

# Role of *LRRK2* in *IDH*-Mutant Grade 4 Astrocytomas: Oncogene or Tumor Suppressor?

**Authors:** \*Michele Persico,<sup>1</sup> Jorge Luis Jimenez Macias,<sup>2</sup> Ishan Mohamed,<sup>2</sup> Saud Alhusaini,<sup>3</sup> Renee Read<sup>2,4,5</sup>

1. Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, USA
2. Department of Pharmacology and Chemical Biology, Emory University School of Medicine, Atlanta, Georgia, USA
3. Department of Neurology, Brown University, Providence, Rhode Island, USA
4. Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, Georgia, USA
5. Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA

\*Correspondence to [michele.persico@emory.edu](mailto:michele.persico@emory.edu)

**Disclosure:** Persico has received a scholarship from the American Academy of Neurology (AAN) for the AAN Annual Meeting 2026 (Future in Neurological Research Award); and is the Editorial Board Member of the AAN: Resident and Fellow Section. Mohamed has received a grant from the American Cancer Society (PF-25-1435269-01-PF-CBI); and support for attending the ACS Research Conference from the American Cancer Society. Read has received support for the present manuscript via federal grant funding (R01NS126348) from NINDS, with payment to the institution; federal grant funding from NINDS (R21NS133633, R01NS132725, and R21NS116639), the Department of Defense (HT9425-24-1-0973 and HT94252310323), and the NCI (P30CA138292), with payment to the institution; support for attending meetings and/or travel from the American Brain Tumor Association and the Center for Scientific Review/National Institutes of Health; and equipment, materials, drugs, medical writing, gifts, or other services from Bausch Health for WINSHIP5070-20 (NCT04590664). The other authors have declared no conflicts of interest.

**Keywords:** Glioma, Parkinson's disease, *LRRK2*, survival, therapy.

**Citation:** *Neurol AMJ*. 2026;3[1]:44-46. <https://doi.org/10.33590/neurolamj/EI91BI3R>

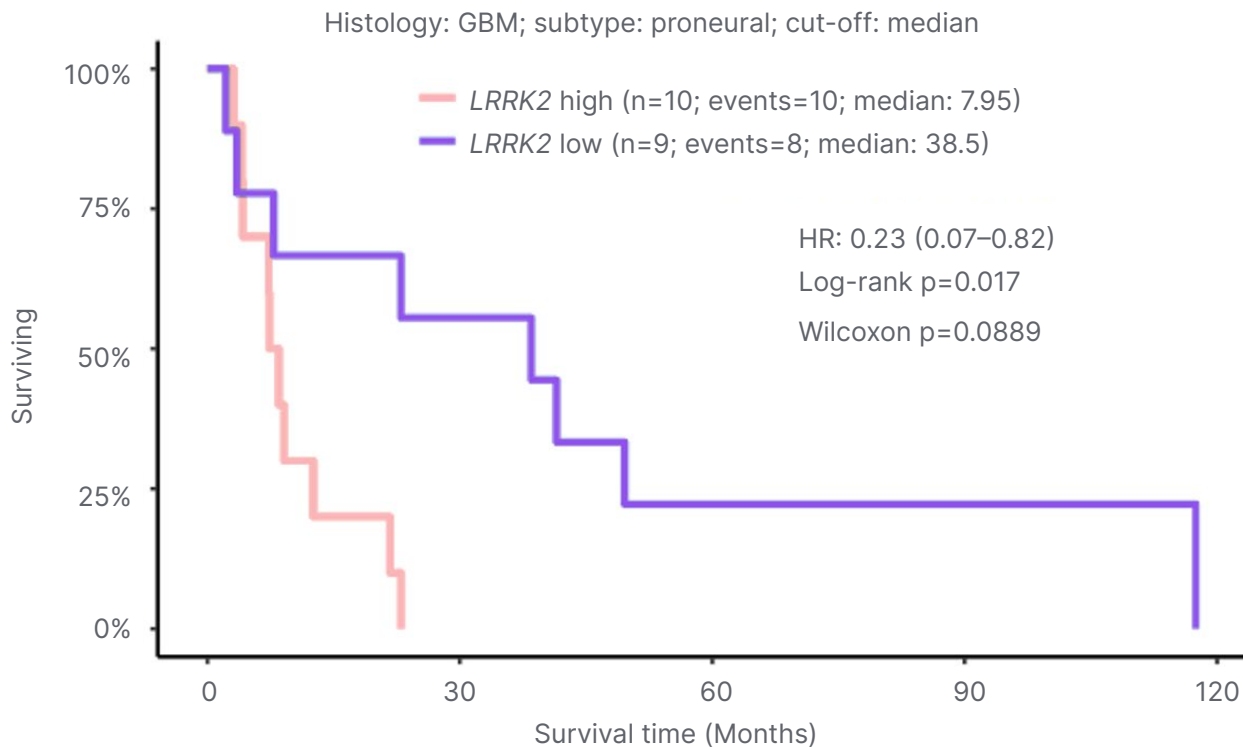
## BACKGROUND AND AIMS

*IDH*-mutant Grade 4 astrocytomas are aggressive brain tumors with limited treatment options.<sup>1</sup> According to the 2021 WHO central nervous system tumor classification, they are defined as diffuse high-grade gliomas characterized by *IDH1/2*, *ATRX*, and *TP53* mutation, and sometimes *CDKN2A/B* deletion.<sup>2</sup> This replaces the old nomenclature of “secondary glioblastomas” (GBM).<sup>2</sup> Leucine-rich repeat kinase 2 (*LRRK2*) was first documented in a Japanese family with autosomal-dominant Parkinson's disease.<sup>3</sup> Park et al.<sup>4</sup> demonstrated that *LRRK2* is overexpressed in up to 40% of GBM specimens, with higher levels correlating with poor patient survival. *LRRK2* is a cytoplasmic kinase that can activate the MAPK cascade, leading to uncontrolled cellular proliferation and resistance to apoptosis.<sup>5</sup>

