ARTICLE

Genetic Insights into Familial Tumors of the Nervous System

GERMAN MELEAN, ROBERTA SESTINI, FRANCO AMMANNATI, AND LAURA PAPI*

Nervous system tumors represent unique neoplasms that arise within the central and peripheral nervous system. While the vast majority of nervous system neoplasm occur sporadically, most of the adult and pediatric forms have a hereditary equivalent. In a little over a decade, we have seen a tremendous increase in knowledge of the primary genetic basis of many of the familial cancer syndromes that involve the nervous system, syndromes that are mostly inherited as autosomal dominant traits. In this review, we discuss the most recent findings on the genetic basis of hereditary nervous system tumors. The identification of genes associated with familial cancer syndromes has in some families enabled a ''molecular diagnosis'' that complements clinical assessment and allows directed cancer surveillance for those individuals determined to be at-risk for disease.

KEY WORDS: familial CNS tumor; NF1; NF2; familial schwannomatosis; familial meningioma; familial glioma; familial posterior fossa brain tumors of infancy; tuberous sclerosis complex; von Hippel-Lindau disease; Li-Fraumeni syndrome; Gorlin syndrome; Carney complex; Turcot syndrome; melanoma-astrocytoma syndrome

INTRODUCTION

Tumors of the nervous system represent a unique, heterogeneous population of neoplasms, and include both benign and malignant forms. Nervous system tumors comprise those that grow within the central nervous system (CNS) (e.g., glioma, medulloblastoma, ependymoma, and meningioma), as well as those that are associated with peripheral nerves (e.g., schwannoma, neurofibroma, and malignant peripheral nerve sheath tumor).

There are a number of familial syndromes that predispose individuals to the development of tumors, often multiple, within the CNS, including neurofibromatosis type 1 and 2, schwannomatosis, the familial syndromes of glioma, meningioma and medulloblastoma, and the familial posterior fossa brain tumors of infancy. Moreover, germline mutations in a number of genes, including *TSC1/TSC2* (tuberous sclerosis complex), *VHL* (von Hippel-Lindau disease), *TP53* (Li-Fraumeni syndrome), *PATCHED* (Gorlin syndrome), *PRKAR1A* (Carney complex), *CDKN2A* (melanoma-astrocytoma syndrome), and *APC* and the mismatch repair genes *hMSH2*, *hMLH1*, and *hPMS2* (Turcot syndrome) predispose individuals to familial cancer syndromes that include the development of CNS primitive tumors. Most genes so far associated with predisposition to nervous system tumors appear to act as tumor suppressors; constitutional alterations associated with somatic loss of the wild-type allele are observed in hereditary tumors, and often, biallelic somatic loss-of-function (LOF) mutations can be found in the corresponding sporadic tumors.

The clinical manifestations and the genes responsible for the conditions reported in this review are summarized in Table I.

NEUROFIBROMATOSES

Neurofibromatoses consist of at least two different autosomal dominant disorders, neurofibromatosis type 1 and type 2, ... It is now clear that they represent two distinct entities, caused by mutations in different genes: the NF1 gene is located on chromosome 17q12, while the NF2 gene is located on 22q12.

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TABLE I. Hereditary Cancer Syndromes Predisposing to Nervous System Tumors

