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# Pediatric low-grade gliomas: How modern biology reshapes the clinical field

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ABSTRACT

Low-grade gliomas represent the most frequent brain tumors arising during childhood. They are characterized by a broad and heterogeneous group of tumors that are currently classified by the WHO according to their morphological appearance. Here we review the clinical features of these tumors, current therapeutic strategies and the recent discovery of genomic alterations characteristic to these tumors. We further explore how these recent biological findings stand to transform the treatment for these tumors and impact the diagnostic criteria for pediatric low-grade gliomas.



## 1. Introduction

Low-grade gliomas (LGGs) are the most common brain tumor of childhood accounting for 35% of all pediatric central nervous system tumors [1,2]. Pediatric LGGs (PLGGs), classified as World Health Organization (WHO) grade I or II [3] represent a heterogeneous group of tumors. PLGGs are classified according to the cellular aspect of the most important constitutive cell type, including astrocytic, oligodendroglial, mixed oligoastrocytic, neuronal, or mixed glioneuronal morphology (Table 1). Although this classification aims to encompass every tumor, a significant number of tumors do not meet the typical criteria for WHO categories or have overlapping histology for multiple categories. In clinical practice, these tumors are often given non-categorical diagnoses with varied and confusing terminology. As such the category of 'low grade glioma, non-otherwise specified' (LGG-NOS) has been formally utilized by several groups including ours as a clinical and research diagnosis for these histologically difficult to classify tumors.

Despite having a similar histological appearance to adult LGG, PLGGs have a distinct and more favorable course and should be considered a different disease entity. Indeed, the majority of children diagnosed with PLGGs are long-term survivors well into adulthood (Bandopadhayay et al., in press, Pediatric Blood and Cancer 2014), imploring treatment strategies that minimize long-term morbidities [4,5]. Therefore, it is crucial to understand the biology of PLGGs to allow the development of targeted therapies with less toxicity.

The explosion of novel technologies and multi-platform integrative genomics in recent years has yielded new insights into the oncogenesis of PLGGs. These findings not only bring a paradigm shift to the traditional histological classification of PLGGs but also reveal new therapeutic targets.

In this review, we highlight the biologic complexity of PLGGs, present current diagnostic and management dilemmas, and propose the natural evolution and augmentation of microscopic histological diagnoses with modern genomic profiles. Increased understanding of the molecular identity of these tumors will help drive the development of target-driven therapies.

## 2. Histopathologic classification

The WHO classifies low-grade gliomas according to their morphological features [3]. Tumors that do not meet the typical criteria of any single category are commonly labeled LGG-NOS for 'not-otherwise

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**Table 1**
Major different subtypes of pediatric low-grade gliomas according to the latest WHO classification.

| | Grade (WHO) |
|---|---|
| *Astrocytic tumors* | |
| Pilocytic astrocytoma (PA) | I |
| Pilomyxoid astrocytoma (PMA) | II |
| Diffuse astrocytoma (DA) | II |
| Pleiomorphic xanthoastrocytoma (PXA) | II |
| *Oligodendroglial oligoastrocytic tumors* | |
| Oligodendroglioma (OD) | II |
| Oligoastrocytoma (OA) | II |
| *Neuronal, mixed neuro-glial neuroepithelial tumors* | |
| Ganglioglioma (GG) | I |
| Desmoplastic infantile tumors | I |
| Dysembryoplastic neuroepithelial tumor (DNT) | I |
| Angiocentric glioma (AG) | I |

specified', which comprise more than a third of all PLGGs [6]. This sometimes results from small biopsy samples that lack sufficient material on which to assign a WHO grade, and at other times, as a result of pathologic features that do not fit any one category. PLGGs typically have a low proliferative index, with MIB-1 scores between 0.1 and 10% [7–11]. This index is often higher in younger children where MIB-1 index higher than 10% can be seen in true PLGGs. However, correlation to either overall or progression-free survival in most studies has been variable and it remains unclear as to whether there is any prognostic significance [7,12–20].

Grade I pilocytic astrocytomas (PAs) are classically characterized by the presence of Rosenthal fibers, biphasic architecture, vascular proliferation, and eosinophilic granular bodies [3]. Eosinophilic granular bodies are often located near cystic areas and may be implicated in cyst formation [21]. Less commonly, PAs contain regions of calcification [22]. Useful positive immunohistochemical markers include oligodendroglial markers OLIG2, myelin basic protein (MBP), platelet-derived growth factor (PDGF) [23–26] as well as the astrocytic marker Glial Fibrillary Acid Protein (GFAP), which is also considered a stem cell marker [27,28]. Gangliogliomas (GGs) are also grade I, and are characterized by perivascular chronic inflammation, granular bodies, binucleated neurons, calcification, and cystic degeneration [29]. DNTs and AGs are recently described subtypes also defined as grade I tumors. Dysembryoplastic neuroepithelial tumors (DNTs) include a specific entity characterized by GFAP-negative oligodendroglia-like cells and floating neurons with a mucinous eosinophilic background [30]. Angiocentric gliomas (AGs), initially described by Tubiana et al., also named angiocentric neuroepithelial tumors (ANET), encompass classically fusiform and bipolar astrocytic cells which stain positively for GFAP and S-100 arranged around blood vessels creating palisade-like structures [31,32]. Microcalcifications are infrequently present.

WHO grade II lesions include diffuse astrocytomas (DAs), pilomyxoid astrocytoma (PMAs), pleomorphic xanthoastrocytoma (PXAs), and oligodendroglial tumors. DAs are characterized by the presence of nuclear atypia, a low mitotic rate, and the absence of vascular proliferation or palisading necrosis. PMAs are characterized by astrocytic pleomorphism, significant cellular atypia, and multinucleated giant cells with intracellular lipid accumulation. PXAs consist of pleomorphic and lipidized cells and tend to follow a more aggressive course with an increased frequency of leptomeningeal disease [33,34]. Oligodendroglial tumors contain monomorphic cells with uniform round nuclei and perinuclear halos, microcalcifications and network of capillaries.

While the WHO classification remains the standard of care in clinical practice for determining management and prognosis, the use of histopathological classification alone has significant limitations in PLGG.

In this group of diseases the criteria are naturally limited by the overlap in histologic and clinical features in patients, inter-observer diagnostic variability, and the intrinsic challenge of tumor heterogeneity. As such the current approach provides little information on prognosis and treatment recommendations for individual patients. A more effective and predictive approach integrating pathology and molecular data emerging from recent genomic profiling is greatly needed. Such an integrative classification system based on the molecular signature of individual tumors is likely to be more accurate and reproducible in guiding diagnostic, prognostic, and management decisions.

## 3. Epidemiology

Brain tumors represent the most common solid tumor of childhood, of which PLGGs are the most frequent [35]. The annual incidence of PLGGs is 2.1 per 100,000 persons in the United States [36,37], accounting for 1600 new diagnosis each year. The relative incidence of each LGG histological subtype varies with age, with clear differences in distribution between pediatric and adult LGGs (Fig. 1). PAs most frequently develop during childhood and are extremely rare in adults. They represent the most common PLGG, accounting for 15% of all pediatric brain tumors [1,6,38–40] (Fig. 2). DAs, oligodendrogliomas and oligoastrocytomas are more common in adults but extremely rare in children, representing less than 5% of PLGG [10,6,27–29]. Similarly, neuronal and mixed glial–neuronal tumors occur more commonly in the pediatric population. Table 2 summarizes the frequency of the major PLGG subtypes reported in recent epidemiologic studies [6,38,39,41–43].

