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Germline genetic landscape of pediatric central nervous system tumors

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Abstract

Central nervous system (CNS) tumors are the second most common type of cancer among children. Depending on histopathology, anatomic location, and genomic factors, specific subgroups of brain tumors have some of the highest cancer-related mortality rates or result in considerable lifelong morbidity. Pediatric CNS tumors often occur in patients with genetic predisposition, at times revealing underlying cancer predisposition syndromes. Advances in next-generation sequencing (NGS) have resulted in the identification of an increasing number of cancer predisposition genes. In this review, the literature on genetic predisposition to pediatric CNS tumors is evaluated with a discussion of potential future targets for NGS and clinical implications. Furthermore, we explore potential strategies for enhancing the understanding of genetic predisposition of pediatric CNS tumors, including evaluation of non-European populations, pan-genomic approaches, and large collaborative studies.

Keywords

genetics | pediatric brain tumor | predisposition | syndromes

Pediatric central nervous system (CNS) tumors are the second most common pediatric malignancy after leukemia and form a heterogeneous group of tumors (eg, medulloblastoma, astrocytoma, ependymoma, atypical teratoid/rhabdoid tumor [AT/RT]; Fig. 1).[1,2] Pediatric CNS tumors are responsible for the highest number of cancer-related deaths in children and are generally associated with poor survival and high morbidity due to their surgically challenging intracranial location.[2,3]

Although some advances have been made over the years in our understanding of pediatric CNS tumor etiology, the role of environmental causes is obscure and characterization of genetic predisposition is incomplete.[4] Indeed, beyond cranial radiation exposure and a limited number of highly penetrant cancer predisposition syndromes, virtually no additional factors have been robustly associated with risk of pediatric CNS tumor development.[4,5] Inter-ethnic differences in incidence of pediatric CNS tumors have previously been described,[6–8] including lower rates among black, Asian, and Hispanic children compared with white children,[6] which may have a genetic basis. Recent developments in next-generation sequencing (NGS) provide new opportunities for studying CNS tumor risk at the genomic level.[9,10] NGS approaches that identify causative gene variants may have potential translational relevance in prognostication and rational therapy design, in addition to determining risk assessment for genetic counseling. The aim of this review is to summarize the current state of knowledge regarding genetic predisposition to pediatric CNS tumors to highlight areas in greatest need for future investigation.

Germline Genetics in Pediatric CNS Tumors

Germline mutations will be discussed by histologic tumor type below. An overview of genes associated with predisposition

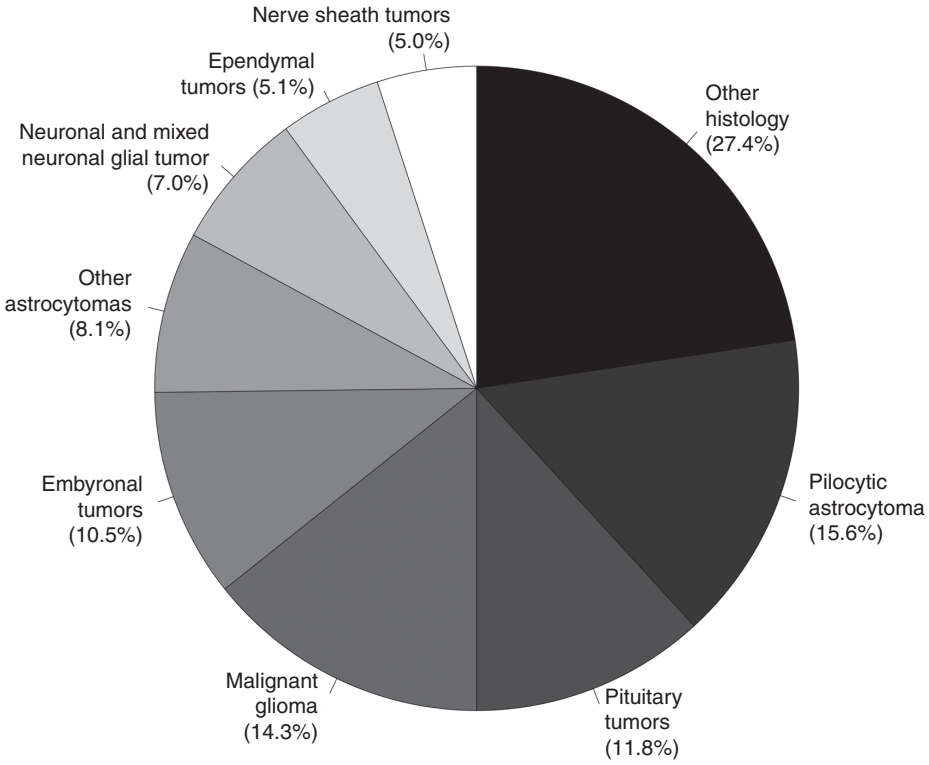

Fig. 1 Distribution of tumor histology for pediatric CNS tumors, adapted from the 2017 CBTRUS statistical report.[2] Relative distribution of pediatric CNS tumors by histology. Embryonal tumors are formed by medulloblastoma (63.6%), AT/RT (14.6%), ETMR (12.6%), and other embryonal tumors (8.9%). A license was obtained for reuse of this figure from Oxford University Press.

to a pediatric CNS tumor when altered in the germline, together with the associated syndrome, appears in Table 1. The prevalence of germline mutations by tumor histology is depicted in Fig. 2.

