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REVIEW PAPER

Molecular Basis of Pediatric Brain Tumors

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Abstract Brain tumors emerge as the second commonest type of pediatric solid tumors following hematologic malignancies. Genomic profiling of low- and high-grade gliomas, ependymomas and medulloblastomas has revealed chromosomal abnormalities and specific gene mutations which have been associated with aberrant activation of crucial signal transduction pathways, including mitogen-activated protein kinase, mammalian target of rapamycin and retinoblastoma tumor suppressor signaling. Furthermore, pediatric high-grade gliomas are associated with chromatin remodeling defects and somatic histone gene mutations that affect prognosis. This review provides an update of the molecular and genetic alterations that characterize pediatric brain tumors, and discusses novel therapeutic approaches targeting these abnormalities.

Keywords Pediatric gliomas · Mutations · MAPK · mTOR · RB

Introduction

Central nervous system (CNS) neoplasms are the most frequent solid tumors in children, representing a primary cause of mortality. Pediatric brain tumors are often accompanied by several clinical manifestations such as headache, nausea, vomiting, vision loss, ataxia, clumsiness and personality changes (Segal and Karajannis 2016). Five-year survival rate varies according to tumor's unique histologic and molecular characteristics and is currently at 73.6% among children under the age of nineteen (Segal and Karajannis 2016).

Previous classification of CNS tumors according to World Health Organization (WHO) was largely dependent on histologic imaging evaluation under the microscope, immunohistochemical expression of lineage-associated proteins and estimation of the corresponding levels of cells' differentiation (Louis et al. 2016). However, the recent update of WHO classification for brain tumors takes into account data from genomic sequencing studies and revises the established guidelines to incorporate molecular characteristics in the revised CNS tumor classification (Louis et al. 2016; Park et al. 2017). Therefore, the main brain tumors (diffuse astrocytic/oligodendroglial and embryonal tumors) are classified into genetically defined subgroups depending on the presence or absence of specific gene alterations [e.g., isocitrate dehydrogenase (*IDH*)-wild-type and *IDH*-mutant glioblastomas] (Louis et al. 2016; Park et al. 2017). In accordance, nowadays the neuropathological evaluation of brain tumors depends on molecular genetic tests not only for their proper classification but also for the monitoring of biological behavior and patients' management. Interestingly, recent whole-genome studies have revealed several genetic alterations that characterize pediatric brain tumors which differ from those found in adults (Glod et al. 2016; Lassaletta et al. 2016; Liu et al. 2017; Park et al. 2017).

In this review, we provide an update of the unique genetic changes observed in pediatric brain tumors, focusing on deregulated signal transduction pathways and gene mutations that contribute to tumor's development.

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Common Features of Brain Tumors in Children

The most frequent types of brain neoplasms in children include distinct clinical entities of glial and non-glial-derived tumors (Northcott et al. 2015). Glial lineage tumors encompass astrocytomas, oligodendrogliomas, oligoastrocytomas and ependymal tumors (Louis et al. 2007). On the other hand, non-glial, neuronal lineage tumors include embryonal tumors, medulloblastomas, craniopharyngiomas, germ cell tumors, lymphomas, meningiomas and others (Northcott et al. 2015).

Regarding the glial lineage tumors, low-grade astrocytomas (WHO grade I and II) are estimated up to 24% of all pediatric brain neoplasms, consisting mainly of pilocytic astrocytomas (PAs, WHO grade I) (Kieran et al. 2010; Segal and Karajannis 2016). PAs demonstrate pilocytic morphology, decreased proliferative activity and low infiltrative rate (Kieran et al. 2010). They are detected mostly in the cerebellum and the optic pathway, exhibiting an excellent 5-year survival (Kieran et al. 2010). On the other hand, high-grade astrocytomas (HGGs, WHO grades III and IV, less than 15% in children) are mainly presented as glioblastoma multiforme (GBM) and diffuse intrinsic pontine gliomas (DIPGs, WHO grade IV) in children below 10 years of age (Kieran et al. 2010). DIPGs in particular are detected in the brainstem and often present a poor 5-year survival (5–10%) (Segal and Karajannis 2016). Ependymomas are generated from radial glial cells, more frequently in boys under 5 years of age, and are commonly detected in the ventricles and the spinal cord with varying survival rate (Segal and Karajannis 2016).

With respect to non-glial origin, medulloblastomas represent the most common neoplasms in children, frequently found at the posterior fossa. They manifest mainly with elevated intracranial pressure and ataxia. Medulloblastomas develop in the fourth ventricle and the cerebellum presenting low differentiation, increased growth and invasiveness with varying survival rates (Segal and Karajannis 2016).

Surgical resection of the tumors comprises the first line of treatment for low-grade gliomas (LGGs) followed by radiation therapy in older children exhibiting high tumor recurrence. Radiation therapy, the gold standard treatment for HGGs and DIPGs, is commonly accompanied with aggressive surgical resection and occasionally chemotherapy. The same combined regimen (surgery, radiation and chemotherapy) is also applied to medulloblastoma patients improving their survival, but it is often associated with adverse clinical manifestations. To this end, genomic sequencing analyses and molecular profiling of brain tumors come to identify tumor-specific gene alterations and intracellular signaling defects that could be pharmaceutically targeted in order to minimize the detrimental side effects of the existing treatment (Segal and Karajannis 2016).

Genetic Basis of Pediatric Brain Tumors

Large efforts have been made over the last years to determine the pathogenic mechanisms underlying pediatric gliomagenesis, revealing both chromosomal abnormalities and molecular defects in signal transduction pathways being associated with specific tumor types (Bax et al. 2010; Jones et al. 2012a; Paugh et al. 2010; Sturm et al. 2012).

Although chromosomal aberrations in pediatric HGGs are less common than in adults, the most frequent change was the gain of chromosome 1q present in approximately 19% of tumors followed by the loss of 16q in 17.5% of HGGs in a study of 63 paraffin-embedded HGGs samples (age <23 years) (Bax et al. 2010). Chromosome 7 gain and 10q loss were less frequently observed in approximately 12.7% of the 63 HGG cases in the same study (Bax et al. 2010; Paugh et al. 2010). In PAs, chromosome 7 gain was often detected (25% of 44 cases) along with gains of chromosomes 5, 6, 11 (10% of 44 samples) (Bergthold et al. 2014; Jones et al. 2006).

