about neurofibromatosis 1
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This brochure is intended to provide an introductory overview of neurofibromatosis type 1 (NF1) for patients, families, and healthcare providers with the hope that readers will seek additional information about the disorder according to their own individual needs. Physicians knowledgeable about NF, local genetics clinics, specialized NF clinics throughout the country, and the Children’s Tumor Foundation all serve as helpful sources of accurate, up-to-date information.

Thanks to advances in NF1 research, new discoveries about the disorder are being made every year. We encourage you to stay informed through the Foundation’s regularly updated website (www.ctf.org), quarterly newsletter, research E-NewsBlast, and brochures covering a wide variety of topics. Physicians who see NF patients are encouraged to attend the Foundation’s annual NF Conference and to visit our website to learn about the NF Clinic Network.

Much can be done to effectively manage NF1 and help affected individuals lead full, healthy lives. We hope this publication will answer many of your questions. If you need further assistance, we welcome you to contact the Foundation at the address, phone number, or e-mail address listed therein.

About Neurofibromatosis (NF)

Neurofibromatosis (NF) is the term for a set of distinct genetic disorders characterized by their tendency to cause multiple, benign (non-cancerous) tumors to grow on nerves. NF affects roughly 100,000 individuals in the U.S. alone. It strikes people of all races and ethnic origins worldwide, and both sexes, equally.
Half of all cases are the result of inheritance from a parent who has NF, while the other 50% occur in families with no history of the disorder.

**Neurofibromatosis 1 (NF1)** is the most common form of NF, affecting one in every 3,000 births. It is one of the most prevalent genetic disorders and the most common of the neurocutaneous disorders (conditions that affect both the skin and nervous system). NF1 was formerly known as peripheral NF or von Recklinghausen’s disease, named after the German physician who recognized the neurological component of the disorder in 1882.

NF1 is characterized by pigmented spots on the skin (café-au-lait spots) and tumors that develop on nerves anywhere in the body. In some cases, tumors can arise in the brain or on the spinal cord. The disorder also can cause non-tumorous complications such as learning disabilities – which affect up to 60% of all individuals with NF1 – as well as bone or skeletal abnormalities and certain cardiovascular defects.

**Neurofibromatosis 2 (NF2),** formerly called central or bilateral acoustic NF, is estimated to affect one in every 25,000 births. The disorder is characterized by tumors (vestibular schwannomas, also called acoustic neuromas) on the eighth cranial nerves of the brain – those that control hearing. NF2 can result in hearing loss. Additional features of NF2 can include other brain tumors, such as meningiomas, and spinal cord tumors.

NF1 and NF2 are quite different disorders, caused by mutations of different genes on different chromosomes, despite the similarity in their names.
**Schwannomatosis** is a more recently recognized form of NF that shares certain, but not other, features of NF2. It generally does not cause hearing loss and is characterized by chronic pain due to tumors (schwannomas) that grow on nerves anywhere in the body. The incidence of Schwannomatosis is estimated to be one in every 40,000 births. It is believed to be predominantly spontaneous (non-inherited), with only an estimated 10% of cases being familial. Little is known about the underlying causes of Schwannomatosis; however, the first candidate gene for the disorder was reported in 2007, which should help accelerate progress in understanding of the disorder.

This brochure will focus on NF1. Separate publications are available from the Children’s Tumor Foundation which provide more information about NF2 and Schwannomatosis. These, as well as brochures on additional topics relevant to NF1, are listed on the back of this brochure.

**COMMON SIGNS OF NF1**

A number of features commonly associated with NF1 are described below. An individual with NF1 may, but will not necessarily, develop all of these features.

**Café-au-lait spots**, one of the most common signs of NF1, are flat, pigmented spots on the skin named after the French term for coffee (café) with milk (lait). They tend to be a few shades darker than the usual color of a person’s
These spots are harmless and often help determine the diagnosis of NF1. There is no correlation between the number of café-au-lait spots that an individual has and the severity, or specific manifestations, of his or her NF1. In general, NF1 tumors are not more likely to appear on regions of the body where there are café-au-lait spots.

People with NF1 almost always have six or more café-au-lait spots, which usually are present at birth or appear within the first several years of life. (Fewer café-au-lait spots may occur in people who do not have NF1; indeed, about 10% of the general population has one or two café-au-lait spots.) The size of the spots that identify NF1 varies from 1/4 inch in children to several inches in diameter, and occasionally may be quite large.

The number of café-au-lait spots that an individual with NF1 has may increase in childhood and, occasionally, later in life. They may be very light in color in infants, darkening as the child gets older or with sun exposure. For some individuals, café-au-lait spots may fade during adulthood.

