Brain Tumors, Genetics

PRIMARY BENIGN and malignant brain tumors are common and occur with an incidence of 12.8 cases per 100,000 according to the Central Brain Tumor Registry of the United States. The relative incidence of brain tumors is age dependent. Intracranial neoplasms, or new tissue growths, represent the most common solid tumors in children younger than age 15. In this age group, primary tumors of the nervous system comprise approximately 20% of all cancers, making them the second most common form of childhood cancer after leukemias.

SPORADIC BRAIN TUMORS

The initiation and progression of brain tumors is associated with a variety of molecular genetic alterations. Most brain tumors result from sporadic genetic alteration. The most common of these include glial tumors, primitive neuroectodermal tumors (PNETs), meningiomas, and schwannomas.

Glial Tumors

Gliomas are a heterogeneous group of mostly sporadic neoplasms derived from glial cells. They account for approximately 40–45% of all intracranial tumors and thus are the most common tumors among the primary central nervous system (CNS) neoplasms. Depending on morphology and histology, gliomas are classified into several subgroups, the most important being astrocytic tumors (including the glioblastoma), oligodendroglial tumors, mixed gliomas (oligoastrocytomas), and ependymal tumors.

Astrocytomas, or astrocytic gliomas, may be subdivided into two major groups: the more common group of diffusely infiltrating tumors, comprising astrocytoma, anaplastic astrocytoma, and glioblastoma, and the less common group of tumors with more circumscribed growth, consisting of pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma of tuberous sclerosis. Astrocytomas are slow-growing tumors that tend to infiltrate surrounding brain. Genetic alterations causing astrocytomas have been mapped to chromosomes 9p, 10, 11p, 17p, 19, and 22 in addition to mutations in the *TP53* gene, and amplification of protooncogenes such as EGFR. Pilocytic astrocytomas constitute a separate clinical and histopathological 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.

Oligodendrogliomas are tumors composed predominantly of neoplastic oligodendrocytes. 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 do astrocytomas.

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 occasionally occur in patients with neurofibromatosis 2 (NF-2). Loss of chromosome 6p is common in the pediatric ependymoma, in addition to 17p and 22q abnormalities.

Primitive Neuroectodermal Tumors

PNETs are 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. Molecular abnormalities on chromosome 9, 11, and 17 have been linked to the development of PNETs. Medulloblastomas represent a subcategory of PNETs. Common genetic abnormalities in medulloblastomas are gains of portions of chromosome 1 and deletion of 1q, 6q, 11p, and 16q. Mutations in the genes encoding Wnt signaling pathway proteins APC and β-catenin occur rarely in sporadic medulloblastomas. Familial medulloblastoma is very rare.

Meningiomas

The meningioma is a tumor composed of neoplastic meningothelial (arachnoid) cells. Several histological variants are recognized, such as meningothelial, fibrous (fibroblastic), transitional, and psammomatous meningioma. Meningiomas are the most common benign brain tumors and account for approximately 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, such as within the ventricular space. Meningiomas frequently occur in patients with NF-2 and less frequently in those with Werner's and Gorlin's syndrome. Genetic linkage studies provide further evidence for the existence of a meningioma locus on chromosome 22 centromeric to the NF-2 gene.

Schwannomas

Schwannomas are encapsulated and sometimes cystic tumors composed of spindle-shaped neoplastic Schwann cells. Schwannomas account for 8% of intracranial tumors and 29% of intraspinal tumors. Vestibular schwannomas are also referred to as acoustic schwannomas or neuromas and commonly occur as single tumors on the vestibular branch of the eighth cranial nerve. Schwannomas are caused by mutation in the NF-2 gene. Schwannomatosis describes a condition of multiple schwannomas and represents a unique class of NF that may or may not involve NF-2 gene mutations.

BRAIN TUMORS AND INHERITED TUMOR SYNDROMES

Brain tumors may occur as part of known inherited cancer syndromes. The most common inherited cancer syndromes are described here.

Neurofibromatosis 1 (NF-1) is a common autosomal dominant disease affecting approximately 1 in 3500 individuals. The NF-1 gene is located on the long arm of chromosome 17 and was identified in 1990. The NF-1 protein neurofibromin is large and functions as a Ras GTPase-activating protein. Neurofibromin action as a tumor suppressor is through its stimulation of GTP hydrolysis on normal but not oncogenic Ras and regulation of the Ras–MAP kinase signaling pathway. Patients with NF-1 typically develop multiple neurofibromas of the peripheral nervous system. Most neurofibromas are benign. Patients with NF-1 may also develop gliomas. 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 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 they rarely occur in the cerebellum or spinal cord. Reports of meningiomas in NF-1 most likely represent the chance association of a common brain tumor with a common genetic disease.