Next-generation sequencing-based tumor profiling and whole-genome association studies have detected combinations of germline and somatic genomic variations in pediatric brain tumors (Mack and Northcott 2017). Whole-genome sequencing identified for the first time *TP53* mutations that code for a nuclear phosphoprotein that regulates cell cycle and affects genetic stability in a sonic hedgehog (SHH) medulloblastoma subgroup, linked to a one-step catastrophic event termed chromothripsis (Rausch et al. 2012). Other genome-wide association studies in medulloblastomas revealed activation of the growth factor independent 1 family of proto-oncogenes (*GFI1*, *GFI1B*) as a prominent oncogenic mechanism mediated through "hijacking" of respective enhancer elements (Northcott et al. 2014). Additional driver gene mutations have also been reported based on NGS-mediated profiling across different tumor subgroups (e.g., *CTNNB1*, *DDX3X* and *PTCH1* in SHH group) (Northcott et al. 2012).

Regarding gliomas, gene mutations are also present in canonical signal transduction pathways including the TP53, the retinoblastoma tumor suppressor (RB) and the tyrosine kinase receptor (RTK)/Ras/PI3K (phosphoinositide 3-kinase) (Table 1, McLendon et al. 2008; Parsons et al. 2008). PAs have been associated with several genetic changes and mechanisms that commonly target the abnormal activation of the mitogen-activated protein kinase (MAPK) pathway (Jones et al. 2008, 2012b), while HGG are often associated with mutations in *PIK3CA* and *PIK3R1* genes affecting the

Table 1 Genetic defects associated with pediatric brain tumors

Type of brain tumor	Molecular Defect/Mutation	Function	Biomarker potential	Investigational drugs	Reference
Low-grade gliomas (LGGs)					
Pilocytic astrocytomas	**NF1** germline mutation (R681X)—microdeletion	Protein truncation—downregulation of the Raf and PI3K transduction pathways	ND	ND	Bergthold et al. (2014, 2015), Garcia et al. (2016), Hernaiz Driever et al. (2010), Costa et al. (2002), Le and Parada (2007), Staedtke et al. (2016) and Zhang et al. (2013)
	KIAA1549–BRAF fusion **BRAF V600E** activating missense mutation **BRAF** duplication of the 3′ portion	Activation of BRAF kinase domain and deregulation of the downstream MAPK pathway. Affect cell proliferation and apoptosis	Positive prognostic and diagnostic marker for PAs	MEK inhibitors, BRAF inhibitors	
Diffuse astrocytomas	**FGFR1** duplication, Gain of function mutations (N546K, K656E), missense (V559M, N544K) and fusions	Activation of downstream signaling pathways Ras–Raf–MEK–ERK and PI3K–Akt–mTOR	ND	ND	Bergthold et al. (2014, 2015), Gajjar et al. (2014), Garcia et al. (2016), Hernaiz Driever et al. (2010), Jones et al. (2013), Northcott et al. (2015), Ramkissoon et al. (2013), Tatevossian et al. (2010), Zhang et al. (2013)
	NF1 germline mutation—microdeletion	Downregulation of the Raf and PI3K transduction pathways	ND	ND	
	MYB amplification Gene rearrangement	Loss of their C-terminal portion	ND	ND	
Pleomorphic xanthoastrocytomas (PXAs)	**BRAF V600E** activating missense mutation	Activation of BRAF kinase domain and dysregulation of the downstream MAPK pathway	Diagnostic for PXAs	BRAF inhibitors	Garcia et al. (2016), Staedtke et al. (2016) and Zhang et al. (2013)
Gangliogliomas (GGs)	**BRAF V600E**	Activation of BRAF kinase domain and dysregulation of the downstream MAPK pathway	Diagnostic for GGs	BRAF inhibitors	Garcia et al. (2016), Staedtke et al. (2016) and Zhang et al. (2013)
Angiocentric gliomas (AGs)	**BRAF V600E**	Activation of BRAF kinase domain and dysregulation of the downstream MAPK pathway	Diagnostic for AGs	BRAF inhibitors	Gajjar et al. (2014), Garcia et al. (2013, 2016), Northcott et al. (2015), Ramkissoon et al. (2013), Staedtke et al. (2016), Tatevossian et al. (2010) and Zhang et al. (2013)
	MYB focal deletions **MYBL1** mutation	Loss of their C-terminal portion			
High-grade gliomas (HGGs)					
Glioblastomas (GBM) and Diffuse pontine gliomas (DIPG)	**H3F3A** **HIST1H3B** **G34V/R** **K27M**	Decrease levels of lysine 27 methylation Change the distribution of lysine 36 methylation	Prognostic and diagnostic role. Associated with worse survival in DIPGs	Epigenetic inhibitors, JMJD3 inhibitor	Becher and Wechsler-Reya (2014), Buczkowicz et al. (2014), Fontebasso et al. (2014a), Fontebasso et al. (2014b), Gajjar et al. (2015), Heaphy et al. (2011), Huse and Rosenblum 2015, Lulla et al. (2016), Schwartzentruber et al. (2012), Schneider et al. (2013), Staedtke et al. (2016), Taylor et al. (2014), Zhang et al. (2013), Paugh et al. (2013), Puget et al. (2012), Roujeau et al. (2007), Schwartzentruber et al. (2012), Taylor et al. (2014) and Wu et al. (2014)

