Molecular Markers in Low Grade Glioma – Toward Tumor Reclassification

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Abstract

Low-grade diffuse gliomas are a heterogeneous group of primary glial brain tumors with highly variable survival. Currently, patients with low grade diffuse gliomas are stratified into risk subgroups by subjective histopathologic criteria with significant interobserver variability. Several key molecular signatures have emerged as diagnostic, prognostic, and predictor biomarkers for tumor classification and patient risk stratification. In this review, we will discuss the impact of the most critical molecular alterations described in diffuse (*IDH1/2*, 1p/19q co-deletion, *ATRX*, *TERT*, *CIC*, *FUBP1*) and circumscribed (*BRAF-KIAA1549*, *BRAF*^{V600E}, *C11orf95–RELA* fusion) gliomas. These molecular features reflect tumor heterogeneity and have specific associations with patient outcome that determine appropriate patient management. This has led to an important, fundamental shift towards developing a molecular classification of WHO grade II-III diffuse glioma.

Introduction

In the United States 28% of all primary brain and central nervous system (CNS) tumors are diagnosed as gliomas [1]. Based on their infiltrative behavior, gliomas are subdivided into two main subgroups: circumscribed and diffuse. The circumscribed gliomas are generally amenable to total surgical resection and patients with these tumors have improved outcomes compared to patients with diffuse gliomas. The aggressive phenotype of diffuse gliomas is attributed to the tendency of the malignant glioma cells to infiltrate the neuropil along axons and travel far away from the primary tumor site (Figure 1). A malignant glioma cell may travel to the opposite cerebral hemisphere. For this reason diffuse gliomas cannot be completely surgically resected (Figure 1c). Diffuse gliomas encompass two main histological subtypes (astrocytoma and oligodendroglioma) of which a third subtype is derived (mixed oligoastroytoma). Histological criteria established by the World Health

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Organization (WHO), further stratify gliomas into four grades of aggressiveness (WHO I-IV) [2]. WHO grade I is reserved for circumscribed glial and glio-neuronal entities usually with favorable prognosis, while diffuse gliomas comprise the more aggressive WHO grades II-IV (Table 1) [2]. Patients with astrocytomas generally have worse outcomes than patients with oligodendrogliomas (Table 2) [1].

While histologic criteria for diagnosing the most aggressive diffuse glioma (i.e. glioblastoma) are clear, there is extreme variability in interpretation of current morphological criteria and in diagnostic reproducibility for grade II and III diffuse glioma among pathologists [3–6]. Several molecular signatures have now been identified in gliomas, with important diagnostic, prognostic, and/or predictive roles. These genetic alterations have led to further stratification of gliomas into several distinct subgroups. The addition of genetic markers offer better prognostic patient stratification compared to WHO grading alone. Guidelines for a combined molecular-morphologic approach to glioma diagnosis are under development [7].

The treatment of WHO grade II-III diffuse gliomas continues to evolve. Retrospective molecular analysis of tumors from patients enrolled in randomized clinical trials have called into question the use of standard histologic grading and have emphasized the relevance of key molecular alterations as important predictive biomarkers with implications for determining appropriate tumor management.

Histopathological classification of WHO grade II-III diffuse glioma

Since Bailey and Cushing's initial attempt at brain tumor classification in 1926 [8, 9], histological examination has been the mainstay method for risk class assignment, patient outcome stratification, therapy guidelines, and stratification for clinical trials [2, 3, 10]. Several potential issues arising during histological examination are responsible for the significant inter-observer variability in achieving diagnostic reproducibility. For example, the current WHO criterion for grade III designation of astrocytomas (i.e. "brisk mitotic activity" [2]) does not clearly specify any mitotic figure cutoffs and is, therefore, ambiguous and subjective and often based on the pathologist's individual experience and bias. Similarly, the criteria for the "mixed oligoastrocytoma" category (i.e. "recognition of neoplastic glial cells with convincing astrocytic or oligodendroglial phenotypes" [2]) are subjective. The pathologist's expertise and experience in neuropathology also significantly impacts accuracy of diagnosis. In a large oncologic center study investigating the rate of diagnosis disagreement after expert neuropathology review, approximately 40% of case reviews had some type of disagreement with the original diagnosis, of which about 9% were serious with immediate impact on treatment [11]. Another potential problem in interpretation can be caused by mistakenly omitting foci of high-grade histology (i.e. missing slides from the resection specimen or alternatively, limited surgical sampling in subtotal resections or biopsies and/or suboptimal specimen sampling of the resected specimen) [3–6, 11]. Due to one or several of these issues, the histopathologic consensus among neuropathologists after a single review is reached in only approximately 50% of cases [5]. Although this number could be improved after several case reviews, [5] it is imperative to implement more objective criteria and/or incorporate ancillary modalities alongside histological parameters in order to significantly

improve the high rate of inter-observer variability in histopathologic diagnosis and classification of diffuse gliomas.

Molecular features of WHO II-III diffuse gliomas

The current WHO classification does not comprehensively reflect diffuse glioma biology and patient outcome. There is extensive evidence that tumors from different patients that have indistinguishable morphology under the microscope do not necessarily share the same biology and do not necessarily reflect similar patient outcomes [12–16]. Molecular subgroups of diffuse glioma, heterogeneous in WHO grade, with different survival outcomes have been described. The use of molecular stratification was superior in predicting outcome compared to the WHO grade alone [15].

Isocitrate dehydrogenase (IDH) mutations in diffuse gliomas

Key molecular markers in WHO grade II-III diffuse glioma include *IDH 1 and 2* (*IDH1/2*) mutations. These genes encode the Krebs/citric acid cycle family of metabolic enzymes [17]. IDH mutations in diffuse glioma were initially described in 2008 [18] but occur at lower frequencies in other malignancies [19–24]. In diffuse glioma *IDH1* mutations occur more commonly (>90%) than *IDH2* mutations and are mutually exclusive. IDH mutations are common in grade II-III diffuse glioma (~65–80%) and secondary glioblastoma (~80%) (i.e. glioblastoma that arise following progression from a grade II or III diffuse glioma) while primary glioblastomas usually lack or show a very low frequency of IDH mutations (~5%) [25–32]. IDH gene family mutations, the most common of which are $IDH1^{R132H}$ and $IDH2^{R172K}$, confer both loss and gain of function that impacts epigenetic regulation through accumulation of 2-hydroxyglutarate and inhibition of α-ketoglutarate-dependent deoxygenases [17, 33–35]. The impact of mutant IDH induces a hypermethylator phenotype [36], the glioma-CpG island methylator phenotype (G-CIMP) [37]. G-CIMP is characteristic of grade II-III diffuse glioma, is associated with improved prognosis, and with a proneural molecular gene expression signature [38, 39].

