Primary Tumors of the Nervous System

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INTRODUCTION

This chapter will review the current knowledge about the molecular genetic alterations associated with the initiation and progression of the most common forms of primary nervous system tumors. These include glial tumors, primitive neuroectodermal tumors (PNETs), meningiomas, and schwannomas. We will briefly review recent epidemiological data and the present histopathological classification of primary nervous system tumors. In addition, we discuss the hereditary syndromes predisposing to the development of tumors of the nervous system.

EPIDEMIOLOGY

Estimates of the incidences of the various tumors of the nervous system vary considerably depending on the source of data (Russell et al., 1989). Tumors of the central nervous system are common and occur with an incidence of 6 to 16 per 100,000 (Polednak, 1991). Consistent with this estimate, according to the Year 2000 Standard Statistical Report of the Central Brain Tumor Registry of the United States (CBTRUS, WWW.CBTRUS.ORG), the overall annual incidence rate for primary benign and malignant brain tumors in the United States is 14.1 cases per 100,000(CBTRUS, 2005). The relative incidence of CNS tumors is age-dependent. Intracranial neoplasms represent the most common solid tumors in the children below the age of 15, among which primary tumors of the nervous system comprise nearly 20% of all cancers, making them the second most common form of childhood cancer next to leukemias (Miller et al., 1995). The incidence of primary brain tumors has apparently increased among the elderly (Grieg et al., 1990; Polednak, 1991) even after correction for improved diagnostic methods (Desmeules et al., 1992).

CLASSIFICATION

There are multiple systems for the classification of brain tumors. Attempts are being made to revise classifications from a morphology-based approach identifying a “cell of origin” or “embryogenetic” phase to a more comprehensive approach incorporating molecular data (Burger et al., 1991). Applications of these approaches may help to validate some of the more recent classification concepts, such as the classification of embryonal tumors. However, many of the original terms are still in clinical use. For example, medulloblastoma was named after the presumed progenitor cell the “medulloblast”. The newer classification systems should increase prognostic accuracy and may provide a basis for developing treatment strategies for specific tumor types.

Several different types of brain tumors can be distinguished based on classic morphologic criteria. Overall the most common type of brain tumor is the glioma, which constitutes more than half of all brain tumors, followed by meningioma and schwannoma, which make up 20% and 10%, respectively. Of the rarer brain tumors only ependymoma and medulloblastoma will be discussed.

The location and histologic type of brain tumors differ in children and in adults. In children, brain tumors occur most frequently in the posterior fossa. The most frequent tumor types are ependymoma, medulloblastoma, and astrocytic

tumors, including spongioblastoma, cerebellar astrocytoma, and optic nerve glioma. In adults, the majority of tumors are supratentorial. Meningiomas and gliomas predominate.

The World Health Organization (WHO) has established a widely-used grading system for classifying CNS tumor malignancy (Kleihues et al., 1993). This classification, based on histopathological tumor typing, also has an optional WHO grading that ranges from WHO grade I (benign) to WHO grade IV (malignant). Tumors with minimal proliferative potential are classified as WHO grade I lesions. Such tumors include pilocytic astrocytomas, subependymomas, myxopapillary ependymomas of the cauda equina, a variety of neuronal and mixed neuronal/glial tumors, schwannomas, and most meningiomas. Tumors with lower mitotic activity and a tendency for recurrence are classified as WHO grade II. Grade II tumors include well differentiated astrocytomas, oligodendrogliomas, mixed gliomas, and ependymomas. Neoplasms with histological evidence of anaplasia, generally in the form of increased mitotic activity, increased cellularity, nuclear pleomorphism, and cellular anaplasia are classified as WHO grade III. WHO grade IV is assigned to mitotically active and necrosis-prone highly malignant neoplasms. Typical examples include glioblastomas and PNETs (Kleihues et al., 1993).

The WHO classification presently is the standard classification system for CNS tumors. The general use of this classification provides a common morphological baseline in neuro-oncology and greatly facilitates comparison of clinical and laboratory results from different institutions around the world. However, Gilles et al. (2000) highlighted certain limitations of the WHO classification of childhood tumors for prognosis. They proposed a classification technique that simultaneously accounts for all reliably recognized histologic features.

INHERITED TUMOR SYNDROMES PREDISPOSING TO CENTRAL NERVOUS SYSTEM TUMORS

Most brain tumors occur in a sporadic fashion. On rare occasions, however, brain tumors may occur as part of known inherited cancer syndromes (Table 1). Most of the time, the germline mutations manifest themselves by the development of non-central nervous system (CNS) malignancies. Occasionally, however, brain tumors may be the presenting tumor in such cancer-prone patients.

In addition to the familial occurrence of brain tumors as part of recognized inherited cancer syndromes, there are rare pedigrees in which several family members develop a specific histologic type of brain tumor consistent with autosomal dominant inheritance, but other signs of phakomatoses or non-CNS malignancies are absent. These pedigrees are described below under the respective tumor type.

Neurofibromatosis 1

Neurofibromatosis 1 (NF1) is transmitted in an autosomal dominant fashion with 50% of patients representing de novo mutations (reviewed in Pulst and Gutmann, 2000). NF1 is a common autosomal dominant disease affecting approximately 1 in 3,500 (Riccardi, 1991). The NF1 gene is located on the long arm of chromosome 17 and was identified in 1990 (Viskochil et al., 1990; Ballester et al., 1990). The NF1 gene encodes a 2,818 amino acid protein called neurofibromin that functions as a Ras GTPase activating protein (Xu et al., 1990). Neurofibromin directly binds Ras and possesses a GAP-related domain that stimulates intrinsic GTPase activity in wildtype but not oncogenic Ras (Lowy and Willumsen, 1993). Patients with NF1 typically develop multiple neurofibromas of the peripheral nervous system. Most neurofibromas, including

the plexiform variant, are benign tumors, but a small fraction may turn into malignant peripheral nerve sheath tumors, which are life-threatening, highly malignant tumors associated with a poor prognosis. Patients with NF1 may also develop gliomas (Riccardi, 1992). These typically involve the optic nerves or optic chiasm and may occur in up to 15% of patients if detailed neuroimaging is used for detection. However, the great majority of these tumors are asymptomatic and show little progression. The histology is typically that of a pilocytic astrocytoma. Gliomas may also occur less frequently in the brainstem and hypothalamus, and rarely in the cerebellum or spinal cord. Reports of meningiomas in NF1 most likely represent the chance association of a common brain tumor with a common genetic disease.

Neurofibromatosis 2

Neurofibromatosis 2 (NF2) is less common than NF1 and affects approximately 1 in 40,000 individuals (Evans et al., 1992). NF2 is autosomal dominant and caused by germline mutation of the NF2 gene which is located at chromosome 22q12 and was cloned in 1993 (Rouleau et al., 1993; Trofatter et al., 1993). NF2 patients are characterized by bilateral vestibular schwannomas, a hallmark feature of the disease. Commonly, NF2 patients have other cranial and spinal schwannomas and meningiomas. Gliomas are also found in patients with NF2, most commonly in the spinal cord (Mautner et al., 1996). Rarely, gliomas may occur in the posterior fossa or in a supratentorial location, and may represent the sole manifestation of NF2 in the occasional patient (Baser et al., 1996). About 80% of gliomas in NF2 patients are intramedullary spinal or cauda equina tumors and the vast majority of these are ependymomas (Louis et al., 1995; Mautner et al., 1995).

