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Syndromes Predisposing to Pediatric Central Nervous System Tumors: Lessons Learned and New Promises

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Abstract Central nervous system (CNS) neoplasms are a leading cause of morbidity and mortality among children with cancer. In contrast to adults, a genetic basis for brain tumors is relatively common in children. A child harboring a germline mutation in a cancer-related gene will be predisposed to develop CNS tumors. These cancer predisposition syndromes are rare but pose overwhelming clinical and psychosocial challenges to families and the treating team. Recent significant advances in our understanding of the biological processes that govern these genetic conditions combined with international efforts to define and treat clinical aspects of these tumors are transforming the lives of these individuals. In this article, we summarize recent progress made for each of the major CNS tumor syndromes. We discuss the biological and clinical relevance of such advances, and suggest a comprehensive approach to a child affected by a predisposition to brain tumors.

Keywords Brain tumor · Cancer predisposition · Child · Central nervous system tumors

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Introduction

Cancer is a rare event in children. Nevertheless, it is still the leading cause of non-accidental mortality beyond the neonatal period. Brain tumors are the most common solid tumors of childhood and are a leading cause of morbidity and mortality in this age group. The causes of most brain neoplasms are not known. However, in contrast to adult brain tumors that are thought to result generally from continuous external insults and multistep tumorigenesis, the etiology of childhood brain tumors is more commonly associated with specific genetic alterations. Germline mutations in specific cancer-related genes are triggering events in up to 50% of certain brain cancers [1, 2•]. Over the last decade, significant advances in our understanding of some genetic predisposition syndromes associated with childhood central nervous system (CNS) tumors have enabled us to better diagnose, develop surveillance protocols, and even design novel therapies for these children. In this article, we focus on syndromes for which such advances have significant implications for the management of these individuals, their families, and the general pediatric population.

Clinically, these cancer syndromes can be divided into two specific subgroups: 1) multisystem syndromes in which cancer is one of other manifestations - the diagnosis is typically made based on the nonmalignant phenotype; and 2) pure cancer predisposition syndromes in which multiple

cancer types can develop at different times throughout the individual's life.

CNS Cancer-Associated Multisystem Syndromes

In these syndromes, the diagnosis is frequently made prior to the development of cancer. Therefore, it is important to be familiar with surveillance protocols available for early detection and management of cancers.

Neurofibromatosis-1

Neurofibromatosis-1 (NF-1) is a common autosomal-dominant disorder with prominent nervous system features, affecting 1 in 2500 to 3000 individuals [3]. Affected individuals develop a combination of dermatologic, skeletal, ophthalmic, and neurologic findings at typical ages of onset, and are diagnosed based on established clinical criteria (Table 1) [4]. Patients with NF-1 harbor germline mutations in the *NF1* gene encoding neurofibromin, located on chromosome 17q11.2 [5]. Importantly, approximately 50% of patients harbor de novo mutations [3] indicating that NF-1 should be suspected even in the absence of a family history. Neurofibromin is a tumor suppressor protein that inhibits Ras and limits cell growth. Recently, two important biological observations expanded our understanding of NF-1 tumorigenesis. First, mutated neurofibromin-induced Ras activation affects downstream signaling of the Akt/mammalian target of rapamycin (mTOR) pathway [6–8]. Furthermore, neurofibromin positively regulates cyclic adenosine monophosphate, which contributes to a reduction in cell growth [9, 10]. These pathways are highly targetable for cancer therapy.

Neoplastic manifestations of NF-1 include optic pathway gliomas (OPGs; typically, World Health Organization grade 1 pilocytic astrocytomas), cutaneous and plexiform neurofibromas (benign peripheral nerve sheath tumors arising from Schwann cells), malignant peripheral nerve sheath tumors, and juvenile myelomonocytic leukemia.

OPGs are by far the most common tumor and manifest in approximately 15% of patients with NF-1, usually before the age of 7 years. Most NF-1–associated OPGs demonstrate slow growth with little, if any, radiologic progression; however, a minority will exhibit rapid progression. Over the last decade, several large clinical trials revealed that NF-1–related OPGs respond better to chemotherapy [11–13] and have a more benign course than sporadic OPGs. Furthermore, surveillance neuroimaging in asymptomatic children has not been shown to reduce the incidence of visual loss in this population [14, 15] and frequent neuro-ophthalmologic examination remains the standard of care [16].