Syndrome [OMIM]	Nervous system tumors	Tumors of other organs and apparatus	Other features	Inheritance	Gene	Locus
Neurofibromatosis type 1 [162200]	Neurofibroma, optic glioma, plexiform neurofibroma, neurofibrosarcoma, astrocytoma, meningioma	Hypothalamic tumor, rhabdomyosarcoma duodenal carcinoid, somatostatinoma, parathyroid adenoma, pheochromocytoma	Cafe-au-lait spots, axillary/inguinal freckling lisch nodules (iris hamartomas); macrocephaly; scoliosis, pseudoarthrosis, sphenoid dysplasia, thinning of long bone cortex, renal artery stenosis, hypertension; aqueductal stenosis; hydrocephalus; Learning disabilities (30%); mild mental retardation (10%)	AD	*NF1*	17q11
Neurofibromatosis type 2 [101000]	Schwannoma, meningioma, ependymoma, astrocytoma, neurofibroma (occasional)		Juvenile posterior subcapsular lenticular capacities, juvenile cortical cataract, retinal hamartoma, occassional cafe-au-lait spots, NF2 plaques, mononeuropathy	AD	*NF2*	22q12
Familial schwannomatosis [162091]	Schwannoma			AD	?	
Familial meningioma [607174]	Meningioma			AD	?	
Familial glioma [137800]	Glioblastoma multiforme (or other astrocytomas)			AD? AR?	?	
Familial posterior fossa brain tumour [601607]	Rhabdoid tumor		Usual onset less than 2 years of age		*SNF5/INI1*	
Tuberous sclerosis [191100]	Ependymoma, giant cell astrocytoma, retinal astrocytoma	Multiple bilateral renal angiomyolipoma, myocardial rhabdomyoma, renal carcinoma, renal cysts, pacial angiofibroma, gingival fibroma	Achromatic retinal patches, pitted dental enamel, cystic areas of bone rarefaction, cafe-au-lait spots, white ash leaf-shaped macules, shagreen patches, subungueal fibromata, subcutaneous nodules, cortical tubers, subependymal nodules, pulmonar lymphangiomyomatosis, mental retardation, epilepsy, autism	AD	*TSC1* *TSC2*	9q34 16p13.3
von Hippel-Lindau [193300]	Cerebellar hemangioblastoma, spinal cord hemangioblastoma	Pulmonary, adrenal, liver hemangiomas; pancreatic and renal hemangioblastoma; bilateral papillary cystadenoma of the epididymis; renal cell carcinoma; hypernephroma; paraganglioma; pheochromocytoma; pancreatic cancer; adenocarcinoma of ampulla of Vater	Multiple renal cysts and pancreatic cysts	AD	*VHL*	3p26-p25
Li-Fraumeni [151623]	Astrocytoma, glioblastoma multiforme	Rhabdomyosarcoma, soft tissue sarcoma, osteosarcoma; breast cancer; leukemia; melanoma; adrenocortical carcinoma; lymphocytic or histiocytic lymphoma; lung adenocarcinoma; gonadal germ cell tumors; prostate and pancreatic carcinoma		AD	*TP53*	17p13

Gorlin (Basal cell nervus syndrome) [109400]	Cerebellar medulloblastoma	Basal cell nevi, basal cell carcinoma, cardiac fibroma, ovarian fibromata, ovarian carcinoma	Facial dysmorphism; mental retardation; bifid, synostotic and hypoplastic ribs; scoliosis, kyphoscoliosis; abnormal cervical vertebrae; brachydactyly; short 4th metacarpal; short thumb terminal phalanx; lung and lymphomesenteric cysts; hamartomatous stomach polyps	AD	*PTCH*	9q22.3
Carney complex [160980]	Psammomatous melanotic schwannoma	Eyelid and atrial myxoma, myxoid subcutaneous tumors, testicular Sertoli cell tumor, pituitary adenoma, pheochromocytoma, mammary ductal fibroadenoma	Profuse pigmented skin lesions; centrofacial/ mucosal lentigines; ephelides; nevi; blue nevi; red hair; adrenocortical nodular hyperplasia (Cushing disease); Acromegaly	AD	*PRKAR1A*	17q23–q24
Melanoma-Astrocytoma syndrome [155755]	Cerebral astrocytoma and other CNS tumors	Cutaneous malignant melanoma		AD	*CDKN2A*	9p21
Turcot [276300]	Medulloblastoma, glioblastoma multiforme, astrocytoma, ependymoma	Colon cancer, basal cell carcinoma gastric cancer	Café-au-lait spots; hyperpigmented spots	AD AR?	*APC MSH2* *MLH1* *PMS2*	5q21 2p22–21 3p21 7p22

ghausen disease spectrum. It is now clear that they represent two distinct entities, caused by mutations in different genes: the *NF1* gene is located on chromosome 17q12, while the *NF2* gene is located on 22q12.

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant disorders in humans, affecting about 1 in 3,000 individuals. The reader is referred to recent reviews on NF1 (see the *American Journal of Medical Genetics*, *Seminars in Medical Genetics*, Volume 89, Issue 1, 1999) for a thorough discussion of NF1; the focus of this review will be limited to NF1-associated nervous system neoplasms. Peripheral

Peripheral neurofibromas are the hallmark of NF1 . . . . They arise from cells in the peripheral nerve sheath and contain a mixture of cell types, such as Schwann cells, fibroblasts, mast cells, and vascular elements.

neurofibromas are the hallmark of NF1; they are soft tumors that appear just before or during adolescence [Gutmann and Collins, 2002], and tend to increase in number and size with age. They arise from cells in the peripheral nerve sheath and contain a mixture of cell types, such as Schwann cells, fibroblasts, mast cells, and vascular elements [Lott and Richardson, 1981]. Neurofibromas may also arise from dorsal nerve roots. About 20% of NF1 individuals develop a more complex, often congenital lesion, called plexiform neurofibroma; it involves the skin, connective tissue, vessels, muscles and nerves, causing overgrowth of surrounding tissues [Waggoner et al., 2000]. In addition, a predisposition to develop nervous system malignancy has been noted in NF1 individuals (reviewed in Korf [2000]).