Von-Hippel-Lindau Disease

Von-Hippel-Lindau VHL)disease is the result of loss of function mutations in the VHL gene on chromosome 3p, which was identified in 1993 (Latif et al., 1993). Hemangioblastomas are found in the majority of patients with von-Hippel-Lindau disease (Filling-Katz et al., 1991) and are frequently a cause of death (Neumann et al., 1992). The majority of hemangioblastomas in von-Hippel-Lindau disease occur in the cerebellum, followed by locations in spinal cord and brainstem (Filling-Katz et al., 1991; Neumann et al., 1992). Approximately one-half of the tumors are asymptomatic (Filling-Katz et al., 1991). Capillary hemangioblastomas in VHL patients tend to manifest in younger patients than sporadic capillary hemangioblastomas and are more often multifocal (Filling-Katz et al., 1991).

Tuberous Sclerosis

Tuberous sclerosis is the second most frequent hereditary tumor syndrome of the nervous system after NF1 (Short et al., 1995). Two different genes have been linked to onset of tuberous sclerosis (TS), TSC1 located at chromosome 9q34, and TSC2 located at 16p13.2 (The European chromosome 16 tuberous sclerosis consortium, 1993; van Slegtenhorst et al., 1997). Neuroimaging studies show CNS lesions in the great majority of patients with tuberous sclerosis, including hamartomas such as cortical tubers and subependymal nodules (Menor et al., 1992). However, only approximately one-fourth of the lesions are tumorous and represent giant-cell astrocytomas. Giant-cell astrocytomas, in contrast to subependymal nodules, show marked enhancement. There are no major differences in the TS phenotypes associated with mutations in TSC1 or TSC2, with the possible exception of mental retardation which may be more frequent in patients with TSC2 mutations (Jones et al., 1997).

Li-Fraumeni Syndrome

The Li-Fraumeni syndrome is a rare dominantly inherited syndrome associated with germline mutations in the TP53 gene (Malkin et al., 1990). Although soft tissue sarcomas and breast cancers predominate, approximately 13% of patients develop brain tumors that typically show the histology of astrocytic glioma, followed by PNETs (Bögler et al., 1995). In addition to patients with the Li-Fraumeni syndrome, TP53 germline mutations have been occasionally identified in patients with non-familial malignancies with early onset or multifocality. First degree relatives of these patients are also at an increased risk of gliomas (Kyritsis et al., 1994, Sameshima et al., 1992).

Gorlin Syndrome

Gorlin syndrome, also called nevoid basal-cell carcinoma syndrome, is an autosomal dominant disorder leading to the development of multiple basal cell carcinomas of the skin as well as palmar and plantar pits, odontogenic keratocysts and skeletal anomalies (Gorlin, 1987). Childhood medulloblastoma, meningioma, craniopharyngioma, and neurofibroma have been described in patients with Gorlin syndrome (Evans et al., 1991a, 1991b; Albrecht et al., 1994). Gorlin syndrome has been linked to mutations in the tumor suppressor gene PTCH, which is the human orthologue of Drosophila patched (Hahn et al., 1996; Unden et al., 1996; Boutet et al., 2003). Somatic mutations in PTCH have been detected in sporadic basal cell carcinomas, PNETs, medulloblastomas, and certain other types of sporadic tumors (Raffel et al., 1997; Wolter et al., 1997; Xie et al., 1997).

Ataxia Telangiectasia

Ataxia telangiectasia is a recessive trait mapped to the ATM gene on chromosome 11q. ATM is a PI3-kinase related protein kinase whose function in cell cycle control is lost by truncating mutations that result in loss of the C-terminally located kinase domain, or by point mutations (Motoyama and Naka 2004; Telatar et al., 1996;). Lymphoid malignancies are frequently seen in patients with ataxia telangiectasia. Although solid tumors occur, primary CNS tumors are infrequent (Anonymous 1975).

Cowden Syndrome

Cowden syndrome, also known as multiple hamartoma syndrome, is an autosomal dominant cancer syndrome that predisposes to a variety of hamartomas and neoplasms. The major CNS lesion associated with the disease is dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease) (Vinchon et al., 1994). Further associated CNS lesions include megaencephaly and gray matter heterotopias. Occasional cases of meningiomas in patients with Cowden disease have also been documented (Lyons et al., 1993). Peripheral manifestations include multiple trichilemmomas of the skin, cutaneous keratoses, oral papillomatosis, gastrointestinal polyps, hamartomas of soft-tissues, thyroid tumors, as well as benign and malignant breast tumors (Hanssen et al., 1995; Weary et al., 1972). Germline mutations in the PTEN tumor suppressor gene at 10q23 have been linked to Cowden disease (Liaw et al., 1997; Pilarski and Eng, 2004).

Werner Syndrome

Werner syndrome is a recessive trait with clinical symptoms resembling premature aging. The responsible gene maps to the short arm of chromosome 8, and has been identified by positional cloning (Yu et al., 1996). In addition to premature aging, some individuals with Werner syndrome develop tumors,

including CNS tumors such as meningiomas and, less frequently, astrocytomas (Epstein et al., 1966; Tsuchiya et al., 1991; Laso et al., 1989).

Turcot Syndrome

Turcot syndrome describes a rare heterogeneous disorder characterized by the association of colonic polyposis and malignant primary neuroepithelial tumors of the CNS. It remains unclear whether Turcot syndrome represents a random association of two distinct diseases or a separate genetic disorder.

Colonic polyposis in patients with Turcot syndrome appears to be the result of mutations in genes encoding Wnt signaling pathway proteins (APC and beta-catenin). Some patients with Turcot syndrome were shown to possess mutations in the gene for familial adenomatous polyposis coli (APC) (Lasser et al., 1994; Mori et al., 1994). A patient with Turcot syndrome and congenital hypertrophy of the pigment epithelium, commonly seen in familial APC, has also been described (Munden et al., 1991). The incidence of glial tumors and medulloblastomas appears to be increased in patients with colonic polyposis (Kropilak et al., 1989 and references therein). On the other hand, somatic APC mutations are not a major cause of brain tumors. Using RNase protection analysis Mori et al. (1994) did not detect any APC gene mutations in 47 medulloblastomas, 8 glioblastomas, 22 astrocytomas, and 2 oligodendrogliomas. Furthermore, mutations in Wnt pathway proteins are less frequent in sporadic medulloblastomas: Huang et al. (2000) detected mutations in the APC or beta-catenin genes in only 6 of 46 of such tumors.

In Turcot patients germline mutations were identified in three different genes. Of 14 families with Turcot syndrome, 10 had germline mutations in the APC gene, and two had mutations in hPMS2 or hMLH1—mismatch repair genes (Hamilton et al., 1995). Mutations in hPMS2 may predispose to extreme DNA instability. One patient was studied who had an inherited hPMS2 missense mutation. Genetic characteriaztion of the patient's tumors, which included one astrocytoma, three colon carcinomas, and two colon adenomas, showed additional mutations in the TGFbetaRII, E2F-4, hMSH3, hMSH6, APC, or TP53 genes (Miyaki et al., 1997).

