

and hepatocellular carcinomas. However, its role in ACC remains unexplored, and understanding its function could provide novel insights into ACC pathogenesis and treatment. **Methods:** Bioinformatic analyses were conducted using GTEx adrenal cortex and The Cancer Genome Atlas (TCGA)-ACC datasets to assess IGSF11 mRNA expression and its correlation with clinical outcomes. Quantitative RT-qPCR and ELISA assays were performed on H295R ACC cell lines transiently transfected with an IGSF11 expression plasmid. Cell proliferation was assessed using live-cell imaging and WST-8 assays. Additionally, IGSF11 protein levels were measured in tissue homogenates from normal adrenal cortex, adrenal adenoma, and ACC samples. **Results:** IGSF11 mRNA expression was significantly lower in ACC tissues compared to normal adrenal cortex ($p < 0.001$). Survival analysis demonstrated that reduced IGSF11 expression correlated with poorer patient outcomes, particularly in the aggressive COC3 TCGA-ACC cluster. In H295R cells, IGSF11 overexpression led to a marked increase in mRNA and protein levels ($p < 0.0001$) and significantly reduced cell proliferation ($p < 0.005$). ELISA assays confirmed significantly reduced IGSF11 protein levels in ACC tissues compared to benign and normal tissues ($p < 0.0001$). Comparative prognostic analysis across 32 TCGA cancer types highlighted a unique role for IGSF11 in ACC, with a hazard ratio of 0.22 ($p = 0.00034$), contrasting with its tumour-promoting role in other cancers. **Conclusion:** IGSF11 exhibits a tumour-suppressive role in ACC, contrasting its immune-inhibitory, tumour-promoting function in other malignancies. Its downregulation in ACC correlates with poorer survival outcomes, positioning it as a promising diagnostic and prognostic biomarker and potential therapeutic target. Restoring IGSF11 expression may offer new avenues for ACC treatment, emphasizing the need for further investigation into its tissue-specific functions and therapeutic potential.

Presentation: Monday, July 14, 2025

Abstract citation ID: bvaf149.281

Adrenal (Excluding Mineralocorticoids)

OR32-04

IGSF11 as a Tumour Suppressor and Potential Diagnostic and Prognostic Biomarker in Adrenocortical Carcinoma: Insights from Clinical and Functional Analyses

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Disclosure: A. Hashmi: None. S. Sidhu: None. G. Hutvagner: None.

Background: Adrenocortical carcinoma (ACC) is an aggressive malignancy with limited diagnostic and prognostic biomarkers and therapeutic options. Immunoglobulin Superfamily Member 11 (IGSF11), a cell adhesion molecule and known ligand of VISTA (V-domain Ig suppressor of T cell activation), has been associated with tumour progression in various cancers due to its role in inhibiting T-cell activation and promoting immune evasion. Elevated IGSF11 expression is linked to poor prognosis in gliomas, colorectal,