Table 1 continued

Type of brain tumor	Molecular Defect/Mutation	Function	Biomarker potential	Investigational drugs	Reference
	ATRX missense mutation (E991K), loss of function	Alternative lengthening of telomeres	Diagnostic role. Closely correlated with *TP53* mutations	ND	
	PDGFRA amplification and gain of function mutations (missense: E229K, C235R, Y288C, C290R, in-frame deletions: E7del, E10del, E10del2, in-frame insertions: C450ins, A491ins, V544ins)	Activates MAPK, PLC/PKC and PI3K/Akt pathways. Regulates proliferation, migration	Prognostic role. Poor outcome	ND	
	TP53—deletions and loss-of-function mutations (frameshift: R156fs; missense: C135Y, V157F, A159V, R175H, G244S, R273C, R273H, R282W, nonsense: E221*)	Regulates cell fate in response to genotoxic stress	Diagnostic role	ND	
	ACVR1—gain of function mutations	Development of fibrodysplasia disorder	ND	ND	
Medulloblastomas					
WNT subgroup	**CTNNB1** deletion of one copy of chromosome 6	Deregulation of WNT downstream target genes	Prognostic and diagnostic role. Favorable prognosis	ND	Gajjar et al. (2015), Jones et al. (2012c), Pugh et al. (2012), Robinson et al. (2012), Segal and Karajannis (2016), Shih et al. (2014), Staedtke et al. (2016) and Wells and Packer (2015)
SHH subgroup	**PTCH1** focal homo-/heterozygous mutations or deletions	Deregulation of SHH pathway. Li–Fraumeni syndrome	ND	SMO inhibitors	
	TP53 mutations	Cell cycle regulation	Prognostic role	ND	
	SMARCA4 mutations	Tumor suppressor. Interferes with ATP-dependent SWI/SNF chromatin remodeling complex	ND	ND	
Group 3	**MYC** amplification	Transcription factor	Poor prognosis	ND	
Group 4	**MYCN** amplification	Regulates cell cycle progression, apoptosis and cellular transformation	Prognostic role. High-risk mutations; associated with reduced survival	Gemcitabine and pemetrexed; BET bromodomain inhibitors	

Table 1 continued

Type of brain tumor	Molecular Defect/Mutation	Function	Biomarker potential	Investigational drugs	Reference
Ependymomas					
Supratentorial ependymomas	C11orf95-RELA gene fusion	Affecting regulation of cell maintenance	ND	ND	Glod et al. (2016), Park et al. (2017) and Segal and Karajannis (2016)
Group A	CPG island methylator phenotype (CIMP high)	Downregulation of differentiation genes			
Group B	CPG island methylator phenotype (CIMP low)	Chromosomal abnormalities			

ND no data available

functional subunits of phosphoinositide 3-kinase (PI3K) and by this way regulating cell growth and differentiation.

Additionally sequencing analysis in 48 pediatric GBM cases has revealed somatic histone H3.3 mutations in almost half of the cases (44%). Along with histone mutations, whole-genome sequencing analyses revealed additional changes in components of the chromatin remodeling pathway, *ATRX* (α-thalassemia/mental retardation syndrome X-linked) and *DAXX* (death domain-associated protein). In particular, most of the cases that harbor *TP53* mutations (86%) also present *H3F3A* and/or *ATRX* mutations (Schwartzentruber et al. 2012). Such alterations have been also identified in DIPGs (Wu et al. 2012) while *ACVR1* mutations are associated with HGGs and DIPGs pathogenesis (Buczkowicz et al. 2014; Fontebasso et al. 2014b; Taylor et al. 2014).

Defects in Signal Transduction Pathways Associated with Pediatric Gliomas

Defects in Neurofibromatosis 1 (NF-1) and Mitogen-Activated Protein Kinase (MAPK) Pathway

Neurofibromatosis 1 (NF-1), a syndrome of autosomal-dominant inheritance, is mainly involved on the onset and progression of neurofibromas and astrocytomas. Up to 15% of children with NF-1 further develop diffuse astrocytomas or PAs, highlighting the strong correlation of NF-1 with low-grade gliomas (Table 1, Hernaiz Driever et al. 2010).

Germline mutations on the tumor suppressor neurofibromin (*NF1*) gene located at the chromosome 17q11.2 are the causative factors of the disease. Neurofibromin is a ubiquitous protein expressed in different tissues during development. It acts as a negative regulator of Ras–Raf–MAPK signal transduction pathway in normal cells by disrupting the functional Ras–GAP-related domain (Ras–GRD) protein, thus enhancing the transition of GTP-bound Ras active form into its GDP-tethered inactive form. *NF1* mutation induces loss of NF-1 function and constitutive activation of the Ras pathway, thus affecting cell proliferation and differentiation of astrocytes, leading to cancer onset (Costa et al. 2002; Le and Parada 2007).

Furthermore, Raf is known to regulate the downstream kinase cascade of MAPK pathway and moderate cell differentiation and proliferation (Dasgupta and Haas-Kogan 2013; Gilheeney and Kieran 2012). Gain of 7q34 chromosomal region containing the *BRAF* locus has been revealed as the most frequent alteration in PLGGs reaching up to 50–100% of the PAs in comparative hybridization studies (Bergthold et al. 2014; Dasgupta and Haas-Kogan 2013; Lawrence et al. 2014). In addition, PLGGs commonly present *BRAF* V600E missense mutations and/or

BRAF duplication/fusions (Ho et al. 2015; penman et al. 2015). The gain of function *BRAF* V600E mutation constitutively activates BRAF kinase and deregulates the MEK/MAP kinase cascade (Bergthold et al. 2014). It has been shown to induce neuronal stem cell transformation and senescence, being implicated in PAs development (Jacob et al. 2011; Raabe et al. 2011).

Zhang et al. (2013) have also detected *BRAF* V600E mutations in pleomorphic xanthoastrocytomas (70%), diffuse astrocytomas (23%), gangliogliomas (33%) and PAs (6%) in a whole-genome sequencing study of 151 PLGG biopsies. The gain of *BRAF*-associated locus in chromosome 7q34 is the most frequent modification in PLGGs which do not present NF-1 and is often observed at the *KIAA1549* gene segment within the *BRAF* fusion transcript (Bergthold et al. 2015, 2014; Hemmati et al. 2003; Jacob et al. 2009). The BRAF protein that is generated by the *KIAA1549:BRAF* fusion is permanently switched on due to the absence of its auto-inhibitory domain (Becker et al. 2015; Jones et al. 2008). Importantly, the *KIAA1549:BRAF* fusion has been shown to induce anchorage-independent cell proliferation in different cell types. There is evidence that around 90% of PAs inside the cerebellum and 50% on the outside harbor *KIAA1549:BRAF* gene fusions in children without NF-1 (Antonelli et al. 2015; Jones et al. 2013; Zhang et al. 2013). Several other *BRAF* fusion genes (*MACF1*, *CLCN6*, *FAM131B*, *GNA11*, *MKRN1*, *SRGAP3* and *RNF130*) have also been reported that do not encode for the inhibitory domain of BRAF N terminus, thus inducing upregulation of the BRAF kinase domain and activation of downstream MAPK effectors, MEK and ERK (Bergthold et al. 2014; Cin et al. 2011; Forshew et al. 2009; Jones et al. 2009, 2013; Lin et al. 2012).

