



Neurofibromatosis

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Institutes of Health

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What is Neurofibromatosis (NF)?

Neurofibromatosis is not a single medical disorder but refers to three different conditions involving the development of tumors that may affect the brain, spinal cord, and the nerves that send signals between the brain and spinal cord and all other parts of the body.

- **Neurofibromatosis type 1 (NF1)**, historically called von Recklinghausen disease
- **Neurofibromatosis type 2 (NF2)**
- **Schwannomatosis (SWN)**

Most tumors are non-cancerous (benign), although some may become cancerous (malignant).

Why tumors develop in these conditions isn't completely known, but it appears to be caused in part by mutations in genes that play key roles in suppressing growth in nervous system cells. These mutations keep the genes—identified as *NF1*, *NF2*, *SMARCB1*, and *LZTR1*—from making normal proteins that control the ability of the cells to function properly. Without the normal function of these proteins, cell growth increases, leading to the formation of tumors.

Neurofibromatosis occurs in both sexes and in all races and ethnic groups.

What is NF1?

Neurofibromatosis 1 (NF1) is the most common of the three conditions. Although many people with NF1 inherit the gene that causes the condition, between 30 and 50 percent of cases arise from a spontaneous genetic mutation in the NF1 gene. Once this mutation has occurred, the abnormal gene can be inherited. Each child of an affected parent has a 50 percent chance of inheriting the gene mutation.

Signs and symptoms of NF1

Children and adults with NF1 can have a variety of symptoms and medical problems which can change across a lifespan. Most people with NF1 have a normal life expectancy. Because many of the other clinical features of NF1 develop as an individual gets older, getting the correct diagnosis may take several years.

To diagnose NF1, a doctor looks for some of the following:

- **Six or more flat, light brown spots on the skin (“café-au-lait” spots)**, which are the most common feature of NF1. These multiple birthmarks measure more than 5 millimeters in diameter in children or more than 15 millimeters across in adolescents and adults. They are seen at birth or develop during the first few years of life. Café-au-lait spots are not dangerous but indicate the possible presence of an NF1 gene change in the person. These skin marks also occur in other conditions (such as Legius syndrome, a genetic condition that involves how cells in the body communicate).

- **Two or more soft, pea-sized bumps involving the skin (cutaneous neurofibromas)**, or one larger neurofibroma that involves multiple nerves (**plexiform neurofibroma**). Neurofibromas are tumors that originate from nerve cells. Plexiform neurofibromas are nerve-associated tumors involving nerves outside of the brain and spinal cord. They can be present at birth or may not become noticeable for many years. Although some cutaneous neurofibromas arise in childhood, most start appearing during or after the teenage years.
- **Freckling in the armpits or the groin.** Freckling usually appears by 3 to 5 years of age. Freckles are similar in appearance to café-au-lait spots but are smaller in size. Freckling can occur in other conditions, but not with the other symptoms and concerns of NF1.
- **Two or more growths on the iris of the eye (known as Lisch nodules or iris hamartomas).** These nodules are harmless, are not usually seen until adolescence, don't affect vision, and do not require monitoring or treatment.
- **A tumor of the optic pathway** (called an optic pathway glioma). These tumors typically first appear by age 6, rarely in late childhood and adolescence, and almost never in adults. Although they can affect vision, most do not become symptomatic.
- **Bone deformities.** Abnormal development of the eye socket (sphenoid) or the tibia (one of the long bones of the shin).
- **A parent, sibling, or child with NF1.**

Additional signs and symptoms of NF1 include:

- **Short stature and larger than normal head circumference.** Children with NF1 are usually shorter than average and have larger heads.
- **Cardiovascular complications,** such as congenital heart defects, high blood pressure (hypertension), and constricted, blocked, or damaged blood vessels.
- **Poor visuospatial skills** and poor performance on academic achievement tests, including those that measure reading and math skills.
- **Behavioral problems,** such as attention deficit hyperactivity disorder (ADHD) and challenges with social skills, are commonly seen in children with NF1.
- **Other neurological problems.** Although common in all people, headaches, pain, and seizures happen more often in people with NF1.
- **Tumors that may become cancerous.** An estimated 10 percent of plexiform neurofibromas may become malignant, requiring aggressive treatment. Cutaneous neurofibromas are not known to become malignant.
- **Malignant glioma** is a type of tumor that can occur (although rarely) in adults with NF1.
- **Other malignancies.** Adult young women with NF1 are at a higher risk for breast cancer arising before the age of 50 years than women in the general public.

