IDH Mutations in Human Glioma

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KEYWORDS

• IDH1 • IDH2 • Glioma • Isocitrate dehydrogenase • GBM • Brain tumor

KEY POINTS

- Isocitrate dehydrogenase-1 (IDH1) mutations are highly conserved to R132 within the enzyme's active site, suggesting that the mutation may have an oncogenic gain of function.
- IDH1 mutations are associated with other prognostically favorable alterations (*TP53* mutations and 1p19q codeletions) and certain gene cluster profiles (proneural).
- IDH1 mutations are found across different molecular and histologic brain tumor subtypes, suggesting they are early genetic alterations in tumorigenesis.
- Novel IDH1 sequencing and staining techniques have allowed this marker to play an increasingly important role in the histologic determination of brain tumor specimens.

INTRODUCTION

The classification of human brain tumors by the World Health Organization (WHO) scale based on tumor histology remains the gold standard in the diagnosis and prognosis of glioma.[1] In addition to the traditional microscopic characteristics that subcategorize these tumor classes, mounting evidence has come to support distinct genetic aberrations associated with individual tumor sets within this grading scheme. For example, mutations in *TP53* are commonly found in astrocytomas (50%–90%) and oligoastrocytomas (40%–50%) but are infrequent in oligodendrogliomas (5%–10%). On the other hand, 1p19q deletions are frequent in oligodendrogliomas (50%–70%) and less common to rare in oligoastrocytomas (30%–50%) and astrocytomas (0%–15%).[2–4] Although both *TP53* mutations and 1p19q codeletions have been associated with improved prognosis, these mutations are mutually exclusive in gliomas, providing molecular evidence to support the histologic stratification of these tumors.

Recently, a sentinel paper by Parsons and colleagues[5] demonstrated the existence of a novel glioma-associated mutation in isocitrate dehydrogenase-1 (IDH1) in 12% of patients with glioblastoma (GBM) via high-throughput gene expression analysis of 20,661 protein coding genes. IDH1 is 1 of 3 metabolic enzymes (along with IDH2 and IDH3) that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) while reducing $NADP^+$ to NADPH (NAD^+ to NADH in the case of IDH3).[6] Mutations in IDH1 were found to be associated with younger age, secondary GBMs (grade IV tumors that arise from biopsy-proven lower-grade predecessors), and increased overall survival (OS). Subsequently, a multitude of retrospective and prospective studies have emerged investigating the frequency, function, and prognostic utility of this mutation in human glioma.[7–36]

IDH1: FUNCTION

IDH1, -2, and -3 are enzymes involved in the citric acid cycle that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) while reducing $NADP^+$ to NADPH (NAD^+ to NADH in the case of IDH3).[37] Although IDH1 is found within

No conflicts of interest to disclose.

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Neurosurg Clin N Am 23 (2012) 471–480

doi:10.1016/j.nec.2012.04.009

1042-3680/12/$ – see front matter Published by Elsevier Inc.

the cytoplasm and peroxisomes, IDH2 and IDH3 are localized solely to the mitochondria.[38] The gene for IDH1 is located on 2q33.3 and is 1 of 5 IDH genes within the human genome.[39] Two of the 5 IDH genes produce homodimeric proteins (IDH1 and IDH2), whereas the remaining 3 IDH gene products constitute the subunits of the heterotetrameric protein IDH3 (2 IDH3α, IDH3β, and IDH3γ).[40] Human IDH1 contains 2 asymmetric active sites formed by small and large domains of each IDH1 molecule and transitions between an inactive open, an inactive semiopen, and a catalytically active closed conformation.[6,41] A critical structure in the enzymatic interaction with the substrate isocitrate is the arginine 132 (R132) found within the active site of IDH1 (arginine is conserved in the functionally analogous R172 of IDH2). This residue is unique among all others involved in the binding of isocitrate in that it forms 3 hydrogen bonds with the α- and β-carboxyl groups of the substrate, whereas other residues form no more than 2.[36] Moreover, it plays a critical role in facilitating the hinge movement between the open and closed conformations.[42,43] The R172 residue in IDH2 plays an identical role because it is the evolutionarily conserved homolog of R132 in IDH1.

