Information about mosaic Neurofibromatosis type 2 (NF2)

NF2 occurs because of a mutation (change) in the NF2 gene. When this change is present at the time of conception the changed gene will be present in all the cells of the baby. When this mutation occurs later in the development of the forming embryo, the baby will go on to have a mix of cells: some with the "normal" genetic information and some with the changed information. This mix of cells is called mosaicism.

Approximately half the people who have a diagnosis of NF2 have inherited the misprinted NF2 gene change from their mother or father who will also have NF2. They will have that misprinted gene in all the cells of their body. When they have their children, there will be a 1 in 2 chance of passing on NF2 to each child they have.

However about half of people with NF2 are the first person in the family to be affected. They have no family history and have not inherited the condition from a parent.

When doctors studied this group of patients more closely they noticed certain characteristics. Significantly they observed that

- fewer children had inherited NF2 than expected
- some people in this group had relatively mild NF2
- NF2 tumours in some patients tended to grow on one side of their body rather than both sides
- that when a blood sample was tested to identify the NF2 gene, the gene change could not be found in 30-40% of people

This lead researchers to conclude that this group of people were most likely to be mosaic for NF2 i.e. to have the NF2 misprint in only a proportion of their cells.

What is mosaic NF2?

Mosaic Neurofibromatosis type 2 (mosaic NF2) is a term used to describe a situation where the genetic misprint that causes NF2 is present in some rather than all of the body's cells.

People with NF2 develop benign tumours in the brain and spine. The majority of people develop tumours called vestibular schwannomas on both nerves of hearing (bilateral vestibular schwannomas). Some people with a diagnosis of

NF2 only have a single hearing nerve tumour (unilateral vestibular schwannoma) but together with other features have sufficient signs of NF2 to confirm a diagnosis. This group of people are most likely to be subsequently diagnosed with mosaic NF2.

When a new diagnosis of NF2 is made, where that person is the first in the family to be affected, and where they have tumours on both hearing nerves, then about 30% of this group of people will have mosaic NF2. If that person is the first in the family to be affected by NF2, and they have a tumour on only one of their hearing nerves, then about 60% of these people will have mosaic NF2.

What does mosaicism mean?
Our body is made up of thousands of cells. Each cell contains a complete set of genes carrying the instructions that make the cell work correctly. In most people, the genes in every cell will contain the same information, whether they are blood cells, skin cells or cells in other tissues such as sperm (in men) and egg cells (in women).

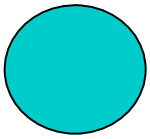
However some people will have a mixture of cells in their body. This mix of cells is called mosaicism. Some cells will contain the correct genetic information. Other cells will have a change in that genetic information. If a gene is changed in some way, it can cause a genetic condition to occur.

The cells that have the changed information in this instance give rise to the genetic condition NF2. Someone with mosaic NF2 therefore will have a mixture of cells: some will have the correct information and others will have the gene change that causes NF2.

Why has this happened?
The very first cell is created when the sperm (from the man) fertilises the egg (from the woman). This single cell contains a complete set of genetic instructions that tells the cell how to behave correctly.

When a baby inherits NF2 from their parent who has NF2, the gene fault that causes NF2 is present at the moment of conception. So the very first fertilised cell will have the genetic misprint (gene change) for NF2. This means that, in time, this baby will develop the characteristic tumours associated with the condition.

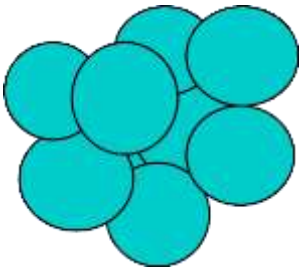
Fertilised single cell with the NF2 misprint



The fertilised cell grows and divides, first into 2 cells then into 4 and so on, faithfully replicating all the information. The complicated genetic information is

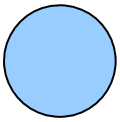
"photocopied" into all the cells that are formed from that first single cell. If the developing baby (embryo) has NF2, then every cell in their body will carry the NF2 misprint (gene fault).

Every cell of this embryo has the NF2 misprint

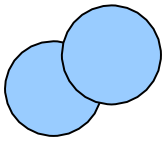


In mosaic NF2 the genetic misprint occurs **later** in the process of the cells dividing.

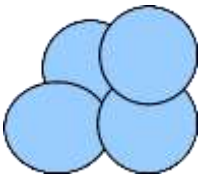
This fertilised cell contains all the genetic information. It does not have the NF2 misprint



The cell divides into 2. All the information is correctly copied

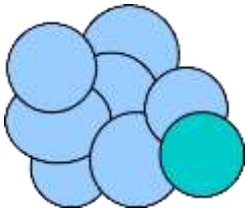


The cell divides again. None of the cells has a misprint at this stage of development of the embryo.

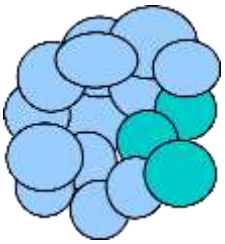


If the genetic misprint occurs at a stage of development of the embryo at say 8 cells, then only the cells photocopied from that 8th cell with the NF2 misprint will carry the same gene fault.

The cells divide again but this time when the genetic information is copied, a misprint occurs. The 8th cell carries the misprint for NF2 (This cell is coloured turquoise to show it clearly).