- **Other tumors.** There is an increased risk of gastrointestinal stromal tumors (GIST) and neuroendocrine tumors, like pheochromocytoma. There also is an increased incidence of benign nerve tumors called glomus tumors.
- **Scoliosis.** Curvature of the spine can be more common and more aggressive in people with NF1.

Treatments for NF1

NF1 cannot be cured, but treatments can help manage signs and symptoms.

Many people with NF1 will not require any prolonged treatment for any manifestation (disease signs or development) during their lives. People with NF1 should be evaluated periodically by an NF1 specialist, even if they are not experiencing symptoms, to evaluate for signs or symptoms that may indicate a need for treatment and to provide reassurance that treatment is not needed when appropriate.

- Surgery may be used to remove tumors that develop symptoms or are of concern for cancer, as well as for tumors that cause significant disfigurement. Several surgical options exist for many of the manifestations of NF1, but there is no general agreement among doctors about when surgery should be performed, or which surgical option is best. Some bone malformations, such as scoliosis, can be corrected surgically or by stabilizing the spine with a brace. Some malformations that affect blood vessels can be successfully addressed with surgery or non-surgical procedures.

- **Chemotherapy** may be used to treat optic pathway or other brain gliomas. The drug selumetinib (Koselugo®) has been approved by the U.S. Food and Drug Administration (FDA) to treat children older than two years old who have symptomatic but inoperable plexiform neurofibromas. Chemotherapy regimens also are a core part of treating cancers that may arise in the setting of NF1, including malignant peripheral nerve sheath tumor (MPNST) and breast cancer.
- Treatments for other conditions associated with NF1 are aimed at controlling or relieving symptoms. Headache and seizures are treated with medications. Since children with NF1 have a higher than average risk for a variety of learning disabilities, ADHD, motor delays, and autism, they should be evaluated by a care team knowledgeable in NF1 and may be advised to have formal neuropsychological assessments to assist in creating individualized educational plans for school.

What is NF2?

Neurofibromatosis 2 (NF2) is less common than NF1. Approximately 50 percent of affected people inherit the abnormal gene (familial); in others the condition is caused by a spontaneous genetic mutation in the NF2 gene. Each child of an affected parent has a 50 percent chance inheriting the abnormal NF2 gene.

Signs and symptoms of NF2 result from the development of:

Benign, slow-growing tumors affecting the cranial, spinal, and peripheral nerves, as well as the covering of the brain and spinal cord (called the meninges).

- **Schwannomas** are tumors made up of Schwann cells—the cells which produce the myelin that covers and protects peripheral nerves throughout the body. They often occur on the eighth cranial nerve, **which has two branches: the acoustic branch** carries the signals for hearing to the brain, and the vestibular branch carries signals for sense of position and balance. Vestibular schwannomas (also historically called acoustic neuromas) are the most recognized form of schwannoma in people with NF2, but schwannomas can involve any of the cranial or peripheral nerves in someone with NF2. Schwannomas also can occur in the skin and appear as bumps under the skin or on the skin surface. Most tumors are benign, although, very rarely, they may become cancerous. Schwannomas may or may not progress over time and many never require treatment.
- **Meningioma** is the second most common tumor type in people who have NF2. Meningiomas form in the tissue covering that surrounds the brain and spinal cord. People with NF2 have both a higher rate of meningiomas than in the general population and can develop multiple meningiomas within the skull and along the spinal column.
- **Ependymoma** tumors occur more frequently in people with NF2 than in the general population. Ependymomas arise within the spinal cord (as opposed to on the surface) and are benign. In many individuals, these tumors produce or show no symptoms.

Visual problems. People with NF2 may develop **cataracts** at an earlier age or changes in the retina that can affect vision.

Peripheral neuropathy. Individuals with NF2 may develop **problems with nerve function**, usually numbness and weakness on both sides of the body (with or without muscle loss) in the arms and legs.

While teenagers and adults often are first seen for hearing and balance problems, young children with NF2 more commonly seek initial medical attention due to vision problems and meningiomas.

Signs and Symptoms of NF2

Signs of NF2 may be present in childhood but can be overlooked, especially in children who do not have a family history of NF2. Children are often first seen by a doctor because of schwannomas in the skin, vision loss from retinal abnormalities or tumors, seizures, or weakness related to spinal cord compression. More commonly, symptoms of NF2 are first noticed **in the second decade of life**.