Tuberous Sclerosis and Defects in mTOR Pathway

Tuberous sclerosis, a genetic disorder that has been associated with formation of benign tumors in almost every organ of the human body, has also been reported to affect the brain. It has been associated with a variety of neurologic symptoms (seizures, developmental delay and behavioral issues), cutaneous lesions and renal manifestations. Tuberous sclerosis demonstrates a causal relationship with germline mutations of hamartin (*TSC1*) or tuberin (*TSC2*) of the tuberous sclerosis complex, strongly connected to subependymal giant cell astrocytoma (SEGA) (Hargrave 2009; Reuss and von Deimling 2009; van Slegtenhorst et al. 1997). *TSC1* and *TSC2* encode for proteins that function as tumor suppressors upstream of mTOR signal transduction. In particular, TSC1/2 complex regulates the status between the active GTP-bound Rheb and its GDP-bound inactive form (Hargrave 2009; Rosner et al. 2008). Mutations on *TSC1* or *TSC2* genes result to downregulation of their tumor suppressing activity, thus leading to activation of Rheb and concomitant induction of the mTOR pathway, facilitating hamartomas progression and SEGAs development (Hargrave 2009; Reuss and von Deimling 2009).

Low-grade gliomas in children are also associated with mutations of the mTOR signaling components suffering from tuberous sclerosis (Table 1). The PI3K/Akt/mTOR signal transduction pathway participates in the integration of intracellular and environmental signals which regulate cell proliferation and growth, as well as survival and autophagy (Hassan et al. 2013). mTOR, a serine-threonine kinase consisting of two protein complexes, mTORC1 and mTORC2, mediates mTORC1 activation by Rheb G-protein in the presence of nutritional adequacy. Upon activation, mTORC1 stimulates p70S6 kinase that leads to activation of phospho-S6 and phospho-4EBP1 that regulates translation and cell growth. Phospho-S6 and phospho-4EBP1 are overexpressed in PLGGs (Dasgupta and Haas-Kogan 2013) and have been associated with poor progression-free survival (Populo et al. 2012). mTORC2 is also regulated by nutrients and controls cellular proliferation by activating the serine–threonine kinase Akt. Akt affects cell growth and metabolism and has been implicated as an oncogene in several types of human malignancies. Activation of Akt is linked with phenotypically aggressive PAs (Rodriguez et al. 2011).

Activation of mTOR and Ras–Raf–MAPK pathways may also occur due to aberrant regulation of the *fibroblast growth factor receptor 1* (*FGFR1*) gene that is commonly amplified in tumors. Most of *FGFR1* alterations including duplication of the 3′ portion of the gene, missense mutations and fusion with transforming acidic coiled-coil (*TACC*) genes have been detected in PAs (Table 1). Point mutations in FGFR1 kinase domain (N546K and K656E) were originally detected in five PAs and were implicated to mind–brain hyperproliferation (Jones et al. 2013). Both mutations were found to alter the autophosphorylation of FGFR1, leading to elevated kinase activity and transformational potential. The necessity of FGF2 ligand along with *FGFR1* mutation to induce tumor formation was revealed by a gene array study of 118 PAs that showed overexpression of FGF2 ligand in PAs compare to 158 normal tissues and other astrocytic tumors. Whole-genome studies also detected intragenic duplication of FGFR1 tyrosine kinase domain in two of 39 PAs and in three of 11 cerebral diffuse gliomas (WHO grade II) being associated with MAPK/ERK and PI3K activation in multiplex immunoassays (Jones et al. 2013; Zhang et al. 2013).

Defects in Retinoblastoma (RB) Tumor Suppressor Pathway

Genetic alterations of the RB pathway are less frequent in pediatric HGGs and vary with respect to tumor location (Table 1). A genome scale study of 63 archival HGGs (age

