Published in final edited form as:

Biochim Biophys Acta. 2014 April ; 1845(2): 294–307. doi:10.1016/j.bbcan.2014.02.004.

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

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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 II³ 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 a PLGGs are long-term survivors well into adulthood (Bandopadhyay et al, in press, *Pediatric Blood and Cancer* 2014), imploring treatment

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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.

Histopathologic classification

The WHO classifies low-grade gliomas according to their morphological features³. Tumors that do not meet the typical criteria of any single category are commonly labeled LGG-NOS for 'not-otherwise specified', which comprise more than a third of all PLGGs⁶. 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 0.1–10%^{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 bodies³. Eosinophilic granular bodies are often located near cystic areas and may be implicated in cyst formation²¹. Less commonly, PAs contain regions of calcification²². 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 degeneration²⁹. 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 background³⁰. Angiocentric gliomas (AGs), initially described by Tubiana et al., also named angiocentric neuroepithelial tumors (ANET), encompasses 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 xanthroastrocytoma (PXAs), and oligodendroglial tumors. DAs are

characterized by the presence of nuclear atypia, a low mitotic rate, and 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, 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.

Epidemiology

Brain tumors represent the most common solid tumor of childhood, of which PLGGs are the most frequent³⁵. 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 (Figure 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} (Figure 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 PLGGs⁶. 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 spine⁴⁴. Pediatric DAs, AGs, PXAs and oligodendrogliomas are most frequently supratentorial^{45–47,48}, GGs occur most frequently within the temporal lobes^{17,18,49} while PAs tend to localize to the cerebellum or the brainstem⁵⁰. 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 PLGGs primary tumors are located in the spine and these are most frequently PAs⁵¹. PLGG can also develop in the cervicomedullary region⁵² as well as in the tectum.

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 NF1⁵³ 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 patients⁵⁹. 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.

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 signs⁶², 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, GGs, DNTs or AGs 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 cases⁷¹.

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 enhancement⁸². PLGGs are not usually associated with peri-tumoral edema or restricted diffusion on diffusion-weighted MRI sequences⁸³. 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 assessment of treatment efficiency and tumor recurrence. GGs typically exhibit contrast enhancement on CT scans and can have variable gadolinium enhancements on MRI – from 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.

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 onset⁸⁴. PLGG 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 study¹⁰⁰. The most significant risk factors for progression identified on multivariate analysis were young age at diagnosis (<1 year), subtotal resection, and DA histology¹⁰¹. 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% (Bandopadhyay et al, in press, *Pediatric Blood and Cancer* 2014). In contrast to adults, PLGGs are characterized by a low incidence of malignant transformation^{102–104}. Importantly, adult survivors of PLGG have low glioma related mortality, suggesting a very low propensity for malignant transformation of PLGG (Bandopadhyay et al, in press, *Pediatric Blood and Cancer* 2014).

Treatment strategies

Given the excellent overall survival for the majority of PLGG patients, the treatment goal is to achieve tumor control while minimizing long-term tumor and treatment related morbidity¹⁰⁵. 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 (Bandopadhyay et al, in press, *Pediatric Blood and Cancer* 2014)^{106–111}.

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^{112–114}, cisplatin¹¹⁵, oxaliplatin¹¹⁶, irinotecan¹¹⁷ alone or in combination with vincristine^{118–126} or etoposide (VP16)¹²⁷ have 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^{128–130}, which can be effectively managed with pre-medication³⁵. 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^{126,131–133}. 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 significance¹²⁶. 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 tamoxifen¹³⁴ or vinblastine¹³⁵ as well as in polychemotherapy regimens with other agents including procarbazine, cyclophosphamide, lomustine, vincristine, VP16 or 5-fluorouracil^{136–139}. Monotherapy using temozolomide^{140–143}, vinblastine^{144–146} or cyclophosphamide¹⁴⁷ have 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/VP16¹⁴⁸ or vincristine/carmustine¹⁴⁹ 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 ¹⁵⁰, vincristine in combination with actinomycin ¹⁵¹, high dose ifosfamide ¹⁵², high dose cyclophosphamide ¹⁵³, bleomycine ¹⁵⁴, topotecan ¹⁵⁵, idarubicin ¹⁵⁶ or lenalinomide ¹⁵⁷.