The most common first symptom is **hearing loss or ringing in the ears** (tinnitus) related to vestibular schwannomas. Less often, the first visit to a doctor will be because of disturbances in balance, visual impairment, focal weakness in an arm or leg, seizures, or skin tumors.

To diagnose NF2, a doctor looks for the following:

- **Vestibular schwannomas**
- **A parent, sibling, or child with NF2** plus a unilateral vestibular schwannoma (on one side of the body) before age 30; or
- Any of the following:
 - ependymoma
 - meningioma

- schwannoma of non-vestibular nerves
- juvenile cataract or retinal abnormalities.

Treatments for NF2

NF2 is best managed at a specialty clinic with an initial screening and annual follow-up evaluations. Magnetic resonance imaging (MRI) of the skull base and internal auditory canal can reveal very small tumors of the vestibular nerve. These tumors usually grow slowly, but can compress the brain stem, resulting in more serious medical problems.

- **Surgery** to remove vestibular schwannomas that produce or show symptoms may help preserve hearing in some circumstances, but surgical options depend on tumor size and extent of hearing loss. There is no general agreement among doctors about when surgery should be performed, or which surgical option is best. Most often, surgery for vestibular schwannomas in the setting of NF2 results in hearing decline or hearing loss on the side of the tumor removal. If hearing is lost during surgery, the surgical placement of a **cochlear implant** (a device placed in the inner ear, or cochlea, that processes electronic signals from sound waves to the auditory nerve) or an **auditory brainstem implant** (a device that stimulates the hearing portions of the brain) may improve hearing.

Surgery for other tumors associated with NF2 is aimed at controlling or relieving symptoms. Surgery also can correct cataracts and retinal abnormalities.

- **Chemotherapy and focal radiation** also are used to manage these tumors. Some people with hearing loss related to a vestibular schwannoma may have hearing improvement and reduced tumor size when treated with the drug bevacizumab. Drugs such as lapatinib and everolimus have shown some biologic activity against some NF2-associated tumors. Individuals should discuss with their doctor the possibility of these treatments and the opportunity to participate in a clinical trial using new targeted therapies for NF2-associated tumors.

Managing the complications of NF2 are critical to maintaining quality of life. Treatment options for facial weakness, dry eye, hoarseness, and difficulty swallowing are often available at specialty clinics.

What is Schwannomatosis?

Schwannomatosis (SWN) is the rarest form of these three conditions and **is genetically and clinically distinct from NF1 and NF2**. In many cases, mutation of the *SMARCB1* or *LZTR1* genes is associated with the disease; however, the genetic cause of SWN in some people is unknown.

Signs and Symptoms of Schwannomatosis

Signs and symptoms of SWN significantly overlap with those of NF2 since they result from the development of slow growing schwannomas of the cranial, spinal, and peripheral nerves and in some cases meningiomas of the brain and spinal cord. About one-third of individuals with schwannomatosis have tumors limited to a

single part of the body, such as an arm, leg, or a segment of the spine. Some people develop many tumors, while others develop only a few. Schwannomas or meningiomas in the setting of schwannomatosis sometimes show no symptoms.

Other symptoms a doctor may look for are:

- **Chronic pain anywhere on the body.**
Chronic pain affects many people with SWN. This pain may or may not be associated with a specific schwannoma.
- **Numbness, tingling, or weakness in the fingers and toes** and/or loss of muscle function.

Treatments for Schwannomatosis

There is no currently accepted medical treatment or drug for schwannomatosis. Surgery may help some people with growing tumors or symptoms that are directly referred to individual schwannomas. However, the potential risk of nerve damage must be weighed carefully against potential benefits of surgery.

How is neurofibromatosis diagnosed?

It may be impossible to distinguish someone with NF2 from SWN, based on clinical features alone. Genetic testing may be needed to correctly diagnose individuals with features of these conditions who lack a known family history or bilateral vestibular schwannomas (those that occur on both sides of the body). Genetic testing can be useful in some situations, such as for prenatal testing or when the clinical diagnosis is inconclusive.

Detailed imaging of the brain and spinal cord by MRI are necessary and additional imaging based on symptoms may reveal schwannomas on peripheral nerves.

What research is being done?

