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Genetic predisposition to peripheral nerve neoplasia: Diagnostic criteria and pathogenesis of neurofibromatoses, Carney complex, and related syndromes

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Abstract

Neoplasms of the peripheral nerve sheath represent essential clinical manifestations of the syndromes known as the neurofibromatoses. Although involvement of multiple organ systems, including skin, central nervous system and skeleton, may also be conspicuous, peripheral nerve neoplasia is often the most important and frequent cause of morbidity in these patients. Clinical characteristics of neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) have been extensively described and studied during the last century, and the identification of mutations in the *NF1* and *NF2* genes by contemporary molecular techniques have created a separate multidisciplinary field in genetic medicine. In schwannomatosis, the most recent addition to the neurofibromatosis group, peripheral nervous system involvement is the exclusive (or almost exclusive) clinical manifestation. Although the majority of cases of schwannomatosis are sporadic, approximately a third occur in families and a subset of these has recently been associated with germline mutations in the tumor suppressor gene *SMARCB1/INI1*. Other curious syndromes that involve the peripheral nervous system are associated with predominant endocrine manifestations, and include Carney Complex and MEN2b, secondary to inactivating mutations in the *PRKARIA* gene in a subset, and activating mutations in *RET* respectively. In this review, we provide a concise update on the diagnostic criteria, pathology and molecular pathogenesis of these enigmatic syndromes in relation to peripheral nerve sheath neoplasia.

Keywords

neurofibromatosis; NF1; NF2; schwannomatosis; Carney complex; multiple endocrine neoplasia; neurofibroma; schwannoma

Introduction

Neoplasms developing from cell components of the peripheral nerve sheath may arise sporadically, but are a frequent manifestation of specific inherited genetic disorders. Some of these syndromes may afflict multiple organ systems; for example, neurofibromatosis type 1 (NF1) (the most frequent of these syndromes) in addition to the development of

neurofibromas and malignant peripheral nerve sheath tumors (MPNST) is associated with neoplastic and developmental disorders of the central nervous and musculoskeletal systems. Carney complex is characteristically associated with additional endocrine manifestations. Other syndromes such as schwannomatosis may be almost entirely restricted to peripheral nerve.

Recent scientific developments have expanded greatly our knowledge of the molecular basis for these disorders (Figure 1). These include increased efficiencies of sequencing technologies, allowing parallel screening for multiple mutations in different genes, as well as the development of relevant animal models that recapitulate the key manifestations of these syndromes with surprising accuracy.

In this review we attempt to summarize the most updated criteria for these problematic syndromes. In addition, we provide updated concepts on their pathogenesis, pathology, and on our molecular understanding of the underlying mechanisms. We have focused this review on the neoplastic manifestations in peripheral nerve. Excellent reviews covering additional clinical manifestations of these multiorgan syndromes are available[33, 38, 55, 68, 69, 92]. Detailed coverage of current concepts on the biological properties and pathogenesis of Schwann cell neoplasms are covered in this same journal issue by Carroll S[20], as well as diagnostic pathology of peripheral nerve sheath tumors by Rodriguez FJ et al.[91]

Neurofibromatosis type 1 (NF1)

Clinical Features and Genetics: the protean manifestations of NF1

NF1 is the most frequent of the inherited genetic syndromes resulting in peripheral nerve sheath tumors. The incidence of this syndrome is approximately 1 in 2,500–3000 births[32, 45, 53, 87], and afflicts individuals of all races and geographic regions. NF1 results from germline mutations in the gene encoding for neurofibromin (*NFI*). The *NFI* gene was identified by positional cloning in 1990[22, 114], and is located in chromosomal region 17q11.2. Neurofibromin is ubiquitously expressed, but the highest levels are found in the nervous system, both central and peripheral, which is prominently involved in the NF1. Neurofibromin is an important tumor suppressor, a GTPase activating protein that regulates ras[24]; therefore, absence of neurofibromin leads to constitutive activation of ras signaling. Neurofibromin may also regulate cAMP levels, although the effects of altered cAMP levels may be more important in central nervous system manifestations of *NFI* deficiency, including optic glioma formation and cognitive deficits in model systems[17, 115].

The diagnosis of NF1 is essentially a clinical one, and diagnostic criteria have been proposed and generally well accepted[1, 34, 44](Table 1). The caveat with these diagnostic criteria schemes, is that some patients present with mosaicism, or findings limited to a specific anatomical region, i.e. so called “segmental” neurofibromatosis. It is possible that an individual can fulfill criteria within a body segment and clinicians need to be aware not to apply the criteria in these situations. A variety of tissues are affected in the form of hyperplasias, hamartomas and neoplasms (Figure 2). Involvement of the skin (café-au-lait spots and axillary freckling), eye (Lisch nodules), bone (dysplasia of sphenoid bone or long bones, kyphoscoliosis), cardiovascular system (cerebral arteriopathy, pulmonary artery stenosis), and central nervous system (learning disabilities) are all important manifestations of the syndrome. However, although it is thought that NF1 penetrance is 100% with appropriate follow-up, extent of organ involvement and clinical manifestations in specific patients, even within families, are variable. Syndromes that present with similar facial and pigmentary features of neurofibromatosis include Noonan syndrome, associated with mutations in various components of the RAS/MAPK signaling pathway[84], and a recently

described NF1-like syndrome associated with *SPRED1* mutations[15, 76], although they are not known to be associated with neoplasms of peripheral nerve.