The anti-VEGF agent bevacizumab has recently been evaluated in combination with irinotecan for PLGG disease progression^{158–160}. A recent phase II study which included 35 recurrent PLGGs reported at 2-year PFS of 47.8% using this treatment strategy ¹⁶⁰. 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 ^{161–163,216,217}. 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 50–59 Gy have been reported in the treatment of non-operable or progressive PLGGs with 5-year PFS ranging from 74%–88% ^{121,164–166}. Over 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 ^{167–169}, gamma-knife stereotactic radiotherapy techniques ^{170–172} and proton beam radiotherapy ^{173,174}.

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.

Genomic alterations in pediatric low-grade gliomas

General genomic features

Recent advances in high-throughput genetic sequencing and gene expression profiling have shed important insights into the genomic alterations of PLGGs¹⁷⁵. 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 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^{176–178}. The most frequent recurrent chromosomal alteration identified was a gain of chromosome 7, especially in PAs^{176,179–181}. Other chromosomal structural abnormalities included gains of chromosome 4, 5, 6, 8, and 11 and deletion of 17p in a subset of PAs, inversion in chromosome 8, and loss of chromosome 1q^{176,179–187}.

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^{188,189}. In contrast, concomitant deletion of chromosome 1p and 19q is rare in children with oligodendrogliomas^{190,191}, and does not confer similar chemosensitivity when present¹⁹². 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^{193,194–198}. 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 gliomas¹⁹⁹. 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^{200,201}.

NF1

The increased risk of LGGs in children with NF1 was one of the first clues that dysregulation of the mitogen-activated protein kinases (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 pathway²⁰². In neurofibromatosis, *NF1* mutations produce a loss of function of neurofibromin that leads to the constitutive activation of the Ras pathway and results in proliferation of astrocytes³⁵, among other phenotypes. Thus, MAPK pathway activation has long been known to contribute to the pathogenesis of LGGs in NF1 patients²⁰³. In addition, constitutive expression of MEK1 causes an increase in astrocytic proliferation.

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 PLGGs³⁵, involving 50–100% of pediatric PAs^{204–206}. The *BRAF* duplication is found more frequently in cerebellar and hypothalamic-chiasmatic tumors²⁰⁶.

The 7q34 gain has been characterized to represent a duplication of *BRAF* with a tandem insertion in the *KIAA1549* gene³⁵. This BRAF duplication results in the activation of the

downstream effectors of the MAPK pathway, MEK and ERK^{207,208}. 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)^{209–212,213,214}. *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 *QKI*, leading to the constitutive activation of MAPK pathway^{209,211,213}. 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 replication²¹⁵. *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^{211,216}. Furthermore, pharmacologic inhibition of MEK1/2 in short-term cultured PLGG cell lines significantly diminishes cell proliferation²⁰⁷, 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.

BRAF V600E and other less frequent mutations

Another frequent genomic alteration in PLGGs is the *BRAF* V600E mutation¹⁶⁹, which also results in deregulation of the MAPK pathway³⁵. This mutation has been described in other cancer subtypes, including melanoma²¹⁷, colorectal cancer²¹⁸, leukemia²¹⁹, and high-grade gliomas²²⁰. *BRAF* is one of the most mutated genes in cancer²²¹. The *BRAF* V600E point mutation occurs most commonly in PXAs, GGs, DAs, and PMAs^{196,209,213,214,222–225} and is only rarely detected in PAs²²⁶. 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*²¹¹. Other rare forms of small amino-acid insertions in *BRAF* have been identified in PAs²¹⁴. The *BRAF* V600E mutation has been shown to promote transformation of human neural stem cells, followed by senescence²²⁷. However, it remains unclear whether this recurrent alteration is sufficient to drive the development of PAs.

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*)^{213,214}. *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 supratentorial 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 FGFR1²¹⁴. 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 DNTs²¹³.

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 PAs²¹⁴. Finally, *KRAS* activating mutations have also been described in 3–5% of sporadic PAs^{209,213,214,228,229} (Table 2).

PI3K and RTK Signaling

After the MAPK pathway, the other most frequently altered pathways in PLGGs include the phosphatidylinositol 3-kinase (PI3K)/AKT/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 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, activation of mTOR through mutations of its upstream inhibitor result 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 activation³⁵. Over-expression of the BRAF-fusion transcript in neural stem cells results in activation of mTOR pathway, leading to the formation of glioma-like lesions and further supports the cross communication between these two pathways²³⁰. 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 proliferation²³¹.

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 speculation that deregulation of the EGFR pathway may play a role in the pathogenesis of disseminated PLGGs²³². Additionally, rare mutations of PDGFRA have been reported in PAs, GGs, and LGG-NOS tumors¹⁹⁶.

