Neurofibromatosis Type 1 Revisited
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Neurofibromatosis Type 1 Revisited

Virginia C. Williams, BS; John Lucas, BS; Michael A. Babcock, BS; David H. Gutmann, MD, PhD; Bruce Korf, MD, PhD; Bernard L. Maria, MD, MBA

ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant condition with a worldwide incidence of ~1 per 2500 to 3000 individuals. Caused by a germ-line-inactivating mutation in the NF1 gene on chromosome 17, the disease is associated with increased morbidity and mortality. In the past several years, significant progress has been made in standardizing management of the major clinical features of neurofibromatosis type 1. Moreover, improved understanding of how the neurofibromatosis type 1 protein, neurofibromin, regulates cell growth recently provided insight into the pathogenesis of the disease and has led to the development of new therapies. In this review, we describe the clinical manifestations, recent molecular and genetic findings, and current and developing therapies for managing clinical problems associated with neurofibromatosis type 1. Pediatrics 2009;123:124–133

CLINICAL FEATURES

After diagnosis, patients with NF1 should undergo a series of evaluations so that physicians can assess disease severity and monitor progression (see Table 2). With assistance from a child neurologist, referrals can be made for cardiovascular, skeletal, neuroophthalmologic, and neuropsychological screenings. The results of these assessments will guide management decisions that must be considered in the context of the individual patient. For this reason, best practices have not yet fully evolved. Continued inquiry into the pathogenesis of the many clinical features associated with NF1 will further the establishment of accepted management practices. The Children’s Tumor Foundation (CTF) is a useful resource for patients diagnosed with NF1. This organization provides information not only to patients and families affected by NF1 but also to NF1 research specialists. Its aim is to define a management algorithm to ensure optimal care for patients with NF1 who are affected by the many symptoms associated with the disease.

Café-au-lait Macules

Although café-au-lait macules are sometimes present at birth, they usually develop between the early months of life and ~2 years of age. Their early appearance is often the first feature of NF1 (see Fig 1). The number of macules per individual may be as high as several dozen, but neither their quantity nor their size has been linked to disease severity. The size and number of these macules is important in the diagnosis of NF1: the presence of ≥6 café-au-lait macules >0.5 cm in diameter before puberty or 1.5 cm in diameter after puberty fulfills 1 diagnostic criterion (see Fig 2). Café-au-lait macules show no tendency toward malignant transformation. For patients disturbed by the cosmetic appearance of these macules, advice can given be on how to camouflage the skin; however, there is no evidence supporting the use of laser therapy for their removal.

Key Words: neurofibromatosis type 1, neurofibroma, malignant peripheral nerve sheath tumor, neurofibromin

Abbreviations

NF1—neurofibromatosis type 1
OPG—optic pathway glioma
CTF—Children’s Tumor Foundation
MPNST—malignant peripheral nerve sheath tumor
FDG-PET—fluorodeoxyglucose positron emission tomography
ADHD—attention-deficit/hyperactivity disorder
UBO—unidentified bright object
mTOR—mammalian target of rapamycin
NF—neurofibromatosis

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TABLE 1 National Institutes of Health Diagnostic Criteria for NF1

| Two or more of the following clinical features signify the presence of NF1 in a patient |
| Six or more café-au-lait macules (>0.5 cm at largest diameter in prepubertal individuals or >1.5 cm in individuals past puberty) |
| Axillary freckling or freckling in inguinal regions |
| Two or more neurofibromas of any type or ≥1 plexiform neurofibroma |
| Two or more Lisch nodules (iris hamartomas) |
| A distinctive osseous lesion |
| A first-degree relative with NF1 diagnosed by using the above-listed criteria |

Data are from the National Institutes of Health.1

**Neurocognitive deficits**
Obtain developmental and neuropsychological assessments before beginning school

**Skeletal dysplasia**
Clinicians should be aware of a range of issues including scoliosis, congenital bone defects leading to pseudoarthroses, sphenoïd wing dysplasia, macrocephaly, and short stature; closely follow linear growth curves and skeletal parameters

