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

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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)