CLINICAL PICTURE:

16 years old female patient presented clinically with bilateral marked diminution of version, mid-dorsal pain, grand mal fits and poor scholastic achievement. Examination revealed bilateral primary optic atrophy, scanty café au lait spots and some cutaneous neurofibromatosis.

RADIOLOGICAL FINDINGS:

RADIOLOGICAL FINDINGS:

Figure 1. Neurofibromatosis type 1. Optic pathway glioma demonstrated as barrel-shaped fusiform dilation of the optic nerves. (optic pathway gliomas in neurofibromatosis type 1 are commonly pilocytic tumors with very slow growth).
Figure 2. Intramedullary cystic astrocytoma demonstrated in this patient. Surgical biopsy demonstrated a pilocytic astrocytoma.

Figure 3. Neurofibromatosis type 1. Scoliosis is demonstrated by plain X ray. Notice the heavily calcified dorsal disc herniation most probably secondary to the scoliotic process.
Figure 4. A 25 years old female with neurofibromatosis type 1 showing non-specific white matter changes (A), bilateral optic nerve glioma (B), dorsal kyphoscoliosis predisposing to early disc degenerative changes (C,D) and cystic spinal pilocytic astrocytoma (E).

Compared with tuberous sclerosis, neuroimaging in NF1 does not have as much importance for diagnosis of the disorder but is more important for monitoring complications. There are no neuroimaging findings included in the diagnostic criteria for NF1. When the consensus criteria for diagnosis of NF1 were formulated in 1987, there was not much experience with MRI, especially in children. MRI T2 hyperintensities may have diagnostic significance, however. In NF1, most young patients have unidentified bright objects (UBOs) on cranial MRI (Fig. 4a), whereas the prevalence of UBOs goes down in older children. The nature of the UBOs remains unclear, and they are postulated to represent hamartomas, dysmyelinated areas, or spongiosis. Most adults with NF1 either do not have UBOs typical for NF1 or have confounding lesions caused by vascular or other disease. DeBella et al [105] used cranial MRI to examine 19 children with NF1 and 19 controls. Of the 19 control children, 11 had UBOs. Of note, the control children all had neurologic disorders. When only the UBOs typical for NF1 were considered (ie, those located in the basal ganglia, cerebellum, and brainstem), their presence was correlated with NF1 to a high degree, yielding a diagnostic sensitivity of 97% and a specificity of 79%. In terms of diagnosis, UBOs are more helpful in young children who have only one criterion for diagnosis (usually multiple café au lait spots). They are less helpful later, because by the age of 5 years, diagnosis can usually be made based on other criteria. Further studies are necessary before typical UBOs can be considered a diagnostic criterion.
Table 1. MRI characteristic of neurofibromatosis type 1

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Optic pathway gliomas</td>
<td>Accounting for 2 to 5 percent of childhood brain tumors. However, up to 70 percent are associated with NF1 [25]. The vast majority of these are WHO grade I pilocytic astrocytomas.</td>
</tr>
<tr>
<td>Kyphoscoliosis with secondary degenerative changes</td>
<td>Vertebral defects, including scalloping from dural ectasias, are not uncommon in NF1 [63]. Approximately 10 percent of affected individuals have scoliosis during late childhood and adolescence [10]. Sometimes this can be severe enough to warrant bracing or surgery and may be associated with the presence of an associated neurofibroma.</td>
</tr>
<tr>
<td>Spinal pilocytic astrocytoma</td>
<td>Uncommon in neurofibromatosis type 1, more common in neurofibromatosis type 2</td>
</tr>
<tr>
<td>Neurofibromatosis white matter patches</td>
<td>Almost characteristic of neurofibromatosis type 1. When only hyperintense white matter patches typical for NF1 were considered (ie, those located in the basal ganglia, cerebellum, and brainstem), their presence was correlated with NF1 to a high degree, yielding a diagnostic sensitivity of 97% and a specificity of 79%. [105]</td>
</tr>
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</table>

**DISCUSSION:**

Type I neurofibromatosis (NF1), also known as von Recklinghausen neurofibromatosis or peripheral neurofibromatosis, is one of the most common autosomal dominant diseases affecting the nervous system. NF1 is now recognized as a single gene defect affecting multiple organ systems (neurologic, dermatologic, orthopedic, etc.) with a particular predisposition to the formation of specific tumors. Historically, descriptions matching the phenotype of NF1 can be found as far back as Hellenic times. Stone renderings have been identified from 300 BC [104] that might have been used as teaching representations of the neurofibromas in NF1 [1]. Other descriptions can be found in the writings of Akenside in the 1600s and others in the 1700s [2]. However, it was not until 1882 that Frederick von Recklinghausen gave the disease its first full description. He recognized the fact that the tumors seen on the skin actually arose from the fibrous tissue surrounding small nerves, thus leading to the term “neurofibroma” [3].