Although the sonic hedgehog pathway is most commonly associated with tumorigenesis of medulloblastoma and high-grade gliomas^{233,234}, a recent study suggests that this pathway could play a role in a subset of pediatric PAs via the over-activity of *PTCH*²³⁵. 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 growth³⁵. 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 types²³⁶. 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.

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 AGs²³⁷. *MYB* is an oncogene that is mutated or altered in T-ALL^{238,239}, breast cancer, pancreatic cancer, and CNS tumors, including primitive neuroectodermal tumors and medulloblastoma^{240,241}. 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^{213,242}. Importantly, this specific duplication-truncation of *MYBL1* has demonstrated tumorigenic properties *in vitro*.

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 cancers²⁴³. Epigenetic regulation of the genome can be defined as heritable modifications in gene expression that do not directly affect the DNA sequence²⁴⁴. Epigenetic modifications include multiple mechanisms affecting the chemical properties of DNA, histones, or other proteins involved in DNA packaging²⁴⁵. The frequency of alterations in epigenetic modifiers in cancer has been shown in multiple cancer types including hematologic tumors^{246,247}, Wilm's tumors²⁴⁸, retinoblastoma²⁴⁹, neuroblastoma, thyroid carcinoma, hepatocellular carcinoma, sarcoma²⁵⁰, and brain tumors such as medulloblastoma²⁵¹ and Atypical teratoid rhabdoid tumors (ATRTs) with *SMARCB1* mutations^{252,253}.

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 GBMs²⁵⁴ as well as DAs and PAs^{213,214}. This suggests that dysregulation of chromatin remodeling effectors are 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^{204,255} and BCR gene rearrangement in one PMA²⁵⁶.

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^{242,252}. 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.

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 resection²⁵⁷. 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 tumors²⁵⁸. 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 pathway²⁵⁹. OIS is a mechanism of tumor suppression that has been implicated in other cancer subtypes²⁶⁰. In contrast, p16 deletion has been identified as a negative prognosticator in 198 PLGG²⁶¹. 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 survival²⁶². The recent discovery of other genomic alterations such as FGFR1 mutations will also enlarge the field of exploration between clinical outcome and biology.

Towards new therapeutic approaches

Our recent increase in understanding the genomic alterations of PLGGs has expanded standard therapeutic approaches into targeted therapies. 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 (Figure 3). The first two agents, vemurafenib and dabrafenib 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 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^{263,264}. 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 prevent the feedback inhibitory loop that results from BRAF targeted agents as discussed above, are 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)²⁶⁵. 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^{266,267}.

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 responses²⁶⁸. 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 activity²⁶⁹. Functional validation in PLGG models or in early clinical trials are 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.

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 behaviour across a larger number of PLGGs will hopefully fill some of these remaining gaps.

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

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

Figure 3.
Targeted therapies currently in evaluation for PLGG treatment

Table 1

Major different subtypes of pediatric low-grade gliomas according to the latest WHO classification

Astrocytic tumors	Grade (WHO)
Pilocytic astrocytoma (PA)	I
Pilomyxoid astrocytoma (PMA)	II
Diffuse astrocytoma (DA)	II
Pleomorphic 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

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

Reference	GRADE (WHO)	WHO International Classification of Diseases	USA	Germany	France	Denmark	Brazil
Number of total CNS tumors		[41] 5200	[6] 20,709	[39] 3268	[38] 1017	[42] 911	[43] 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							
PA	I	14.8	15.5	16.4	23.1	16.5	18.2
DA	II	1.8	5.2	NA	1		
PXA	II	0.4	NA		0.3	13	6.2
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 neuro-glial 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

Table 3

Summary of the different chemotherapy strategies evaluated in PLGGs

Regimen course	Reference	Study length	Number of patients	First line	Eligibility Recurrence/progression	Response			OS		PFS	
						CR (%)	PR (%)	MR/SD (%)	PD (%)	year	%	year
CBP-VCR	Packer et al 1993	NA	60	yes	yes	2	37	50	11	NA	NA	NA
	Packer et al 1997	1989–1993	78	yes	yes	5	28	60	6	3	97	3 68
	Demaerel et al 2002	NA	9	yes	no	0	55	45	0	NA	NA	NA
	Gnekow et al 2004	1996–2004	123	yes	no	2	6	76	7	5	87	5 61
	Ronghe M et al 2010	1996–2006	16	yes	yes	6	50	38	6	NA	NA	NA
	Ater et al 2012	1997–2000	137	yes	yes	CR/PR: 35		32	33	5	86	5 39
CBP/VP16 CPP/VCR Iomustine/PC/VCR	Bruggers et al 2007	NA	10	yes	yes	20	10	70	0	NA	NA	NA
PC/CBP VP16/CisP VCR/CCP	Laithier et al 2003	1990–1998	85	no	yes	0	42	45	13	5	89	5 34
CBP/VP16	Castello et al 1995	NA	13	yes	no	8	0	70	22	NA	NA	NA
CBP/tamoxifene	Walther et al 2011	NA	13	yes	no	0	15	69	15	3	69	3 47
CBP/vinblastine	Jakacki et al 2011	2006–2008	26	yes	yes	0	5	81	14	NA	NA	NA
CBP or Ibroplatine	Friedman et al 1992	1986–1990	12	yes	yes	0	0	75	25	NA	NA	NA
CisP/VCR	Massimino 2002	1991–2000	34	yes	no	3	32	65	0	3	100	3 78
	Massimino 2010	2001–2007	37	yes	no	0	47	20	33	3	97	3 65
CBP	Moghrabi et al 1993	NA	6	no	yes	0	0	100	0	NA	NA	NA