Embryonal Tumors

Medulloblastoma

Medulloblastoma is currently defined by 4 major subgroups: sonic hedgehog (SHH) activated (either tumor protein p53 [*TP53*] mutant or wildtype), wingless (WNT) activated, and the consensus Groups 3 and 4.[11]The subgroups were determined by a combination of age at diagnosis, patient sex, tumor factors, histology, immunophenotype, and associated molecular and cytogenetic alterations.[11,12] For example, SHH-activated pathway tumors are most common in adolescent males, WNT-activated tumors typically demonstrate catenin beta-1 (*CTNNB1*) mutations and monosomy 6, Group 3 or 4 tumors may demonstrate amplification of *MYC/MYCN* and a high frequency of isodicentric 17q chromosomes.[11,12]

Certain syndromes with characteristic germline mutations have been suggested to be risk factors for medulloblastoma and tend to associate with specific subgroups. In particular, Gorlin syndrome (also known as nevoid basal cell carcinoma syndrome) increases the risk of SHH-activated medulloblastoma, and mutations associated with familial adenomatous polyposis (FAP) increase the risk of WNT-activated medulloblastoma.[13–15]

Waszak et al recently compared the prevalence of putative causal germline mutations in their medulloblastoma cohort with data from the Exome Aggregation Consortium (ExAC).[13,16] They found that germline *suppressor of fused homolog (SUFU)*, Patched 1 (*PTCH1*), partner and localizer of BRCA2 (*PALB2*), breast cancer 2 (*BRCA2*), and *TP53* mutations were associated with increased risk of SHH-activated medulloblastoma, with *SUFU* mutations in particular conferring an extremely high risk of disease (relative risk > 1000).[13] Several other studies have identified mutations in the same genes among SHH-activated medulloblastoma patients.[13,17–22] In one recent large-scale sequencing study of pediatric cancers, among 42 SHH-activated medulloblastoma patients, 1 harbored a germline *SUFU* mutation, while another harbored a *PTCH1* mutation.[17] This suggests that germline *SUFU* and *PTCH1* mutations are responsible for only a small portion of SHH-activated medulloblastoma cases. Germline *TP53* mutations have been associated with chromothripsis (ie, chromosomal shattering and subsequent rearrangement), which is thought to result in SHH-activated *TP53*-mutant medulloblastoma.[23] Germline mutations in *PALB2*, which are associated with several adult cancers and Fanconi anemia, also contribute to the risk of SHH-activated medulloblastoma.[13,21,24]

Table 1 Summary table for pediatric CNS tumors and genes that may contribute to predisposition when mutated in the germline, listed together with their associated syndrome

Tumor Group	Tumor	Gene	Associated Syndrome	Pathway/Function
Embryonal tumors	Medulloblastoma	PTCH1[13]	Gorlin syndrome	Hedgehog (responsible for early development)
		SUFU[13]	Gorlin syndrome	Hedgehog (responsible for early development)
		GLI3[31]	Gorlin syndrome	WNT (responsible for early development)
		APC[13,14]	FAP	Tumor suppressor
		PALB2[13,21]	Fanconi anemia	Tumor suppressor
		NBN[35]	Nijmegen breakage syndrome	Damaged DNA-repair
		CREBBP[33]	Rubinstein–Taybi	Chromatin modifier
		TP53[23]	Li–Fraumeni	Tumor-suppressor gene
		NF2[17]	NF2	Tumor-suppressor gene
		SDHA[17]	NA	Tumor-suppressor gene
		VHL[17]	von Hippel–Lindau	Protein degradation
		BRCA2[17]	HBOC	Tumor-suppressor gene
	AT/RT	SMARCB1[17]	RTPS	Gene expression through SWI/SNF
		SMARCA4[44]	RTPS	Gene expression through SWI/SNF
	ETMR	TP53[47]	Li–Fraumeni	Tumor-suppressor gene
Low-grade gliomas	Pilocytic astrocytoma	NBN[51,52]	Nijmegen breakage syndrome	DNA-repair
		PTPN11[49]	Noonan syndrome	Ras-MAPK signaling
		BRCA2[17,53]	HBOC	Tumor-suppressor gene
		TSC2[17,53]	Tuberous sclerosis complex	Tumor-suppressor gene
	Optic glioma	NF1[54,57]	NF1	Ras-MAPK signaling
	Ependymoma	APC[64,65]	FAP	Tumor suppressor gene
		NF2[63]	NF2	Tumor-suppressor gene
		NF1[53]	NF1	Ras-MAPK signaling
		TP53[53]	Li–Fraumeni	Tumor-suppressor gene
	Subtype not specified	NF1[53]	NF1	Ras-MAPK signaling
		RUNX1[53]	Platelet disorder	Control of hematopoiesis
		PMS2[53]	cMMRD	MMR
High-grade gliomas	GBM	PMS2[67]	cMMRD, HNPCC	MMR
		MLH1[67]	cMMRD, HNPCC	MMR
		MSH2[67]	cMMRD, HNPCC	MMR
		MSH6[67]	cMMRD, HNPCC	MMR
		TP53[18,66]	Li–Fraumeni	Tumor-suppressor gene