Freckling in specific body areas may also occur in individuals with NF1. In those who do not have NF1, freckling usually occurs in areas of skin exposed to sun; with NF1, freckling can be present in other areas, including the armpit (axillary freckling) and the groin (inguinal freckling). The freckles are often first noted around three or four years of age. Such freckling is not seen in every person with NF1, but when present it is considered strong evidence of the disorder.
Lisch nodules are clumps of pigment in the colored part of the eye (iris) that usually appear around puberty. They do not cause medical problems or affect vision. The presence of Lisch nodules can be helpful in confirming a diagnosis of NF1. Lisch nodules can be distinguished from iris freckles (commonly seen in people without NF) by a simple procedure called a slit-lamp examination. This is typically performed by an ophthalmologist.

Neurofibromas, the most common tumors in NF1, are benign growths that typically develop on, or just underneath, the surface of the skin; however, they may also occur in deeper areas of the body. Neurofibromas are composed of tissue from the nervous system (neuro) and fibrous tissue (fibroma). There are two major types of neurofibromas.

Dermal neurofibromas, also known as cutaneous neurofibromas, are small, nodule-like tumors on the surface of the skin (pictured here). These may appear at any age, though are most likely to start developing in adolescence. Dermal neurofibromas rarely, if ever, become cancerous.

Plexiform neurofibromas grow diffusely or as nodules under the skin surface or deeper in the body. They may be present from birth, but not initially be noticeable. Plexiform neurofibromas can develop in any part of the body and tend to grow and intertwine with normal body tissues. They have approximately a 10% chance of
becoming cancerous. Sudden growth or pain in a plexiform neurofibroma can be a sign of malignancy.

The presence of multiple neurofibromas is an important diagnostic sign of NF1. (A single neurofibroma may occur in a person who does not have NF.) The number of neurofibromas varies widely among affected individuals – from only a few to, in rare cases, thousands.

At present, there is no way to predict how many neurofibromas a person will develop. In some people, the size or number of neurofibromas increases during puberty and pregnancy, reflecting a possible hormonal effect. In general, the number of dermal neurofibromas tends to increase with age. There is no evidence that diet, exercise, or vitamins affect the growth of neurofibromas.

**DIAGNOSIS OF NF1**

Primary care physicians will refer patients to a geneticist, neurologist, or NF clinic to confirm the diagnosis of NF1. The disorder is diagnosed by the presence of two or more of the following criteria, provided that no other disease accounts for the findings:

- Six or more café-au-lait spots, each over 5 mm (1/5 inch) in greatest diameter among children who have not yet reached puberty; or each over 15 mm (2/3 inch) in greatest diameter among post-pubertal individuals.
- Two or more neurofibromas of any type, or one plexiform neurofibroma.
- Multiple freckles in the axillary (armpit) or inguinal (groin) regions.
• A distinctive osseous (bone) lesion, such as sphenoid dysplasia (absence of bone surrounding the eye) or bowing of the tibia of the lower leg with or without pseudarthrosis (incomplete healing of a fracture).

• Optic glioma (tumor of the optic nerve).

• Two or more Lisch nodules (in the iris of the eye) on slit-lamp examination.

• A first-degree relative (parent, sibling, or offspring) with NF1, diagnosed by the above criteria.

Occasionally, the signs of NF1 are not easy to identify. Members of families in which NF1 has occurred are often concerned about whether they may have inherited the disorder (or whether they may have passed on NF1 to their children), even if they have no obvious signs. An examination by a physician familiar with the signs of NF1 is usually the best way to determine whether the disorder is present.

If a family member is found to have a few features of NF1 but not enough to make a diagnosis (for example, two or three café-au-lait spots only), it may be helpful to perform a direct gene test. However, it is extremely rare for an individual to inherit NF1 yet show no detectable signs of the disorder.

**Genetic Testing**

In most affected individuals, NF1 can be diagnosed by the above clinical criteria. In these cases a genetic test is not necessary. In other cases, genetic testing of the patient’s blood may be useful to confirm a diagnosis. Laboratory tests are now available to determine pre-symptomatic (when the individual has no clinical symptoms of NF1) and prenatal diagnosis. Direct gene testing
from a blood sample is available for diagnosing NF1. At present, the test is 95% effective in diagnosing the disorder. However, the test cannot determine the severity of NF1 or the likelihood of any specific physical symptoms developing. To learn the latest about NF testing, we suggest that you consult your physician, the Children’s Tumor Foundation, your nearest genetics center, or a designated NF clinic.

