

What are the neurofibromatoses?

The neurofibromatoses are a group of three genetically distinct disorders that cause tumors to grow in the nervous system. Tumors begin in the supporting cells that make up the nerve and the myelin sheath (the thin membrane that envelops and protects the nerves), rather than the cells that actually transmit information. The type of tumor that develops depends on the type of supporting cells involved. Scientists have classified the disorders as neurofibromatosis type 1 (NF1, also called von Recklinghaus disease), neurofibromatosis type 2 (NF2), and a type that was once considered to be a variation of NF2 but is now called schwannomatosis. An estimated 100,000 Americans have a neurofibromatosis disorder, which occurs in both sexes and in all races and ethnic groups. The most common nerve-associated tumors in NF1 are neurofibromas (tumors of the peripheral nerves), whereas schwannomas (tumors that begin in Schwann cells that help form the myelin sheath) are most common in NF2 and schwannomatosis. Most tumors are benign, although occasionally they may become cancerous. Why these tumors occur still isn't completely known, but it appears to be related mainly to mutations in genes that play key roles in suppressing cell growth in the nervous system. These mutations keep the genes—identified as NF1, NF2 and SMARCB1/INI1—from making normal proteins that control cell production. Without the normal function of these proteins, cells multiply out of control and form tumors.

What is NF1?

NF1 is the most common neurofibromatosis, occurring in 1 in 3,000 to 4,000 individuals in the United States. Although many affected people inherit the disorder, between 30 and 50 percent of new cases result from a spontaneous genetic mutation of unknown cause. Once this mutation has taken place, the mutant gene can be passed to succeeding generations.

What are the signs and symptoms of NF1?

To diagnose NF1, a doctor looks for two or more of the following: six or more light brown spots on the skin (often called "café-au-lait" spots), measuring more than 5 millimeters in diameter in children or more than 15 millimeters across in adolescents and adults; two or more neurofibromas, or one plexiform neurofibroma (a neurofibroma that involves many nerves); freckling in the area of the armpit or the groin; two or more growths on the iris of the eye (known as Lisch nodules or iris hamartomas); a tumor on the optic nerve (called an optic nerve glioma) abnormal development of the spine (scoliosis), the temple (sphenoid) bone of the skull, or the tibia (one of the long bones of the shin); a parent, sibling, or child with NF1.

What other symptoms or conditions are associated with NF1?

Many children with NF1 have larger than normal head circumference and are shorter than average. Hydrocephalus, the abnormal buildup of fluid in the brain, is a possible complication of the disorder. Headache and epilepsy are also more likely in individuals with NF1 than in the healthy population. Cardiovascular complications associated with NF1 include congenital heart defects, high blood pressure (hypertension), and constricted, blocked, or damaged blood vessels (vasculopathy). Children with NF1 may have poor language and visual-spatial skills, and perform less well on academic achievement tests, including those that measure reading, spelling, and math skills. Learning disabilities, such as attention deficit hyperactivity disorder (ADHD), are common in children with NF1. An estimated 3 to 5 percent of tumors may become cancerous, requiring aggressive treatment. These tumors are called malignant peripheral nerve sheath tumors.

When do symptoms appear?

Symptoms, particularly the most common skin abnormalities-café-au-lait spots, neurofibromas, Lisch nodules, and freckling in the armpit and groin-are often evident at birth or shortly afterwards, and almost always by the time a child is 10 years old. Because many features of these disorders are age dependent, a definitive diagnosis may take several years.

What is the prognosis for someone with NF1?

NF1 is a progressive disorder, which means most symptoms will worsen over time, although a small number of people may have symptoms that remain constant. It isn't possible to predict the course of an individual's disorder. In general, most people with NF1 will develop mild to moderate symptoms. Most people with NF1 have a normal life expectancy. Neurofibromas on or under the skin can increase with age and cause cosmetic and psychological issues.

How is NF1 treated?

Scientists don't know how to prevent neurofibromas from growing. Surgery is often recommended to remove tumors that become symptomatic and may become cancerous, as well as for tumors that cause significant cosmetic disfigurement. Several surgical options exist, but there is no general agreement among doctors about when surgery should be performed or which surgical option is best. Individuals considering surgery should carefully weigh the risks and benefits of all their options to determine which treatment is right for them.

Treatment for neurofibromas that become malignant may include surgery, radiation, or chemotherapy. Surgery, radiation and/or chemotherapy may also be used to control or reduce the size of optic nerve gliomas when vision is threatened. Some bone malformations, such as scoliosis, can be corrected surgically. 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 learning disabilities, they should undergo a detailed neurological exam before they enter school. Once these children are in school, teachers or parents who suspect there is evidence of one or more learning disabilities should request an evaluation that includes an IQ test and the standard range of tests to evaluate verbal and spatial skills.