Table 1 Continued

Tumor Group	Tumor	Gene	Associated Syndrome	Pathway/Function
	Subtype not specified	MUTYH[70]	MAP	DNA repair
		NBN[53]	Nijmegen breakage syndrome	DNA repair
		NF1[17]	NF1	Ras-MAPK signaling
		VHL[17]	von Hippel–Lindau	Protein degradation
		LZTR1[17]	Schwannomatosis	Unknown
		BRCA2[17]	HBOC	Tumor-suppressor gene
		TSC2[17]	Tuberous sclerosis type 2	Potentially involved in cell growth and size
		ATM[69]	NA	Development of CNS
Other CNS tumors	Dysplastic cerebellar gangliocytoma	PTEN[89]	Cowden syndrome	Tumor-suppressor gene
	Pineoblastoma	DICER1[86]	DICER1 syndrome	miRNA processing
		RB1[87]	NA	Tumor-suppressor gene
	Choroid plexus carcinoma	TP53[74]	LFS	Tumor-suppressor gene
	MPNST	NF1[84]	NF2	Ras-MAPK signaling
	Schwannoma	NF2[63]	NF2	Tumor-suppressor gene
	Meningioma	NF2[63]	NF2	Tumor-suppressor gene
		SMARCE1[71,72]	Coffin–Siris syndrome	Gene expression through SWI/SNF
	Retinoblastoma	RB1[77,79,80]	Retinoblastoma	Tumor-suppressor gene

Abbreviations: HBOC: hereditary breast and ovarian cancer syndrome, HNPCC: hereditary nonpolyposis colorectal cancer, MAP: MYH associated polyposis, MMR: mismatch-repair; MPNST: malignant peripheral nerve sheath tumor, NA: not available.
This table depicts pediatric CNS tumors and genes that may result in cancer predisposition when mutated in the germline. Syndromes and pathways associated with germline mutations in these genes are also described.

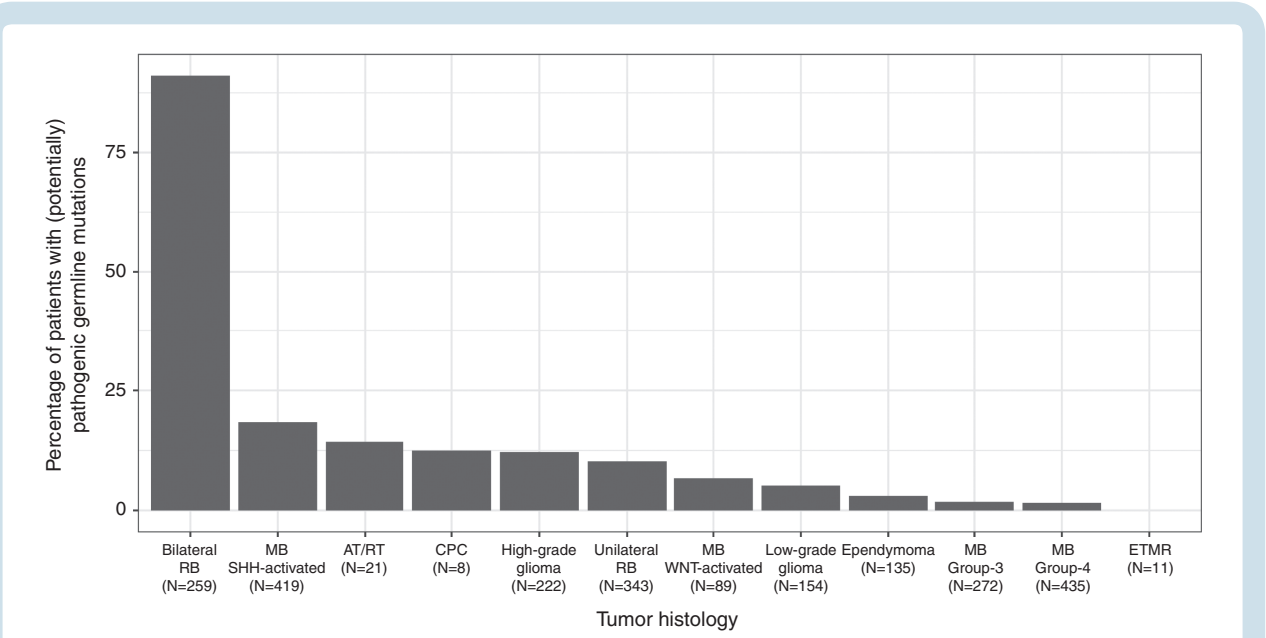

Fig. 2 Bar chart depicting the percentage of patients with putative pathogenic germline mutation by CNS tumor subtype. This bar chart depicts the fraction of cases affected by germline putative pathogenic mutations in cancer predisposition genes based on combining data from various studies.[13,17,53,77,78,121] MB: medulloblastoma; RB: retinoblastoma.

