Overview of NF2

The term Schwannomatosis is an umbrella term for several genetic conditions that cause the development of benign tumours to grow on nerves through out the body.

Most common types of Schwannomatosis are:

- *NF2*-related Schwannomatosis
- *SMARCB1*-related Schwannomatosis
- *LZTR1*-related Schwannomatosis

What is *NF2*- Related Schwannomatosis (NF2)?

NF2 is a rare genetic condition that causes benign (non-cancerous) tumours to develop on the nerves, typically affecting the nervous system (brain and spine) and on peripheral nerves. The most common tumours in *NF2*-related schwannomatosis are called vestibular schwannomas on the nerve that carries sound and balance information from the inner ear to the brain (the eighth cranial nerve). Schwannomas are tumours that arise from the Schwann cells, which are the cells that produce the insulating myelin sheath covering nerves.

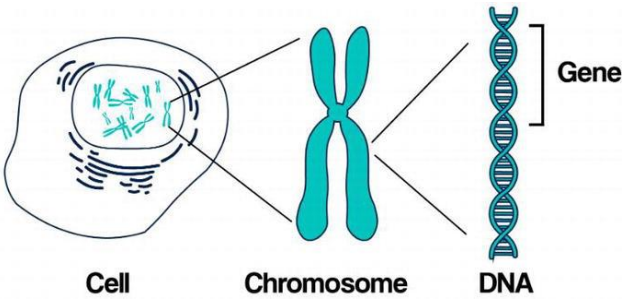
In NF2 these tumours often affect both ears and may lead to partial or complete hearing loss. NF2 can also cause schwannomas to develop on other nerves in the brain and spine or nerves in other places in the body, including on the skin. People with NF2 can also develop other tumours, including meningiomas (tumours in the lining of the brain and spinal cord), ependymomas (tumours that develop from cells lining the ventricles of the brain and centre of the spinal cord).

Most NF2 tumours are slow-growing and may cause minimal problems for years. Although they are non-cancerous their position may produce significant symptoms.

How common is NF2?

Birth incidence of NF2 is approximately one in 25,000–33,000 worldwide, women and men are equally affected. The number of people affected in UK at a particular point in time is estimated to be 1 in 60,000.

Causes of *NF2*- Related Schwannomatosis



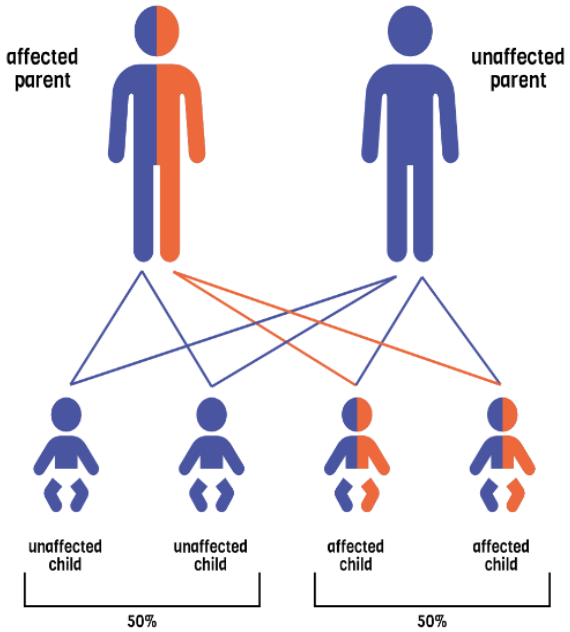
NF2-related schwannomatosis is caused by a pathogenic variant (a gene change that causes the gene to stop working correctly) in the *NF2* gene located on chromosome 22.

The *NF2* gene provides instructions to produce a protein called merlin, also known as schwannomin. This protein is made in the nervous system, particularly in specialised cells called Schwann cells that wrap around and insulate nerves.

Merlin helps regulate several key signalling pathways that are important for controlling cell shape, cell growth, and the attachment of cells to one another (cell adhesion). This protein functions as a tumour suppressor, preventing cells from growing and dividing too fast or in an uncontrolled way. When it is not working properly due to gene fault, cells may start dividing uncontrollably, leading to the formation of tumours in the nervous system.

How is NF2 Inherited?