Mutations in IDH1 and IDH2 are generally mutually exclusive, and there has only been one report of simultaneous IDH1 and IDH2 mutations to date.[34] Interestingly, apart from rare case reports, the mutations of IDH1 and IDH2 occur exclusively at these arginine residues (most commonly replaced by histidine, R132H in IDH1), which are highly conserved across species and malignancies that involve the mutation of isocitrate dehydrogenase.[44–46] The mutations are missense substitutions, with no evidence of inactivating nonsense deletions of base pairs. This slight modification in the active site of the enzyme disrupts the aforementioned hydrogen bonding of the critical R132 and results in a shift in the enzymatic equilibrium to favor the closed configuration and subsequently increased affinity for nicotinamide adenine dinucleotide phosphate (NADPH).[42] In addition, with the change in the active site conformation, there is a markedly reduced affinity for isocitrate. As a result of these changes, R132 mutations result in a greater than 80% reduction in activity compared with the wild-type (wt) enzyme.[36]

IDH1 MUTATIONS IN HUMAN GLIOMA

Following the first report that IDH1 mutations were found more frequently in secondary GBMs (sGBM) compared with primary GBMs (pGBM), other studies showed similar findings and elucidated other associations between IDH1 mutation status and WHO classification (**Table 1**). Indeed, IDH1 mutations are more frequently found in sGBMs, with reported frequencies ranging from 50% to 86% compared with pGBMs, which contain the mutation only 4% to 21% of the time.[8,9,18,21,24,25,28,31,34,35,47–50] sGBMs were frequently cited as being associated with younger patients; prognostically favorable genetic alterations, including 1p19q deletions and *TP53* mutations; and an improved clinical course.[5,18,24,26,35] The association between IDH1 mutations and favorable overall prognosis was so striking that some groups argued that sGBMs lacking these characteristics may in fact be pGBMs that were underdiagnosed as anaplastic tumors on initial discovery; the molecular similarities with pGBMs of these IDH1 mutation-negative sGBMs and the fact that all said tumors were initially found as anaplastic gliomas supported this assertion.[24]

Table 1
Frequency of IDH1 mutations in various glial tumors based on results from direct sequencing

Tumor Type	Cases Studied	Mutations Detected	Frequency (%) (Range)
Diffuse astrocytoma[8,16,18,21,23,25,28,30,31,35,48,50–53,86]	887	669	75 (59–100)
Oligodendroglioma[8,16,18,23,28,35,47,48,51,53,86]	623	485	78 (67–93)
Oligoastrocytoma[8,16,18,23,28,35,47,48,51,53,86]	371	291	78 (50–100)
Anaplastic astrocytoma[8,9,16,18,21,23,25,28,30,31,34,35,48,50,51,53,86]	1084	674	62 (0–100)
Anaplastic oligodendroglioma[8,16,18,23,28,35,48,50,51,86]	721	482	67 (49–86)
Anaplastic oligoastrocytomas[8,16,18,21,28,32,34,35,48,50,86]	849	547	64 (63–100)
Secondary GBM[8,9,18,24,25,31,35,47,50,51]	134	96	72 (50–86)
Primary GBM[9,21,25,28,34,47–51,86]	1837	121	7 (4–21)
Pediatric GBM[8,27,35,51]	85	9	11 (0–16)

The reported rates of IDH1 mutation in low-grade gliomas (LGG) are comparable with those of sGBMs, ranging from 59% to 100% in diffuse astrocytomas, 67% to 93% in oligodendrogliomas, and 50% to 100% in oligoastrocytomas. WHO grade III tumors seem to share a similar rate of IDH1 mutations (0%–100% in anaplastic astrocytomas, 49%–86% in anaplastic oligodendrogliomas, and 63%–100% in anaplastic oligoastrocytomas); however, when calculated and compared across numerous series, they seem to have a lower overall frequency (see **Table 1**).[8,16,18,21,23,25,26,28,30,31,35,47,48,51–53] The ubiquitous nature of the mutation across histologic grades and traditionally dichotomized tumor groups (eg, oligodendroglial and astrocytic tumors) separated it from previously described genetic alterations and sparked great interest in elucidating its role in tumorigenesis and its value as a prognostic marker.