Loss-of-function germline mutations, including deletions, in *PTCH1* and *SUFU* cause Gorlin syndrome.[25–27] In family studies, germline *SUFU* mutations have also been associated with a 20-fold higher chance of developing medulloblastoma compared with patients with *PTCH1* mutations, as well as earlier presentation and worse outcomes.[26,28] However, limitations of these smaller studies with potential ascertainment bias due to recruitment of family members of probands are noted and warrant cautious interpretation.

Combined, germline alterations of *PTCH1* or *SUFU* are present in approximately 2% of medulloblastoma patients overall.[13,15] *PTCH1* and *SUFU* proteins are both vital components of the SHH signaling pathway,[29] which plays an important role in embryonic CNS development and the genesis of various malignancies.[30] In the absence of the SHH molecule, *PTCH1* inhibits Smoothened (*SMO*) and permits *SUFU* and *GLI* to form a complex that prevents *GLI* from activating the hedgehog target genes,[29] including *PTCH1, CCND2, JUP, PAX6, NKX2-2,* and *BMI1*, effectively creating a negative feedback loop.[30] Germline mutations in *GLI3*, a negative regulator in the SHH pathway, causes Greig syndrome, which may also co-occur with medulloblastoma.[31,32]

Waszak et al also found that germline adenomatous polyposis coli (*APC*) mutations, which cause FAP, were associated with a relative risk greater than 100 for developing WNT-activated medulloblastoma.[13] However, germline *APC* mutations were identified in only 1 out of 21 sporadic WNT-activated medulloblastoma patients, and not among other subtypes of medulloblastoma, in a recent NGS study,[17] suggesting that FAP does not underlie a large proportion of *overall* medulloblastoma diagnoses.[13] Another patient with WNT-activated medulloblastoma was found to have a mutation in *VHL*,[17] which causes another cancer predisposition syndrome known as von Hippel–Lindau disease.

Bourdeaut et al suggested that cAMP response element binding protein (*CREBBP*) germline mutations may predispose to Group 3 medulloblastoma based on a case report in a child with Rubinstein–Taybi syndrome.[33] Germline mutations in the chromatin modifying gene *CREBBP* cause Rubinstein–Taybi syndrome, which manifests in motor organ dysfunction, craniofacial dysmorphism, and psychomotor retardation in addition to increased cancer risk.[33,34] In another study, 1 patient out of 60 with Group 3 medulloblastoma carried a germline *BRCA2* mutation, but no potentially pathogenic *CREBBP* germline mutations were identified.[17] With regard to Group 4 medulloblastoma, among 107 patients, 3 germline mutations were identified in *SUFU,* 1 in neurofibromatosis (*NF*) type 2, and 1 in succinate dehydrogenase A (*SDHA*).[17] Heterozygous mutations in nibrin (*NBN*), a DNA repair gene that underlies Nijmegen breakage syndrome, have been identified in 7 out of 104 Group 3 and Group 4 medulloblastoma patients.[35] It is clear, therefore, that a diverse set of genes may underlie the germline risk for predisposition to the various subtypes of medulloblastoma.

Atypical Teratoid/Rhabdoid Tumor

The vast majority of AT/RTs arise as a result of homozygous inactivation of *SMARCB1*[36,37] or *SMARCA4*,[38] which are both members of the SWItch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex. The median age at diagnosis for patients with germline mutations in *SMARCB1* is 6 months compared with 1–2 years for