Although rare in this population, high-grade gliomas have been reported and should be considered in patients whose tumors arise in an uncharacteristic location or demonstrate particularly aggressive behavior, and may be an indication for biopsy [17, 18].

Based on elucidation of the molecular pathogenesis of NF-1, current phase 2 trials are evaluating the efficacy of tipifarnib, a farnesyltransferase inhibitor, which prevents post-translational isoprenylation of Ras, a requirement for its translocation and subsequent activation [19]. The use of mTOR inhibitors is also being considered for the treatment of NF-1–related tumors; phase 2 trials conducted by the Neurofibromatosis Consortium are underway evaluating mTOR inhibitors for chemotherapy-refractory progressive gliomas and plexiform neurofibromas. Surgical intervention has a role in relieving hydrocephalus and tumor debulking, whereas radiotherapy should be discouraged because of the incidence of secondary malignancies, in addition to vasculopathy and further neurocognitive morbidities [16].

In summary, data gathered in the last decade stress the need for conservative management in NF-1–related OPG and the potential of biological-based targeted therapies. Nevertheless, most NF-1 patients with progressive OPG will still have significant visual loss and other morbidities, highlighting the need for new tools to predict outcome and intervene accordingly.

Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome)

Nevoid basal cell carcinoma syndrome (NBCCS) is a multisystem, autosomal-dominant condition that affects approximately 1 in 57,000 individuals [20]. NBCCS is caused by a germline mutation in the homologue of the *Drosophila melanogaster* Patched gene, *PTCH*, a tumor suppressor gene located at 9q22.3 [21]. *PTCH* mutations are found in 85% of patients fulfilling clinical diagnostic criteria. *PTCH* encodes a transmembrane receptor for sonic hedgehog (SHH). SHH binding relieves inhibition by PTCH on the smoothened (SMOH) transmembrane receptor, which then transmits downstream signals via a number of proteins, including GLI, ultimately leading to activation of genes involved in embryonic development and differentiation of many tissues, including the brain [22]. Further knowledge of the pathway enabled discovery of other genes, such as *SUFU*, associated with germline predisposition to medulloblastoma [23].

NBCCS is characterized by multiple developmental anomalies and early-onset neoplasms. Diagnostic criteria include the presence of bifid or fused ribs, jaw cysts, palmar/plantar pits, and congenital facial abnormalities (Table 1) [24]. Multiple basal cell carcinomas are distinctive, in addition to ovarian fibromas and a number of CNS tumors; namely, medulloblastoma, meningioma, and infrequently glial neoplasms [25]. Medulloblastoma has been described in 1% to 5% of individuals with NBCCS [20].

Table 1 Summary of clinical signs and cancers in syndromes with predisposition to pediatric CNS tumors

