Familial cancer syndromes involving the peripheral nervous system

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The neurofibromatoses are members of the group of neurocutaneous disorders which also include tuberous sclerosis, neurocutaneous melanosis, hypomelanosis of Ito, incontinentia pigmenti, Sturge-Weber syndrome and von Hippel-Lindau disease. Collectively, these conditions have also been referred to as "phakomatoses," a term is derived from the Greek phakos, meaning a lentil or birthmark. All but Sturge-Weber syndrome, which is sporadic in occurrence, have an autosomal dominant pattern of inheritance. Only neurofibromatosis type I and II as well as schwannomatosis show significant involvement of the peripheral nervous system.

Neurofibromatosis is characterized by multiple lesions of diverse type affecting a variety of tissues. These processes include hyperplasias, hypoplasias, hamartomas, and both benign and malignant neoplasms. Most lesions are neuroectodermal or mesenchymal in derivation. No gender or racial predilections are seen. Although the existence of as many as 8 neurofibromatosis variants has been proposed, three principal genetic and clinicopathologic forms are recognized. Termed neurofibromatosis types 1 and 2 (NF1 and NF2) as well as schwannomatosis, each is characterized by distinctive clinical abnormalities; overlap in manifestations is minor except in NF2 and schwannomatosis. Both NF1 and 2 result from genetic alterations of affecting tumor suppressor genes. The risk of developing a malignant neoplasm is ten-fold higher in patients with either condition. The key features of NF1 and NF2 are summarized in Table 1. The importance of distinguishing these conditions cannot be overstressed.

NEUROFIBROMATOSIS 1 (NF1)

The full expression of this more frequently occurring disorder, also termed peripheral neurofibromatosis or von Recklinghausen disease, has long been recognized. The responsible mutation resides in the large, NF1 gene on the 17q11.2, in close proximity to that of the nerve growth factor receptor gene. Spanning 350 kb of genomic DNA and consisting of 60 exons, the NF1 gene encodes neurofibromin, a 2818 amino acid protein. Evidence indicates that it functions as a tumor suppressor and that it also plays a role in cell proliferation and differentiation. Neurofibromin is normally expressed in many different tissues.

NF1 is among the most common of mendelian disorders, sparing no races and showing a population incidence of 1 in 3,000. Since the pattern of inheritance is autosomal dominant, approximately half of affected individuals have a family history of the disorder. Its penetrance is high, but expression is variable. The remaining cases appear to be sporadic in occurrence given the high mutation rate of the NF1 gene. Despite the high (100%) rate of penetrance, just over half of patients are only mildly affected.

Although in isolation, none of the manifestations of NF1 is pathognomonic of the disorder, a clinical diagnosis can be confirmed if a patient has two or more of the findings listed below. As a rule, the expression of NF1 is variable, even among members of the same family. Nonetheless, concordant manifestations have been reported in affected monozygotic twins, and in members of the same family. Among the earliest manifestations of NF1 and occasionally congenital are
pigmented cutaneous macules termed **café-au-lait spots**, which tend to enlarge and become more pigmented over time. Occasional macules are two-toned with both dark and pale areas. **Axillary freckling**, a form of pigmentation affecting intertriginous skin, is of particular diagnostic significance. Pigmentation in café-au-lait spots and freckles is not due to an increase in melanocytes; rather, to an excess of melanin in the form of melanosome-containing phagolysosomes. Referred to as ‘macromelanosomes’ or ‘melanin macroglobules’, they are not limited to melanocytes, but may be seen in keratinocytes, Langerhans cells, and macrophages as well. Since café-au-lait spots are commonly found in normal persons and occur in unrelated diseases, such as the McCune-Albright syndrome (polyostotic fibrous dysplasia), their size, contour, and number must be taken into account when considering a clinical diagnosis of NF1. The typical **NF1 facies** includes a broad forehead, triangular face, and dark infraorbital discoloration. Pigmented iris hamartomas, termed **Lisch nodules**, are also a common feature of NF1, thought to occur in 95% of patients over age 6 years. They are readily visualized on slit lamp examination as brown, often bilateral nodules.