Neurofibromas and MPNSTs in NF1: pathology and pathogenesis

The main neoplasms that develop in the setting of NF1 predominantly involve the peripheral nerve, in particular benign neurofibromas (Figure 2b). Neurofibromas can be of different clinicopathologic types according to the WHO classification[67, 97], including cutaneous (localized or diffuse), intraneural (localized) or plexiform. Histologically, the main cell type in neurofibromas is the Schwann cell, but they also contain a variety of cellular nerve components, including fibroblasts, mast cells, axons and perineurial cells[97]. Cellularity in conventional neurofibromas is low, and they contain a variable myxoid stroma associated with collagen fiber bundles (Figure 2c). When involving a peripheral nerve trunk, they cause a characteristic, diffuse fusiform expansion. Diffuse neurofibromas may be encountered in NF1 patients, although they are not exclusive of the syndrome (Figure 2d). They usually present as large cutaneous plaques that infiltrate dermis and subcutaneous tissues, and entrap cutaneous adnexal structures. Occasionally, they contain pseudo-meissnerian corpuscles, i.e. small structures resembling the specialized Wagner-Meissner sensory bodies(Figure 2e). Diffuse neurofibromas may also arise in deep locations and even involve internal organs.

Plexiform neurofibromas are complex neoplasms that by definition involve many peripheral nerve fascicles or components of a large nerve plexus (Figure 2f). The gross appearance of these tumors is characteristic, which may exhibit a “worm-like” mass tangle. Deep plexiform neurofibromas involving large nerves or nerve plexuses occur almost exclusively in the setting of NF1 syndrome[97, 119]. In addition to be associated with increased morbidity, plexiform neurofibromas have a propensity for malignant degeneration and represent a precursor to MPNST, an important cause of mortality in NF1 patients. However, it should be noted that on rare occasions localized intraneural neurofibromas may also undergo malignant degeneration.

MPNSTs are usually high grade spindle cell neoplasms with various degrees of Schwann cell differentiation, with a high propensity for metastasis (Figure 2g). They occur in 8–13% of patients with NF1[30]. Divergent differentiation (i.e. mesenchymal or epithelial “heterologous” components) may be present, in particular in the setting of NF1[27], including skeletal muscle, smooth muscle, cartilaginous, osseous, angiosarcomatous or glandular differentiation[27, 89, 117, 118] (Figure 2h,i). Another rare neurofibroma variant that is strictly limited to the NF1 syndrome is the massive soft tissue neurofibroma (Figure 2j,k,l), which can reach an enormous size and lead to distortion of the soft tissues or even a whole extremity[119]. Histologically, it infiltrates diffusely into soft tissue, including skeletal muscle and nerve fascicles, and may contain regions packed with cells containing high nuclear cytoplasmic ratios (Figure 2l), as well as pseudo-meissnerian corpuscles. In spite of its increased and alarming cellularity at the histological level, and negative cosmetic effects, the massive soft tissue neurofibroma usually follows a benign course. However, a plexiform component is present in some instances, and therefore a low potential for malignant degeneration exists.

Internal organs may be involved in NF1, predominantly the gastrointestinal tract, in the form of neurofibromas, ganglioneuromatosis, or gastrointestinal stromal tumors. Glomus tumors have recently been added to the NF1 spectrum[16], although they rarely involve peripheral nerve.

Numerous advances have been made in recent years regarding the biology of nerve sheath tumors in NF1. Neurofibromas exhibit genetic alterations in S100 positive Schwann cells, which demonstrate loss of heterozygosity in the *NF1* gene[82]. However, early observations

have demonstrated a variety of cellular components in neurofibromas in addition to Schwann cells, including perineurial cells, fibroblasts as well as hematopoietic components such as mast cells. Mouse knockout experiments have highlighted the importance of the tumor microenvironment in the development of neurofibromas, since haploinsufficient microenvironment cell components are required for neurofibroma development[121]. Recently, *NF1* heterozygous multipotent precursor cells, presumably hair follicle-derived, have been isolated from neurofibromas, and may aid in the development of cutaneous tumors[56].

Timing and precise location of *Nf1* inactivation in neurofibroma has been tested in various mouse models, with *Nf1* loss in the embryonic period[64], perinatal period or even adulthood resulting in neurofibromas[72]. Some investigators have proposed nonmyelinating Schwann cell progenitors (p75+) as the cell of origin of plexiform neurofibroma[125]. However, this finding is controversial since *Nf1* loss in Schwann cell precursors expressing desert hedgehog also leads to plexiform neurofibromas[120]. In addition, a cutaneous neural stem cell/progenitor, which is neural crest derived but outside of the Schwann cell lineage, may give rise to cutaneous neurofibromas[63]. Malignant peripheral nerve sheath tumors, in addition to *NF1* loss, develop alterations in additional tumor suppressors and amplification/overexpression in receptor tyrosine kinases such as the epidermal growth factor receptor[65, 83, 124]. Detailed updates in the biology of these tumors is covered in recent reviews, including a comprehensive one by Carroll S. in the current issue[20].

Neurofibromatosis type 2 (NF2)

Clinical Features, Diagnostic Criteria, and Genetics

NF2 occurs at a lesser frequency than NF1, with an estimated incidence of 1 in 33–40,000 births[29]. NF2 has also been referred historically as “central” neurofibromatosis, a currently discouraged term, which emphasized the predilection of NF2 associated neoplasms for the central nervous system and craniospinal axis, compared with NF1 (Figure 3a,b). The *NF2* gene was identified in 1993[93, 111]. The protein product of *NF2* is also known as Merlin or schwannomin, another tumor suppressor with numerous cellular functions, particularly associating with cell junction complexes.

