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ACCS mRNA Expression and Promoter Methylation as Independent Prognostic Determinants in Glioma

Background: *ACCS* (1-aminocyclopropane-1-carboxylate synthase homolog) remains functionally obscure in cancer biology, and its transcriptional and epigenetic behavior in glioma has yet to be systematically investigated. It is unclear whether *ACCS* expression, together with its promoter methylation status, delineates a molecularly and clinically distinct subgroup of gliomas.

Methods: We integrated genomic, transcriptomic, and DNA methylation profiles from the TCGA low-grade glioma cohort using cBioPortal and UCSC Xena. Promoter methylation was captured through the individual CpG probe cg20240860 (TSS1500, N-shore), which correlated inversely and robustly with *ACCS* mRNA levels ($R = -0.44$, $p < 2.2 \times 10^{-16}$), alongside a composite methylation score averaged across probes covering the *ACCS* core promoter. Tumors were categorized according to the WHO 2021 molecular classification, and survival outcomes, multivariate Cox modeling, and Hallmark GSEA were used to characterize the *ACCS*-defined subgroups.

Results: Tumors with elevated *ACCS* expression and reduced methylation at cg20240860 (as well as the promoter-wide average) were markedly enriched for *IDH*-wildtype glioblastoma, skewed toward older patients, and disproportionately carried *EGFR* amplification, homozygous *CDKN2A/B* deletion, combined chromosome 7 gain/10 loss, and *MGMT* promoter unmethylation—together with worse overall survival and higher mortality ($p < 0.05$ throughout, predominantly $p < 0.001$). Both *ACCS* mRNA expression and cg20240860 methylation varied significantly across WHO subtypes (Kruskal-Wallis $p < 2.2 \times 10^{-16}$). After adjustment for clinical and molecular covariates in multivariate Cox regression, cg20240860 methylation each remained independently predictive of outcome. Hallmark GSEA further indicated that the *ACCS*-high, hypomethylated phenotype was accompanied by activation of proliferative and mesenchymal gene expression programs, in line with a more aggressive tumor biology.

Conclusions: Elevated *ACCS* expression coupled with cg20240860 (TSS1500) hypomethylation characterizes an aggressive, *IDH*-wildtype-predominant glioma subtype. These findings position cg20240860 as a promising methylation-based biomarker amenable to targeted assay development, reinforcing *ACCS* as an independent determinant of glioma prognosis.