VARIABILITY OF NF1

Symptoms of NF1 are highly variable from one person to another. At present, there is no way to predict how serious a case of NF1 an individual will have. The severity ranges from very mild cases in which the only signs of the disorder in adulthood may be multiple café-au-lait spots and a few dermal neurofibromas, to more severe cases in which other kinds of tumors or other more serious complications may develop.

NF1 is a congenital disorder; that is, it has its origins as the child develops before birth. Many of the serious problems in NF1 mentioned below are evident at birth or develop prior to adolescence. People with NF1 who have reached adulthood without having certain problems are unlikely to develop them. These include curvature of the spine (scoliosis); congenital defects of the bone; problems associated with puberty, growth, or head size; and optic glioma (a tumor on the nerve that controls vision). Neurological impairment leading to learning disabilities, and in rare cases mental retardation, is also typically evident in early childhood.

It is important to note that the majority of people with NF1 lead healthy, productive lives. For many, coping with the uncertainties surrounding NF1 presents a unique, yet conquerable challenge.
OTHER POTENTIAL MANIFESTATIONS OF NF1

Learning Disabilities

Learning disabilities are approximately five times more common in children with NF1 than in other children and may be associated with speech problems, motor deficits, or Attention Deficit Hyperactivity Disorder (ADHD). About 50-60% of children with NF1 will have learning difficulties of some type requiring special assistance at school. At the same time, it is important to remember that roughly half of all individuals with NF1 will not have learning disabilities.

NF1-associated learning disabilities are often first noticed when a child starts school. There are specific characteristic problems performing tasks such as reading, writing, or the use of numbers. These issues can occur in children with NF1 who have normal, or even above average, intelligence.

A child with NF1 who is suspected of having a learning problem should be evaluated at the youngest possible age by a psychologist, pediatric neurologist, developmental pediatrician, or other professional with special knowledge of learning disabilities. Many school systems provide referrals to such specialists, and developmental services are available even for infants and pre-schoolers.

Although a learning disability is a lifelong condition, many adults have found ways to adapt and successfully overcome specific deficits. Additional brochures are available from the Children’s Tumor Foundation with specific information about NF1, learning disabilities, and enhancing success in school, for use by parents and educators.
Optic Glioma

An optic glioma is a tumor of the optic nerve in the brain which controls vision. This kind of tumor occurs in about 15% of patients with NF1 and usually appears in childhood, with a peak onset age of about 3-4 years old. Optic gliomas may be suspected because of failing vision or an abnormal eye exam, and they are detected by means of a screening MRI scan. Therefore, children with NF1 should have routine eye exams – at least annually – by an ophthalmologist who is familiar with NF1 and optic gliomas. Fortunately, the majority of optic nerve gliomas never affect vision and do not require any treatment. If there is evidence that the optic glioma is progressing (getting worse or affecting vision), the current most common treatment recommended is chemotherapy.

Bone Defects

Abnormal bone development occurs in approximately 14% of individuals with NF1. Most bone defects of NF1 will be evident at birth or shortly thereafter (some, such as vertebral defects, can occur later). They can occur in almost any bone, but are seen most often in the skull and limbs. They include:

- Congenital absence, or partial absence, of the sphenoid bone (the bone normally surrounding the orbit of the eye), also known as sphenoid wing dysplasia. This may cause slight bulging of the skin around the eye.
• Congenital bowing of the leg bones, called tibial dysplasia, can occur in the bones of the lower leg (tibia or fibula). This affects about 3-5% of people with NF1. Tibial dysplasia is usually noticed in the first year of life, so children older than this are very unlikely to develop it. The affected bones may be thinner than normal. If a fracture occurs, healing may be slow or incomplete, causing pseudarthrosis (a “false joint” or non-healing fracture). In rare cases, pseudarthrosis may involve other bones such as the ulna of the forearm. Management of pseudarthrosis is a difficult problem, requiring the supervision of an orthopedic surgeon who is familiar with NF1. NF research is underway to determine the best way to manage pseudarthrosis.

• Bone cysts occasionally occur at the end of bones in the arms and legs, and they can sometimes cause pain or discomfort.

• Osteopenia (decreased bone density), which is the primary cause of osteoporosis, is more common in individuals with NF1 than in those of the general population. Prevention strategies can be discussed with one’s doctor.

**Scoliosis**

Scoliosis, or lateral curvature of the spine, is relatively common in NF1 – occurring in about 10% of patients. In most cases the scoliosis is mild and appears in early childhood. A subset of children with NF1 may develop an unusual type of scoliosis with a sharp angle to the curve rather than a
smooth S-shaped curve. A child with scoliosis will need periodic spinal imaging and physical examinations to determine whether corrective measures are needed. In some cases, a brace may be used to prevent progression of the problem. The sharply angulated form of scoliosis is more likely to require correction by surgery.