**Cardiovascular abnormalities**
Annual blood pressure screening and heart examination

**Adapted from refs 7–9, 11, 16, 22, 24, 25, 27, 28, 35, 36, 42, and 45.**

### Table 2 Evaluation and Management for Features of NF1

<table>
<thead>
<tr>
<th>NF1 Diagnostic Feature</th>
<th>Evaluation</th>
<th>Management</th>
</tr>
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<tbody>
<tr>
<td>Café-au-lait macules</td>
<td>Early diagnostic feature (0–2 years of age); hyperpigmented macules, typically ranging from 1.0 to 3.0 cm in diameter</td>
<td>No evidence supporting laser therapy for removal; cosmetic advice can be given on skin camouflaging</td>
</tr>
<tr>
<td>Skinfold freckling</td>
<td>Diagnostic feature (3–5 y of age): freckling in axillary and inguinal areas most common, with freckling sometimes extending beyond these regions. Freckles are typically small (&lt;93 mm in diameter). Additional sites for freckling include the area above the eyelids, around the neck, and under the breasts. In some affected individuals, freckling may extend beyond these regions.3</td>
<td>No follow-up necessary</td>
</tr>
<tr>
<td>Lisch nodules</td>
<td>Diagnostic feature: pigmented iris hamartomas on slit-lamp examination</td>
<td>Refer to ophthalmologist</td>
</tr>
<tr>
<td>Cutaneous neurofibroma</td>
<td>Diagnostic feature (childhood or early adolescence): benign peripheral nerve sheath tumors; may present with localized pruritus</td>
<td>Surgical removal for lesions causing pain or cosmetic disfigurement depending on size and location; carbon-dioxide laser therapy may be helpful for removing small superficial lesions; after removal of lesions, patients are at risk for recurrence, hypertrophic scarring, and neurologic deficit</td>
</tr>
<tr>
<td>Plexiform neurofibroma</td>
<td>Diagnostic feature: peripheral nerve sheath tumors involving multiple nerve fascicles; may extend into surrounding structures with varying growth rates and patterns; deep lesions may only be detected on radiologic examination</td>
<td>Regular follow-up with special attention given to signs and symptoms of transformation to MPNST; FDG-PET may distinguish benign plexiform neurofibromas from MPNSTs; surgical excision for symptomatic tumors; radiotherapy is contraindicated</td>
</tr>
<tr>
<td>MPNSTs</td>
<td>Often arise from preexisting plexiform neurofibromas; consult an NF1 specialist for persistent pain for &gt;1 mo or pain that disrupts sleep, new or unexplained neurologic deficit (alteration in neurofibroma texture from soft to hard), or rapid increase in neurofibroma size</td>
<td>Complete resection with tumor-free margins is ideal; however, tumor location dictates surgery; adjuvant radiotherapy is useful for partially resectable, aggressive, or &gt;5-cm tumors; benefit of chemotherapy as second adjuvant remains controversial; regular (every 3–4 months) follow-up for metastases (ie, chest computer tomography scans, bone pain follow-up)</td>
</tr>
<tr>
<td>Skeletal dysplasia</td>
<td>Clinicians should be aware of a range of issues including scoliosis, congenital bone defects leading to pseudoarthroses, sphenoïd wing dysplasia, macrocephaly, and short stature; closely follow linear growth curves and skeletal parameters</td>
<td>Scoliosis may require use of a brace, corrective surgery, or spinal fusion depending on severity; pseudoarthroses typically respond poorly to surgery and amputation may be necessary, although early bisphosphonate therapy maybe beneficial</td>
</tr>
<tr>
<td>OPG</td>
<td>MRI for visual or endocrinologic signs and symptoms</td>
<td>MRI at 3- to 12-mo intervals with regular neuroophthalmologic and endocrinologic evaluations; standard chemotherapy includes carboplatin and vincristine; radiotherapy is contraindicated</td>
</tr>
<tr>
<td>Neurocognitive deficits</td>
<td>Obtain developmental and neuropsychological assessments before beginning school</td>
<td>Develop an individual education plan (IEP); obtain yearly assessments and follow with a special educational needs coordinator</td>
</tr>
<tr>
<td>Cardiovascular abnormalities</td>
<td>Annual blood pressure screening and heart examination</td>
<td>Renal arteriography and 24-h urinary excretion of total plus fractionated catecholamines and metabolites for high blood pressure; refer patients with murmurs to cardiology</td>
</tr>
</tbody>
</table>