The mission of the National Institute on Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and use that knowledge to reduce the burden of neurological disease. NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

NINDS conducts and sponsors science and studies aimed at understanding normal and abnormal development of the brain and nervous system, as well as clinical trials to improve the diagnosis and treatment of neurological disorders, including neurofibromatosis. Other NIH institutes, the Department of Defense, and private foundations have provided critical support for NF research and clinical trials.

Current basic and clinical research is not only aimed at understanding how defects in the responsible genes cause the diverse conditions and medical problems encountered in children and adults with NF, but also how better to predict which clinical features will arise in any given person (personalized or precision medicine). In addition, studies in NF1, NF2, and SWN have revealed numerous important insights for investigators working in other fields, including brain cancer, sarcoma, autism, learning disabilities, nerve regeneration, chronic pain, and targeted therapies.

Genetic studies. The gene for NF1 is located on chromosome 17. The NF1 gene makes a protein called *neurofibromin*, which regulates cell division in the nervous system and functions as a kind of molecular brake to keep cells from growing out of control. The gene for NF2 is located on chromosome 22. The NF2 gene product is a tumor-suppressor protein (called *merlin* or *schwannomin*).

Ongoing NINDS-sponsored research continues to discover additional genes and molecular pathways that may play a role in NF-related tumor suppression or growth. Continuing research is starting to reveal how this novel family of growth regulators controls how and where tumors form and grow, which may lead to the development of new drugs and therapies for NF.

Clinical trials. The NINDS supports clinical trials aimed at understanding tumor growth and cognitive impairments in children.

- Studying the natural history of tumors in NF2 can help scientists determine possible factors that may regulate their growth. NINDS-supported researchers are using a variety of tests, including diagnostic imaging, eye examinations, hearing and balance tests, neurologic examinations, blood and genetic testing, and quality of life assessments to characterize the impact of NF2 on individuals and better understand disease progression.
- The NINDS supports clinical trials involving a large group of children with NF1 to find associations between brain abnormalities

and specific cognitive disabilities. Finding these links could help doctors anticipate cognitive impairments and inform early intervention programs.

Current basic and clinical research is aimed at understanding how the genetic mutations that cause NF1 tumors also cause neurons and neural networks to form abnormally during fetal development, which later result in the learning disabilities and cognitive deficits of children with the disorder. The NINDS also encourages research to develop improved methods to diagnose the neurofibromatoses and identify factors that contribute to the wide variations of symptoms and severity of the disorders.

Several options have been tested or are under investigation for treating NF tumors. Ongoing clinical studies on drugs that block the enzyme mitogen-activated protein kinase (that affects how some cells grow and develop) show great promise in treating NF1-associated tumors, especially in children. Because schwannomas are particularly hard to treat tumors, NINDS researchers are developing and testing a new treatment option, which uses a virus to kill tumor cells. Researchers are also testing some chemotherapy drugs as treatments for NF2-related schwannomas.

How can you help research?

Join a clinical trial

Many neurological disorders do not have effective treatment options. Clinical trials offer hope for many people and an opportunity to help researchers find better ways to safely detect, treat, or prevent disease. In addition, they may offer access to treatments approved for non-NF indications that may not be available through standard clinical practice. For information about finding and participating in a clinical trial, please contact the **NIH's Patient Recruitment and Public Liaison office** at 800-411-1222. You can find information about clinical trials for neurofibromatosis, and other neurological and other disorders at **ClinicalTrials.gov**, <https://clinicaltrials.gov>.

Donate brain tissue

NINDS supports the **Human Brain and Spinal Fluid Resource Center**. This bank supplies investigators around the world with tissue from individuals with neurological and other disorders. Tissue from those with NF1, NF2, or Schwannomatosis is needed to enable scientists to study these disorders more effectively.

Donors may contact:

Human Brain and Spinal Fluid Resource Center

310-268-3536

24-hour pager: 310-636-5119

<http://brainbank.ucla.edu>

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's **Brain Resources and Information Network (BRAIN)** at:

BRAIN

P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information is also available from the following organizations:

Children's Tumor Foundation

Tel: 800-323-7938; 212-344-6633
<https://www.ctf.org>

Neurofibromatosis Network

Tel: 630-510-1115; 800-942-6825
www.nfnetwork.org

Neurofibromatosis Clinical Trials Consortium

<https://www.uab.edu/nfconsortium/>

Department of Defense Neurofibromatosis Research Program

<https://cdmrp.army.mil/nfrp/default>



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Neurological Disorders
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Prepared by:
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Department of Health and Human Services
Bethesda, Maryland 20892-2540