Like café-au-lait spots, **neurofibromas** are hallmark lesions of NF1. All cells of NF1 patients harbor one nonfunctional NF1 gene (germline mutation). Neurofibromas arise as a result of a 2\(^{nd}\), somatic mutation. Loss or mutation of one or more tumor suppressor genes underlies transformation of neurofibroma to malignant peripheral nerve sheath tumor (MPNST). Neurofibromas may occasionally be present at birth, but most develop later in life. Hyperpigmentation may be seen overlying cutaneous and massive soft tissue neurofibromas, but the locations of the tumors and pigmentation do not necessarily coincide. Both peripheral and visceral nerves may be affected by neurofibromas. Small nerves of skin and subcutaneous tissue are preferentially involved. A single localized cutaneous neurofibroma is of no significance in terms of establishing a diagnosis of NF1. In contrast, **numerous localized cutaneous neurofibromas, plexiform, and massive soft tissue variants** are considered diagnostic of NF1.

In rare instances wherein a plexiform neurofibroma occurs in a patient without other stigmata of NF1 or a family history of the disorder, the tumor is likely the result of a local somatic mutation. This is also the mechanism underlying so-called **localized or segmental neurofibromatosis**, an anatomically limited form of NF1. Such cases often feature cutaneous or subcutaneous neurofibromas as well as café-au-lait spots limited to one portion of the body, typically one limb or even a single dermatome. These patients do not transmit the condition to their progeny. Other localized forms of NF1 include hemifacial hypertrophy and visceral neurofibromatosis.

So-called **visceral neurofibromatosis** is a rare condition in which patients often exhibit few external manifestations of NF1. The pathobiology of visceral neurofibromatosis is unclear but it may be a result of anatomically selective NF1 gene expression or nerve growth factor effect. Aside from visceral neurofibromatosis as the sole manifestation of NF1, various organ systems may be affected in the generalized form of the disease. Mainly affected is the gastrointestinal tract, which shows great case-to-case variation in manifestations. The upper gastrointestinal (GI) tract is most often involved, but colon and rectum can be affected. The spectrum of NF1-associated GI lesions includes ganglioneuromatosis, neurofibromas of both localized and plexiform type, GIST, and various neuroendocrine neoplasms. **Ganglioneuromatosis**, whether localized or diffuse, results in a Hirschsprung-like picture in children and in pseudo-obstruction or megacolon in adults. It is characterized by an increase in ganglion cells and their processes
which affects primarily the submucosal plexus. Even "giant ganglia" featuring neurons of varying size and number may be seen. As in multiple endocrine neoplasia (MEN) IIb, the mucosa may also be involved, particularly the lower lamina propria. The degree to which the myenteric plexus is affected varies, ranging from markedly hypertrophic to diminished. Patients with neurofibromatosis are also prone to develop gastrointestinal stromal tumors. Other miscellaneous tumors associated with NF1 include bilateral pheochromocytoma, duodenal paraganglioma and carcinoid tumor, rhabdomyosarcoma, juvenile chronic myelogenous leukemia, juvenile xanthogranuloma, and non-ossifying fibroma of bone.

NEUROFIBROMATOSIS 2 (NF2)
Also termed central or bilateral acoustic neurofibromatosis, NF2 is inherited in an autosomal dominant manner and exhibits a penetrance of almost 100% at age 60. Fifty percent of cases represent new or sporadic mutations. The NF2 gene has been cloned on 22q12, spanning 110 kb of genomic DNA and encoding for merlin (schwannomin), a member of the protein 4.1 family. Its function is to mediate communication between the extracellular milieu and the cytoskeleton.

NF2 is much less common than NF1. Most patients present in the second or third decade, but some cases are late onset. Although NF2 is often more clinically devastating than NF1, two forms of NF2 are encountered, the mild Gardner variant usually restricted to vestibular schwannomas and a severe, earlier onset type associated with meningiomas. Indeed, intracranial meningiomas increase the relative risk of mortality 2.5-fold. A clinicopathologic comparison of both forms of NF1 and NF2 is presented in Table 1.

