NEUROFIBROMATOSIS TYPE 1

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Important points

- Neurofibromatosis type 1 (NF1) is a different condition from neurofibromatosis type 2 (NF2)
- NF1 is a very common genetic condition and affects about 1 in 3,000 to 5,000 people
- NF1 has a wide range of severity and many people with the condition will only be mildly affected. 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
- Most common features include having 6 or more flat, coffee-coloured 'birth marks' on the skin (*cafe-au-lait patches); neurofibromas* (harmless soft pink small lumps that can grow on nerves anywhere in the body; freckles in areas that are not usually exposed to sunlight; *Lisch nodules* (harmless small brown spots on the iris of the eye)
- People with NF1 have a change in one of their *NF1* gene copies that makes the gene faulty
- The pattern of inheritance in families of the faulty gene causing NF1 is described as **autosomal dominant inheritance**
- When one of the parents has the faulty *NF1* gene copy ie. has NF1, they have 1 chance in 2 (or 50% chance) **in every pregnancy** of having a child with NF1
- In about 50% of the cases, NF1 is inherited from an affected parent
- In up to 50% of the cases, the person with NF1 is the first in the family with the condition and results from a change that occurred in one copy of the *NF1* gene during the formation of the egg or sperm, during or shortly after conception (a spontaneous mutation that occurred for unknown reasons)
- If spontaneous mutation occurred shortly after conception of the person, not all of the person's cells may contain the gene change: the person is said to be '**mosaic**' for the faulty *NF1* gene. People who have this rare form of mosaic NF1 often have symptoms that are restricted to one part of their body (see Genetics Fact Sheet 13).
  - If a **child of a parent who is mosaic** for NF1 inherits the faulty *NF1* gene, they may be more severely affected by NF1 as the child would have the faulty gene in all the cells of their body. That child also has a 50% risk of passing on the faulty gene to his or her children
- The diagnosis of NF1 is based on clinical features and genetic testing is not required: most people with NF1 will have enough signs of the condition by age 5 years for a specialist to diagnose them with confidence
- Genetic testing for changes in the *NF1* gene is not widely available and is currently expensive but can be helpful in some situations such as testing a baby in pregnancy for NF1 where one of the parents is affected (see Genetics Fact Sheet 17C). It is highly recommended that considerations for this testing be discussed in the context of genetic counselling (see Genetics Fact Sheet 3).

There are two types of neurofibromatosis:

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

The two types are completely separate genetic conditions, with a different genetic basis.

This Fact Sheet describes NF1; Genetics Fact Sheet 52 discusses NF2.

Neurofibromatosis type 1 (NF1):

- Affects about 1 in 3,000 to 5,000 people
- Is also known as Von Recklinghausen disease as it was first described by a German doctor named Frederich von Recklinghausen in 1882
- Is one of the more common genetic conditions

What are the characteristics of neurofibromatosis type 1 (NF1)?

NF1 has a wide range of severity and many people with the condition will only be mildly affected.

For most people, with NF1 symptoms are not severe but for a few, 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.

The range of features that are characteristic of NF1 are listed below in order from those that occur frequently to those that are less common:

- Flat, coffee-coloured 'birth marks' on the skin (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 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
- *Neurofibromas* are harmless soft pink small lumps that can grow on nerves anywhere in the body. Neurofibromas are most visible in the skin and most commonly, first appear around adolescence but by age 30 years almost all people with NF1 will have several (and some have hundreds). Over time, they often slowly grow in size. They rarely cause any problems

except some people may have concerns over their cosmetic impact. They are usually absent or few in childhood and generally increase in number during puberty or pregnancy
- The appearance of freckles in areas that aren't usually exposed to sunlight, particularly the armpits and groin region. Again, these are harmless.
- *Lisch nodules* are harmless small brown spots on the iris (the coloured part of the eye). Lisch nodules are not often visible, except to an eye specialist looking with a special eye examination microscope called a slit lamp. They do not affect vision
- Specific learning disabilities where a child of normal intellect has specific problems in certain areas of their learning eg reading, mathematics or spelling occur in around half of people with NF1. Most are usually weak in only one or two areas and can cope in a normal classroom
- Children may have short attention spans, low muscle tone, reduced co-ordination and may be slower to mature emotionally than their peers. They respond to treatments for these problems the same way as any other child
- A larger head size than usual
- Being shorter than would be expected by looking at the rest of the family
- *Plexiform neurofibromas* (localised areas where a tangle of extra nerve tissue sits within normal tissues) can occur anywhere in the body. They are found in around one in four people with NF1 and, in about 5% of these people, will cause a major problem with their appearance. They almost always develop before birth and most become obvious by two years of age
- *Optic gliomas* (non-cancerous growths of the optic nerve that connects each eye to the brain) affect a small number of children, and can slowly impair vision. They are rare over ten years of age
- *Bone problems*. About 15% 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% 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

What causes NF1?

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.

If a gene is changed so that it does not work properly, the gene is described as being faulty. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

Everyone has two copies of each gene located on the chromosomes numbered 1-22 (the autosomes). Everyone has two copies of a gene located on chromosome 17 that are called the *NF1* gene. The *NF1* gene contains the information for a protein called NF1 which has a role in cancer protection in the body (a *tumour suppressor* gene).