Syndrome	Mutation	Clinical manifestations	Associated brain tumors	Other tumors	Suggested references
Neurofibromatosis-1	Gene: *NF1* Chromosome: 17q11.2 Protein: neurofibromin	*CNS*: neurocognitive defects (developmental delay, learning deficits, language deficits, fine and gross motor coordination deficits), ADHD, neurofibromatous (symmetrical sensory) neuropathy, idiopathic precocious puberty, macrocephaly *Dermatologic*: café-au-lait macules, axillary and inguinal freckling *Musculoskeletal*: sphenoid dysplasia, pseudoarthroses, scoliosis, kyphosis, dural ectasia *Ophthalmologic*: melanocytic iris hamartomas (Lisch nodules) *Other*: vasculopathy (stenoses, aneurysms, AV malformations), hypertension, congenital heart disease; constitutional short stature	Optic pathway glioma (juvenile pilocytic astrocytoma) Infrequently: high-grade glioma	Cutaneous and plexiform neurofibromas, malignant peripheral nerve sheath tumors, JMML, pheochromocytoma, neuroblastoma	[3, 4]
Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	Gene: *PTCH* Chromosome: 9q22.3	*Characteristic facies*: frontoparietal bossing, hypertelorism, macrocephaly, cleft lip/palate *Dermatologic/musculoskeletal*: keratocyst of jaw, palmar/plantar pits, bifid/fused/splayed ribs, pectus deformity, vertebral anomalies, bridging of sella turcica, calcification of falx cerebri, bone lucencies *Ophthalmologic*: congenital cataract, microphthalmia, coloboma	Medulloblastoma, meningioma Infrequently: astrocytoma, craniopharyngioma, oligodendroglioma	Basal cell carcinoma, ovarian fibroma	[25]
Tuberous sclerosis complex	Gene: *TSC1* Chromosome: 9q34 Protein: hamartin *or* Gene: *TSC2* Chromosome:16p13 Protein: tuberin	*CNS*: subependymal nodules, cortical tubers, infantile spasms, cognitive delay, autism spectrum disorders *Mucocutaneous*: facial angiofibromas, hypomelanotic macules, periungual fibroma, shagreen patch, confetti skin lesion, dental pits, gingival fibroma, hamartomatous rectal polyps	Subependymal giant-cell astrocytoma, cortical tubers	Renal angiomyolipoma, renal cell carcinoma, cardiac rhabdomyoma	[35, 38]

Table 1 (continued)

Syndrome	Mutation	Clinical manifestations	Associated brain tumors	Other tumors	Suggested references
		Other: bone cysts, renal cysts, retinal achromic patch, pulmonary lymphangiomyomatosis			
Fanconi anemia	Gene: *FANCD1/BRCA2, FANC-N,* or *PALB2*	*Congenital anomalies*: short stature, microcephaly, café-au-lait macules/abnormal pigmentation, thumb/radial anomalies, structural renal anomalies *Hematologic*: Bone marrow failure	Medulloblastoma PNET	Leukemias, Wilms tumor, breast cancer, squamous cell carcinoma in older patients	[44–46]
Brain tumor-polyposis syndrome-1	Gene: *MLH1, MSH2, MSH6, PMS2*	*Dermatologic*: irregular café-au-lait macules. May present as NF-1.	Glioblastoma Other: astrocytoma, medulloblastoma, supratentorial PNET	Hematologic (lymphomas and leukemias; particularly T-cell), early-onset colorectal adenoma and carcinoma	[55, 56•]
Brain tumor-polyposis syndrome-2	Gene: *APC* Chromosome: 5q21	Retinal pigment hypertrophy, dental anomalies, osteosclerotic jaw lesions	Medulloblastoma Astrocytoma Ependymoma Pinealoblastoma	Colorectal and gastric polyposis and carcinoma, hepatoblastoma, aggressive fibromatosis	[63, 67]
Neurofibromatosis-2	Gene: *NF2* Chromosome: 22q12 Protein: merlin	*Dermatologic*: café-au-lait macules (uncommon) *Ophthalmologic*: posterior subcapsular cataract, retinal hamartoma	Vestibular schwannoma Meningioma (intracranial/spinal) Ependymoma (intracranial/spinal) Infrequently: astrocytoma, neurofibroma	Neurofibromas	[69, 72, 74]
Li-Fraumeni syndrome	Gene: *TP53* Chromosome: 17p13.1	None	Gliomas: mostly malignant Choroid plexus carcinoma Medulloblastoma	Multiple early-onset tumors: sarcomas, breast cancer, adrenocortical carcinoma, leukemia	[48, 50, 53•]
Rhabdoid tumor predisposition syndrome	Gene: *hSNF5/INI1* Chromosome: 22q11	None	Atypical teratoid/rhabdoid tumors	Renal and extrarenal rhabdoid tumors, schwannomas? other sarcomas?	[2•, 79]
Other syndromes:					
Von Hippel-Lindau disease	Gene: *VHL* Chromosome: 3p25	*CNS*: hearing loss/tinnitus, cerebrovascular disease	Hemangioblastoma (intracranial/spinal)	Renal cell carcinoma, pheochromocytoma, pancreatic	[87, 88]

Table 1 (continued)