IDH family mutations are early [25, 40] and consistent [40, 41] molecular events in the development of a glioma and are complemented by subsequent mutually exclusive glioma lineage specific genetic alterations, such as *TP53* and *alpha thalassemia/mental retardation syndrome X-linked (ATRX)* mutations. These latter mutations are associated with the astrocytic phenotype [42–47]. On the other hand, 1p/19q co-deletion [39, 43, 46] is associated with mutations in *the homolog of Drosophila capicua gene (CIC)* [42, 48] and/or *far-upstream binding protein 1 gene (FUBP1)* and with the oligodendroglial phenotype [42, 49]. These molecular markers strongly support the predominant monoclonal origin of mixed oligoastrocytomas demonstrated by microdissection studies. [41, 50, 51] These molecular markers may help to further classify this controversial mixed glioma category into specific subclasses of either astrocytoma or oligodendroglioma [52].

In addition to its important diagnostic role, IDH mutations also have a significant prognostic role in high-grade diffuse glioma (WHO grade III and IV) independent of WHO grade in some instances [29, 30, 32, 42, 53–56]. On the other hand, the prognostic role of IDH mutations in WHO grade II diffuse glioma has not been completely elucidated [40, 57–63]. These mutations

do not appear to have prognostic significance in non-CNS malignancies [21, 23]. Similarly, the predictive role of IDH mutations has not been clarified. Very few studies suggest a potential advantage of the use of IDH mutations for determining treatment response in anaplastic diffuse gliomas. Two randomized phase III clinical trials [Radiation Therapy Oncology Group (RTOG) 9402 and European Organisation for the Research and Treatment of Cancer (EORTC) 26951] have now reported a similar improved overall survival benefit to a combined regimen using radiotherapy and PCV specifically in patients with anaplastic gliomas that are IDH mutant and 1p/19q non-co-deleted [64, 65]. The predictive role of IDH mutations remains to be further investigated along with the possible prognostic implication of the IDH driven G-CIMP in grade II-III gliomas [37, 38, 66, 67]. Of note, a promising IDH1^{R132H} specific inhibitor drug (AGI-5198) has shown significant activity in pre-clinical models [68] and is currently in phase 1 clinical trials for solid tumors [69, 7069, 7069, 7069, 70][69, 70][69, 70][69, 70][69, 7029, 84]. Multiple other agents targeting mutant IDH are also under investigation.

IDH^{R132H} mutation can be easily detected clinically by immunohistochemistry (Figure 1C). The expression of mutated IDH1^{R132H} protein confirms mutation. Cases that are IDH1^{R132H} immunonegative can be further interrogated by DNA sequencing for other *IDH1* or *IDH2* mutations. Since mutations are mainly present in codons 132 and 172 respectively, sequencing can be limited to these codons [17]. At our institution all grade II-III diffuse gliomas and glioblastomas in young patients (less than age 50) are interrogated in this manner [71].

Chromosomes 1p/19q loss of heterozygosity in diffuse gliomas

Another important molecular marker in diffuse glioma is the presence of 1p/19q co-deletion, the molecular signature of oligodendroglioma, initially described in 1994 [4, 39, 48, 72–74]. The proposed mechanism of formation of this chromosomal abnormality is a translocation between 1p and 19q leading to the derivative chromosome, der(1;19)(q10;p10). This derivative chromosome was demonstrated in a small number of tumors leading to the hypothesis that subsequent der(1;19)(p10;q10) formation leads to 1p/19q loss of heterozygosity [75, 76]. Importantly, 1p/19q co-deletion is only present if IDH mutations are present [77]; therefore, this implies an association with the G-CIMP and proneural expression phenotypes [38, 39], an association that was demonstrated in grade II-III oligodendrogliomas [39, 66]. Several studies showed that 1p/19q co-deletion can aid in risk stratification of IDH mutant gliomas with IDH mutant, 1p/19q co-deleted gliomas having the best prognosis, followed by IDH mutant, 1p/19q non-co-deleted gliomas and lastly by IDH wild-type, 1p/19q non-co-deleted tumors with the worst outcome [39, 57, 63, 64, 78].

Besides prognostic significance, 1p/19q co-deletion is a marker of chemotherapeutic response [79–83]. Patients with 1p/19q co-deleted diffuse gliomas responded better to adjuvant chemotherapy [either procarbazine (Matulane®, Sigma Tau Pharmaceuticals, Gaithersburg, MD)/lomustine (CCNU) (CeeNU®, Bristal-Myers Squib Company, Princeton, NJ)/ vincristine (Oncovin®, Eli Lilly and Company, Indianapolis, IN) (PCV) regimen; or temozolomide (TMZ)] [79, 81–90]. The mechanism for the associated chemosensitivity remains

unknown and whether 1p/19q co-deletion leads to loss of a chemoresistant gene(s) or is merely a marker of more chemosensitive clones remains to be determined.

One of the most popular methods for detection of 1p/19q co-deletion is fluorescent in situ hybridization (FISH). FISH permits pathologists to correlate chromosomal arm copy number findings with tissue morphology and does not require the use of normal control samples (Figure 2). Polymerase chain reaction-based loss of heterozygosity assays or array comparative genomic hydridization (CGH) are also utilized in different laboratory settings [91, 92].

ATRX and telomerase reverse transcriptase (*TERT*) promoter mutations in gliomas

Two distinct telomere maintenance mechanisms have been recently described mainly in IDH mutant grade II-III diffuse glioma and primary glioblastoma. Telomeres are repetitive guanine-rich nucleotide sequences situated at each chromatid end. They are required for chromosome stability and shorten with each cell division. [93] In cancer, the length of telomere sequences is maintained either by telomerase enzyme activity or by a mechanism independent of telomerase activity called alternative lengthening of telomeres (ALT). [94, 95] Two mutually exclusive telomere maintenance mechanisms appear associated with IDH mutant WHO grade II-III diffuse gliomas. An ALT mechanism may be triggered by loss of the normal ATRX protein function of maintaining chromatin integrity for DNA replication. *ATRX* or *death-associated protein 6* (*DAXX)* mutations cause dysfunctional ATRX-DAXX protein complexes that are unable to carry their normal histone chaperone function, leading to chromatin breakage, and abnormal DNA replication. [96–98] Telomeric DNA double-strand breakage may trigger ALT.[43, 99–102] This mechanism is encountered in IDH mutant, 1p/19q non co-deleted grade II-III diffuse glioma [43, 44, 46, 103].