Further advances in our understanding of this disorder came in the early twentieth century when the autosomal dominant pattern of inheritance was recognized in the landmark monograph of Crowe, Schull, and Neel in 1956 [4]. They also recognized the high incidence, the high spontaneous mutation rate, the usefulness of the café-au-lait spot as a diagnostic feature, and the recognition of the wide range of clinical features that can occur in this syndrome. In 1937, Karl Lisch, a Viennese ophthalmologist, suggested that the iris hamartoma was a frequent clinical sign in adults with NF1 [5].

The 1970s witnessed the birth of the integrated comprehensive NF clinic where individuals affected with NF1 were managed by a team of physicians familiar with the protean manifestations of the disorder. Despite a growing awareness of the clinical features associated with NF1, considerable confusion remained about which signs were required to render a diagnosis of NF1. The NF Consensus Panel organized by the National Institutes of Health in 1986 codified the diagnostic criteria for NF1 [6]. With the establishment of reliable criteria, it became possible to clinically diagnose affected individuals reliably and consistently. Lastly, with the advent of molecular genetics, the gene for NF1 and its protein, neurofibromin, were identified, which permitted clinicians and researchers to begin to unravel the pathogenesis of NF1-associated abnormalities and to begin to consider the design of targeted and rational therapies for specific clinical problems in individuals affected with NF1.

- Clinical syndrome
  - Incidence
It is difficult to accurately quantify the incidence of NF1 chiefly because it is often not diagnosed at birth. Multiple population studies from the United States [4], Russia [7], Denmark [8], and Wales [9] have estimated the disease prevalence at approximately 1 in 2500 to 1 in 5000. The Russian study provided a lower estimate of 1 in 7800, but this figure may underestimate the true frequency of NF1. When under-ascertainment and increased mortality are considered, the true birth incidence of NF1 is probably between 1 in 3000 and 1 in 4000. Approximately 50 percent of individuals with NF1 lack a family history and are presumed to represent new mutations. As expected for a genetic disorder with such a high incidence of spontaneous mutations, the frequency of NF1 does not vary among different races or ethnic groups.

**Diagnostic criteria**

The diagnosis of NF1 is rarely difficult to establish by an experienced clinician using the NIH Consensus criteria. The diagnosis of NF1 is rendered when two or more of the following are present:

1. Six or more café-au-lait spots
   - 1.5 cm or larger in postpubertal individuals
   - 0.5 cm or larger in prepubertal individuals
2. Two or more neurofibromas of any type OR One or more plexiform neurofibromas
3. Freckling of armpits or groin
4. Optic glioma (tumor of the optic pathway)
5. Two or more Lisch nodules (benign iris hamartomas)
6. A distinctive bony lesion
   - Dysplasia of the sphenoid bone
   - Dysplasia or thinning of long bone cortex
7. First-degree relative with NF1

With these criteria, the diagnosis of NF1 can be rendered confidently in the vast majority of cases. In small children or infants without a positive family history of NF1, often only one diagnostic feature is present (typically café-au-lait macules), and the diagnosis of NF1 cannot be established. For this reason, it is important to recognize the age-dependent appearance of NF1-associated features. Manifestations and management are as follows:

1. Discrete Neurofibromas
2. Learning Disabilities
3. Plexiform Neurofibromas
4. Pain
5. Optic Pathway Gliomas
6. Scoliosis
7. Seizures
8. Headache/Migraine
9. Bowel or bladder complications (usually secondary to pelvic plexiform neurofibroma)
10. Primary Aqueductal Stenosis
11. Stroke (cerebrovascular abnormalities)

In young children, close attention should be paid to the presence of bony deformities (e.g., leg length discrepancy, orbital abnormalities), café-au-lait macules, plexiform neurofibromas, and optic pathway gliomas. As they age, signs of precocious puberty and learning disabilities may manifest. During adolescence, neurofibromas typically appear with gradually increasing numbers during puberty and later during pregnancy [10]. Adults with NF1 may have neurological problems associated with neurofibroma growth and, rarely, malignant tumors. Awareness of the development and age-dependent appearance of NF1-associated features is critical to the anticipatory management and treatment of individuals with NF1.

- Clinical features

Perhaps the most obvious visible features of NF1 are the pigmentary abnormalities, the most classic being the café-au-lait spots (CALS). CALs are flat, evenly pigmented macules that are often apparent at birth, but increase in number and size during the first two years of life (Fig. 5). As many as 25 percent of the normal population will have one or two café-au-lait spots [11]. In contrast to those seen in NF1, non-NF1-associated café-au-lait macules may have variegated color and irregular borders. The presence of six or more café-au-lait spots is highly suspicious for NF1, providing the size criteria listed are closely followed. Microscopically, the melanocytes within the café-au-lait spot often display an increased number of macromelanosomes, although this is not diagnostic for NF1 [12]. Later in life, the café-au-lait spots may fade making it difficult, or nearly impossible, to identify them in older individuals. The use of a Wood's lamp is quite helpful in this regard.

