

NF1 Mutations/Neurofibromatosis type 1

Brought to you by the National Society of Genetic Counselors, Cancer Special Interest Group

What you should know about Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is an inherited syndrome caused by mutations in the *NF1* gene. NF1 is characterized by changes in skin coloring (pigmentation) and the growth of tumors along nerves in the skin, brain, and other parts of the body. The signs and symptoms of this condition vary among individuals. Almost all people with NF1 have multiple café-aulait spots (flat, pigmented birthmarks), which are typically present from childhood. Freckles in the underarms and groin typically develop later in childhood. Lisch nodules (benign tumors of the iris) are found in almost all adults with NF1. Most individuals with NF1 develop neurofibromas, which are noncancerous (benign) tumors that are usually located on or just under the skin. These tumors may also occur in nerves near the spinal cord or along nerves elsewhere in the body. Approximately 10% of individuals with NF1 develop cancerous tumors that grow along nerves called malignant peripheral nerve sheath tumors. People with NF1 also have an increased risk of developing other cancers, outlined below.

Tumor Risk / Feature	Typical Age of Onset	Lifetime Risk
Neurofibromas	Childhood, increase with age	Nearly 100%
Plexiform neurofibromas (benign)	Childhood – adolescence	50%
Plexiform neurofibromas (cancerous)	Adolescence – adulthood	10%
Optic nerve gliomas	Childhood	15-20%
Brain gliomas	Childhood	< 10%
Leukemia	Childhood	Rare
Pheochromocytoma	Adulthood	Rare
Gastrointestinal stromal tumors (GISTS)	Adulthood	Rare
Breast cancer	Adulthood	5-fold increased risk for women < 50 y.o.

Cancer Risks and Features Associated with Neurofibromatosis Type 1

Additional features of NF1 include short stature, macrocephaly, bone changes (such as sphenoid dysplasia, tibial pseudoarthrosis, and osteoporosis), and skeletal abnormalities such as scoliosis. Hypertension is also common, and while usually "essential" (meaning the cause is unknown) can also be related to vascular changes such as renal artery stenosis or a type of adrenal neuroendocrine tumor called a pheochromocytoma. Although most people with NF1 have normal intelligence, learning disabilities and attention deficit disorder occur frequently.

Genetics and Inheritance of Neurofibromatosis Type 1

Genes are our body's instructions. They provide our body with information about how to grow and develop. When there is a mutation in a gene, it can cause the gene to no longer function correctly. Each person has two copies of every gene. One copy is inherited from their mother and the other copy is inherited from their father.

NF1 is due to a mutation in the *NF1* gene. Cancer risks associated with *NF1* are inherited in an autosomal dominant manner. This means that children, siblings and parents of individuals with an *NF1* mutation have a 50% (1 in 2) chance of having the mutation as well. Both males and females can inherit an *NF1* mutation and can pass it on to their children. Approximately 50% of the time an individual with NF1 is the first person in the family to have the condition.



Managing Cancer Risks

The American Academy of Pediatrics and the American College of Medical Genetics (ACMG) have published guidelines for surveillance of children with NF1. The ACMG has also published guidelines for adults. The following are recommended:

- Annual physical examination by a physician who is familiar with the individual and with NF1
- Annual ophthalmologic examination in early childhood; less frequent examination in older children and adults
- Regular developmental assessment by screening questionnaire (in childhood)
- Regular blood pressure monitoring
- Other studies (e.g., MRI) only as indicated on the basis of clinically apparent signs or symptoms
- Monitoring of those who have abnormalities of the central nervous system, skeletal system, or cardiovascular system by an appropriate specialist

In addition, the National Comprehensive Cancer Network (NCCN) recommend that mammography be performed annually beginning at age 30 and that breast MRI be considered between ages 30 and 50 years in women with NF1.

Genetic Counseling

In many families, the cancer history may be due to a combination of genetic and environmental factors. In addition, other genetic conditions (i.e. other gene mutations) may appear clinically similar to NF1. For this reason, a detailed review of the family history by a genetics professional is important before pursuing genetic testing. A genetic counselor can help determine which, if any, genetic tests may be helpful for a family and review the benefits, risks and limitations of genetic testing. Genetic testing is usually performed through a blood or saliva sample.

Genetic test results can be complicated and are most useful when interpreted by a genetics professional in the context of an individual's personal and family history. To locate a genetic counselor near you, please visit <u>www.nsgc.org</u> and click on the 'Find a Genetic Counselor' link.

Genetic Discrimination

The Genetic Information Nondiscrimination Act (GINA) was signed into federal law in 2008. GINA prohibits health insurers and most employers from discriminating against individuals based on genetic information (including the results of genetic tests and family history information). According to GINA, health insurance companies cannot consider genetic information to be a preexisting condition, nor can they use it to make decisions regarding coverage or rates. GINA also makes it illegal for most employers to use genetic information in making decisions about hiring, firing, promotion, or terms of employment. It is important to note that GINA does not offer protections for life insurance, disability insurance, or long-term care insurance. More information about GINA can be found by contacting a local genetic counselor or by visiting <u>www.ginahelp.org</u>.

Resources

- NF Network: <u>https://nfnetwork.org/</u>
- Children's Tumor Foundation: <u>https://www.ctf.org/</u>

References

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