RELATIVE RISK OF CANCER IN FIRST-DEGREE RELATIVES

In epidemiologic studies only a small increased risk for brain tumors was detected for relatives of patients with brain tumors. Choi et al. (1970) found a ninefold increase in the incidence of brain tumors among relatives of glioma patients compared to controls. However, even this increased relative risk translated into the relatively small absolute risk of 0.6% in this study. In other studies the increased relative risk was less significant (Burch et al., 1987; Hill et al., 2003). Gold et al. (1994) compared several risk factors in 361 children with brain tumors to 1083 matched controls. Although a family history of tumors did not contribute to an increased risk of brain tumors in children, a modest increase in risk of childhood brain tumors was associated with a maternal family history of birth defects. Kuijten et al (1993) found a modestly increased risk of childhood cancers only in relatives of cases with primitive neuroectodermal tumors, whereas for relatives of astrocytoma cases this risk was not significantly increased.

GLIAL TUMORS

Gliomas are a heterogeneous group of mostly sporadic neoplasms derived from glial cells. They account for about 40 to 45% of all intracranial tumors

and thus are the most common tumors among the primary CNS neoplasms (Russel et al., 1989). Depending on morphological appearance and presumed histogenesis, gliomas are subdivided into several subgroups, the most important being astrocytic tumors (including the glioblastoma), oligodendroglial tumors, mixed gliomas (oligoastrocytomas), and ependymal tumors.

A genetic predisposition for the development of gliomas is seen in NF1 and NF2, Li-Fraumeni syndrome, tuberous sclerosis, Gorlin syndrome, and Turcot syndrome, and ataxia telangiectasia. The specific type of glioma or its location may vary depending on the disorder. For example, pilocytic astrocytoma of the optic nerve is typical for NF1, whereas ependymoma of the spinal cord is characteristic for NF2. Of 282 children with astrocytoma examined by Kibirige et al. (1989), 21 had a diagnosis of NF1, and 4 had tuberous sclerosis. Familial glioma not associated with a specific genetic syndrome does occur but is infrequent, and it is exceedingly rare to see more than two first-degree relatives with glioma. Vieregge et al. (1987) reviewed 39 reports of familial glioma and concluded that 60% involved affected siblings. Although gliomas are seen in familial APC and Turcot syndrome, somatic mutations in the APC gene in primary brain tumors are rare and were not detected in 91 neuroepithelial tumors including gliomas (Mori et al., 1994).

Astrocytoma and glioblastoma

Astrocytoma is a generic term applied to diffusely infiltrating tumors composed of well differentiated neoplastic astrocytes (Kleihuis et al., 1993). The astrocytomas, or astrocytic gliomas, may be subdivided into two major groups: 1) The more common group of diffusely infiltrating tumors, comprising astrocytoma, anaplastic astrocytoma, and glioblastoma. 2) The less common group of tumors with more circumscribed growth consisting of pilocytic astrocytoma, pleomorphic xanthoastrocytoma (PXA), and subependymal giant cell astrocytoma of tuberous sclerosis. Astrocytomas tend to infiltrate surrounding brain. Therefore, despite their slow growth, even well-differentiated astrocytomas (corresponding to grade II histologically) tend to recur. Anaplastic (malignant) astrocytomas show diffuse anaplasia (e.g., increased cellularity, pleomorphism, nuclear atypia and mitotic activity). Histologically they correspond to grade III. Glioblastoma is an anaplastic, often cellular brain tumor composed of poorly differentiated, fusiform, round or pleomorphic cells and occasional multinucleated giant cells. Essential for the histologic diagnosis is the presence of prominent vascular proliferation and/or necrosis. Histologically, glioblastomas correspond to grade IV. Astrocytomas and glioblastomas account for about 17% of primary brain tumors in adults, whereas in children they account for only 4%.

The most malignant type of glioma, the glioblastoma (WHO grade IV), is also the most common, making up close to 50% of all gliomas (Walker et al., 1985). The incidence of glioblastomas peaks between 45 and 60 years of age. In adults, glioblastomas share a preferential supratentorial location with the other diffuse astrocytomas. By CT and magnetic resonance imaging (MRI), these tumors usually appear as a ring structure with a hypodense center (necrosis) surrounded by a ring of contrast-enhancing vital tumor tissue and edema. Macroscopically, typical glioblastomas are largely necrotic masses with a peripheral zone of fleshy gray tumor tissue. Intratumoral hemorrhage is a frequent finding. Histologically, glioblastomas are cellular tumors that may show a variety of tissue and cell differentiation patterns.

Although histologically indistinguishable, there are genetically distinct subtypes of primary and secondary glioblastoma. Primary glioblastomas account for the vast majority of cases in adults older than 50 years. After a short clinical history of usually fewer than 3 months, they manifest de novo without clinical or histologic evidence of a less malignant precursor lesion. In contrast, secondary glioblastomas usually develop in younger patients less than 45 years of age with malignant progression from grade II or III astrocytoma. The interval of progression may be from less than one year to as long as 10 years with a median interval of 4 to 5 years (Kleihues et al., 2002). The prognosis of glioblastoma patients is extremely poor, with a median postoperative survival time of only 12 months (Burger et al., 1987).

Molecular Genetics of Astocytic Gliomas

Several molecular mechanisms have been implicated in the development of gliomas and their progression to more malignant histologic grades upon recurrence. These involve activation of dominantly acting oncogenes as well as inactivation of recessive tumor suppressor genes. Among primary glioblastomas, 60% have overexpression of the epidermal growth factor receptor (EGFR) and 40% have EGFR amplification. EGFR vIII, a mutant EGFR receptor, is co-expressed in nearly 50% of glioblastomas with EGFR amplification (Ekstrand et al., 1992). Other genetic alterations observed in primary glioblastomas include overexpression of the MDM2 (murine double minute 2) gene and mutation loss of the tumor suppressor protein PTEN. Secondary glioblastomas typically have mutations of the p53 tumor suppressor gene and overexpression of platelet-derived growth factor (PDGF) ligands and receptors (Kleihues et al., 2002). Genetic alterations on chromosomes 9p, 10q, 11p, 17p, 19q and 22 have also been associated with events leading to gliomas.

As we observe these molecular genetic alterations of tumors, efforts are targeted at correlating these changes with clinical parameters including prognosis and response to treatment. As an example, we can look more closely at the MGMT gene located on chromosome 10q26, which encodes a DNA-repair protein that removes alkyl groups from the O6 position of guanine. High levels of MGMT activity diminish the therapeutic effects of alkylating agents. Loss of MGMT expression occurs by epigenetic silencing of the MGMT gene by promoter methylation. In a series of 206 glioblastomas, the MGMT promoter was methylated in 45%. This change correlated with a statistically significant increase in median overall survival of 18.2 months compared with 12.2 months in those without promoter methylation. Moreover, those patients with the MGMT promoter methylation status benefited from a combination of chemotherapy with an alkylating agent, temozolomide, and radiation with a median survival of 21.7 months compared to radiation alone with a median survival of 15.3 months (Hegi et al. 2005).

Genetic alterations leading to glioma formation are described below in greater detail, and a simplified summary of events leading to glioma formation and progression is shown in Figure 1.

Chromosome 9p

The critical gene on chromosome 9 is the CDKN2A (MTS1) tumor suppressor gene which encodes p16 (p16INK4a), a negative regulator of cell cycle progression (Liggett and Sidransky, 1998). CDKN2A mutations have been identified in melanoma, astrocytoma, and glioblastoma (Greene, 1999; Rasheed et al., 1999). The p16 protein normally binds the cyclin D-cyclin-dependent kinase 4 or 6 (Cdk4, Cdk6) complex, thereby inactivating the retinoblastoma protein Rb resulting in cell-cycle arrest (Lukas et al., 1995).