Neurofibromatosis 2 (NF-2) is less common than NF-1 and affects approximately 1 in 40,000 individuals. NF-2 is inherited as an autosomal dominant trait and caused by germline mutation of the NF-2 gene. The NF-2 gene is located at chromosome 22q12 and was identified in 1993. NF-2 patients are characterized by bilateral vestibular schwannomas, a hallmark feature of the disease. Commonly, NF-2 patients have other cranial and spinal schwannomas and meningiomas. Gliomas are also found in patients with NF-2, most commonly in the spinal cord. Approximately 80% of gliomas in NF-2 patients are intramedullary spinal or cauda equina tumors, and the vast majority of these are ependymomas.

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. Hemangioblastomas are found in the majority of VHL patients and are frequently a cause of death. The majority of hemangioblastomas in VHL disease occur in the cerebellum, followed by locations in spinal cord and brainstem. Approximately one-half of the tumors are asymptomatic. Capillary hemangioblastomas tend to manifest in younger VHL patients than do sporadic capillary hemangioblastomas and are more often multifocal.

Tuberous sclerosis (TS) is the second most frequent hereditary tumor syndrome of the nervous system after NF-1. Two different genes have been linked to onset of TS: TSC1 located at chromosome 9q34 and TSC2 located at 16p13.2. Neuroimaging studies show CNS lesions in the majority of patients with TS, including hamartomas such as cortical tubers and subependymal nodules. 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.

The Li–Fraumeni syndrome is a rare dominantly inherited syndrome associated with germline mutations in the TP53 gene. 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. In addition to patients with the Li–Fraumeni syndrome, TP53 germline mutations have occasionally been identified

in patients with nonfamilial malignancies with early onset or multifocality. First-degree relatives of these patients are also at an increased risk of gliomas.

Gorlin's 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 and palmar and plantar pits, odontogenic keratocysts, and skeletal anomalies. Childhood medulloblastoma, meningioma, craniopharyngioma, and neurofibroma have been described in patients with Gorlin's syndrome. This syndrome has been linked to mutations in the tumor-suppressor gene *PTCH*, which is the human ortholog of *Drosophila patched*. Somatic mutations in *PTCH* have been detected in sporadic basal cell carcinomas, PNETs, medulloblastomas, and certain types of sporadic tumors.

Ataxia telangiectasia is a recessive trait mapped to the ATM gene on chromosome 11q. Lymphoid malignancies are frequently seen in patients with ataxia telangiectasia. Although solid tumors occur, primary CNS tumors are infrequent.

Cowden's 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 the dysplastic gangliocytoma of the cerebellum. Additional associated CNS lesions include megaencephaly and gray matter heterotopias. Occasional cases of meningiomas in patients with Cowden's disease have also been documented. 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. Germline mutations in the *PTEN* tumor-suppressor gene at 10q23 have been linked to Cowden's disease.

Werner's 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. In addition to premature aging, some individuals with Werner's syndrome develop tumors, including CNS tumors such as meningiomas and, less frequently, astrocytomas.

Turcot's syndrome describes a rare heterogeneous disorder characterized by the association of colonic polyposis and malignant primary neuroepithelial tumors of the CNS. Colonic polyposis in patients with Turcot's syndrome appears to be the result of mutations in genes encoding Wnt signaling pathway proteins (APC and *β*-catenin). Turcot's syndrome has also been linked to mutations in the mismatch repair genes h*PMS2* and h*MLH1*.

KNUDSON'S TWO-HIT MODEL AND LOSS OF HETEROZYGOSITY

Inherited cancer syndromes are often characterized by loss of two alleles at a disease-causing locus. This is known as the Knudson two-hit model of tumorigenesis and is most commonly observed in syndromes caused by loss of function of a recessive tumor-suppressor gene. When observed, the patient is heterozygous at the disease-causing locus, possessing one normal and one mutated allele. Sporadic loss of the normal allele at that locus leaves only the mutated recessive allele. When sporadic deletion or chromosomal rearrangement cause the second "hit," the resulting tumor is said to have undergone loss of heterozygosity.

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See also–Brain Tumors, Biology; Brain Tumors, Clinical Manifestations and Treatment; Childhood Brain Tumors; Genetic Testing, Molecular; Glial Tumors; Meningiomas; Migraine, Genetics of; Nerve Sheath Tumors; Neurogenetics, Overview; Tuberous Sclerosis Complex (TSC); Von Hippel-Lindau Disease

Further Reading

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Brancher Deficiency
see Glycogen Storage Diseases