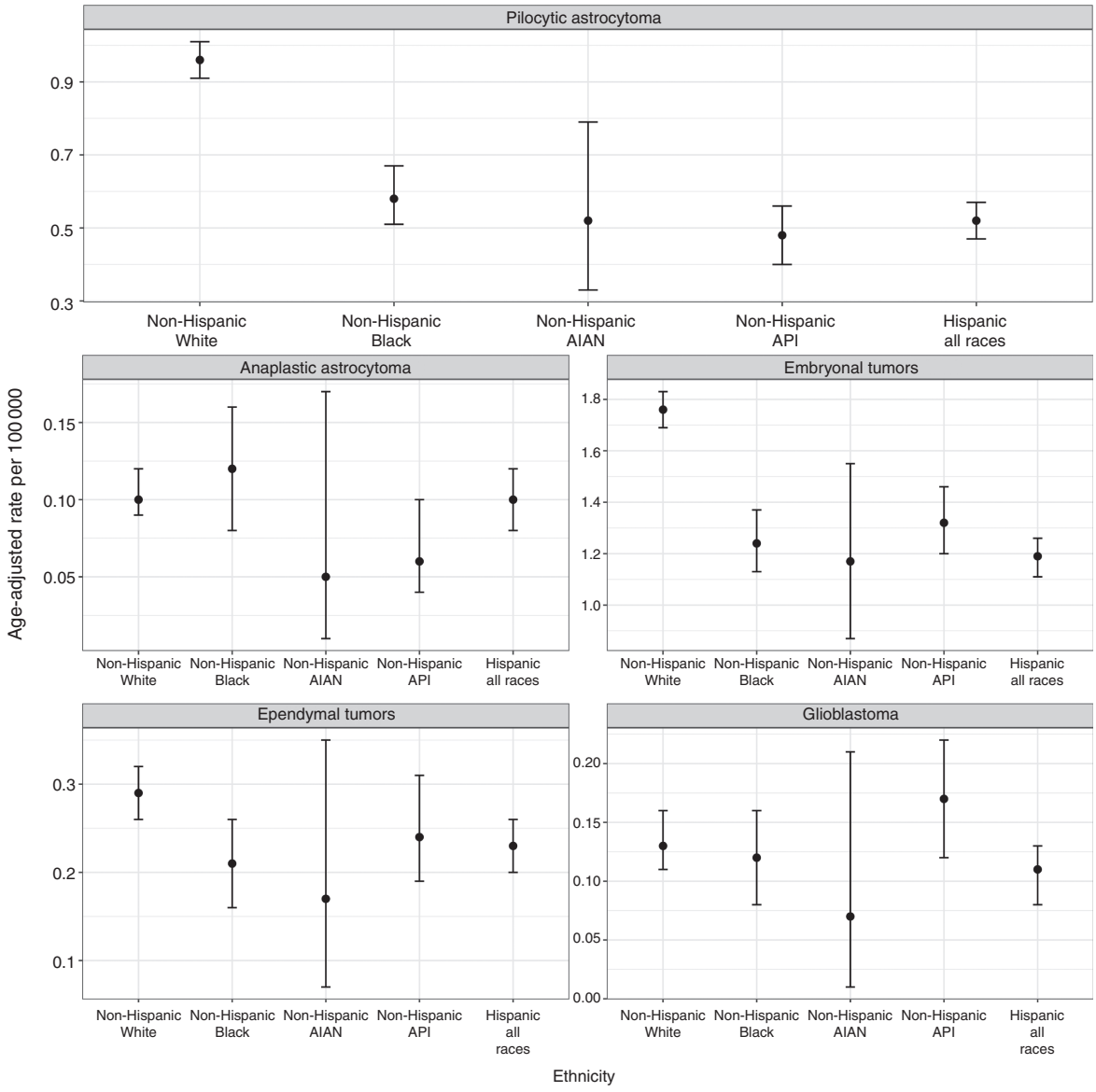

Fig. 3 Age-adjusted incidence rates for various pediatric brain tumor subtypes by ethnicity (SEER data). Age-adjusted incidence rates per 100 000 with 95% CIs are depicted for PA (ICD-O-3: 9421, 9425), anaplastic astrocytoma (ICD-O-3: 9401), embryonal tumors (ICD-O-3: 8963, 9364, 9470–9474, 9480, 9490, 9500–9502, 9508), ependymal tumors (ICD-O-3: 9383, 9391, 9392, 9393, 9394), and GBM (ICD-O-3: 9440, 9441, 9442). Age-adjusted incidence rates were derived from SEER (years: 1992–2016, age: 0–19 y). AIAN: American Indian or Alaska Native, API: Asian or Pacific Islander.

patients with sporadic AT/RT.[39,40] Patients may present with synchronous tumors in the brain and kidney or other soft tissue sites due to the presence of a germline mutation in *SMARCB1*.[40] Germline *SMARCB1* mutations are also associated with significantly poorer survival (2-year overall survival: 0% versus 48% for germline mutation and wildtype, respectively),[40] although a more recent report suggests that survival rates are not different between these groups with intensive therapy.[41] While inherited *SMARCB1* and *SMARCA4* mutations have been described,[36,38] a large portion of germline mutations and deletions in the *SMARCB1* locus appear de novo with no family history of disease.[36,40]

Germline mutations in *SMARCB1* are also associated with familial schwannomatosis.[42] Genotype-phenotype studies have demonstrated that deletions or truncating mutations of *SMARCB1* are more often seen in AT/RT, whereas loss-of-function mutations in exon 1 and splice site mutations are more often seen in schwannomatosis.[42] Interestingly, several families have been reported in whom the index cases presented with AT/RT, whereas the parents or grandparents developed schwannomas later in life.[42] This led to the hypothesis of an early developmental window in which AT/RTs were more likely to occur, which is now supported by genetically engineered murine models of AT/RT.[43] Although a small number of patients with

germline *SMARCA4* mutations have been reported, it has been suggested that patients with *SMARCA4*-mutated AT/RT carry a germline mutation more often than *SMARCB1*-mutated tumors.[38,44,45]

Embryonal Tumors with Multilayered Rosettes

ETMRs are a group of tumors that are suggested to develop from primitive or undeveloped nerve cells in the CNS with a distinction made between those with amplification of the miRNA cluster C19MC and non-amplified tumors.[12,46] Germline mutations in *TP53* have been identified in 3 pediatric CNS ETMRs.[47,48] Recent evaluations with targeted sequencing of oncogenes in 13 ETMR patients identified no germline alterations that were deemed likely to be pathogenic.[17,21]