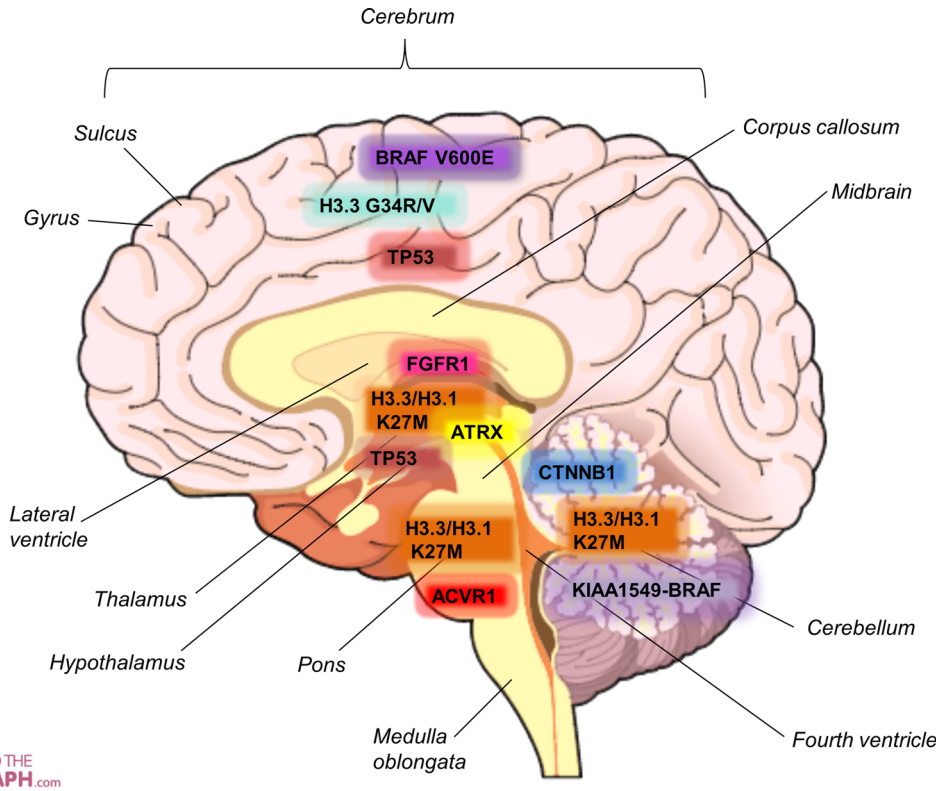

Fig. 1 Mutations associated with different neuroanatomical sites in pediatric brain tumors. Pediatric high-grade gliomas are distinguished into subgroups based on specific mutations that appear in different neuroanatomical sites. HGGs are frequently arising as DIPG in the pons and thalamus areas. *BRAF* mutations (*BRAF V600E*) and *H3* mutations (*G34R/V*) mainly characterize cerebral cortical tumors. *ACVR1* mutations are associated with *H3.1 K27M* and they are predominantly found in midline locations such as DIPG. In thalamic HGGs, *FGFR1* mutations are present, whereas *ATRX* mutations are seen in G34V/R tumors. Furthermore, *TP53* mutations are associated with *G34R/V* and *K27M* tumors while *CTNNB1* mutations are found in the area of cerebellum

<23 years) employing paraffin-embedded samples revealed that homozygous deletions of *cyclin-dependent kinase inhibitor 2A* (*CDKN2A*) were present in 25% of non-brain-stem-HGGs (NBS-HGGs) (Bax et al. 2010). Another whole-genome, whole-exome and whole-transcriptome sequencing analysis of 127 fresh pediatric tumor tissues (57 DIPGs and 70 NBS-HGGs) reported focal amplification of the cyclin/CDK complex components including *cyclin D1*, *D2* or *D3*, *CDK6* and *CDK4* that phosphorylate RB at the cell cycle G1 checkpoint, predominantly detected in DIPGs (Wu et al. 2014). Several studies report that *CDKN2A* deletion is only present in NBS-HGGs (Paugh et al. 2011; Qu et al. 2010; Wu et al. 2014). Although one-third of HGGs exhibit loss of chromosome 13q, loss-of-function mutations of both *RB* alleles are not frequent in HGGs, indicating a therapeutic potential of CDK 4/6 inhibitors for both NBS-HGGs and DIPGs (Buczkowicz et al. 2014; Fontebasso et al. 2014a; Schwartzentruber et al. 2012; Taylor et al. 2014).

Gene Mutations Associated with Pediatric Gliomas

Serine/Threonine Protein Kinase B-Raf (BRAF) Mutations

A genome-wide study investigating the predominance of *BRAF* V600E mutations in 1320 pediatric CNS tumors, reported high frequency in pleomorphic xanthoastrocytomas (66% in 42 of 64 cases) and pleomorphic xanthoastrocytomas with anaplasia (65% in 15 of 23 cases) while gangliogliomas presented a lower frequency of 18% (14 of 77 cases) and PAs of 9% (9 of 97 cases). Gliomas and glioblastomas exhibited an even lower frequency or absence of mutations (Table 1; Fig. 1, Knobbe et al. 2004; Schindler et al. 2011).

However, a higher frequency of *BRAF* V600E mutation (54%) was reported in GBMs with histologic features of epithelioid differentiation (7 of 11 cases) in a study of 24 patients (age range 4–67 years, 11 < 18 years) employing both frozen and paraffin-embedded tissues (Kleinschmidt-DeMasters et al. 2013). Additionally, *BRAF* V600E mutation was detected in pediatric cortical HGGs (~10%), less often in thalamic HGGs, but not in DIPGs (Bautista et al. 2014; Huillard et al. 2012; Nicolaides et al. 2011; Schwartzentruber et al. 2012).

Another genome-wide sequencing analysis performed in a panel of 33 fresh pediatric astrocytoma tissues (age 1–18 years, WHO grades II–IV) revealed that ~20% of astrocytomas grade II–IV carry the *BRAF V600E* mutation, with concomitant presence of the homozygous deletion of the *CDKN2A* locus, encoding p19ARF and p16Ink4a (Schiffman et al. 2010; Wu et al. 2014). Therefore, the combination of these genetic changes may possible define a subset of malignant astrocytomas.

Myeloblastosis (MYB) Mutation

The proto-oncogene *MYB* has been previously implicated in gliomagenesis, and *MYB* mutations have been detected in several LGG types. In a study cohort of 57 pediatric LGGs and 59 HGGs frozen tissue specimens (age 1–9 years), Affymetrix SNP arrays were employed to investigate MYB copy number aberrations while gene amplification was confirmed by dual-color interphase fluorescence in situ hybridization. *MYB* amplification was detected in 2/14 diffuse astrocytomas and focal deletions of *MYB* terminal region occurred in 1 of 2 angiocentric gliomas.

MYB expression was found upregulated at the protein levels using RT-PCR and immunohistochemistry in 60% of diffuse LGGs, in 41% of PAs and 19% of HGGs indicating the important role of *MYB* in a subset of pediatric tumors (Tatevossian et al. 2010; Gajjar et al. 2014).

Additionally, a high-resolution analysis of copy number of 44 paraffin-embedded PLGGs revealed that 28% of diffuse astrocytomas grade II exhibited a partial duplication of the transcription factor *MYBL1* with truncation in its regulatory C-terminal domain. The truncated *MYBL1* transcripts were further found to induce anchorage-independent growth of 3T3 cells and tumor formation in vivo (Ramkissoon et al. 2013; Zhang et al. 2013; Table 1).

Platelet-Derived Growth Factor Receptor Alpha (PDGFRA) and Tumor Protein 53 (TP53) Mutations

Platelet-derived growth factor (PDGF) and its tyrosine kinase receptors have a critical developmental role being involved in proliferation, migration and survival of several cell types (Paugh et al. 2013). Genomic analyses of pediatric brain tumors have detected a focal gene amplification of *platelet-derived growth factor receptor alpha* (*PDGFRA*) in HGGs inside and outside the brainstem, followed by elevated mRNA levels and protein overexpression (Paugh et al. 2010, 2011).