In addition to the defined groups of tumors, LGG-NOS tumors represent the second most prevalent diagnosis and have been reported to account for at least 17% of all PLGGs [6]. This is despite the fact that in most historical studies and governmental databases, this category is not included. This highlights the increasing need for integration of histology with molecular data to improve categorization of PLGG tumors.

Although PLGG tumors can occur anywhere throughout the CNS, different subtypes demonstrate predilection for specific sites within the brain or the spine [44]. Pediatric DAs, AGs, PXAs and oligodendrogliomas are most frequently supratentorial [45–48], GGs occur most frequently within the temporal lobes [17,18,49] while PAs tend to localize to the cerebellum or the brainstem [50]. A small fraction of PLGG can arise in the optical pathway as well as in the diencephalic/hypothalamic region; the incidence of those tumors is significantly higher in patients with neurofibromatosis type 1 (NF1). Five percent of all PLGG primary tumors

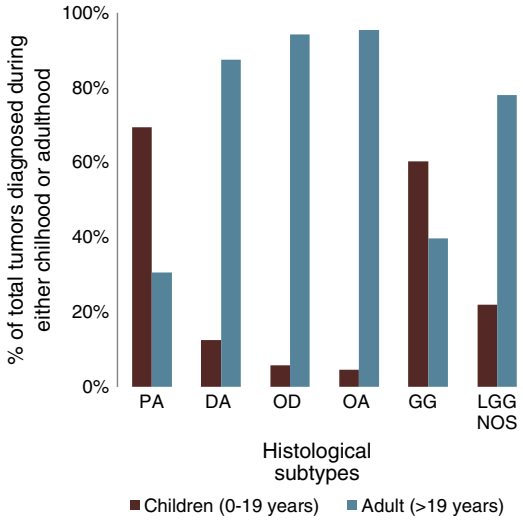


**Fig. 1.** Comparison of the distribution of histological subtypes developing during childhood (0–19 years) and adulthood, according to the CBTRUS Statistical Report, 2012.

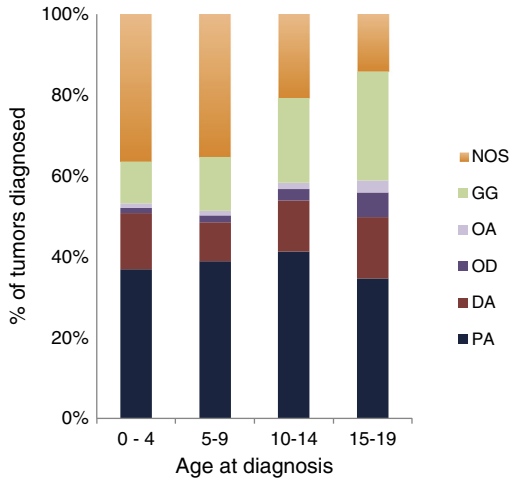


**Fig. 2.** Distribution of PLGGs histological subtypes during 4 stages of development, according to the CBTRUS Statistical Report, 2012.

are located in the spine and these are most frequently PAs [51]. PLGG can also develop in the cervicomedullary region [52] as well as in the tectum.

## 4. Genetic predisposition syndromes

Initial insight into the molecular characteristics of PLGGs was derived from the subset of non-sporadic tumors associated with genetic syndromes. Among these, the most frequent association is with NF1, also known as von Recklinghausen disease. PAs and DAs are the most common subtypes associated with NF1 [53] and most commonly involve the optic pathway and hypothalamus [54–56]. NF1 is characterized by a germline mutation of *neurofibromin 1* (*NF1*), located on chromosome 17q, which results in activation of the RAS/MAPK signaling pathway. Importantly, only 30% of the tumors become symptomatic and require treatment, which suggests a unique biology underlying these tumors [57,58].

Tuberous sclerosis (TS) is another neuro-cutaneous disorder with increased predilection for LGG, with brain tumors found in 5–14% of patients [59]. The most frequent brain tumor associated with TS is sub-ependymal giant cell astrocytoma (SEGA) [60]. TS is caused by mutations in two tumor suppressor genes, *TSC1* (hamartin, on chromosome 9q34) and *TSC2* (tuberin, on chromosome 16p13) [61]. These genes are part of the Rheb–mTOR pathways that function in regulation of cell proliferation.

These genetic syndromes contributed to our understanding of the importance of the Ras/mTOR pathway in the oncogenesis of PLGGs. Additional findings from recent genomic studies have added further insights into the vital role of this pathway in the pathogenesis of PLGGs.

## 5. Clinical presentation

The clinical presentation of PLGGs is dictated by their location. Tumors in the posterior fossa typically present with acute signs and symptoms of elevated intracranial pressure secondary to obstructive hydrocephalus, as well as cerebellar signs [62], whereas LGGs of the optic pathway impair vision. PLGGs affecting the cerebral cortex typically present with focal neurological manifestations such as seizures or behavioral changes. Seizures are particularly associated with temporal, frontal, or parietal localization and oligodendrogliomas, GG, DNT or AG subtypes [63–67]. Tumors involving the hypothalamus manifest with endocrinopathies or the diencephalic syndrome [68–70]. Tectal gliomas are often associated to hydrocephalus due to their expansion to the periaqueductal space. Compared to sporadic PLGGs, the clinical spectrum of NF1-related PLGGs diverges. NF1 patients more commonly present with multifocal tumors compared to sporadic cases [71].

PLGGs are most frequently localized at diagnosis, although they can present with disseminated disease. Leptomeningeal dissemination is reported in approximately 3–5% of children at presentation, especially in the setting of spinal cord or diencephalic/hypothalamic lesions [72–74], and may be associated with inferior overall survival compared to those who present with localized disease [75–77].

Radiological features of PLGGs are variable. These neoplasms are usually hypodense on CT compared to more malignant neoplasms. Grade I PLGGs are typically well-circumscribed tumors, with T1-hypointensity and T2-hyperintensity on MRI imaging. Following gadolinium administration, grade I astrocytomas usually demonstrate homogeneous enhancement. In contrast, grade II gliomas, especially DAs, are typically non-enhancing and may be less circumscribed [78–82]. PMAs express usually heterogeneous enhancement [82]. PLGGs are not usually associated with peri-tumoral edema or restricted diffusion on diffusion-weighted MRI sequences [83]. Magnetic resonance spectrometry (MRS), diffusion-weighted MRI (DWI) and diffusion tensor imaging (DTI) serve as useful adjuncts in further characterizing PLGGs. PET-scan and single-photon emission CT (SPECT) may also aid in the assessment of treatment efficiency and tumor recurrence. GGs typically exhibit contrast enhancement on CT scans and can have variable gadolinium enhancements on MRI — from the absence of contrast enhancement to nodular or circumferential. Similar to astrocytomas and oligodendroglial tumors, they appear T1-hypointense and T2-hyperintense on MRIs. The contrast enhancement for oligodendroglial tumors is variable and is related to the infiltrative aspect of the tumors with a higher gadolinium contrast enhancement in solid and non-invasive tumors. DNTs do not displace brain structures but tend to infiltrate and usually have low or no contrast enhancement. They appear as bright T2-weighted and hypointense T1 tumors with typically neither mass effect nor peritumoral edema. Their slow growth may be associated with skull deformation when located in the cortex.