Syndrome	Mutation	Clinical manifestations	Associated brain tumors	Other tumors	Suggested references
		Ophthalmologic: retinal angioma *Other*: liver and renal cysts, pancreatic cysts	Endolymphatic sac tumors	cysts, neuroendocrine tumors, reproductive cystadenomas	
Cowden syndrome (multiple hamartoma syndrome)	Gene: *PTEN* Chromosome: 10q23	*Mucocutaneous*: Oral mucosal papillomatosis, palmar/plantar keratosis, acral keratosis	Cerebellar dysplastic gangliolioma Infrequent: meningioma	Hamartomas of CNS, eyes, gastrointestinal tract, genitourinary tract and bones, breast cancer, endometrial cancer, epithelial thyroid cancer	[89–91]
Rubinstein-Taybi syndrome	Gene: *CREBBP* Chromosome: 16p13.3 Protein: CREB-binding protein	*Characteristic facies*: highly arched eyebrows, downslanting palpebral fissures, beaked nose, highly arched palate *Other*: developmental delay, microcephaly, broad thumbs/halluces, congenital heart defect	Medulloblastoma and other PNET	Neuroblastoma, leukemia, rhabdomyosarcoma, and osteosarcoma	[92]
Ataxia telangiectasia	Gene: *ATM* Chromosome: 11q22.3	*CNS*: cerebellar ataxia, choreoathetosis±dystonia *Dermatologic:* oculocutaneous telangiectasia *Other*: immunodeficiency	Medulloblastoma	Lymphoproliferative: most commonly T-cell leukemia and lymphoma	[93–95]

ADHD attention deficit hyperactivity disorder; *AV* atrioventricular; *CNS* central nervous system; *JMML* juvenile myelomonocytic leukemia; *PNET* primitive neuroectodermal tumor

The mean age of onset is 2 years, distinguishing it from sporadic medulloblastoma, which usually presents around 6 years of age [20]. Another notable feature is the preponderance of the desmoplastic subtype. All described NBCCS patients with medulloblastoma have desmoplastic pathology [26]. Importantly, medulloblastoma is commonly the first malignant manifestation of NBCCS, and some authors suggest that the presence of desmoplastic medulloblastoma in a child younger than 2 years of age should be considered a major criterion for the diagnosis of NBCCS [26].

Traditionally, management of NBCCS-associated medulloblastoma has been identical to that of sporadic forms, and a more favorable outcome in patients with NBCCS has been reported [26, 27]. However, the use of radiation in this population is associated with an unacceptable rate of numerous invasive basal cell carcinomas in the radiation field. Moreover, there have been a number of reports describing the development of other CNS tumors in the radiation field, including meningioma and anaplastic astrocytoma [26, 28]. The striking favorable outcome of desmoplastic medulloblastomas in young children who were not irradiated [29] highlights the need for judicious use of postoperative radiotherapy in this population [28].

Inhibitors of SHH, including cyclopamine derivatives, have been investigated as potential therapies for medulloblastoma in experimental models [30]. Treatment with the SHH pathway antagonists (GDC-0449 and LDE225) are already in clinical trials for medulloblastoma [31] and have also shown encouraging although not sustained results in relapsed cases [32]. NBCCS patients may benefit in the future from targeted therapies and from avoiding radiation therapy. Moreover, since up to 35% of medulloblastomas have constitutively activated SHH [33], NBCCS demonstrates how knowledge of genetic predisposition syndromes can help develop rational novel therapies for sporadic forms of the disease.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal-dominant disorder caused by mutations in the *TSC1* or *TSC2* tumor suppressor genes. TSC affects 1 in 6000 individuals [34]. Diagnosis is established by satisfying defined major and minor clinical criteria, whereas genetic testing is corroborative [35]. Furthermore, 15% to 20% of patients meeting clinical diagnostic criteria will have no identifiable mutation, and 65% to 85% of cases represent new mutations [36, 37].

TSC1 and *TSC2* gene products form a heterodimer that inactivates the mTOR signaling cascade via inhibition of Rheb (Ras homologue expressed in brain). The mTOR pathway has a central role in the control of cell growth and cancer development via ribosome biosynthesis in response to growth factors and nutrients.