**Large Head Size**

Children and adults with NF1 often have large head circumference. This usually does not indicate any significant medical problem. Rarely, large head circumference results from hydrocephalus, a serious condition which may require surgery. Imaging of the brain with CT scan or MRI can help determine if head enlargement is serious or not. Head circumference in children with NFI should be periodically measured.

**Headache & Other Pain**

Many people with NF1 have frequent headaches, particularly migraine headaches. Features may include throbbing pain on one side of the head, nausea, and sensitivity to light. Migraine can also cause stomach pain, with or without headache. These can be relieved using the same types of medications used to treat migraines in persons without NF1. Severe or recurrent pain of any type, anywhere in the body, should be evaluated by a physician.

Pain is a treatable condition and many different therapeutic options are available for its management. Importantly, new pain in a plexiform neurofibroma can be a sign of malignancy and should be evaluated right away.
High Blood Pressure (Hypertension)

People with NF1 can have hypertension for reasons completely unrelated to NF1. However, two rare problems associated with NF1 may result in hypertension: renal artery stenosis (narrowing of the artery to the kidney) and pheochromocytoma (a rare and usually benign tumor of the adrenal gland). Both of these problems are treatable. It is important that routine physical exams for children and adults with NF1 include blood pressure checks.

LESS COMMON COMPLICATIONS OF NF1

The complications mentioned below may occur in NF1, but usually in less than 10% of patients. It should be emphasized that most people with NF1 will not experience these symptoms. Many are treatable.

• Early or late onset of puberty (can be associated with optic glioma).

• Problems with growth (individual is too short or too tall). It is important to note that, as a group, people with NF1 are slightly shorter than the general population – with average height around the 25th percentile rather than the 50th percentile.

• Mental retardation (this is seen in 5-8% of those with NF1, compared to 3-5% in the general population).

• Epilepsy (seizure disorder).

• Cerebrovascular occlusion (stroke), due to blockage of the blood vessels supplying the brain.
• Abnormalities of blood vessels, including aneurysm (weakening of the blood vessel wall, resulting in bulging) in the renal arteries or in the brain.

• Congenital heart defects, such as a small hole between chambers of the heart (VSD) or narrowing of the pulmonary artery (pulmonic stenosis).

• Malignant tumors (cancer). NF1-related malignancy is estimated to occur in about 7-12% of affected individuals. People with NF1 have a somewhat higher risk for certain rare malignant tumors that occur along peripheral nerves, in the brain, or in the spinal cord. One specific type, called MPNST (malignant peripheral nerve sheath tumor), can grow within a plexiform neurofibroma. NF1 patients probably have the same risk for certain common cancers (such as cancer of the lung or colon) as does the general population. However, early research indicates a possible increase in the incidence of breast cancer among women with NF1.

• Brain tumors (other than optic glioma), such as astrocytomas or brain stem gliomas.

• Leukemia. Children with NF1 have more than a 200-fold increase in the risk of developing an uncommon type of leukemia called juvenile myelomonocytic leukemia (JMML). This affects less than 1% of NF1 patients. Adults with NF1 are not at increased risk of developing leukemia or related cancers.

• Neurological dysfunction (motor or sensory).

• Itching of the skin (pruritis).
In some cases, NF1 can be disfiguring. Some adults may have large enough numbers of dermal neurofibromas to cause cosmetic problems. Occasionally, large plexiform neurofibromas may grow around the eye or eyelid, or affect one side of the face. Scoliosis can affect appearance when it is severe. Growths can occur around the nipple (areolar neurofibromas), which may be distressing. Rarely, an overgrowth of skin or bone causes enlargement of an arm or leg.

Disfigurement, and the fear of becoming disfigured in the future, is often a major concern for those with NF1. Yet not everyone reacts the same way to complications that affect appearance. Some people find that café-au-lait spots or a small number of neurofibromas on the skin are hard to live with, while others are able to cope well with more severe involvement.

Most physicians do not recommend routine removal of dermal neurofibromas, unless they are causing pain, rubbing against clothing, or causing significant cosmetic concern. If desired, a plastic surgeon may be consulted to determine whether a particular tumor or group of tumors can be removed by conventional or laser surgery. Some patients are exploring the technique of electro-dessication, or use of an electric current to dry out and remove dermal neurofibromas. All of these procedures pose the risk of possible scarring, and none have been proven to result in permanent tumor removal. They should always be performed by a physician who is experienced in treating patients with NF1.
Plexiform neurofibromas around the eye are often managed jointly by an eye (ophthalmic) surgeon and a plastic surgeon. Large plexiform neurofibromas are often difficult to remove completely, since they are enmeshed with normal tissues such as nerves and blood vessels.