The other telomere maintenance mechanism involves point mutations in the *TERT* promoter. *TERT* encodes the catalytic subunit of telomerase. Telomerase is a RNA-dependent polymerase composed of two subunits: TERT (the catalytic subunit) and TERC (the telomerase RNA component which serves as a template for telomere extension) [104, 105]. Two consistent and mutually exclusive *TERT* promoter point mutations (C228T and C250T) have been described in gliomas [77, 106]. These mutations have been also frequently found in other non-CNS tumors, with C228T being by far more common (~80%) than C250T (~20%) overall [103, 107, 108]. Point mutations in the *TERT* promoter region create binding sites for the E-twenty-six (Ets) family of transcription factors, [107–110] which upon binding cause two to four fold increase in transcriptional activity [107] with subsequent increased TERT mRNA expression [77]. This increased mRNA expression seems to be positively correlated with the tumor's *CIC* mutational status [77], likely because *CIC* regulates the Ets family of transcription factors [111]. Chen et al. demonstrated *in vitro* that the increase in TERT transcriptional activity is maintained under hypoxic conditions and under treatment with TMZ [112]. This second telomere maintenance mechanism is also characteristic of IDH mutant, 1p/19q co-deleted grade II-III diffuse glioma (and therefore of molecular oligodendroglioma) [103, 106, 113]. In the diffuse glioma category, it is not yet clear if *TERT* promoter mutations confer additional prognostic benefit to the presence of IDH mutations

and 1p/19q co-deletion. Most studies demonstrate improved survival in patients with IDH mutant, *TERT* promoter mutated grade II-III diffuse gliomas [77, 113, 114] ; however after stratification for 1p/19q co-deletion status, *TERT* promoter mutations demonstrate a prognostic advantage only to the 1p/19q non-co-deleted subset [114]. Interestingly, *TERT* promoter mutations are negative prognostic biomarkers in the IDH wild-type grade II-III diffuse gliomas subset [77, 113, 114] and in primary glioblastoma [77, 103, 112, 113]. In addition to obtaining IDH mutation and 1p/19q co-deletion status, identifying *ATRX* and *TERT* promoter mutations status should further enhance the stratification of diffuse gliomas.

IDH mutation– driven subgroups of WHO grade II-III diffuse glioma

There is evidence that the presence or absence of IDH mutation is an important branch point towards grade II-III diffuse glioma subclassification. Gorovets et al. subclassified 101 grade II and III diffuse gliomas of astrocytic morphology by IDH mutation status. IDH mutant tumors were enriched in *TP53* mutations, *PTEN* promoter methylation, and gains of 8q. Based on expression signatures, IDH mutant grade II-III astrocytomas were also subdivided into two subgroups: neuroblastic and early progenitor-like, the former enriched in mature neuronal and the latter enriched in developmental gene signatures. The early progenitor-like subgroup components were associated with *TP53* mutations and several chromosomal copy number abnormalities (gains of 7p and 15q, and losses of 4q34.3, 9p23, 11p, 12q21.33, 13q, and 19q).

On the other hand IDH wild-type grade II-III astrocytomas shared *EGFR* amplifications, *PTEN* losses, PI3K/AKT molecular pathway activation, and gains of 7p and losses of 9p and 10q [15]. Partial or total loss of 10q and 9p loss have been previously associated with dismal prognosis in WHO II-III diffuse glioma [115–117]. This is important because the latter signatures are characteristic molecular markers of primary glioblastoma [18, 118–120]. This suggests that a subgroup of grade II-III astrocytomas confined to the IDH wild-type genetic subclass is biologically identical to glioblastoma. This same group also demonstrated that these specific tumors clustered within a separate, heterogeneous subgroup defined based on expression profiling that, not surprisingly, was called pre-glioblastoma [15]. Similarly Yan et al., defined an IDH wild-type subgroup based on expression profiling that was also predominantly composed of primary glioblastomas and also clustered several grade II-III diffuse gliomas [16].

A proposed classification scheme based on a summary of the molecular analysis to date for WHO II-III diffuse gliomas is shown in Figure 3. This schema may more accurately reflect underlying biology and be more representative of patient outcome than the WHO grade alone. The Cancer Genome Atlas (TCGA) [121] group is currently working on analyzing a large cohort of WHO grade II-III diffuse gliomas of all morphologies. Extensive data derived from multiple molecular platforms were analyzed and their results are expected shortly. We can speculate that similar molecular findings will be reported as have been reported previously and that emphasize a significant difference between groups of tumors that are primarily separated by the IDH mutation status.

Susceptibility loci for the development of diffuse glioma

Several large genome-wide association studies (GWAS) have been performed to identify genetic variants associated with the risk of development of a glioma. These GWAS studies have identified several risk single nucleotide polymorphism (SNP) loci. The reported loci with the strongest glioma risk association were rs78378222 (*TP53*, 17p13), rs4295627 and rs55705857 (*CCDC26*, 8q24.21), rs2736100 (*TERT*, 5p15.33), rs1920116 (*TERC*, 3q26.2), rs4977756 (*CDKN2B*, 9p21.3), rs6010620 and rs2297440 (*RTEL1*, 20q13.33), and rs498872 (*PHLDB1*, 11q23.3) [122–131]. Of these, rs4295627, rs55705857 (*CCDC26*, 8q24.21) and rs498872 (*PHLDB1*, 11q23.3) are strongly associated with low-grade disease, IDH mutations [132] and 1p/19q co-deletions [127]. For the former two SNPs, the risk for developing oligodendroglioma was also shown by Jenkins et al [128, 129]. High-grade disease, IDH wild-type, *EGFR* amplification, *CDKN2A p16INK4a* homozygous deletion, 9p and 10q loss were linked to rs2736100 (*TERT*, 5p15.33) and rs6010620 (*RTEL1*, 20q13.33) [127]. An additional SNP locus associated with high-grade glioma was rs2297440 (*RTEL1*, 20q13.33) [128].

Molecular features of well-circumscribed gliomas

BRAF genetic alterations are shared by pilocytic astrocytoma, ganglioglioma, and pleomorphic xanthoastrocytoma. *BRAF-KIAA1549* fusion-duplication, a possibly prognostic marker [133], is frequent in younger patients [134] with cerebellar pilocytic astrocytomas (~60–80%), intermediate in frequency for brainstem, hypothalamic, and optic pathway tumors (~60%) [135], and low (~20%) in supratentorial cortical tumors [136]. *BRAF^V600E^* mutations are common in pleomorphic xanthoastrocytoma (~60–80%) involving the temporal lobes, ganglioglioma (~30–50%) [137–139], and less commonly found in pilocytic astrocytoma (~2 to 30% depending on location). Most common locations include diencephalon, followed by cerebral cortex and brainstem, and least common in cerebellar tumors) [137].

Location-specific subgroups of ependymomas with characteristic genetic signatures have been described. Supratentorial ependymomas (~70–75%) are enriched in *C11orf95–RELA* fusion, driver of NF-kB cell signaling [140, 141]. Posterior fossa ependymomas are comprised of two genetically and clinically distinct subgroups, group A (PFA) and B (PFB). The more aggressive PFA group is enriched in cancer-related signal transduction pathway gene signatures, exhibits the CIMP phenotype (distinct from G-CIMP), while the PFB group is CIMP negative and enriched in chromosomal number aberrations [142–144].