Glioma

Low-Grade Gliomas

The most common low-grade glioma in pediatric patients is pilocytic astrocytoma (PA), which makes up 15.6% of all pediatric CNS tumors.[2] Patients with PA rarely harbor putative pathogenic germline mutations.[17] It has been reported that PA may occur in patients with germline mutations in Ras/mitogen-activated protein kinase (MAPK) pathway genes *NF1* and *PTPN11,* the latter of which is associated with Noonan syndrome.[49–51] *NBN* germline mutations have also been identified among PA patients, though at a lower frequency than among medulloblastoma patients.[52] Additional germline mutations that are likely to be pathogenic in pediatric PA patients have been identified in *BRCA2* and *TSC2*.[17,53]

A specific group of pediatric low-grade glioma patients develop optic pathway gliomas (OPGs), which occur in 15–20% of NF1 patients and tend to present in the first decade of life.[54–57] These patients harbor loss-of-function germline mutations in the *NF1* gene, which is a negative regulator of the Ras-MAPK pathway.[56] It has been suggested that germline mutational heterogeneity in the *NF1* gene influences optic glioma tumor characteristics and behavior in both mice and humans.[58] Indeed, Xu et al showed that among 215 NF1 patients, mutations in the cysteine/serine rich domain of *NF1* were associated with higher risk of developing OPG, whereas mutations in the HEAT-like region were associated with decreased risk compared with patients with mutations in other *NF1* domains.[59] Similarly, mutations in the 5′ region of *NF1* have been associated with increased OPG risk.[59–61] However, Hutter et al found no genotype-phenotype correlation among NF1 patients with regard to optic glioma development based on whole exome sequencing among 77 unrelated NF1 patients.[62] Ethnically, data also suggest that black and Asian pediatric NF1 patients have reduced odds of brain tumor diagnoses compared with white patients, although the underlying mechanism remains unexplored.[7]

NF2 patients, harboring germline *NF2* mutations, may present with ependymoma in childhood, but may also present with schwannomas and meningiomas.[63] Case reports have also described the occurrence of multiple ependymomas in patients with germline *APC* mutations.[64,65] Zhang et al identified germline mutations in *NF1, NF2,* and *TP53* that were deemed pathogenic among 67 ependymoma cases based on a panel decision.[53] However, another study that sequenced a selection of oncogenes in 59 ependymoma patients identified no germline mutations that were likely to be pathogenic.[17]

One study that evaluated low-grade gliomas that were not further specified found mutations in *NF1, RUNX1,* and *PMS2*.[53]

High-Grade Gliomas

Pedigree analyses of families with Li–Fraumeni syndrome, caused by germline *TP53* mutations, found that gliomas, including glioblastomas (GBMs), were the most common CNS tumors arising in their study population, followed by choroid plexus carcinoma (CPC), medulloblastoma, and ependymoma.[18,66] The majority (81%) of the brain tumors in this unique population occurred in childhood.[18,66]

Pediatric GBM has also been associated with constitutional mismatch repair deficiency (cMMRD), which is suggested to result in a tumor with the highest mutational load of any CNS tumor, especially when co-occurring with somatic mutations in the polymerase epsilon gene (*POLE*).[67,68] CMMRD is caused by homozygous or compound heterozygous germline mutations in postmeiotic segregation increased 2 (*PMS2*), mutL homolog 1 (*MLH1*), mutS homolog 2 (*MSH2*), and *MSH6*.[67] Biallelic mutations occurring in these genes confer a near fully penetrant CNS tumor predisposition phenotype.[67] Germline mutations in pediatric high-grade glioma patients have also been identified in *ATM, MUTYH, NF1, NBN, LZTR1, BRCA2, TSC2,* and *VHL*.[17,21,52,53,69,70]

Other Tumors

Meningioma

Two studies have identified germline *SMARCE1* mutations in pediatric and adult clear cell meningioma patients.[71,72] Patients with NF2 may also develop meningiomas during childhood.[63] It has also been suggested that spinal meningiomas occur more often in NF2 patients.[73]

Choroid Plexus Carcinoma

The prevalence of *TP53* mutations appears to be particularly high in CPC, which has been suggested to be as high as 36.4%, and patients with *TP53*-mutated CPCs show significantly poorer survival.[74,75] As mentioned above, CPCs are a common tumor among Li–Fraumeni families.[18,66]

Retinoblastoma

Retinoblastoma is generally classified as non-heritable or heritable, the latter of which is typically caused by germline *RB1* mutations, and is generally believed to follow the

"two-hit" tumor model.[76] Retinoblastoma may present unilaterally or bilaterally, and germline *RB1* mutations occur in ~10% and ~90% of cases, respectively.[77,78] Bilateral retinoblastoma comprises approximately one quarter of all cases and presents at a relatively earlier age.[77–80] Patients harboring an *RB1* mutation and successfully treated for retinoblastoma are also at considerable risk of developing secondary cancers later in life, especially soft-tissue sarcomas.[53,81–83]

