

Neurofibromatosis

Posted 11-29-04

Key Points

- Neurofibromatosis type 1 (NF1) is a single-gene disorder that occurs in about one in 3000 births and usually presents in childhood.
- Clinical manifestations are variable, and include skin changes ([café au lait spots](#) and [neurofibromas](#)), neuropathies secondary to neurofibromas, optic glioma, skeletal dysplasia, and malignant tumors of neuroectodermal origin.
- NF1 is inherited as an autosomal dominant condition.
- Genetic testing is available but has limitations.

Learning Objectives

Participants will be able to:

- Understand how a clinical diagnosis of NF1 is made;
- Recognize that clinical manifestations occur over time, with sufficient findings for diagnosis usually present by reproductive age;
- Recognize the role of diagnosis in planning appropriate clinical management;
- Understand the potential uses and limitations of DNA-based testing for NF1.

Summary

NF1 is a genetic condition caused by mutations in the *NF1* gene [[GeneReview: NF1](#)]. Clinical manifestations include skin changes ([café au lait spots](#) and [neurofibromas](#)), neuropathies secondary to neurofibromas, optic glioma, skeletal dysplasia, and malignant tumors of neuroectodermal origin. Learning disabilities (from mild to severe) occur in approximately 50% of affected individuals. Café au lait spots and axillary and inguinal freckling are usually first noted in early childhood; skin neurofibromas are usually first noted in adolescence. The severity of the condition is highly variable, with manifestations ranging from a few skin lesions to major disabilities due to skin, neurologic, or other complications.

Neurofibromatosis type 2 (NF2) is a separate, distinct genetic disorder [[GeneReview: NF2](#)]. Individuals with NF2 may also have a few café au lait spots and (rarely) skin neurofibromas, but the primary complications of NF2 are acoustic neuromas and neurofibromas affecting the spinal cord. NF2 is caused by mutations in a separate gene, designated NF2, and has a much lower prevalence than NF1.

Mode of inheritance: [Autosomal dominant](#). About 50% of affected individuals represent a new, or de novo mutation, not previously present in their family.

Prevalence at birth: Approximately 1/3000

Diagnosis. Diagnosis of NF1 is made on the basis of two or more of the following clinical findings.

- Six or more [café au lait macules](#) over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
- Two or more [neurofibromas](#) of any type or one [plexiform neurofibroma](#)
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
- A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria

Genetic testing. Mutations in the *NF1* gene can be detected by several molecular methods. Most laboratories offer testing with approximately 70% sensitivity, although there is now a multi-step testing method available with an estimated 95% sensitivity [[GeneReview: NF1, Table 1](#)]. When an NF1 patient (one in whom the clinical diagnosis has been established) has a negative test result, the patient is assumed to have a mutation that is difficult to detect by current technology, because of its location or structure.

Testing has three potential uses:

- As a diagnostic test in a patient with suggestive findings
- As a means of identifying additional affected family members after the diagnosis is made in an index case
- In prenatal diagnosis

Testing strategies need to take into account the limitations in test sensitivity.

Family History Issues

About half of NF1 patients have a de novo mutation , and thus do not have a family history of NF1. The other half have a family history of one or more first-degree relatives with clinical manifestations of NF1.

Red Flags



Clinical findings suggestive of NF1 include:

- Café au lait macules
- Neurofibromas
- Freckling in the axillary or inguinal regions
- Optic glioma
- Lisch nodules (iris hamartomas); identification of Lisch nodules generally requires a slit lamp examination
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis

Case 40. Does this child have neurofibromatosis?

At 12 months, Joe D is noted to have mild developmental delay. He was born after an uneventful pregnancy and vaginal delivery and has had no other health problems. His physical exam reveals eight café au lait spots of over 5 mm in diameter, but no other abnormalities. He is the youngest child of Mary and Roger D; their two older children, Eleanor (age 10) and Robert (age 4) are both healthy and without history of developmental problems or physical anomalies. Because of Joe's café au lait spots, the question of neurofibromatosis type 1 (NF1) has been raised.