What is NF2?

This rare disorder affects about 1 in 25,000 people. Approximately 50 percent of affected people inherit the disorder; in others the disorder is caused by a spontaneous genetic mutation of unknown cause. The hallmark finding in NF2 is the presence of slow-growing tumors on the eighth cranial nerves. These nerves have two branches: the acoustic branch helps people hear by transmitting sound sensations to the brain; and the vestibular branch helps people maintain their balance. The characteristic tumors of NF2 are called vestibular schwannomas because of their location and the types of cells involved. As these tumors grow, they may press against and damage nearby structures such as other cranial nerves and the brain stem, the latter which can cause serious disability. Schwannomas in NF2 may occur along any nerve in the body, including the spinal nerves, other cranial nerves, and peripheral nerves in the body. These tumors may be seen as bumps under the skin (when the nerves involved are just under the skin surface) or can also be seen on the skin surface as small (less than 1 inch), dark, rough areas of hairy skin. In children, tumors may be smoother, less pigmented, and less hairy. Although individuals with NF2 may have schwannomas that resemble small, flesh-colored skin flaps, they rarely have the café-au-lait spots that are seen in NF1. Individuals with NF2 are at risk for developing other types of nervous system tumors, such as ependymomas and gliomas (two tumor types that grow in the spinal cord) and meningiomas (tumors that grow along the protective layers surrounding the brain and spinal cord). Affected individuals may develop cataracts at an earlier age or changes in the retina that may affect vision. Individuals with NF2 may also develop problems with nerve function independent of tumors, usually symmetric numbness and weakness in the extremities, due to the development of a peripheral neuropathy.

What are the signs and symptoms of NF2?

To diagnose NF2, a doctor looks for the following: bilateral vestibular schwannomas; or a family history of NF2 (parent, sibling, or child) plus a unilateral vestibular schwannoma before age 30; or any two of the following: o glioma;o meningioma,o schwannoma;oro juvenile posterior subcapsular/lenticular opacity (cataract) or

juvenile cortical cataract.

When do symptoms appear?

Signs of NF2 may be present in childhood but are so subtle that they can be overlooked, especially in children who don't have a family history of the disorder. Typically, symptoms of NF2 are noticed between 18 and 22 years of age. The most frequent first symptom is hearing loss or ringing in the ears (tinnitus). Less often, the first visit to a doctor will be because of disturbances in balance, visual impairment (such as vision loss from cataracts), weakness in an arm or leg, seizures, or skin tumors.

What is the prognosis for someone with NF2?

Because NF2 is so rare, few studies have been done to look at the natural progression of the disorder. The course of NF2 varies greatly among individuals, although inherited NF2 appears to run a similar course among affected family members. Generally, vestibular schwannomas grow slowly, and balance and hearing deteriorate over a period of years. A recent study suggests that an earlier age of onset and the presence of meningiomas are associated with greater mortality risk.

How is NF2 treated?

NF2 is best managed at a specialty clinic with an initial screening and annual follow-up evaluations (more frequent if the disease is severe). Improved diagnostic technologies, such as magnetic resonance imaging (MRI), can reveal tumors of the vestibular nerve as small as a few millimeters in diameter. Vestibular schwannomas grow slowly, but they can grow large enough to engulf one of the eighth cranial nerves and cause brain stem compression and damage to surrounding cranial nerves. Surgical options depend on tumor size and the extent of hearing loss. There is no general agreement among doctors about when surgery should be performed or which surgical option is best. Individuals considering surgery should carefully weigh the risks and benefits of all options to determine which treatment is right for them. Surgery to remove the entire tumor while it's still small might help preserve hearing. If hearing is lost during this surgery, but the auditory nerve is maintained, 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) may be an option to improve hearing. As tumors grow larger, it becomes harder to surgically preserve hearing and the auditory nerve. The development of the penetrating auditory brain stem implant (a device that stimulates the hearing portions of the brain) can restore some hearing in individuals who have completely lost hearing and do not have an auditory nerve present. Surgery for other tumors associated with NF2 is aimed at controlling or relieving symptoms. Surgery also can correct cataracts and retinal abnormalities.

What is schwannomatosis?

