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# IDH1 and IDH2 Mutations in Gliomas

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## Abstract

Mutations in isocitrate dehydrogenase (IDH) 1 and 2, originally discovered in 2009, occur in the vast majority of low grade gliomas and secondary high grade gliomas. These mutations, which occur early in gliomagenesis, change the function of the enzymes, causing them to produce 2-hydroxyglutarate, a possible oncometabolite, and to not produce NADPH. IDH mutations are oncogenic, although whether the mechanism is through alterations in hydroxylases, redox potential, cellular metabolism, or gene expression is not clear. The mutations also drive increased methylation in gliomas. Gliomas with mutated IDH1 and IDH2 have improved prognosis compared to gliomas with wild-type IDH. Mutated IDH can now be detected by immunohistochemistry and magnetic resonance spectroscopy. No drugs currently target mutated IDH, although this remains an area of active research.

### Keywords

Isocitrate dehydrogenase; astrocytoma; oligodendroglioma; glioblastoma; 2-hydroxyglutarate; carcinogenesis; prognosis; mutations

## Introduction

Diffuse gliomas are the most common primary brain tumor in adults, affecting about 20,000 people in the US each year [1]. Most gliomas are astrocytic (70%) or oligodendroglial tumors (9%), which include classic oligodendrogliomas and mixed oligoastrocytomas [1]. Three pathways of glioma development have been identified: primary glioblastoma that arise de novo without lower grade precursors, astrocytomas that start as grade 2 or 3 and then transform into secondary glioblastoma, or oligodendrogliomas that can transform into anaplastic oligodendroglioma. Infiltrating gliomas are incurable with current treatment modalities: surgery, radiation, and chemotherapy. While several important genetic alterations in gliomas have been known for some time, new technologies have allowed much

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deeper genetic and epigenetic analyses of larger numbers of glioma samples, leading to a number of novel discoveries in the past few years. One of the most exciting and clinically relevant observations was the discovery that a high percentage of lower grade gliomas (and a lower percentage of higher grade gliomas) harbor mutations in the genes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2). Growing data indicate that these mutations play a causal role in gliomagenesis, have a major impact on tumor biology, and also have clinical and prognostic importance

## Glioma histopathologic and molecular classification

Diffuse gliomas can be categorized according to grade; low grade (grade II), anaplastic (grade III), and glioblastoma (GBM, grade IV). Traditionally, GBMs have been classified as primary or secondary on the basis of clinical presentation [2]. Secondary GBMs display evidence of progression from a lower-grade tumor, whereas primary GBMs present as advanced cancers at diagnosis. Secondary GBMs are predominantly found in younger patients (median age of ~45 years compared with median age of ~60 years for primary GBM) and tend to occur less frequently than primary GBMs, making up ~5% of total GBMs [3]. Despite the differences in their ontology, these high grade tumors are histopathologically indistinguishable [3].

Recently, large scale efforts have been made to identify the major genetic and epigenetic alterations and to define important molecular subtypes in GBM and lower grade gliomas [4, 5]. Publications from the Cancer Genome Atlas (TCGA) effort have identified 4 subgroups of GBM based on dominant gene expression patterns, which were called Proneural, Neural, Mesenchymal, and Classical [5]. Individual gene expression subtypes were associated with specific genetic and epigenetic alterations. Secondary GBMs are virtually always Proneural, while primary GBM can be any of the subtypes.

As discussed below, mutations in one of the IDH genes are tightly linked with the Proneural phenotype and secondary glioblastomas. Virtually all tumors with IDH mutation are of the Proneural gene expression subtype. In addition, IDH mutation was observed to be associated with increased DNA methylation, called G-CIMP for Glioma CpG Island Methylation Phenotype [6]. Thus, both IDH mutation and G-CIMP phenotype are seen almost exclusively in secondary GBMs. Developing data regarding the metabolic and biologic consequences of IDH mutation have led to significant increases in our understanding of the development and clinical behavior of these different molecular subtypes of glioma.

