1 chance in 2 (ie. 2 chances in 4) or 50% chance that their child will inherit a copy of the faulty *NF2* gene and will therefore be affected by NF2 at some time in their life
- An equal chance (ie. 1 chance in 2) or 50% that their child will inherit the working copy of the gene from his/her affected parent as well as a working copy from his/her unaffected parent. In this case, the child will not develop NF2 and cannot pass on the faulty *NF2* gene copy to any of his/her children.

While *Figure 52.1* shows the father as the parent carrying the faulty *NF2* gene, the same situation would arise if it was the mother. NF2 usually affects men and women equally.

When a person with NF2 is the first in the family to have the condition

In about 50% of cases, there are no other affected family members and the diagnosis of NF2 is made on clinical features.

- NF2 in this person is caused by a new change that occurred for unknown reasons in the *NF2* gene copy on chromosome 22 during the formation of the egg cell or sperm cell from which they arose, or during or shortly after conception
- These changes are called 'spontaneous mutations' and the condition is described as occurring sporadically
- The affected person is then the first person in a family to have NF2. That person will then be able to pass on the faulty *NF2* gene copy to his/her children

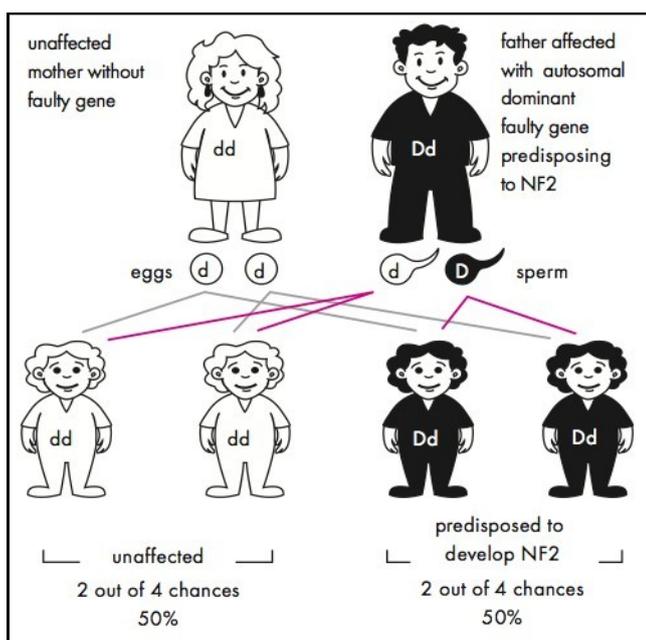


Figure 52.1: Autosomal dominant inheritance when one parent has the faulty *NF2* gene copy. The faulty *NF2* gene copy is represented by 'D'; the working copy by 'd'.

In these situations, the chance of passing on the faulty gene may not always be 50%.

- If the spontaneous mutation in the *NF2* gene copy occurred shortly after conception of the person, not all their 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 and so the chance that a child will inherit the faulty gene is less than 50%
- 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)

If a child inherits the faulty *NF2* gene from a parent who is mosaic for NF2, the child will be more severely affected by the condition than their parent as the child would have the faulty gene in all the cells of their body. That child also now has a 50% risk of passing on the faulty gene copy to his or her children.

Genetics Fact Sheet 13 provides more information about mosaicism.

Can a person determine if they have inherited the faulty *NF2* gene?

The *NF2* gene normally has a 'tumour protection' role in the cells. Children of an individual with NF2 have a 50% risk of having NF2 and developing NF2 related tumours. Screening for tumours starts early in a child's life.

Genetic testing (see Genetics Fact Sheets 21) to determine if a person has inherited the faulty *NF2* gene copy requires the identification of the variation in the gene, in a family member who has NF2.

- This testing is complex, time consuming and expensive and the variation making the gene faulty may not be found in the gene or in the DNA regulating how the gene works even if it is present
- Once the gene variation is identified, family members who are at up to 50% risk of having inherited the faulty gene, but who do not have any symptoms of the condition, can have 'presymptomatic' genetic testing

Family members who have not inherited the *NF2* faulty gene copy do not need screening for the symptoms of NF2 as they will not develop the condition

In most families with more than one affected member, the test would involve looking at 'markers' in the DNA that are close to the gene. The results of such tests together with determining the typical age at which symptoms start in family members with NF2 may be used to provide the likelihood that the faulty gene has been inherited.

This type of genetic testing is called indirect DNA testing or linkage and is described in Genetics Fact Sheet 21. Genetic counselling in conjunction with specialist familial cancer services may be useful in providing the most up-to-date information and advice about the availability and implications of genetic testing (see Genetics Fact Sheet 3).

Genetic testing for changes in the *NF2* gene may be helpful in situations such as determining who should have screening. It can also be used for testing a baby in pregnancy or an embryo before pregnancy (see Genetics Fact Sheets 17C & 18). It is highly recommended that all considerations of this testing be carried out in the context of genetic counselling (see Genetics Fact Sheet 3).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 13, 17C, 18, 21, 37