Regimen course	Reference	Study length	Number of patients	First line	Eligibility		Response				OS		PFS	
					Recurrence/progression	CR (%)	PR (%)	MR/SD (%)	PD (%)	year	year	year	year	%
CisP	Aquino et al 1999	1992–1996	12	no	yes	0	33	50	17	3	83	NA	NA	
	Gururangan et al 2002	1993–2000	81	no	yes	2	21	82	15	3	84	3	64	
	Hsu et al 2008	1992–2007	16	no	yes	0	25	31	44	5	94	5	56	
oxaliplatin	Beatty et al 2010	2004–2006	9	no	yes	0	0	38	62	NA	NA	NA	NA	
CisP/VCR	Sawamura et al 2009	1992–2008	15	no	yes	7	53	40	0	NA	NA	NA	NA	
VP16-VCR	Pons et al 1992	NA	20	yes	yes	0	0	71	29	NA	NA	NA	NA	
VCR/VP16/CPP/5-FU	Lee et al 2006	1999–2004	13	no	yes	8	38	23	31	6	100	6	67	
TMZ	Nicholson et al 2007	1998–1999	22	no	yes	0	5	95	0	NA	NA	NA	NA	
	Gururangan et al 2007	1999–2005	30	no	yes	0	10	43	47	4	71	4	17	
	Khaw et al 2007	1999–2005	13	no	yes	15	23	23	38	NA	NA	3	57	
	Bartels et al 2011	2000–2006	28	no	yes	NA	NA	NA	NA	2	71	NA	NA	
TPDCV	Prados et al 1997	1984–1992	42	yes	yes	0	36	59	5	5	78	NA	NA	
	Mishra et al 2010	1984–1992	33	yes	yes	0	NA	NA	76	15	71	15	23	
TPCV	Lancaster et al 2003	NA	10	no	yes	NA	NA	78	NA	NA	NA	NA	NA	
BCNU/VCR/MTX-JT	Ater et al 2012	1997–2000	137	yes	yes	CR/PR: 30		36	34	5	87	5	52	
vinblastin	Sumer et al 1978	NA	6	NA	NA	NA	NA	50	NA	NA	NA	NA	NA	
	Lafaye-Cousin et al 2005	NA	9	no	yes	11	56	22	11	NA	NA	NA	NA	
	Bouffet et al 2012	2002–2009	51	no	yes	2	34	38	26	5	93	5	43	

Regimen course	Reference	Study length	Number of patients	Eligibility		Response				OS		PFS	
				First line	Recurrence/progression	CR (%)	PR (%)	MR/SD (%)	PD (%)	year	%	year	%
CPP	Kadota et al 1999	1996–1997	15	no	yes	7	0	57	36	NA	NA	NA	NA
CBP/VCR VCR/VP16 TPCV vinblastine	Scheinmann et al 2011	1985–2009	38	no	yes	NA	NA	NA	NA	5	86	;	37
bevacizumab/trinotecan	Packer et al 2009	2006–2008	10	no	yes	11	44	45	0	NA	NA	NA	NA
	Coucec et al 2012	2007–2010	11	no	yes	0	63	0	37	NA	NA	NA	NA
nimotuzumab	Saurez et al 2009	2005–2007	4	no	yes	0	0	50	50	NA	NA	NA	NA
erlotinib/rapamycin	Yalon et al 2013	2007–2010	21	no	yes	0	6	35	59	NA	NA	NA	NA
everolimus	Krueger et al 2010	2009–2010	28	no	yes	0	75	25	0	NA	NA	NA	NA