Bilateral vestibular schwannomas are the hallmark of NF2. The clinical severity of NF2 varies considerably. Genotype-phenotype correlations are reflected in age of onset. Virtually all such vestibular schwannomas are benign. Although bilateral in most patients, they often present metachronously, years elapsing before the appearance of symptoms of the second tumor. The demonstration of vestibular schwannomas or the exclusion of their presence requires thin-slice (3 mm) MRI examination. Aside from vestibular examples, schwannomas in patients with NF2 affect sites similar to those of sporadic tumors, but differ in several ways. These include multifocality within a nerve, prominent myxoid change, peritumoral nerve edema, a distinctly nodular microscopic growth pattern, an association with peritumoral arachnoidal cell proliferation, and the rare occurrence of a mixed schwannoma-meningioma phenotype. Cutaneous schwannomas occur in approximately 50% of NF2 patients, their prevalence and number varying with disease severity. In contrast, superficial schwannomas in schwannomatosis are subcutaneous in location. Although plexiform neurofibromas are not a component of NF2, approximately 5% of plexiform schwannomas occur in this setting. It is of note that the majority of sporadic schwannomas also show mutations in the NF2 gene.

Meningiomas occur in the majority of patients with NF2. Indeed, multiple meningiomas may be the only feature of the disorder. They arise earlier in life than sporadic examples, are often multiple or multicentric, and sometimes take the form of ‘meningiomatosis’ in which diffuse or multifocal lesions involve both the cranial and spinal meninges. Multifocal meningiomas are not, however, pathognomonic of NF2. The variants of meningioma occur with similar frequency in NF2 as among sporadic meningiomas, but multiple lesions (57%) and intraventricular tumors (13%) were more often observed. Meningioangiomatosis is an NF2-associated, rare lesion, in
which meningotheelial cells surrounding leptomeningeal and cortical vessels form single or multiple, firm, pale lesions that literally replace a segment of cerebral cortex. Some are associated with an overlying coarse calcification which often occupies a sulcus. Meningiomas may supervene upon meningoangiomatosis. In the setting of NF2, gliomas occur less commonly than either vestibular schwannomas or meningiomas. They involve the spinal cord or, less frequently, the cerebrum or cerebellum. Fully 70% are ependymomas and often present as multiple lesions with a tendency to affect cervicothoracic levels. In addition, ependymomas may involve the filum terminale, a site also prone to the development of multiple schwannomas. Pilocytic or diffuse fibrillary astrocytomas of optic nerve, brainstem, cerebellum, or cerebrum are far less common in NF2 than in NF1. The majority of patients with NF2 die of CNS complications of the disorder. Most patients survive for longer periods. There appear to be two distinct clinical presentations. One, associated with a rapid disease course was described by Wishart and is characterized by the early onset of multiple tumors in addition to bilateral vestibular schwannomas. More protracted is the Gardner-Frazier type, the onset of which is late and features bilateral vestibular schwannomas alone. A study of 55 members of an NF2-kindred with bilateral acoustic schwannomas found that 71% of patients in whom a cause of death was known died of bilateral acoustic schwannomas, attributed to brainstem compression, elevated intracranial pressure, or complications of surgery. The 2nd major cause of death is due to spinal ependymomas, which occur in the cervicothoracic region.

Particularly unusual are tumors composed of an intimate admixture of schwannoma and meningioma, a complex lesion most often associated with NF2. To date, 10 cases have been published, all in the setting of NF2. The distribution of the two components varies from an admixture to very distinct zones of both tumor patters. The pathogenesis of the lesion remains to be determined. The common cytogenesis of Schwann cells and some leptomeninges from neuroectoderm may provide an explanation. It is also tempting to consider mixed schwannoma-meningioma to be simply collision tumors, particularly in a setting wherein both lesions occur multifocally. Bona fide examples have been reported. Also of relevance are reports of florid meningotheelial reaction in leptomeninges surrounding optic gliomas in NF1, as well as at 8th nerve schwannomas, both in association with NF2 and in sporadic examples.