NF1 patients have a 10% lifetime risk for developing malignant peripheral nerve sheath tumor (MPNST) or neurofibrosarcoma, which is one of the characteristic complications of NF1 [Evans et al., 2002]. It usually arises within a plexiform neurofibroma, and it is a very aggressive and often fatal malignancy. However, the most common CNS tumor seen in NF1 individuals is optic glioma. This tumor involves the optic nerve and/or chiasma and can be unilateral or bilateral. It usually arises in children under the age of six. By MRI scan, about 15–20% of children affected by NF1 have radiographic evidence of optic glioma, but the majority of these children never become symptomatic. Moreover, in NF1 individuals there is a moderately increased risk of CNS malignancies, mainly astrocytomas.

Neurofibromatosis Type 2

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome that predisposes to the development of nervous system tumors. Bilateral vestibular schwannomas are pathognomonic of the disorder; schwannomas arise from the nerve sheath and consist of Schwann cells in a collagenous matrix. Patients often develop schwannomas of other cranial, spinal, and peripheral nerves, as well as intracranial and intraspinal meningiomas; less frequently, NF2 patients develop low grade gliomas and ependymomas. Other features often associated with the disease are neuronopathy (mainly affecting the facial nerve) and ophthalmic signs such as juvenile posterior subcapsular lenticular opacities (60–80% of patients), and retinal hamartomas. Cutaneous features in NF2 are less evident than in NF1: café-au-lait spots and skin tumors can be found in about 45% and in 70% of patients, respectively. The most frequent skin tumor is a plaque-like lesion (NF2 plaque), which is intracutaneous, raised, and slightly pigmented compared to the adjacent skin. Occasionally, intracutaneous tumors similar to those of NF1 can be found; however, they are usually schwannomas and only rarely neurofibromas.

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NF2 displays variable age of onset, with most affected individuals presenting manifestations in the second to third decade of life. However, clinical variability is seen in the syndrome, and two distinct phenotypic subtypes can be identified: the severe form is characterized by a young age at onset, rapid progression of hearing loss, and multiple associated tumors, while the mild form occurs at an older age, and shows a slower deterioration of hearing and few associated tumors [Parry et al., 1994].

The birth incidence of NF2 is 1 in 33,000 to 1 in 40,000, with a penetrance close to 100% by the age of 60 years [Evans et al., 1992]. Approximately 50% of NF2 patients do not have a family history of the disease, representing de novo mutations.

The disease is caused by mutations in the *NF2* tumor suppressor gene, located in 22q12 [Rouleau et al., 1993; Trofatter et al., 1993]. *NF2* is a large gene made up of 17 exons distributed over approximately 110 kb of genomic DNA. Since its identification, germline mutations have been identified in 34–84% of NF2 patients investigated in different studies (NF2 mutation map: http://neurosugery.mgh.harvard.edu/NFclinic/NFresearch.htm). These include single basepair substitutions, small deletions, and insertions in exons 1–15 of the *NF2* coding sequence and in the corresponding intron-exon boundaries, as well as large deletions encompassing the gene [Bruder et al., 2001]. The majority of mutations are thought to encode for truncated proteins.

A genotype-phenotype correlation has been described. Missense mutations have been mainly associated with a mild phenotype, while nonsense and frameshift mutations have been correlated with severe disease, regardless of their position in the gene [Evans et al., 1998]. The phenotype is more variable in patients with splice-site mutations.

Recent evidence suggests that up to 25–30% of de novo patients represent somatic mosaics [Kluwe et al., 2003; Moyhuddin et al., 2003]. However, only two single cases of germline mosaicism in a clinically normal individual have been reported [Parry et al., 1996; Sestini et al., 2000]. Mosaicism may be common in sporadic NF2 patients with mild phenotypes, which might be the result of the lower number of mutated cells in the individual.

The *NF2* gene encodes for a 595-amino acid protein called "merlin" [Trofatter et al., 1993], due to its similarity to three proteins of the ezrin, radixin, moezin (ERM) family (Merlin means "moezin, ezrin, radixin-like" protein); it is also known as "schwannomin" [Rouleau et al., 1993]. The ERMs are believed to organize specialized membrane domains by linking membrane-associated proteins to the actin cytoskeleton. The discovery that merlin is closely related to ERM proteins raised the question of how a protein localized in the cytoplasm could control cell proliferation. Although several studies have shown that merlin does indeed control cell proliferation, the specific pathways involved in transducing its growth-suppressive signal are still poorly understood (reviewed in McClatchey [2003]).