Glioblastomas frequently show deletions of one or both copies of the CDKN2A tumor suppressor gene on 9p21. Schmidt et al. found homozygous deletion of CDKN2A in 41% and hemizygous loss of CDKN2A in 28% of primary glioblastomas (Schmidt et al., 1994). In glioblastoma cell lines, the incidence of homozygous CDKN2A loss seems to be even higher, reaching 70% (He et al., 1994). In addition, inactivation of CDKN2A either by point mutation or by 5' CpG island methylation has been found in some glioblastomas (Costello et al., 1996; Ichimura et al., 1996). Chromosome 9p deletions are not exclusive to malignant astrocytomas, and may occur in lower grade astrocytomas and oligodendrogliomas (Bello et al. 1994).

Chromosome 10

Monosomy 10 is a frequently detected karyotypic abnormality in gliomas, and typically associated with a more malignant histologic type. Using comparative genomic hybridization, Schrock et al. (1994) demonstrated chromosome 10 loss in one of two astrocytomas and seven of seven glioblastomas. The incidence of chromosome 10 loss in glioblastomas varies between different studies, ranging from 60% to over 90% of the cases (Collins and James, 1993). Loss of heterozygosity in gliomas for chromosome 10 genetic markers often involves markers spanning the whole chromosome. However, partial deletions have recently been identified (Karlbom et al., 1993).

Three different regions on both arms of chromosome 10 have been implicated as potential sites of glioblastoma-associated tumor suppressor genes (Karlbom et al., 1993). The region most frequently deleted is located at distal 10q and spans approximately 5 cM between the loci D10S587 and D10S216 (Rasheed et al., 1995). A candidate tumor suppressor gene designated DMBT1 ("deleted in malignant brain tumors 1"), has recently been cloned and mapped to this region (Mollenhauer et al., 1997). Intragenic homozygous deletions in DMBT1 were found in about 23% of glioblastomas (Mollenhauer et al., 1997). Another candidate gene from distal 10q is the MXI1 gene, which codes for a negative regulator of the Myc oncoprotein. Mutations of MXI1 have been detected in prostate cancer (Eagle et al., 1995). Glioblastomas have not been studied in detail for MXI1 mutations. In contrast, somatic mutations in the PTEN tumor suppressor gene at 10q23 have been detected in about one third of glioblastomas (Bostrom et al., 1998; Li et al., 1997; Steck et al., 1997). PTEN is also altered in some breast carcinomas, prostate carcinomas, and malignant melanomas (Li et al., 1997; Steck et al., 1997).

Chromosome 11p

Eleven of 43 malignant astrocytomas showed loss of heterozygosity (LOH) of markers in 11p (Fults et al., 1992). The HRAS gene that maps to this region was excluded as a candidate gene by single strand conformation polymorphism (SSCP) analysis. Loss is detected in low as well as high grade gliomas, suggesting that these events occur early in tumorigenesis.

Chromosome 17p and TP53

Loss of chromosome 17p is an early and frequent event in astrocytomas, and losses are frequently accompanied by mutation in the TP53 gene which is located in 17p13.1. This was not surprising since the occurrence of glial tumors in patients with the Li-Fraumeni syndrome pointed to the importance of the TP53 gene in the formation of sporadic gliomas. In addition, Kyritsis et al. (1994) identified TP53 germline mutations in 6 of 19 patients with multifocal glioma, including two with family history of cancer, one with another primary malignancy, and two with all three risk factors; one of four patients with unifocal glioma, another primary malignancy, and a family history of cancer;

and 2 of 15 patients with unifocal glioma and a family history of cancer but no second malignancy. In a family ascertained through the occurrence of childhood adrenocortical carcinoma a mutation of codon 307 in exon 8 was identified in the proband's tumor as well as in an astrocytoma from the proband's father (Sameshima et al., 1992). However, van Meyel et al. (1994) did not identify germline mutations in 26 members of 16 families with glioma in exons 5 through 9 of the TP53 gene.

The wild-type TP53 gene product is a nuclear phosphoprotein that suppresses cell and tumor growth. In a study of 120 primary brain tumors, TP53 mutations were only detected in the 59 astrocytic tumors (Wu et al., 1993). Of these, six tumors with TP53 mutations were either anaplastic astrocytomas or glioblastomas. Four of the six tumors had lost heterozygosity for 17p markers as well. Del Arco et al. (1993) suggested a two-step model for inactivation of the TP53 gene in astrocytomas. A single TP53 mutation seemed to occur in the initial stage of tumorigenesis, since low-grade astrocytomas were heterozygous for the mutation; loss of the remaining wild-type allele was associated with a higher degree of malignancy. Sidransky et al. (1992) proposed that histologic progression of astrocytomas was associated with a clonal expansion of cells that had previously acquired a mutation in the TP53 gene. By studying low-grade tumors that had recurred as more malignant tumors they could show that a subpopulation of cells in the initial tumor that contained TP53 mutations made up the majority of cells in the recurrent tumor which had progressed to glioblastoma. However, inactivation of TP53 may not be an obligatory step since 4 of 13 glioma cell lines contained a non-mutated TP53 gene with wild-type function in a functional assay using transcriptional elements that are induced by wild type but not mutant TP53 (van Meir et al., 1994). However, these tumors may contain amplifications of the MDM2 gene (see below).

Wild-type p53 has a short half-life, and is present in such small quantities in normal cells that it cannot be detected immunocytochemically. Mutations in the TP53 gene are associated with slower turnover and may result in abnormal expression leading to p53 accumulation in the cell nucleus so that staining can be detected by immunocytochemistry. Aberrant or increased expression of p53 has been observed in many astrocytic tumors (Karamitopoulo et al., 1993). Haapasalo et al. (1993) stained sections of 102 astrocytic tumors with two antibodies to wildtype and mutant TP53. None of the grade 1 astrocytomas were positive, but 29% of grade 2 tumors, and 49% of grade 3 to 4 astrocytomas. However, some mutations in the conserved TP53 exons may be missed by immunocytochemistry, and p53 accumulation may occur independent of mutations in these exons (Louis et al., 1993).

Chromosome 19

LOH on chromosome 19p is a common alteration found in astrocytomas (Ritland et al., 1995; von Deimling et al., 1992). Ritland et al. (1995) showed LOH at 19p13.2-pter in 17 of 23 studied astrocytomas, consistant with findings of the previous work by von Deimling et al. (1992). Alterations on chromosome 19q are also less commonly linked to the development of astrocytomas, involving 19q13.2 - q13.4 (Von Deimling et al., 1994).

Chromosome 22

Using comparative genomic hybridization, Schrock et al. (1994) identified loss and gain of chromosome 22 in malignant gliomas. Five of nine tumors had lost all or part of chromosome 22q. A novel amplification site was mapped to chromosome 22q12.

Gene Amplifications

The most commonly amplified gene in glioblastomas is the gene coding for the epidermal growth factor receptor (EGFR) on chromosome 7 correlating with the frequent observation of trisomy 7 in glioblastomas. EGFR is a transmembrane protein with tyrosine kinase activity. Its extracellular domain binds EGF and transforming growth factor (TGF)-α. EGFR may interact with its ligands in an autocrine fashion leading to an increase in cell proliferation.

EGFR abnormalities are specifically associated with glioblastoma multiforme (Agosti et al., 1992) and EGFR amplification is associated with a shorter median survival (Hurtt et al., 1992). In a study of 58 glioblastomas, von Deimling et al. (1992) detected EGFR gene amplification only in tumors with loss of chromosome 10 suggesting that EGFR abnormalities follow chromosome 10 loss in the cascade of tumor progression.