Extremely Rare Pediatric CNS Tumor Types

Germline mutations in predisposition genes have also been identified in pediatric CNS tumor types that are extremely rare in the population. For example, malignant peripheral nerve sheath tumors have been found in pediatric NF1 patients.[84] Pathogenic germline *DICER1* mutations have been identified among pineoblastoma patients, with a mutation being present in approximately 17% of cases.[85,86] Pineoblastoma patients may also harbor germline *RB1* mutations, which also form a predisposition for retinoblastoma.[87] Dysplastic cerebellar gangliocytoma, also known as Lhermitte–Duclos disease, is an extremely rare CNS tumor that may also present in childhood and is pathognomonic for Cowden syndrome, caused by germline mutations in phosphatase and tensin homolog (*PTEN*).[88,89]

Implications of a Germline Genetic Diagnosis

Although varying by tumor type, approximately 10% of children with apparently sporadic CNS tumors harbor a germline mutation in a predisposition gene, based on analysis of known cancer predisposition genes.[17] In children with a known cancer predisposition syndrome, the chances of developing a CNS tumor may be extremely high, as seen with cMMRD (48%) or NF1 (20%).[54–56,67,90,91]

For some tumor types, germline mutations may result in earlier presentation, worse survival, multifocal disease, and higher chance of recurrence, as seen, for example, with medulloblastoma and AT/RT.[26,28,39,40] Pediatric CNS tumors may also be the first presentation of oncologic predisposition syndromes, such as Li–Fraumeni.[18,66] It may, therefore, be advisable to screen primary pediatric CNS tumor patients for potentially pathogenic germline mutations and provide enhanced surveillance for disease relapse or development of secondary cancers. Identification of pathogenic germline mutations, especially when accompanied by somatic copy-neutral loss of heterozygosity, may also provide targets for personalized medicine in rare scenarios where a drug targeting the altered pathway is available, as seen with immune checkpoint inhibition in patients with cMMRD.[67] However, as patients with germline mutations are more likely to get a secondary cancer, radiation therapy is preferably not applied.[92] An important caveat to consider is that not all institutions may have the financial capacities to provide all patients with genetic screening, or they may lack access to advanced sequencing technologies. Urgency regarding the potential clinical consequences and the preferences of patients and their families may also play a key role when genetic screening is being considered.

Family members of pediatric cancer patients who harbor a putative pathogenic germline mutation may also be prime candidates for genetic screening for the presence of the same mutation (ie, cascade screening), which would indicate a cancer predisposition syndrome. Similarly, pediatric cancer survivors who harbor germline mutations, whether inherited or de novo, may be counseled regarding the potential transmission of that mutation to their future offspring. Many genes described earlier may also predispose to a range of other adult-onset malignancies, which may have clinical consequences.[14,39,40,44] This has been best studied in the context of Li–Fraumeni syndrome, which necessitates long-term screening (eg, routine whole-body MRI) for early cancer detection.[93] The clinical management of childhood cancer survivors with other germline mutations is less well developed and merits future research.

Future Approaches to the Study of Pediatric CNS Predisposition

Much remains to be discovered regarding the germline genetics of pediatric CNS tumors. Most previous studies included only small numbers of patients and mixed histologic groupings, whereas recent larger studies have focused on pediatric tumors in general and have evaluated predominantly known cancer predisposition genes, which likely underestimates the true contribution of germline predisposition to cancer risk. Additionally, these studies have all been limited in their assessment of the role of germline genetics in contributing to variation in patient outcomes.[17,53] Future studies that aim to evaluate germline genetics using NGS or other methods of evaluating germline genetics for specific pediatric CNS tumors are, therefore, likely to be of value. Efforts to provide access and standardize such genetic screening should be facilitated via national and international oncology groups, particularly important for rare subtypes.

Highly penetrant germline mutations have been assessed in many pediatric CNS tumors, but low penetrance genetic variants that may be discovered by genome-wide association studies have not been identified for any pediatric CNS tumor. A more targeted approach along these lines may be evaluation of low penetrance alleles that are known to be associated with CNS tumors in adults, as common variants associated with adult glioma risk showed some evidence of association with pediatric brain tumors in a small case-control study.[94] Thus, larger studies are warranted to investigate the shared genetic basis of pediatric and adult CNS tumors.[94] Genetic research for new genome-wide association study discovery in pediatric CNS tumors will need to overcome the challenges of many disparate histopathologic subtypes, which reduces power for genome-wide analysis. These studies may be improved through linkage of biobanks and cancer registries as well as creation of dedicated (international) networks that can capture enough of each rare subtype to have sufficient statistical power. One example of this is the Gabriella Miller Kids First Pediatric Research Program, which collects DNA

and RNA samples from children with cancer or structural birth defects.[95] Other international consortia for childhood cancers, including the International Childhood Cancer Cohort Consortium[96] and the Childhood Leukemia International Consortium,[97] may help facilitate collaboration and the collection of sufficient subjects for study.