FAMILIAL SCHWANNOMATOSIS

Schwannomatosis is characterized by the onset of multiple intracranial, spinal, or peripheral schwannomas, without involvement of the vestibular nerve.

Schwannomatosis is characterized by the onset of multiple intracranial, spinal, or peripheral schwannomas, without involvement of the vestibular nerve, which is instead pathognomonic of NF2 [Jacoby et al., 1997]. Only a few cases of familial schwannomatosis have been reported; in these, an autosomal dominant pattern of inheritance with incomplete penetrance and variable expressivity has been noted [Evans et al., 1997; MacCollin et al., 2003].

The schwannomatosis phenotype has been shown to be linked to the chromosome 22q12.2 region, containing the *NF2* gene, in two large families [Evans et al., 1997]. Moreover, in some schwannomatosis patients without germinal mutations of *NF2*, the analysis of multiple tumors revealed the same *NF2* gene mutation in different tumors associated with the loss of the second allele [Honda et al., 1995; Jacoby et al., 1997]. It was, therefore, concluded that some schwannomatosis patients are somatic mosaics for *NF2* gene changes.

However, further studies have shown that some schwannomatosis patients, particularly those with a positive family history, may have an inherited predisposition to the development of tumors that carry somatic alterations of the *NF2* gene, which appear not to be related to *NF2* germline mutations. MacCollin et al. [2003] have demonstrated the occurrence of different *NF2* mutations in the same allele in schwannomas arising in members of the same family. These *NF2* mutations were accompanied by loss of the *trans* allele in all tumors. Although the family data were consistent with linkage of this trait to the *NF2* locus, the study implied that the primary event in the tumors lay outside the coding region of the *NF2* gene. From these data, two different hypotheses can be invoked to explain the molecular genetic basis of schwannomatosis. The first hypothesis posits the existence of a second tumor suppressor gene, *SCH*, that lies near *NF2* on chromosome 22; according to this hypothesis schwannoma development should be dependent on four "hits" (two in the *SCH* and two in the *NF2* tumor suppressors). The inactivating *SCH* mutation would cause the schwannomatosis condition; the acquired loss of the *trans* chromosome 22 would induce tumorigenesis by eliminating the normal copies of both *SCH* and *NF2*. The second hypothesis, based on the observation that loss of heterozygosity (LOH) events always occur *trans* to the inherited *SCH* allele, posits that the germinal event involves a structural element whose alteration predisposes to LOH on the *trans* chromosome 22. The molecular genetic basis of schwannomatosis is probably even more complex, taking into account that schwannomatosis patients showing different somatic *NF2* mutations not associated with LOH of chromosome 22 have been observed, e.g., family 9 in MacCollin et al. [2003], and our observation of a sporadic patient in which the analysis of five different schwannomas showed three different *NF2* somatic mutations without LOH on 22q (Papi et al., unpublished data).

FAMILIAL MENINGIOMAS

Meningiomas are common CNS human tumors; although they are usually classified as benign, about 25% cannot be treated due to their inaccessible anatomical location or to their invasiveness [Heinrich et al., 2003]. While the vast majority of meningiomas are sporadic, a few cases of familial meningioma have been reported in families with no evidence of neurofibromatosis [Sieb et al., 1992; Maxwell et al., 1998]. The mode of transmission was apparently autosomal dominant. Additionally, linkage studies indicate that the *NF2* gene is not involved in familial meningiomas [Pulst et al., 1993; Maxwell et al., 1998].

FAMILIAL GLIOMAS

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Gliomas are CNS neoplasms derived from glial cells and comprise astrocytomas, glioblastoma multiforme, oligodendrogliomas, and ependymomas. Gliomas are known to occur in association with several well-defined hereditary tumor syndromes such as NF1 and NF2, tuberous sclerosis, Li-Fraumeni syndrome, and Turcot syndrome.

In addition, familial clustering of gliomas in the absence of these tumor syndromes has also been described. In most cases, the familial pattern is not typical, the cancers do not involve multiple generations, and early onset is not apparent [Grossman et al., 1999]. On the basis of segregation analyses, both autosomal recessive and multifactorial mendelian models have been suggested [Malmer et al., 2001; de Andrade et al., 2001].

Several candidate genes for familial glioma have been investigated. The *TP53* tumor suppressor gene has been the most frequently investigated candidate gene, but mutations have only seldom been found in the germ line of glioma families without Li-Fraumeni syndrome [Tachibana et al., 2000]. Other candidate genes studied, namely *PTEN*, *CDKN2A*, and *CDK4*, have not been found to harbor mutations in the germ line of familial glioma patients [Paunu et al., 2001].