**SCHWANNOMATOSIS**

As previously noted, NF1 and 2 both share a predisposition to the developments of nerve sheath tumors. A recent addition to the neurofibromatosis spectrum is schwannomatosis, an uncommon condition (estimated prevalence 1 in 40,000) characterized by the occurrence of multiple, but not vestibular schwannomas. Although it was long debated whether schwannomatosis is an attenuated form of NF2, it is now accepted as a separate syndrome. The key feature of schwannomatosis is the occurrence of multiple schwannomas, showing considerable variation in structure. Initially, it was thought to be the only neoplastic manifestation associated with this syndrome, however, recent reports suggest that schwannomatosis is also associated with menigiomas. Most cases are sporadic (85%), the remainder familial. Clinically, pain is a key feature and may be disabling. The vast majority of patients present in the 2nd–3rd decade. The distribution of schwannomas varies; in fully 30% of cases it is segmental. Peripheral, mainly spinal nerves are far more often affected (75%) than are subcutaneous or cranial nerves.
All schwannomas have biallelic inactivation of NF2 gene, but only patients with NF2 have a germline mutation detectable in all tumors and non-tumor tissues from the same patient and in tumors of different affected individuals in a family. NF2 gene loss in schwannomatosis is not germline. It is detectable in tumors, but differs among various lesions in any one patient and in tumors from other affected family members. Lineage studies of schwannomatosis kindred have placed the schwannomatosis locus centromeric to NF2 on chromosome 22q, and mutation analysis of familial schwannomatosis normal and tumor tissues has found germline mutations of the \textit{SMARCBI/INI1} gene. Mutations in the latter occur in 30% of sporadic and in 8% of familial schwannomatosis cases. The schwannomas of schwannomatosis are similar to those of NF2 including the occurrence of plexiform/multinodular examples. Their microscopic appearance often differs from conventional schwannoma in featuring myxoid change, often patchy, and peritumoral nerve edema in many instances. The immunophenotype of schwannomatosis-associated schwannomas is largely the same as that of conventional schwannomas. The differential diagnosis includes most importantly \textit{neurofibroma}, a tumor capable of malignant transformation. In contrast, schwannomas of any kind only rarely become malignant.

Lastly, schwannomatosis lesions often show partial loss of INI-1 staining (mosaic pattern), more so in familial (93%) than in sporadic examples (50%). NF2-associated schwannomas also often (83%) show a mosaic pattern of staining. In contrast, conventional schwannomas are only infrequently (5%) mosaics. Interestingly, atypical teratoid rhabdoid tumor, a highly malignant brain tumor of childhood defined by its mutation of the SMARCB1 gene and INI-1 immunonegativity, only very rarely occurs in the setting of familial schwannomatosis. We have also observed an example.