**Lisch Nodules**
Lisch nodules are melanocytic iris hamartomas that do not affect vision. They typically present in patients between 5 and 10 years of age and are most reliably identified on slit-lamp examination by an experienced ophthalmologist.10 Lisch nodules are pathognomonic of NF1 and should be distinguished from iris nevi observed in the general population.8

**Neurofibromas**
Neurofibromas are benign Schwann cell tumors that arise from the fibrous tissue surrounding peripheral nerve sheaths and are composed of Schwann cells, fibroblasts, perineural cells, and mast cells. NF1-deficient Schwann cells are considered to be the primary source of neurofibromas. They typically respond poorly to surgery and amputation may be necessary, although early bisphosphonate therapy may be beneficial.
Localized pruritus is sometimes reported by patients with NF1-associated neurofibromas, perhaps resulting from mast-cell activation and subsequent degranulation. The use of mast-cell stabilizers for relief from itching remains unclear, and controversy exists as to whether antihistamines are beneficial. Ferner et al reported that antihistamines generally do not reduce itching, whereas the CTF has indicated that localized pruritus can be treated with antihistamines. Emollients are recommended, and to prevent irritation it is recommended that extreme heat be avoided.

Despite the lack of a standard classification system, neurofibromas may be subdivided according to their appearance and location into 4 groups: focal or diffuse cutaneous; subcutaneous; nodular or diffuse plexiform; or spinal. The location and number of neurofibromas is unpredictable, varying among individuals even within a family. Focal cutaneous or dermal neurofibromas typically appear in late childhood or early adolescence, rarely cause pain or neurologic deficits, and do not transform into malignant tumors (see Fig 2). Cutaneous neurofibromas causing patient discomfort or extreme cosmetic disfigurement can be removed by a surgeon with expertise in their removal. Patients with NF1 should be advised of the risk of recurrence and hypertrophic scarring after surgical excision. For removal of neurofibromas occurring on the head and neck, a plastic surgery consult is advised. Carbon-dioxide laser therapy may be helpful for the removal of small lesions, but no proven

![Figure 1](image1.png)

**FIGURE 1**
NF1 consists of, but is not limited to, the clinical features listed, which are arranged according to their corresponding age of onset. Data are from the National Institutes of Health.

![Figure 2](image2.png)

**FIGURE 2**
NF1 clinical features: A, Axillary freckling; B, discrete dermal neurofibromas; C, café-au-lait macules; D, OPG; E, skeletal dysplasia. (All photographs are courtesy of co-author Dr Korf.)
benefit exists to support the use of this treatment over surgical removal of larger and more invasive neurofibromas.9

The removal of subcutaneous neurofibromas is more likely to result in neurologic deficit and should be overseen by a skilled soft tissue tumor surgeon.9 These subcutaneous lesions can be noted on palpation of the skin and may present with tenderness or tingling distributed along the affected nerve. Spinal neurofibromas may occur at single or multiple nerve roots and can be associated with both sensory and motor neurologic deficits.14

**Plexiform Neurofibromas**

Plexiform neurofibromas differ from focal cutaneous neurofibromas in that they arise from multiple nerve fascicles and tend to grow along the length of a nerve. These lesions typically present at birth but may continue to appear through late adolescence and early adulthood. They occur in ~30% of patients with NF1, although this does not account for internal lesions that remain undetected in the absence of radiologic evaluation.15 Although their growth rates are considered unpredictable, growth patterns have been recognized, with periods of rapid growth common during adolescence, followed by periods of apparent inactivity.9 Plexiform neurofibromas extend into surrounding structures including skin, fascia, muscle, bone, and internal organs and, thus, may cause pain. Categorized according to growth into 3 categories (superficial, displacing, and invasive), these tumors can be measured volumetrically with MRI. Displacing and invasive plexiform neurofibromas pose the largest threat because of their ability to transform into malignant peripheral nerve sheath tumors (MPNSTs).