Furthermore, in a cohort of 90 pediatric HGG employing both frozen and paraffin-embedded tissues, sequencing analysis of all *PDGFRA* coding exons showed that somatic activating *PDGFRA* mutations were present in 14.4% (13 of 90) of non-brainstem HGGs and in 4.7% (2 of 43) of DIPGs. *PDGFRA* mutations included several missense mutations (E229K, C235R, Y288C and C290R), three in-frame deletions (E7del, E10del and E10del2) and three in-frame insertions (C450ins, A491ins and V544ins) (Table 1, Paugh et al. 2010, 2011, 2013). Interestingly, a 40% of pediatric HGGs exhibited both *PDGFRA* amplification and mutations (Puget et al. 2012, 2013; Schwartzentruber et al. 2012). Other studies also report a concurrent amplification of *PDGFRA* with receptor tyrosine kinase proto-oncogene *MET* and *insulin-like growth factor 1* (*IGF1R*) (Bax et al. 2010; Paugh et al. 2010, 2011; Puget et al. 2012; Qu et al. 2010).

Of importance, activated PDGFR signal transduction is mediated via critical downstream pathways such as MAPK, PLC/PKC and PI3K/Akt with well-established tumorigenic roles.

In pediatric HGGs, frequent mutations are also observed in the tumor suppressor gene *p53* which regulates cell fate in response to genotoxic stress. Whole-genome sequencing of 26 fresh DIPG biopsies (mean age 6.5 years) identified somatic *TP53* mutations in 42% (11 of 26) of patients samples (frameshift: R156fs; missense: C135Y, V157F, A159V, R175H, G244S, R273C, R273H, R282W, nonsense: E221*)(Buczkowicz et al. 2014; Fontebasso et al. 2014a; Schwartzentruber et al. 2012; Taylor et al. 2014; Wu et al. 2014).

Additionally, a target gene of TP53, the TP53-induced phosphatase *PPMID* that impairs the TP53-dependent G1 checkpoint was also found mutated in 23% of DIPGs (6 of 26) (frameshift: P428fs, R429fs, T483fs; nonsense: S468*, C478*, L513*) suggesting its implication as a downstream *TP53* effector in DNA damage response (Kleiblova et al. 2013; Taylor et al. 2014; Wu et al. 2014).

Histone Gene Mutations

A significant number of pediatric GBM and DIPG samples present highly recurrent histone hotspot mutations affecting two distinct residues of histone 3 (glycine 34 replacement by valine or arginine (G34V/R), or substitution of lysine 27 by methionine (K27M) (Table 1; Fig. 1, Lulla et al. 2016; Waldmann and Schneider 2013). These mutations are taking place in the non-canonical histone gene *H3F3A*, as well as at the canonical histone genes *HIST1H3B* and *HIST1H3C* which encode histone H3.3 and H3.1 (Khuong-Quang et al. 2012; Schwartzentruber et al. 2012; Sturm et al. 2012; Wu et al. 2012). These mutations have demonstrated a spatial heterogeneity, with K27M substitutions occurring almost exclusively in midline tumors (i.e., those in the thalamus, brainstem or spine) and G34R/V substitutions restricted to hemispheric GBMs. Although *G34* mutations typically co-occur with *ATRX* mutations and alternative lengthening of telomeres (a potential point of targeted interference), they are less frequently co-expressed in tumors carrying K27M substitutions (Yuen and Knoepfler 2013). Whole-exome sequencing of 48 pediatric GBM detected 31% of tumors to harbor these mutations, targeting specific residues on the histone tail and participating in post-translational modifications (Downing et al. 2012; Schwartzentruber et al. 2012). There is a strong association between histone mutation, clinical patient characteristics and distinct molecular features (Fontebasso et al. 2013; Khuong-Quang et al. 2012; Sturm et al. 2012). *H3F3A* mutations were uncovered to

characterize pediatric GBM implying their association to diffuse high-grade tumors (Gielen et al. 2013). In addition, the mutation *H3F3A K27M* has been detected in only three (1.9%) thalamic LGGs by whole-genome sequencing of 39 fresh samples (Zhang et al. 2013). Another study of whole-genome, whole-exome and whole-transcriptome sequencing of 26 fresh DIPG biopsies reported *K27M* mutations to occur in approximately 88% (23 of 25) of DIPGs (Taylor et al. 2014). *K27M* mutations were present in both *H3F3A* (58%) and *HIST1H3B* (31%), while *G34V/R* mutations involved exclusively *H3F3A* (Buczkowicz et al. 2014; Waldmann and Schneider 2013; Wu et al. 2012).

Histone gene mutations are related to tumor location and patient's age. *K27M* mutant tumors arise in midline locations such as the spinal cord, thalamus and pons. *H3F3A K27M* has been detected in a 6% of thalamic PAs (3 of 48) followed by *NF1* and *FGFR1* mutations (Jones et al. 2013; Ryall et al. 2016). In contrast, *G34V/R* mutations occur in tumors located in hemispheric regions (Bjerke et al. 2013; Fontebasso et al. 2014b; Sturm et al. 2012; Wu et al. 2012, 2014). A considerable number of these tumors have mutations in *TP53* and in chaperone genes *ATRX* and *DAXX* (Schwartzentruber et al. 2012; Sturm et al. 2012), frequently showing an alternative lengthening of telomeres (ALT) phenotype and DNA hypomethylation (Sturm et al. 2012).

With respect to patient's age, younger children (peak age 7 years) usually present *H3.1K27M* tumors which are often combined with *ACVR1* mutations (Becher and Wechsler-Reya 2014; Fontebasso et al. 2014b; Roujeau et al. 2007; Taylor et al. 2014). On the other hand, *H3.3K27M* tumors are more frequent in infants and older children (median age, 11 years), whereas *G34V/R* mutations predominate in adolescents and young adults (median age, 20 years) (Gerges et al. 2013; Khuong-Quang et al. 2012; Schwartzentruber et al. 2012).

Tumors with *H3.1* mutations are associated with decreased survival compared to patients harboring *H3.3* mutations. Reduced survival has also been observed in patients with the *K27M* mutation compared to those with the *G34V/R* mutation which exhibit a slightly prolonged overall survival (Bjerke et al. 2013; Fontebasso et al. 2014b; Khuong-Quang et al. 2012; Sturm et al. 2012; Taylor et al. 2014; Wu et al. 2014). Although *G34V/R* tumors are more accessible by surgery, a dismal prognosis has been associated with patients bearing *K27M* tumors regardless of their location, indicating an extremely aggressive subtype of HGGs (Sturm et al. 2012).