Figure 5. Café-au-lait macule in a young child with NF1.

The second most common pigmentary abnormality in children with NF1 is skinfold freckling. The occurrence of freckles in axillary, groin, and intertriginous non-sun-exposed areas was first pointed out by Crowe and is a useful diagnostic feature [13]. Skinfold freckles are also seen under the chin and in the inframammary regions in adults [10]. Unlike the café-au-lait spot, skinfold freckling is usually not apparent at birth but appears later in childhood. In addition to café-au-lait macules and skinfold freckling, the Lisch nodule is also an important diagnostic finding and is nearly pathognomonic for NF1. Lisch nodules are raised, pigmented hamartomas of the iris [14, 15]. They do not interfere with vision and are not associated with any clinical symptoms. Lisch nodules are often difficult to detect on bedside examination, especially in individuals with dark irides. Careful inspection by an experienced ophthalmologist using a slit lamp can facilitate their detection during childhood. Nearly all adults with NF1 manifest Lisch nodules, making it an extremely useful clinical sign.

- Neurofibromas

Neurofibromas are the tumors from which this disorder takes its name. Peripheral neurofibromas are benign peripheral nerve sheath tumors characterized by unpredictable patterns of growth, variable cellular composition, and diverse appearances [16,17]. Classified as WHO grade 1 tumors, these lesions are rarely if ever present at birth, but tend to develop during adolescence, often heralding the onset of puberty [16]. Clinically, dermal neurofibromas tend to arise as discrete masses from a single nerve as exophytic or subcutaneous tumors (Fig. 6A). Dermal neurofibromas may cause discomfort or itching but are rarely associated with neurologic deficit. They are benign tumors without the risk of associated malignant transformation [18]. Nearly all adults with NF1 will develop neurofibromas at some time during their lives. They tend to increase in both size and number with age, but their rates of growth can be extremely variable. Some women with NF1 report an increase in the appearance or rate of
growth of neurofibromas during pregnancy. This observation, along with the common presentation of neurofibromas around puberty, suggests that these tumors may be stimulated by changes in hormones. Pathologically, these lesions are composed of a mixture of cell types including Schwann cells, fibroblasts, mast cells, and vascular elements. There is a subset of patients that have firmer and sometimes painful neurofibromas along the course of peripheral nerves, which can be difficult to manage surgically. Even more challenging are the spinal neurofibromas arising from the dorsal nerve roots, which can lead to pain as well as neurological compromise [19]. Discrete neurofibromas can be surgically excised, but these tumors may reappear in the same site after surgery.

Another type of neurofibroma is the diffuse, or plexiform, neurofibroma (Fig. 6B). This tumor is thought to be a congenital lesion, although it may not be recognized for many years. In many clinic-based studies, the incidence of plexiform neurofibromas has been estimated somewhere between 25 to 50 percent of NF1 patients, with most series suggesting an incidence of 25 to 30 percent [10,20]. Plexiform neurofibromas are complex tumors that may diffusely involve nerve, muscle, connective tissue, vascular elements, and overlying skin [17]. These tumors can arise in various regions of the body, including the trunk, limbs, head, and neck. Plexiform neurofibromas may be detected in various ways. First, they can remain clinically silent for many years, only to be revealed as incidental findings on imaging studies. In this fashion, they may grow to large sizes prior to clinical detection. In one study of 126
individuals age 16 or older with NF1, plexiform neurofibromas were found in the chest of 20% of patients and in the abdomen and pelvis of 44% of patients [21]. Second, plexiform neurofibromas may be detected by their effects on associated organs or structures. Leg length discrepancy, sphenoid wing dysplasia, and unexplained internal pain may be the presenting sign of a plexiform neurofibroma. When plexiform neurofibromas involve the orbit, they are often associated with sphenoid wing dysplasia, and may extend into the cranial vault, accompanied by pulsating exophthalmos. Spinal cord compression with associated neurologic dysfunction can also occur. Lastly, plexiform neurofibromas may be noted by an asymmetry on physical examination in a child.