CBP: carboplatin, VCR: vincristine, VP16: etoposide, CPP: cyclophosphamide, PC: procarbazine, CisP: cisplatin, 5-FU: 5-fluorouracil, 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

Table 4

Summary of all the major mutations described in PLGGs

Reference	Number of tumors analyzed	Mutation	Histology
Sharma et al 2005	21	KRAS	5% PA
Janzarik et al 2007	25	KRAS	4% LGA
Jones et al 2008	44	KIAA-BRAF dup (3 fusion types)	66% PA
Jones et al 2009	44	SRGAPS-RAF1 dup	7% PA
		BRAF V600E	2% PA
Jacob et al 2009	36	BRAF V600E	20% GG
Forsheew et al 2009	50	KIAA-BRAF dup (6 fusion types)	94% PA
			9% DA
			22% PM
		SRGAP3-RAF1 dup	3% PM
		BRAF V600E	9% DA
		KRAS	100% PXA 3% PA
Sievert et al 2009	28	KIAA-BRAF dup	77% PA
			50% DA
McConail et al 2009	117	BRAF V600E	57% GG
			23% NDS
			2% PA
		MYC	2% PA
			7% GG
		PIK3CA	2% PA
		CUBN	2% NOS
		CUBN	4% PA
		CTNNB1	2% PA
		TP53+PKHD1	2% NOS
Yu et al 2010	79	KIAA-BRAF dup (3 fusion types)	2% NOS
			PDGFRA
Dougherty et al 2010	27	BRAF V600E	60% PA
			25% PXA 50% GG
Schindler et al 2011	133	BRAF V600E	9% PA
			69% PXA
			13% GG
Dias-Santagata et al 2011	11	BRAF V600E	64% PXA

Reference	Number of tumors analyzed	Mutation	Histology
Lin et al 2012	106	KIAA-BRAF dupl (5 fusion types)	60% PA
			24% DOS
			36% GN
			33% PMA
Padovani et al 2012	24	IDH1 mutation	1 OA
Ramkissoon et al 2013	45	KIAA-BRAF dup	22% GG
			10% NOS
		BRAF V600E	75% GG
			71% NOS
		MYBL1 rearrangement	36% DA
Zhang et al 2013	148	KIAA-BRAF dup	28% DA
			76% PA
		BRAF-MACF1 dup	11% GG
			11 %GG
		RAF fusions	2% PA
		NF1 mutation	2% PA
		V600E mutation	3% DA
			5.5% PA
			70% PXA
			33% GG
		FGFR1 duplication (TDK)	12% DA
			24% DA
			3% PA
			100% DNT
		FGFR1-TACC1 translocation	1% PA
		FGFR1 mutation	9% DA
			2% PA
Jones DT et al 2013	96 PA	KRAS mutation	3% DA
			1%PA
		MYB/MYBL1 rearrangement	21% DA
			100% AG
		IDH1 mutation	3% DA
		H3F3A mutation	9% DA
		NTRK2 fusion -NAV1	3% DA
		KIAA-BRAF dup	70%
		BRAF other rearrangements (-FAM131B, -RNF130, -CLCN6, -MKRN1, -GNAI1)	5.5%
		BRAF ins599T	1%
		BRAF p.R506 insVLR	1%

Reference	Number of tumors analyzed	Mutation	Histology
		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%

Table 5

Summary of all the different fusions types of BRAF and RAF1 described in PLGGs

KIAA – BRAF duplication-translocation	
KIAA Ex 15 - BRAF Ex 9	Jones et al 2008&2009
KIAA Ex 16 - BRAF Ex 11	Forsheew et al 2009
KIAA Ex 16 - BRAF Ex 9	Sievert et al 2009
KIAA Ex 15 - BRAF Ex 11	Yu et al 2010
KIAA Ex 17 - BRAF Ex 10	Lin et al 2012
KIAA Ex 16 - BRAF Ex 10	Lin et al 2012
	Dahiya et al 2012
RAF1 duplication-translocation	
SRGAP3 Ex 11-RAF1 Ex8	Forsheew et al 2009
SRGAP3 Ex 12-RAF1 Ex10	Jones et al 2009
SRGAP3-RAF1	Jones et al 2009
QK1 - RAF1	Zhang et al 2013 Zhang et al 2013
Other fusion types	
FAM131B-BRAF	Cin et al 2011
MACF1 - BRAF	Jones et al 2013
RNF130 Ex 3 - BRAF Ex 9	Zhang et al 2013
CLCN6 – BRAF (intrachromosomal)	Jones et al 2013
MKRN1 - BRAF	
GNAI1 - BRAF	