Conclusions

Grade II-III diffuse gliomas are heterogeneous tumors. Based on current published data, IDH mutations and 1p/19q co-deletion are major drivers of gliomagenesis and in determining outcome for grade II-III diffuse gliomas. Diffuse glioma subgroups defined based on these two molecular alterations will require further characterization in order to identify additional important biomarkers as well as for therapeutic target discovery. Continued endeavors to further characterize grade II-III glioma characterization should not only offer important information regarding many accepted clinical observations but also provide mechanisms regarding these observations. For example, why are 1p/19q co-deleted

tumors more chemosensitive? Why is the improved overall survival in those patients receiving chemoradiation observed late after the median overall survival has already been reached? How should 1p/19q non-co-deleted tumors be treated? It is anticipated in the near future that preclinical/laboratory efforts paired with clinical results obtained from large collaborative studies and clinical trials will likely provide answers to these important questions regarding appropriate patient management. In the near future, the use of combined molecular-histopathological criteria will improve glioma risk stratification, aid in trial design, and ultimately be used to guide therapy for patients with diffuse gliomas.

Acknowledgments

References

1. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011. Neuro-oncology. 2014; 16(Suppl 4):iv1–iv63. [PubMed: 25304271]

2. Louis, DN.; Ohgaki, H.; Wiestler, OD., et al. WHO Classification of tumors of the central nervous system. Lyon (France): IARC; 2007.

3. van den Bent MJ. Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective. Acta Neuropathol. 2010; 120(3):297–304. [PubMed: 20644945]

4. Aldape K, Burger PC, Perry A. Clinicopathologic aspects of 1p/19q loss and the diagnosis of oligodendroglioma. Arch Pathol Lab Med. 2007; 131(2):242–51. [PubMed: 17284109]

5. Coons SW, Johnson PC, Scheithauer BW, et al. Improving diagnostic accuracy and interobserver concordance in the classification and grading of primary gliomas. Cancer. 1997; 79(7):1381–93. [PubMed: 9083161]

6. Kros JM, Gorlia T, Kouwenhoven MC, et al. Panel review of anaplastic oligodendroglioma from European Organization For Research and Treatment of Cancer Trial 26951: assessment of consensus in diagnosis, influence of 1p/19q loss, and correlations with outcome. J Neuropathol Exp Neurol. 2007; 66(6):545–51. [PubMed: 17549014]

7. Louis DN, Perry A, Burger P, et al. International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading. Brain Pathol. 2014

8. MacKenzie DJ. A Classification of the Tumours of the Glioma Group on a Histogenetic Basis With a Correlated Study of Prognosis. Can Med Assoc J. 1926; 16(7):872.

9. Bailey, P.; Cushing, H. A Classification of the Tumours of the Glioma Group on a Histogenetic Basis With a Correlated Study of Prognosis. Philadelphia: J. B. Lippincott Co; 1926.

10. NCCN. Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 2. 2014. [updated 3/11/2014; cited 2014 9/1/2014]. Available from: http://www.nccn.org

11. Bruner JM, Inouye L, Fuller GN, et al. Diagnostic discrepancies and their clinical impact in a neuropathology referral practice. Cancer. 1997; 79(4):796–803. [PubMed: 9024718]

12. Li A, Walling J, Ahn S, et al. Unsupervised analysis of transcriptomic profiles reveals six glioma subtypes. Cancer Res. 2009; 69(5):2091–9. [PubMed: 19244127]

13. Gravendeel LA, Kouwenhoven MC, Gevaert O, et al. Intrinsic gene expression profiles of gliomas are a better predictor of survival than histology. Cancer Res. 2009; 69(23):9065–72. [PubMed: 19920198]

14. Vitucci M, Hayes DN, Miller CR. Gene expression profiling of gliomas: merging genomic and histopathological classification for personalised therapy. Br J Cancer. 2011; 104(4):545–53. [PubMed: 21119666]

15. Gorovets D, Kannan K, Shen R, et al. IDH mutation and neuroglial developmental features define clinically distinct subclasses of lower grade diffuse astrocytic glioma. Clin Cancer Res. 2012; 18(9):2490–501. [PubMed: 22415316]

16. Yan W, Zhang W, You G, et al. Molecular classification of gliomas based on whole genome gene expression: a systematic report of 225 samples from the Chinese Glioma Cooperative Group. Neuro-oncology. 2012; 14(12):1432–40. [PubMed: 23090983]

17. Ichimura K. Molecular pathogenesis of IDH mutations in gliomas. Brain Tumor Pathol. 2012

18. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008; 321(5897):1807–12. [PubMed: 18772396]

19. Shibata T, Kokubu A, Miyamoto M, et al. Mutant IDH1 confers an in vivo growth in a melanoma cell line with BRAF mutation. Am J Pathol. 2011; 178(3):1395–402. [PubMed: 21356389]

20. Kang MR, Kim MS, Oh JE, et al. Mutational analysis of IDH1 codon 132 in glioblastomas and other common cancers. Int J Cancer. 2009; 125(2):353–5. [PubMed: 19378339]

21. Boissel N, Nibourel O, Renneville A, et al. Prognostic impact of isocitrate dehydrogenase enzyme isoforms 1 and 2 mutations in acute myeloid leukemia: a study by the Acute Leukemia French Association group. J Clin Oncol. 2010; 28(23):3717–23. [PubMed: 20625116]

22. Borger DR, Tanabe KK, Fan KC, et al. Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. Oncologist. 2012; 17(1):72–9. [PubMed: 22180306]

23. Amary MF, Bacsi K, Maggiani F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011; 224(3):334–43. [PubMed: 21598255]

24. Hartman DJ, Binion D, Regueiro M, et al. Isocitrate dehydrogenase-1 is mutated in inflammatory bowel disease-associated intestinal adenocarcinoma with low-grade tubuloglandular histology but not in sporadic intestinal adenocarcinoma. Am J Surg Pathol. 2014; 38(8):1147–56. [PubMed: 25029120]

25. Watanabe T, Nobusawa S, Kleihues P, et al. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. Am J Pathol. 2009; 174(4):1149–53. [PubMed: 19246647]

26. Nobusawa S, Watanabe T, Kleihues P, et al. IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. Clin Cancer Res. 2009; 15(19):6002–7. [PubMed: 19755387]

27. Hartmann C, Meyer J, Balss J, et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. Acta Neuropathol. 2009; 118(4):469–74. [PubMed: 19554337]

28. Horbinski C, Kofler J, Kelly LM, et al. Diagnostic use of IDH1/2 mutation analysis in routine clinical testing of formalin-fixed, paraffin-embedded glioma tissues. J Neuropathol Exp Neurol. 2009; 68(12):1319–25. [PubMed: 19915484]

29. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009; 360(8):765–73. [PubMed: 19228619]

30. Sonoda Y, Kumabe T, Nakamura T, et al. Analysis of IDH1 and IDH2 mutations in Japanese glioma patients. Cancer science. 2009; 100(10):1996–8. [PubMed: 19765000]

31. Sanson M, Marie Y, Paris S, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol. 2009; 27(25):4150–4. [PubMed: 19636000]

32. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol. 2010; 120(6):707–18. [PubMed: 21088844]