Clinical manifestations of TSC include characteristic dermatologic manifestations such as facial angiofibromas and hypopigmented macules, renal angiomyolipomas, cardiac rhabdomyomas and CNS lesions including subependymal nodules, cortical tubers, and subependymal giant-cell astrocytomas (SEGAs), each of which manifest at distinct developmental periods (Table 1). Other neurologic features include epilepsy—particularly infantile spasms, cognitive delay, and autism spectrum disorders [38].

The story of treatment of SEGA is fascinating and worth elaboration. SEGAs are low-grade, benign tumors, which present in approximately 5% to 15% of patients with TSC [39]. SEGAs typically arise in the foramen of Monro projecting into the ventricle and remain asymptomatic until either acute or chronic obstructive hydrocephalus develops. They tend to exhibit slow progressive growth, but can rarely display more aggressive features including parenchymal invasion. Surgical resection has traditionally been considered standard therapy for SEGAs, as gross total resection is curative; however, residual lesions frequently regrow and procedures may present significant morbidity risks depending on tumor size and location. A pilot study revealed that the mTOR inhibitor sirolimus resulted in tumor regression in all patients [40]. Larger studies using everolimus confirmed these observations and demonstrated a dramatic reduction in the need for surgery in the management of these patients [40, 41••]. Strikingly, mTOR inhibition also results in improvement of seizure frequency, skin lesions, and angiomyolipomas, in addition to other life-threatening manifestations of TSC [42••, 43]. Therefore, TSC is an enlightening example of how understanding the molecular pathway of a cancer predisposition syndrome can change its course and manifestations.

Fanconi Anemia

Fanconi anemia (FA) is a rare autosomal-recessive disorder of defective DNA repair, with characteristically variable clinical expression, including various congenital malformations, bone marrow failure, and leukemias (Table 1). In addition, a variety of solid tumors have long been recognized to develop with increasing frequency.

The FA complementary group of proteins play a central role in DNA damage repair and homologous recombination [44]. These proteins are involved in recognition, processing, and repair of DNA alterations. Interestingly, several members of the downstream FA genes were recently reported to be associated with pediatric tumors presenting at a young age. These include *FANCD1* (or *BRCA2*), *FANC-N*, and the FANCD1 binding protein, *PALB2* [45–47]. The tumors include leukemias, Wilms tumor, and brain tumors—primarily medulloblastoma. Identification of these patients is crucial because children with FA will have unacceptable and even

life-threatening side effects from ionizing radiation and chemotherapy. These children present with brain tumors as an initial manifestation in 25% of cases. Therefore, meticulous clinical examination looking for the specific dermal, skeletal, and other abnormalities is warranted, especially in cases of consanguinity. Because these observations are relatively recent, the full spectrum of brain tumors in these syndromes and the role of somatic FA mutations in medulloblastoma are still unknown.

Cancer Syndromes Without Other Clinical Manifestations

In these devastating cancer predisposition syndromes, there are usually no other phenotypic manifestations to guide clinicians. Consequently, careful documentation of a comprehensive family history of cancer and a high index of suspicion can facilitate a lifesaving diagnosis.

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a prototypic autosomal-dominant cancer predisposition syndrome characterized by the development of multiple early-onset tumors, including sarcomas, premenopausal breast cancer, adrenocortical carcinoma, leukemia, and brain tumors [48].

LFS affects 1 in 5000 to 10,000 individuals and is caused by constitutional mutations of the *TP53* tumor suppressor gene [49]. *TP53* is located at chromosome 17p13.1. It is referred to as the "guardian of the genome" and is one of the major proteins that control genome integrity in the context of DNA damage, hypoxia, and other stressors. *TP53* activation results in cell cycle arrest, senescence, and apoptosis. Somatic inactivation of *TP53* is a key event in most cancers.