Abnormalities of the EGFR gene in glioblastomas include most commonly amplification and overexpression, but also rearrangements and deletions resulting in abnormal binding of ligands (Agosti et al., 1992; Ekstrand et al., 1991; Wong et al., 1992). Most frequently, rearrangements are deletions affecting the 5'-end (coding for the extracellular domain) and, more rarely, the 3'-end (coding for the intracellular domain)(Collins, 1995). The most common of these rearrangements, an in-frame deletion of 801 bp resulting in the aberrant splicing of exon 1 to exon 8, causes the expression of a truncated receptor molecule lacking parts of the extracellular domain necessary for ligand binding. Functional characterization of this EGFR variant has revealed that it shows constitutive tyrosine kinase activity and may thereby confer enhanced tumorigenicity on human glioma cells (Collins, 1995).

In addition to EGFR, the cellular MDM2 (murine double minute 2) gene on 12q is amplified in a large percentage of human sarcomas and in other human tumors. The gene product can complex with p53 and inhibit its function (Finlay, 1993). Reifenberger et al. (1993) studied 157 primary brain tumors and found that the MDM2 gene is amplified and overexpressed in 8 to 10% of anaplastic astrocytomas and glioblastomas. No TP53 mutations or LOH for 17p were detected in these tumors, suggesting that MDM2 amplification may be an alternative mechanism for abnormally regulated p53 growth control. Reifenberger et al. (1994) showed that 15% of astrocytomas and glioblastomas show amplification of 12q13-14 and identified some tumors that had amplicons not containing MDM2, but CDK4 and SAS. More recently, another murine double minute gene, MDM4, has been shown to be amplified in gliomas lacking TP53 mutations that lacked MDM2 amplification (Riemenschneider et al., 1999). Other genes including NMYC and MET may be amplified as well, albeit at a much smaller frequency (Bigner et al., 1988, Wullich et al., 1994).

Pilocytic astrocytomas constitute a separate clinical and histopathologic entity and are the most common astrocytic tumors in children. In contrast to adult astrocytomas, allelic losses on chromosomes 10, 17p, and 19q are not found in pilocytic astrocytomas nor are alterations in the EGFR gene. However, von Deimling et al. (1993) detected loss of alleles on 17q in 4 of 20 tumors. One tumor contained an interstitial deletion encompassing the region of the NF1 gene. Mutations of the TP53 gene were not identified in 12 juvenile pilocytic astrocytomas (Ohgaki et al., 1993).

Oligodendroglioma

Oligodendroglioma is a tumor composed predominantly of neoplastic oligodendrocytes (Kleihues et al., 1993). Oligodendrogliomas are typically slow growing and usually occur during adulthood. They are most commonly located in the cerebral white matter and deep gray structures. Oligodendrogliomas have a lesser tendency to malignant transformation than astrocytomas. Histologically, oligodendrogliomas most often correspond to WHO grade II, while the anaplastic oligodendrogliomas are WHO grade III.

Most oligodendendroglial tumors are sporadic neoplasms. Occasional cases of familial clustering have been reported by Parkinson and Hall (1962) (oligodendroglioma in two brothers), Roosen et al. (1984), (oligodendroglioma in a mother and her daughter), Roelvink et al. (1986) (oligodendroglioma in twin sisters), and Ferraresi et al. (1989) (oligodendroglioma in a father and his son). In addition, a family with polymorphous oligodendrogliomas in brother and sister has been shown, whose tumors were immunoreactive for p53, suggesting that each tumor was associated with a mutation in the TP53 gene (Kros et al., 1994).

Molecular Genetics of Oligodendrogliomas

There are multiple molecular mechanisms that account for the development of oligodendrogliomas. Genetic alterations on chromosomes 1, 10, and 19 have been associated with events leading to oligodendrogliomas. Amplification of EGFR has also been observed in oligodendrogliomas, however EGFR amplification is considerably more infrequent than in other glial tumor types, while EGFR overexpression is common. Loss of heterozygosity (LOH) on the chromosome arms 1p and 19q is frequent in oligodendroglial tumors. LOH of chromosome 1p or combined loss involving chromosomes 1p and 19q is statistically significantly associated with both chemosensitivity and longer recurrence-free survival after chemotherapy (Cairncross et al., 1998). LOH on 1p and 19q in patients with anaplastic oligodendroglial tumors treated with chemotherapy with or without radiation had a median time to progression of 86 months and a median overall survival of 91 months compared to those without LOH who had a median time to progression of 39 months and a median overall survival of 46 months (Felsberg et al., 2004).

Chromosome 1

Loss of alleles on the short arm of chromosome 1 are common in oligodendroglial neoplasms. Reifenberger et al. (1994) showed LOH on 1p in 67% (14/21) of studied tumors. Bello et al. (1994) found LOH on 1p in 6 of 6 oligodendrogliomas and 5 of 6 anaplastic oligodendrogliomas. Kraus et al. (1995) detected LOH in 3 of 9 oligodendrogliomas and 3 of 6 anaplastic oligodendrogliomas.

In anaplastic oligodendrogliomas, when chromosome 1p deletions are absent, chromosome 9p deletions often occur, and loss of CDKN2A, which encodes a cell cycle regulatory molecule (p16INK4A). CDKN2A has a close homologue, CDKN2C, located at chromosome 1p32. Tipped by these reciprocal 1p/9p deletions, Pohl et al. (1999) demonstrated homozygous deletions of the CDKN2C gene on the short arm of chromosome 1 in a subset of oligodendrogliomas, suggesting CDKN2C may be oncogenic in these tumors.

Chromosome 10

Wu et al. (1993) report a patient presenting with an oligodendroglioma that recurred with the histology of a glioblastoma 5 months later. DNA analysis

of the initial tumor showed loss of alleles on chromosome 10, which is typically found in more malignant gliomas. The authors suggested that loss of chromosome 10 alleles may be predictive of malignant tumor growth even when morphologic criteria of aggressive growth are absent. Chromosome 10 deletions in low grade oligodendrogliomas were more recently narrowed to 10q25-26 (Maier et al., 1997).

Chromosome 19

The most frequent genetic alteration in oligodendrogliomas is LOH on the long arm of chromosome 19 (Ransom et al., 1992; von Deimling et al., 1992, 1994; Rosenberg et al., 1996). Ritland et al. (1995) examined region specific LOH and its relation to the morphologic type of glioma. Whereas in astrocytomas allelic loss was most commonly observed for 19p, loss of alleles in 19q and retention of alleles in 19p was associated with oligodendrogliomas and mixed oligoastrocytomas (Ritland et al., 1995).

Allelic loss on 19q showed a striking association with LOH on 1p, a finding suggesting a synergistic effect of both alterations in providing a selective growth advantage (Bello et al., 1995; Kraus et al., 1995; Reifenberger et al., 1994; Smith et al., 1999).

Amplification of EGFR

EGFR gene amplifications are the most common amplifications found in glioblastomas. EGFR amplifications are relatively uncommon in oligodendrogliomas, while overexpression of EGFR protein is a common feature of oligodendrogliomas. Reifenberger et al. (1996) studied 13 grade II oligodendrogliomas and 20 grade III anaplastic oligodendrogliomas for EGFR gene amplification. They observed EGFR gene amplification in only one anaplastic tumor. However Reifenberger et al. (1996) also observed that overexpression of EGFR mRNA is relatively common in both low and high grade oligodendrogliomas (6 of 13 oligodendrogliomas, and 10 of 18 anaplastic oligodendrogliomas).