The clinical manifestations of NF2 in many instances may be associated with increased morbidity compared with those of NF1, and include a variety of neoplasms (schwannoma, meningioma, ependymoma), as well as cutaneous (Figure 3c) and eye manifestations (posterior subcapsular cataracts, retinal hamartomas, epiretinal membranes). Peripheral nerve manifestations include a polyneuropathy in addition to schwannomas[48]. The development of bilateral vestibular schwannomas is a hallmark of NF2, and a useful diagnostic criterion (Table 2). However, NF2 mosaicism has been extensively reported, and the presence of unilateral vestibular schwannoma in the presence of other NF2 manifestations should raise this possibility. The presence of NF2 mosaicism is particularly an issue in patients without family history (i.e. de novo), where it occurs in 20–30% of patients[61, 77]. Clinical manifestations may also vary in patients with different mutations in the *NF2* gene. For example, several studies have demonstrated a more severe NF2 phenotype (earlier onset of symptoms, higher tumor burden, earlier death) in patients with nonsense or frameshift mutations resulting in abnormal protein expression, compared with mutations/large deletions resulting in complete Merlin loss[75, 99], or Merlin retention [75, 99].

Abnormalities in skin pigmentation (i.e. café au lait spots), and development of cutaneous neoplasms occurs to a lesser extent in NF2 than in NF1[28]. A characteristic lesion

occurring in NF2 with hamartoma-like features that demonstrates involvement of the brain cortex proper is meningioangiomatosis. This uncommon, epilepsy-associated lesion is characterized by downgrowth of meningotheial or meningotheial-like cells in association with leptomeningeal and superficial cortical vessels. Occasionally they coexist with meningiomas. The clinical manifestations of NF2 have been embodied in contemporary diagnostic criteria [1, 34, 44, 78], which have emphasized clear, objective separation of NF2 from NF1[1, 2, 8, 28, 44](Table 2). Recent interest to incorporate genetic information to clinical classification schemes have been developed in Baser's criteria (Table 3)[1, 2, 8, 28, 44].

Peripheral nerve pathology in NF2: Schwannoma as a model of impaired cell junctions in tumorigenesis

The development of multiple schwannomas is one of the hallmarks of the NF2 syndrome (Figure 3d). As in the sporadic setting, these benign neoplasms are characterized by a compact proliferation of neoplastic Schwann cells (Figure 3e). Unlike neurofibroma, non-neoplastic nerve sheath components and infiltration of peripheral nerve are lacking. Histologically, schwannomas demonstrate a well formed capsule, as well as alternating Antoni A (cellular, collagen rich) and Antoni B (loose, mucopolysaccharide rich) areas (Figure 3f). Verocay bodies, distinctive palisades in Antoni A areas, are variable in frequency but one of the diagnostic hallmarks (Figure 3g). Additional histologic features of schwannomas include degenerative vascular changes with hyalinization and perivascular hemosiderin. Immunohistochemical stains demonstrate strong expression of S100 and collagen IV (pericellular), while EMA is limited to the peripheral perineurium and neurofilament protein highlights peripheral axons. Plexiform schwannoma is a rare variant with a predilection for cutaneous sites, and characterized by a multinodular pure Schwann cell neoplastic growth. Multiple plexiform schwannomas may be identified in NF2 patients[85, 112], although they are not specific to the syndrome (in contrast to large or multiple plexiform neurofibromas in NF1).

In general, syndrome-associated schwannomas are similar to sporadic examples. Although no formal large pathologic studies are available, some features described at increased frequency in NF2-associated tumors include the formation of whorls (Figure 3h) and multifocal involvement within a single nerve[97], as well as juxtaposition with meningiomas (Figure 3i). In addition, patchy loss of INI1 immunohistochemical staining ("mosaic" pattern) has been reported in the majority of syndrome associated schwannomas, including both NF2 and schwannomatosis [81].

Although malignant degeneration in schwannomas, including the NF2 setting, is an extremely rare phenomenon, this has been reported in NF2 patients, in particular after radiation therapy[31]. Also, it should be noted that cutaneous neurofibromas may also occur in NF2. Although, the presence of neurofibromas has been used in the past as a clue to distinguish NF2 from schwannomatosis, neurofibromas have been reported in two patients satisfying clinical criteria for schwannomatosis[90].

At the molecular level, the neoplastic manifestations of NF2 are explained by initial Merlin loss. A critical function of Merlin is its participation in *contact-dependent inhibition*, whereby cell proliferation is suppressed with increased cell density and formation of intercellular adhesions[26]. However, Merlin associates with many different proteins in diverse cells types, and additional functions include regulation of cell surface and intracellular signaling cascades[9, 60], as well as actin-cytoskeleton interactions[62].

Schwannomatosis

The new neurofibromatosis: background and diagnostic criteria

Schwannomatosis is the most recent addition to the neurofibromatosis group. The incidence of schwannomatosis in the general population may be similar to NF2[5], but is probably less well recognized. Schwannomatosis, as NF2, is characterized by the development of multiple schwannomas (Figure 4a,b). Unlike NF2, schwannomas in schwannomatosis spare the vestibular nerves and the majority of the patients lack a family history. Ocular involvement has not been described and the typical NF2 intracutaneous plaque lesions [28] also do not appear to be part of the schwannomatosis phenotype. The main clinical manifestation and indication for surgery is pain, which in these patients may be debilitating[70].

Although our understanding of this enigmatic syndrome continues to evolve, practical diagnostic criteria have been developed[70]. Age is a critical factor in the diagnosis of schwannomatosis, and a cutoff of age 30 to document absence of vestibular schwannomas (and therefore NF2) has been proposed (table 4). Some investigators have advocated the use of high resolution MRI studies with special protocols focusing on the internal auditory canals, to exclude small vestibular schwannomas which are diagnostic of NF2 [70]. Other investigators advocate molecular testing, particularly young patients, to exclude NF2 including mosaics[8].