**FINDING MEDICAL CARE FOR NF1**

Individuals with NF1 should regularly see a physician for evaluation and follow-up care who is knowledgeable about the disorder and its complications – or is at least willing to learn and identify colleagues with the required expertise as needed. Specialists from many disciplines may be knowledgeable about specific aspects of NF1; those most likely to be familiar with the disorder as a whole include geneticists, neurologists, and pediatric neurologists.

The Children’s Tumor Foundation has established an NF Clinic Network that includes major centers for NF care throughout the U.S. For more information about where to seek help, contact the Foundation’s national headquarters or your local chapter or affiliate, or visit www.ctf.org.

**MEDICAL EVALUATION & FOLLOW-UP: CHILDREN**

The role of the pediatrician who follows a child with NF1 is to monitor the child’s growth and development much as is ordinarily done for any other child. The physician ideally will be able to accomplish this without unduly emphasizing potential difficulties, which may or may not become problems for any given child. A medical evaluation for anyone with NF1 should include looking at family medical history.
Healthy children with NF1 are usually examined at 6- or 12-month intervals for height, weight, and head circumference; blood pressure; vision and hearing; evidence of normal sexual development; signs of learning disability, hyperactivity, or speech and motor deficits; evidence of scoliosis; and for café-au-lait spots and neurofibromas. The causes of any unusual growth pattern are generally investigated. Further diagnostic evaluations, including blood tests and imaging, are usually needed only to investigate suspected problems.

Many NF specialists feel there is no need to do routine screening MRI scans of the brain or spine in healthy patients with NF1 who have no symptoms. Others will recommend a “baseline” MRI scan in children to check for optic nerve gliomas or spinal tumors and for use as a reference point to compare future scans. All physicians are in agreement that MRI scans and other imaging should be used if patients are having specific symptoms.

**MEDICAL EVALUATION & FOLLOW-UP: ADULTS**

In addition to the standard physical evaluation, routine check-ups for adults with NF1 generally include an examination of the skin, the spine (for scoliosis), blood pressure, vision, and hearing. Attention is given to any mass that is rapidly enlarging or causing new pain, as these signs can indicate malignancy. Specific tests can be performed if a medical problem develops. Adults with NF1 who are otherwise healthy usually have check-ups at 12-month intervals.
TREATING TUMORS IN NF1

Neurofibromas, depending on their location and size, can sometimes be removed surgically if they become painful, invasive, infected, or cosmetically troublesome. A tumor sometimes appears where one has been removed, particularly if that tumor was not removed completely. There is no evidence that removal of dermal neurofibromas will increase the rate of appearance of new growths, or cause incompletely removed tumors to change from benign to cancerous.

Subcutaneous (under the skin) neurofibromas are more difficult to remove completely. This is especially the case for plexiform neurofibromas. Partial removal may be recommended if they are causing symptoms or pushing on important structures, which can result in loss of neurological function.

World-class NF research is underway to identify and test candidate drugs that could potentially lead to treatments that enable shrinking or stopping the growth of tumors associated with NF1. The speed of progress in NF1 research, from discovery of the NF1 gene in 1990 to the start of clinical trials more recently, should give individuals with the disorder good reason for optimism.

Information about current NF1 clinical trials can be found on the Children’s Tumor Foundation website. The Foundation funds pioneering NF research through its Young Investigator Awards, Drug Discovery Initiative Awards, NF Preclinical Consortium, and special awards for specific areas of study. Through its annual NF Conference and other scientific meetings, the Foundation also fosters vital research collaborations.
The potential complications and uncertainties of NF1 can be stressful for many affected individuals. Decisions about whether, or what, to tell friends, teachers and employers – and whether to have children – are examples of concerns expressed by many. Anxiety about the need for medical treatments, a sense of losing control, and the feeling of being different from others also are common. Because of the stress of medical problems and learning disabilities associated with NF1, social and psychological problems may also develop.

The disorder can place emotional burdens not only on the individual affected, but also on the whole family – including unaffected siblings. Parents may be troubled by unfounded, yet natural feelings of guilt about the child’s difficulties. The financial cost of caring for a child with NF1 complications can be considerable. Individual or family counseling by a social worker or psychotherapist is often helpful.

To help ease these multiple pressures, the Children’s Tumor Foundation and its local chapters and affiliates have organized support groups that help those with NF overcome their sense of isolation. Support groups offer an opportunity to share feelings and learn more about the disorder in an atmosphere of mutual understanding. Many people report that becoming actively involved in efforts to advance NF research, provide support services, or raise awareness of NF can bring an added sense of hope, community, and empowerment.
DECIDING WHETHER TO HAVE A CHILD

For couples in which one person has NF1, there is a 50-50 chance of passing on the disorder with each pregnancy. The decision whether to conceive children will involve emotional introspection as well as the gathering of facts. No one can make this personal decision for anyone else.