Clinical Care Issues

A child with NF1 is at risk of developing all complications of the disorder; other than skin findings, however, most complications occur in only a

minority of patients [[GeneReview: NF1](#)]. A diagnosis of NF1 would lead to specific screening recommendations as outlined in [Interventions](#) below.

An NF1 diagnosis in the family would also raise the possibility that other family members are affected, and that the parents might be at risk of having additional children affected with NF1.

However, café au lait spots can occur in the absence of NF1, as an isolated and benign skin finding.

Risk Assessment

Diagnosis of NF is made on the basis of two or more of the following findings:

- Six or more [café au lait macules](#) over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
- Two or more [neurofibromas](#) of any type or one [plexiform neurofibroma](#)
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas), identified by slit lamp examination
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
- A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria

Joe has one finding (six or more café au lait spots over 5 mm in diameter), so one additional finding would confirm the diagnosis. However, some findings of NF1 (e.g., neurofibromas; Lisch nodules) typically do not appear until puberty or adulthood. Joe should be carefully examined, and his medical history reviewed, to determine whether other diagnostic findings are present.

In addition to an examination of Joe, most geneticists would recommend a careful evaluation of both parents and a directed family history. If either parent had clinical findings diagnostic of NF1, the diagnosis could be made in Joe as well. Findings of NF1 can be subtle, so a diagnosis of NF1 can be missed without a complete skin examination. Use of the Wood's lamp to detect pigment change is often helpful.

Genetic Counseling and Testing

If Joe is diagnosed to have NF1, genetic counseling would focus on two issues:

- **Ongoing monitoring of Joe for complications of NF1.** See specific screening recommendations as outlined in [Interventions](#) below. Because Joe has been noted to have a mild developmental delay, careful monitoring of his developmental progress is warranted, with appropriate interventions as indicated. (This follow-up is indicated irrespective of a diagnosis of NF1).
- **Risk of NF1 in other family members**
 - If careful evaluation reveals findings of NF1 in one of Joe's parents, this diagnosis would confirm inheritance of NF1. Other children in the family would be at 50% risk of inheriting NF1, and should be carefully examined. In future pregnancies, there would also be a 50% risk of inheriting NF1.
 - If the parents' examinations reveal no evidence of NF1, Joe's condition would most likely represent a de novo mutation and the recurrence risk to his parents would be very low (in some instances the NF1 mutation has arisen in gonadal tissue [testes or ovary] of the parent. This occurrence is called gonadal mosaicism and is rare). Joe's children would be at 50% risk of inheriting NF1 from him.

If examination of Joe and his parents does not provide diagnostic information to confirm NF1, genetic testing could be considered. A positive genetic test result would confirm the diagnosis, **but a negative test result would not rule it out. Thus, a negative test would not alter recommendations for following Joe clinically.**

Careful clinical follow-up provides an alternative to genetic testing in this situation. In the absence of a positive family history, few children with NF1 have full diagnostic clinical findings at age one, but most do by age eight.

Genetic testing. Genetic testing has three potential uses:

- As a diagnostic test in a symptomatic patient
- As a means of identifying additional affected family members after the

diagnosis is made in an index case

- In prenatal diagnosis

Mutations in the *NF1* gene can be detected by several molecular methods. Most laboratories offer testing with approximately 70% sensitivity, although there is now also a multi-step testing method available with an estimated 95% sensitivity [[GeneReview: NF1, Table 1](#)].

- **Diagnosis.** If an individual has clinical findings that suggest NF1 but are insufficient to confirm the diagnosis (as in Joe's case), genetic testing may sometimes confirm NF1. However, this approach may be problematic.

