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about
neurofibromatosis

NF1

OVERVIEW OF NEUROFIBROMATOSIS TYPE 1 (NF1)

Neuro fibroma tosis
ASSOCIATION OF IRELAND

Contents

Professor Green
Director, Centre of Medical Genetics

"I am delighted to support and endorse the new information sheets for people with Neurofibromatosis 1 and their families. The information will be of great help to the many families in Ireland with NF1, and will help those families to understand better the many ways in which Neurofibromatosis 1 can affect people. The National Centre for Medical Genetics is delighted to be associated with the Neurofibromatosis Association of Ireland, and that the Neurofibromatosis Association of Ireland has funded a genetic counsellor to run a specialised NF clinic in the NCMG. The NCMG has a wealth of experience with Neurofibromatosis and sees many families with the condition throughout Ireland. The NCMG holds genetics clinics in Dublin, Cork, Limerick and Galway, and is happy to see families with NF1, with a referral from their own doctor.

Prof. Andrew Green

NEUROFIBROMATOSIS CLINIC

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INTRODUCTION

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 condition according to their own individual needs. Physicians knowledgeable about NF and NFA Ireland serve as helpful sources of accurate, up-to-date information. Much can be done to effectively manage NF1 and help affected individuals lead full, healthy lives. Thanks to advances in NF1 research, new discoveries about the condition are being made every year and we encourage you to stay informed. We hope that this publication will answer many of your questions.

ACKNOWLEDGEMENT

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ABOUT NEUROFIBROMATOSIS (NF)

Neurofibromatosis (NF) is the term for a set of distinct genetic conditions characterized by their tendency to cause multiple, benign (noncancerous) tumours to grow on nerves. NF affects roughly 2,500 individuals

in the ROI alone. It affects 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 condition.

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 recognised the neurological component of the condition in 1882).

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

COMMON SIGNS OF NF1

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

Café-au-lait patches, 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 colour of a person's skin. These spots are harmless and often help determine the diagnosis of NF1. There is no correlation between the number of café-au-lait patches that an individual has and the severity, or specific manifestations, of his or her NF1.

In general, NF1 tumours are not more likely to appear on regions of the body where there are café-au-lait patches.

People with NF1 almost always have six or more café-au-lait patches, which usually are present at birth or appear within the first several years of life. Fewer café-au-lait patches may occur in people who do not have NF1; indeed, about 10% of the general population has one or two café-au-lait patches. 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 patches that an individual with NF1 has may increase in childhood. They may be very light in colour in infants, darkening as the child gets older or with sun exposure. For some individuals, café-au-lait patches 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 condition.

Lisch nodules are clumps of pigment in the coloured 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 an ophthalmologist.

Neurofibromas, the most common tumours 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 tumours on the surface of the skin. 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 malignant. Sudden growth or pain in a plexiform neurofibroma should be investigated by a physician.

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

GPs will refer patients to a geneticist or dermatologist, to confirm the diagnosis of NF1. The condition 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 patches, each over 5mm (1/5 inch) in greatest diameter among children who have not yet reached puberty; or each over 15mm (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 (tumour 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 condition (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 condition is present.

Genetic Testing

Genetic testing for NF1 is not part of the routine diagnostic process but can be useful in a small number of cases if the diagnosis of NF1 is uncertain. Some families wish to consider prenatal testing in a pregnancy or an In-Vitro Fertilisation (IVF) technique called Pre-implantation Genetic Diagnosis (PGD).

Before these procedures can proceed genetic testing is needed in order to find the exact gene alteration which has caused the condition in the parent.

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 condition in adulthood may be multiple café-au-lait patches and a few dermal neurofibromas, to more severe cases in which other kinds of tumours or other more serious complications may develop.

NF1 is a congenital condition; 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 tumour on the nerve that controls vision). Learning difficulties, if present, are 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 Difficulties
Learning difficulties in NF1 may be associated with 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 difficulties.

NF1-associated learning difficulties 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 developmental paediatrician and educational psychologist, or other professional with special knowledge of learning difficulties. Many adults find ways to adapt and successfully overcome specific difficulties. Additional brochures are available from NFA Ireland with specific information about NF1, learning difficulties, and enhancing success in school, for use by parents and educators.

Optic Glioma

An optic glioma is a tumour of the optic nerve in the brain which controls vision. This kind of tumour 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 treatment. If there is evidence that the optic glioma is progressing, the current most common treatment recommended is chemotherapy.