Ependymoma

Ependymoma is a tumor composed predominantly of neoplastic ependymal cells. Ependymomas are moderately cellular with low mitotic activity. They are thought to arise from the ependymal or subependymal cells surrounding the ventricles, the central canal or within the filum terminale. Ependymomas usually present as a posterior fossa mass in children between the ages of 2 and 10 years, but are also found in the spinal canal.

Ependymomas may occur in patients with NF2 and have been described in one individual who was part of a sibship with autosomal dominant meningiomas (Sieb et al., 1992). Familial ependymoma occurred in a family of 11 siblings (Honan et al., 1987). Four siblings developed ependymomas or subependymomas, and one additional sibling had a brain tumor with unverified histology. Gilchrist and Savard (1989) described ependymomas in two sisters and their maternal male cousin.

Since ependymomas are found in patients with NF2, the NF2 gene was a likely candidate for an ependymoma gene. However, loss of chromosome 22 in sporadic ependymomas is rarely determined by cytogenetic or molecular studies (James et al., 1990; Weremowicz et al., 1992; Rubio et al., 1994). Rubio et al. (1994) detected loss of chromosome 22 alleles and mutation in the NF2 gene in

only one out of eight ependymomas. Segregation analysis with chromosome 22 markers identified chromosome 22pter-22q11.2 as a region containing the ependymoma locus, and clearly excluded the NF2 gene locus (Hulsebos et al., 1999) This is consistent with the finding in a single patient of an ependymoma-associated constitutional translocation, t(1;22)(p22;q11.2) (Rhodes et al., 1997). It should be noted that ependymomas in NF2 patients usually occur in the spine, whereas most sporadic tumors have an intracranial location.

Mutations in the TP53 gene are also rare in ependymomas. In 15 ependymomas, only one contained a silent mutation in exon 6. Metzger et al. (1991) detected a germline mutation in codon 242 of the TP53 gene in a patient with a malignant ependymoma of the posterior fossa. Several of the relatives had died at a young age from a variety of cancers. Similarly, in a survey of relatives of 195 children under age 15 with soft-tissue sarcomas, only one sib died from an ependymoma (Pastore et al., 1987).

Evidence for other ependymoma loci has come from several different approaches. In addition to chromosome 22 abnormalities, cytogenetic analyses of ependymomas have shown abnormalities of chromosomes 6, 11, 16, and 17 (Neumann et al., 1993, Sainati et al., 1992, Rogatto et al., 1993). Comparative genomic hybridization studies and cytogenetic analysis have shown that loss of chromosome 6p is common in the pediatric ependymoma, in addition to 17p and 22q abnormalities (Kramer et al., 1998; Reardon et al., 1999). By immunocytochemical investigation of ependymomas using antibodies directed against schwannomin, Huynh et al. (1997) divided ependymomas into two groups: one group with lack of staining suggesting that loss or mutation of both NF2 alleles had occurred, and a second group with normal staining suggesting that mutation in other genes caused ependymoma formation (Fig. 2). An ependymoma locus in addition to NF2 was also suggested by genetic linkage analysis of a family with autosomal dominant meningiomas and ependymomas (Pulst et al., 1993).

Molecular Predictors of Glioma Progression

In gliomas more than in any other type of brain tumor, recurrence is associated with a more malignant histologic type, and response to treatment may vary greatly despite identical histologic classification. Patients with EGFR gene amplification in their gliomas, were found to have a significantly shorter survival than those without amplification ($P < 0.01$, Hurtt et al., 1992). Analysis of tumor cells in a plaque assay allowed Sidransky et al. (1992) to detect a subpopulation of tumor cells that contained mutations in the TP53 gene. Progression to a more malignant histology in the recurring tumor was due to clonal expansion of those cells containing TP53 mutations. In a long term follow-up study of 52 patients with low grade astrocytomas, a trend towards more aggressive growth was detected for patients with p53 positive tumors (Iuzzolino et al., 1994). Five years after diagnosis the survival estimate with the Kaplan-Meier method was 21% for p53 positive patients, but 46% for patients whose tumors lacked p53 immunoreactivity. Glioblastomas in patients with Turcot syndrome caused by mutations in mismatch repair genes may have a prolonged survival (Hamilton et al., 1995).

PRIMITIVE NEUROECTODERMAL TUMOR AND MEDULLOBLASTOMA

The WHO classification defines primitive neuroectodermal tumors (PNETs) as small-cell, malignant tumors of childhood with predominant location in the cerebellum and a noted capacity for divergent differentiation, including neuronal, astrocytic, ependymal, muscular, and melanotic (Kleihues et al.,

1993). A major subcategory of PNETs is the medulloblastoma. Medulloblastomas are malignant, embryonal childhood tumors located in the cerebellum and composed of densely packed cells with round to oval, or carrot-shaped nuclei and scanty cytoplasm. Most medulloblastomas express neuronal marker proteins (Kleihues et al., 1993). Medulloblastomas account for the vast majority of PNETs and make up about 20% to 25% of all intracranial tumors in children (Russel et al., 1989). Medulloblastomas have a peak incidence between 3 and 5 years of age of approximately 1-100,000/year.

Genetic disorders associated with medulloblastoma include Gorlin syndrome (Evans et al., 1991a, 1991b; Gorlin 1987), familial adenomatous polyposis coli and Turcot syndrome (Hamilton et al., 1995). One patient in a family with von-Hippel-Lindau disease presented with a primitive neuroectodermal tumor with multipotent differentiation in the cerebellum (Becker et al., 1993).

Familial medulloblastoma is very rare, but has been reported in two newborn sisters and identical twin girls (Belamaric and Chau, 1969). Another sib pair was recently reported by Hung et al. (1990) including a review of the relevant literature. One study detected a germline TP53 mutation in two siblings with cerebral PNETs (Reifenberger et al., 1994).

Molecular Genetics of Primitive Neuroectodermal Tumors

Molecular abnormalities on chromosome 9, 11, and 17 have been linked to the development of PNETs. Other common genetic abnormalities in medulloblastomas are gains of portions of chromosome 1, and deletions of 1q, 6q, 11p, and 16q (Bigner et al., 1988; Fults et al., 1992; Kraus et al., 1996; Thomas and Raffel, 1991). Mutations in the genes encoding Wnt signaling pathway proteins APC and beta-catenin occur rarely in sporadic medulloblastomas (Huang et al., 2000; Vortmeyer et al., 1999) No mutations in the APC gene were detected in 91 neuroepithelial tumors including medulloblastomas (Mori et al., 1994). However, 12% of sporadic medulloblastomas (of 86 tumors plus 11 cell lines investigated) had Axin1 gene deletions (Dahmen et al., 2001). The Axin1 gene is located at 16p13.3 and its gene product Axin is a negative regulator of Wnt signaling.

Chromosome 9

LOH of chromosome 9q involving the Gorlin syndrome gene locus at 9q22 (PTCH) has been found in a subset of medulloblastomas, including desmoplastic variants (Albrecht et al., 1994; Schofield et al., 1995). In addition, somatic mutations in the PTCH gene have been found in about 10% to 15% of medulloblastomas (Raffel et al., 1997; Wolter et al., 1997).