There are three types of brain tumors associated with LFS: high-grade gliomas, choroid plexus carcinoma (CPC), and medulloblastoma. Because the prevalence of LFS among patients with CPC is extremely high, it is currently considered an LFS-defining tumor and genetic counseling should be offered to all patients with the disease [50]. Furthermore, *TP53* alterations may be associated with worse survival in patients with CPC [1], medulloblastoma [51], and malignant gliomas [52]. Perhaps the most important advance in the management of LFS patients in the last decade was the establishment of a surveillance protocol and the potential for such a protocol to reduce mortality through early detection and therapeutic intervention [53•]. Most of the patients who benefitted from early detection in this study were children with malignant brain tumors. Finally, there is a growing volume of evidence to suggest an increased risk of second malignancies in the radiation field of patients with LFS. These observations imply that genetic counseling followed by an aggressive surveillance protocol may change our management and the need for toxic therapies for tumors, which may have a significant beneficial effect on survival and quality of life of individuals with LFS.

Turcot Syndrome

Since its original description in 1959 [54], Turcot syndrome has been reclassified into two distinct syndromes with specific molecular aberrations, each characterized by colorectal polyps/adenocarcinoma and malignant brain tumors [55].

Brain Tumor-Polyposis Syndrome-1

This autosomal-recessive cancer syndrome is caused by biallelic germline mutations in one of the mismatch repair (MMR) genes, and is usually found in consanguineous families. This is a unique syndrome because heterozygote carriers have a very different phenotype termed Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Lynch syndrome is inherited in an autosomal-dominant manner with primarily gastrointestinal malignancies. Brain tumor-polyposis syndrome-1 (BTPS-1) patients present with a very different spectrum of tumors than their parents and other family members. This extended spectrum of malignancies includes hematologic and malignant CNS cancers [56•].

MMR genes play essential roles in maintaining genome integrity by correcting errors that arise during DNA replication. Mismatch recognition is mediated by two heterodimers: MSH2 and MSH6 (MutSα) are involved in repairing base/base mismatches and single nucleotide misalignments, and MSH2 and MSH3 (MutSβ) are involved in recognizing larger insertion-deletion loops. These heterodimers interact with MutLα (composed of MLH1 and PMS2) and EXO1 to remove aberrant DNA [56•]. Accordingly, mutations in MMR genes lead to accumulation of somatic mutations in other genes including cancer-related ones.

Astrocytomas, primarily glioblastomas, are the most prevalent brain tumors in patients with biallelic MMR mutations, although medulloblastoma and supratentorial primitive neuroectodermal tumors have also been reported [56•]. Hematologic malignancies include acute lymphoblastic leukemia, particularly of T-cell lineage, and non-Hodgkin's lymphoma. Of note, patients with this syndrome have been reported to share phenotypic features of NF-1, in particular multiple café-au-lait spots, [57]. The *NF-1* gene has been shown to be a mutational target of MMR deficiency [58]. Early onset of colorectal cancers (mean age, 16 years), in addition to multiple (> 10) colorectal adenomas and small bowel adenocarcinoma are frequent in this population [59]. Individuals with this devastating syndrome rarely reach adulthood.

Screening for a germline mutation of the four MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) should be pursued in children and adolescents with hematologic, CNS, or Lynch-syndrome–associated neoplasms if they also have consanguineous parents, a history of Lynch syndrome on one side of the family, atypical café-au-lait spots, a second non-NF-1–associated malignancy, or a sibling with childhood cancer [56•]. Clinical surveillance guidelines are available for Lynch syndrome [60], and recently a protocol has been developed for patients with biallelic MMR mutations, in an effort to detect glial tumors and lymphomas at an early stage [61]. Targeted therapies are lacking for this complex syndrome; however, a recent case report describes the use of retinoic acid as effective "chemoprevention" in a patient with a constitutional homozygous mutation of *PMS2* [62]. This syndrome highlights the role of careful family history and index of suspicion because individuals with "atypical NF-1" and suggestive family history can benefit from early diagnosis and surveillance.

Brain Tumor-Polyposis Syndrome-2 (Familial Adenomatosis Polyposis Coli)

The second group of patients initially classified as having "Turcot syndrome" have since been found to have germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21, and manifest autosomal-dominant inheritance. In this population, the characteristics of colorectal adenoma are typical of familial adenomatosis polyposis coli (FAP); patients develop hundreds to thousands of colonic adenomas from early adolescence, with inevitable progression to colorectal carcinoma by an average of 40 years of age [63]. CNS tumors reported to be associated with FAP include medulloblastoma and rarely astrocytoma, ependymoma, and pinealoblastoma [64, 65].