FAMILIAL POSTERIOR FOSSA BRAIN TUMORS OF INFANCY

Malignant rhabdoid tumors (MRT) are aggressive malignancies that usually develop in infants and young children. They are formed, partially or totally, by rhabdoid cells, and their most common locations are the CNS and the kidney. Differential diagnosis is challenging, because in the brain, MRT often contain

areas of primitive neuroepithelial cells, and/or mesenchymal tissue, and/or epithelial tissue; such lesions might be confused with medulloblastomas or primitive neuroectodermal tumors and, to a lesser extent, with choroid plexus carcinomas or germ-cell tumors [Rorke et al., 1996; Burger et al., 1998]. Acquired mutations of the *hSNF5/INI1/SMARCB1* gene, localized in 22q11, have recently been reported in CNS, renal, and soft-tissue rhabdoid tumors [Versteege et al., 1998; Biegel et al., 2002a], and germline mutations have been described in several infants with MRT [Biegel et al., 1999; Sevenet et al., 1999]. The hSNF5/INI1/SMARCB1 protein is part of the ATP-dependent SW1/SNF chromatin remodeling complex; this multiprotein complex has a role in remodeling nucleosomes and, therefore, in regulating the access of transcription factors to several different promoters (reviewed in Biegel et al. [2002b]).

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome, characterized by the development of hamartomas and benign tumors in the brain, heart, and kidney, sometimes associated with cognitive defects, epilepsy, and autism. The prevalence of TSC is 1 in 6,000 to 1 in 10,000 live births [Kwiatkowski, 2003]; it is inherited in an autosomal dominant manner, with 65–85% of all cases representing new mutations [Weiner et al., 1998].

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CNS lesions of TSC include tubers in the cerebral cortex, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SGCAs). Cortical or subcortical tubers can be found in 70% of TSC individuals [Goodman et al., 1997]; they are static lesions that represent regions of cortical dysplasia that might result from aberrant neuronal migration during corticogenesis. SENs, which occurs in approximately 90% of TSC patients [Shepherd et al., 1991], are nodular regions that grow into the ventricles and are usually asymptomatic; however, they can expand, and when they do, they are called SGCAs. SGCAs arise in 6–14% of TSC individuals, with a mean age at diagnosis of 9.4 years [Torres et al., 1998]; their most common locations are the borders of the lateral ventricles, particularly the region of the foramen of Monro. SGCAs may grow and produce obstructive and pressure lesions.

TSC occurs due to mutations in one of two genes: *TSC1* on chromosome 9q34 [van Slegtenhorst et al., 1997] and *TSC2*, on 16p13.3 [European Chromosome 16 Tuberous Sclerosis Consortium, 1993]. *TSC1* has 23 exons, encoding for an 1,164-amino acid protein called "hamartin"; *TSC2* has 42 exons, and the corresponding "tuberin" contains 1,807 amino acids. Roughly, 50% of TSC families are linked to *TSC1* and 50% to *TSC2* [Povey et al., 1994]. Mutations in *TSC1* or *TSC2* can be identified in 60–80% of TSC patients [Jones et al., 1999; Dabora et al., 2001]. Most of the germline mutations identified in *TSC1* and *TSC2* are unique; almost all identified *TSC1* mutations are truncating, while about 20% of the *TSC2* mutations are missense. *TSC1* and *TSC2* large chromosomal rearrangements have been reported, too. Among sporadic cases there is a higher incidence of *TSC2* than *TSC1* mutations, 65% and 10%, respectively [Jones et al., 1999; Dabora et al., 2001].

Recent evidence has shown that hamartin forms heterodimers with tuberin; the intracellular signaling pathways regulated by hamartin and tuberin have been recently reviewed [Krymskaya, 2003]. Briefly, hamartin and tuberin control cell growth by negatively regulating S6 kinase and eukaryotic initiation factor 4E binding protein 1, potentially through their upstream modulator mammalian target of rapamycin (mTOR). Moreover, tuberin displays guanosine 5′-triphosphatase (GTPase) activating (GAP) activity for Rap1 and Rab5, while hamartin interacts with cytoskeleton proteins such as neurofilament-L and ERM proteins. These latter interactions raise the questions: 1) Do tuberin and hamartin have a role in cytoskeleton rearrangement? 2) Is the GAP activity of tuberin critical for its tumor suppressor function?

VON HIPPEL-LINDAU SYNDROME

von Hippel-Lindau syndrome (VHL) is an autosomal dominant condition predisposing individuals to the development of a variety of malignant and benign neoplasms, most frequently retinal, cerebellar, and spinal hemangioblastomas, renal cell carcinomas, pheochromocytomas, and pancreatic tumors. Its incidence is estimated at 1 in 36,000 births per year [Maher et al., 1991]; about 20% of cases are due to new mutations.