## 6. Natural history

The natural history of pediatric LGGs is distinct from that of adult LGGs. On the whole, PLGGs exhibit slow rates of growth. Thus, the majority of children are diagnosed at least six months after symptom onset [84]. PLGGs have been reported to spontaneously regress, especially in patients with NF1 [85–89], who have been reported to have superior outcomes compared to sporadic cases [90–92]. Tumors that can be completely resected often require no further therapy highlighting the importance of location on outcome. In a recent prospective population-based study of a large cohort of 639 PLGGs, the 5-year PFS (progression free survival) was 69.4% [93], which is comparable to other studies [84,94–99]. Given the fact that two thirds of NF1 patients never progress, the recurrence rate of sporadic PLGGs is near 55%, as reported in the recent COG study [100]. The most significant risk factors for progression identified on multivariate analysis were young age at diagnosis (<1 year), subtotal resection, and DA histology [99]. Due in part to a better chance of complete resection, tumors involving the optic nerve or cerebellum have better progression-free survival (PFS) compared to those involving the chiasm and hypothalamus. Even if progression occurs, children diagnosed with PLGG have an excellent overall survival long-term, as described in a recent analysis of the SEER (Surveillance Epidemiology and End Results) database showing a 20 year overall survival of 87% (Bandopadhayay et al., in press, Pediatric Blood and Cancer 2014). In contrast to adults, PLGGs are characterized by a low incidence of malignant transformation [101–103]. Importantly, adult survivors of PLGG have low glioma related mortality, suggesting a very low propensity for malignant transformation of PLGG (Bandopadhayay et al., in press, Pediatric Blood and Cancer 2014).

## 7. Treatment strategies

Given the excellent overall survival for the majority of PLGG patients, the treatment goal is to achieve tumor control while minimizing

**Table 2**
Overview of six epidemiological studies including PLGGs performed in various countries around the world.

| | GRADE (WHO) | WHO International Classification of Diseases | USA | Germany | France | Denmark | Brazil |
|---|---|---|---|---|---|---|---|
| Reference | | [41] | [6] | [39] | [38] | [42] | [43] |
| Number of total CNS tumors | | 5200 | 20,709 | 3268 | 1017 | 911 | 1058 |
| Type of study | | Retrospective | Retrospective CBTRUS Statistical Report | Retrospective German Childhood Cancer Registry | Prospective French Brain Tumor Database | Retrospective Multi-institution | Retrospective Single-institution Hospital das Clinicas of Sao Paulo |
| Age | | 0–19 years | 0–19 years | 1–15 years | 0–19 years | 0–15 years | 0–21 years |
| Follow-up period | | 1980–1999 | 2005–2009 | 1990–1999 | 2004–2006 | 1960–1984 | 1974–2003 |
| Frequency of tumors (%) | | | | | | | |
| Astrocytic tumors | | | | 16.4 | | | |
| PA | I | 14.8 | 15.5 | | 23.1 | 16.5 | 18.2 |
| DA | II | 1.8 | 5.2 | NA | 1 | 13 | 6.2 |
| PXA | II | 0.4 | NA | | 0.3 | | |
| Oligodendroglial tumors | | | | | | | |
| Oligodendroglioma | II | 1.4 | 1.1 | 1.1 | 4 | 1.6 | 0.9 |
| Oligoastrocytic tumors | | | | | | | |
| Oligoastrocytoma | II | 0.6 | 0.7 | NA | 1.1 | NA | NA |
| Neural and mixed neuroglial tumors | | | | | | | |
| GG | I | 2.5 | | 3.2 | 4.6 | 2.2 | 3.6 |
| Desmoplastic infantile astrocytoma | I | NA | 7 | NA | 0.1 | NA | 0.3 |
| DNT | I | NA | | NA | 3.1 | NA | 1.3 |
| LGG-NOS tumors | I, II | 0.1–6 | 11.3 | NA | 1.8 | 0.4 | NA |

long-term tumor and treatment related morbidity [104]. Most patients require only surveillance after surgery. If progression, recurrence and/or symptoms occur, then treatment modalities including surgery, chemotherapy (including biologic therapy), or less frequently, radiation therapy are indicated.

Surgical resection remains the cornerstone of PLGG management. Patients with gross total resection of tumor typically do not need further treatment. However, gross total resection is not always achievable without significant neurological impairment for some tumor locations, such as the optic pathway, hypothalamus, diencephalon, and brainstem. In these instances, the goal of surgery is to achieve maximal resection without risking severe neurologic deficits. Even in the event of a subtotal resection, the overall survival of patients remains excellent (Bandopadhayay et al., in press, Pediatric Blood and Cancer 2014) [105–110].

Chemotherapy is usually initiated for radiological and/or symptomatic progression. Over the last few decades, many protocols using either monotherapy or poly-chemotherapy have been tried for PLGG, as shown in Table 3. Platinum-based chemotherapy such as carboplatin [111–113], cisplatin [114], oxaliplatin [115], iproplatin [116] alone or in combination with vincristine [117–124] or etoposide (VP16) [125] has been widely utilized and evaluated. The combination of vincristine and carboplatin is commonly used as first-line therapy, with 5-year overall and progression-free survival rates of 86 to 97% and 39 to 61% (Table 3). Carboplatin hypersensitivity is the most frequent adverse event [126–128], which can be effectively managed with pre-medication [35]. Ototoxicity is another issue that is important to monitor during treatment with platinum compounds. A combination of thioguanine, procarbazine, lomustine, and vincristine (TPCV) is another well-established chemotherapy regimen for progressive PLGG [129–131]. A prospective randomized clinical trial comparing outcomes of vincristine/carboplatin versus TPCV revealed that treatment with TPCV had a trend towards superior 5-year event-free survival (EFS) compared to vincristine/carboplatin (52% vs 39%, respectively), although this did not reach statistical significance [100]. However, the potential long-term morbidity associated with alkylating agents such as infertility and increased risk of secondary malignancy has led most oncologists to use vincristine/carboplatin as a first-line therapy over TPCV. Hematologic dyscrasias are other potential complications, especially of alkylating agents.

Alkylating agents have also been tested in combination with tamoxifen [132] or vinblastine [133] as well as in polychemotherapy regimens with other agents including procarbazine, cyclophosphamide, lomustine, vincristine, VP16 or 5-fluorouracile [134–137]. Monotherapy using temozolomide [138–141], vinblastine [142–144] or cyclophosphamide [145] has been used in progressive PLGGs with variable results in terms of outcome, depending on the ages of the children and the tumor locations enrolled in the studies.

