Transcriptomic Analysis Identifies the PVT1-miR-34a Axis as a Novel Non-Coding RNA Therapeutic Target in Diffuse Intrinsic Pontine Glioma

Ayesha Farooq[1,4], Hurmat Haroon[1], Faisal F. Khan[1,3]

1. CECOS-RMI Precision Medicine Lab, RMI Laboratory Building, Hayatabad, Peshawar, Pakistan
2. Institute of Integrative Biosciences, CECOS University, Hayatabad, Peshawar, Pakistan
3. Centre for Genomic Sciences, Rehman Medical Institute, Peshawar, Pakistan
4. Khyber Medical College, University Road, Peshawar, Pakistan

Introduction

Diffuse Intrinsic Pontine Glioma (DIPG) is a lethal pediatric brainstem tumor with a median survival of less than 12 months, as it is inoperable and resistant to chemotherapy (1). Non-coding RNAs (ncRNAs) are key gene regulators that, when dysregulated, can drive tumor progression and therapy resistance. This makes these aberrant ncRNAs promising targets for novel RNA-based treatments in DIPG (2). Although oncogenic lncRNAs such as XIST and H19 have been identified in DIPG, the regulatory landscape of **ncRNAs axes** remains largely unexplored (3,4).

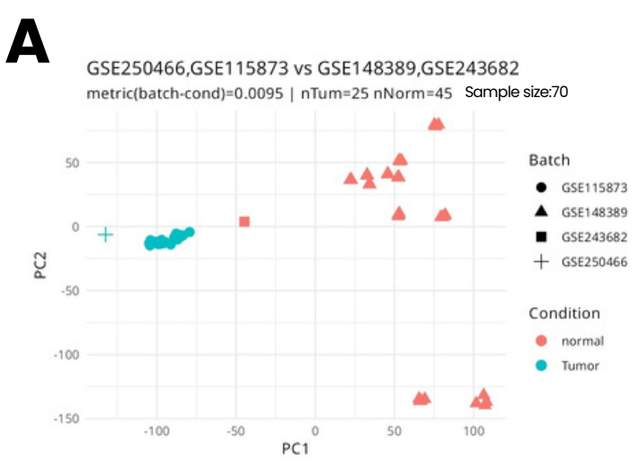
Objectives

- To identify dysregulated **lncRNA–miRNA–mRNA** regulatory axes in DIPG through integrated transcriptomic analysis.
- To computationally validate the lncRNA-miRNA-mRNA regulatory axes and investigate its downstream impact on cancer-related pathways.

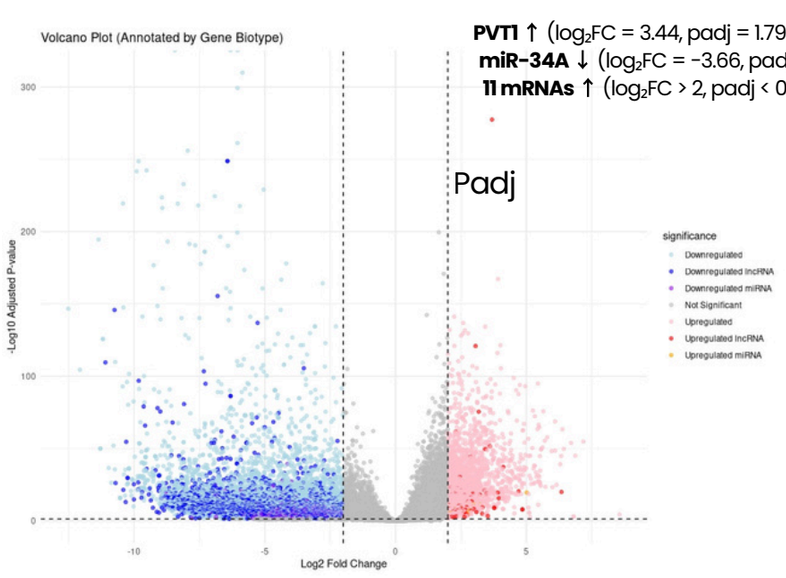
Methodology

1. Literature Search
2. Data Acquisition and Preprocessing
3. Differential Expression Analysis
4. Target Prediction: LncRNA-miRNA
5. Target Prediction: miRNA-mRNAs
6. Network Construction
7. Enrichment Analysis
8. Spearman correlation Analysis