33. Olar A, Raghunathan A, Albarracin CT, et al. Absence of IDH1-R132H mutation predicts rapid progression of nonenhancing diffuse glioma in older adults. Ann Diagn Pathol. 2011

34. Xu W, Yang H, Liu Y, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer cell. 2011; 19(1):17–30. [PubMed: 21251613]

35. Chowdhury R, Yeoh KK, Tian YM, et al. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. EMBO reports. 2011; 12(5):463–9. [PubMed: 21460794]

36. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer cell. 2010; 18(6):553–67. [PubMed: 21130701]

37. Turcan S, Rohle D, Goenka A, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature. 2012; 483(7390):479–83. [PubMed: 22343889]

38. Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer cell. 2010; 17(5):510–22. [PubMed: 20399149]

39. Mur P, Mollejo M, Ruano Y, et al. Codeletion of 1p and 19q determines distinct gene methylation and expression profiles in IDH-mutated oligodendroglial tumors. Acta Neuropathol. 2013; 126(2): 277–89. [PubMed: 23689617]

40. Juratli TA, Kirsch M, Robel K, et al. IDH mutations as an early and consistent marker in low-grade astrocytomas WHO grade II and their consecutive secondary high-grade gliomas. J Neurooncol. 2012

41. Lass U, Numann A, von Eckardstein K, et al. Clonal analysis in recurrent astrocytic, oligoastrocytic and oligodendroglial tumors implicates IDH1- mutation as common tumor initiating event. PloS one. 2012; 7(7):e41298. [PubMed: 22844452]

42. Jiao Y, Killela PJ, Reitman ZJ, et al. Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. Oncotarget. 2012; 3(7):709–22. [PubMed: 22869205]

43. Kannan K, Inagaki A, Silber J, et al. Whole-exome sequencing identifies ATRX mutation as a key molecular determinant in lower-grade glioma. Oncotarget. 2012; 3(10):1194–203. [PubMed: 23104868]

44. Killela PJ, Pirozzi CJ, Reitman ZJ, et al. The genetic landscape of anaplastic astrocytoma. Oncotarget. 2013

45. Liu XY, Gerges N, Korshunov A, et al. Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. Acta Neuropathol. 2012; 124(5):615–25. [PubMed: 22886134]

46. Wiestler B, Capper D, Holland-Letz T, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. Acta Neuropathol. 2013; 126(3):443–51. [PubMed: 23904111]

47. Cai J, Yang P, Zhang C, et al. ATRX mRNA expression combined with IDH1/2 mutational status and Ki-67 expression refines the molecular classification of astrocytic tumors: evidence from the whole transcriptome sequencing of 169 samples samples. Oncotarget. 2014

48. Yip S, Butterfield YS, Morozova O, et al. Concurrent CIC mutations, IDH mutations, and 1p/19q loss distinguish oligodendrogliomas from other cancers. J Pathol. 2012; 226(1):7–16. [PubMed: 22072542]

49. Sahm F, Koelsche C, Meyer J, et al. CIC and FUBP1 mutations in oligodendrogliomas, oligoastrocytomas and astrocytomas. Acta Neuropathol. 2012

50. Dong ZQ, Pang JC, Tong CY, et al. Clonality of oligoastrocytomas. Hum Pathol. 2002; 33(5):528–35. [PubMed: 12094379]

51. Qu M, Olofsson T, Sigurdardottir S, et al. Genetically distinct astrocytic and oligodendroglial components in oligoastrocytomas. Acta Neuropathol. 2007; 113(2):129–36. [PubMed: 17031656]

52. Sahm F, Reuss D, Koelsche C, et al. Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma. Acta Neuropathol. 2014

53. Beiko J, Suki D, Hess KR, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro-oncology. 2014; 16(1):81–91. [PubMed: 24305719]

54. van den Bent MJ, Dubbink HJ, Marie Y, et al. IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: a report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. Clin Cancer Res. 2010; 16(5):1597–604. [PubMed: 20160062]

55. Weller M, Felsberg J, Hartmann C, et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. J Clin Oncol. 2009; 27(34):5743–50. [PubMed: 19805672]

56. Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol. 2009; 27(35):5874–80. [PubMed: 19901110]

57. Houillier C, Wang X, Kaloshi G, et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology. 2010; 75(17):1560–6. [PubMed: 20975057]

58. Mukasa A, Takayanagi S, Saito K, et al. Significance of IDH mutations varies with tumor histology, grade, and genetics in Japanese glioma patients. Cancer science. 2012; 103(3):587–92. [PubMed: 22136423]

59. Kim YH, Nobusawa S, Mittelbronn M, et al. Molecular classification of low-grade diffuse gliomas. Am J Pathol. 2010; 177(6):2708–14. [PubMed: 21075857]

60. Metellus P, Coulibaly B, Colin C, et al. Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis. Acta Neuropathol. 2010; 120(6):719–29. [PubMed: 21080178]

61. Ahmadi R, Stockhammer F, Becker N, et al. No prognostic value of IDH1 mutations in a series of 100 WHO grade II astrocytomas. J Neurooncol. 2012

62. Okita Y, Narita Y, Miyakita Y, et al. IDH1/2 mutation is a prognostic marker for survival and predicts response to chemotherapy for grade II gliomas concomitantly treated with radiation therapy. Int J Oncol. 2012; 41(4):1325–36. [PubMed: 22825915]

63. Hartmann C, Hentschel B, Tatagiba M, et al. Molecular markers in low-grade gliomas: predictive or prognostic? Clin Cancer Res. 2011; 17(13):4588–99. [PubMed: 21558404]

64. Cairncross JG, Wang M, Jenkins RB, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. J Clin Oncol. 2014; 32(8):783–90. [PubMed: 24516018]

65. Erdem-Eraslan L, Gravendeel LA, de Rooi J, et al. Intrinsic molecular subtypes of glioma are prognostic and predict benefit from adjuvant procarbazine, lomustine, and vincristine chemotherapy in combination with other prognostic factors in anaplastic oligodendroglial brain tumors: a report from EORTC study 26951. J Clin Oncol. 2013; 31(3):328–36. [PubMed: 23269986]

66. van den Bent MJ, Gravendeel LA, Gorlia T, et al. A hypermethylated phenotype is a better predictor of survival than MGMT methylation in anaplastic oligodendroglial brain tumors: a report from EORTC study 26951. Clin Cancer Res. 2011; 17(22):7148–55. [PubMed: 21914791]

67. Christensen BC, Smith AA, Zheng S, et al. DNA methylation, isocitrate dehydrogenase mutation, and survival in glioma. J Natl Cancer Inst. 2011; 103(2):143–53. [PubMed: 21163902]

68. Rohle D, Popovici-Muller J, Palaskas N, et al. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. Science. 2013; 340(6132):626–30. [PubMed: 23558169]