Schwannomatosis pathology and the *SMARCB1/INI1* gene

Schwannomas presenting in the setting of schwannomatosis share many of the histologic features with those occurring in NF2 or sporadically. These features include alternating cellular and loose areas (Antoni A and Antoni B respectively), Verocay bodies, hyalinized vessels and the presence of a capsule. However, features that appear to be overrepresented in schwannomatosis associated tumors include myxoid changes, intraneural growth, and peritumoral nerve edema[70](Figure 4c).

An important hallmark in our understanding of schwannomatosis was the identification of an inactivating germline mutation in the *SMARCB1/INI1* gene in a family with the syndrome [52]. This was a somewhat surprising finding, given that germline mutations in this key tumor suppressor gene have been described in families predisposed to high grade malignant tumors, in particular atypical teratoid rhabdoid tumors[11]. More recently, different somatic (but not germline) NF2 mutations in separate schwannomas, in addition to a *SMARCB1/INI1* germline mutation, were described in a family suggesting a “four-hit” mechanism for schwannoma tumorigenesis in some schwannomatosis patients[100]. Indeed, this inactivation of both NF2 and *SMARCB1/INI1* appears to be the typical mechanism in schwannomas from *SMARCB1/INI1* germline mutated individuals[46]. Similar findings were reported in a multiple meningioma family[23], although *SMARCB1/INI1* mutations seem very rare in multiple meningioma patients[46]. Immunohistochemical testing for INI1 is feasible in pathologic specimens. Curiously, a “mosaic” pattern of immunostaining, where a subset of tumor cells are positive while others are negative, has been described in syndrome associated schwannomas, including both NF2 and schwannomatosis[81](Figure 4d). This contrasts with INI1 loss in atypical teratoid rhabdoid tumor, where the loss occurs in most, if not all tumor cells. This may correlate with the different genotypes in schwannomatosis patients which are often missense mutations indicating the possibility of hypomorphic mutations.

Although patients with schwannomatosis were felt to be predisposed to multiple schwannomas only, a recent schwannomatosis family with a *SMARCB1* mutation and multiple meningiomas has been recently described[7], adding multiple meningiomas to the schwannomatosis spectrum. Similarly, cutaneous neurofibromas were thought not to be part

of the syndrome, but the recent report of two schwannomatosis patients with superficial neurofibromas[90] suggests caution in the interpretation of the schwannomatosis patient with isolated cutaneous neurofibromas.

Carney Complex

Background

Carney complex (CNC) is a rare multiple neoplasia syndrome first described by Dr. J. Aidan Carney in 1985 as ‘the complex of myxomas, spotty pigmentation, and endocrine overactivity’ and inherited in an autosomal dominant manner; Dr. Carney recognized that patients with syndromes that had been previously described as LAMB (lentigines, atrial myxoma, myxoid neurofibroma and ephelide) or NAME (nevi, atrial myxoma, blue nevi) had the same condition [6, 86]. To this date, over 500 patients of diverse ethnicity from all continents have been registered by the NIH-Mayo clinic (USA) and the Cochin Hospital (France); 43% are males and 57% are females; approximately 70% are familial cases [107].

Diagnosis and Clinical Manifestations of CNC

The diagnosis of CNC is made if two or more major manifestations of the syndrome are present (Table 5) [12, 71, 95, 107]. These must be confirmed by histology, biochemical testing, and imaging. However, one can also make the diagnosis when only one of the major criteria is present if the patient is a carrier of a known inactivating mutation of *PRKARIA* [13]. Additionally, a considerable number of clinical and biochemical manifestations listed in Table 4 are suggestive, but not diagnostic, of CNC.

Cutaneous Manifestations—Pigmented skin lesions are reported in the majority of CNC patients (over 80%). They constitute one of the three major criteria of CNC and are diagnostically very important because, easily recognizable and occurring early in life, they may lead to early detection of a potentially life threatening disease. The most common skin lesions are lentigines (they are present in 70–75% of cases). Morphologically, lentigines are flat, poorly circumscribed, brown-to-black macules usually measuring less than 0.5 cm in diameter. Histologically, lentigines show hyperpigmentation of the basal cell layer associated to melanocytic hyperplasia and hypertrophy. In contrast, the pigmentation in common freckles is the result of increased melanin production, usually without melanocytic hyperplasia [105] [51]. Even though lentigines may be the first sign of CNC at birth, they usually do not acquire their typical intensity and characteristic distribution (lips, conjunctiva and inner and outer canthi; vaginal and penile mucosa) until the late prepubertal and early peripubertal period [10, 71]. The second most frequent skin manifestations in CNC patients are blue nevi, and in particular, epithelioid blue nevi[10, 51], followed by cutaneous myxomas [10, 71]. Early identification of cutaneous myxomas is essential since it is estimated that almost 80% of CNC patients with a lifethreatening cardiac myxoma had presented earlier in life with cutaneous myxoma [10, 71, 107].

Other CNC-related skin manifestations include: café-au-lait spots (typically less pigmented than those seen in McCune Albright syndrome) or depigmented lesions that can also be present at birth or develop during childhood; melanocytic and atypical nevi, and the so called Spitz nevus.

Neoplasms in Carney Complex

Cardiac myxomas, which can appear as early as in infancy, are responsible for over 50% of the disease-specific mortality of CNC patients. Early detection and regular screening for cardiac myxomas by echocardiography is essential, as these tumors can lead to sudden death

by embolism, strokes, or cardiac failure. Cardiac myxomas are the most common, clinically significant non-cutaneous lesions in CNC patients.