Inherited From Parent- In half of all cases of NF2, the faulty gene is passed from a parent to their child. We have two copies of the genes in our body, one from each parent, including the *NF2* gene. In NF2 it only takes a faulty gene in one copy of the gene to cause the condition; the second copy of the gene from the other parent will not have a fault and is working correctly. This is called an **autosomal dominant** pattern of inheritance. In general, a parent with an autosomal dominant disorder (such as NF2) has a 50% chance of passing along the condition to a child.



Autosomal Dominant Inheritance (https://www.jnetics.org/jewish-genetic-disorders/dominant-disorders)

Spontaneous NF2- In the other 50% of the people with NF2, the faulty gene appears to develop spontaneously, with them being the first person in their family to be diagnosed. This is referred to as sporadic or de novo occurrence.

NF2 is a variable and unpredictable condition affecting different people in different ways.

NF2 Tumours

- **Vestibular Schwannomas -** The most common tumours in NF2 are called vestibular schwannomas which develop on the nerve that carries sound and balance information from the inner ear to the brain (the eighth cranial nerve). Having vestibular schwannomas on both hearing and balance nerves is the hall mark feature of NF2.

- **Other Schwannomas-** NF2 can also cause schwannomas to develop on other nerves in the brain and spine or nerves in other places in the body, including on the skin.

- **Meningiomas** – These are tumours in the lining of the brain and spinal cord. They occur in about 80% of people with NF2-SWN at some point in their lifetime but don't always cause noticeable symptoms. Symptoms of meningiomas can include headaches, seizures, blurred vision, weakness, or numbness. Many meningiomas in people with NF2 never require treatment, but they are often monitored by MRI scans. Surgery is the primary treatment for meningiomas.

- **Ependymomas**- Tumours that develop from cells lining the ventricles of the brain and centre of the spinal cord. Spinal ependymomas may cause pain, sensory changes, or weakness but are most commonly asymptomatic. If needed, surgery is the primary treatment for ependymoma, although other treatments, such as radiation therapy or chemotherapy, may occasionally be considered.

Most NF2 tumours are slow-growing and may cause minimal problems for years. Although they are non-cancerous their position may produce significant symptoms

Symptoms of *NF2*-related Schwannomatosis

There are different ways that NF2-related schwannomatosis can initially be suspected, for example, there may be a concern with hearing or balance. NF2 is sometimes diagnosed before any symptoms develop, either because it was suspected due to family history or if NF2 tumours were found incidentally (unexpectedly) on a body scan obtained for another reason (for example, a brain scan is done after a head injury, and reveals a vestibular schwannoma tumour).

Most of the symptoms in NF2 are caused by the growing benign tumours resulting an increased pressure in and around the brain and spine.

Most people with NF2 develops vestibular schwannoma. These usually cause symptoms such as:

- Progressive hearing loss
- Tinnitus (ringing or buzzing in the ears)
- Difficulties with balance, especially in low light or on uneven surfaces.

Other symptoms may include,

- Weakness in the arms and legs
- Persistent headaches.
- Vision problems
- Difficulty in swallowing
- Facial weakness
- Foot or hand drop and squint.
- Numbness and tingling in the feet or hands, burning, stabbing or shooting pain due to nerve damage.

Diagnosis of NF2-related Schwannomatosis

If NF2 is suspected, further tests – such as scans, hearing tests, sight tests or blood tests – may be recommended.
Genetic testing is not always necessary to make a diagnosis of *NF2*-related schwannomatosis, as the diagnosis can often be made just based on clinical features. However, NF2 testing is highly recommended for,

- Confirmation of the diagnosis
- Understanding and predicting the severity of NF2
- Allowing testing of family members who are at risk.
- Family planning for future children.

Testing may be done in a blood or saliva sample but can also sometimes require tumour tissue, if available.

With this type of test, there are three possible results -

1.The test will identify a significant gene change in-keeping with full or mosaic NF2.

2. Test may not identify any significant gene changes on the *NF2* gene. This might be because the altered gene is only present in some of a person's cells, or because there may be genetic alterations involved in NF2 that our technology cannot yet detect.

3. Test may identify a gene change of uncertain significance, which is difficult to fully interpret using current scientific knowledge.