Plexiform neurofibromas may occasionally undergo malignant transformation and develop into Malignant Peripheral Nerve Sheath Tumors (MPNSTs) [22]. Pathologically these are spindle cell Schwann cell malignancies. They represent particularly aggressive and almost universally fatal cancers that can arise anytime during the life of an individual with a plexiform neurofibroma. The most predictive sign of a MPNST is the development of sudden pain or the appearance of a new neurological deficit, either of which should always prompt investigation in an individual with a plexiform neurofibroma. Other features not reliably associated with transformation include sudden growth and a change in the consistency of the tumor or the coloration of the overlying skin. Recent experience suggests that 18-fluoro-deoxyglucose-positron emission tomography (PET) may distinguish between benign and malignant peripheral nerve sheath tumors [23]. Our ability to detect these tumors early may improve survival if extensive surgical excision with clean margins can be performed. There are some long-term survivors with limb MPNSTs who underwent amputations. Unfortunately, these malignancies are also relatively resistant to conventional chemotherapy and radiation [24]. They can metastasize and are associated with a low five-year survival rate.

- **Optic pathway gliomas**

The most commonly recognized tumor of NF1 is the optic pathway tumor, or optic glioma (Fig. 7). Optic pathway tumors are rare in the young only accounting for 2 to 5 percent of childhood brain tumors. However, up to 70 percent are associated with NF1 [25]. The vast majority of these are WHO grade I pilocytic astrocytomas. Pathologically, pilocytic astrocytomas located here diffusely expand the optic nerve producing a fusiform mass [1,26–28]. Two architectural forms are seen at both the gross and microscopic level: (1) diffuse expansion and obscuration of the optic nerve without extensive subarachnoid spread, and (2) predominant infiltration of the subarachnoid space leaving the mildly involved nerve surrounded by a rim of tumor tissue [27,28].

![Figure 7. Optic pathway glioma in a young child with NF1. Significant enhancement is noted upon gadolinium infusion in the left optic nerve.](image)

Typically, optic pathway gliomas in NF1 arise exclusively in young children. The median age is 4.9 years [29,30]. The incidence of optic pathway glioma in children with NF1 varies based on referral bias, with estimates ranging from 1.55% in a population based study [21] to 15% in each of two NF1 referral centers [29–31]. However, in the latter study, all children with NF1 had screening brain neuroimaging. Of those children with radiographically identified optic gliomas, only 52% ultimately developed any signs or symptoms of these lesions.
Most children with symptomatic optic pathway gliomas present with visual abnormalities. Young children may not have any clear symptoms; however, ophthalmologic abnormalities that can be found include decreased visual acuity, abnormal pupillary function, decreased color vision, and optic atrophy [29,30]. Only a minority of children will develop proptosis from a rapidly enlarging intraorbital tumor. In addition, some children present with accelerated linear growth as the first manifestation of precocious puberty. In a comprehensive study of children with NF1, precocious puberty was found exclusively in children who had optic pathway gliomas involving the hypothalamus [32].

NF1 children who present with symptoms of an optic pathway glioma should receive an MRI with contrast enhancement. In addition, these children should be followed closely for signs of precocious puberty (accelerated linear growth, secondary sexual characteristics). Guidelines for management and treatment have been published [25]. Serial ophthalmologic and neurologic exams should be performed in concert. Therapy is indicated for patients who exhibit progressive proptosis or progressive loss of vision, or those who develop clear radiologic progression. Options include surgery, radiation, or chemotherapy [25]. Surgery is reserved for isolated intra-orbital tumors in which vision has been lost, and the tumor is removed for cosmetic reasons or to potentially prevent further extension to the chiasm. Approximately 80 percent of patients treated with radiotherapy will have either disease stability or tumor shrinkage, although maximum tumor shrinkage may not be seen until 6 months to 1 year following radiotherapy [25]. Unfortunately, there are significant potential sequelae to radiotherapy from its effects on the normal brain, including neurocognitive and endocrinologic sequelae. For this reason, chemotherapy has been used increasingly as a first line of therapy. The combination of carboplatinum and vincristine has shown great promise in the management of optic gliomas in NF1 [33,34].

- **Malignancies**

In addition to the optic pathway, NF1 patients are at risk for other CNS tumors, especially astrocytomas. In a 1986 study, Blatt and colleagues retrospectively evaluated the frequency and distribution of tumors in 121 children with NF1 between 1953 and 1984 at Children's Hospital of Pittsburgh. They discovered that of 22 “clinically significant” tumors among the cohort, 18 involved the central nervous system, 9 were optic gliomas and 5 represented “other” astrocytomas [35]. Recent studies by Rasmussen and Friedman suggest that high-grade malignancies may be more common in older adults with NF1 than previously recognized [36].

Patients with NF1 are susceptible to malignancies outside of the nervous system, including pheochromocytomas and leukemias. Even among individuals with NF1, pheochromocytomas are rare [37]. However, in several series of patients with pheochromocytomas, the proportion of individuals with NF1 has been estimated between 4 and 23 percent [38–40]. Pheochromocytomas are detected in NF1 patients presenting with signs of malignant hypertension, but both young and old patients tend to have causes of hypertension other than pheochromocytomas.