Pigmented nodular adrenocortical disease (PPNAD) is the most frequent endocrine manifestation in CNC patients. Adrenocorticotrophic hormone-independent Cushing syndrome (CS), is present in 25–30% of CNC patients [104]. PPNAD is named after the macroscopic appearance of the adrenal glands that is characterized by small, cortisol-producing, pigmented micro-nodules (less than 1 cm in diameter) of the adrenal cortex. Diagnosis of CS due to PPNAD is often difficult because hypercortisolism can develop progressively over years and may be periodic: cyclical and atypical CS is more often the rule, rather than the exception among patients with CNC [104, 107]. Pathological investigation reveals that adrenal glands from patients with PPNAD are usually normal in size and weight; it is for this reason, that one out of three patients has essentially normal-appearing adrenal glands on computed tomography (CT-scan). The remaining patients may have visible round micronodules (smaller than 1 cm in diameter) or, rarely, macronodules (larger than 1 cm) within the background of hyperplasia.

Psammomatous melanocytic schwannoma (PMS) was present in 8% of CNC patients studied by Bertherat and al, and four patients died of metastatic PMS [10]. PMS may occur anywhere in the peripheral nervous system, but it is most frequently found in the gastrointestinal tract (esophagus and stomach) and the paraspinal sympathetic chain. Schwannomas in CNC are characterized by their heavy pigmentation (melanin), frequent calcifications, and multicentricity (Figure 5). PMS is unlike any of the schwannomas seen in the other conditions reviewed in this article [18, 19, 107].

In contrast to conventional schwannomas, melanotic schwannomas usually lack Verocay bodies, microcysts, a well formed capsule and thick-walled hyalinized vessels. Psammoma bodies may be focal and only identifiable after extensive search. However, their recognition is important since approximately half of patients with PMS have CNC, and the syndrome association is even higher when multiple tumors are present. In addition these tumors frequently contain large cytoplasmic vacuoles simulating adipose tissue. Another important distinction with conventional schwannoma is that a subset of melanotic schwannomas (up to 15% reported cases) are associated with malignant clinical behavior [25, 36, 54, 94]. Strict criteria of malignancy in melanotic schwannoma are not well developed, although a combination of worrisome histologic features (large vesicular nuclei with macronucleoli, brisk mitotic activity and necrosis) raises concern of aggressive behavior.

The differential diagnosis of melanotic schwannoma is largely restricted to melanocytic tumors ranging from melanocytoma to primary and metastatic melanoma. Melanocytic immunohistochemical markers (e.g. S100, melanA, HMB45) are not useful in this distinction, since they are frequently expressed in both tumor categories. The identification of pericellular basement membrane by histochemical (reticulin) and immunohistochemical (Collagen IV, laminin) stains or by electron microscopy is more specific for melanotic schwannoma (Figures 5 and 6), although this important diagnostic feature is not as accentuated as in conventional schwannomas[97].

Additional tumors and tumor-like manifestations of CNC include growth hormone secreting pituitary hyperplasia and adenomas, large-cell calcifying Sertoli cell tumors (*LCCSCT*), thyroid gland disease[103], ovarian cysts [80, 106] and osteochondromyxoma.

Pathogenesis of Carney Complex

Genetic linkage analysis identified two independent loci for CNC, CNC1 located on chromosome 17p22–24 and CNC2 located on chromosome 2p16 [58, 102]. The genetic

defect responsible for CNC at locus 2p16 remains unknown. In most cases, CNC is caused by inactivating mutations in the regulatory subunit type 1 alpha gene (*PRKAR1A*) located at 17q22–24 which encodes the most widely expressed of the protein kinase A (PKA) regulatory subunits [107]. Thus, *PRKAR1A* is a key component of the cAMP signaling pathway. *PRKAR1A*'s genomic region is approximately 21 kblong and the open reading frame contains 11 exons that code for a protein that totals 384 amino acids. The peptide consists of a dimerisation/docking domain and two cAMP binding domains (A and B) that are essential for its function within the PKA tetramer (see below).

To date, over 100 disease-causing pathogenic sequence variants, spread all over the coding length of the gene, have been identified. These coding variants show no preference for a particular genomic region or exon. A recent extensive update by Horvath and al., reviewed all the known *PRKAR1A* mutations. The majority of CNC-causing *PRKAR1A* mutations are base substitutions, small deletions and insertions or rearrangements [107]. Rarely, large *PRKAR1A* deletions can occur [50]. The phenotype of these depends on their intronic versus exonic sequences that are involved and whether additional genes are involved. Over 70% of CNC patients with a classical phenotype show a *PRKAR1A* mutation which leads to a premature stop codon and subsequently non-sense mediated mRNA decay (NMD) [10, 107] and, thus, *PRKAR1A* haploinsufficiency. The mutations that escape NMD are significantly less frequent and lead to the expression of an abnormal and defective *PRKAR1A* protein [42, 50, 74, 113]. The *in vitro* effect of a certain number of these expressed mutations has been evaluated and confirmed their pathogenic potential [39, 74].

Until recently, no genotype-phenotype correlations had been found for the stop codon mutations that lead to *PRKAR1A* haploinsufficiency. This is because most of the *PRKAR1A* mutations in CNC patients are family or patient specific and only three mutations have been identified in more than three kindreds: c.82t, c.491–492delTG in exon 5 and c.709-7del6 in intron 7 [42, 107]. Recently, Bertherat and al. reported a genotype-phenotype study in 353 CNC patients of which 73% were positive for a *PRKAR1A* mutation [10]. *PRKAR1A* mutations were observed in 80% of the familial cases compared to 37% of the sporadic CNC patients. The overall penetrance of CNC in *PRKAR1A* mutated patients was 97.5%. Patients with *PRKAR1A* mutations more frequently had myxomas, skin lesions, thyroid and gonadal tumors and these clinical manifestations appeared at an earlier age compared to CNC patients that did not have *PRKAR1A* mutations or deletions. Acromegaly, cardiac myxoma, lentigines and PMS were more often associated with exonic mutations. An ongoing study, by the same group, is evaluating the clinical implications of the co-occurrence of phosphodiesterase 11A (*PDE11A*) mutations in CNC patients with *PRKAR1A* mutations. The *PDE11A* locus was identified by a genome-wide SNP genotyping study in individuals with adrenocortical hyperplasia leading to Cushing's syndrome that was not caused by known genetic defects [49]. More CNC-causing genes remain to be identified as over 60% and 25% of respectively sporadic and familial cases are negative for *PRKAR1A* mutations.