## MATERIALS AND METHODS

*In silico* analyses were performed using *GlioVis*, a web application for data visualization and analysis to explore brain tumor expression datasets.<sup>6</sup> *LRRK2* mRNA was examined in relation to overall survival and key high-grade glioma diagnostic and prognostic markers (*CDKN2A/B*, *ATRX*, *PDGFRA*, *TERT*, *MGMT*, *TP53*). Subgroup analyses were performed across transcriptional subtypes (classical, mesenchymal, and proneural).<sup>7</sup> The proneural subtype is characterized by *IDH1* and *PDGFRA* mutations, whereas the classical and mesenchymal subtypes are *IDH*- and *PDGFRA*-wild-type.<sup>7</sup> *GlioVis* does not strictly follow the 2021 WHO classification of central nervous system tumors. As such, a GBM diagnosis in this

**Figure 1: Kaplan–Meier survival curves for *LRRK2* expression in female patients with GBM stratified by proneural subtype.**



GBM: glioblastoma.

study refers to the GliOVis classification framework rather than the WHO 2021 criteria.

## RESULTS

In female patients with GBM, proneural subtype, low *LRRK2* mRNA expression levels are associated with improved survival (hazard ratio: 0.23;  $p=0.017$ ; Figure 1). *LRRK2* mRNA expression levels showed statistically significantly lower expression in the classical and mesenchymal subtypes compared to the proneural subtype (diff: 0.65,  $p=0.00$ ; diff: 0.52,  $p=0.00$ ) and statistically significantly higher *LRRK2* expression levels in glioma-CpG island methylator phenotype (G-CIMP; diff: 0.77;  $p=0.00$ ). *LRRK2* mRNA expression levels revealed a correlation in the proneural

subtype with *CDKN2A* ( $r=-0.37$ ;  $p=0.04$ ), *ATRX* ( $r=0.59$ ;  $p=0.00$ ), *PDGFRA* ( $r=0.26$ ;  $p=0.03$ ), *TERT* ( $r=-0.26$ ;  $p=0.00$ ), and *MGMT* ( $r=-0.49$ ;  $p=0.01$ ). No statistically significant correlations were identified with *TP53* and *CDKN2B*.

## DISCUSSION

Elevated *LRRK2* mRNA expression, particularly in proneural GBM, is associated with worsened overall survival, which raises the question of *LRRK2*'s potential oncogenic role (Figure 1). *LRRK2* mRNA expression levels appear more elevated in the proneural subtype of GBM, which is associated with *IDH1* mutations.<sup>7</sup> This evidence is solidified by the higher *LRRK2* mRNA expression levels

in G-CIMP, which are associated with an *IDH*-mutant genotype.<sup>8</sup> In addition, a positive correlation with *PDGFRA*, whose higher mRNA expression levels are associated with *IDH*-mutant Grade 4 astrocytomas,<sup>9</sup> and a negative correlation with *CDKN2A*, whose deletions are a diagnostic criterion for *IDH*-mutant Grade 4 astrocytomas,<sup>2</sup> demonstrate that higher *LRRK2* expression levels correlate with an *IDH*-mutant Grade 4 astrocytoma genotype. This is further supported by the negative correlation with *TERT*, whose higher expression levels are associated with *TERT* promoter mutation, which is atypical of *IDH*-mutant Grade 4 astrocytomas.<sup>10</sup> *LRRK2* has a negative correlation with *MGMT* in the proneural subtype. In *IDH*-mutant Grade 4 astrocytomas, *MGMT* promoter methylation is not prognostic or predictive of response to temozolomide.<sup>1</sup> Hence, the clinical significance of the negative correlation between *LRRK2* and *MGMT* mRNA expression levels in *IDH*-mutant Grade 4 astrocytomas remains unclear.

## CONCLUSION

*LRRK2* may represent a key oncogene in *IDH*-mutant Grade 4 astrocytomas. *LRRK2* inhibition could represent a potential therapeutic strategy in these types of high-grade gliomas.

## References

1. Youssef G et al. Prognostic significance of O6-methylguanine-DNA methyltransferase promoter methylation status in isocitrate dehydrogenase-mutant glioma. *Neuro Oncol.* 2026;28(3):752-64.
2. Louis DN et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol.* 2021;23(8):1231-51.
3. Funayama M et al. A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. *Ann Neurol.* 2002;51(3):296-301.
4. Park S et al. Suppression of glioblastoma stem cell potency and tumor growth via *LRRK2* inhibition. *Int J Stem Cells.* 2024;17(3):319-29.
5. Bahar ME et al. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. *Signal Transduct Target Ther.* 2023;8(1):455.
6. Bowman RL et al. GlioVis data portal for visualization and analysis of brain tumor expression datasets. *Neuro Oncol.* 2017;19(1):139-41.
7. Verhaak RG et al.; Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in *PDGFRA*, *IDH1*, *EGFR*, and *NF1*. *Cancer Cell.* 2010;17(1):98-110.
8. Turcan S et al. *IDH1* mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature.* 2012;483(7390):479-83.
9. Rautajoki KJ et al. Genomic characterization of *IDH*-mutant astrocytoma progression to grade 4 in the treatment setting. *Acta Neuropathol Commun.* 2023;11(1):176.
10. Jiang H et al. Unraveling the heterogeneity of WHO grade 4 gliomas: insights from clinical, imaging, and molecular characterization. *Discov Oncol.* 2025;16(1):111.