69. Clinical trials website. [cited 2014 October 22]. Available from: http://clinicaltrials.gov

70. Agios pharmaceuticals website. [cited 2014 October 22]. Available from: http://www.agios.com/pipeline-idh.php

71. Olar A, Aldape KD. Biomarkers classification and therapeutic decision-making for malignant gliomas. Current treatment options in oncology. 2012; 13(4):417–36. [PubMed: 22956341]

72. Reifenberger J, Reifenberger G, Liu L, et al. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol. 1994; 145(5):1175–90. [PubMed: 7977648]

73. Scheie D, Cvancarova M, Mork S, et al. Can morphology predict 1p/19q loss in oligodendroglial tumours? Histopathology. 2008; 53(5):578–87. [PubMed: 18983467]

74. Cairncross G, Jenkins R. Gliomas with 1p/19q codeletion: a.k.a. oligodendroglioma. Cancer J. 2008; 14(6):352–7. [PubMed: 19060598]

75. Jenkins RB, Blair H, Ballman KV, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer Res. 2006; 66(20):9852–61. [PubMed: 17047046]

76. Griffin CA, Burger P, Morsberger L, et al. Identification of der(1;19)(q10;p10) in five oligodendrogliomas suggests mechanism of concurrent 1p and 19q loss. J Neuropathol Exp Neurol. 2006; 65(10):988–94. [PubMed: 17021403]

77. Labussiere M, Di Stefano AL, Gleize V, et al. TERT promoter mutations in gliomas, genetic associations and clinico-pathological correlations. Br J Cancer. 2014

78. Frenel JS, Leux C, Loussouarn D, et al. Combining two biomarkers, IDH1/2 mutations and 1p/19q codeletion, to stratify anaplastic oligodendroglioma in three groups: a single-center experience. J Neurooncol. 2013; 114(1):85–91. [PubMed: 23681562]

79. Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol. 2006; 24(18):2707–14. [PubMed: 16782910]

80. Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst. 1998; 90(19):1473–9. [PubMed: 9776413]

81. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013; 31(3):337–43. [PubMed: 23071247]

82. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol. 2006; 24(18):2715–22. [PubMed: 16782911]

83. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol. 2013; 31(3):344–50. [PubMed: 23071237]

84. Kaloshi G, Benouaich-Amiel A, Diakite F, et al. Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome. Neurology. 2007; 68(21):1831–6. [PubMed: 17515545]

85. Kesari S, Schiff D, Drappatz J, et al. Phase II study of protracted daily temozolomide for low-grade gliomas in adults. Clin Cancer Res. 2009; 15(1):330–7. [PubMed: 19118062]

86. Tosoni A, Franceschi E, Ermani M, et al. Temozolomide three weeks on and one week off as first line therapy for patients with recurrent or progressive low grade gliomas. J Neurooncol. 2008; 89(2):179–85. [PubMed: 18431544]

87. Chinot OL, Honore S, Dufour H, et al. Safety and efficacy of temozolomide in patients with recurrent anaplastic oligodendrogliomas after standard radiotherapy and chemotherapy. J Clin Oncol. 2001; 19(9):2449–55. [PubMed: 11331324]

88. Hoang-Xuan K, Capelle L, Kujas M, et al. Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. J Clin Oncol. 2004; 22(15):3133–8. [PubMed: 15284265]

89. van den Bent MJ, Taphoorn MJ, Brandes AA, et al. Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971. J Clin Oncol. 2003; 21(13):2525–8. [PubMed: 12829671]

90. Lassman AB, Iwamoto FM, Cloughesy TF, et al. International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors. Neuro-oncology. 2011; 13(6):649–59. [PubMed: 21636710]

91. Jansen M, Yip S, Louis DN. Molecular pathology in adult gliomas: diagnostic, prognostic, and predictive markers. Lancet neurology. 2010; 9(7):717–26.

92. Yip S, Iafrate AJ, Louis DN. Molecular diagnostic testing in malignant gliomas: a practical update on predictive markers. J Neuropathol Exp Neurol. 2008; 67(1):1–15. [PubMed: 18091559]

93. Aubert G, Lansdorp PM. Telomeres and aging. Physiol Rev. 2008; 88(2):557–79. [PubMed: 18391173]

94. Bryan TM, Englezou A, Dalla-Pozza L, et al. Evidence for an alternative mechanism for maintaining telomere length in human tumors and tumor-derived cell lines. Nat Med. 1997; 3(11):1271–4. [PubMed: 9359704]

95. Heaphy CM, Subhawong AP, Hong SM, et al. Prevalence of the alternative lengthening of telomeres telomere maintenance mechanism in human cancer subtypes. Am J Pathol. 2011; 179(4):1608–15. [PubMed: 21888887]

96. Drane P, Ouararhni K, Depaux A, et al. The death-associated protein DAXX is a novel histone chaperone involved in the replication-independent deposition of H3.3. Genes Dev. 2010; 24(12): 1253–65. [PubMed: 20504901]

97. Lewis PW, Elsaesser SJ, Noh KM, et al. Daxx is an H3.3-specific histone chaperone and cooperates with ATRX in replication-independent chromatin assembly at telomeres. Proc Natl Acad Sci U S A. 2010; 107(32):14075–80. [PubMed: 20651253]

98. Goldberg AD, Banaszynski LA, Noh KM, et al. Distinct factors control histone variant H3.3 localization at specific genomic regions. Cell. 2010; 140(5):678–91. [PubMed: 20211137]

99. Lovejoy CA, Li W, Reisenweber S, et al. Loss of ATRX, genome instability, and an altered DNA damage response are hallmarks of the alternative lengthening of telomeres pathway. PLoS genetics. 2012; 8(7):e1002772. [PubMed: 22829774]

100. Bower K, Napier CE, Cole SL, et al. Loss of wild-type ATRX expression in somatic cell hybrids segregates with activation of Alternative Lengthening of Telomeres. PloS one. 2012; 7(11):e50062. [PubMed: 23185534]

101. Heaphy CM, de Wilde RF, Jiao Y, et al. Altered telomeres in tumors with ATRX and DAXX mutations. Science. 2011; 333(6041):425. [PubMed: 21719641]

102. Abedalthagafi M, Phillips JJ, Kim GE, et al. The alternative lengthening of telomere phenotype is significantly associated with loss of ATRX expression in high-grade pediatric and adult astrocytomas: a multi-institutional study of 214 astrocytomas. Mod Pathol. 2013; 26(11):1425–32. [PubMed: 23765250]

103. Killela PJ, Reitman ZJ, Jiao Y, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci U S A. 2013; 110(15):6021–6. [PubMed: 23530248]

104. Theimer CA, Feigon J. Structure and function of telomerase RNA. Curr Opin Struct Biol. 2006; 16(3):307–18. [PubMed: 16713250]

105. Weinrich SL, Pruzan R, Ma L, et al. Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT. Nat Genet. 1997; 17(4):498–502. [PubMed: 9398860]

106. Arita H, Narita Y, Fukushima S, et al. Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol. 2013; 126(2):267–76. [PubMed: 23764841]

107. Huang FW, Hodis E, Xu MJ, et al. Highly recurrent TERT promoter mutations in human melanoma. Science. 2013; 339(6122):957–9. [PubMed: 23348506]

108. Rachakonda PS, Hosen I, de Verdier PJ, et al. TERT promoter mutations in bladder cancer affect patient survival and disease recurrence through modification by a common polymorphism. Proc Natl Acad Sci U S A. 2013; 110(43):17426–31. [PubMed: 24101484]

109. Horn S, Figl A, Rachakonda PS, et al. TERT promoter mutations in familial and sporadic melanoma. Science. 2013; 339(6122):959–61. [PubMed: 23348503]

110. Nault JC, Mallet M, Pilati C, et al. High frequency of telomerase reverse-transcriptase promoter somatic mutations in hepatocellular carcinoma and preneoplastic lesions. Nature communications. 2013; 4:2218.