How do *PRKAR1A* defects cause CNC and its tumors? In its inactive form, cyclic AMP (cAMP)-dependent protein kinase (or PKA) is a holotetramer composed of two regulatory (R) and two catalytic (C) homodimers. The tetramer is dissociated into two regulatory and two free enzymatically active catalytic subunits when intra-cellular cAMP levels increase and two molecules of cAMP bind to each of the regulatory subunits [57, 110]. In turn, free catalytic subunits phosphorylate a variety of cellular target substrate proteins, that regulate a wide range of cellular processes: transcription, metabolism, cell cycle progression and apoptosis [98, 101]. So far, four different regulatory subunits (*PRKAR1A*, *PRKAR1B*, *PRKAR2A*, and *PRKAR2B*) and four catalytic subunits (*PRKACA*, *PRKACB*, *PRKACG* and *PRKX*) have been identified. It is the *PRKAR1A* gene coding for the PKA type I-A

regulatory subunit (R-1 α) that is mutated in CNC and *PRKAR1A* is the only PKA subunit in which mutations have been found to lead to human disease. *PRKAR1A* haploinsufficiency leads to excess cellular cAMP signaling in affected tissues [58, 88]. Loss of R-1 α leads to an increase in total (but not PKA specific) cAMP-stimulated kinase activity [21, 58].

The role of R1 α has been explored in several different cancer tissues and cell lines, including colorectal, breast, renal, and ovarian cancer [14, 35, 47, 66, 73, 79, 116]. The CNC data suggest that *PRKAR1A* is a tumor suppressor gene, as tumors from CNC patients frequently carry both the germline mutation and LOH of the 17q22–24 *PRKAR1A* locus. However, a few CNC tumors did not show *PRKAR1A* LOH [21, 58]. Mouse models have shed some light into the role of *PRKAR1A* haploinsufficiency in tumor formation in cAMP responsive tissues. *Prkar1a* knock-out (KO) animals die *in utero* due to failed cardiac morphogenesis [4]. Heterozygous KO (HetKO) mice develop tumors in cAMP-responsive tissues (non pigmented schwannomas, bone lesions and thyroid neoplasias) but they lack some characteristic CNC lesions, like cardiac and skin myxomas, and pituitary adenomas. However, compared to human CNC tumors, cAMP signaling in HetKO mouse cells is only modestly increased, which may explain the lower susceptibility of the mouse pituitary, heart and skin in tumor formation [59]. A different mouse model, which led to significantly higher *PRKAR1A* downregulation, showed higher cAMP signaling and an overall more severe phenotype, including endocrine manifestations such as hypercorticotesteronemia and thyroid cancer, and an overall shorter lifespan [40, 41]. Tissue-specific, pituitary and cardiac, complete *Prkar1a*-KO mice, did develop pituitary adenomas and cardiac lesions that resembled human myxomas, respectively [122, 123].

A recent mouse model studied the effect of *PRKAR1A* haploinsufficiency on tumor formation in the background of other known tumor suppressor gene defects and chemically induced skin papillomas. Interestingly, *Prkar1a*^{+/-}*Trp53*^{+/-} and *Prkar1a*^{+/-}*Rb1*^{+/-} double heterozygote mice developed more sarcomas and grew more and larger pituitary and thyroid tumors compared to the single HetKO *Trp53*^{+/-} and *Rb1*^{+/-} heterozygous mice, respectively. Similarly, HetKO *Prkar1a*^{+/-} mice developed more papillomas than wild-type animals after chemical induction [3]. Thus, *Prkar1a* haploinsufficiency augmented the previously described phenotype for the respective mouse models without causing any new tumors in other cAMP-responsive or other, tissues. In the same study, *Wnt* signaling and cell cycle abnormalities were identified by whole-genome transcriptome profiling as the main pathways activated by abnormal cAMP signaling confirming recent data from human studies which identified somatic beta catenin (*CTNNB1*) mutations in *PRKAR1A*-haploinsufficient tumors [37, 108]. These studies showed that *PRKAR1A* haploinsufficiency maybe an overall relatively weak tumorigenic signal, unless it is associated with other tumor suppressor gene defects, Wnt signaling activation, and cell cycle dysregulation, mainly an increase in the expression of cyclin D1 and the transcription factor *E2F1* [3].

Miscellaneous Syndromes: hamartomatous proliferations of nerve

The peripheral nervous system may also be involved in the form of pseudoneoplastic, hamartomatous growths in inherited genetic syndromes. Prominent among these, is the syndrome of multiple endocrine neoplasia 2b (MEN 2b). In MEN 2b the primary manifestations include the development of endocrine neoplasms affecting most importantly the thyroid (medullary carcinoma), as well as parathyroid (hyperplasia) and adrenal gland (pheochromocytoma). Two important conditions affecting the peripheral nervous system in this syndrome are mucosal neuromas and intestinal ganglioneuromatosis, resulting from hypertrophy of autonomic nervous system components (i.e. nerve plexuses and ganglia).