APC encodes a tumor suppressor protein that acts as an antagonist of the Wnt/Wingless signaling pathway, which has important roles in promoting cell proliferation, and differentiation, in addition to apoptosis depending on the cellular context. With *APC* loss, Wnt signaling constitutively promotes cell survival and inhibits cell death [66].

Although the risk of medulloblastoma for individuals with germline *APC* mutations is 92 times that of the general population [65], it is still a rare event and does not necessitate routine surveillance. Targeted surveillance of patients with segment 2 mutations of the *APC* gene (which is associated with higher risk of medulloblastoma formation) may be a reasonable approach given their correlation with the medulloblastoma phenotype [67]. As with Gorlin syndrome, knowledge of this genetic aberration resulted in further understanding of medulloblastoma. The Wnt pathway is activated in 5% to 10% of tumors and reveals excellent survival in current protocols [68]. These biological observations may be beneficial for individuals with brain tumor-polyposis syndrome-2 (BTPS-2) because they may be treated with a less aggressive approach.

Neurofibromatosis-2

Neurofibromatosis-2 (NF-2) is an autosomal-dominant syndrome that occurs in 1 in 25,000 live births [69]. Although the hallmark of NF-2 is bilateral vestibular schwannomas, it is in fact a multiple neoplasia syndrome, resulting from a germline mutation in the *NF2* tumor suppressor gene on chromosome 22q12. The *NF2* gene encodes merlin [70], which is activated by phosphorylation and leads to downstream regulation of oncogenic pathways involved in promotion of cell growth and protein translation, mainly through the phosphatidylinositol-3 kinase and mitogen-activated protein kinase pathways. Furthermore, $NF2^{-/-}$ schwannomas were shown to be highly responsive to vascular endothelial growth factor (VEGF) inhibition in vitro and in vivo [71], suggesting attractive targets for clinical trials for NF-2 patients.

Apart from vestibular schwannomas, other nervous system tumors include intracranial and spinal meningiomas and ependymomas, schwannomas of other central and peripheral nerves, and rarely, astrocytomas and neurofibromas. Revised diagnostic criteria (the Baser criteria) have very recently been proposed with improved sensitivity and without compromise of specificity, lending particular utility to patients without bilateral acoustic schwannomas or a family history of NF-2 [72]. This represents significant progress in the management of NF-2 patients, since half of patients have de novo mutations of the *NF2* gene [73]. Earlier diagnosis in these groups can be accompanied by the institution of clinical surveillance and improved clinical care. Presymptomatic genetic testing is recommended at age 10 years to correspond with the onset of MRI surveillance, although earlier testing is offered based on the needs of individual families [74, 75].

Treatment of vestibular schwannomas traditionally includes surgical resection or radiation therapy; however, although both may achieve control of tumor growth, they are invariantly associated with hearing loss and facial nerve damage [74]. Clinical trials are ongoing to assess the efficacy of drugs targeting pathways associated with aberrant *NF2* gene expression, including a phase 2 trial of lapatinib, an inhibitor of epidermal growth factor (EGF). Erlotinib, another EGF inhibitor, was not shown to produce radiographic or audiologic responses in patients with progressive vestibular schwannoma, although it did contribute to prolonged stable disease in a subset of patients [76]. More encouraging results were recently reported using bevacizumab, an anti-VEGF monoclonal antibody. Volume of vestibular schwannoma tumor was reduced and associated with

improved hearing in some patients [77•, 78•]. Management of children with NF-2 and growing schwannomas is still very complex but prevention or delay of the devastating effects of tumor growth and surgical interventions could have a dramatic effect on the quality of life of these patients.