The α-Thalassemia/Mental Retardation Syndrome X-Linked (ATRX) Mutations

The ATRX multiprotein chromatin remodeling complex that commonly involves the death domain-associated protein 6 (DAXX) participates in epigenetic regulation of chromatin assembly, nucleosome positioning and deposition of histone H3.3. The ATRX–DAXX complex facilitates heterochromatin H3.3 release at telomeres. Overall, H3.3 deposition is associated with the repression of telomeric RNA transcription and occurs near specific active genes (Goldberg et al. 2010). Loss-of-function *ATRX* mutations have been recently detected in different types of malignancies such as neuroblastomas, pancreatic neuroendocrine tumors and alpha-thalassemia as part of the ATRX syndrome.

Recent studies demonstrate the presence of ATRX mutations in pediatric HGGs being implicated in alternative telomere lengthening (Heaphy et al. 2011; Schwartzentruber et al. 2012). Primary GBM and oligodendroglial *IDH-CIC/FUBP1* mutants are also characterized by mutually exclusive telomerase reverse transcriptase (*TERT*) promoter mutations (*C228T*, *C250T*) which mediate telomere elongation (Table 1; Fig. 1). On the other hand, children with HGGs lack *TERT* promoter mutations, being possibly associated with age (Buczkowicz et al. 2014; Fontebasso et al. 2014b; Wu et al. 2014).

Isocitrate Dehydrogenase 1, 2 (IDH1, IDH2) Mutations

Although *IDH1* and *IDH2* mutations were (R132, R172) discovered in 70–80% of adult type II and III infiltrating gliomas, oligodendrogliomas and IDH-mutant GBMs, they are rarely detected in children with LGGs, possibly because LGGs do not often progress to develop high-grade tumors (Buccoliero et al. 2012; Park et al. 2017).

Genetic Mutations Associated with Medulloblastomas

Medulloblastomas being the most frequent pediatric brain tumors are classified into four subgroups based on their molecular profiling. These include Group 1 that is characterized of wingless (WNT)-associated alterations, Group 2 being associated with sonic hedgehog (SHH) alterations, Group 3 with MYC activation and Group 4 without a unifying pathway. The 80% of WNT medulloblastomas exhibit a deletion in chromosome 6 (monosomy 6) and mutations in the principal effector of WNT pathway, the *CTNNB1* gene that encodes for β-catenin 1 (Jones et al. 2012c; Pugh et al. 2012; Robinson et al. 2012). CTNNB1 is involved in chromatin remodeling by recruiting protein complexes to its C terminus and promotes gene transcription of WNT-related genes. In addition, *CTNNB1* gene mutations render β-catenin 1 resistant to proteolysis and allow its accumulation to the nucleus. This tumor subtype is often detected in older children with rare metastatic potential and excellent

prognosis (5-year disease-free survival >90%) (Table 1, Fattet et al. 2009; Gajjar et al. 2015).

Group 2 tumors comprise the 25% of medulloblastomas that arise in the cerebellar hemispheres with low metastatic potential in infants and adults (Gajjar et al. 2015). This subgroup harbors deletions of 9q and mutations in the sonic hedgehog (SHH) signaling pathway that normally starts with binding of SHH ligand to the receptor Patched 1 (PTCH1) which further results in derepression of smoothened (SMO) activity and activation of the transcription factors GLI. Mutations in *PTCH1* gene are commonly detected in this subgroup along with *TP53* mutations with a negative effect on prognosis compared to WNT-associated tumors. Interestingly, patients with SSH-associated tumors without a *TP53* mutation present with a far better prognosis (Gajjar et al. 2015).

Group 3 comprises approximately 25% of medulloblastomas with high metastatic potential and the worst prognosis of all previous subgroups (Taylor et al. 2014; Wells and Packer 2015). A multicentric study investigating molecular biomarkers on 673 medulloblastomas tissue microarray using FISH detected several gene alterations that characterize these tumors. These include amplification of *MYCC* (~17% of tumors), mutations of the transcription activator BRG1 gene *SMARCA4* and isochromosome 17q being the most frequent, with promoting effects over cell proliferation and associated with poor patients' prognosis (Gajjar et al. 2015).

Group 4 encompasses the majority of medulloblastomas rising up to 35%, being characterized by diversified molecular alterations without a clear-cut molecular profile (Jones et al. 2012c; Pugh et al. 2012; Robinson et al. 2012). Cytogenetic analysis from the above-mentioned multicentric study and others detected upregulation of isochromosome 17q and *MYCN* as the most common findings in Group 4 without, however, severely affecting prognosis (Gajjar et al. 2015; Shih et al. 2014; Wells and Packer 2015). In a study of 1087 medulloblastomas, tandem duplications of the Parkinson's disease gene *synuclein alpha interacting protein* (*SNCAIP*) were identified on chromosome 5, characterizing specifically this subgroup (Northcott et al. 2012).

Biomarkers

A series of biomarkers emerge as prognostic and predictive factors in subclasses of pediatric brain tumors (Table 1). Highly sophisticated genome-associated methods have been employed to retrieve molecular information from a confined subset of tissues. In order to evaluate the molecular profile of highly heterogeneous tumors such as HGGs and medulloblastomas, an overall profiling of the tumors is needed with modern high-throughput methods, such as next-generation sequencing and whole-exome sequencing (Huse and Rosenblum 2015; Staedtke et al. 2016).

Pediatric HGGs commonly harbor chromatin remodeling defects and specifically mutations in histone *H3F3A* with K27M substitution being present in 78% of DIPGs while one-third of non-brainstem HGGS carry *G34V/R* or *K27M* mutations (Venneti et al. 2013, 2014). The presence of these mutations has a prognostic role since they have been associated with poor outcome (Table 1). Mutations in *ATRX* and *TP53* are also frequently observed in HGGs and could have a diagnostic significance but with unclear predictive or prognostic value (Liu et al. 2012). *PDGFRA* mutations may also have a prognostic role in HGGs since they are relatively frequent and are commonly associated with poor patient's survival (Paugh et al. 2013).