Mucosal neuromas are important from the diagnostic standpoint, since they may be subjected to biopsy, and their correct identification may lead to life saving prevention of more ominous manifestations of the syndrome such as medullary thyroid carcinoma. Histologically, mucosal neuromas represent tortuous, abnormal enlargements of nerves at submucosal sites (Figure 7). It should be noted that multiple neuromas were the subject of a curious report in a patient with a germline *PTEN* mutation[96], therefore in rare occasions they may arise independent of MEN 2b. Gastrointestinal ganglioneuromatosis consists of a similar enlargement and tortuosity of submucosal and myenteric plexuses in the intestine. Although, gastrointestinal ganglioneuromatosis may be present in other syndromes such as Cowden, Juvenile polyposis, and NF1, extensive and diffuse involvement of all intestinal layers is relatively specific to MEN 2b[97].

The main genetic change in MEN 2b is an activating mutation in the *RET* protooncogene. *RET* was identified originally as a chimeric oncogene using transfections assays with neoplastic DNA, therefore its name “rearranged during transfections”[109]. The *RET* gene, located in chromosomal region 10q11.2, encodes a membrane bound receptor tyrosine kinase. The most frequent mutation in MEN 2b is caused by a substitution of the methionine at residue 918 by a threonine in the kinase domain. This leads to increased downstream signaling by several molecular mechanisms, including ligand-independent activation, increased ATP binding affinity, and loss of normal autoinhibition[43].

Conclusion

The peripheral nerve sheath is an important site for neoplastic development in a variety of inherited or sporadic tumor syndromes. The spectrum of neoplasms and pseudoneoplastic growths is wide, encompassing both benign and malignant tumors, and consequently leading to marked morbidity, and even mortality in patients afflicted by them. Recent advances have started to expand our genetic and molecular understanding, and hopefully will lead to most needed novel, directed therapies for these devastating disorders.

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Figure 1. Molecular basis of inherited tumor syndromes of nerve

Inherited predisposition to nerve sheath neoplasia involves germline mutations in key tumor suppressor genes. In NF1, neurofibromin loss leads to constitutive MEK/ERK pathway activation. NF2 is associated with Merlin loss, a tumor suppressor with multiple complex effects, regulating RAC, PI3K and receptor tyrosine kinases (including PDGFR). Less is currently known about the genetic basis of schwannomatosis, which is sporadic in most cases. Germline mutations in the *SMARCB1* gene, encoding a component of the SWI/SNF chromatin remodeling complex, are present in approximately one third of familial cases and 10% of sporadic ones. Carney complex frequently results from mutations in the *PRKAR1A* gene, which encodes a regulatory subunit of protein kinase A. Conversely, MEN2b, caused by activating mutations in the *RET* oncogene, does not result in true neoplasms in the peripheral nerve, but rather hamartomatous growths.

Figure 2. Neurofibromatosis type 1: clinical and pathologic features

The most typical CNS manifestation of neurofibromatosis is optic nerve glioma (a, arrows), which almost always is a pilocytic astrocytoma. Multiple cutaneous neurofibromas are frequent in NF1 (b), and characterized by a proliferation of neoplastic schwann cells, fibroblasts and perineurial cells with associated wavy collagen (c). Diffuse neurofibromas are larger neoplasms that entrap adnexa and infiltrate fat (d), and may undergo conspicuous aggregation of pseudo-meissnerian corpuscles (e). Plexiform neurofibromas are defined by involvement of several nerve fascicles leading to « worm-like » growth (f). Malignant peripheral nerve sheath tumors are cellular, usually high grade spindle cell neoplasms (g). Heterologous elements, such as rhabdomyoblasts, may be present (h). Specific

immunohistochemical markers are confirmatory (myogenin, i). Massive soft tissue neurofibromas are large, benign distinctive neoplasms characterized by diffuse soft tissue infiltration (j). A cellular, round cell component may be present, but has no adverse prognostic implications (k,l).

Figure 3. Neurofibromatosis type 2 : clinical and pathologic features

Bilateral vestibular schwannomas represent a pathognomic finding of NF2(a).

Ependymomas are an important CNS manifestation of NF2 (b, same patient as in a). Hairy cutaneous plaques are part of the NF2 syndrome (c), and a clinical finding allowing separation from schwannomatosis. Most sporadic or NF2 associated schwannomas are well circumscribed, tan-white appearing neoplasms with variable yellowish areas (d). Compact aggregates of schwann cells represent the most important feature (e). Alternating compact (Antoni A) and loose (Antoni B) areas in schwannomas are distinctive (f). Palisades of cells in schwannomas with empty cores are known as Verocay bodies (g). Although syndrome associated and sporadic schwannomas have many overlapping features, well formed whorls

reminiscent of meningioma may be overrepresented in syndrome associated cases, including NF2 (h). Meningiomas (arrowheads) and schwannomas (arrows) may co-exist in the spine (i).

Figure 4. Schannomas in schwannomatosis

Whole body MR scans may demonstrate multiple schwannomas (arrows) in schwannomatosis patients (a)(Photo courtesy of Dr. Jaishri Blakeley). Schwannomas in schwannomatosis are usually circumscribed, but often expand the adjacent nerve (b). Myxoid patterns are also present in a subset of these schwannomas (c) as well as adjacent nerve. A mosaic pattern of INI1 immunoreactivity is present in the majority of syndrome associated schwannomas, including those of schwannomatosis (d)(Photo courtesy of Dr. Arie Perry).