## IDH Mutations and Alterations in IDH Function

In 2008, a multi-group collaboration sequenced over 20,000 genes in 22 GBMs and identified a common point mutation in the metabolic gene *IDH1* in 12% of the samples analyzed [7]. Further studies found that this mutation is present in ~80% of grade II-III gliomas and secondary GBM [8-14]. Mutations in *IDH2* have also been identified in gliomas, although they are much less common and are mutually exclusive with mutations in *IDH1* [10, 15, 14]. All mutations identified to date have been a single amino acid missense mutation in IDH1 at arginine 132 (R132) or the analogous residue in IDH2 (R172). Before these observations, mutation of IDH genes had never been linked to cancer. However,

subsequent studies have identified IDH mutations in acute myelogenous leukemia, cholangiocarcinoma, cartilaginous tumors, prostate cancer, papillary breast carcinoma, acute lymphoblastic leukemia, angioimmunoblastic T-cell lymphoma, and primary myelofibrosis indicating that these genes may be important players in multiple tumor types [16-23].

Five genes encode for three human IDH catalytic isozymes: IDH1, IDH2, and IDH3. IDH1 and 2 form homodimers while IDH3 forms a heterotetramer containing two α, one β, and one γ subunit [24]. IDH3 functions in the Kreb cycle to convert isocitrate to α-ketoglutarate (α-KG) and NAD+ to NADH. The IDH1 and IDH2 proteins in the cytosol and mitochondria, respectively, generate reduced nicotinamide adenine dinucleotide phosphate (NADPH) from NADP+ by catalyzing the oxidative decarboxylation of isocitrate to α-KG outside of the Kreb cycle [25]. NADPH is mainly produced by glucose 6-phosphate dehydrogenase (G6PDH), malate dehydrogenase, and IDH. Upon exposure to free radicals and reactive oxygen species (ROS), cells with low levels of IDH became more sensitive to oxidative damage [26]. These studies demonstrated that in addition to being a major enzyme in the citric acid cycle, IDH may also function to maintain the cellular redox state and suggests that IDH plays an important role in cellular defense against oxidative stress.

All mutations in *IDH1* in glioma appear to effect amino acid residue 132, with the vast majority (>85%) containing a heterozygous missense mutation of arginine to histidine (R132H) [27]. This residue is located in the active site of the enzyme and is critical for isocitrate binding [28]. The mutation at R132 inactivates the protein's ability to bind isocitrate and abolishes its normal catalytic activity. The net result is reduced levels of α-KG and NADPH, which is an important cofactor that is necessary to maintain normal levels of reduced glutathione (GSH) to combat ROS [29, 30].

## IDH Mutations and Oncogenesis

One question that always arises in studies of gene mutations in cancer is whether that specific gene is a key driver of tumor formation (oncogenesis), whether the mutation arises as a step in tumor progression, or whether it is an incidental consequence of impaired DNA repair in tumors (e.g. a carrier mutation). Two lines of evidence support the concept that IDH mutation is a direct driver of oncogenesis. First, somatic mosaicism for IDH1 or IDH2 at R132 causes the enchondromatosis syndromes, Ollier's disease and Maffucci syndrome, which are characterized by hemangiomas and cartilaginous tumors and which carry an increased risk for gliomas [18, 31, 32]. Second, introduction of mutated IDH into normal cells causes increased proliferation, increased colony formation, and inability to differentiate [33-35].

Exactly how IDH mutation contributes to oncogenic transformation remains controversial. Initial reports suggested that the mutant protein functions in a dominate-negative fashion by heterodimerizing to wild-type IDH1 and impairing its activity [36-38]; however, more recent *in vitro* studies have shown that the mutated IDH1 protein acquires the ability to convert α-KG to R(-)-2-hydroxyglutarate (2-HG) [39, 40]. This is supported by the findings that 2-HG levels are elevated in gliomas containing an *IDH1* mutation [39]. These findings led to the hypothesis that mutant *IDH* is an oncogene and 2-HG is an 'oncometabolite' [41].