Treatment for *NF2*-related Schwannomatosis

Treatment involves regular monitoring and treating any problems as they occur. Because NF2 is a rare and complex condition, patients diagnosed with NF2 are treated at one of the four specialist centres. These centres are based at Cambridge, Manchester, London and Oxford.

Monitoring

Regular monitoring of NF2 patients is crucial to manage the condition effectively. This typically involves:

1. Regular Check-ups: Periodic medical check-ups to assess the overall health and monitor for any emerging symptoms or complications related to NF2.

2. Hearing Tests: Since NF2 often affects hearing, regular audiograms are essential to detect any changes in hearing.

3. Imaging Studies: Regular MRI (Magnetic Resonance Imaging) scans are conducted to monitor the growth of tumours in the nervous system.

4. Balance and Neurological Assessments: Regular assessments of balance and neurological functions to help detect any changes or abnormalities.

5. Eye health checks: Regular eye check-ups are crucial for the early detection and management of potential issues related to NF2, helping to preserve vision and address any complications promptly.

5.Genetic Counselling: For individuals with NF2, ongoing genetic counselling can provide support, information, and guidance on managing the genetic aspects of the condition.

Depending on your symptoms, more-frequent tests may sometimes be required.

If you experience new symptoms or a worsening of existing ones between check-ups please contact us.

Treating Tumours

Treatment plans involves a multidisciplinary approach and are often individualized based on the specific characteristics of the tumours, their locations, and the overall health of the patient.

Surgery

Surgical intervention aims to remove tumours that may be causing symptoms or posing a risk to the individual's health. The goal is often to achieve the best possible balance between tumour removal and preserving neurological function. Surgery to remove vestibular schwannoma carries a risk of complete loss of hearing. Therefore, Neurosurgeons carefully assess the risks and benefits of surgery, considering the location of tumours and potential impact on surrounding structures.
After surgery, individuals with NF2 may undergo rehabilitation to address any functional deficits resulting from the procedure. This may include physical therapy, occupational therapy, or other supportive measures.
Due to the nature of NF2, which often involves the development of multiple tumours over time, individuals may require more than one surgical procedure throughout their lives.

Radiation Therapy

In cases where complete surgical removal is challenging, radiation therapy may be used to shrink or control the growth of tumours by using focused beams of radiation to target and damage the tumour cells.
Unlike surgery, radiation therapy is a non-invasive treatment method. In NF2, there are two types of radiation therapy used. These are:

Fractionated Radiation, which involves dividing the total radiation dose into smaller, more manageable fractions.

In **Gamma knife surgery**, a tightly focused beam of gamma radiation is commonly used. This helps minimise damage to surrounding healthy tissues.

Like surgery, there are risks associated with this treatment. There is a small possibility that gamma radiation could lead to the transformation of new tumours into cancerous ones, which should be taken into account when considering treatment options.

Medical management using Bevacizumab

Bevacizumab, commonly known by the brand name Avastin, is a medication that targets blood vessel growth and is sometimes used in the management of *NF2*-related vestibular schwannomas (a type of tumour affecting the balance and hearing nerve).

Bevacizumab is an anti-angiogenic drug, meaning it inhibits the growth of new blood vessels. In NF2, this property is utilized to limit the blood supply to tumours, potentially slowing their growth.

Regular monitoring through imaging studies, such as MRIs, is essential to evaluate the response to Bevacizumab treatment and adjust the therapy plan as needed.

Like any medication, Bevacizumab can have side effects, and the decision to use it involves a careful consideration of potential risks and benefits. Common side effects may include high blood pressure, bleeding, and an increased risk of infection and damage to kidneys.

The use of Bevacizumab in NF2 is often part of an individualized treatment plan, and decisions are made based on factors such as the specific Tumour growth criteria, the individual's overall health, and their response to previous treatments.

Treating hearing problems

Since hearing loss is common in NF2, lip reading and British Sign Language (BSL) can be learned to enhance communication. Hearing aids or surgically implanted hearing devices may be recommended to improve or restore hearing.

There are 2 types of hearing implants used in NF2:

1. **Cochlear implants (CI)** - Cochlear implants can be considered for individuals with NF2 who experience significant hearing loss due to vestibular schwannomas or other tumours affecting the auditory nerves. Cochlear implants are electronic devices that bypass damaged inner ear sections, directly stimulating the auditory nerve to enable sound perception, especially in cases of profound sensorineural hearing loss.