PUTATIVE ROLE OF IDH1 MUTATIONS IN GLIOMAGENESIS

It was initially thought that the loss of IDH1 enzymatic ability and subsequent decreased production of α-KG was a form of dominant negative activity and the driving force behind this mutation's oncogenic properties. Indeed, α-KG has critical ancillary roles aside from those of metabolism, as it is required by prolyl hydroxylases (PHD), enzymes that aid in the degradation of hypoxia induced factor-1α (HIF-1α). HIF-1α in turn serves as a key modulator of the transcription factor HIF-1, which is responsible for expressing genes implicated in tumor progression (eg, glucose metabolism, angiogenesis, and invasion) in response to low oxygen levels.[54] It seemed plausible that the loss of α-KG, resulting in the destabilization of PHDs and the accumulation of HIF-1α, could result in tumorigenesis as is seen in 2 other metabolic enzymes that have been found to serve as oncogenes: succinate dehydrogenase and fumarate hydratase.[55] Although initial work reported elevated levels of HIF-1α in IDH1 mutant tumors,[36] subsequent studies involving genome array, immunohistochemical, and fluorodeoxyglucose positron emission tomography analyses did not find significantly elevated levels of HIF-1α in IDH1 mutated gliomas.[23,31,56] Moreover, because the tumors associated with the loss of succinate dehydrogenase and fumarate hydratase are vascular because of the activated angiogenesis pathways, the lack of vascularity in IDH1-mutated LGG (tumors most frequently carrying the mutation) further argues against this as an underlying mechanism in their gliomagenesis.[57]

Other biochemical arguments against the role of reduced α-KG in gliomagenesis stem from the reasoning that a significant percentage of IDH1 molecules would need to exist as heterodimers in order for this mutation to exert dominant negative activity in vivo. A study by Jin and colleagues[58] demonstrated that although IDH1 R132 mutants have equal binding affinity for IDH1 wt proteins, IDH2 R172 mutants (which exhibit the same clinical and molecular profiles as IDH1 mutants) have little affinity for their IDH2-wt counterparts. This finding is supported by other studies that have shown that IDH1/2 containing glioma do not have significantly reduced levels of α-KG.[42,59]

Notwithstanding the controversial role of diminished oxidative decarboxylation of isocitrate to α-KG, IDH1/2 mutants do gain a neomorphic ability to convert α-KG to D-2-hydroxyglutarate (2-HG). This ability is likely secondary to the newly developed high affinity for NADPH by the R132/R172 mutant enzyme, which changes the equilibrium of the active site state to kinetically allow, and even favor, the conversion of α-KG to 2-HG.[42] Assays of 2-HG have shown increases in its concentration from 100- to 300-fold in glioma cells harboring IDH1 mutations.[42,59–61] Furthermore, the addition of 2-HG alone into glioma cells has been shown to decrease proliferation without inducing apoptosis as was found in IDH1 R132 mutant cells[61]; the addition of this metabolite also induced global metabolic changes in IDH1-wt glioma on metabolomic analysis, akin to those found in IDH1-R132H expressing cells.[62] The existence of a highly conserved mutation site without complete inactivation of the gene product, combined with data showing that the knockdown of IDH1-wt does not produce downstream changes shared by 2-HG–injected or IDH1-R132 mutant glioma, gives further credence to the idea that the isocitrate dehydrogenase gene serves as an oncogene with gain of function through its mutation.[6,57,62]