MRI can now be used to characterize the superficial or invasive nature of plexiform neurofibromas. In clinical trials, volumetric measurement allows practitioners to determine if new therapeutic agents are halting the growth of lesions that are invasive or inoperable. The results of such studies will prove beneficial given the current standard of care for plexiform neurofibromas. Symptomatic plexiform neurofibromas can be treated surgically, but their diffuse infiltrative nature often precludes complete resection. There have been reports that resection of small and medium superficial plexiform neurofibromas occurring in childhood may prevent complications associated with these lesions later in life.15 Recent volumetric MRI analyses performed by Dombi et al16 confirmed that plexiform neurofibromas grow more quickly in young children. Thus, it may prove beneficial to remove superficial plexiform neurofibromas at an earlier age. Friedrich et al17 reported that early surgical intervention was tolerated well by 7 children with NF1, and during a 3-year clinical and radiologic follow-up there was no evidence of tumor regrowth. However, the risk of neurologic deficit associated with removal of these tumors still guides the current clinical practice of monitoring for signs of MPNST transformation, and additional research is necessary before new recommendations are warranted.

**Malignant Peripheral Nerve Sheath Tumors**

Patients with NF1 harbor a 10% lifetime risk of developing a highly aggressive spindle cell sarcoma termed MPNST.18 Typically MPNSTs arise from preexisting plexiform neurofibromas; however, King et al19 documented that 36% of 30 patients from a cohort of 1475 developed MPNSTs without a previous history of plexiform neurofibromas. Patients with MPNSTs commonly present with pain and neurologic deficits. Recent experience with fluorodeoxylucose positron emission tomography (FDG-PET) imaging has proven it to be a sensitive and specific test to differentiate benign plexiform neurofibromas from MPNSTs.20,21 In addition, although tumor grade and histopathology correlate poorly with prognosis, FDG-PET measurements of MPNSTs are significantly related to survival.22 MPNSTs are frequently resistant to therapy and frequently metastasize and have a poor overall prognosis. Standard of care for MPNSTs typically consists of wide surgical excision with postoperative radiotherapy. Although this regimen does not improve long-term survival rates, it does delay the time to local recurrence.23 The use of chemotherapy as a second adjuvant option in the treatment of MPNSTs remains controversial.24

**Neurofibromatous Neuropathy**

It is important to distinguish the sensorimotor deficits occurring as a result of multiple spinal neurofibromas from those of neurofibromatous neuropathy, which affects 1.3% of patients with NF1.25 Although a rare manifestation of NF1, this distal, symmetrical neuropathy is characterized clinically by the early development of large numbers of cutaneous and subcutaneous neurofibromas. In contrast to the neuropathy associated with neurofibromatosis type 2, the neurofibromatous neuropathy associated with NF1 has been documented as primarily a sensory deficit with no evidence of clinical or neurophysiologic deterioration. It is recommended that neurophysiologic studies be performed on patients with evidence of peripheral neuropathy. All possible causes of peripheral neuropathy must be ruled out before diagnosing neurofibromatous neuropathy in a patient with NF1.25

**Skeletal Dysplasia**

Osseous lesions in patients with NF1 include short stature, dystrophic scoliosis, tibial pseudoarthrosis, and sphenoid wing dysplasia. As many as 14% of patients with NF1 are 2 SDs below the mean height for their age.10 Scoliosis affects 10% to 26% of patients with NF1, and children should undergo yearly spinal examination.26 A brace can be used to prevent progression of the disease in mild cases. For more severe cases, corrective surgery may be necessary. Dystrophic scoliosis, the most severe form, is marked by early onset, rapid progression, and the need for early spinal fusion.27 This severe form occurs in fewer than 10% of people with NF1 and scoliosis but can cause spinal cord compression.28,29 Neurologic complications resulting from spinal cord compression include, but are not limited to, limb paralysis and
myelopathic symptoms such as bowel and bladder dysfunc-
tion.\textsuperscript{30}