Many in this position choose to conceive and feel confident that, whether or not their child is born with NF1, they have made the decision that is right for them. Others may decide to have prenatal testing to determine whether the unborn child has NF1.

This testing is available either by amniocentesis (performed at 15-16 weeks in the pregnancy) or by chorionic villous sampling (performed at 10-12 weeks). Unfortunately, prenatal testing can only tell whether the child has inherited NF1 from the parent; it does not give any information about the expected degree of severity.

Some couples have chosen “preimplantation genetic diagnosis,” a complicated and expensive procedure using in vitro fertilization techniques. Eggs are fertilized outside the body and those that do not have an NF1 mutation are selected to implant back into the uterus.

The “50-50 Risk”

With every pregnancy, an individual with NF1 faces a 50% risk of conceiving a child with the disorder – the same odds as flipping a coin. This risk can be compared to the 4-7% risk that any couple in the general population faces of bearing a child with a serious medical problem.
Unaffected parents who have a child born with NF1 because of a “spontaneous genetic mutation” do not have a 50% risk in future pregnancies. Their chance of bearing another child with NF1 is about that of any couple in the general population (some studies show a slightly higher risk). For NF1, this chance is one in 6,000. (One additional birth in every 6,000 results in a child who has inherited NF1 from a parent with the disorder. Thus, a total of two children in 6,000 – or one in 3,000 – are born with NF1.)

However, in order for unaffected parents who have a child with NF1 to accurately assess their risk of conceiving another child with NF1, it is essential to know for certain whether they themselves in fact have NF1. These parents should be examined by a knowledgeable physician to make sure that neither of them has a mild, undiagnosed case of NF1.

Help with Making the Decision

Genetic counseling can help couples work through the decision-making process. Counselors do not tell anyone what to do; rather, they provide information, clarify issues, answer questions, and explain possible options including prenatal testing, adoption, or artificial insemination. The counselor encourages the couple to arrive at a decision that is right for them. Most major hospitals and university-based medical centers offer genetic counseling services.
NF1 is caused by a change (mutation) in a single gene located on chromosome 17. Another form of NF, called NF2, is caused by a mutation in an entirely different gene located on chromosome 22. The odds of one person, or members of one family, having both NF1 and NF2 are extremely low; this possibility should not be of concern. An individual with NF1 cannot pass on NF2 to his or her child, nor can someone with NF2 pass on NF1.

When a person with NF1 is said to have the NF1 gene, what this really means is that the individual has a mutation in at least one of the two copies of the NF1 gene that people normally have. Individuals who were not born with NF1 have two normal (or unaffected) copies of the NF1 gene.

The NF1 gene can be inherited from an affected parent (who has NF1) or it may arise by chance in an individual with no family history of NF1. In the latter case, NF1 results from a change in the gene called a spontaneous mutation. About half of those with NF1 have inherited it from a parent who has the disorder; the other half are affected because of a spontaneous mutation and have no affected parent. NF1 has an unusually high spontaneous mutation rate. It can appear in any family, regardless of race or ethnicity.

Once an individual has a change in the NF1 gene – whether by inheritance or because of a spontaneous mutation – there is a 50-50 chance, each time he or she has a child, that the changed gene will be passed on. There is also a 50-50 chance, each time, that the changed gene will not be passed on. In this
latter case, the child will be completely free of NF1 and will never develop signs of the disease. This child, therefore, cannot pass on the disorder; NF1 cannot “skip a generation.”

Variability

The extreme variability in NF1 symptoms is seen even within families. The same NF1 gene mutation present in different members of the same family – brothers and sisters, grandparents, parents and children – can result in NF1 cases with widely varying degrees of severity and very different symptoms. For example, a parent who has a mild case of NF1 may have a severely affected child. The reverse situation can also occur: a severely affected parent may have a child with very mild NF1. At present, there is no way to predict how seriously affected any person in any family with NF1 will be, or which NF1 complications may develop.

Genes

Our body is made up of trillions of cells. Each cell nucleus contains a set of chemical structures known as chromosomes. There are 46 chromosomes, arranged in 23 pairs, in each cell of the body. One chromosome of each pair was contributed by the father, and the other by the mother.