Hemangioblastomas are benign and usually cystic tumors which represent the most characteristic and frequent lesion of the syndrome, affecting 60–80% of all patients; moreover, VHL patients often develop more than one hemangioblastoma [Filling-Katz et al., 1991]. Hemangioblastomas are localized in the brain in 80% of VHL patients, while the spinal cord is involved in only 20% of cases; rarely, they develop from spinal roots or peripheral nerves. Hemangioblastomas represent less than 2% of all CNS tumors [Richard et al., 1998]; the average age at presentation is about 33 years in the VHL-related cases and 43 years in the sporadic ones [Maher et al., 1990]. Therefore, the

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The syndrome is caused by germinal mutations in the *VHL* gene, located in 3p26, which comprises three exons and spans approximately 10 kb of genomic DNA [Latif et al., 1993]. *VHL* codes for a 213-amino acid protein, pVHL, which is expressed in most cells; it is mainly located in the cytoplasm, although it can be shuttled to the nucleus. pVHL has been implicated in a variety of functions at the transcriptional and posttranscriptional level [Kaelin and Maher, 1998]. Many studies suggest that the protein regulates the transcription of hypoxia-inducible genes by altering the stability of their mRNA. Unless a cell is oxygen deprived, pVHL normally shuts down the release of these factors; therefore, pVHL inactivation results in overexpression of hypoxia-inducible mRNAs, including vascular endothelial growth factor (VEGF) [Kondo and Kaelin, 2001]. This is concordant with the high vascularization of VHL-related tumors.

A wide spectrum of germinal mutations in the *VHL* gene have been identified. Complete and partial gene deletions can be found in 28% of VHL patients, while nonsense, missense, and splice-site mutations that affect any of the three exons (except the first 54 codons) are found in the remaining 72% of patients [Stolle et al., 1998].

LI-FRAUMENI SYNDROME

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant disease that predisposes individuals to a wide range of cancers: typically, premenopausal breast cancer, sarcomas, acute leukemia, brain tumors, and adrenal cortex cancer, but also other tumors. Two different forms of LFS can be recognized: 1) classic LFS meets the following criteria: a proband with a sarcoma diagnosed before 45 years of age, a first-degree relative with any cancer diagnosed before 45 years of age, and a first- or second-degree relative with any cancer diagnosed before 45 years of age or a sarcoma at any age [Li et al., 1988]; 2) Li-Fraumeni-like syndrome (LFL) is defined by the presence of a proband with any childhood tumor or sarcoma, brain or adrenocortical tumor before 45 years of age, plus a first- or second-degree relative with a typical LFS tumor at any age, and another first- or second-degree relative with any cancer before the age of 60 years [Birch, 1994].

Breast carcinomas are the most frequent tumors in LFS (24%), followed by bone sarcomas (12.6%), brain tumors (12%), and soft tissue sarcomas (11.6%) [Kleihues et al., 1997]. The mean age of onset of brain tumors in LFS is 25 years [Kleihues et al., 1997], and several LFS families with a high incidence of CNS tumors have been described [Dockhorn-Dworniczak et al., 1996; Lynch et al., 2000]. Clustering of specific tumor types in some LFS families may reflect the different genetic background of the respective kindred, even though environmental factors can also play a role.

The underlying genetic defect in many LFS families is a germline mutation in the *TP53* gene [Malkin et al., 1990; Srivastava et al., 1990]. *TP53* is a tumor suppressor gene that codifies for p53, a checkpoint protein that plays a crucial role in DNA damage repair and apoptosis. Following DNA damage, p53 can activate the transcription of downstream genes to promote DNA repair or it can direct signals to a sensor molecule in order to proceed with apoptosis [Vousden and Lu, 2002].

TP53 germline mutations are found in 71–77% of classic LFS families, and in 22–40% of LFL families, when all exons are sequenced [Varley, 2003]. Most *TP53* mutations are found within exons 5–8, including the splice-site junctions, with the majority being missense changes (Institute Curie Database; http://p53.curie.fr).

Recently, it has been proposed that germline mutations in the checkpoint gene *CHEK2* can also cause LFS [Bell et al., 1999]. *CHEK2* is a tumor suppressor gene that acts as a checkpoint gene, activated in response to DNA damage; it codifies for a serine/threonine-protein kinase that phosphorylates p53 (reviewed in Bartek et al. [2001]). However, results of subsequent studies indicate that *CHEK2* mutations probably do not predispose to LFS, but only to the breast cancers that arise within the context of certain LFS/LFL families in which no *TP53* mutations can be identified [Sodha et al., 2002].