Rhabdoid Tumor Predisposition Syndrome

Rhabdoid tumor predisposition syndrome (RTPS) is a relatively "new" syndrome. Therefore, information regarding the exact prevalence and tumor types involved in this syndrome is still evolving. Historically, two apparently orphan tumors had been diagnosed in very young children. These tumors were renal and extrarenal rhabdoid tumors and atypical teratoid/rhabdoid tumors (ATRT) of the brain. Both tumors carried a dismal prognosis and were often confused with other malignant neoplasms. The observation of concomitant rhabdoid kidney tumors and ATRTs in the same individuals and cytogenetic molecular findings of loss of the long arm of chromosome 22 among these tumors led to the recognition of this "rhabdoid predisposition syndrome" [79].

The *SMARCB1* (previously denoted *INI1/hSNF5*) gene was cloned in 1998 [80] and is located on chromosome 22q11. Heterozygous germline loss-of-function mutations of the gene were first described in 1999 [79]. This facilitated the definition of ATRT and permitted assessment of the risk of germline mutations in individuals with ATRT. A recent publication analyzed matched tumor and blood samples and found germline mutations in 35% of cases [2•]. All patients with both CNS and extracranial tumors harbored a germline mutation. The exact function of *INI1* is still not completely understood. However, disruption of the gene is involved in defective spindle checkpoint and high rate of chromosomal instability. The recent observation that loss of *INI1* leads to activation of the *SHH* pathway is intriguing [81] because it may suggest a target for novel therapies.

Importantly, a high proportion of germ-cell mosaicism or de novo mutations was suggested based on negative germline testing among the vast majority of parent pairs. These findings highlight the necessity for genetic screening of patients with rhabdoid tumors, in addition to renal ultrasound for children with ATRT to provide genetic counseling and inform treatment decisions.

The management of sporadic ATRTs has presented significant challenges, with a median survival of only 6 to 11 months [82•]. However, recent studies, which identified this unique subpopulation and designed therapy accordingly, have demonstrated long-term survival in subsets of patients with the use of maximal resection followed by an aggressive multimodal approach including high-dose chemotherapy [82•, 83•, 84, 85]. As with other "new" syndromes, the recent observation of germline *INI1* mutations in familial schwannomatosis adds a new dimension to this story [86]. Because until recently, most patients with RTPS did not survive, the cancer spectrum and lifetime risk of other malignancies in carriers remains unknown. Taken together, RTPS represents an example of the evolving effect of cancer genetics on the field of pediatric oncology.

A Clinician's Approach to Children with Cancer Predisposition Syndromes

The three pillars of the clinical approach to childhood cancer predisposition include alertness and high index of suspicion, genetic counseling to establish a diagnosis, and long-term planning with consideration of different approaches to treat each tumor in the context of the specific genetic alteration. Because these pillars require different expertise, a multidisciplinary team approach is necessary. For a pediatrician attending to a child with a brain tumor, alertness could lead to the determination of which syndromes are to be considered in the context of the patient's specific tumor type (Table 1). Referral to genetic counseling is highly recommended. Additional tools to establish the diagnosis include comprehensive family history, and complete physical examination with assessments from other physicians, such as geneticists, dermatologists, ophthalmologists, and cardiologists. Physical examination of other family members may also be helpful. Finally, specific immunohistochemical and molecular analysis of the tumors can help direct which molecular tests should be undertaken. Timing of these steps may be crucial because treatment decisions may be required without delay. These issues highlight the indispensable role of the primary physician in advocating for and coordinating this complex process. Because these syndromes are rare, we would suggest contacting international experts for more intricate management issues. Perhaps the most important component of the management of such children is the understanding that these individuals, and in many cases other family members, will require continuous care, monitoring, social and psychological support even after the initial tumor is treated.

Conclusions

In this article we highlighted recent progress made in childhood cancer predisposition syndromes affecting the CNS. For a more comprehensive review of each specific syndrome and other syndromes not presented here we recommend reference to the papers noted in Table 1. As presented above, the evolution of novel technologies and clinical knowledge generated by cooperative studies are improving survival and transforming the lives of children and families

with cancer predisposition syndromes. We believe that astute clinical observation of individuals harboring germline mutations in cancer-related genes combined with our knowledge of somatic alterations in these genes will substantially benefit these families and the general population affected by these devastating tumors.

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