The notion that 2-HG may serve as an oncogenic metabolite in IDH1/2 mutated gliomas was appealing given the existence of congenital conditions, such as L-2HG aciduria whereby germ-line mutations of IDH result in the accumulation of the L-enantiomer of 2-HG, with some of these patients developing malignant brain tumors.[63,64] However, brain tumors are not found in the form of 2-HG aciduria that accumulates the D-enantiomer, although some suggest that because it is the more clinically severe form, these patients may not live long enough to develop intracranial neoplasms.[65,66] There is some evidence that the accumulation of 2-HG in cells may lead to epigenetic alterations because high levels of 2-HG have been shown to reduce the activity of histone

demethylases and Translocated in liposarcoma, Ewing's sarcoma and TATA-binding protein-associated factor 15 (TET) 5-methylcyosine hydroxylases, which are 2 enzymes that have recently been implicated in the epigenetic control of gene transcription, although the exact mechanism is unclear.[60] Further studies are required to resolve the role of 2-HG in gliomagenesis.

IDH1 MUTATIONS AND OTHER GLIOMA-ASSOCIATED GENETIC CHARACTERISTICS

With mounting evidence that IDH1 mutations in glioma are associated with favorable molecular profiles and clinical outcomes, many studies began reporting on its association with other known significant genetic aberrations in human brain tumors. Traditionally, O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, *TP53* mutation, and deletions of 1p19q have been associated with improved outcomes in patients with glial tumors.[67–69] IDH1 mutations were found to be strongly associated with 1p19q codeletions in numerous studies,[18,22–24,28,32,70] although a few others did not find any significant relationship between the two.[8,14] Most of the published work to date regarding the association between these two genetic phenomena have indicated a high incidence of co-occurrence, with reported rates of 90% to 100% of IDH mutations in gliomas that have 1p19q deletions.[22,28] The correlation between *TP53* and IDH1 mutations is not as robust[8,11,14,15,28]; however, the trend of evidence does suggest a high rate of simultaneous mutations in gliomas that have been studied to date.[10,19,23,24,31,35,48] MGMT promoter methylation was similarly found to be associated with IDH1 mutation in numerous studies,[10,15,28,29,31,32] although others did not find any significant relationship.[30,71,72]

The overwhelming presence of IDH1 mutations with 1p19q deletion and *TP53* mutation, 2 events that have been classically dichotomized with distinct histologic and molecular groups, namely oligodendroglial and astrocytic tumors, alluded to an early genetic event that occurred before the differentiation of neural progenitor cells into these various tissue types. In the case of recurrent gliomas whereby multiple biopsies were taken, investigators were able to discern the presence of these genetic events in temporal sequence. In many cases, IDH1 mutations were found to be simultaneously present with *TP53* mutations or 1p19q deletions, whereas in others, IDH1 mutations preceded them. In no case did *TP53* mutations or 1p19q deletions precede the mutation of IDH1, indicating that this was indeed an early event in the development of glioma.[25,35,70] Watanabe and colleagues[26] analyzed a series of glioma from patients with Li-Fraumeni syndrome, who on account of their disease have germ-line *TP53* mutations, and found that 71% of their patients had an IDH1 mutation. Of note, 100% of these mutations were R132C substitutions, a rarer form of mutation (3.6%–4.6%) compared with R132H (~90%),[12] suggesting that this mutation may be the favored gliomagenic pathway in patients with preexisting mutations of TP53.[26] These findings indicate that although there seems to be a predilection for IDH1 mutations to be an early step in the formation of glioma, it is not the exclusive pathway in IDH1 mutation based gliomagenesis.