**REFERENCES:**
Gutmann DH et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. \textit{JAMA.} 1997; 278:51-7

**TABLE 1. COMPARATIVE FEATURES OF NEUROFIBROMATOSIS 1 AND 2**

<table>
<thead>
<tr>
<th></th>
<th>NF1 von Recklinghausen’s Disease</th>
<th>NF2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>1/3000</td>
<td>1/40,000</td>
</tr>
<tr>
<td>Prevalence</td>
<td>60/100,000</td>
<td>0.01/100,000</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Sporadic occurrence</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Chromosome location</td>
<td>17q11.2</td>
<td>22q12</td>
</tr>
<tr>
<td>Encoded protein</td>
<td>Neurofibromin</td>
<td>Merlin (schwannomin)</td>
</tr>
<tr>
<td>Café-au-lait spots (6 or more)</td>
<td>Often multiple and large</td>
<td>Small, rarely more than 6</td>
</tr>
<tr>
<td>at least 0.5 cm (prepubertal)</td>
<td>At least 70% of patients</td>
<td>40% of patients</td>
</tr>
<tr>
<td>one or more 1.5 cm (postpubertal)</td>
<td>About 90% of patients</td>
<td></td>
</tr>
<tr>
<td>Cutaneous neurofibromas</td>
<td>Most patients</td>
<td>Rare</td>
</tr>
<tr>
<td>Cutaneous schwannomas</td>
<td>Not associated</td>
<td>70%</td>
</tr>
<tr>
<td>Multiple Lisch nodules</td>
<td>Very common</td>
<td>Not associated</td>
</tr>
<tr>
<td>Skeletal malformations</td>
<td>Common</td>
<td>Not associated</td>
</tr>
<tr>
<td>Astrocytomas (optic, cerebellar, cerebral)</td>
<td>Moderate incidence</td>
<td>Not associated</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Occasionally seen</td>
<td>Not associated</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>Approximately 5%</td>
<td>Not seen</td>
</tr>
<tr>
<td>Intellectual impairment</td>
<td>Common</td>
<td>Not associated</td>
</tr>
<tr>
<td>Vestibular schwannoma</td>
<td>Not associated</td>
<td>Most cases (usually bilateral)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Not associated</td>
<td>Common</td>
</tr>
<tr>
<td>Spinal cord ependymoma</td>
<td>Not associated</td>
<td>Common</td>
</tr>
<tr>
<td>Meningoangiomatosis</td>
<td>Not associated</td>
<td>Occasional</td>
</tr>
<tr>
<td>Schwannosis</td>
<td>Not associated</td>
<td>Common</td>
</tr>
<tr>
<td>Glial hamartomas</td>
<td>Occasional</td>
<td>Very common</td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>Not associated</td>
<td>Associated</td>
</tr>
<tr>
<td>Posterior subcapsular cataracts</td>
<td>Not associated</td>
<td>Common (60-80%)</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>Occasional</td>
<td>Not associated</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor (GIST)</td>
<td>Occasional</td>
<td>Not associated</td>
</tr>
<tr>
<td>Paraganglioma, including duodenal gangliocytic variant</td>
<td>Occasional</td>
<td>Not associated</td>
</tr>
<tr>
<td>Foregut carcinoid tumor, including duodenal calcifying somatostatinoma</td>
<td>Occasional</td>
<td>Not associated</td>
</tr>
<tr>
<td>Juvenile xanthogranuloma</td>
<td>Occasional</td>
<td>Not associated</td>
</tr>
<tr>
<td>Juvenile leukemia (CML)</td>
<td>Occasional</td>
<td>Not associated</td>
</tr>
</tbody>
</table>
Familial cancer syndromes involving the peripheral nervous system

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Phakomatoses

• Neurofibromatoses#
• Tuberous sclerosis
• Neurocutaneous melanosis
• Hypomelanosis of Ito
• Incontinentia pigmenti
• Sturge-Weber syndrome*
• von Hippel-Lindau disease

all except * are autosomal dominant

# significant involvement of the peripheral nervous system
NEUROFIBROMATOSIS 1 (NF1)

- the most common of mendelian disorder
- sparing no races
- population incidence of 1 in 3,000
- autosomal dominant: high penetrance, variable expression (half of patients are only mildly affected)
- half of affected individuals have a family history of the disorder
- remaining cases appear to be sporadic in occurrence given the high mutation rate of the NF1 gene
Neurofibromatosis

• multiple lesions of diverse type (neuroectodermal or mesenchymal derivation): hyperplasias, hypoplasias, hamartomas, benign and malignant neoplasms
• No gender or racial predilections
• 3 principal genetic and clinicopathologic forms are recognized:
  – Neurofibromatosis type 1 (NF1)
  – Neurofibromatosis type 2 (NF2)
  – Schwannomatosis
• NF1 & NF2:
  – genetic alterations affecting tumor suppressor genes.
  – 10x- higher risk of developing a malignant neoplasm
Manifestations of NF1

- Café-au-lait spots*
- Axillary freckling *
- NF1 facies
- Lisch nodules
- Neurofibromas:
  - numerous localized cutaneous neurofibromas
  - plexiform
  - massive soft tissue variant

* Pigmentation is due to an excess of melanin (melanosome-containing phagolysosomes) in melanocytes, keratinocytes, macrophages.
Café-au-lait spots
Axillary freckling
Lisch nodules
Lisch nodules
Localized Cutaneous Neurofibroma

Dermal / subcutaneous neurofibromas are dome-shaped, discrete, and movable.