111. Dissanayake K, Toth R, Blakey J, et al. ERK/p90(RSK)/14-3-3 signalling has an impact on expression of PEA3 Ets transcription factors via the transcriptional repressor capicua. Biochem J. 2011; 433(3):515–25. [PubMed: 21087211]

112. Chen C, Han S, Meng L, et al. TERT promoter mutations lead to high transcriptional activity under hypoxia and temozolomide treatment and predict poor prognosis in gliomas. PloS one. 2014; 9(6):e100297. [PubMed: 24937153]

113. Killela PJ, Pirozzi CJ, Healy P, et al. Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas. Oncotarget. 2014; 5(6):1515–25. [PubMed: 24722048]

114. Chan AK, Yao Y, Zhang Z, et al. TERT promoter mutations contribute to subset prognostication of lower-grade gliomas. Mod Pathol. 2014

115. van Thuijl HF, Scheinin I, Sie D, et al. Spatial and temporal evolution of distal 10q deletion, a prognostically unfavorable event in diffuse low-grade gliomas. Genome biology. 2014; 15(9): 471. [PubMed: 25245118]

116. Houillier C, Mokhtari K, Carpentier C, et al. Chromosome 9p and 10q losses predict unfavorable outcome in low-grade gliomas. Neuro-oncology. 2010; 12(1):2–6. [PubMed: 20150361]

117. Bissola L, Eoli M, Pollo B, et al. Association of chromosome 10 losses and negative prognosis in oligoastrocytomas. Ann Neurol. 2002; 52(6):842–5. [PubMed: 12447941]

118. Cancer, Genome, Atlas, et al. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008; 455(7216):1061–8. [PubMed: 18772890]

119. Olar A, Aldape KD. Using the molecular classification of glioblastoma to inform personalized treatment. J Pathol. 2014; 232(2):165–77. [PubMed: 24114756]

120. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013; 19(4):764–72. [PubMed: 23209033]

121. Chin L, Hahn WC, Getz G, et al. Making sense of cancer genomic data. Genes Dev. 2011; 25(6): 534–55. [PubMed: 21406553]

122. Shete S, Hosking FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet. 2009; 41(8):899–904. [PubMed: 19578367]

123. Chen H, Chen Y, Zhao Y, et al. Association of sequence variants on chromosomes 20, 11, and 5 (20q13.33, 11q23.3, and 5p15.33) with glioma susceptibility in a Chinese population. Am J Epidemiol. 2011; 173(8):915–22. [PubMed: 21350045]

124. Egan KM, Thompson RC, Nabors LB, et al. Cancer susceptibility variants and the risk of adult glioma in a US case-control study. J Neurooncol. 2011; 104(2):535–42. [PubMed: 21203894]

125. Rajaraman P, Melin BS, Wang Z, et al. Genome-wide association study of glioma and meta-analysis. Hum Genet. 2012; 131(12):1877–88. [PubMed: 22886559]

126. Melin B, Dahlin AM, Andersson U, et al. Known glioma risk loci are associated with glioma with a family history of brain tumours -- a case-control gene association study. Int J Cancer. 2013; 132(10):2464–8. [PubMed: 23115063]

127. Di Stefano AL, Enciso-Mora V, Marie Y, et al. Association between glioma susceptibility loci and tumour pathology defines specific molecular etiologies. Neuro-oncology. 2013; 15(5):542–7. [PubMed: 23161787]

128. Jenkins RB, Wrensch MR, Johnson D, et al. Distinct germ line polymorphisms underlie glioma morphologic heterogeneity. Cancer genetics. 2011; 204(1):13–8. [PubMed: 21356187]

129. Jenkins RB, Xiao Y, Sicotte H, et al. A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendroglial tumors and astrocytomas with IDH1 or IDH2 mutation. Nat Genet. 2012; 44(10):1122–5. [PubMed: 22922872]

130. Walsh KM, Codd V, Smirnov IV, et al. Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. Nat Genet. 2014; 46(7):731–5. [PubMed: 24908248]

131. Stacey SN, Sulem P, Jonasdottir A, et al. A germline variant in the TP53 polyadenylation signal confers cancer susceptibility. Nat Genet. 2011; 43(11):1098–103. [PubMed: 21946351]

132. Rice T, Zheng S, Decker PA, et al. Inherited variant on chromosome 11q23 increases susceptibility to IDH-mutated but not IDH-normal gliomas regardless of grade or histology. Neuro-oncology. 2013; 15(5):535–41. [PubMed: 23361564]

133. Hawkins C, Walker E, Mohamed N, et al. BRAF-KIAA1549 fusion predicts better clinical outcome in pediatric low-grade astrocytoma. Clin Cancer Res. 2011; 17(14):4790–8. [PubMed: 21610142]

134. Hasselblatt M, Riesmeier B, Lechtape B, et al. BRAF-KIAA1549 fusion transcripts are less frequent in pilocytic astrocytomas diagnosed in adults. Neuropathol Appl Neurobiol. 2011; 37(7):803–6. [PubMed: 21696415]

135. Jacob K, Albrecht S, Sollier C, et al. Duplication of 7q34 is specific to juvenile pilocytic astrocytomas and a hallmark of cerebellar and optic pathway tumours. Br J Cancer. 2009; 101(4): 722–33. [PubMed: 19603027]

136. Lin A, Rodriguez FJ, Karajannis MA, et al. BRAF alterations in primary glial and glioneuronal neoplasms of the central nervous system with identification of 2 novel KIAA1549:BRAF fusion variants. J Neuropathol Exp Neurol. 2012; 71(1):66–72. [PubMed: 22157620]

137. Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol. 2011; 121(3):397–405. [PubMed: 21274720]

138. Dias-Santagata D, Lam Q, Vernovsky K, et al. BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications. PloS one. 2011; 6(3):e17948. [PubMed: 21479234]

139. Koelsche C, Sahm F, Wohrer A, et al. BRAF-mutated pleomorphic xanthoastrocytoma is associated with temporal location, reticulin fiber deposition and CD34 expression. Brain Pathol. 2014; 24(3):221–9. [PubMed: 24345274]