Bone Defects

Most bone defects of NF1 will be evident at birth or shortly thereafter (some 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. 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 orthopaedic 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. Head circumference in children with NF1 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 phaeochromocytoma (a rare and usually benign tumour 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 emphasised 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. 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.
- Moderate to severe intellectual impairment (this is seen in 4-6% of those with NF1).
- Epilepsy (seizure disorder is seen in 6-7% of those with NF1).
- 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 tumours (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 tumours that occur along peripheral nerves, in the brain, or in the spinal cord. One specific type, called MPNST (malignant peripheral nerve sheath tumour), 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, evidence now

shows an increase in the incidence of breast cancer among women with NF1. Early mammography from 40 – 50 years of age is recommended.
- Brain tumours (other than optic glioma), such as astrocytomas or brain stem gliomas.
- Leukaemia. Children with NF1 have an increased risk of developing an uncommon type of leukaemia called juvenile myelomonocytic leukaemia (JMML). This affects less than 1% of NF1 patients. Adults with NF1 are not at increased risk of developing leukaemia.
- Neurological dysfunction (motor or sensory).
- Itching of the skin (pruritis).

COSMETIC CONCERNS

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 patches 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. A plastic surgeon may be

consulted to determine whether a particular tumour or group of tumours can be removed by conventional or laser surgery. All of these procedures pose the risk of possible scarring, and none have been proven to result in permanent tumour 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 condition 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 condition as a whole include geneticists, neurologists, paediatric neurologists, and dermatologists.

MEDICAL EVALUATION & FOLLOW-UP: CHILDREN

The role of the paediatrician who follows a child with NF1 is to monitor the child's growth and development much as is ordinarily done for any other child. Annual review by a paediatrician throughout childhood is recommended. A medical evaluation for anyone with NF1 should include looking at family medical history.

Healthy children with NF1 are usually examined at 12-month intervals for height, weight, and head circumference; blood pressure; vision and hearing; evidence of normal sexual development; signs of learning difficulty, hyperactivity, or speech and motor deficits; evidence of scoliosis; and for café-au-lait patches 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. All physicians are in agreement that MRI scans and other imaging can be useful 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 GP check-ups at 12-month intervals.

TREATING TUMOURS IN NF1

Neurofibromas, depending on their location and size, can sometimes be removed surgically if they become painful, invasive, infected, or cosmetically troublesome. A tumour sometimes appears where

one has been removed. There is no evidence that removal of dermal neurofibromas will increase the rate of appearance of new growths, or cause incompletely removed tumours 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 tumours 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 condition good reason for optimism.

PSYCHOLOGICAL & SOCIAL ISSUES OF NF1

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 difficulties associated with NF1, social and psychological problems may also develop.

The condition 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. Further information may be available from a social worker and individual or family counselling by a counsellor or psychotherapist is often helpful.

DECIDING WHETHER TO HAVE A CHILD

For couples in which one person has NF1, there is a 50-50 chance of passing on the condition 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 consider having prenatal testing to determine whether the pregnancy is affected with NF1.

This testing is available either by Chorionic Villous Sampling (performed at 11-13 weeks) or by amniocentesis (performed at 15-16 weeks in the pregnancy). Prenatal testing can only be carried out if a mutation is found in the parent with NF1. Also, it does not give any information about the expected degree of severity.

Some couples have chosen "pre-implantation genetic diagnosis," a complicated and expensive procedure using *in vitro* fertilisation techniques. Eggs are fertilised 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 condition – the same odds as flipping a coin. This risk can be compared to the 2-3% 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 condition. 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 counselling can help couples work through the decision-making process. Counsellors 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 counsellor encourages the couple to arrive at a decision that is right for them.

THE GENETICS OF NF1

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 condition; 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, ethnicity, or gender.

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 condition; 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 colour; 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 "tumour 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 condition to appear; the action of the unaffected gene which is paired with the dominant gene cannot prevent the condition. Because one gene is enough to cause the condition, NF1 can be passed from one generation to the next when only one parent has the mutation.

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.

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.

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.

A person who has NF1 makes two different kinds of reproductive cells, one which will – if it happens to be used in conception – cause a child to have NF1, and the other which will produce an unaffected child if it is the one that happens to be used. When a person with NF 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. 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
Tumours that arise from brain cells called astrocytes.

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

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

CHEMOTHERAPY
Treatment of tumour growth by chemical agents.

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

COMPUTERISED TOMOGRAPHY
(Also known as CT or CAT scan) A computerised 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 condition. An identical, paired gene need not be present.

FIBROMA
A tumour 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.

GLIOMA
A type of brain tumour.

GLIOBLASTOMA
A type of malignant brain tumour.

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 DIIFFICULTY
A problem with a specific cognitive function necessary for learning in spite of average or above average intelligence. Learning difficulties can affect one's ability to listen, think, read, write, spell, speak and/or compute maths.

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 tumour 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 tumour caused by proliferation of Schwann cells and fibroblasts.