Other protocols including vincristine/VP16 [146] or vincristine/carmustine [147] associated with intrathecal injection of methotrexate have shown 50–70% tumor control (defined as radiologic response or stable disease) in progressive PLGGs. Other chemotherapy regimens tested include vincristine alone [148], vincristine in combination with actinomycin [149], high dose ifosfamide [150], high dose cyclophosphamide [151], bleomycin [152], topotecan [153], idarubicin [154] or lenalidomide [155].

The anti-VEGF agent bevacizumab has recently been evaluated in combination with irinotecan for PLGG disease progression [156–158]. A recent phase II study which included 35 recurrent PLGGs reported at 2-year PFS of 47.8% using this treatment strategy [158]. Bevacizumab is generally well tolerated, however, patients need close monitoring for the development of hypertension or proteinuria and there are concerns for premature ovarian failure.

Radiation therapy was once standard-of-care for PLGG, however its use has decreased in PLGGs with increased awareness of its devastating long-term morbidities including cognitive deficits, increased risk of secondary high-grade malignancies, vasculopathy, endocrinopathy,

and effects on growth [159–161,214,215]. Given the excellent overall survival of children with PLGG and the numerous available chemotherapy regimens, the use of radiation therapy for PLGG is generally avoided to minimize long-term and irreversible morbidity, and is used for those in whom disease control cannot be achieved with either surgery or chemotherapy (including targeted therapies). Several protocols using conformal external beam radiotherapy at doses between 50 and 59 Gy have been reported in the treatment of non-operable or progressive PLGGs with 5-year PFS ranging from 74% to 88% [120,162–164]. Over the last decade, through the advances in radiotherapy techniques, significant progress has been made in minimizing scatter doses to normal brain. These techniques include stereotactic conformational external radiotherapy [165–167], gamma-knife stereotactic radiotherapy techniques [168–170] and proton beam radiotherapy [171,172].

While numerous treatment options for PLGG patients are available, all of these current approaches have acute and/or long-term toxicity, have frequent recurrences and are based on non-tumor specific mechanisms of action. With the development of new molecular technologies, the opportunity to dissect the molecular basis of PLGGs might assist in the improved classification of these lesions. More importantly, the identification of specific pathways also provides for the potential institution of tumor specific targeted therapy.

## 8. Genomic alterations in pediatric low-grade gliomas

### 8.1. General genomic features

Recent advances in high-throughput genetic sequencing and gene expression profiling have shed important insights into the genomic alterations of PLGGs [173]. Table 4 summarizes the major mutations and chromosomal rearrangements that have been described in different cohorts of PLGGs. One important limitation to these studies is the lack of

**Table 3**
Summary of the different chemotherapy strategies evaluated in PLGGs. CBP: carboplatin, VCR: vincristine, VP16: etoposide, CPP: cyclophosphamide, PC: procarbazine, CisP: cisplatin, 5-FU: 5-fluorouracile, TMZ: temozolomide, TPDCV: five-drug regimen consisting of 6-thioguanine, procarbazine, dibromodulcitol, 1-(2-chloro- ethyl)-3-cyclohexyl-1-nitrosourea (CCNU), and vincristine, TPCV: thioguanine, procarbazine, lomustine, and vincristine, BCNU: carmustine, MTX-IT: intrathecal injection of methotrexate, CR: complete response, PR: partial response, MR/SD: minor response/stable disease, PD: progressive disease, OS: overall survival, PFS: progression free survival.

| Regimen course | Reference | Study length | Number of patients | Eligibility | | CR (%) | Response | | PD (%) | OS | | PFS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | First line | Recurrence/progression | | PR (%) | MR/SD (%) | | Year | % | Year | % |
| CBP–VCR | [117] | NA | 60 | Yes | Yes | 2 | 37 | 50 | 11 | NA | | NA | |
| | [118] | 1989–1993 | 78 | Yes | Yes | 5 | 28 | 60 | 6 | 3 | 97 | 3 | 68 |
| | [119] | NA | 9 | Yes | No | 0 | 55 | 45 | 0 | NA | | NA | |
| | [120] | 1996–2004 | 123 | Yes | No | 2 | 6 | 76 | 7 | 5 | 97 | 5 | 61 |
| | [121] | 1996–2006 | 16 | Yes | Yes | 6 | 50 | 38 | 6 | NA | | NA | |
| | [100] | 1997–2000 | 137 | Yes | Yes | CR/PR:35 | | 32 | 33 | 5 | 86 | 5 | 39 |
| CBP/VP16 | [135] | NA | 10 | Yes | Yes | 20 | 10 | 70 | 0 | NA | | NA | |
| CPP/VCR | | | | | | | | | | | | | |
| Lomustine/PC/VCR | | | | | | | | | | | | | |
| PC/CBP | [134] | 1990–1998 | 85 | No | Yes | 0 | 42 | 45 | 13 | 5 | 89 | 5 | 34 |
| VP16/CisP | | | | | | | | | | | | | |
| VCR/CCP | | | | | | | | | | | | | |
| CBP/VP16 | [125] | NA | 13 | Yes | No | 8 | 0 | 70 | 22 | NA | | NA | |
| CBP/tamoxifene | [132] | NA | 13 | Yes | No | 0 | 15 | 69 | 15 | 3 | 69 | 3 | 47 |
| CBP/vinblastine | [133] | 2006–2008 | 26 | Yes | Yes | 0 | 5 | 81 | 14 | NA | | NA | |
| CBP or iproplatin | [116] | 1986–1990 | 12 | Yes | Yes | 0 | 0 | 75 | 25 | NA | | NA | |
| CSP/VCR | [123] | 1991–2000 | 34 | Yes | No | 3 | 32 | 65 | 0 | 3 | 100 | 3 | 78 |
| | [124] | 2001–2007 | 37 | Yes | No | 0 | 47 | 20 | 33 | 3 | 97 | 3 | 65 |
| CBP | [111] | NA | 6 | No | Yes | 0 | 0 | 100 | 0 | NA | | NA | |
| | [112] | 1992–1996 | 12 | No | Yes | 0 | 33 | 50 | 17 | 3 | 83 | NA | |
| | [113] | 1993–2000 | 81 | No | Yes | 2 | 21 | 62 | 15 | 3 | 84 | 3 | 64 |
| CisP | [114] | 1992–2007 | 16 | No | Yes | 0 | 25 | 31 | 44 | 5 | 94 | 5 | 56 |
| Oxaliplatin | [115] | 2004–2006 | 9 | No | Yes | 0 | 0 | 38 | 62 | NA | | NA | |
| CisP/VCR | [122] | 1992–2008 | 15 | No | Yes | 7 | 53 | 40 | 0 | NA | | NA | |
| VP 16–VCR | [146] | NA | 20 | Yes | Yes | 0 | 0 | 71 | 29 | NA | | NA | |
| VCR/VP16/CPP/5-FU | [136] | 1999–2004 | 13 | No | Yes | 8 | 38 | 23 | 31 | 6 | 100 | 6 | 67 |
| TMZ | [138] | 1998–1999 | 22 | No | Yes | 0 | 5 | 95 | 0 | NA | | NA | |
| | [139] | 1999–2005 | 30 | No | Yes | 0 | 10 | 43 | 47 | 4 | 71 | 4 | 17 |
| | [140] | 1999–2005 | 13 | No | Yes | 15 | 23 | 23 | 38 | NA | | 3 | 57 |
| | [141] | 2000–2006 | 28 | No | Yes | NA | NA | NA | NA | 2 | 71 | NA | |
| TPDCV | [130] | 1984–1992 | 42 | Yes | Yes | 0 | 36 | 59 | 5 | 5 | 78 | NA | |
| | [131] | 1984–1992 | 33 | Yes | Yes | 0 | NA | NA | 76 | 15 | 71 | 15 | 23 |
| TPCV | [129] | NA | 10 | No | Yes | NA | NA | 78 | NA | NA | | NA | |
| | [100] | 1997–2000 | 137 | Yes | Yes | CR/PR:30 | | 36 | 34 | 5 | 87 | 5 | 52 |
| BCNU/VCR/MTX-IT | [147] | NA | 6 | NA | NA | NA | NA | 50 | NA | NA | | NA | |
| Vinblastine | [142] | NA | 9 | No | Yes | 11 | 56 | 22 | 11 | NA | | NA | |
| | [143] | 2002–2009 | 51 | No | Yes | 2 | 34 | 38 | 26 | 5 | 93 | 5 | 43 |
| CPP | [145] | 1996–1997 | 15 | No | Yes | 7 | 0 | 57 | 36 | NA | | NA | |
| CBP/VCR | [137] | 1985–2009 | 38 | No | Yes | NA | NA | NA | NA | 5 | 86 | 5 | 37 |
| VCR/VP16 | | | | | | | | | | | | | |
| TPCV | | | | | | | | | | | | | |
| Vinblastine | | | | | | | | | | | | | |
| Bevacizumab/irinotecan | [156] | 2006–2008 | 10 | No | Yes | 11 | 44 | 45 | 0 | NA | | NA | |
| | [157] | 2007–2010 | 11 | No | Yes | 0 | 63 | 0 | 37 | NA | | NA | |
| Nimotuzumab | [265] | 2005–2007 | 4 | No | Yes | 0 | 0 | 50 | 50 | NA | | NA | |
| Erlotinib/rapamycin | [262] | 2007–2010 | 21 | No | Yes | 0 | 6 | 35 | 59 | NA | | NA | |
| Everolimus | [263] | 2009–2010 | 28 | No | Yes | 0 | 75 | 25 | 0 | NA | | NA | |