Another non-CNS malignancy seen disproportionately in NF1 patients is leukemia [41]. Although these childhood myeloid leukemias in NF1 are exceptionally rare malignancies, individuals with NF1 harbor a greatly increased risk of developing myeloid cancers, such as juvenile chronic myeloid leukemias (JCML) and myelodysplastic syndromes (MDS). Typically, lymphocytic leukemias predominate at a 4:1 ratio over non-lymphocytic (myeloid) leukemias in children without NF1. However, in individuals affected with NF1, there is a 20:9 ratio of non-lymphocytic to lymphocytic leukemias [37]. Most of the children with NF1 and malignant myeloid disorders reported in the literature are boys under ten years of age.

**Other neurological complications**

Although not specific enough to be a part of the clinical criteria, patients with NF1 often develop other clinical complications that involve the nervous system, including macrocephaly, hydrocephalus, cognitive impairment, headaches, seizures, and cerebral ischemia (Table 2). Macrocephaly, with occipital-frontal circumference greater than 3 standard deviations from the norm, is a common feature in NF1. Most often, in the absence of any neurologic signs or symptoms, NF1-associated macrocephaly does not warrant further investigation.

**Table 2: Age Dependant Manifestations and Management**

<table>
<thead>
<tr>
<th>1–2 years:</th>
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<tr>
<td>- Café-au-lait macules</td>
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</table>
- Plexiform neurofibromas
- Tibial Dysplasias (anterolateral bowing of lower leg): may require orthopedic referral

3–5 years:

- Skinfold Freckling
- Lisch nodules
- Optic Pathway Gliomas: requires serial neurologic, ophthalmologic, and MRI scans once detected. Further management is warranted if there is tumor progression.
- Learning disabilities: requires planning with parents and teachers and early intervention if detected.
- Precocious puberty: requires endocrinologic and radiographic evaluation
- Plexiform Neurofibromas: requires regular follow-up

Late Childhood and Early Adolescence

- Dermal Neurofibromas
- Plexiform Neurofibromas: requires regular follow-up
- Scoliosis: requires orthopedic evaluation for possible bracing and/or surgery

Lifelong

- Neurofibromas
- Pain
- Plexiform Neurofibromas: requires regular follow-up
- Malignant Peripheral Nerve Sheath Tumor (MPNST)
- Other Malignant Neoplasms

Learning disabilities are common in children with NF1, but frank mental retardation (IQ<70) is uncommon. Standard IQ testing reveals a downward shift of scores by 5 to 10 IQ points in children with NF1 [42]. Specific learning disabilities are found in approximately 50 percent of children with NF1 [43,44]. There has been much controversy regarding what specific type of learning disabilities predominate in children with NF1. Several studies have been conducted to evaluate this, and it appears that language-based learning problems are at least as common as non-language based deficits [42,44–47]. However, these children have a particular problem with visuospatial function using the Judgment of Line Orientation (JLO) test [48]. In all studies of children with NF1, the JLO is consistently abnormal [45,49–51]. Because of this increased risk of learning disabilities, parents of an affected child should be counseled early about this potential problem.

The use of brain MRI has identified signal abnormalities seen on T2-weighted images in children with NF1. These high signal intensities occur in 60–70% of children with NF1 and are seen most commonly in the basal ganglia, optic tracts, brainstem, and cerebellum. They tend to disappear sometime during the second and third decades of life [52–58]. (Fig. 8.9) At one point, these “unidentified bright objects” (UBO) were incorrectly thought to be hamartomas. While their effect on the clinical picture is still unclear, they are not associated with the severity of disease, nor do they cause any focal deficits [42,55]. However, there is some question as to their contribution to the NF1-associated learning disabilities. Several studies have been published that show a correlation between the presence of UBOs and cognitive dysfunction [42,43,45,48]. However, other studies found no such relationship [59,60]. In one such study, further analysis showed a significant association between deficits in IQ, memory, motor function and attention span and UBOs in the thalamus [60]. Thus, it is still unclear at this point whether these T2-
Seizures develop in 5–7% of children with NF1 and have the same etiologies and response to therapy as non-NF1-associated seizures [10]. Similarly, individuals with NF1 may develop headaches, which are rarely disabling. New headaches associated with an abnormal neurological examination should heighten the suspicion for an intracranial mass. Aqueductal stenosis leading to hydrocephalus is a known, albeit uncommon, complication of NF1. Lastly, cerebrovascular abnormalities (“Moya-moya”) are rarely seen in NF1, but are known to occur at an increased frequency and may lead to stroke [10,61].

- **Non-neurologic features of NF1**

Children with NF1 have other associated features that are non-neurologic, including short stature. Careful studies of adult height suggest that individuals with NF1 are, on the average, about 3 inches shorter than predicted by their family background [10,62].