People with NF1 have a change in **one of their NF1 gene copies** that makes the gene faulty. They have one faulty *NF1* gene copy and one working *NF1* gene copy.

Studies of the *NF1* gene have shown a number of different changes in the information contained in the gene in people affected with NF1.

What is the pattern of inheritance of NF1 in families?

In about 50% of the cases, NF1 is inherited from an affected parent. Two factors influence the pattern of inheritance of the faulty *NF1* gene in these families.

1. The *NF1* gene is located on chromosome 17, an autosome (one of the numbered chromosomes)
2. The effect of the change in the *NF1* gene is 'dominant' over the information in the working copy of the gene on the partner chromosome 17 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty gene causing NF1 is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In *Figure 37.1* the autosomal dominant faulty gene causing NF1 is represented by 'D'; the working copy by 'd'. Where one of the parents has NF1 due to the faulty *NF1* gene, there are four possible combinations of the genetic information that is passed on by the parents. This means that, **in every pregnancy**, there is

- 1 chance in 2 (ie. 2 chances in 4) or 50% chance that their child will inherit a copy of the faulty *NF1* gene and will therefore be affected by NF1
- An equal chance (ie. 1 chance in 2) or 50% that their child will inherit the working copy of the *NF1* 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 NF1 and cannot pass on the faulty *NF1* gene copy to any of his/her children

While *Figure 37.1* shows the father as the parent with the faulty *NF1* gene copy, the same situation would arise if it was the mother. NF1 usually affects men and women equally.

When neither parent has NF1 but they have a child with the condition.

In up to 50% of cases, the person with NF1 is the first in the family with the condition. In these people, the condition resulted from a change that occurred in one copy of the *NF1* gene on chromosome 17 during the formation of the egg or sperm, during or shortly after conception.

- These changes that make the *NF1* gene copy faulty are called 'spontaneous mutations'
- Spontaneous mutations are not caused by any action of the parents but arise by chance, as a new change
- Once a person has NF1 he/she will then be able to pass on the faulty *NF1* gene copy to his/her children as described

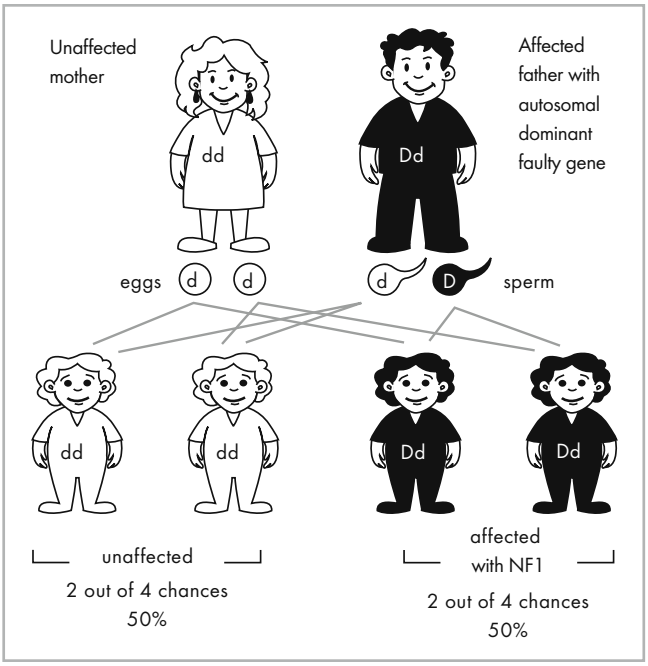

Figure 37.1: *Autosomal dominant inheritance where one parent has the faulty NF1 gene copy. The faulty gene copy is represented by 'D'; the working copy by 'd'.*

The chance that it would happen again in further pregnancies is low.

If the change in the *NF1* gene copy that makes it faulty occurred shortly after conception of the person, not all their cells may contain the gene change: this individual is said to be '**mosaic**' for the faulty *NF1* gene. The faulty gene might not be in all their egg or sperm cells and so the chance that their children will inherit the faulty gene is less than 50% (see Genetics Fact Sheet 13).

- Individuals who have this rare form of mosaic NF1 often have symptoms that are restricted to one part of their body
- The mosaic form of NF1 occurs in 1 in 36,000 to 1 in 40,000 people
- If a **child of a parent who is mosaic** for NF1 inherits the faulty *NF1* gene copy, they will be more severely affected by NF1 than their parent will as the child would have the faulty gene in all the cells of their body. That child also has a 50% risk of passing on the faulty gene copy to his or her children

Can a person determine if they have inherited the faulty NF1 gene?

The diagnosis of NF1 is based on clinical features.

- Even though NF1 is a genetic condition, genetic testing is not needed to diagnose the condition after birth because most people with NF1 will have enough signs of the condition by age 5 years for a specialist to diagnose them with confidence
- Genetic testing for changes in the *NF1* gene is not widely available and is currently expensive

Genetic testing can however be helpful in some situations such as testing a baby in pregnancy for NF1 where one of the parents is affected (see Genetics Fact Sheet 17C & 21).

It is highly recommended that considerations of this testing be discussed 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, 21, 52

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