Neurofibromas affecting the palm/sole are rare outside the setting of NF1.
Innumerable Localized Cutaneous Neurofibromas
Typical facial features in NF1
Plexiform Neurofibroma

Soft and compressible, lesions are often likened to a “bag of worms”

Massive digital enlargement (“localized gigantism”)
Large plexiform neurofibromas massively enlarged nerves and often have intervening diffuse neurofibromatous tissue.
Plexiform Neurofibroma
Plexiform Neurofibroma
Neurofibroma with Schwannomatous Nodules
Multiple Bilateral Nerve Roots Neurofibromas
Massive Neurofibroma in NF1 (plaque)
Massive Neurofibroma in NF1

Cape-like flaps

Massive diffuse examples affect an entire limb, a lesion once referred to as “elephantiasis neuromatosa”
Massive Soft Tissue Neurofibroma
Other forms of Neurofibromatosis

• Localized or segmental neurofibromatosis
  – cutaneous/subcutaneous neurofibromas, café-au-lait spots limited to one portion of the body (limb or single dermatome)
  – do not transmit the condition to their progeny

• Hemifacial hypertrophy

• Visceral neurofibromatosis
  – anatomically selective NF1 gene expression
  – exhibit few external manifestations of NF1
Segmental neurofibromatosis – trigeminal nerve distribution

NF1 – local somatic mutation
Visceral neurofibromatosis
NF1-associated GI lesions

- Ganglioneuromatosis
- Neurofibromas (localized or plexiform type)
- GIST
- Various neuroendocrine neoplasms
GI Neurofibromas in NF1
NEUROFIBROMATOSIS 2 (NF2)

Central or Bilateral Acoustic Neurofibromatosis

- autosomal dominant, 100% penetrance
- 50% represent new or sporadic mutations
- The NF2 gene: merlin (schwannomin), a member of the protein 4.1 family, mediating communication between the extracellular milieu and the cytoskeleton.
- 2 clinical forms of NF2:
  - mild variant usually restricted to vestibular schwannomas
  - severe, earlier onset type associated with meningiomas
Manifestations of NF2

- Bilateral vestibular schwannomas
  - multifocality within a nerve
  - prominent myxoid change (predominant Antoni B)
  - peritumoral nerve edema
- Meningiomas
- Meningioangiomatosis
- Mixed schwannoma-meningioma
- Ependymomas
Bilateral vestibular schwannomas
Multiple Schwannomas in NF2

Multiple cranial or spinal nerve root schwannomas arising in cauda equina nerve roots

multinodular lesion median nerve
Multiple Meningiomas in NF2
Meningioangiomatosis
Multiple Spinal Cord Ependymomas in NF2

Whole mount longitudinal section of the spinal cord
SCHWANNOMATOSIS

- recent addition to the neurofibromatosis spectrum
- Rare: prevalence 1 in 40,000; 2\textsuperscript{nd}-3\textsuperscript{rd} decade
- multiple schwannomas, but not vestibular schwannomas
- also associated with meningiomas.
- Most cases sporadic (85%), remainder familial
- Clinically: pain is a key feature and may be disabling.
SCHWANNOMATOSIS

• Distribution:
  – 30% of cases it is segmental.
  – Peripheral, mainly spinal nerves are far more often affected (75%) than are subcutaneous or cranial nerves.

• Genetics:
  – NF2 gene loss in schwannomatosis is not germline
  – germline mutations of the SMARCB1/INI1 gene (30% of sporadic and in 8% of familial): loss of INI-1 staining (mosaic pattern) by IHC
Schwannomas in Schwannomatosis

(A) conventional globular lesions arising in a single fascicle,
(B) multiple examples affecting the same fascicle
(C-E) multiple tumors affecting multiple fascicles
Tumors affecting a single fascicle may be separated by normal nerve or abut one another

1/25/2012
MRI T2-WEIGHTED IMAGES: coexistent plexiform- (arrows) and conventional (asterisk) appearing lesions
Schwannomas in Schwannomatosis

Schwannoma residing within a single fascicle, with 3 accompanying normal fascicles

endoneurium edema surrounding the tumor
Loss of immunoreactivity for INI1, often partial due to mosaicism