A gene is a small section of a chromosome composed of DNA, a molecule that encodes the building blocks of proteins that direct our cells. Just as the chromosomes occur in pairs, genes also come in pairs. An estimated 30,000 genes are arranged in a very specific order on the 23 chromosome pairs. One of these pairs, called the sex chromosomes, differs in males and
females; the other 22 pairs, called autosomes, are the same in both sexes.

What Genes Do

When a gene is activated, a variety of events can occur in the cell, depending on the particular function of that gene. Some genes are responsible for obvious traits such as eye color; others control the production of substances essential to chemical processes inside our bodies. Certain genes simply act as on-off switches for other genes. The sum total of these reactions – which are like orders to the cell – are all the instructions needed for the first cell to develop into a human being and for the body to carry on all the functions of life.

Gene Mutation

A mutation is simply a change or alteration. Gene mutations have occurred since the beginning of time and continue to do so. Most are not detectable, and many are not harmful. In fact, gene mutations can be beneficial in allowing species to adapt and ultimately survive changes in the environment. When a mutation occurs in a gene, it can alter the structure of the gene, and the gene’s “instructions” to the cell are changed or even stopped completely. An alteration of this kind can have serious effects, and may result in a genetic disorder.

NF1 is the result of such a changed gene. This change is not caused by any factor under a person’s control, such as drug or X-ray exposure; rather, it is caused by an error in the process of copying genetic information, typically when sperm or egg cells form.
Due to advances in research, much information is now known about how the NF1 gene acts at a molecular level. The NF1 gene normally produces a protein called “neurofibromin,” which acts through a pathway in the cell (called the Ras pathway) to signal cells whether to keep dividing and multiplying. This type of gene is also called a “tumor suppressor” gene.

**Mosaic or Segmental NF**

Occasionally, a mutation in the NF1 gene can occur after conception, later in embryonic development. It therefore affects only a certain percentage of cells in the body, but not others. Such cases, which always result from a spontaneous mutation, are called mosaic NF1. Segmental NF1 is a form of mosaicism in which only one portion of the body is affected with features of NF1.

**Autosomal Dominant Disorders**

NF1 is an autosomal dominant disorder. Autosomal means the gene is located on one of the 22 numbered pairs of chromosomes called autosomes. Since these chromosomes are the same in males and females, the gene can be present in either sex, and it can be passed on from either a mother or a father to a son or a daughter. The term dominant means that the presence of only one changed or affected gene causes the disorder to appear; the action of the unaffected gene which is paired with the dominant gene cannot prevent the disorder. Because one gene is enough to cause the disorder, NF1 can be passed from one generation to the next when only one parent has the gene.
The 50-50 Odds of Passing on NF1

Why are the odds of a child inheriting NF1 from an affected parent 50-50?

The explanation for this lies in the process that brings egg cells and sperm cells to maturity. These cells carry our genetic heritage from one generation to the next. Before reaching maturity each of these sperm and egg cells contains 23 pairs of chromosomes, the full complement of genetic material just like any other body cell. As they approach maturity, however, these cells go through a special cell division process (meiosis) that results in each egg or sperm having a single chromosome from each pair – or half of its original genetic material. It happens this way:

1. Chromosomes line up in pairs inside the egg or sperm cell.

2. The pairs separate.

3. The cell divides.

4. Two cells are produced, each with one member of every chromosome pair.

When an egg and sperm – each with 23 single chromosomes – unite, a new cell is formed which contains the 46 chromosomes (23 pairs) required for normal human development.
This diagram shows the only pair of chromosomes which include the NF1 gene and its unaffected partner:

When a person with NF1 has children with an unaffected individual, there are four possible combinations of cells. Two will yield a child with NF1, and two will yield an unaffected child. This is how it happens:

Thus, there is a 50% chance with each pregnancy for the child to receive the NF1 gene; there is also a 50% chance for the child to receive two unaffected genes and be free of NF1.
GLOSSARY OF MEDICAL TERMS RELATING TO NF1

ASTROCYTOMA
Tumors that arise from brain cells called astrocytes.

AUTOSOMAL DOMINANT INHERITANCE
The process by which one gene of a pair causes the expression of a trait or disorder. Such a gene has a 50% chance of being passed on to each child of an affected parent.

CAFÉ-AU-LAIT SPOTS
Pigmented, flat spots which are variable in shape and size. Six or more spots are usually a sign of NF1.

CHEMOTHERAPY
Treatment of tumor growth by chemical agents.

CHROMOSOMES
Bearers of genes, the basic units of heredity. The nucleus of each body cell contains 23 pairs of chromosomes.

COMPUTERIZED TOMOGRAPHY
(Also known as CT or CAT scan) A computerized X-ray, which provides detailed images of internal organs, head and limbs.