GORLIN SYNDROME

Gorlin syndrome (GS), also known as nevoid basal cell carcinoma syndrome (NBCCS), is characterized by the association of developmental abnormalities and an increased incidence of malignancy. Neoplastic manifestations are mainly basal cell carcinomas, medulloblastoma, and, occasionally, meningiomas [Gorlin, 1995; Kimonis et al., 1997]. It is inherited in an autosomal dominant manner, but about 20–30% of the probands represent de novo mutations. The prevalence of the syndrome is thought to be about 1 in 57,000 [Evans et al., 1991].

Individuals with GS are at increased risk of developing childhood medulloblastoma: lifetime risk appears to be about 3–5% [Evans et al., 1991]. Moreover, medulloblastomas develop earlier in GS individuals than in the general population; in fact, the mean age at onset of medulloblastoma in GS patients is two years, as compared to seven years in the sporadic counterpart [Kimonis et al., 1997].

The susceptibility gene for NBCC has been identified as the human homolog of the *Drosophila melanogaster* Patched gene, *PTCH*, which is located on 9q22.3 [Hahn et al., 1996; Johnson et al., 1996]. Mutations in *PTCH* are found in approximately 85% of the cases fulfilling the diagnostic criteria; they are spread throughout the entire gene with no apparent clustering, and the majority result in premature protein truncation [Wicking et al., 1997].

PTCH encodes for the patched protein homolog 1 protein (Patched1), a transmembrane receptor for the secreted ligand sonic hedgehog (*SHH*) [Ingham, 1998]; moreover, Patched1 may associate with another transmembrane receptor, known as smoothened (SMOH). In the absence of bound SHH, SMOH and PTCH form an

inactive complex; when SHH binds to PTCH, the complex is altered, and SMOH becomes free and able to transduce the signal into the cell. According to this model, the inhibition of *SMOH* signaling is relieved following mutational inactivation of *PTCH* in basal cell nevus syndrome. However, the mechanism by which activation of the hedgehog pathway leads to carcinogenesis is not entirely known (reviewed in di Magliano and Hebrok [2003]). *GLI* genes have a role in mediating the carcinogenic effect of hedgehog activation: *GLI1* acts as an oncogene in brain tumors including medulloblastomas, and mouse models overexpressing *gli1* or *gli2* in epidermis develop tumors resembling basal cell carcinomas.

CARNEY COMPLEX

Carney complex (CNC) is a rare, multiple neoplasia syndrome characterized by the presence of skin pigmentary abnormalities associated with a predisposition to develop endocrine as well as cardiac, cutaneous, and neural tumors [Carney and Stratakis, 1998]. CNC is inherited in an autosomal dominant manner, but about 30% of the probands have a de novo mutation.

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Psammomatous melanotic schwannoma (PMS) is a rare nerve sheath tumor that differs from other schwannomas because of its high melanin pigmentation and the presence of psammoma bodies. About 10% of CNC patients develop PMS [Carney and Stratakis, 1998], which is often multicentric and may be localized anywhere in the central and peripheral nervous system; in 28% of cases there is involvement of the spinal nerve roots [Watson et al., 2000], but PMS can also affect the skin, the stomach, and the esophagus [Carney, 1990]. Moreover, PMS is one of the few CNC-associated tumors that may assume an aggressive behavior and metastasize to distant sites, mainly the lung and CNS, with a significant mortality rate [Watson et al., 2000].

Linkage analysis in CNC families showed genetic heterogeneity, with at least two main loci involved. About 30% of CNC families have been linked to 2p15-p16 [Stratakis et al., 1996], but the gene contained in this region has yet to be isolated. In about 40% of the families, CNC is linked to chromosome 17q24 [Casey et al., 1998]. This region contains the *PRKAR1A* locus, which has been recognized as a CNC-predisposing gene [Kirschner et al., 2000a]. *PRKAR1A* gene mutations have been identified in about 41% of individuals with CNC [Kirschner et al., 2000b], and are mostly truncating. *PRKAR1A* encodes for the regulatory subunit Iα of the protein kinase A, the main mediator of cAMP signaling pathways [Stergiopoulos and Stratakis, 2003]. The absence of the PRKAR1A protein in CNC tumors is associated with a greater PKA response to cAMP [Kirschner et al., 2000b].

MELANOMA-ASTROCYTOMA SYNDROME

A few families that are characterized by the presence of malignant cutaneous melanoma and nervous system tumors, such as astrocytoma, neurofibroma, schwannoma, and meningioma have been described [Kaufman et al., 1993; Bahuau et al., 1997; Petronzelli et al., 2001; Randerson-Moor et al., 2001; Prowse et al., 2003]. This association has been termed melanoma-astrocytoma syndrome, due to the presence of astrocytomas in the first family recognized [Kaufman et al., 1993].