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

NEURONS
Electrically active cells of the nervous system responsible for controlling behaviour and body function.

OPTIC GLIOMA
Tumour 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 centre of the central nervous system, toward the surface of the body.

PIGMENTED
Having colour, in the case of café-au-lait patches a few shades darker than one's regular skin colour.

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 condition.

SARCOMA
Malignant soft tissue tumour.

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

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

VON RECKLINGHAUSEN'S DISEASE
Another name for NF1.

About Neurofibromatosis 1
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NF1 BROCHURES
- OVERVIEW OF NEUROFIBROMATOSIS TYPE 1
- A GUIDE FOR EDUCATORS
- LEARNING & COGNITIVE DIFFICULTIES
- NEUROFIBROMATOSIS TYPE 1 FOR TEENS
- THE CHILD WITH NEUROFIBROMATOSIS TYPE 1
- TALKING TO YOUR CHILD
- READERS 100 QUESTIONS ANSWERED

LEAFLETS
- NF1 REVIEW CHECKLIST FOR CHILDREN & ADULTS
- NEUROFIBROMATOSIS – A BRIEF INTRODUCTION
- SCHWANNOMATOSIS
- CONTACT FORM

CLINICAL GUIDELINES FOR MANAGING NF1
- FOR ADULTS
- FOR HEALTH PROFESSIONALS

NEUROFIBROMATOSIS TYPE 2 BROCHURES
- FOR FAMILIES
- FOR HEALTH PROFESSIONALS

HANDBOOK
- NF IRELAND HANDBOOK

Neurofibromatosis is a Little Known Genetic Condition and Can Manifest Itself in a Whole Lot of Different Ways

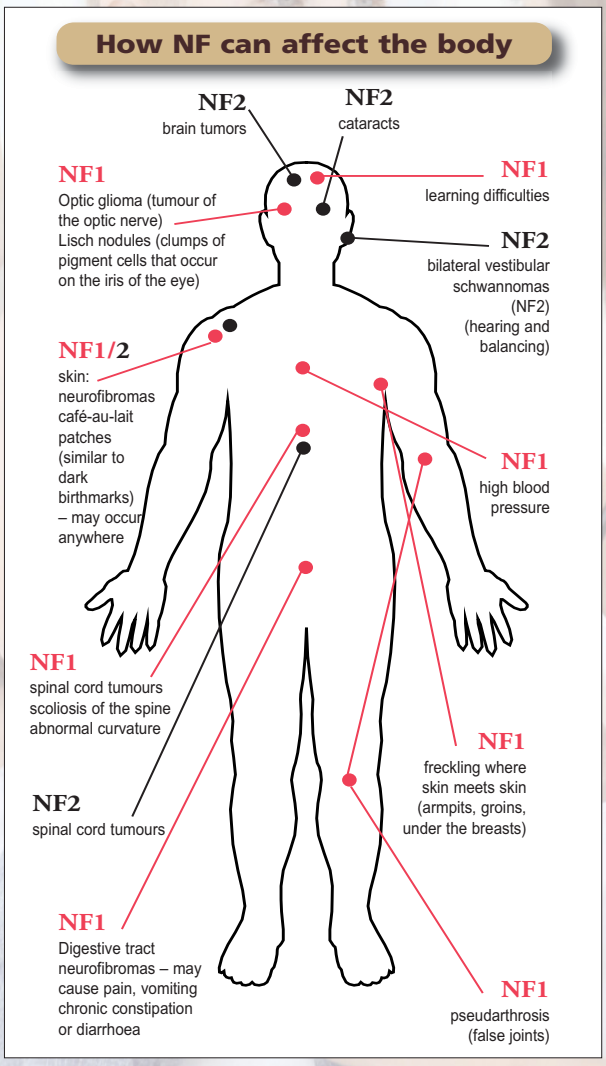
The care of persons with NF is made complex by the wide range of expression of the disorder. It is difficult to predict the specific problems that will occur in a particular individual. Diagnosis is made if an individual has two or more of the following features.

