**WHAT ARE CHROMOSOMES, GENES AND VARIANTS?**

Chromosomes are the packages of our genetic information. Within each cell of the body are 46 chromosomes arranged in 23 pairs. One chromosome in each pair is inherited from the mother and the other from the father. The pairs are numbered by size. The number 1 chromosome pair is the largest and the number 22 is the smallest. The last pair of chromosomes (sex chromosomes) help to determine whether an individual is a male or a female. Genes are small areas along the chromosomes, and are the body’s blueprints or instructions. We have approximately 20,000 genes that control how we grow and develop and what we look like. Each gene can be thought of as a sentence made up of four letters (A, T, C and G). Pathogenic variants (previously called mutations), are changes in a gene’s letters that disrupt a gene’s function. There are several different types of changes including translocations or inversions (rearranging the letters of the sentence), deletions (taking letters out), duplications (adding extra letters in), or substitutions (changing a letter or word in the sentence).

**WHAT IS THE GENE INVOLVED IN NF1?**

Neurofibromatosis type 1 (NF1) is a genetic condition caused by changes in the NF1 gene on chromosome 17. Individuals with NF1 have a change in one of their two NF1 genes. This gene is an important gene in regulating cell growth and development. A few types of genetic variants are present in many people with NF1, but a vast majority are unique to a specific family.

**WHAT IS AN NF1 MICRODELETION?**

When the entire NF1 gene is missing, it is referred to as NF1 gene deletion or NF1 microdeletion. Approximately 5% of individuals with a diagnosis of NF1 have a deletion that includes the entire NF1 gene. Other than the NF1 gene, there are usually other nearby genes that are also missing.

**WHAT DOES IT MEAN TO HAVE AN NF1 MICRODELETION?**

In addition to the NF1 gene, individuals with NF1 microdeletion typically have other genes in the region of chromosome 17 deleted. There are often more than ten other genes missing. These genes are important for cognitive functioning and body development, and also have other important purposes such as stopping growth of tumors. The NF1 microdeletion is often, but not always, characterized by a more severe presentation than is observed in other individuals with NF1. The loss of several missing genes is thought to contribute to the more significant findings. Similar to NF1 in general, NF1 microdeletion is variable, affecting each...
individual differently and therefore not all individuals will develop all features or have similar complications.

Individuals with the NF1 microdeletion often have earlier onset and higher number of neurofibromas. These may be externally visible, or internal. There is also an increased risk of transformation of plexiform neurofibromas into a malignant/cancerous form or a tumor. The specific risks of cancer in NF1 microdeletion are not well defined, but the increased risk is supported in many medical reports and may be as high as 25% (compared to 8-13% in individuals having other types of gene variants).

More individuals with NF1 microdeletion have heart defects than in the general NF1 population. These types of heart defects vary and may involve a narrowing or dysfunction of a valve (pulmonic stenosis or mitral valve prolapse), narrowing of a blood vessel (aortic stenosis), a hole between the chambers of the heart (atrial septal defect or ventricular septal defect) or a thickened heart muscle making it difficult for the heart to pump blood (hypertrophic cardiomyopathy).

Bone findings such as scoliosis may be more common in NF1 microdeletion patients.

In addition, there is an increased frequency of connective tissue findings such as flexible joints (joint hypermobility) and decreased muscle tone (hypotonia). This may lead to deficiencies with skills involving the joints such as walking, writing, etc. and may cause joint fatigue and discomfort.

Many individuals with NF1 microdeletion have more significant learning and developmental challenges than in the general NF1 population. Intellectual disability may be present. This often requires early intervention and school accommodations.

Other observed findings are subtle to most people and do not cause medical issues, but are simply observed more often in individuals with the NF1 gene deletion. Compared to other individuals with NF1, people with NF1 microdeletion tend to be tall and have large hands and feet. Some individuals also have unique physical features including a broad neck, wide-spaced eyes (hypertelorism) and down-slanting eyes.

ARE THERE DIFFERENT TYPES OF NF1 MICRODELETIONS?

Three different sizes of NF1 microdeletions have been described and are measured in a unit of length called a megabase.

1. **Type 1 microdeletion** This is the largest of the microdeletions, and includes 1.4 megabases of DNA. There are 14 genes deleted in addition to the NF1 gene. This is the most common of the microdeletions, and is seen in 80% of those who have an NF1 microdeletion.

2. **Type 2 microdeletion** This is the next largest microdeletion, and includes 1.2 megabases of DNA and 13 deleted genes. Type 2 microdeletions may be present in only
a percentage of the body's cells. This is called mosaicism.

3. **Type 3 microdeletion** 
   This is a very rare deletion of 1.0 megabases of DNA and 9 deleted genes. They account for only about 1-4% of those with NF1 microdeletions.

Other than these three types of microdeletions, some individuals have varying sizes of microdeletions. These are often referred to as **atypical microdeletions**. Information is continually updated and there may be more information available about additional types of microdeletions in the future.

**HOW DOES A DIAGNOSIS OF NF1 MICRODELETION AFFECT MEDICAL CARE?**

There is no universal approach to caring for individuals with NF1 microdeletion so each healthcare provider may approach care slightly differently. Because of the increased risks of certain complications in NF1 microdeletion, your doctor may order scanning of different parts of the body (such as MRI, PET scan, X-rays) or a detailed look at the heart (echocardiogram). In addition, developmental assessment and ongoing monitoring may be recommended. As with the general type of NF1, routine eye exams are typically performed.

It is important to be aware of the signs or symptoms of concerns and call your NF doctor with any changes. These include a new onset of pain or loss of function, or change of an existing tumor such as a difference in texture or increase in pain, itching or size.

**HOW IS NF1 DELETION INHERITED?**

NF1 microdeletions are more likely to occur as a **de novo**, or new, gene variant rather than inherited from a parent. However, for any individual with an NF1 gene deletion, the risk of passing it on to future generations is the same as for other individuals with NF1. It follows an autosomal dominant inheritance pattern with a 50% risk to the offspring of individuals with NF1 microdeletion.

**HOW DO YOU KNOW IF YOU/YOUR CHILD HAS NF1 MICRODELETION?**

The only way to confirm whether a person has an NF1 gene deletion is by genetic testing. This usually involves a blood or saliva sample. Families should be educated about the benefits, costs, possible outcomes, and limitations prior to pursuing genetic testing. Genetic testing is expensive and often requires pre-authorization from insurance companies before the sample is obtained. Genetic testing does not always identify a genetic change to explain clinical features, and predictions cannot be made based on the result of genetic testing alone. Talk to a genetic counselor for more information about genetic testing.

**WHERE CAN YOU GET MORE INFORMATION ABOUT NF1 MICRODELETION?**

The information discussed in this resource is for general information only. Like in other NF1 mutations, there is a great deal of variability in NF1 gene deletion and predictions in any one individual are not possible.

Contact your NF provider for individualized medical care and up to date information about NF1 gene deletion. To locate an NF Clinic in your area, go to: [www.ctf.org/doctor](http://www.ctf.org/doctor).