IDH-mutant glioma

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IDH-Mutant Glioma Classification (WHO 2021)

The classification of IDH-mutant gliomas according to the World Health Organization Classification of Tumors of the Central Nervous System 2021 is summarized in the table below:

Tumor Type	IDH Status	1p/19q Status	Key Features	Available Grades
Astrocytoma IDH-mutant	Mutant	Intact	ATRX loss, TP53 mutation	Grade 2, 3, or 4
Oligodendroglioma IDH-mutant and 1p/19q-codeleted	Mutant	Codeleted	TERT promoter mutation, ATRX retained	Grade 2 or 3
Glioblastoma	Wildtype	—	TERT/EGFR amplification or +7/−10 signature, or necrosis/microvascular proliferation	Always Grade 4

Additional Notes

- The term `glioblastoma, IDH-mutant` is no longer used. These tumors are now classified as `Astrocytoma, IDH-mutant, Grade 4`.
- The presence of CDKN2A/B homozygous deletion upgrades astrocytoma, IDH-mutant to WHO Grade 4 even in the absence of necrosis or microvascular proliferation.

Although IDH-mutant glioma generally has a better prognosis than its IDH-wildtype counterparts, considerable prognostic heterogeneity persists among patients with the same IDH mutation. A study of Wang et al. has primarily focused on the different IDH statuses or grades, while the metabolic heterogeneity within IDH-mutant gliomas remains insufficiently characterized. This study aims to

identify transcriptomic metabolic subtypes and associated immune microenvironment differences to better understand survival variability and potential therapeutic targets in IDH-mutant glioma.

Patients with IDH-mutant gliomas were included from four public datasets (TCGA, n = 373; CGGA325, n = 167; CGGA693, n = 333; GLASS, n = 100), supplemented by 22 cases from Beijing Tiantan Hospital as an independent cohort. Consensus clustering was used to define novel metabolic subtypes. Clinical features were assessed using chi-square tests and Kaplan-Meier analysis. Metabolic profiles were characterized through enrichment analysis and GSVA; immune infiltration was analyzed using CIBERSORTx and ESTIMATE. Tumor samples from the independent cohort underwent untargeted metabolomics for validation. LASSO regression was applied to select metabolic signatures, and the CGP2014 drug library was used for drug screening.

Three metabolic subtypes (C1-C3) with distinct prognoses ($p < 0.05$) were identified. C1 exhibited enhanced carbohydrate and nucleotide metabolism; C2 displayed upregulated amino acid and lipid metabolism; and C3 demonstrated elevated lipid, nucleotide, and vitamin metabolism. These patterns were validated in the independent cohort. Subtypes were also correlated with immune infiltration. A 13-gene metabolic signature was established to stratify prognostic risk and suggest subtype-specific drug sensitivities.

The study provided a novel metabolic subtype for IDH-mutant glioma and highlighted these patients' metabolic heterogeneity and potential therapeutic strategies [1)]

Wang et al. provide compelling evidence that metabolic subtyping in IDH-mutant gliomas is biologically meaningful and prognostically informative. Despite the limitations of validation scope and functional depth, the study opens promising avenues for metabolism-guided precision neuro-oncology.

IDH-Mutant Glioma Subtypes

IDH-mutant gliomas, although generally associated with better prognosis, show considerable biological and clinical heterogeneity. Recent transcriptomic and metabolic profiling has revealed distinct subtypes with prognostic and therapeutic implications.

Molecular Subtypes (Traditional WHO Classification)

Subtype	IDH Status	1p/19q Status	Common Features	WHO Grades
Astrocytoma, IDH-mutant	Mutant	Intact	TP53 mutation, ATRX loss	Grade 2, 3, or 4
Oligodendroglioma, IDH-mutant	Mutant	Codeleted	TERT promoter mutation, ATRX retained	Grade 2 or 3

Metabolic Subtypes (Wang et al., 2025)

Subtype	Dominant Metabolism	Prognosis	Immune Microenvironment	Notes
C1	Carbohydrate & nucleotide metabolism	Poor	Less immune infiltration	Higher proliferation signature
C2	Amino acid & lipid metabolism	Intermediate	Moderate immune activity	May benefit from lipid metabolism-targeted drugs
C3	Lipid, nucleotide & vitamin metabolism	Favorable	Higher immune infiltration	Most differentiated; possible immunogenic role

Summary

- These subtypes are defined by transcriptomic and metabolic profiling, not by histopathology alone.
- A 13-gene metabolic signature has been proposed to distinguish these subtypes and guide potential treatment.
- Future therapy may be subtype-specific, focusing on metabolism and immune modulation.

1)
Wang P, Wang J, Fang Z, Chen Q, Zhang Y, Qiu X, Bao Z. Novel metabolic subtypes in IDH-mutant gliomas: implications for prognosis and therapy. BMC Cancer. 2025 Apr 30;25(1):815. doi: 10.1186/s12885-025-14176-y. PMID: 40307749.