sufficient tumor tissue from rarer subtypes of PLGGs such as tectal gliomas, thalamic and optic pathway tumors.

A striking finding of PLGGs is the low number of genetic alterations present in the tumors. Early cytogenetic studies revealed almost normal diploid karyotypes across multiple subtypes of PLGGs [174–176]. The most frequent recurrent chromosomal alteration identified was a gain of chromosome 7, especially in PAs [174,177–179]. Other chromosomal structural abnormalities included gains of chromosomes 4, 5, 6, 8, and 11 and deletion of 17p in a subset of PAs, inversion in chromosome 8, and loss of chromosome 1q [174,177–185].

Genetic alterations in pediatric LGGs differ from adult LGGs. Concomitant deletion of chromosome 1p and 19q is one of the most frequent recurrent genetic alterations in adult oligodendrogliomas, aiding in diagnosis as well as serving as a favorable prognostic marker [186,187]. In contrast, concomitant deletion of chromosomes 1p and 19q is rare in children with oligodendrogliomas [188,189], and does not confer similar chemosensitivity when present [190]. Similarly, mutations in TP53, a tumor suppressor gene that codes for a nuclear phosphoprotein and regulates cycle cell arrest, apoptosis, and genetic stability, are frequently found in adult but rarely in pediatric LGGs [191–196]. IDH1 and IDH2 mutations are also rarely observed in PLGGs while they are frequent in adults. In a recent study examining *IDH1* and *IDH2* in 445 CNS tumors and 494 non-CNS tumors, *IDH1/2* mutations were described to occur with a frequency of more than 70% in adult patients across a variety of glial tumors including low-grade astrocytomas, anaplastic astrocytomas, oligodendrogliomas and oligoastrocytomas and secondary glioblastomas derived from the lower-grade gliomas [197]. In contrast, *IDH1/2* mutations are rare in children, although when found in adolescent patients they may be a harbinger of the adult form of the disease, meriting concordant treatment recommendations [198,199].

### 8.2. NF1

The increased risk of LGGs in children with NF1 was one of the first clues that dysregulation of the mitogen-activated protein kinase (MAPK) pathway may be important in the pathogenesis of PLGGs. *NF1* encodes neurofibromin, which is ubiquitously expressed at variable levels in different tissue types during development. Structurally, neurofibromin contains a central domain homologous to Ras-GTPase-activating (Ras-GAP) proteins and acts as a negative regulator of the Ras–Raf–MEK–ERK pathway [200]. In neurofibromatosis, *NF1* mutations produce a loss of function of neurofibromin that leads to the constitutive activation of the Ras pathway and results in the proliferation of astrocytes [35], among other phenotypes. Thus, MAPK pathway activation has long been known to contribute to the pathogenesis of LGGs in NF1 patients [201]. In addition, constitutive expression of MEK1 causes an increase in astrocytic proliferation.

### 8.3. BRAF duplication–fusions

Genetic rearrangements of the oncogene *BRAF* are the most common genomic alterations found in sporadic PLGGs. Early studies utilizing comparative genomic hybridization (CGH) identified a gain of the specific chromosomal region 7q34 containing the *BRAF* locus as the most frequent copy number alteration in PLGGs [35], involving 50–100% of pediatric PAs [202–204]. The *BRAF* duplication is found more frequently in cerebellar and hypothalamic–chiasmatic tumors [204].

The 7q34 gain has been characterized to represent a duplication of *BRAF* with a tandem insertion in the *KIAA1549* gene [35]. This BRAF duplication results in the activation of the downstream effectors of the MAPK pathway, MEK and ERK [205,206]. Subsequently, variants of the fusion transcript involving *BRAF* gene have been described, involving not only *KIAA1549* but also other fusion partners, *SRGAP3*, *FAM131B*, MACF1, RNF130, CLCN6, MKRN1 and GNAI1 (Table 5) [207–212]. *RAF1*, which encodes a protein that leads to the stabilization and activation of *BRAF*, has also been described to harbor gene fusions with *SRGAP3* and *QK1*, leading to the constitutive activation of MAPK pathway [207,209,211]. These *BRAF* rearrangements tend to occur frequently in cerebellar lesions, Strikingly, all of the fusion protein variants are characterized by loss of the N-terminal inhibitory domains of BRAF, resulting in constitutive activation of the BRAF kinase and downstream activation of MAPK and its effectors, MEK and ERK.