Chromosome 11

Three of 11 PNETs showed LOH of markers in 11p (Fults et al., 1992). The c-HRAS gene that maps to this region was excluded as a candidate gene by SSCP analysis.

Chromosome 17 and TP53

Isochromosome 17q has been consistently observed in cytogenetic studies of PNETs, which has been detected in about 30% to 50% of the tumors (Biegel et al., 1989; Bigner et al., 1988). Isochromosome 17q results in the loss of one copy of 17p, and molecular studies have indeed confirmed LOH on 17p in a similar percentage of medulloblastomas (Cogen et al., 1990; James et al., 1990; Raffel et al., 1990). However, loss of 17p in medulloblastomas is usually not associated with TP53 mutation (Biegel et al., 1992; Cogen et al.,

1992; Cogen et al., 1990; Ohgaki et al., 1991; Phelan et al., 1995; Saylors et al., 1991). Mutations in the TP53 gene are relatively infrequent in medulloblastomas. Although 4 of 22 tumors had lost 17p, only two harbored mutations in the TP53 gene, and the mutation was homozygous in only one of these tumors(Badiali et al., 1993). Intense overexpression of p53 by immunocytochemical analysis of tumor sections was associated with a significantly reduced survival (Jaros et al., 1993). The infrequent mutation of TP53, together with the finding of LOH at distal 17p not including the TP53 locus, suggest the existence of a second, not yet identified, tumor suppressor gene located at 17p13.3 (Biegel et al., 1992; Watling et al., 1995). The HIC-1 gene is a good candidate for this suspected tumor suppressor gene (Wales et al., 1995; Steichen-Gersdorf et al., 1997), but further studies are needed to substantiate the role of this gene in PNETs.

SCHWANNOMA (NEURILEMMOMA, NEURINOMA)

Schwannomas are encapsulated and sometimes cystic tumors composed of spindle-shaped neoplastic Schwann cells (Kleihues et al., 1993). Tumors contain cellular areas with compact elongated cells, often with pallisading, (Antoni A areas) and less dense areas with cells containing lipid (Antoni B).

Schwannomas account for 8% of intracranial tumors and 29% of intraspinal tumors. Vestibular schwannomas (VSs) are also (somewhat erroneously) referred to as acoustic schwannomas or neuromas and occur commonly as single tumors on the vestibular branch of the eighth cranial nerve. They have an incidence of around 13/million/year (Tos and Thomsen, 1984). In patients with NF2, vestibular schwannomas are often bilateral and occur at a much earlier age than in patients with sporadic unilateral tumors. About 4% of vestibular schwannomas are bilateral, and virtually all of these patients have NF2. Schwannomas also occur on other cranial and spinal nerves. When magnetic resonance imaging (MRI) imaging is used, spinal schwannomas are as common in NF2 as vestibular schwannomas (Mautner et al., 1995, 1996). A proband presenting with multiple spinal schwannomas harboring a deletion in the NF2 gene has been described (Kluwe et al., 1995). Two relatives carrying the same deletion were subsequently shown to have asymptomatic bilateral vestibular schwannomas. A second pedigree with autosomal dominant spinal tumors, but lacking vestibular schwannomas or other CNS tumors by autopsy or MRI, has also been described (Pulst et al., 1991).

Frequent loss of alleles in 22q12 in sporadic vestibular schwannomas and NF2 tumors indicated a common pathogenetic mechanism for these tumors (Seizinger et al., 1987). These findings were further supported by establishing linkage of NF2 to genetic markers on chromosome 22 (Rouleau et al., 1987), leading to the subsequent cloning of the NF2 gene in 1993 (Rouleau et al., 1993, Trofatter et al., 1993). The NF2 gene product, designated schwannomin or merlin (see Welling and Chang, 2000), is a 595 amino acid protein of the protein 4.1 superfamily of proteins, with highest similarity to the ERM protein family (including ezrin, radixin, and moesin) which link the cell membrane and the cytoskeleton.

The action of the NF2 gene is that of a classical tumor suppressor. Inactivation or loss of the second allele and lack of the NF2 gene product could be demonstrated in most schwannomas (Sainz et al., 1994, see below). Reduction of schwannomin synthesis in Schwann cells by use of antisense oligonucleotides leads to morphologic changes and loss of cell attachment (Huynh et al., 1996). Schwannomin is known to directly interact with a variety of proteins including ezrin, moesin, radixin, betaII-spectrin, actin, HRS, eIF3c, CD44, paxillin, N-WASP, magicin, PIKE-L, and EBP50/NHE-RF (Fernandez-

Valle et al., 2002; Manchanda et al., 2005; Morrison et al., 2001; Murthy et al., 1998; Reczek et al., 1997; Rong et al., 2004; Scoles et al., 1998; Scoles et al., 2000; Scoles et al., 2002; Wiederhold et al., 2004; Xu and Gutmann, 1998).

In addition, schwannomin co-localizes and forms complexes that may or may not be direct with betaI-integrin (Obremski et al., 1998), and CD44 (Sainio et al., 1997).

The majority of NF2 gene mutations identified in vestibular schwannomas are deletions leading to a premature stop codon (Bianchi et al., 1994; Irving et al., 1994; Jacoby et al., 1994; Lekanne-Deprez et al., 1994; Ruttledge et al., 1994, 1996; Sainz et al., 1994; Sainz et al., 1995; Twist et al., 1994). Although no clear hot spots for mutations have been identified, C to T transitions leading to change of an arginine codon to a stop codon occur more commonly than expected (Table 2) (Sainz et al., 1995). With the exception of an increased frequency of C to T transitions (Sainz et al., 1995) and mutations resulting in skipping of exon 4 (Sainz et al., 1996) recurrent mutations are rare in the germline or in schwannomas (MacCollin et al., 1994).

Most NF2 mutations are expected to result in loss of the majority of interactions between schwannomin and other proteins. NF2 mutation also significantly decreases schwannomin stability. Sainz et al. (1994) demonstrated absence of schwannomin staining in all of 30 immunohistochemically stained vestibular schwannomas. Two other studies demonstrated loss of schwannomin expression in 93% of stained schwannomas, 75% of meningiomas, and 33% of ependymomas (Huynh et al., 1997; Gutmann et al., 1997). Thus, in contrast to meningiomas and ependymomas, mutations in the NF2 gene appear to be the major if not exclusive molecular event leading to schwannoma formation.

Schwannomatosis describes a condition of multiple schwannomas and represents a unique class of NF that may or may not involve NF2 gene mutations (Pulst et al., 1997). Patients with schwannomatosis lack vestibular schwannomas, and some cases show multiple schwannomas localized to just the spine. Some patients with schwannomatosis have been characterized to possess no identifiable NF2 gene mutations (Bruder et al., 1999). In another study, pedigree analysis of 20 families with spinal schwannomatosis revealed truncating NF2 gene mutations and LOH (Jacoby et al., 1997). Some patients proved to be sporadic mosaics for NF2 gene mutations, while others had familial NF2

MENINGIOMA

Meningioma is a tumor composed of neoplastic meningothelial (arachnoid) cells (Kleihues et al., 1993). Several histologic variants are recognized, such as meningothelial, fibrous (fibroblastic), transitional, and psammomatous meningioma.

Meningiomas are the most common benign brain tumors, and account for about 15% of all intracranial tumors and 25% of intraspinal tumors. The frequency of meningioma increases with advancing age and meningiomas are more common in women. Although meningiomas are frequently attached to the dural membranes, they may occur in unusual sites, for example within the ventricular space.