Whether it is 2-HG or mutated IDH or both that promotes cancer remains unclear. An increased risk of gliomas has been observed for patients with inborn errors of metabolism that result in increased levels of S-2-HG but not R-2-HG, although interestingly people with R-2-hydroxyglutaric aciduria can have IDH2 mutations but never IDH1 mutations [42, 43]. Furthermore, It was recently discovered that the wild-type IDH1 can also catalyze the conversion of α-KG to 2-HG, albeit less efficiently than mutant IDH [44].

New evidence suggests that by antagonizing α-KG, 2-HG competitively inhibits the activity of many α-KG-dependent dioxygenases, including but not limited to histone demethylases (e.g. collagen prolyl-4-hydroxylase, prolyl hydroxylases, and the ten-eleven translocation (TET) family of DNA hydroxylases) [45, 35, 46]. As described above, profiling of GBM from the TCGA demonstrated an association between IDH mutation and increased promoter methylation (G-CIMP) [6], which generally results in transcriptional silencing of the associated genes [47].

Two recent independent studies demonstrated that the G-CIMP phenotype was not only correlated with IDH mutation but that IDH mutation alone is actually the cause of the G-CIMP hypermethylation phenotype in diffuse gliomas [48, 49]. In these studies, introduction of mutant *IDH1* into immortalized primary human astrocytes was found to be sufficient to cause the hypermethylator phenotype [50]. One possible implication of these findings is that reduced α-KG and increased 2-HG (from IDH mutation) may predispose cells harboring mutant IDH to malignant transformation via genome-wide epigenetic changes. However, further studies are needed to determine the precise link between these effects of IDH mutation and actual oncogenic transformation as development of CIMP phenotype in astrocytes after introduction of IDH mutations did not result in tumor formation.

## IDH Mutations and the Hypoxia Pathway

Prolylhydroxylase domain enzymes (PHD) are important for the hydroxylation and degradation of hypoxia-inducible factor 1α (HIF-1α). These enzymes require α-KG and divalent ferrous iron ($Fe^{2+}$). One of the effects of IDH mutation is the depletion of α-KG and oxidation of ferrous iron by ROS. Reduced levels of α-KG and $Fe^{2+}$ in mutant *IDH* cells may therefore promote cellular accumulation of HIF-1α. Activation of this pathway leads to the induction of HIF-1 target genes that affect angiogenesis, metabolism, growth and differentiation, apoptosis and autophagy, as well as cell motility [51]. Zhao *et al*. found that overexpression of mutant *IDH* in U87MG glioma cells increased HIF-1α protein levels and induced HIF-1α target gene expression. This effect was abolished after exogenous administration of α-KG. In addition, HIF-1α protein expression was found to be higher in gliomas with *IDH1* mutations compared with those containing wild-type IDH [38]. These observations suggest that IDH mutation can lead to activation of the hypoxia pathways in the presence of normoxia, a process termed “pseudohypoxia. However, other studies by Koivunen *et al.* found that R-2-HG, could substitute for α- KG in late passage immortalized astrocytes expressing mutant IDH to stimulate the activity of the HIF-1α PHD proteins EGLN1, 2 and 3 that promote the degradation of HIF-1α. Furthermore, analysis of gene expression data from TCGA showed that tumors harboring mutant IDH had reduced expression of HIF target genes relative to tumors containing wild-type IDH [33].

Inconsistencies in these findings suggest that effects of IDH mutation on the hypoxia pathway may be context dependent and further studies are required to determine the association between mutant IDH expression and HIF activity in gliomas.