Vertebral defects, including scalloping from dural ectasias, are not uncommon in NF1 [63]. Approximately 10 percent of affected individuals have scoliosis during late childhood and adolescence [10]. Sometimes this can be severe enough to warrant bracing or surgery and may be associated with the presence of an associated neurofibroma. Long bone complications, such as tibial bowing, are also seen in individuals with NF1, particularly in young children. These long bone deformities may result from thinning of the cortex and lead to pathological fracture, severe difficulties with nonunion of the fragments, and the formation of a pseudarthrosis, or false joint, rendering the limb severely compromised.

- **Variant presentations of NF1**

There are several unusual presentations of NF1 that warrant separate discussion. One of these is known as...
segmental, or mosaic, NF1 [64]. In general, mosaicism occurs when one of the two NF1 genes sustains a mutation during fetal development, such that only a localized region of the developing fetus is affected. Patients with a mosaic form of NF1 will only have features of NF1 affecting those body parts or tissue types with the NF1 mutation. The areas of involvement are variable. In most affected individuals, it is unilateral sometimes affecting only one narrow strip, others a quadrant, and occasionally one half of the body. In other cases, both sides of the body can be involved in either a symmetric or asymmetric fashion. One can see neurofibromas, plexiform neurofibromas, café-au-lait macules, and even Lisch nodules if the iris is affected. This condition is generally under-diagnosed, as most signs are thought to represent an odd birthmark or a harmless nodule and are never brought to a physician’s attention. Some patients with mosaic NF1 have children with generalized NF1 indicating gonadal tissue involvement. These patients are referred to as gonosomal mosaics [65–67].

Another variant of NF1 (called Watson’s syndrome) that appears to “breed true” in certain families involves multiple café au lait spots, dull intelligence, short stature, pulmonary valvular stenosis, and only a small number of neurofibromas [68]. Individuals with Watson syndrome may also have Lisch nodules. Molecular studies performed on these families demonstrate mutations involving the NF1 gene. At this point, there appear to be no differences in the NF1 mutations causing Watson syndrome and those associated with NF1.

Another particularly interesting variant of NF1 is the Neurofibromatosis-Noonan Syndrome (NFNS). In this syndrome, children with NF1 also display features reminiscent of Noonan Syndrome, such as pectus excavatum, mild hypertelorism, and short stature [69]. Linkage studies of autosomal dominant Noonan syndrome occurring in the absence of NF1 have indicated no linkage to markers in the NF1 region on chromosome 17. Thus, a mutation on chromosome 17 close to the NF1 gene causing a Noonan syndrome is highly unlikely.

Another phenotype that mimics generalized NF1 is spinal neurofibromatosis. In this rare presentation, families have a predominance of spinal neurofibromas but relatively few cutaneous manifestations of NF1 [19]. It is not known whether all cases of spinal NF arise from mutations in the NF1 gene.

**GENETICS**

It is always important with genetic diseases to establish the inheritance pattern. In 1918, Preiser and Davenport surveyed the literature and found that approximately 50 percent of those affected with NF1 had children who were also affected [70]. They also found numerous cases of male-to-male transmission. With these findings, they established that the disease follows an autosomal dominant inheritance pattern. Hall discovered a curious phenomenon in 1981 [71]. He suggested that the sex of the affected parent might have an impact on the severity of the disease. In his study, children of affected mothers tended to be more affected than children of affected fathers. Subsequent studies and analyses of this issue have failed to confirm this maternal effect.

Of those individuals with NF1, 30 to 50 percent do not have an affected parent [4,8,9]. These individuals presumably represent spontaneous mutations. Many examples of de novo alterations in the NF1 gene have been found in such individuals. Given that NF1 is a common disease and that so many patients have new mutations, the mutation rate must be unusually high and is estimated at approximately 1074 per generation.

The penetrance of NF1 is essentially 100 percent in individuals who have reached adulthood and have been carefully examined (including a slit-lamp examination) by an experienced physician. Despite its nearly 100% penetrance, NF1 exhibits highly variable expressivity. Families with multiple affected individuals are likely to demonstrate a wide range of severity and complications. In addition, the variability within a family of significant size with the identical NF1 mutation is similar to the variability seen when compared to different families with distinct NF1 mutations, indicating that specific germ-line mutations at the NF1 locus do not accurately predict the phenotype of a particular individual. In order to distinguish between genetic influences and environmental and/or chance influence, studies on monozygotic twins were performed by Easton and coworkers [72]. They compared twins concordant for NF1 with other pairs of first-degree affected relatives. They found a significant correlation in the number of café-au-lait spots and neurofibromas between identical twins, with a lower correlation in first-degree relatives and almost no correlation between more distant relatives. This suggests that these features may be controlled by other genetic influences, but that the specific mutation in the NF1 gene plays a minor role. Other complications including optic glioma, scoliosis, epilepsy, and learning disability were concordant in twin pairs, but plexiform neurofibromas were not. The presence of one complication did not predict the occurrence of another, except that MPNSTs occur almost exclusively in individuals with plexiform neurofibromas.