In addition to isolated changes in chromosome copy and gene mutations, some studies have investigated the relationship between IDH1 mutations and glioma genetics on a genome level. Recently, there has been mounting interest in chromosome methylation profiles of individual neoplasms. The cancer genome atlas project first identified DNA methylation, primary sequence, copy number, and gene expression changes characteristic of GBM tumors in 2008.[73] Noushmehr and colleagues[74] analyzed more than 200 gliomas for their glioma-CpG island methylator phenotype (G-CIMP) to ascertain if there was any relationship between IDH1 mutations and overall DNA methylation profiles. They found a tight association between G-CIMP with IDH1-mutation-containing tumors (18/23; 78%), whereas all 184 G-CIMP-negative tumors were IDH1-wt. They analyzed an additional 100 gliomas of all WHO grades and independently confirmed the strong relationship between IDH1-mutant tumors and G-CIMP (35/48; 72.9%). Similarly, Christensen and colleagues[10] clustered gliomas into separate groups based on their methylation status and found that only 2 distinct methylation classes had IDH1 or IDH2 mutants and that more than 98% of the tumors in these 2 classes possessed the mutation. Moreover, these methylation profiles were stable across the evolution of the tumor into more malignant grades, suggesting that these changes occurred early during gliomagenesis,[75] giving further credence to the idea that the mutation of IDH1 may have a role in the epigenetic modulation of gene expression.

Other cluster analyses based on overall gene expression have found that a high percentage of IDH1-mutants were associated with a proneural gene expression profile, a genetic gestalt that is commonly associated with younger age and improved prognosis compared with other expression constitutions (mesenchymal, neural, and classical).[74,76] Finally, recent reports have

described the association between IDH1 mutation and internexin-α, a proneural gene encoding a neurofilament interacting protein that has previously been shown to be tightly related to 1p19q codeletions and a predictor of favorable outcomes in anaplastic oligoastrocytomas and anaplastic oligodendrogliomas.[77,78] Further studies will likely help add to the list of IDH1 mutation-associated genetic changes that interact in the oncogenesis of these unique tumors.

ROLE OF IDH1 MUTATION IN PROGNOSIS AND RESPONSE TO TREATMENT IN HUMAN GLIOMA

Since the publication of the first report on improved survival in patients with GBM with IDH1 mutations (45.6 vs 13.2 months in IDH1-mutations vs IDH1-wt respectively) by Parsons and colleagues,[5] numerous groups have been able to replicate similar findings.[12,18,22,24,28,31,32,34,35] In addition to improved OS, Sanson and colleagues[28] were able to demonstrate improved progression free survival (PFS) as well in their set of patients with GBM, with 55 months PFS in patients with IDH1 mutation versus 8.8 months PFS in those without it. The analysis was extended to anaplastic (WHO grade III) tumors because many groups were readily able to show an improved OS in grade III tumors that harbored the IDH mutation compared with those that did not in both univariate[18] and multivariate analyses.[22,28,32] In a prospective analysis, Wick and colleagues[34] found that grade III astrocytomas that possessed the IDH1 mutation were associated with greater PFS regardless of the treatment arm and conferred a stronger risk reduction than any other factor in multivariate analysis, including histology.

The evidence for LGG and the prognostic value of IDH1 mutations is slightly more controversial. Two independent groups found that IDH1 mutations in LGG were associated with significantly improved OS,[11,23] whereas others could not find any significant association.[18,70] Weller and colleagues[33] found improved PFS with IDH1 mutation in univariate and multivariate analyses but no significant improvement in OS in multivariate analysis.

It is still unclear if IDH1 mutational status is a prognostic indicator or a predictive measure of response to treatment. Houillier and colleagues[17] stratified a cohort of LGG into 3 groups based on prognostic factors based on the presence of 1p19q deletion, IDH1 mutation, or both together. They found that each of these factors was an independent predictor of improved clinical outcome in response to treatment with the chemotherapeutic agent temozolomide and that the group of patients with both mutations had the best treatment response (objective response in 80% with both mutations, 61% of IDH1-mutants without 1p19q deletion, 17% without either mutation). In a similar fashion, Hartman and colleagues[14] found that in their cohort of patients that received adjuvant therapies, IDH1 mutation status was the single most important predictor of PFS and OS; this was not seen in their cohort of patients that did not receive adjuvant therapy. These findings support the notion that IDH1 mutations may be an important predictor to treatment response. However, van de Bent and colleagues[32] reported that improved prognosis was found regardless of adjuvant therapy when investigating IDH1-mutant glioma in response to procarbazine (Matulane), lomustine (CCNU), and vincristine (Oncovin) chemotherapy. Future studies are necessary to better determine the prognostic versus predictive role of IDH1 status in human glioma.