Schwannomatosis is a rare form of neurofibromatosis that is genetically and clinically distinct from NF1 and NF2. Inherited forms of the disorder account for only 15 percent of all cases. Researchers have identified a mutation of the SMARCB1/INI1 gene that is associated with the familial form of the disease but don't fully understand what causes the intense pain that characterizes this disorder.

What are the signs and symptoms of schwannomatosis?

The distinguishing feature of schwannomatosis is the development of multiple schwannomas everywhere in the body except on the vestibular nerve. The dominant symptom is pain, which develops as a schwannoma enlarges, compresses nerves, or presses on adjacent tissue. Some people experience additional neurological symptoms, such as numbness, tingling, or weakness in the fingers and toes. Individuals with schwannomatosis do not have neurofibromas. 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 schwannomas, while others develop only a few.

What is the prognosis for someone with schwannomatosis?

Anyone with schwannomatosis experiences some degree of pain, but the intensity varies. A small number of people have such mild pain that they are never diagnosed with the disorder. Most people have significant pain, which can be managed with medications or surgery. In some extreme cases, pain will be so severe and disabling it will keep people from working or leaving the house.

How is schwannomatosis treated?

There is no currently accepted medical treatment or drug for schwannomatosis, but surgical management is often effective. Pain usually subsides when tumors are removed completely, although it may recur should new tumors form. When surgery isn't possible, ongoing monitoring and management of pain in a multidisciplinary pain clinic is advisable.

Are there prenatal tests for the neurofibromatoses?

Clinical genetic testing can confirm the presence of a mutation in the NF1 gene. Prenatal testing for the NF1 mutation is also possible using amniocentesis or chorionic villus sampling procedures. Genetic testing for the NF2 mutation is sometimes available, but is accurate only in about 65 percent of those individuals tested. Prenatal or genetic testing for schwannomatosis currently does not exist.

What research is being done on the neurofibromatoses?

The National Institute of Neurological Disorders and Stroke (NINDS), one of the National Institutes of Health (NIH), is the primary federal supporter of research on neurological diseases. The Institute sponsors basic 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. In conjunction with the other NIH institutes, the NINDS supports research focused on finding better ways to prevent, treat, and ultimately cure the neurofibromatoses. In the mid-1990s, research supported by the NINDS located the exact position of the NF1 gene on chromosome 17. The gene has been cloned and its structure continues to be analyzed. The NF1 gene makes a large and complex protein called neurofibromin, which is primarily active in nervous system cells as a regulator of cell division and functions as a kind of molecular brake to keep cells from over-multiplying. In addition to work on NF1, intensive efforts have led to the identification of the NF2 gene on chromosome 22. As in NF1, the NF2 gene product is a tumor-suppressor protein (called merlin or schwannomin). Ongoing NINDS-sponsored research continues to discover additional genes that appear to play a role in NF-related tumor suppression or growth. Continuing research on these genes and their proteins is beginning to reveal how this novel family of growth regulators controls tumors formation and growth. Understanding the molecular pathways and mechanisms that govern these key proteins and their activities will offer scientists exciting opportunities to design drugs that could replace the missing proteins in people who have the neurofibromatoses, and return their cell production to normal. Current basic and clinical research is aimed at understanding how the genetic mutations that cause the benign tumors of NF1 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. The NINDS is supporting ongoing research with a large group of children with NF1 to find associations between brain abnormalities and specific cognitive disabilities. Finding these links would give doctors an indication of the kinds of learning disabilities parents and their children could anticipate and help them develop early intervention programs. The NINDS supports clinical research aimed at understanding the natural history of tumors in NF2 and determining possible factors that may regulate their growth patterns. Using diagnostic imaging, eye examinations, hearing and balance tests, neurologic examinations, blood and genetic testing, and quality of life assessments, researchers hope to better characterize the impact of NF2 on individuals and look for possible factors that may affect disease progression.

How can I help research?

The NINDS contributes to the support of the Human Brain and Spinal Fluid Resource Center in Los Angeles. This bank supplies investigators around the world with tissue from individuals with neurological and other

disorders. Tissue from individuals with NF1 or NF2 is needed to enable scientists to study these disorders more effectively. Prospective donors may contact: Human Brain and Spinal Fluid Resource Center Neurology Research (127A)W. Los Angeles Healthcare Center 11301 Wilshire Blvd., Bldg. 212 Los Angeles, CA 90073 310-268-3536 24-hour pager: 310-636-5199 www.loni.ucla.edu/uclabrainbank/ Interested individuals may also contact the NIH's Patient Recruitment and Public Liaison office at 800-411-1222 to ask about participating in clinical studies on the neurofibromatoses.

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:

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