## IDH mutation distribution and significance in human glioma

Several lines of evidence suggest that *IDH1* mutations are an early event in glioma development. As described above, IDH1 mutations are seen in a high percentage of grade II and III astrocytomas and oligodendrogliomas and secondary GBM tumors. Mutations in *IDH2* have been found in fewer than 3% of glial tumors, with similar distributions related to grade. *IDH* mutations are rare in primary GBM [14]. In lower grade gliomas with a high percentage of IDH mutation, differences in other tumor mutations and copy number alterations have been found associated with histologic subtypes. *IDH1* mutations often occur with a *TP53* mutation in astrocytic tumors, and these tumors rarely demonstrate loss of chromosomes 1p and 19q. On the other hand, IDH mutation is seen in virtually all oligodendrogliomas with 1p/19q co-deletion, and these tumors rarely demonstrate p53 mutation [13, 14, 52]. Thus, even though IDH1 is highly associated with both *TP53* mutation and loss of 1p/19q, these alterations are generally mutually exclusive in gliomas. These findings suggest that IDH mutation is an early event in glioma formation and occurs prominently in low grade tumors of both astrocytic and oligodendroglial lineage. Indeed, studies of the timing of *IDH1* mutations relative to others in gliomas indicate that IDH mutations precede *TP53* mutations in 63% of diffuse astrocytomas [13, 30] and 80% of glioblastomas and anaplastic astrocytomas with *IDH* mutations also had a mutation of *TP53* [14]. Mutations in the *TP53* tumor suppressor gene were first implicated in gliomagenesis twenty years ago when an increased incidence of gliomas was observed in patients with Li-Fraumeni syndrome, a rare cancer-predisposing disorder caused by mutations in *TP53* [53]. Interestingly, IDH mutations found in astrocytomas that developed in Li-Fraumeni syndrome families contained the less common R132C substitution, suggesting a difference in selection in cells that already harbor *TP53* mutations [27]. While commonly seen with alterations associated with low grade glioma, IDH mutation is rarely observed with genetic alterations commonly seen in high frequency in primary GBMs (e.g., *EGFR*), supporting the idea that IDH mutation is not a driver of tumor initiation in these GBM subtypes [13].

Thus, there appear to be three pathways to the development of glioma. One pathway starts with IDH mutation followed by TP53 mutation and results in astrocytic lineage tumors. These gliomas start as grade 2 astrocytomas, have the G-CIMP phenotype, and presumably then acquire other genetic alterations that result in progression to higher grade tumors. Another pathway starts with IDH mutation followed by loss of 1p/19q, which is associated with mutation in the Capicua (CIC) gene. These alterations result in development of grade 2 oligodendrogliomas, which can then acquire other genetic alterations to become anaplastic oligodendrogliomas. The third pathway includes those gliomas that are wild-type for IDH. These gliomas appear to rapidly acquire multiple complex genetic alterations, including amplification or mutation of EGFR, and loss of the PTEN gene, and become glioblastomas very early in their development (See figure 1). It should be noted that the cell of origin for these tumors remains unknown, and it also remains unclear whether there is a common cell of origin, or different cells of origin for the different lineage and molecular subtypes.

People with gliomas with mutated IDH are, on average, several years younger than people with gliomas with wild-type IDH. On the other hand, IDH mutations are rare in gliomas in young children, although they are common in gliomas in adolescents 14 years-old or older [54, 55]. About 20-25% of people with IDH-mutated gliomas carry the rs55705857 single nucleotide polymorphism (SNP) on chromosome 8q24, compared with 5% of the general population. [56]In a prospective analysis, grade II-IV glioma patients whose tumors harbored mutant *IDH1* or *IDH2* had significantly longer overall survival than patients without *IDH* mutation [12]. This finding has been confirmed independently by others [57, 58, 14]. The prognostic importance of IDH mutation is independent of other known prognostic factors, including age, grade, and MGMT methylation status [12].

However, it remains to be determined whether *IDH* mutation is a prognostic factor only or whether it is predictive of outcome to specific treatments or mechanistically related to treatment response. *In vitro*, induction of mutated IDH increased the sensitivity of gliomas to radiation [59]. Small retrospective series have suggested that the response rate to alkylating chemotherapy is also higher in IDH mutated grade 2 tumors than in wild-type tumors and that progression free survival after radiation or alkylating chemotherapy is higher for people with IDH-mutated tumors than for people with wild type tumors [60-62]. In the German Glioma Group retrospective study, IDH mutation influenced survival only in those patients who received radiation or chemotherapy immediately after surgery [63]. IDH mutation does not predict progression free survival for temozolomide treatment in low grade astrocytomas that had previously received radiation [64]. However, their retrospective nature and lack of control groups limits the conclusions that can be drawn from these studies.