Another distinctive osteopathy of NF1 is sphenoid
wing dysplasia, which typically presents as a unilateral
defect affecting the orbital plate and frontal bone.\textsuperscript{31}
Sphenoid wing dysplasia is most often detected in
asymptomatic individuals on careful physical examina-
tion followed by radiographic studies. Some patients
with sphenoid wing dysplasia have pulsating enophthal-
mos with cerebral herniation into the orbit.\textsuperscript{10} Long-bone
dysplasia, such as congenital tibial dysplasia with
pseudarthrosis, is also seen with NF1 (see Fig 2). Iden-
tified in infancy, congenital tibial dysplasia presents as
anterolateral bowing of a leg. The bone displays cortical
thinning, which predisposes affected individuals to
pathologic fractures on weight-bearing within the first
year of life.\textsuperscript{32} Repeated fracture and failure to heal can
result in a pseudoarthrosis (false joint).

Pseudoarthroses typically respond poorly to surgery,
in part because of an attenuated healing response sec-
ondary to localized osteopenia, and some patients re-
quire limb amputation. Early therapy with bisphospho-
nates has yielded positive results.\textsuperscript{26} In addition to
localized osteopenia, patients with NF1 exhibit an over-
al decrease in bone mineral density. Peak bone mass is
the most important determinant for adult bone health,
and this generalized osteopenia may predispose individ-
uals to osteoporosis and fracture later in life.\textsuperscript{26,33} Starting
children on exercise regimens aimed at improving bone
acquisition may be warranted.\textsuperscript{31}

**Optic Pathway Gliomas**

OPGs, typically low-grade pilocytic astrocytomas, are the
most common type of intracranial malignancy in pa-
tients with NF1.\textsuperscript{34} Compared with sporadic OPGs, NF1-
associated OPGs are located most often along the optic
nerve (see Fig 2), whereas sporadic OPGs are more fre-
cently chiasmal or postchiasmal.\textsuperscript{35} OPGs are found in
\(\sim 15\%\) of children with NF1 and usually arise in the first
decade of life. Most NF1-associated OPGs have a benign
course,\textsuperscript{36} and only one third to one half of patients with
NF1 with an OPG develop visual symptoms.\textsuperscript{37} Symptom-
atic OPGs can cause proptosis, visual loss, and precocious
puberty resulting from hypothalamic encroachment.\textsuperscript{10} When compared with symptoms associated with spo-
radic OPGs, the symptoms of NF1-associated OPGs more
commonly manifest as precocious puberty, whereas
signs of intracranial pressure are less common. Precoc-
ious puberty is seen in 12\% to 40\% of children with
chiasmal tumors, and clinicians should keep accurate
growth charts, because increased linear growth is often
the first sign.\textsuperscript{33} Children often do not complain of vision
loss, and an annual ophthalmologic examination by an
experienced ophthalmologist is a crucial part of manage-
ment, especially for children <6 years of age.\textsuperscript{34} These
children are at greatest risk for developing OPGs, and
children >6 years of age who have not been diagnosed
with OPG can be followed by routine ophthalmologic
examination less frequently. Baseline MRI to detect
asymptomatic OPGs is not warranted.\textsuperscript{35} Yearly neu-
roophthalmologic observation is the accepted manage-
ment protocol for lesions that present asymptotically.

Progressive disease is less common than in sporadic
OPGs, and initiation of treatment should only be con-
sidered for patients with ocular or endocrinologic
symptoms and signs.\textsuperscript{35} The current first-line therapy
for aggressive NF1-associated OPG includes a baseline
MRI for characterization of growth rate and chemono-
therapy with the combination of carboplatin and vin-
 christine.\textsuperscript{36} Radiation therapy, although historically ef-
fective in controlling OPG growth after progression, is
discouraged for children with NF1 because of the in-
creased risk of radiation-induced second malignancies
and vascular stenosis.\textsuperscript{39}

Gliomas also occur in the brainstem, diencephalon,
and cerebellum in up to 3.5\% of patients with NF1.\textsuperscript{9,40}
Compared with brainstem gliomas in the general popu-
lation, lesions in the NF1 population frequently present
with a more indolent course and may regress spontane-
ously. They can manifest occasionally as high-grade as-
 trocytomas, and for this reason we recommend MRI
follow-up studies to characterize growth patterns for
aggressive nonoptic glial tumors and tumor-like masses
in patients with NF1.\textsuperscript{9,40} Surgical treatment is not recom-
mended unless the lesion exhibits rapid growth or the
patient’s clinical state deteriorates. As with OPGs, tumor
location dictates an individualized surgical approach
when necessary.