DETECTION OF IDH1 MUTATIONS

There are 6 amino acid base pair substitutions at R132 of IDH1 that have been identified to date in human glioma: R132H (88.2%–92.7%), R132C (3.6%–4.6%), R132L (0.4%–4.3%), R132 G (0.6%–3.8%), R132S (0.8%–2.5%), and R132P (0.4%).[8,9,12,16,25,26,35] The identity of the amino acid does not seem to have any bearing on the function of the mutant enzyme as long as the arginine is replaced.[8] The R132C substitution has been found in greater frequency in astrocytomas[12,18] and gliomas associated with Li-Fraumeni syndrome, which were diffuse and anaplastic astrocytomas.[26] Recently Pusch and colleagues[44] identified 3 cases of R100Q substitutions within the IDH1 gene. In line with the preexisting dogma that it was the conformational alteration of the IDH1 protein that allowed neomorphic enzymatic activity, R100 is within the active site involved in binding isocitrate. Regardless of the location of the amino acid substituted, each of the identified IDH1 mutations seems to share the same molecular and clinical properties.

Given the increasing importance of IDH1 mutation status in glioma research, there has been considerable effort to develop novel ways to quickly and reliably detect this mutation in tissue specimens. Traditionally, and in most of the literature to date, IDH1 status was detected through traditional Sanger sequencing and polymerase chain reaction (PCR). Although this has the clear advantage of being able to detect non-R132H mutations, it is time consuming and requires there to be at least 20% mutant allele frequency within

the tissue specimen for reliable detection.[51] Pyrosequencing is an alternative to traditional sequencing that allows for rapid high-throughput analysis of IDH1 mutations. This method has been recently used to detect IDH1 mutations in gliomas and demonstrated an advantage over classic Sanger sequencing in that it can detect mutated allele frequencies down to 5%.[71,79]

Derived cleaved amplified polymorphic sequence analysis is another alternative to DNA sequencing that uses mismatched primers for specific mutations, which, following PCR amplification, will create differing restriction endonuclease sites depending on the presence of the mutation.[80] The advantage of the technique is that it uses supplies commonly found in most laboratories, obviating expensive sequencing equipment. However, unlike sequencing, the method is limited in that it can only detect mutations being queried. Other PCR-based techniques include coamplification at lower temperature (COLD) PCR with high-resolution melting (HRM) and real-time PCR and post-PCR fluorescent melting curve analysis (FMCA). Through COLD PCR combined with HRM, Boisselier and colleagues[81] were able to detect mutant allele concentrations of 0.25% in a span of only 3 hours. However, because the technique requires the new mutation to have a T_m that is lower than IDH1-wt, it theoretically may not be able to detect R132 G mutations. Real-time PCR with post-PCR FMCA was shown by Horbinski and colleagues[82] to be more sensitive than Sanger sequencing with detection rates of as little as 10% mutant DNA and a processing time of 80 minutes.

A monoclonal antibody to detect IDH1-R132H mutations (mIDH1R132H) was developed with a reported sensitivity and specificity of 94% and 100%, respectively.[47,53] Other antibodies for R132H followed, including IMab-1[83] and DIA-H09,[15] with one report indicating that DIA-H09 was superior to IMab-1 in that it was generally crisper with better signal-to-noise ratio.[84] Proponents of immunohistochemistry-based antibody staining argue that the use of these antibodies to identify IDH1 mutations may even be superior to direct sequencing because there are reported cases in which these antibodies detect mutations missed by direct sequencing, likely because of poor tissue preservation of samples.[15,30] Their ability to detect even single IDH-mutant-containing tumor cells and distinguish them from non-neoplastic brain tissue or tissue contaminants, such as reactive gliosis, radiation necrosis, hemorrhage, and brain tumors with known absence of IDH-mutations (in addition to the technical simplicity of this method), make it a favorable alternative for clinical use.[53,85,86] However, because the antibodies are mutation specific, it can be expected that those designed to bind R132H will fail to detect IDH1 mutants approximately 10% of the time. Moreover, Ikota and colleagues[86] found that these antibodies may sometimes give false positives by staining antimitochondrial antibodies in the cytoplasm of certain cells, so microscopic interpretation should be done with caution to ensure that the antibody stains both the nucleus and the cytoplasm. Although there are other available antibodies to detect the less frequent mutations (eg, R132S),[87] current immunohistochemistry techniques may need to be complemented by other detection techniques to increase their sensitivity to 100%.[30]

