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Promoter Methylation-Based Stratification of *ABCA5* Expression Reveals a High-Risk Glioma Subtype

Background: The ATP-binding cassette transporter *ABCA5* has established roles in lipid transport and stem-cell biology, but its transcriptional regulation and prognostic relevance in glioma remain uncharacterized. Whether *ABCA5* mRNA expression and site-specific promoter methylation jointly define a clinically distinct glioma subtype is unknown.

Methods: Genomic, transcriptomic, methylation data and clinical information for the The Cancer Genome Atlas (TCGA) low-grade glioma cohort were retrieved from cBioPortal and University of California Santa Cruz (UCSC) Xena. Promoter methylation was evaluated using the single CpG probe cg06409153 (TSS1500, S-shore) and the mean methylation across probes spanning the *ABCA5* promoter region (TSS200, TSS1500). Tumors were classified by WHO 2021 molecular subtype, and Kaplan-Meier analysis, multivariate Cox regression, and Gene Ontology (GO) and Hallmark Gene Set Enrichment Analysis (GSEA) were performed.

Results: High *ABCA5* mRNA expression and hypomethylation at both cg06409153 and the promoter-averaged probes were each significantly associated with *IDH*-wildtype status, older age, *EGFR* amplification, combined *CDKN2A/B* deletion, combined chromosome 7 gain/10 loss, *MGMT* promoter unmethylation, and shorter overall survival with higher mortality (all $p < 0.05$, most $p < 0.001$). In multivariate Cox regression adjusting for clinical and molecular covariates, cg06409153 methylation retained independent prognostic value, supporting locus-specific methylation profiling. GO and Hallmark GSEA showed that high-expression/hypomethylated tumors were enriched for EMT and inflammatory-response pathways, and these associations were reproduced in the CGGA validation cohort.

Conclusions: *ABCA5* overexpression and cg06409153 (TSS1500) hypomethylation define a high-risk, *IDH*-wildtype-enriched glioma subtype. cg06409153 represents a clinically actionable methylation biomarker suitable for targeted assays, supporting *ABCA5* as an independent prognostic indicator in glioma.