- **Identification of the NF1 gene and its protein product, neurofibromin**

Perhaps one of the greatest strides made in the field of neurofibromatosis 1 was the identification of the NF1 gene.
By linkage analysis on thousands of individuals from hundreds of families with NF1, the responsible gene was localized to chromosome 17q11.2. Identified by positional cloning, the NF1 gene spans approximately 300,000 nucleotides of genomic DNA and contains an open reading frame of 8454 nucleotides [73,74]. The messenger RNA is 11,000 to 13,000 nucleotides in length and is detectable at varying levels in all tissues examined.

With the identification of the NF1 gene, it became possible to determine the structure and function of the NF1 gene product. The predicted amino acid sequence failed to reveal any nuclear localization signals or transmembrane domains, suggesting that the NF1 protein resides in the cytoplasm. Upon complete sequencing of the NF1 gene, a small region in the central portion of the protein demonstrated sequence similarity with the functional domain of a family of proteins termed GTPase-Activating Proteins (GAPs; Fig. 10) [75].

![Figure 10. NF1 gene product, neurofibromin. Alignment of the predicted protein sequence of the NF1 gene reveals a small region in the central portion of neurofibromin (denoted by the grey shaded area) with significant sequence similarity to the function RAS-GAP domain of several mammalian, non-vertebrate, and yeast molecules, including fruit fly neurofibromin (Dr-neurofibromin), the other mammalian RAS-GAP (p120-GAP), and two yeast GAPs (IRA1 and IRA2).](image)

Using antibodies generated against fusion proteins and synthetic peptides, a unique 220–250-kDa protein was identified [76–78]. Consensus agreement resulted in assignment of the name, neurofibromin, to the NF1 gene product. As its predicted sequence suggested, neurofibromin was localized to the cytoplasm by differential centrifugation, glycerol gradients, and indirect immunofluorescence. The tissue distribution of neurofibromin mRNA was originally shown to be present at some level in all tissues; however, subsequent analysis by Western blotting, immunoprecipitation, and immunohistochemistry demonstrated that the highest levels of neurofibromin expression were in the brain, spleen, kidney, testis, and thymus [76]. Neurofibromin is highly expressed in the dendritic processes of central nervous system neurons, axons of peripheral nervous system neurons, nonmyelinating Schwann cells, oligodendrocytes, and dorsal root ganglia [76,79]. It is expressed at lower levels in astrocytes, microglia, and myelinating Schwann cells.

The predicted amino acid sequence of neurofibromin demonstrated sequence similarity with a family of GAP molecules. This predicted homology was verified by multiple methods, arguing that one of the functions of neurofibromin was to function as a GAP. GAP proteins in both mammals and yeast regulate the activation state of the cellular p21-RAS proto-oncogene [80–83]. GAP molecules accelerate the hydrolysis of p21-RAS-GTP to p21-RAS-GDP converting RAS from its GTP-bound, active form to an inactive, GDP-bound form (Fig. 11) [84,85]. In this regard, neurofibromin appears to function as a tumor suppressor by down-regulating the activity of RAS. In mammalian cells, activation of RAS is associated with increased cell proliferation. Loss of neurofibromin function in specific cells in individuals with NF1 would be hypothesized to result in increased RAS activity, which in turn, would provide an increased growth advantage and promote tumor formation.
As is true for other tumor or cancer predisposition syndromes, loss of both copies of the NF1 gene is required for tumor formation (Fig. 12). In the case of NF1, affected individuals would inherit one mutated NF1 gene, but only develop tumors when a somatic mutation renders the one remaining wild-type NF1 gene non-functional. This “two hit” hypothesis was originally espoused by Alfred Knudson while describing the tumor predisposition of retinoblastoma [86,87].

The ability of neurofibromin to function as a tumor suppressor has been demonstrated by a number of elegant studies. This capacity to inhibit cell proliferation and facilitate tumor formation is primarily reflected in the ability of neurofibromin to function as a RAS-GAP. Loss of neurofibromin expression in neurofibromas, astrocytomas, and myeloid cancers in patients with NF1 is associated with increased RAS activity [88–90]. Inhibition of RAS activity results in reduced cellular proliferation and attenuated tumor progression. Although other functions of neurofibromin may be identified as further studies focus on regions of the protein outside of the RAS-GAP domain, the correlation between neurofibromin function and RAS pathway activation is compelling enough to warrant the design of clinical trials that target RAS pathway activity.