DOMINANT
Pertains to a gene, which by itself causes the expression of a trait or disorder. An identical, paired gene need not be present.

FIBROMA
A tumor composed mainly of fibrous or connective tissue.

GENE
The basic unit of heredity. Thousands of genes, arranged in specific linear order, form a chromosome. Genes, like chromosomes, come in pairs; one of each pair is located on one chromosome, with the matching gene on the other chromosome of that pair.

GLIOBLASTOMA
A type of malignant brain tumor.
HAMARTOMA
A benign growth consisting of an overgrowth of the tissues which normally occur in an area. A neurofibroma is an example of a hamartoma.

HEMIHYPERTROPHY
Overgrowth of one half of the body or of a part of the body, such as the face. Rarely, this may occur in NF1.

LEARNING DISABILITY
A problem with a specific cognitive function necessary for learning in spite of average or above average intelligence. Learning disabilities can affect one’s ability to listen, think, read, write, spell, speak and/or compute math.

LISCH NODULES
Small, harmless clumps of pigment on the iris of the eye, often seen in NF1. They do not cause problems with vision.

MAGNETIC RESONANCE IMAGING (MRI)
A diagnostic technique which uses magnetic energy to image the brain and body.

MENINGIOMA
A benign tumor of the covering of the brain.

MUTATION
A permanent change in genetic material, usually in a single gene.

NEURO
Denotes relationship to a nerve or nerves, or to the nervous system.

NEUROFIBROMA
A benign tumor caused by proliferation of Schwann cells and fibroblasts.

NEUROFIBROMATOSIS TYPE 1 (NF1)
(pronounced neuro-fibroma-tosis)
A genetic disorder characterized by developmental changes in the nervous system, muscles, bones and skin and marked superficially by the formation of multiple soft tumors (neurofibromas) and by areas of pigmentation (café-au-lait spots). Formerly called von Recklinghausen’s disease.

NEURONS
Electrically active cells of the nervous system responsible for controlling behavior and body function.
OPTIC GLIOMA
Tumor affecting the optic (visual) nerve.

ORBIT
Bony cavity of the skull in which the eyeball is located.

PLEXIFORM NEUROFIBROMA
A diffuse, flat type of growth. Usually occurs below the skin internally.

PERIPHERAL
Situated away from the center of the central nervous system, toward the surface of the body.

PIGMENTED
Having color, in the case of café-au-lait spots a few shades darker than one’s regular skin color.

PSEUDARTHROSIS
Failure of a fracture to heal, resulting in a “false joint.”

RECESSIVE
Pertaining to a gene, a pair of which is generally required for full expression of a trait or disorder.

SARCOMA
Malignant soft tissue tumor.

SCHWANN CELL
The cell of which myelin (the insulation of peripheral nerves) is composed.

SCHWANNOMA
A benign tumor caused by proliferation of Schwann cells.

SCOLIOSIS
Lateral deviation in the normally straight vertical line of the spine.

SPONTANEOUS MUTATION
A change in a gene, occurring with no identifiable cause.

VESTIBULAR SCHWANNOMA
(ACOUSTIC NEUROMA)
Benign tumor of the eighth cranial nerve that causes hearing impairment, a common tumor in NF2.

VON RECKLINGHAUSEN’S DISEASE
Another name for NF1.
The mission of the Foundation is to:

- Find effective treatments and a cure for NF by sponsoring world-class research and promoting collaboration between scientists in the field;
- Improve clinical care for patients with NF and encourage the development of NF clinics nationwide;
- Provide information and support services for affected patients and families, including youth programs;
- Raise public awareness of NF to generate better understanding and resources to improve the lives of those born with the disorder.

Become Involved!

Your participation, whether as a volunteer or donor, will help “solve the NF puzzle” by enabling pioneering research aimed at ending NF. Until a cure is found, you also will be helping to provide hope and support for those with NF.

To become involved and learn about local Foundation activities in your area, please visit our website or contact us at the address or number on the back of this brochure.
Brochures Available

- About NF1
- About NF2
- About Schwannomatosis
- The Child with NF1
- NF1: For Adults
- NF1: For Teens
- NF1: For Educators
- NF1: About Learning Disabilities
- NF2: For Teens
- NF2: About Hearing Loss
- NF: Genetic Testing
- Mosaic & Segmental NF
- Children’s Tumor Foundation: About Us

Other Resources

Stay up-to-date on information about NF:

- Visit our website at http://www.ctf.org
- Contact us (see back) to receive our quarterly newsletter and regular e-mail news updates!
Founded in 1978, the Children's Tumor Foundation is a national, not-for-profit health organization dedicated to meeting the unique needs of individuals with neurofibromatosis (NF) and their families.