Title: Differential Prognostic Impact of PIK3R1 Expression Across Glioma Grades: A TCGA PanCancer Atlas Analysis

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Background:

Gliomas represent a diverse category of primary brain tumors spanning from relatively indolent lower-grade gliomas (LGG) to glioblastoma (GBM), the most aggressive form associated with rapid clinical deterioration and limited survival. Aberrant activation of th e PI3K/AKT pathway is a hallmark of glioma pathogenesis. *PIK3R1* encodes the p85 r egulatory subunit of PI3K, which controls pathway activity through its interaction with t he p110 catalytic component. Although genomic alterations of PIK3R1 have been descr ibed in various malignancies, their clinical and grade-dependent significance in glioma has not been comprehensively established. To address this gap, we investigated the m utational landscape, expression patterns, and clinical significance of *PIK3R1* across LG G and GBM to clarify its grade-dependent biological and prognostic roles.

Methods:

A comprehensive analysis of *PIK3R1* alterations and their clinical correlations was perf ormed on the TCGA PanCancer Atlas glioma cohorts via cBioPortal. Specifically, Kapla n–Meier survival modeling and expression distribution mapping were conducted to dete rmine the grade-specific impact of PIK3R1 on patient outcomes.

Results:

PIK3R1 mutations were identified in both LGG (~4–5%) and GBM (~7–8%), with a slig htly higher frequency in GBM. Recurrent hotspot alterations were enriched within the i nter-SH2 (iSH2) region, a key regulatory interface for p110 interaction, and GBM demo nstrated a greater proportion of truncating and splice-site variants. However, mutation s tatus was not associated with overall survival in either LGG ($p = 0.853$) or GBM ($p = 0.818$). In contrast, transcriptional expression of PIK3R1 demonstrated a distinct grade -dependent prognostic association. In LGG, elevated expression levels were significantl y linked to prolonged survival and displayed a graded survival advantage across incre asing expression strata. No comparable survival relationship was observed in GBM.

Conclusion:

Although *PIK3R1* mutations cluster within functional regulatory domains, they do not ap pear to influence survival outcomes in either LGG or GBM. Instead, the prognostic rel evance of PIK3R1 in glioma is primarily reflected in its transcriptional activity, with high

er expression associated with improved survival specifically in LGG. These findings su ggest a grade- dependent biological role for *PIK3R1* driven more by expression dyna mics than by mutational events. Given the relatively low mutation frequency and potent ial confounding by established LGG molecular subtypes, further studies using larger co horts and multivariate analyses are warranted.