Studies on NF1-associated neurofibromas have demonstrated loss of NF1 gene expression in the Schwann cells, suggesting that loss of neurofibromin results in increased RAS activity and promote tumor formation. In contrast, the development of MPNSTs may involve additional cooperating genetic mutations involving the p53, p16 and p27-
Experimental treatments

agents that target specific biochemical abnormalities in NF1 tumors with increased RAS activity. Clinical trials using farnesyltransferase protein inhibitors as well as other activation [102,103]. Farnesylation target is inhibition of RAS farnesylation, a reaction necessary for RAS membrane localization and subsequent activation [100,101]. Third, increased RAS activity was detected in a single NF1-associated astrocytoma associated with loss of neurofibromin expression [90]. Since only a minority of NF1-associated astrocytomas exhibit clinical progression, it is likely that additional genetic alterations are necessary for the development of symptomatic, clinically progressive optic pathway tumors in NF1.

MANAGEMENT OF NEUROFIBROMATOSIS 1

The management of individuals affected with NF1 often requires the expertise of many medical and surgical subspecialists coordinated by one physician, or team of physicians, most familiar with NF1. Because of this, the establishment of neurofibromatosis clinics has made great strides in advancing the care of these patients. These clinics not only involve the physicians most closely aware of NF1 (geneticists), but also other subspecialties including ophthalmologists, neurologists, plastic surgeons, neurosurgeons, otolaryngologists, psychiatrists, social workers, child psychologists, orthopedic surgeons, dermatologists, and oncologists. The NF clinic not only treats the patient, but also educates the child as well as the family of the patient about their condition. This is accomplished during the regular office visits as well as by communication through the various local and national neurofibromatosis associations.

The approach to the new patient suspected of having NF1 requires obtaining a complete medical history and examination. This is a time consuming process that begins prior to the appointment, thus allowing time to review the patient's specific clinical features and family history. This discussion often precipitates the individual further delving into their own family histories. When possible, outside records including autopsies and surgical pathology reports should be requested.

Once in the clinic, the patient is carefully examined by one of the NF1 physicians. A detailed dermatological examination is performed, looking for neurofibromas, skinfold freckling, and café-au-lait spots. Specific attention should be focused on the skeletal system to detect any abnormal spinal curvatures or bowing of the extremities, especially in young children. Suspicious extremities are examined by plain x-rays and affected patients should be referred to an orthopedic surgeon. A directed neurological exam on all affected individuals should be performed during each visit with special attention to subtle neurologic or visual abnormalities. In addition, an ophthalmologic exam should be performed on all children starting at one year and continuing annually for at least the first decade. Abnormalities on the visual examination should prompt MRI evaluation looking for optic pathway gliomas. Radiologic evaluation of children and adults with NF1 should be performed only when clinically indicated. This is especially true with the use of brain imaging studies. There is no utility in “screening” or “baseline” MRI evaluations, as they are not predictive [62]. Recommendations for the evaluation of children and adults with NF1 have been published [61]. Patients with NF1 also deserve close follow-up for ongoing development of tumors and other medical problems [61].

An often forgotten, but important, part of the care of the NF1 patient is genetic counseling. A genetic counselor educates the family about all aspects of NF1, which provides a basis for continuing education as well as dispelling common misperceptions. Explanations are given not only for what is seen now, but what can be expected to come in the future especially as it relates to puberty and pregnancy. Issues about genetic transmission and recurrence risks of having a child with NF1 are discussed, and the emotional aspects of the disease are addressed.

- Experimental treatments

The development of rational and targeted treatments is the ultimate goal of basic science research in NF1 (Fig. 13). The application of drugs that interfere with RAS activity would be predicted to have a beneficial effect. One such target is inhibition of RAS farnesylation, a reaction necessary for RAS membrane localization and subsequent activation [102,103]. Farnesylation-blocking agents have already shown promise in the laboratory in treating tumors with increased RAS activity. Clinical trials using farnesyltransferase protein inhibitors as well as other agents that target specific biochemical abnormalities in NF1-associated tumors may one day find their place in the
Neurofibromatosis 1 is one of the most common genetic conditions affecting the nervous system. Individuals with NF1 are predisposed to the development of peripheral nerve sheath tumors (neurofibromas and MPNSTs), astrocytomas (optic pathway gliomas), learning disabilities, seizures, strokes, macrocephaly, and vascular abnormalities. The NF1 tumor suppressor gene encodes a large protein (neurofibromin) that functions primarily as a RAS negative regulator, suggesting that targeted therapy for NF1 might derive from inhibition of the RAS signaling pathway.

Table 5. Genetics of neurofibromatosis
Addendum

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<th>Gene location</th>
<th>Gene function</th>
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<td>Long arm of chromosome 17</td>
<td>Putative tumor suppressor function</td>
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<td>Merlin</td>
<td>Long arm of chromosome 22</td>
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