2. **Auditory brainstem implants (ABI**)- ABIs are an option for individuals with NF2 who have tumours affecting both auditory nerves and are not suitable candidates for cochlear implants. Unlike cochlear implants, ABIs bypass the damaged auditory nerve and directly stimulate the cochlear nucleus in the brainstem. This allows individuals to perceive sound. While ABIs can provide auditory sensation, the quality of sound perception may be different from natural hearing, and the outcomes can vary among individuals.

Family Planning

Pregnancy planning options are available to people who want to prevent the faulty gene from being passed on. Points to consider:

Genetic Counselling: A genetic counsellor can provide information about the likelihood of passing on NF2 to children and discuss available options.

Prenatal Testing: For those who are already pregnant or planning to become pregnant, testing in early pregnancy can be an option to determine whether the developing foetus has inherited the NF2 mutation.

In Vitro Fertilization (IVF) with Preimplantation Genetic Diagnosis (PGD): IVF with PGD allows for the screening of embryos for genetic conditions before implantation, reducing the risk of passing on NF2.

Adoption or Surrogacy: Some individuals or couples with NF2 may choose adoption or surrogacy as alternative family-building options.

Regular Monitoring during Pregnancy: If a woman with NF2 becomes pregnant, close monitoring by healthcare professionals is important to address any potential complications associated with the condition.

Close collaboration between multidisciplinary team is crucial for optimal management in NF2. Regular follow-up appointments and ongoing communication with the medical team are key components of NF2 tumour treatment.

The NF2 Multidisciplinary Team

Consultant Neurologist- Neurologist play a crucial role in the comprehensive care of individuals with NF2, contributing to diagnosis, annual neurological assessment, symptom management, treatment planning, and ongoing care coordination.

Consultant Geneticist - The role of a consultant geneticist in NF2 involves providing genetic counselling, coordinating genetic testing, assessing genetic risk, supporting family planning decisions and collaborating with other specialists.

ENT (Ear, Nose, Throat) Surgeons and Neurosurgeons - The surgeon's role in NF2 involves tumor removal, surgical planning, risk assessment, minimizing impact on function, follow-up care, reconstructive procedures, multidisciplinary collaboration, and ongoing evaluation.
Radiologist- They will look at the scans in detail, interpreting images and writing reports and provide their expert opinion at the multidisciplinary team meeting.

Audiologist – They conduct regular hearing assessments to monitor changes in hearing, recommend hearing aids for individuals with hearing loss, assess suitability for Cochlear implants and Auditory Brain Stem Implants and provide regular assessments and follow up post implantation.

Oncologist- The role of oncologist in NF2 involves evaluation, treatment planning and management of benign and malignant tumour. They provide expertise to the MDT on radiotherapy and use of Bevacizumab.

Ophthalmologist – Ophthalmologist undertakes the monitoring and treatment of eyes and vision.

NF2 Specialist Nurses- The NF2 specialist nurse coordinates patient care between multiple clinicians and locations, they support patients with the management of their

disease by providing expert advocacy for newly diagnosed patients or those in acute need.

Physiotherapist - The role of a physiotherapist in NF2 involves assessing and addressing physical challenges and designing personalised exercise programs. Their contribution is essential in improving functional outcomes and enhancing the overall quality of life for individuals with NF2.

Clinical Psychologist - Clinical psychologists play a vital role in providing emotional support, offering coping strategies, enhancing quality of life, addressing family dynamics, and contributing to overall well-being. Their expertise helps individuals and families navigate the psychological aspects of living with NF2.

Speech and Language Therapists - Qualified and registered speech and language therapists work within the NF2 MDT. Our speech and language therapists provide assessment, advice, and management for individuals experiencing changes to their voice, swallow, speech or communication secondary to NF2

Coping with a diagnosis of NF2 can be difficult at any stage of life. While NF2 poses unique challenges, advances in medical care and supportive interventions contribute to improved outcomes and quality of life for people living with this condition. Engaging with a healthcare team and building a support network can help people with NF2 navigate the various aspects of their lives successfully.

Meet Our Team

For support and information, Contact NF2 Clinical Nurse Specialists on

0161 276 4619.