Although the BRAF fusion protein has been shown to result in a tandem duplication of the *BRAF* locus, further studies are necessary to explain the precise mechanism by which the fusions contribute to the formation of tumor and the specific role of KIAA1549 and SRGAP3 segments within the BRAF fusion transcripts. One recent study reported that regions flanking the breakpoints of the RAF gene fusion are enriched with microhomologous sequences. This has led to the hypothesis that tandem duplications of the *RAF* gene might be generated by microhomology-mediated break-induced replication [213]. In vitro evaluation of the effect of the BRAF fusion protein has suggested that this protein has oncogenic properties and is able to activate the MAPK pathway. The short form of KIAA1549-BRAF fusion induces anchorage-independent growth in multiple cell lines [209,214]. Furthermore, pharmacologic inhibition of MEK1/2 in short-term cultured PLGG cell lines significantly diminishes cell proliferation [205], supporting a role of the MAPK pathway in promoting proliferation. Taken together, *BRAF* and *RAF1* fusion transcripts, leading to constitutive activation of MAPK pathway, may play a crucial role in the pathogenesis of sporadic PAs and may also present potential therapeutic targets for PLGGs.

### 8.4. BRAF V600E and other less frequent mutations

Another frequent genomic alteration in PLGGs is the BRAF V600E mutation [167], which also results in deregulation of the MAPK pathway [35]. This mutation has been described in other cancer subtypes, including melanoma [215], colorectal cancer [216], leukemia [217], and high-grade gliomas [218]. BRAF is one of the most mutated genes in cancer [219]. The BRAF V600E point mutation occurs most commonly in PXAs, GGs, DAs, and PMAs [194,207,211,212,220–223] and is only rarely detected in PAs [224]. Thus BRAF duplications and V600E point mutation are almost always mutually exclusive. The *BRAF* V600E alteration confers constitutive BRAF kinase activation, and transforms NIH3T3 fibroblasts in vitro [209]. Other rare forms of small amino-acid insertions in *BRAF* have been identified in PAs [212]. The BRAF V600E mutation has been shown to promote transformation of human neural stem cells, followed by senescence [225]. However, it remains unclear whether this recurrent alteration is sufficient to drive the development of PAs.

### 8.5. Other mutations and rearrangements involving the MAPK pathway

Recent landmark sequencing projects including large cohorts of PLGGs identified recurrent genomic alterations in fibroblast growth factor receptor type 1 (FGFR1) [211,212]. *FGFR1* genomic alterations have also been described in breast cancer, lung cancer, and glioblastomas. *FGFR1* point mutations (N546K and K656E) were found in 5% of supra-tentorial PAs. Both mutations have been described to transform cells in vitro. In 2% of cases, *FGFR1* mutations were associated with the presence of a *PTPN11* mutation, another downstream effector of FGFR1 [212]. In the same study, one PA possessed a tandem duplication of *FGFR1*. Importantly, gene expression analysis revealed that FGF2, a ligand of FGFR1, was significantly over-expressed in PAs compared to other astrocytic tumors, suggesting that the FGF/FGFR pathway alteration plays an important role in tumorigenesis of PLGGs. Additionally, *FGFR1* mutations and duplication of its tyrosine kinase domain have also been described in PAs, DAs, and DNTs [211].

Alterations of other MAPK members have also been described in PLGG. These include genomic alterations affecting the kinase domain

of neurotrophic tyrosine kinase type 2 (*NTRK2*), which have been described in pediatric PAs [212]. Finally, *KRAS* activating mutations have also been described in 3–5% of sporadic PAs [207,211,212,226,227] (Table 2).

### 8.6. PI3K and RTK signaling

After the MAPK pathway, the other most frequently altered pathways in PLGGs include the phosphatidylinositol 3-kinase (PI3K)/AKT/

**Table 4**
Summary of all the major mutations described in PLGGs.

| Reference | Number of tumors analyzed | Mutation | Histology |
|---|---|---|---|
| [226] | 21 | KRAS | 5% PA |
| [227] | 25 | KRAS | 4% LGA |
| [214] | 44 | KIAA–BRAF dup (3 fusion types) | 66% PA |
| [209] | 44 | SRGAP3–RAF1 dup | 7% PA |
| | | BRAF V600E | 2% PA |
| [204] | 36 | BRAF V600E | 20% GG |
| [207] | 50 | KIAA–BRAF dup (6 fusion types) | 94% PA |
| | | | 9% DA |
| | | | 22% PM |
| | | SRGAP3–RAF1 dup | 3% PM |
| | | BRAF V600E | 9% DA |
| | | | 100% PXA |
| | | KRAS | 3% PA |
| [206] | 28 | KIAA–BRAF dup | 77% PA |
| | | | 50% DA |
| [194] | 117 | BRAF V600E | 57% GG |
| | | | 23% NOS |
| | | | 2% PA |
| | | MYC | 2% PA |
| | | | 7% GG |
| | | PIK3CA | 2% PA |
| | | | 2% NOS |
| | | CUBN | 4% PA |
| | | CTNNB1 | 2% PA |
| | | TP53 + PKHD1 | 2% NOS |
| | | PDGFRA | 2% NOS |
| [126] | 79 | KIAA–BRAF dup (3 fusion types) | 60% PA |
| [221] | 27 | BRAF V600E | 25% PXA |
| | | | 50% GG |
| [223] | 133 | BRAF V600E | 9% PA |
| | | | 69% PXA |
| | | | 13% GG |
| [222] | 11 | BRAF V600E | 64% PXA |
| [208] | 106 | KIAA–BRAF dupl | 60% PA |
| | | (5 fusion types) | 24% NOS |
| | | | 36% GN |
| | | | 33% PMA |
| [199] | 24 | IDH1 mutation | 1 OA |
| [240] | 45 | KIAA–BRAF dup | 22% GG |
| | | | 10% NOS |
| | | BRAF V600E | 75% GG |
| | | | 71% NOS |
| | | | 36% DA |
| | | MYBL1 rearrangement | 28% DA |
| [211] | 148 | KIAA–BRAF dup | 76% PA |
| | | | 11% GG |
| | | BRAF–MACF1 dup | 11% GG |
| | | RAF fusions | 2% PA |
| | | NF1 mutation | 2% PA |
| | | | 3% DA |
| | | V600E mutation | 5.5% PA |
| | | | 70% PXA |
| | | | 33% GG |
| | | | 12% DA |
| | | FGFR1 duplication (TDK) | 24% DA |
| | | | 3% PA |
| | | | 100% DNT |
| | | FGFR1–TACC1 translocation | 1% PA |
| | | | 9% DA |
| | | FGFR1 mutation | 2% PA |
| | | | 3% DA |
| | | KRAS mutation | 1% PA |
| | | | 3% DA |
| | | MYB/MYBL1 rearrangements | 21% DA |
| | | | 100% AG |
| | | IDH1 mutation | 3% DA |
| | | H3F3A mutation | 9% DA |
| | | NTRK2 fusion–NAV1 | 3% DA |
| [212] | 96 PA | KIAA–BRAF dup | 70% |

**Table 4** (*continued*)

| Reference | Number of tumors analyzed | Mutation | Histology |
|---|---|---|---|
| | | BRAF other rearrangements (-FAM131B, -RNF130, -CLCN6, -MKRN1, -GNAI1) | 5.5% |
| | | BRAF ins599T | 1% |
| | | BRAF p.R506 insVLR | 1% |
| | | V600E mutation | 4% |
| | | KRAS point mutations | 2% |
| | | NTRK2 fusions (QKI or NACC2) | 3% |
| | | FGFR1 mutations | 5% |
| | | FGFR1 tandem duplication | 1% |
| | | PTPN11 mutation | 2% |
| | | H3F3A mutation | 1% |

mammalian target of rapamycin (mTOR) pathway, the epidermal growth factor receptor (EGFR) pathway, sonic hedgehog (SHH) signaling, and the vascular endothelial growth factor (VEGF) signaling pathway.