**Cardiovascular Abnormalities**

Cardiovascular manifestations of NF1 include congenital
heart disease, vasculopathy, and hypertension. Coro-
nary heart disease occurs at a higher-than-expected fre-
cuency compared with that in the general population,
with pulmonary artery stenosis representing 25\% of
these malformations.\textsuperscript{31} At diagnosis, children should un-
dergo a thorough cardiac examination with auscultation
and blood pressure measurement. Any murmur should
be evaluated by a cardiologist and examined by echo-
cardiography.\textsuperscript{41}

NF1 vasculopathy includes stenoses, aneurysms, and
arteriovenous malformations and is the second leading
cause of death in this population.\textsuperscript{42} Vasculopathy usually
attacks the arterial system, and renal artery stenosis is
the most common manifestation, occurring in at least
1\% of patients with NF1. Renal arteriography is indi-
cated for any patient with hypertension and NF1.\textsuperscript{41} Ce-
rebrovascular disease, especially in younger patients,
usually results from stenoses or occlusions and is diag-
nosed most often in children with a clinical picture of
weakness, involuntary movements, headaches, or sei-
zures secondary to ischemia. It is important to note that
any patient who presents with sudden-onset neurologic
deficit should be evaluated for cerebrovascular disease.\textsuperscript{41}
Histologically, vascular lesions show fibromuscular dys-
plasia with intimal thickening and proliferation of
Schwann cells without atherosclerosis.\textsuperscript{31,42}

Hypertension is significantly associated with mortality
in the NF1 population, and blood pressure should be
checked annually with a target of <140/90 mm Hg.\textsuperscript{9,41}
Renal artery stenosis is the most common cause, espe-
cially in the pediatric population. However, coarctation of the aorta and pheochromocytoma represent important differentials. Pheochromocytomas occur at a frequency of 0.1% to 5.7%. Most (90%) are benign and typically occur in the adult population.\(^4\) However, because of the risk of malignancy, any patient with hypertension, especially paroxysmal hypertension or with symptoms of catecholamine excess such as headache, sweating, palpitations, or anxiety, should undergo measurement of 24-hour urinary excretion of total plus fractionated catecholamines and their metabolites.\(^9,4\) Only after the presence of a pheochromocytoma has been biochemically confirmed should MRI be used to localize the tumor.\(^4\) There is an association between pheochromocytomas and carcinoid tumors, usually of the duodenum, and the presence of one should prompt the clinician to seek the other.\(^9,4\)

### Neurocognitive Deficits

Neurocognitive deficits are the most frequently reported complication of NF1. Children with NF1 should undergo neuropsychological assessments as soon as possible for educational planning.\(^4\) Learning deficits in children with NF1 may include visuospatial and visuomotor deficits and language disorders. In addition to the specific nonverbal and verbal language deficits seen in 30% to 65% of children with NF1, both fine and gross motor-coordination deficits are common.\(^4,4\)

The cognitive phenotype of NF1 is marked by a higher incidence of attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, behavioral abnormalities, and psychosocial issues. In an assessment of the frequency and severity of specific cognitive deficits in children with NF1, Hyman et al\(^4\) showed that patients were 3 times more likely to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for ADHD than their siblings. Under experienced supervision, children with ADHD typically respond well to methylphenidate.\(^4\) In addition, cognitive behavioral therapy can be helpful. Patients with NF1 usually show IQ levels in the low-average range, and the frequency of mental retardation is increased among these individuals.\(^4\) Children with NF1 should be followed by a specialist-needs coordinator who maintains a close relationship with teachers, educational psychologists, occupational therapists, and pediatricians. To ensure proper support, yearly assessments of the child's ability to focus on an activity, social interaction, and fine and gross motor skills should be made.\(^9\)