140. Parker M, Mohankumar KM, Punchihewa C, et al. C11orf95-RELA fusions drive oncogenic NF-kappaB signalling in ependymoma. Nature. 2014; 506(7489):451–5. [PubMed: 24553141]

141. Pietsch T, Wohlers I, Goschzik T, et al. Supratentorial ependymomas of childhood carry C11orf95-RELA fusions leading to pathological activation of the NF-kappaB signaling pathway. Acta Neuropathol. 2014; 127(4):609–11. [PubMed: 24562983]

142. Witt H, Mack SC, Ryzhova M, et al. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer cell. 2011; 20(2):143–57. [PubMed: 21840481]

143. Wani K, Armstrong TS, Vera-Bolanos E, et al. A prognostic gene expression signature in infratentorial ependymoma. Acta Neuropathol. 2012; 123(5):727–38. [PubMed: 22322993]

144. Hoffman LM, Donson AM, Nakachi I, et al. Molecular sub-group-specific immunophenotypic changes are associated with outcome in recurrent posterior fossa ependymoma. Acta Neuropathol. 2014; 127(5):731–45. [PubMed: 24240813]
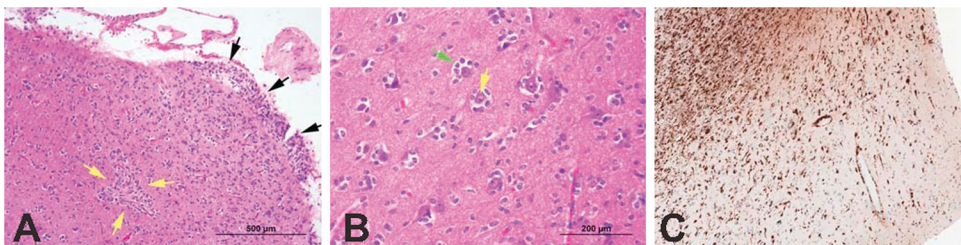
Figure 1.
Diffuse gliomas are aggressive neoplasms that tend to infiltrate along dendrites and axons and travel long distances from the primary site of origin. Malignant glioma cells are shown infiltrating the cortex and forming aggregates along a blood vessel (yellow arrows) extending all the way to the leptomeningeal surface (black arrows) (**A – H&E, Obj: 100X**). A higher power of the cortex highlights neoplastic glioma cells (green arrow) surrounding the neurons (yellow arrow) (**B – H&E, Obj: 200X**). A special immunohistochemical stain for the mutated IDH-R132H protein highlights (in brown) malignant glioma cells infiltrating the normal (pale) subcortical and cortical tissue – note how the subcortex has an incresed density of glioma cells (left upper corner) compared to the superficial cortex (right lower corner) (**C – IDH1-R132H, Obj: 40X, scale not available**).
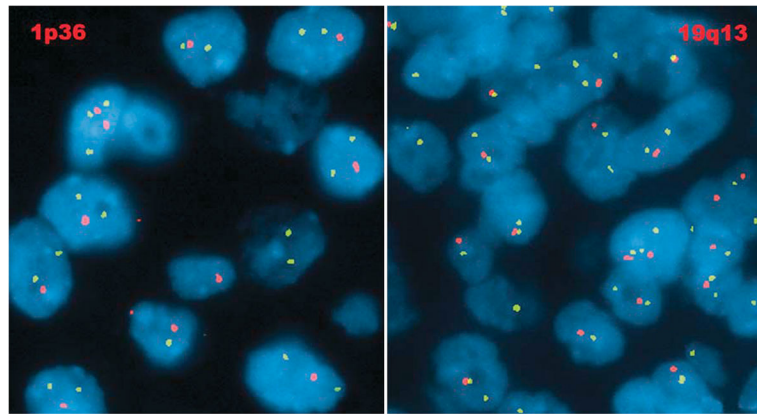
Figure 2.
Diffuse glioma with 1p/19q co-deletion. The locus-specific identifier (LSI) probe, 1p36 (SpectrumOrange) and corresponding LSI 1q25 (SpectrumGreen) show two normal green signals and single abnormal orange signal in a subpopulation of interphase cells suggestive of 1p loss (left). LSI probe, 19q13 (SpectrumOrange) and corresponding LSI 19p13 (SpectrumGreen) show two normal green signals and single abnormal orange signal in a subpopulation of oligodendroglioma interphase cells suggestive of 19q loss (right) (Photographs courtesy of Prof. Dr. Adekunle Adesina, Texas Children's Hospital, Houston, TX, USA).

WHO grade II-III diffuse glioma		
IDH1/2 mutant		IDH1/2 wild-type
1p/19q co-deleted	1p/19q non-co-deleted	
TERT promoter	ATRX	TERT promoter
FUBP1/CIC	TP53	EGFR amplification PTEN loss 10q, 9p loss PI3K/AKT pathway activation
Molecular Oligodendroglioma	Molecular Astrocytoma	Molecular Glioblastoma
Best prognosis	Intermediate prognosis	Worse prognosis

Figure 3.
Proposed molecular classification of WHO grade II-III diffuse glioma.

Table 1

Classification and assigned grading of gliomas after the current WHO system [2].

		WHO grade
Circumscribed	**Astrocytic**	
	Subependymal giant cell astrocytoma	I
	Pilocytic astrocytoma	I
	Pilomyxoid astrocytoma	II
	Pleomorphic xanthoastrocytoma	II
	Ependymal	
	Subependymoma	I
	Myxopapillary ependymoma	I
	Ependymoma	II
	Anaplastic ependymoma	III
Diffuse	Diffuse astrocytoma	II
	Oligodendroglioma	II
	Mixed oligoastrocytoma	II
	Anaplastic astrocytoma	III
	Anaplastic oligodendroglioma	III
	Anaplastic mixed oligoatrocytoma	III
	Glioblastoma	IV
Other	Angiocentric glioma	I
	Desmoplastic infantile astrocytoma	I
	Chordoid glioma of the third ventricle	II
Mixed glio-neuronal tumors	Ganglioglioma	I
	Anaplastic ganglioglioma	III
	Desmoplastic infantile ganglioglioma	I
	Papillary glioneuronal tumour	I
	Rosette-forming glioneuronal tumour of the fourth ventricle	I
	Dysembryoplastic neuroepithelial tumour	I

Table 2

Five-year relative survival rates for patients with diffuse glioma [1].

Diffuse glioma (WHO grade)	5-Year relative survival rate (%)(95% Confidence Interval)
Oligodendroglioma (II)	79.5 (77.9–81)
Mixed oligoastrocytoma (II-III)	61.1 (58.6–63.6)
Anaplastic oligodendroglioma (III)	52.2 (49.1–55.1)
Astocytoma (II)	47.4 (46–48.8)
Anaplastic astrocytoma (III)	27.3 (25.6–28.9)
Glioblastoma (IV)	5 (4.8–5.4)