PI3K is an intracellular protein that is recruited to the cell membrane after stimulation of a transmembrane growth receptor such as EGFR or platelet derived growth factor receptor A (PDGFRA — which also signals along the Ras–Raf–MEK–MAPK pathway), resulting in the activation of downstream effectors, such as AKT and mTOR, to induce cell proliferation and inhibition of apoptosis. As initially suggested by early studies of tuberous sclerosis, the activation of mTOR through mutations of its upstream inhibitor results in increased predisposition for PLGGs, in particular the SEGA subtype. In a series of PLGG, 44% of tumors were demonstrated to have evidence of PI3K/Akt/mTOR pathway activation [35]. Over-expression of the BRAF-fusion transcript in neural stem cells results in the activation of mTOR pathway, leading to the formation of glioma-like lesions and further supports the cross communication between these two pathways [228]. Additionally, the deregulation of Rheb and further mTOR activity in TS patients is another important insight for the role of MAPK pathway in PLGGs as mTOR pathway is connected to the MAPK pathway. In contrast, MEK1/2 knockdown in mice results in the absence of glial cell differentiation and proliferation [229].

The activation of the EGFR pathway has been shown in a small series of PLGGs. Comparative genomic hybridization and fluorescent in situ hybridization (FISH) studies of six disseminated PLGGs demonstrated EGFR amplification, while none was observed in a cohort of localized tumors. This led to a speculation that deregulation of the EGFR pathway may play a role in the pathogenesis of disseminated PLGGs [230]. Additionally, rare mutations of PDGFRA have been reported in PAs, GGs, and LGG-NOS tumors [194].

**Table 5**
Summary of the different fusion types of BRAF and RAF1 described in PLGGs.

| KIAA–BRAF duplication–translocation | Reference |
|---|---|
| KIAA Ex 15–BRAF Ex 9 | [214,209] [207] |
| KIAA Ex 16–BRAF Ex 11 | [206] [126] |
| KIAA Ex 16–BRAF Ex 9 | [208] |
| KIAA Ex 15–BRAF Ex 11 | [208] |
| KIAA Ex 17–BRAF Ex 10 | |
| KIAA Ex 16–BRAF Ex 10 | [259] |
| RAF1 duplication–translocation | |
| SRGAP3 Ex 11–RAF1 Ex8 | [207] |
| SRGAP3 Ex 12–RAF1 Ex10 | [209] |
| SRGAP3–RAF1 QK1–RAF1 | [211] |
| Other fusion types | |
| FAM131 B–BRAF | [210] [212] |
| MACF1–BRAF | [211] |
| RNF130 Ex 3–BRAF Ex 9 | [212] |
| CLCN6–BRAF (intrachromosomal) | |
| MKRN1–BRAF | |
| GNAI1–BRAF | |

Although the sonic hedgehog pathway is most commonly associated with tumorigenesis of medulloblastoma and high-grade gliomas [231,232], a recent study suggests that this pathway could play a role in a subset of pediatric PAs via the over-activity of *PTCH* [233]. In this series of 20 pediatric PAs, 45% of tumors demonstrated over-expression of *PTCH* mRNA. Interestingly, a significant inverse correlation between *PTCH* expression level and patient age suggests that the SHH pathway is more frequently activated in young patients.

Finally, the potential role of angiogenesis is highlighted through studies involving the VEGF pathway, one of the major signaling pathways in cancer biology, contributing to neovascularization which is essential for tumor growth [35]. Comparative analysis of vessel architecture in 59 pediatric PAs and adult high-grade gliomas showed that vessel immaturity and instability are present in both tumor types [234]. Another study of 17 pediatric PAs demonstrated immunohistochemical reactivity for activated VEGF receptors. However, further validation studies are necessary to confirm altered VEGF signaling in pediatric PAs.

### 8.7. Transcription factors

Genomic alterations affecting key transcription factors have been described in PLGGs. These include *MYB* amplification in DAs and focal deletions of *MYB* in AGs [235]. *MYB* is an oncogene that is mutated or altered in T-ALL [236,237], breast cancer, pancreatic cancer, and CNS tumors, including primitive neuroectodermal tumors and medulloblastoma [238,239]. In PLGGs, *MYB* expression has been shown to be up-regulated in a proportion of diffuse LGGs (60%) and PAs (41%). Its role in the normal development of the CNS and tumorigenesis remains unknown.

More recently, a novel recurrent genetic rearrangement involving another member of the MYB transcription factor family, *MYBL1*, was identified in a cohort of grade II DAs and AGs [211,240]. Importantly, this specific duplication–truncation of *MYBL1* has demonstrated tumorigenic properties in vitro.

### 8.8. Epigenetic analysis of pediatric low-grade gliomas

Aberrant epigenetic regulation has been increasingly described in human cancers and has become a major focus in a number of pediatric cancers [241]. Epigenetic regulation of the genome can be defined as heritable modifications in gene expression that do not directly affect the DNA sequence [242]. Epigenetic modifications include multiple mechanisms affecting the chemical properties of DNA, histones, or other proteins involved in DNA packaging [243]. The frequency of alterations in epigenetic modifiers in cancer has been shown in multiple cancer types including hematologic tumors [244,245], Wilm's tumors [246], retinoblastoma [247], neuroblastoma, thyroid carcinoma, hepatocellular carcinoma, sarcoma [248], and brain tumors such as medulloblastoma [249] and atypical teratoid rhabdoid tumors (ATRTs) with *SMARCB1* mutations [250,251].