On MRI, children with NF1 frequently harbor hyperintense regions on T2-weighted sequences, sometimes termed “unidentified bright objects” (UBOs). UBOs are sometimes difficult to distinguish from non–contrast-enhancing low-grade gliomas. Initially, UBOs were proposed as radiologic biomarkers for cognitive disabilities in children with NF1; however, recent studies have challenged this view.\(^4,9,5\)

### Genetics and Genetic Testing

All individuals with NF1 are born with 1 functional and 1 nonfunctional (mutated) copy of the \(NF1\) gene in every cell in their body.\(^3\) Approximately half of all NF1 cases are diagnosed without a known family history and are thought to represent new mutations. It is estimated that 80% of newly occurring nondeletion \(NF1\) mutations are paternal in origin.\(^5\) A hallmark feature of \(NF1\) is the variable expression of clinical manifestations, which makes counseling and prognostic determinations difficult. The condition arises from a germ-line mutation in the \(NF1\) gene located on chromosome 17q11.2.\(^5,4\)

Mosaic NF1, a variation of NF1 initially termed “segmental neurofibromatosis” by Riccardi and Eichner,\(^5\) results from early somatic mutations and can present with a wide range of clinical features. Because of the varying degrees of mosaicism, Ruggieri and Huson\(^5\) categorized individuals with mosaic NF1 into 1 of 3 groups: (1) mild generalized disease; (2) localized disease; and (3) pure gonadal mosaicism. Individuals who are mosaic for NF1 are at a lower risk of developing severe medical complications.\(^5\) There are clinical conditions that overlap with the NF1 phenotype but are not yet fully understood at the molecular level: familial café-au-lait spots and familial spinal neurofibromatosis.\(^5\) Recently, mutations in the \(SPRED1\) gene were found in several families segregating autosomal dominant multiple café-au-lait spots.\(^5\)

Approximately 5% of patients with NF1 have a deletion of the entire, or nearly entire, \(NF1\) gene. These patients display a more severe phenotype, including earlier onset, large load of neurofibromas, greater likelihood of cognitive deficiency, dysmorphic facial features, increased risk of malignancy, and connective tissue involvement, with joint laxity, hyperextensible skin, and mitral valve prolapse. Echocardiography to screen for mitral valve prolapse should be considered for individuals with NF1 microdeletions.\(^5\)

Genetic testing in NF1 is challenging because of the large number of possible mutations in the large gene. Linkage analysis can be offered but is not helpful for sporadically affected individuals.\(^6\) Messiaen et al\(^6\) showed that use of a set of complementary techniques permits detection of ~95% of mutations in patients who fulfill diagnostic criteria. GeneTests (www.genetests.org), a publicly funded Web site, accepts and displays listings of commercial and research laboratories that conduct \(NF1\) gene testing.

### Neurofibromin

The protein product of the \(NF1\) gene (neurofibromin) is a cytoplasmic protein that is 2818 amino acids long. Because patients with NF1 are prone to developing benign and malignant tumors, neurofibromin is hypothesized to function as a tumor suppressor or negative growth regulator. In this regard, neurofibromin normally limits cell growth, and its absence or reduced expression leads to increased cell growth. Analysis of the predicted sequence of neurofibromin revealed that it likely functions as a negative regulator of Ras, a key intracellular signaling protein that is important for regulating cell growth and survival. Neurofibromin inhibits the activity of Ras GTPase proteins by catalyzing the hydrolysis of active guanosine triphosphate–bound Ras
to inactive guanosine diphosphate–bound Ras (see Fig 3). Loss of neurofibromin results in unopposed Ras activity and constitutive downstream signaling and increased cell growth.\(^{57,62}\) Deregulated Ras activity leads to activation of several important downstream signaling intermediates, including the mammalian target of rapamycin (mTOR) protein. In addition to regulating Ras, neurofibromin also functions to positively regulate cyclic adenosine monophosphate (AMP) levels.\(^{63,64}\) Increased cyclic AMP levels are associated with reduced cell growth, likely through interference with multiple mitogenic signaling pathways.