In EORTC 26951, a randomized trial comparing the addition of chemotherapy with procarbazine, CCNU, and vincristine to adjuvant radiation in anaplastic oligodendrogliomas, the presence of IDH mutation predicted prolonged survival in the chemotherapy group, but the presence of IDH mutation nearly completely overlapped with 1p/19q deletion, so the independent effect of these genetic alterations in grade 3 oligondendrogliomas cannot be determined [65]. The NOA-04 trial compared radiation with alkylating chemotherapy as up front treatment of grade 3 gliomas. IDH mutation was associated with improved PFS in both treatment groups approximately equally [66]. The ongoing CATNON trial should provide important additional data to address the question of the predictive association with IDH mutation and specific treatments in non-1p/19q deleted grade 3 gliomas.

## Detection of IDH mutation in glioma

Initial studies of IDH mutations used direct sequencing [14]. Pyrosequencing has remained clinically valuable for detection of IDH mutations in hematologic malignancies, particularly AML. While sequencing remains the gold standard for IDH mutation testing, more rapid and easy to apply methods have been developed for initial screening in gliomas. The development of a monoclonal antibody against IDH1 R132H allows the detection of the most common mutation seen in gliomas by immunohistochemistry from paraffin embedded sections, and this method is being used with increasing frequency for clinical classification of tumors [67].

In addition to detection of IDH mutation in tissue, the increased levels of 2-hydroxyglutarate in IDH mutated tumors have led several groups to develop non-invasive imaging methods for detection of IDH-mutated gliomas. Indeed, 2-hydroxyglutarate has a distinctive magnetic resonance spectrum that is detectable by *in vivo* magnetic resonance spectroscopy (MRS) [68]. MRS may therefore be useful for distinguishing gliosis from low grade gliomas, potentially avoiding biopsy in ambiguous cases. However, additional prospective studies are needed to further define the sensitivity and specificity of these imaging approaches.

## Models of IDH-mutated glioma

Study of IDH-mutated gliomas has been limited by a lack of appropriate mouse models. There are no models of spontaneous IDH-mutated glioma-producing mice. Expression of mutated IDH1 in the brains of transgenic mice causes death soon after birth due to intercerebral hemorrhage [46]. *In vitro* cell lines with IDH mutation can be transiently produced but do not persist in non-immortalized cells. In standard cell culture conditions, IDH-mutated gliomas cells from IDH-mutated patient tumors generally do not grow well [69]. Moreover, there may be a selection pressure against IDH-mutated glioma cells in culture because, in contrast to the effect on normal cells, introduction of mutated IDH into IDH wild-type glioma cells decreases the proliferation rate [70]. Despite these challenges, IDH-mutated primary glioma neurospheres have been isolated from a human tumor and propagated in stem cell conditions by at least one group [71].

## Targeting IDH mutations

The discovery of IDH mutation in glioma has resulted in a number of novel ideas for therapeutic approaches. The concept of 2-HG being an “oncometabolite” has led several investigators to try to devise strategies to either restore normal IDH function or block production or downstream effects of 2-HG. Indeed, in an *in vitro* model, suppression of expression of mutated IDH decreases growth and clone formation in an IDH-mutated fibrosarcoma cell line [72]. While there are currently no direct IDH inhibitors in clinical trials, a number of investigators and drug companies are working on bringing specific inhibitors to the clinic. *In vitro*, the production of 2-HG by mutated IDH2 can be inhibited by metabolites such as oxaloacetate [73].

Another approach that is being considered is targeting the downstream signaling pathway alterations and epigenetic changes that are induced by IDH mutation. For example, IDH-mutated glioblastomas have increased activation of the hedgehog pathway, so use of a hedgehog inhibitor is of potential interest in these tumors [74]. Alternatively, hypomethylating agents or other epigenetic modifiers may be rational to try to target the G-CIMP hypermethylation phenotype induced by mutated IDH [75]. One potential caveat of this approach is that the general activation of expression of many genes through a decrease in methylation could also increase expression of deleterious ones such as oncogenes.