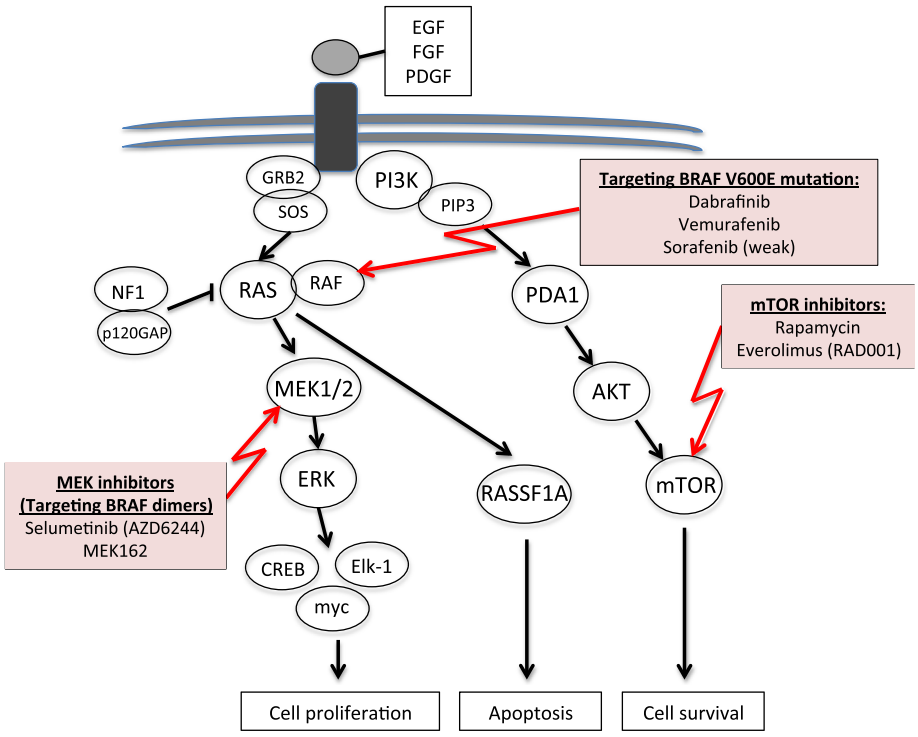


**Fig. 3.** Targeted therapies currently in evaluation for PLGG treatment.

The evidence that epigenetics is a major factor in pediatric glioma biology is extremely strong. Direct mutations in the chromatin modifier H3F3A have been described in pediatric GBMs [252] as well as DAs and PAs [211,212]. This suggests that dysregulation of chromatin remodeling effectors is also acting with genomic alterations in the tumorigenesis of a subset of PLGGs. Other genomic alterations include HIPK2 genomic gains and increased mRNA expression level in a subset of sporadic PAs arising from the cerebellum [202,253] and BCR gene rearrangement in one PMA [254].

The role of epigenetic dysregulation of tumor suppressor gene expression has been described in multiple adult LGGs. Several lines of evidence also support a role of epigenetics in PLGGs. First, the spectrum and frequency of mutations in PLGGs is limited, compared to adult tumors [240,250]. Moreover, most of these mutations are not oncogenic independently. Recent in vivo studies suggest that *BRAF* alterations in gliomas are not sufficient to induce tumor formation. Additionally, the natural history of PLGGs suggests regulation in addition to somatic DNA mutations that controls PLGG tumor behavior. PLGGs appear to enter growth arrest after the teenage years, which are unlikely to be driven by somatic changes. These mechanisms remain to be characterized in PLGGs. Thus, epigenetic profiling of PLGGs presents great potential to further the understanding of the pathophysiology underlying these heterogenic and poorly understood tumors.

### *8.9. Prognostic implications*

Recently attempts have been made to correlate specific genomic alterations to clinical outcome with controversial results. A multivariate analysis of 146 patients reported that the presence of KIAA1549-BRAF fusion protein was the most significant favorable prognostic factor in pediatric PAs following subtotal resection [255]. Another study including 106 PLGGs, most of which were sporadic PAs, showed no statistical superior progression-free survival rates among tumors with the BRAF-duplication compared to the wild-type tumors [208]. The observation that BRAF duplicated tumors behave differently than the others remains an open question, especially with the recent discovery of new BRAF fusion types that might have biased the previous studies. Further larger and controlled or prospective analyses are needed to address this question. It has been hypothesized that improved outcome in PAs conferred by the BRAF duplication may be due to oncogene-induced senescence (OIS), which occurs through the activation of p16Ink4a pathway [256]. OIS is a mechanism of tumor suppression that has been implicated in other cancer subtypes [257]. In contrast, p16 deletion has been identified as a negative prognosticator in 198 PLGG [258]. This remains to be further validated. Similarly, a recent study performed on GGs has showed that the presence of the V600E point mutation was associated with significant lower recurrence-free survival [259]. The recent discovery of other genomic alterations such as FGFR1 mutations will also enlarge the field of exploration between clinical outcome and biology.

### *8.10. Towards new therapeutic approaches*

Our recent increase in understanding the genomic alterations of PLGGs has expanded standard therapeutic approaches into targeted therapies. The identification of frequent and recurrent alterations of BRAF resulting in MAPK pathway activation across many PLGGs offers great potential as a therapeutic target. There are currently three drugs, which target various members of the MAPK pathway undergoing evaluation for a potential role in PLGG treatment (Fig. 3). The first two agents, vemurafenib and dabrafinib are BRAF inhibitors currently in early phase clinical trials for PLGGs that harbor the BRAFV600E mutation. The BRAF inhibitor sorafenib is another commercially available albeit a weak BRAF inhibitor. Based on the known MAPK feedback loops that regulate BRAF inhibition, patients with the V600E mutation, which signal as monomers, should be very sensitive to BRAF inhibitors. By contrast, when these same compounds are used to down-regulate BRAF dimers, they cause a paradoxical amplification in signaling due to these feedback loops and thus would be expected to stimulate tumor growth rather than inhibit it [260,261]. Treating PLGG patients with BRAF inhibitors should therefore not be undertaken until the tumor has been profiled and the appropriate targets identified. The second group, MEK1/2 inhibitor, which prevents the feedback inhibitory loop that results from BRAF targeted agents as discussed above, is currently being evaluated in early phase clinical trials for PLGGs with

the *BRAF* duplication. The third group include the mTOR inhibitors rapamycin and everolimus which have also been used in PLGGs. Rapamycin has also been used in combination with erlotinib, an anti-EGFR agent, in a cohort of 21 progressive PLGGs, with limited clinical benefit with only 6% partial response (PR) and 35% residual disease/stable disease (RD/SD) [262]. Single-drug therapy using everolimus, an mTOR targeted agent, has recently been successfully used in the treatment of pediatric subependymal giant-cell astrocytomas in TSC and is now approved for this indication [263,264].

EGFR pathway activation in a subset of PLGG has also brought insights to evaluate anti-EGFR targeted agents in those tumors. A pilot study using nimotuzumab in 4 PLGGs reported partial responses [265]. The recent discovery of FGFR1 alterations in PAs and other PLGG subtypes represents another potential target in the treatment of those tumors. Preclinical and early phase trials using a FGFR1 targeted agent, dovitinib (TKI258) in FGFR1 amplified breast cancer models has already shown antitumor activity [266]. Functional validation in PLGG models or in early clinical trials is needed to support the role of these genomic alterations in PLGG tumorigenesis.

Although the identification of genomic alterations represents a major milestone in the biology of PLGGs, many unanswered questions remain. Further investigation is needed to unveil the mechanisms that govern the unique clinical course of PLGGs, notably their lack of malignant transformation and quiescence after attaining adulthood. In addition to genomic alterations, epigenetic mechanisms, which vary with development, may potentially influence the growth of PLGGs. One major caveat to move forward is the lack of relevant preclinical model.

## 9. Conclusions

Low-grade gliomas, the most common brain tumor of childhood, encompass a heterogeneous group of WHO grade I and II tumors. Although they are associated with excellent overall survival rates, children can suffer morbidity from both the tumor and therapy. The striking predominance of the RAS/RAF/MAPK pathway alteration in PLGG tumorigenesis may help redefine traditional histopathological classifications and also represents exciting new avenues for the development of novel targeted therapies. Many unanswered questions remain regarding the biology of these tumors. Further analysis of the interplay between genetic, epigenetic alterations, and clinical behavior across a larger number of PLGGs will hopefully fill some of these remaining gaps.

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