Meningiomas occur frequently in patients with NF2 (Evans et al., 1992; Parry et al., 1994; Mautner et al., 1996), and less frequently in Werner and Gorlin syndrome. Many reports of familial meningioma may represent patients with NF2 that were inadequately evaluated for the presence of small vestibular

or spinal schwannomas or lens opacities. For example, Delleman et al. (1978) reported a family with four members in two generations with meningiomas. Other signs of NF2 were missing. A fifth member of the pedigree, however, had multiple meningiomas and vestibular schwannomas. Since it is advisable to remove vestibular schwannomas before they lead to loss of hearing, signs of NF2 should be carefully sought in all cases of familial meningioma, multiple meningiomas or meningiomas in young patients. Dominantly inherited meningioma without other evidence of NF2, however, does occur (Pulst et al., 1993; Bolger et al., 1980, and references therein).

Molecular Genetics of Meningiomas

Chromosome 22

Zang and Singer (1967) reported the loss of chromosome 22 in short term cultures of fresh meningiomas. Subsequently, Seizinger et al. (1987) reported loss of heterozygosity of chromosome 22 DNA markers in 17 of 40 meningiomas. Molecular studies of sporadic meningiomas and meningiomas from NF2 patients have confirmed these findings (Dumanski et al., 1987; Seizinger et al., 1987). Inactivating mutations in the NF2 gene have been detected in 20 to 30% of sporadic meningiomas, often accompanied by mutations or loss in the second allele (Lekanne-Deprez et al., 1994; Ruttledge et al., 1994). Schwannomin staining is absent in more than half of sporadic meningiomas (Huynh et al., 1997; Gutmann et al., 1997, see above).

Additional genes may be involved in meningioma pathogenesis both on chromosome 22. A translocation (4;22) observed in a meningioma cell line recently led to the identification of a gene, dubbed MN1, which is also involved in translocations with the tel gene in the pathogenesis of leukemias (Zwarthoff et al., 1993). This gene is centromeric but in close proximity to the NF2 gene. What role MN1 plays in the formation or progression of most meningiomas is still unresolved. Other genes more recently linked to meningiomas pathogenesis include DAL1 and protein 4.1R (Perry et al., 2004)

In a screen of 81 meningiomas for mutations in the NF2 gene, LOH for chromosome 22 markers was detected only in those meningiomas that also had NF2 gene mutations (Leone et al., 1999). Of the 81 meningiomas, 44 had LOH of 22q, 29 had LOH of 1p, and 23 had LOH of 14q (Leone et al., 1999). The authors concluded that the formation of aggressive meningiomas follows a multi-step tumor progression model involving genes on 1p, 14q, and 22q. Immunocytochemical studies of meningiomas support this hypothesis. Schwannomin immunoreactivity was absent in more than half of meningiomas, whereas the remainder showed strong schwannomin staining suggesting that the NF2 gene was not mutated (Huynh et al., 1997; Gutmann et al., 1997).

Genetic linkage studies provide further evidence for the existence of a second meningioma locus. Analysis of a pedigree with autosomal-dominant meningiomas and ependymomas excluded the mutation from the NF2 region (Pulst et al., 1993). The region excluded by linkage analysis encompassed the region centromeric to NF2 that contains the MNI gene.

Chromosome 1

Cytogenetic studies had indicated that next to loss of chromosome 22, deletions of chromosome 1p are common in meningiomas. Bello et al. (1994) studied 50 meningiomas and identified 13 meningiomas with loss of chromosome 1 alleles of which 12 had also lost alleles on chromosome 22. Most of these tumors showed aggressive growth. Analysis of 16 anaplastic meningiomas detected loss of chromosome 1p alleles at almost the same frequency as chromosome 22

loss (Lindblom et al., 1994) confirming a role of genes in 1p in the progression of meningiomas. Comparative genomic hybridization has shown that a meningioma locus maps to a distal chromosome 1p region (Maruno et al., 1998). Analysis of 157 blood/tumor pairs showed LOH for 1p in 34% of cases, and high-resolution deletion mapping defined a 1.5 cM region within 1p32 as a candidate meningioma locus (Sulman et al., 1998). More recently, loss of expression of the alkaline phosphatase ALPL which maps to 1p36.1-p34 was shown to be involved in meningioma progression (Muller et al., 1999).

Chromosome 14

There is considerable evidence supporting the existence of a meningioma locus on chromosome 14q. Aberrations including LOH on 14q are common in low- and high-grade meningiomas (Menon et al., 1997; Tse et al., 1997; Leone et al., 1999). As for changes in chromosome 1p alleles, alterations of the chromosome 14q locus may not be causative, but rather may be related to in tumor progression, because many tumors also displayed LOH of the NF2 locus (Menon et al., 1997; Leone et al., 1999).

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Fig. 131-1. Simplified schematic representation of glioma pathogenesis and progression. **(A)** Fibrillary astrocytoma with low cellularity and microcyst formation; **(B)** anaplastic astrocytoma with nuclear atypia, and frequent mitoses; **(C)** glioblastoma with small, anaplastic tumor cells, vascular proliferation, and necrotic areas with pseudopalisading of tumor cells. Mut.: mutation, amplif.: amplification. Parentheses indicate a minor or less well established role of a particular genetic change in the pathogenesis of gliomas. (From Kleihuis et al., 1993, with permission).

Fig. 131-2. Detection of schwannomin in normal human vestibular nerve and ependymomas. **(A)** Staining of a paraffinized section of normal human vestibular nerve with an antibody raised against schwannomin (Huynh et al., 1997). White and black arrows indicate cytoplasm of a vestibular neuron (N) and a satellite cell (Sa), respectively. Schwannomin is present in the cytoplasm of both vestibular neurons and satellite cells. **(B)** Staining of the adjacent section with the same antibody after pre-absorption. **(C)** Detection of schwannomin in an ependymoma. In this ependymoma, endothelial cells (**E**, at arrow) and tumor ependymal cells were stained. **(D)** Absence of schwannomin in another ependymoma as indicated by negative antibody staining in tumor cell cytoplasm (note nuclear counterstain). Cell nuclei in all sections were counterstained with aqueous hematoxylin.

Table 1. Inherited Cancer Syndromes and Tumors of the Nervous System

Syndrome	Gene	Location	Predominant Tumor Type
Neurofibromatosis 1 peripheral	NF1	17q11.2	neurofibroma, malignant Nerve sheath tumor, optic glioma
Neurofibromatosis 2 ependymoma	NF2	22q12	schwannoma, meningioma,
von-Hippel-Lindau disease	VHL	3p25	capillary hemangioblastoma, renal cell carcinoma, pheochromocytoma
Tuberous sclerosis astrocytoma	TSC1	9q34	subependymal giant cell
	TSC2	16p13.3	
Li-Fraumeni syndrome	p53	17p13.1	soft tissue and bone sarcomas, Breast carcinoma, glioma, Leukemia, PNET
Gorlin syndrome	PTCH	9q22	basal cell carcinoma, PNET, meningioma
Ataxia-telangiectasia	ATM	11q22-23	lymphoid tumors
Cowden syndrome	PTEN	10q23	dysplastic gangliocytoma of the cerebellum, meningioma
Werner syndrome	WRN	8p12	meningioma, astrocytoma
Turcot syndrome	APC	5q21	colon carcinoma, glioblastoma,
	hPMS2	7p22	PNET
	hMLH1	3p21.3-p23	