IDH MUTATIONS IN OTHER BRAIN TUMORS

Multiple studies have reported the rate of IDH1 mutations in tumors other than glioma. In regard to central nervous system (CNS) tumors, IDH1 mutations do seem to favor glial tumors because the highest frequencies of mutations are found in astrocytic and oligodendroglial tumors of WHO grades II, III, and IV, as mentioned previously. Juvenile pilocytic astrocytomas do not seem to fall under the predilection of IDH1 mutations because there have been no reports of this gene mutation in this tumor type to date.[18,21,35] This finding suggests that despite their glial origin, these tumors arise from a distinct mechanism than other gliomas. Other CNS tumors that conspicuously lack IDH1 mutations include medulloblastomas,[8,18,35] dysembryoplastic neuroepithelial tumors,[18,51,53] schwannomas,[18] meningiomas,[51,53,86] pleomorphic xanthoastrocytomas,[8,35,51,71] subependymal giant cell astrocytomas,[8,35,51] and ependymomas.[8,18,25,35]

IDH1 mutations have been found with moderate frequency within gangliogliomas, and have been shown to confer a poorer prognosis in these patients. In a large-scale multi-institutional analysis of 98 gangliogliomas, Horbinski and colleagues[49] found that 8.2% (8/98) of the gangliogliomas harbored the R132H IDH1 mutation, and that these patients were older (46.1 vs 25.5 years of age), had greater risks of adverse outcomes (high-grade transformation or death), and shorter recurrence-free survival. On multivariate analysis, the presence of the IDH1 mutation was found to be the most powerful risk factor after age.

Pediatric gliomas have been reported to possess IDH mutations less frequently than their adult counterparts.[7,19] However, when analyzed across numerous studies, they seem to have a frequency comparable to primary GBM in adults

(see **Table 1**).[8,27,35,51] Although they too are associated with older age,[88,89] they seem to have increased PFS and OS[27] when compared with patients possessing IDH-wt tumors. This finding was highlighted in a study by Pollack and colleagues[27] whereby 100% of their IDH mutations were in children aged older than 14 years (7/20, 35%), whereas none of their patients aged younger than 14 years were positive for the mutation. Given the paucity of studies, further reports will be needed before the exact frequency and prognostic value of IDH1 mutations in the pediatric population can be determined.

SUMMARY

The discovery of IDH1/2 mutations in gliomas was arguably one of the most significant breakthroughs in our understanding of the oncogenesis and classification of gliomas in the past decade. The presence of the mutation in both astrocytic and oligodendroglial tumor types suggests that it is an early event in the pathogenesis of brain tumors and has added novel insight in the way we view gliomas and their origins. Its value as a molecular prognosticator is becoming increasingly evident as more and more studies are published regarding its value in the clinical setting. Its ability to serve as a marker for improved clinical outcome over traditional measures, such as tumor grade and histopathology, has caused some to suggest it be added to the next addition of the WHO tumor classification scheme.[15] The use of IDH1 status to predict clinical outcome, aid diagnosis in histopathology, and illuminate the mechanisms underlying oncogenesis have been invaluable steps in glioma research to date. Future research will need to continue exploring these avenues to help further our understanding of this novel mutation and aid the development of novel therapies to target brain tumors that harbor it.

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