What is Neurofibromatosis (NF)?

There are three different types of neurofibromatosis: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. The common features of each condition are listed below:

**NF1**
- Brown spots (café au lait spots) on the skin
- Freckling in the armpits or groin
- Tumors that grow along nerves, sometimes associated with overgrowth of part of the body (plexiform neurofibromas)
- Bumps on or under the skin (cutaneous neurofibromas)
- Bone problems, including curvature of a bone (pseudarthrosis of a long bone, scoliosis of the spine), bowing of the leg (tibial dysplasia), or deformity of the bones around the eye (orbital dysplasia)
- Eye abnormalities including Lisch nodules (tan bumps on the iris) or abnormalities of the vascular layer of the eye (choroid)
- Tumor of the optic nerve (optic nerve glioma)

**NF2**
- Tumors on the eighth cranial nerves (vestibular schwannomas), which can cause ringing in the ears, hearing loss, or dizziness
- Other tumors in or around the brain or spinal cord (meningiomas, schwannomas, or ependymomas)
- Cataracts in the eyes

**SCHWANNOMATOSIS**
- Benign tumors of the lining around the nerves (schwannomas or hybrid nerve sheath tumors) that can develop on nerves anywhere in the body
- Severe pain that can be difficult to manage
**What is Segmental NF?**

Individuals with segmental NF have only a certain area of the body that shows signs of NF. Any part of the body can be affected.

**Segmental NF1** - Individuals with segmental NF1 most commonly have the skin findings associated with NF1, such as café au lait spots, skin fold freckles, or neurofibromas, that are confined to a certain area (for example, only an arm or only a restricted area of the abdomen). Some individuals may have an isolated tumor involving the nerves without other signs of NF1. It is not known whether such isolated tumors represent true cases of segmental NF, or whether they may have other causes.

**Segmental NF2** - Individuals with segmental NF2 have some of the tumors associated with NF2 confined to a restricted region, such as only one side of the body.

**Segmental Schwannomatosis** - Individuals with segmental schwannomatosis have tumors associated with schwannomatosis confined to a restricted region, such as only one limb or a part of the spine.

**What causes segmental NF?**

All three types of neurofibromatosis are genetic conditions; NF1 is due to a pathogenic variant (previously called a mutation), which is a change in the \(NF1\) gene. Likewise, NF2 is due to a pathogenic variant in the \(NF2\) gene. The genetic causes for schwannomatosis are so far linked to two different genes, called \(SMARCB1\) and \(LZTR1\). Individuals with the classic forms of NF (non-segmental) generally carry these pathogenic variants in all cells of the body, since the variant was present from the time of conception in the fertilized embryo. In contrast, for individuals with segmental NF, the pathogenic variant is present only in some cells of the body. This happens if the gene change occurred sometime after conception, leading to the body having a mixture of cells, some with the abnormal gene and some without. This is referred to as *mosaicism*. In individuals with segmental NF, the region of the body in which cells have the pathogenic variant often shows features of NF, whereas other regions of the body (those with cells that do not have the abnormal gene) do not show features of NF. The earlier in embryo development that the pathogenic variant occurs, the more cells that will be affected.

**What are the complications of segmental NF?**

Individuals with segmental forms of NF can develop any of the related complications in the regions of the body that include cells with the pathogenic variant. These can be very mild, or, in some cases, can include more significant complications. Many individuals with segmental NF1 never develop any clinical features other than café au lait spots or freckles confined to a specific region, but others can develop neurofibromas in the affected area. In the other types of NF, an
individual may develop only a few tumors which do not lead to significant medical problems, while others may have more extensive involvement. Although it may appear that signs are limited to just one area, there is no way to be sure that there aren’t additional cells carrying the variant elsewhere in the body; therefore, additional complications of NF are possible, although less likely than in someone with non-segmental NF.

**How is segmental NF managed?**

Because segmental NF can be associated with any of the clinical features of NF1, NF2 or schwannomatosis, it is recommended that affected individuals are followed regularly by a physician familiar with the condition, ideally in an NF specialty clinic. At the present time, clinical management focuses on the specific manifestations that affect a particular affected individual and they are managed in a manner similar to classic NF. In some cases, follow-up may require a multidisciplinary care approach that includes referrals to other specialities such as orthopedics, oncology, ophthalmology, neurosurgery, or plastic surgery, as needed.

**Is there a diagnostic test for segmental NF?**

Genetic testing for all three types of neurofibromatosis is available and typically done using a blood or saliva specimen to detect the pathogenic variant responsible for the disorder. In some individuals with segmental NF, the pathogenic variant can be detected by genetic analysis of the blood; however, in others, the variant may only be present in the affected tissues (and not in the blood). Therefore, testing of the affected tissue, such as skin or tumor tissue, may be required. This is often done by taking a biopsy of the affected tissue. Genetic testing is useful to confirm a diagnosis of NF, including segmental NF. If genetic testing is done, it is important that the results are reviewed with a physician or genetic counselor who has experience in interpreting and explaining information obtained from genetic testing.

**What are the genetic implications of segmental NF?**

**Parents of an individual with segmental NF** - Typically a person with segmental NF is the first to be affected in the family; one does not expect to see signs of the disorder in either parent. This is because the NF variant occurred after conception, and was not present in the sperm or egg cell that formed that person. Therefore, it is rare for parents of a child with segmental NF to have another child with NF.

**Children of an individual with segmental NF** - A person with segmental NF may be at risk of passing along the NF gene variant to a child. This would be the case if germ cells (sperm or egg cells) carry the variant. This risk is difficult to predict, but could be as high as 50% if the germ cells carry the variant. Alternatively, the risk could be lower if only some or no germ cells are affected.
Genetic testing can sometimes reveal the gene variant in the germ cells by testing a male’s sperm. However, it is more invasive and difficult to retrieve and test eggs from a female. It is important to realize that, if a variant is passed on to the embryo, it will be present in all of the cells of the child. Therefore, the child will have “the classic form” or generalized NF, not segmental NF. This individual would be at risk for having any of the clinical features associated with NF and may have more significant manifestations than what are present in the parent. Therefore, individuals with segmental NF should be aware of the wide range of manifestations seen in non-segmental forms of NF.

Understanding this information can be complicated, and families are encouraged to meet with a genetic counselor to talk about risks to pass NF on to an offspring. Also, in some cases, prenatal testing or other reproductive options may be available.

**What is the difference between segmental NF and mosaic NF?**

Segmental NF and mosaic NF are similar in that there is a mixture of cells with and without the NF gene change. These variants occur after conception leading to a combination of normal and affected cells. Contrary to segmental NF, in mosaic NF the affected area may not be confined to a specific area of the body, but instead might appear as a less severe case of NF, or may affect various areas throughout the entire body. Mosaicism is quite common in NF2, but can occur in the other types of NF as well. Individuals with mosaic NF have the same genetic implications as those with segmental NF (see above).

**How can I learn more?**

You can learn more about all forms of neurofibromatosis, as well as search our NF Clinic Network for a doctor near you, at the Children’s Tumor Foundation website, www.ctf.org.

**About the Children’s Tumor Foundation**

Founded in 1978, the Children’s Tumor Foundation (CTF) began as the first grassroots organization solely dedicated to finding treatments for NF. Today, CTF is a highly recognized national nonprofit foundation, the leading force in the fight to end NF, and a model for other innovative research endeavors.

**Our Mission**

Drive research, expand knowledge, and advance care for the NF community.

**Our Vision**

End NF.