The cells continue to divide. Some will be "normal" cells with all information correctly copied. A proportion will have the NF2 genetic misprint. (Cells with the NF2 misprint are coloured turquoise here)



The stage of development when the genetic misprint occurs dictates the proportion of cells that carries the genetic misprint and their distribution around the body.

What is the significance of this type of NF2?
NF2 is a condition that causes benign (non cancerous) tumours to grow on nerves controlling hearing and balance. People can also develop tumours on nerves elsewhere in their body, mostly within the central nervous system (the brain and the spine) and sometimes on other nerves. The types of tumours associated with NF2 are called schwannomas, meningiomas and ependymomas. This becomes clear when tumour cells are examined under a microscope.

In half the cases of NF2, a child will inherit the condition from their parent who has the same condition. In the other half of cases, where neither parent is affected, NF2 crops up as a first event "out of the blue". This is called a spontaneous gene mutation. There is currently no known explanation as to why this has happened. It is a chance event.

Within this group of people with no family history of NF2, where NF2 has occurred by chance, about 30% of people will not have the NF2 misprint in all the cells of their body. This is because the genetic misprint has occurred at a later stage of the cells being "photocopied" i.e. after conception as described in the process of cell division above.

A person who has a diagnosis of mosaic NF2 therefore tends to have a milder form of NF2. The tumours may favour one side of the body rather than both sides. The characteristic tumours may develop rather later than most people with NF2.

How is mosaic NF2 diagnosed?
Doctors familiar with NF2 can sometimes be fairly sure of the diagnosis of mosaic NF2 after a careful physical examination, neurological tests and scans. If this demonstrates that the NF2 tumours are all located on the same side of the brain and/or spinal cord, this is evidence to suggest a diagnosis of mosaic NF2. However if the tumours are on both sides of the body, doctors cannot diagnose mosaic NF2 without further tests. This is because NF2 is variable, and separate intrinsic factors influence its course such as the specific type of gene change (mutation) in a person.

It can be helpful to think of this gene change as "spelling mistakes" where the

letters forming a word are omitted, transposed or muddled up. Research has shown that different mutations are associated with correspondingly mild or more severe course of disease. So initially it may be unclear whether a person has a gene change that tends to develop a milder course of generalised NF2 or whether they could have a mosaic form.

It is also important to be certain that the tumours identified are consistent with a diagnosis of NF2. The overwhelming majority of people who develop a tumour on one hearing nerve will not have NF2, but a diagnosis of a single vestibular schwannoma. Differentiating this diagnosis from either generalised NF2 or mosaic NF2 is clearly important because health monitoring and management will be different to reflect the differing health implications.

The next step to clarify the diagnosis is usually to take a blood test to look for the NF2 gene change. In someone with mosaic NF2, the result of this test will usually be "normal" because the blood cells do not have sufficient quantity of the NF2 gene change to detect it.

Occasionally an NF2 change is identified but only in a proportion of the blood cells. If this is the case, it confirms that person has NF2.

The final stage of the diagnosis is to look for the gene change in the actual NF2 tumour itself. If a tumour is removed during surgery, regardless of whether it is a vestibular tumour, a spinal tumour or even a skin schwannoma, the cells that form the tumour will definitely have the gene change. Testing tumour tissue for NF2 gives doctors additional significant information.

Being clear about the exact diagnosis is important. Firstly it helps to guide the healthcare for that patient. Secondly it informs couples planning a family and gives a clearer understanding of the chance of passing NF2 on to their children.

Can mosaic NF2 be passed on (inherited)?

For those at risk of inheriting NF2, guidelines have been developed to help with genetic testing and screening. This is particularly helpful to those individuals where a diagnosis of NF2 has not been proved but where they are "at risk". This can be because they have an affected parent with NF2 or they have some signs of NF2 but insufficient to confirm a diagnosis. In this situation referral to one of the specialist NF2 centres or regional genetics service is advised.

If a parent has NF2 in all their cells, the chance of passing it on to each of their children is described as 50% or a 1 in 2 chance with every pregnancy. This is irrespective of whether they are a mother or a father with NF2.

If a parent has mosaic NF2 the chance of passing on NF2 to a child is less. The level of risk depends on a number of factors. Calculating specific risk figures is now possible depending on individual circumstances.

If this is an area of concern to couples, they should seek advice about risks in pregnancy and discuss the current options available **at an early stage in their planning** (including testing in pregnancy and pre-implantation genetic

diagnosis or PGD). This discussion will take place in a regional genetics clinic or one of the specialist NF2 nationally funded centres (Cambridge, London, Manchester and Oxford).

If a child inherits NF2 from a parent who has a mosaic form of the condition, they will inevitably have the NF2 misprint in **all their cells** and therefore will have more NF2 related health problems compared to their parent.

Once this child reaches adulthood and wants to have children themselves, they then have a 1 in 2 or 50% chance of passing on the NF2 gene to each of their children.

More information about NF2

NF2 care and treatment is co-ordinated through four main specialist centres in England. These are located at hospitals in Cambridge, London, Manchester and Oxford. The teams include consultant clinical geneticists and genetic counsellors who can offer specific individual advice and information about this complicated aspect of NF2.

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RA January 2012

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