**NOVEL THERAPIES**

New therapies for NF1-associated tumors can be grouped into those that target “deregulated” signaling pathways within NF1-deficient tumor cells or those that target stromal contributions from NF1\(^{+/-}\) cells in the tumor microenvironment. In addition, strategies based on correcting Ras signaling are currently being proposed for the treatment of cognitive deficits in children with NF1.

**Targeting Tumor Cells**

Because neurofibromin functions as a Ras inhibitor, initial treatment studies focused on Ras inhibitors. Tipifarnib is a farnesyl protein transferase inhibitor, which inhibits the farnesylation and geranylgeranylation of Ras required for its translocation to the cell membrane and subsequent activation.\(^{65}\) A phase I trial with tipifarnib conducted in children with either refractory solid tumors or NF1 plexiform neurofibromas was completed recently, and the drug was well tolerated in children and adults at a similar maximum tolerated dose. A phase II trial of tipifarnib in patients with NF1-associated plexiform neurofibroma is ongoing.\(^{65}\)

Because neurofibromin regulates mTOR signaling, the use of rapamycin and related analogs are being considered for the treatment of tumors in individuals with NF1. Rapamycin was first described as an immunosuppressive drug that bound its target FKBP12, a suppressor of mTOR signaling. Excitement for the use of rapamycin was fueled recently by the report that oral rapamycin caused regression of subependymal giant-cell astrocytomas in a small number of patients with tuberous sclerosis complex.\(^{66}\)

**Targeting Stromal Contributions**

Antihistaminic agents such as ketotifen fumarate were used initially to treat plexiform neurofibromas on the basis of the idea that mast cells may contribute to neu-
rofibroma growth. Unfortunately, the results from this trial have been difficult to assess, considering that entry and outcome criteria were not clearly defined. Although this and subsequent trials were largely considered to be ineffective, patients reported some subjective symptomatic relief.

Plexiform neurofibromas maintain a robust vascular supply, suggesting that chemotherapeutic agents that target the tumor vasculature might be effective. α-Interferon was first evaluated in a large phase II trial; however, after 18 months of treatment there was tumor stabilization, but very few patients reported decreased tumor size. AZD2171 is a small-molecule inhibitor of the vascular endothelial growth factor receptor (VEGFR) family of receptor-tyrosine kinases. The VEGFR family and its ligands are primarily known for their role as mediators of angiogenesis. Other angiogenesis inhibitors, such as thalidomide, have shown promise in the treatment of MPNSTs.

The past decade has seen major advancements in the treatment of NF1-related learning disabilities. Ultimately, the rapid emergence of new molecular targets in NF1 coupled with the use of small-animal models will allow treatment to progress beyond symptomatic confines.

New Treatment for Learning Disabilities
Recent clinical studies by Li et al. revealed a reversal of the cognitive deficits associated with NF1 after treatment of nf1−/− mice with lovastatin. The p21/Ras/mitogen-activated protein kinase (MAPK) biochemical pathway plays a common pathophysiologic role underlying the cognitive deficits seen in patients with NF1, and it is thought that lovastatin lowers the abnormally increased levels of p21/Ras in the nf1−/− mice. After treatment with lovastatin, nf1−/− mice performed equally as well as wild-type mice on various spatial, behavioral, and learning tasks. The nf1−/− mice receiving placebo or no treatment performed significantly lower on these tasks, signaling that the cognitive phenotype of nf1−/− mice had been reversed.

CONCLUSIONS
The current management of NF1 focuses on genetic counseling and symptomatic treatment of specific complications. Despite early encouraging results from potential pharmacologic- and biological-based therapies, new modes of therapeutic development are needed to move the field forward. Although clinical trials are the gold standard of therapeutic testing, there is significant interest in using small-animal models of NF1-associated clinical features. Preclinical models of NF1 will allow investigators to more rapidly screen potential molecularly targeted agents for specific diseases or stages of disease. Small-animal genetically engineered NF1 mouse models can be used in conjunction with small-animal imaging modalities to allow investigators to follow disease progression in a clinically relevant manner. In fact, even robust small-animal mouse models exist for NF1-associated learning disabilities. Ultimately, the rapid emergence of new molecular targets in NF1 coupled with the use of small-animal models will allow treatment to progress beyond symptomatic confines.
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