If the test identifies a definitive disease-causing mutation, it confirms NF1, **but a negative test does not rule out the diagnosis**. Based on clinical findings, a high likelihood of NF1 may remain, even if the test result is negative. Because molecular testing is generally expensive, and insurance coverage variable, testing in this situation may not be cost-effective. The test also sometimes identifies a "gene variant of unknown clinical significance" — that is, a mutation not previously described that could represent either normal DNA variation or a disease-causing mutation. This result is confusing and, like a negative result, adds no additional information concerning diagnosis. Over time, some of these variants may become known as either disease-causing or normal variants.

Given the uncertainties and expense of genetic testing, many experts recommend the alternative of clinical follow-up in a child with suspected NF1; over time other clinical findings will emerge if the child is affected, making a definitive diagnosis possible.

- **Testing of an at-risk family member.** If an *NF1* mutation is identified in a patient with the condition, genetic testing can be used to determine whether other family members have inherited the mutation. This testing process can be helpful in assessing the status of a relative with limited clinical findings that are suggestive of, but not diagnostic for, NF1. However, the severity of clinical manifestations of NF1 is highly variable, and a positive genetic test does not provide prognostic information concerning age of onset or disease severity.
- **Prenatal diagnosis.** Prenatal diagnosis of NF1 by direct DNA testing is available for pregnancies in which one of the parents is affected and a

specific mutation has been identified in the family. Prenatal diagnosis can also be done by linkage analysis if the family includes enough unequivocally affected and/or unaffected members to establish linkage. DNA can be extracted from fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or amniocentesis at 16-18 weeks' gestation. [[GeneReview: NF1, Prenatal Testing](#)].

Interventions


Follow-up of patients with NF1 includes the following:

- Annual physical examination by a physician who is familiar with the patient and (ideally) with the disease
- Annual ophthalmological examination in childhood, to monitor for the potential complications of NF1. Ophthalmological examination as indicated by clinical features or usual screening recommendations in adults
- Regular developmental assessment
- Regular blood pressure monitoring in both children and adults, because renovascular hypertension may occur as a rare complication. The prevalence of essential hypertension may be increased in adults as well.
- Other studies only as indicated on the basis of clinically apparent signs or symptoms

Ethical/Legal/Social/Cultural Issues

Stigma. For many patients with NF1, stigma is an unfortunate consequence of the diagnosis. Most NF1 patients have visible skin neurofibromas; these lesions usually increase in number over time. Plexiform neurofibromas can be large and disfiguring. Facial or other visible skin changes can result in unwanted attention. Some NF1 patients are very reluctant to participate in activities such as swimming that would require them to expose most of their skin to public view. Adolescents with many neurofibromas are likely to view themselves as socially impaired. Because many patients with NF1 look 'different' they are sometimes treated as though they are cognitively impaired — though mental retardation is a complication in fewer than 10% of patients — or assumed to have other disabilities. Patients with NF1 have also been denied jobs involving exposure to the public, because of their noticeable skin abnormalities. These experiences represent an important burden of NF1; for many patients, these social consequences are more significant than the clinical effects of the disorder.

Resources

- **National Library of Medicine Genetics Home Reference**
[Neurofibromatosis type 1](#)
- **GeneTests Online Medical Genetics Information Resource**
- ***GeneReviews*, GeneTests Online Medical Genetics Information Resource**
- **GeneTests Resources for NF1** 

References

American Academy of Pediatrics Committee on Genetics (1995) Health supervision for children with neurofibromatosis. *Pediatrics* 96:368-72 [[Medline](#)]

Eichenfield LF, Levy ML, Paller AS, Riccardi VM (1997) Guidelines of care for neurofibromatosis type 1. American Academy of Dermatology Guidelines/Outcomes Committee. *J Am Acad Dermatol* 37:625-30 [[Medline](#)]

Friedman JM and Birch PH (1007) Type 1 neurofibromatosis: a descriptive analysis of the disorder in 1728 patients. *Am J Med Genet* 70:138-43 [[Medline](#)]

Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D (1997) The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 278:51-7 [[Medline](#)]