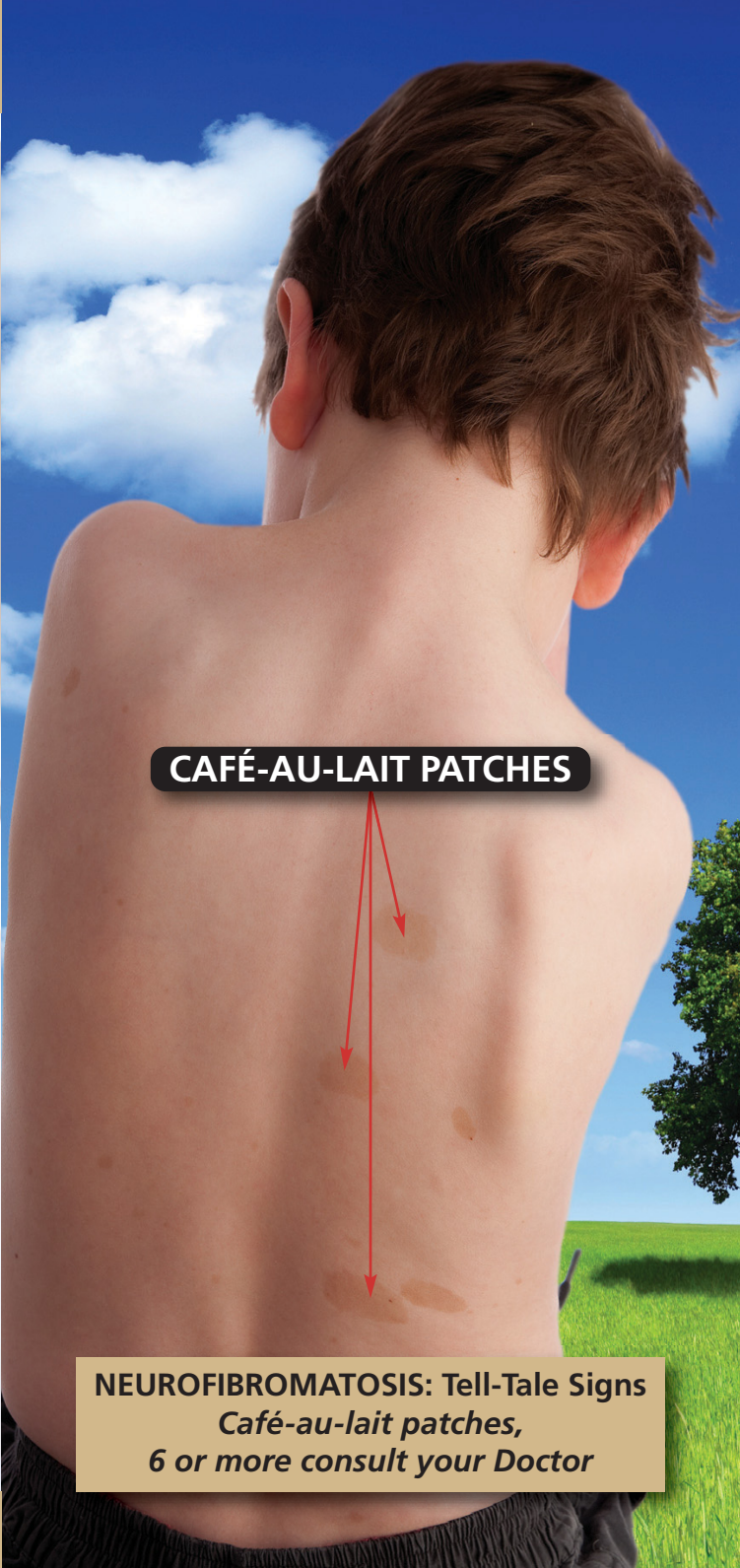
The diagnosis is based on the following clinical criteria:

1. **Six or more (café au lait)** coffee coloured patches sized 5mm or over in pubertal individuals and over 15mm in size in post pubertal individuals.
2. **Freckling** under the **arm** or in the **groin** area.
3. **Two or more Neurofibromas** of any type (growth of tumours on nerve tissue anywhere on the body) usually first seen on the skin.
4. **Plexiform Neurofibromas –** large bundle of nerves are thickened and appear as a soft tissue mass under the skin, these growths often large, can change the normal shape of the body.
5. **Optic Glioma –** Thickening of the optic nerve.
6. **Lisch Nodules –** clumps of pigment cells that occur on the iris of the eye.
7. **Orthopaedic** problems include **scoliosis** (curvature of the spine) **abnormal bone development**, such as overgrowth in long bones causing bowing and deformity that result in fractures, which fail to heal.
8. **First-degree relative with NF** e.g. parent, sibling, offspring.
9. **Learning Difficulties**. As many as 50% of children with NF have short attention span, appear clumsy and uncoordinated. Problems particularly with arithmetic and spelling are common.

Neurofibromatosis Type 2

Another rarer type of Neurofibromatosis and distinct in its clinical feature is **NF2.** The gene for **NF2** is located on chromosome 22, Features include: **Vestibular schwannomas** (tumour on hearing nerve). **Schwannoma** (type of tumour of the substance that covers nerve fibres). **Meningomas** (tumour of the covering of the brain). **Cataract**.





NEUROFIBROMATOSIS: Tell-Tale Signs
Café-au-lait patches,
6 or more consult your Doctor

Neuro
fibroma
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