The chromosomal region 9p21 is a major locus for predisposition to melanoma [Kamb et al., 1994]. In this region, two different candidate genes were mapped: *CDKN2A*, which encodes the $p16^{INK4A}$ and $p14^{ARF}$ proteins, through the use of an alternative exon 1 (1β), and *CDKN2B*, coding for p15 [Kamb et al., 1994; Stone et al., 1995]. $p16^{INK4A}$ is encoded by three exons [exons 1α, 2, and 3], whereas $p14^{ARF}$ is encoded by the alternative exon 1β, which splices into *CDKN2A* exon 2, but is translated into an alternative reading frame. Germline mutations of *CDKN2A* account for a proportion of melanoma kindreds [Dracopoli and Fountain, 1996]. In two melanoma-astrocytoma families, large deletions of 9p21 involving *CDKN2A* have been observed [Bahuau et al., 1998]; another family with a deletion involving exclusively *CDKN2A* exon 1β has been described [Randerson-Moor et al., 2001]. Recently, two kindreds with melanoma and neurofibroma carrying splice-site mutations, predicted to remove exon 2 and thus affecting $p16^{INK4A}$ as well as $p14^{ARF}$, have been identified [Petronzelli et al., 2001; Prowse et al., 2003]. It is therefore attractive to speculate that the cooperative effects of $p16^{INK4A}$ and $p14^{ARF}$ inactivation or the inactivation of $p14^{ARF}$ alone, might be responsible for the development of nervous system tumors in these families. $p16^{INK4A}$ and $p14^{ARF}$ have different functions: $p16^{INK4A}$ acts, with p15, in the retinoblastoma pathway as a specific *CDK4/CDK6* inhibitor [Roussel, 1999], while $p14^{ARF}$ acts in both p53 and retinoblastoma pathways via a common protein, MDM2 [Xiao et al., 1995; Weber et al., 1999].

TURCOT SYNDROME

Turcot syndrome (TS) is characterized by the occurrence of a primary brain tumor and multiple colorectal adenomas and/or colorectal adenocarcinoma. In Turcot patients, the most frequent brain tumors are astrocytomas, glioblastomas and medulloblastomas; ependymoma, spongioblastoma, gliosarcoma, and oligodendroglioma have also been reported [Hamada et al., 1998].

Recently, TS has been divided in two subgroups. One subgroup has hundreds to thousands of polyps in the

colon and has a greatly increased risk of medulloblastoma [Hamilton et al., 1995; Paraf et al., 1997]. These patients tend to have mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21 [Hamilton et al., 1995]. On the other hand, some patients present fewer polyps of the colon and develop colorectal cancer and glial tumors. These patients have mutations in the DNA mismatch repair (MMR) genes, such as *hMSH2*, *hMLH1*, and *hPMS2* [Lucci-Cordisco et al., 2003]. Patients with germline mutations in MMR genes do not appear to have an increased risk of medulloblastoma, and sporadic medulloblastomas do not show microsatellite instability, the hallmark of MMR mutations [Hamilton et al., 1995; Lee et al., 1998]. Although the distinction between these two forms of TS is attractive, it might be an oversimplification. Indeed, there are reports of medulloblastoma, colon cancer, and glioblastoma occurring in the same patient [McLaughlin et al., 1998], and the family originally described by Turcot et al. [1968] included a glial tumor as well as a medulloblastoma in two siblings born from a consanguineous marriage. The mode of inheritance of TS syndrome (autosomal recessive or dominant) has been a controversial issue for some time. From this point of view, a TS patient which was a compound heterozygote for *PMS2* mutations has been described [De Rosa et al., 2000].

CONCLUSIONS

In conclusion, in this short review, we have presented the most recent findings on the genetics of hereditary tumors of the nervous system. Although rare, hereditary tumor syndromes need to be recognized in individual patients, as they can alter clinical management. For example, omitting or limiting radiation therapy in individuals with NF2 and GS should be considered. Moreover, families will require information concerning the risk of additional neoplasms in the proband and the possibility of disease in other family members. It is likely that in the future additional familial syndromes associated with nervous system tumors will be identified, thus providing further insights into the pathogenesis of these aggressive tumors. The challenge for the future will be to expand our knowledge into a more complete understanding of the normal functions of the genes involved in the inherited predisposition to nervous system tumors; this should ultimately translate into significant improvements in the management of affected patients, possibly through the development of new therapies based on the discovery of new molecular targets.

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