An intriguing clue and area ripe for discovery is the varied incidence of pediatric CNS tumors among different ethnicities.[6–8,98] For instance, the incidence of PA and embryonal tumors appears considerably higher among non-Hispanic whites (Surveillance, Epidemiology, and End Results [SEER] registry data; Fig. 3). This is similar to adult glioma, as the incidence of adult glioma is also highest among non-Hispanic whites in the US.[2] The variation in incidence may be the result of both environmental and genetic factors, resulting from different allele frequencies of risk alleles between groups and interactions between race/ethnicity-related exposures and underlying genetic susceptibilities.[99] A few studies have investigated links between environmental exposures and childhood brain tumors, including the role of pesticides, diet, and vitamin supplements, although, aside from ionizing radiation, evidence is inconsistent and limited.[4] Apart from studies showing sensitivity to ionizing radiation from subjects carrying high penetrance mutations, there is a dearth of information on genetic modifiers of environmental exposures, including those involved in metabolism, DNA repair, or other factors that may influence tumor initiation or progression.

In addition to their potential important contributions to disease etiology, gene–environment interactions may in part explain the heterogeneity in findings from previous assessments on the link between environmental exposures and childhood brain tumors. Exposures during early life may be particularly impactful, as children have a disproportionately greater exposure due to their smaller body mass and less efficient ability to metabolize toxicants. Children experience rapid development of the CNS, including greater rates of cell proliferation and differentiation that may leave them more vulnerable to the mutagenic and epigenetic alterations induced by environmental toxicants and stressors.[100] Genes involved in DNA repair pathways, including mismatch repair, have been previously associated with pediatric brain tumor susceptibility,[35,51–53,67,70,101] consistent with the hypothesis that individuals already susceptible to carcinogenesis may be at even greater risk when exposed to environmental factors that cause chromosomal aberrations, DNA breaks, DNA adducts, and other damage that requires repair. Interaction effects that have been suggested to contribute to greater risk of childhood brain tumors to date include: pesticide exposure and genes involved in toxin metabolism and detoxification,[102,103] air pollutant exposure and genes involved in DNA repair,[104] cured meat consumption and genes involved in the inactivation of N-nitroso compounds,[105] and folic acid supplementation and genes involved in the folate pathway.[106] However, these studies are limited in sample size and lack replication. Additional efforts with integrative approaches from multiple disciplines are necessary to further clarify the multifactorial etiology of childhood brain tumors involving the potential interaction of environmental factors and germline susceptibility. These may include employing a comprehensive bioinformatics method prioritizing previously identified environmentally responsive genes or those associated with biological functions involving xenobiotic metabolism, DNA repair, and immune and inflammatory responses[107]; verification of suspected interaction effects with model systems and functional studies to complement population-based epidemiologic findings[108,109]; and, most importantly, collection of high-quality comprehensive exposure data alongside germline genetic data.

Common genetic variation that naturally differs by ancestral populations may also partially explain varying incidence rates for pediatric brain tumors by ethnicity as seen in adult brain tumors,[110–112] but this has not been evaluated to date. Therefore, genetic association studies of pediatric CNS tumors may also be improved by inclusion of individuals from diverse genetic/ancestral backgrounds, thereby leveraging differences in linkage disequilibrium across multi-ethnic groups and fine-mapping candidate causal or functional variants.[113] Future studies may benefit from improved power by meta-analysis of variants across multiple ethnicities, particularly among subjects of African ancestry who harbor greater genetic diversity,[113] and from admixture mapping, which involves screening individuals of mixed ancestry for chromosomal regions with greater frequency of alleles from parental populations with higher CNS risk compared with the parental population with lower risk.[113]

With regard to rare variants, rare founder mutations may yield insight, as seen with elevated colorectal cancer risk in whites from Kentucky harboring a common *MSH2* mutation.[114] Indeed, the p.R337H founder mutation in *TP53* is observed in about 1 out of 375 Brazilian children[115] and is responsible for the elevated CPC incidence observed in this population.[116] That additional CNS tumors are associated with low-penetrance founder mutations in cosmopolitan populations is entirely possible and warrants further exploration.

We also believe it is of great importance to evaluate the penetrance of putative pathogenic mutations, as highlighted by the recently reported higher-than-expected frequency of pathogenic or likely pathogenic *TP53* mutations in the general population.[117] Other ways of further improving NGS analysis may be through utilization of publicly available datasets such as the Genome Aggregation Database (gnomAD)—for example, as controls for gene-burden testing to pinpoint novel predisposition genes for CNS tumors and other childhood cancers, although this is still controversial.[13,16,118,119] Utilizing and combining other data sources such as organ-specific gene expression data (eg, the Genotype-Tissue Expression, GTEx project) may result in further identification of genes or noncoding regions of interest.[120] NGS data may also be studied to identify genotype–phenotype interactions as seen with OPG in NF1 patients.[59–61] Other genotype–phenotype interactions that may warrant future studies are age of presentation as seen in AT/RT,[39,40] tumor location as seen in meningioma,[73] co-occurrence of mutations, response to therapy, and patient outcomes as seen in CPC.[74]

In conclusion, the current state of knowledge regarding genetic predisposition to pediatric CNS tumors highlights the need for collaboration to identify sufficient numbers of cases and to study rare variants across the genome among

multiple ethnicities. This review can serve as a guide and starting point for candidate-gene, gene-pathway, and risk variant analyses for targeting in future sequencing studies.

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