Figure 5. Melanotic Schwannomas

Pigmented schwannomas represent the hallmark of peripheral nerve sheath neoplasia in Carney complex, lobulated melanin rich tumors (a). Cytologic atypia in the form of large, violaceous nucleoli may be present, particularly in some aggressive examples (b). The presence of psammoma bodies is typical of melanotic schwannomas in the setting of Carney syndrome (c)(photo courtesy of Dr. Caterina Giannini). Although expression of markers of melanocytic differentiation is the rule in these neoplasms, the presence of perilobular/pericellular reticulin suggests the diagnosis (d). Collagen IV immunoreactivity is variable in these tumors, and may highlight tumor lobules (e) or rarely be pericellular (f).

Figure 6. Ultrastructural features of melanotic schwannomas (Photo courtesy of Dr. Caterina Giannini)

Electron microscopy is an useful adjunct in the diagnosis of melanotic schwannomas, demonstrating dual melanocytic and schwannian differentiation. Electron dense intracytoplasmic melanosomes are conspicuous (a,b). The presence of surface basal lamina, often duplicated, (c) is an important diagnostic feature, which is absent in melanomas and melanocytomas.

Figure 7. Mucosal neuromas in MEN 2B (Photo Courtesy of Dr. J. Aidan Carney)
Mucosal neuromas are characterized by severely hypertrophic, rather than neoplastic, nerves (a,b)

Table 1**Diagnostic criteria for Neurofibromatosis type 1 (NIH 1991)**

<u>Two or more of the following features:</u>
1-Café au lait macules (6), with a diameter of 0.5 cm in children, or 1.5 cm after puberty
2-Cutaneous or subcutaneous neurofibromas (2) or plexiform neurofibroma
3-Freckling of the axillary or groin region
4-Glioma of the optic pathways
5-Lisch nodules identified by slit lamp examination (2)
6-Dysplasias of the skeletal system (sphenoid wing, long bone bowing, pseudoarthrosis)
7-Diagnosis of NF1 in a first degree relative

Table 2

Diagnostic criteria for Neurofibromatosis type 2 (Manchester criteria, Evans DG et al. 1992)

A.	Bilateral Vestibular Schwannoma
OR	
B.	NF2 in first degree relative PLUS unilateral vestibular schwannoma, or any two of the following neurofibroma, meningioma, glioma, schwannoma, posterior subcapsular lens opacity
OR	
C.	Unilateral Vestibular Schwannoma PLUS any two of: neurofibroma, meningioma, glioma, schwannoma, posterior subcapsular lens opacity
OR	
D.	Two or more meningiomas PLUS unilateral vestibular schwannoma, or any two of: neurofibroma, glioma, schwannoma, or cataract

Table 3

Baser's criteria for neurofibromatosis type 2 (Baser ME 2011)

Feature	Present age 30 years	Present age >30 years
NF2 in first degree relative	2	2
Vestibular Schwannoma (unilateral)	2	1
Vestibular Schwannoma (second)	4	3
Meningioma	2	1
Meningioma (second)	2	1
Cutaneous schwannoma (s)	2	1
Neoplasm of cranial nerves	2	1
Mononeuropathy	2	1
Cataract (s)	2	0

Points added:

Points 6: Definite NF2

Points 4–5: NF2 mutational analysis required

Points<4: NF2 unlikely

Table 4

Diagnostic criteria for Schwannomatosis (Baser ME et al. *Neurology* 2006)

<u>Definite Schwannomatosis</u>
A. Age> 30 years PLUS two or more schwannomas (not dermal), at least one with histologic confirmation
B. Schwannoma (pathologically confirmed) PLUS first-degree relative who meets the above criteria
<u>Possible schwannomatosis</u>
A. Age <30 years PLUS two or more schwannomas (not dermal), at least one with histologic confirmation
B. Age>45 years PLUS two or more schwannomas (not dermal), at least one with histologic confirmation
C. Evidence of a schwannoma (by radiaology) and first degree relative meeting the criteria for definite schwannomatosis

(All individuals must lack NF2 by criteria, lack vestibular schwannoma (by high resolution MRI), lack NF2 in first degree relative, and lack germline *NF2* mutations)

Table 5**Diagnostic criteria for Carney Complex (CNC)**

<i>Major Diagnostic criteria for CNC</i>
1. Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosal)
2. Myxoma [*] (cutaneous and mucosal)
3. Cardiac myxoma [*]
4. Breast myxomatosis [*] or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
5. PPNAD [*] or paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle's test
6. Acromegaly due to GH-producing adenoma [*]
7. LCCST [*] or characteristic calcification on testicular ultrasound
8. Thyroid carcinoma [*] or multiple, hypoechoic nodules on thyroid ultrasound in a young patient
9. Psammomatous melanotic schwannomas [*]
10. Blue nevus, epithelioid blue nevus [*]
11. Breast ductal adenoma [*]
12. Osteochondromyxoma [*]
<i>Supplementary criteria</i>
1. Affected first-degree relative
2. Inactivating mutation of the PRKARIA gene
<i>Findings suggestive of or possibly associated with CNC, but not diagnostic for the disease</i>
1. Intense freckling (without darkly pigmented spots or typical distribution)
2. Blue nevus, common type (if multiple)
3. Café-au-lait spots or other "birthmarks"
4. Elevated IGF-I levels, abnormal GTT, or paradoxical GH response to TRH testing in the absence of clinical acromegaly
5. Cardiomyopathy
6. Pilonidal sinus
7. History of Cushing's syndrome, acromegaly, or sudden death in extended family
8. Multiple skin tags or other skin lesions; lipomas
9. Colonic polyps (usually in association with acromegaly)
10. Hyperprolactinemia (usually mild and almost always combined with clinical or subclinical acromegaly)
11. Single, benign thyroid nodule in a young patient; multiple thyroid nodules in an older patient (detected on ultrasound)
12. Family history of carcinoma, in particular of the thyroid, colon, pancreas, and ovary; other multiple benign or malignant tumors

^{*} After histological confirmation