## Conclusion

The story of IDH mutations in gliomas is one of the successes of mapping the human genome. In the three years since their discovery, our understanding of the biochemistry,

genetics, and epigenetics of IDH mutations has grown. It is now clear that mutations in IDH1 and IDH2 are driver mutations in low grade gliomas, likely through 2-HG production. These mutations lead to a hypermethylation phenotype as well as changes in cellular metabolism and response to hypoxic and oxidative stress. IDH mutations have a definite effect on prognosis and may be predictive of response to radiation and/or alkylating chemotherapy. Our ability to target gliomas with IDH mutations remains limited, however. Thus, while our understanding of IDH mutation and its biology has increased dramatically in a relatively short time period, it is clear more investigation is necessary to determine optimal therapeutic strategies to target the IDH mutated subsets of gliomas.

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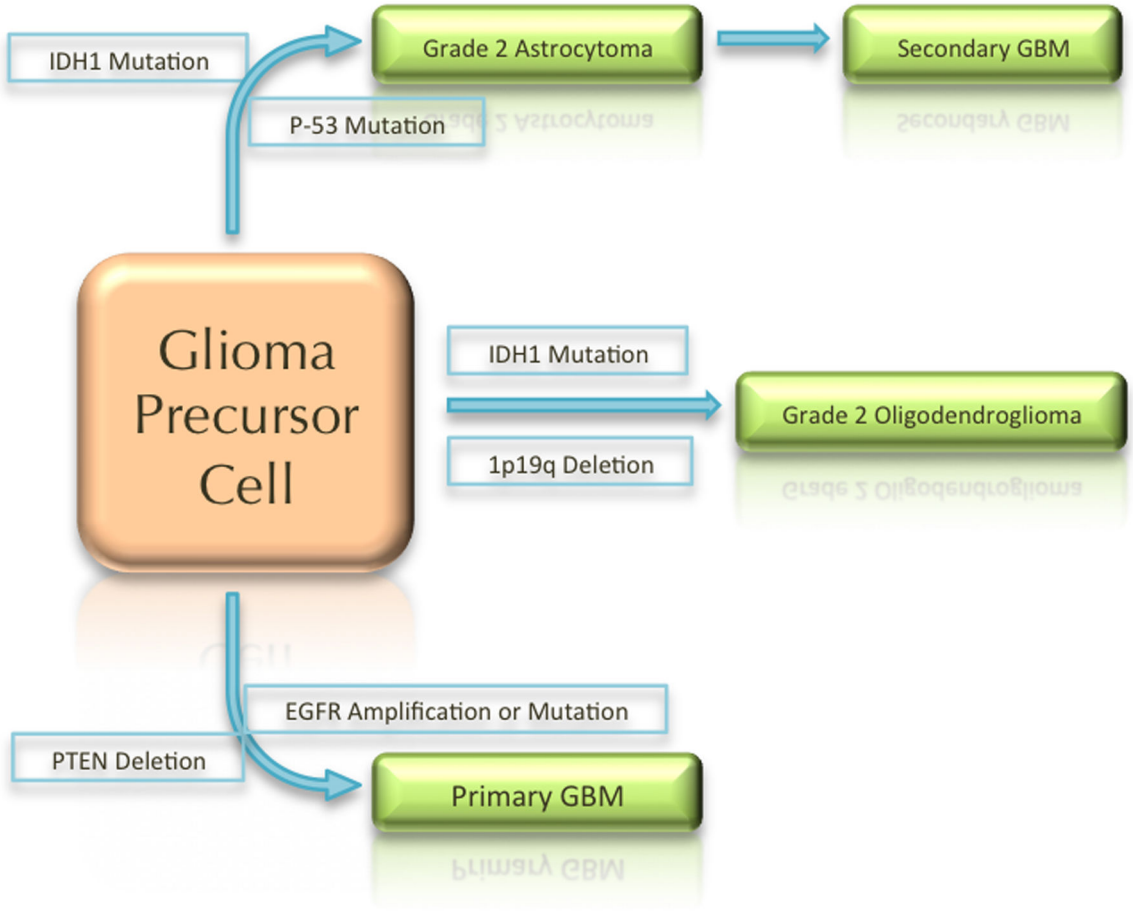


**Figure 1.**
Schematic of the three possible paths of gliomagenesis based on IDH mutation status.