Results

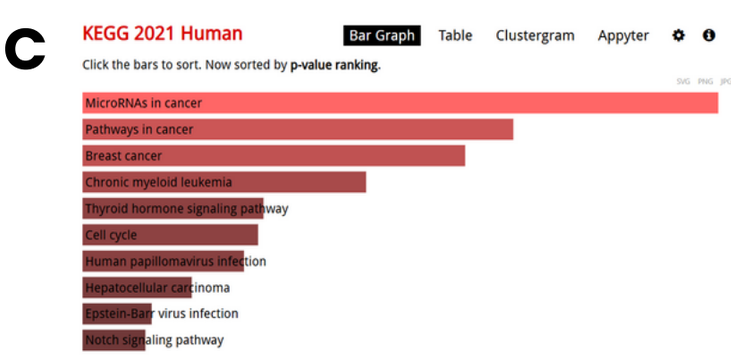


A. PCA distinctly separates DIPG from normal brain tissue, indicating clear molecular divergence

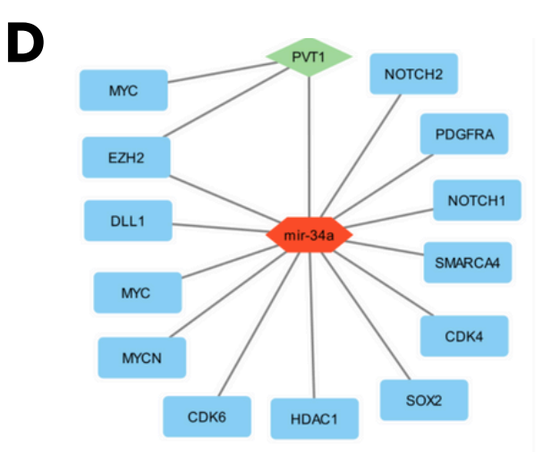


PVT1 ↑ ($log_2FC = 3.44$, padj = 1.79E-18),
miR-34A ↓ ($log_2FC = -3.66$, padj = 0.03);
11 mRNAs ↑ ($log_2FC > 2$, padj < 0.05).

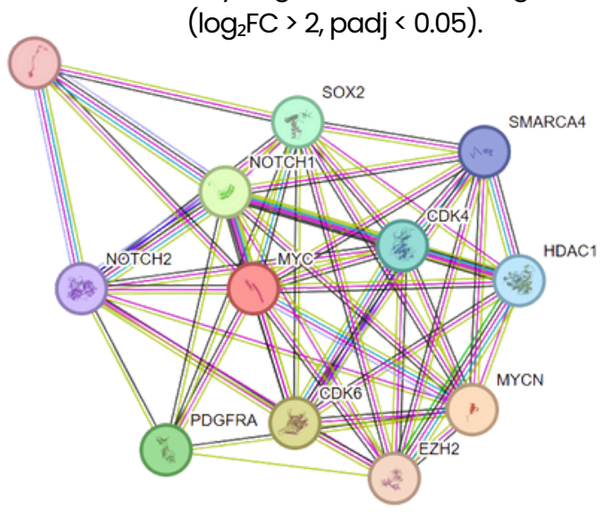
B. Differential expression analysis reveals significant number of dysregulated non-coding RNAs. ($log_2FC > 2$, padj < 0.05).



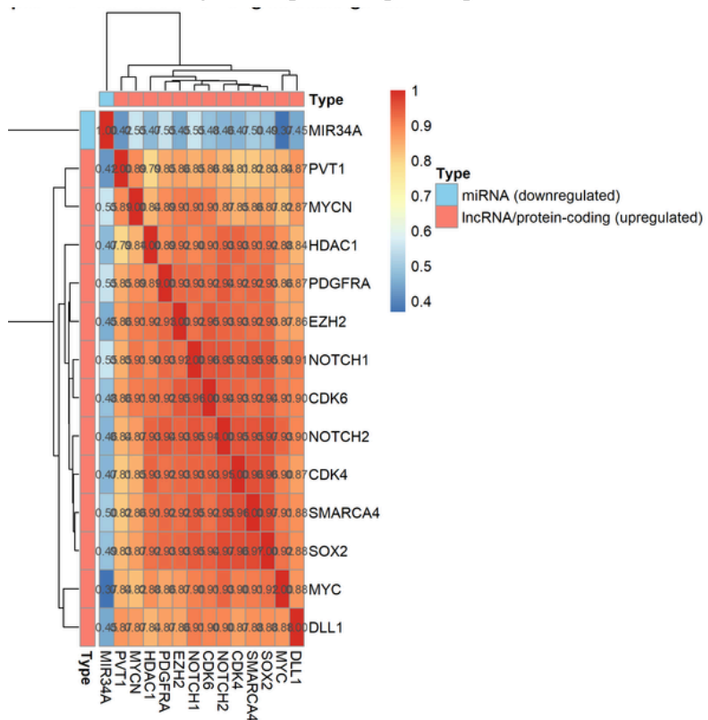
C. Pathway enrichment shows target genes cluster in key oncogenic signaling cascade



D. The integrated network shows **PVT1** as a central sponge regulating **miR-34a** and downstream **oncogenic mRNAs**.



E. PPI analysis of target genes reveals tightly connected cancer-related module



F. PVT1 expression positively correlates with 11 oncogenes, while miR-34A shows inverse correlation, confirming a functional PVT1–miR-34a axis driving DIPG

Conclusion

Transcriptomic analysis identifies a dysregulated **ceRNA axis** in DIPG. PVT1 is upregulated 3.44-fold while miR-34a is downregulated 3.66-fold, supporting PVT1-mediated sequestration of miR-34a and de-repression of oncogenic mRNAs, with clear potential for therapeutic targeting.

Way Forward

- Experimentally validate PVT1-miR-34a interaction using luciferase assays and test miR-34a mimics/PVT1 Anti-sense Oligos in DIPG cell lines.
- Evaluate therapeutic efficacy in patient-derived xenografts as monotherapy and combined with radiotherapy.

References

(1) Warren KE et al. *Front Oncol.* 2012
(2) Julia Latowska et al. *J. Int J Mol Sci*. 2020
(3) Velázquez-Flores MÁ et al. *Clin Transl Oncol.* 2021
(4) Roig-Carles D et al. *Int J Mol Sci*. 2021

Acknowledgements

I am deeply grateful to PML and Dr. Faisal Khan for this invaluable opportunity, Mr. Tauheed for his expert guidance, Mr. Arsalan for his crucial assistance with the data, and fellow electives for their constant support.