LGGs on the other hand are mainly characterized by oncogenic activation of BRAF. The fusion gene *KIAA1549:BRAF* that is found in 50–70% of PAs is generated by tandem duplication at 7q34 leading to deregulation of MAPK signaling pathway and affecting cell proliferation, differentiation and apoptosis. Although the prognostic significance of this fusion gene is still unclear, there is some evidence of improved survival in some studies. Furthermore, the frequent *BRAF* alterations in PAs may have a diagnostic role in differentiating PAs from grade II gliomas. However, *BRAF V600E* mutations are found both in LGGs and in HGGs with limited diagnostic and predictive value (Staedtke et al. 2016).

Medulloblastomas have been linked to inherent molecular differences that have allowed their classification into the four main subtypes. WNT tumors are very frequently harboring *CTNNB1* mutations that affect WNT signaling and may possess both diagnostic and prognostic role with most often favorable survival of patients. SHH tumors are usually characterized by *PCTCH1* mutations that activate SHH signaling and may have a diagnostic role. However, other genetic aberrations are also found rendering SHH tumors rather heterogeneous. *TP53* mutations play a decisive role upon disease prognosis since SHH/TP53 mutant tumors have a very poor outcome. *MYCN* amplification may also play a prognostic role, often associated with reduced survival (Staedtke et al. 2016).

Epigenetic changes are also critical during development of pediatric gliomas and constitute a distinct set of biomarkers that characterizes subdivisions of these tumors (Hovestadt et al. 2014). For example, childhood ependymomas demonstrate a CpG island methylator phenotype (CIMP). Such DNA hypermethylation is mediated by the polycomb group of proteins and targets differentiation genes that are transcriptionally controlled by marks on H3K27. Agents against these alterations proved to be efficacious in vitro and in vivo (Mack et al. 2014).

Finally, the vascular endothelial growth factor (VEGF) that reflects enhanced tumor angiogenesis was recently acknowledged as a noninvasive circulating biomarker in children with brain tumors. Sobol-Milejska et al. (2017) reported significantly elevated VEGF expression in blood samples of 106 children diagnosed with brain tumors compared to the control group. VEGF expression has been also found upregulated in UW402 medulloblastoma cells upon hypoxia (Cruzeiro et al. 2017). In accordance, strong expression of VEGFR has been associated with gadolinium enhancement in MRI of pediatric patients with medulloblastomas, a feature with prognostic significance (Hervey-Jumper et al. 2014). Response from anti-VEGF treatment with the monoclonal antibody bevacizumab varies with radiographic and clinical improvement in low-grade gliomas, but with little clinical impact for high-grade gliomas and ependymomas. A logical reasoning is that bevacizumab should be tested at the time of the initial diagnosis rather than in recurrent pediatric brain tumors, since these tumors carry different oncogenic mutations that confer resistance to anti-angiogenic treatment (Sie et al. 2014).

Molecular Therapeutic Targeting of Pediatric Brain Tumors

Continuous research studies on the genetic background of pediatric brain tumors have identified several efficient molecular targets including MEK and BRAF V600E inhibitors such as vemurafenib, dabrafenib and trametinib (Table 1, Gajjar et al. 2015). Additionally, everolimus, an mTOR pathway inhibitor, had a beneficial treatment outcome in tuberous sclerosis-associated subependymal giant cell tumors (Krueger et al. 2013) and is currently evaluated in other low-grade brain tumors (Gajjar et al. 2015).

For HGGs, several innovative targeted approaches such as inhibitors for histone deacetylases, histone modifications, *BRAF V600E*, Ras/Akt pathway and telomerase are under investigation (Wells and Packer 2015).

O^6-alkylguanine DNA alkyltransferase (MGMT) pathway inhibitors have been used in HGGs in combination with temozolomide to sensitize tumors; however, their therapeutic relevance in children is still unclear. Immunotherapeutic approaches employing converted viruses or vaccines are currently investigated in adults with also a potential effectiveness to pediatric patients (Wells and Packer 2015).

Inhibitors of histone methyltransferase, EZH2 can be used for the treatment of medulloblastomas and ependymomas that exhibit elevated PRC2 activity (Dubuc et al. 2013; Mack et al. 2014; Robinson et al. 2012).

Furthermore, JQ, a BET bromodomain inhibitor was proved efficient in MYC-driven medulloblastoma models (Bandopadhayay et al. 2014) and in SMO inhibitor-resistant SHH medulloblastomas with potential efficiency in GFI1/1B-activated medulloblastomas (Northcott et al. 2014; Tang et al. 2014).

Additionally, an SMO inhibitor for efficient targeting of specific mutations upstream of SHH pathway is currently investigated. High-throughput screening has revealed the potential effectiveness of pemetrexed and gemcitabine for Group 3 medulloblastomas with the worst prognosis, being currently under clinical trial (Wu et al. 2014).

However, genomic profiling data are still in demand to elucidate any non-coding regions, structural alterations, transcriptome and epigenetic modifications of brain tumors. Genetic characterization of posterior fossa ependymomas and medulloblastomas (Groups 3 and 4) is highly demanded in order to improve patients' prognosis.

Conclusions

The molecular and genetic landscape of pediatric brain tumors is under extensive investigation and rapid evolution over the last years. Studies have successfully elucidated novel mutations and molecular pathways that have a significant role in pediatric neoplasia. Interestingly, different genes and molecular signaling cascades from those implicated in adult brain tumorigenesis have been detected leading to the requirement of different therapeutic strategies. The high sensitivity of children brains to the damaging effects of radiation urges the development of novel, less toxic and more effective regimes.

Although improvements in chemotherapy, radiation and neurosurgery techniques have advanced the survival of medulloblastoma patients, several other pediatric brain tumors such as primitive neuroectodermal tumors, high-grade gliomas and atypical rhabdoid/teratoid tumors still have a very poor prognosis.

Molecularly targeted agents that can work in association with conventional therapeutic strategies to reduce their toxicity present the future of these devastating neoplasms. High-throughput molecular and genetic studies focused on each tumor type are highly demanded to underpin their specific molecular profile in order to develop effective targeted therapeutic regimens.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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