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The influence of SINEs as potential regulatory element on chromatin structures in human brain cancer cells

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Motivation and Aim: High-grade gliomas are notably aggressive and malignant brain tumors [1, 2]. Although they account for about one-fourth of all brain tumors, they demonstrate a high tendency for recurrence, often leading to a short median progression-free survival of only 1.8 months after recurrence [3, 4]. Despite surgical resection being a primary treatment strategy, the invasive nature of these tumors into surrounding healthy brain tissue makes complete removal challenging, thereby reducing the likelihood of successful long-term management. Moreover, despite significant advancements in medical research, high-grade gliomas continue to pose a formidable challenge, with many aspects of their underlying genetic and epigenetic mechanisms remaining elusive [5]. One area of study is the role of SINEs in genomic regulation [6–8]. This group of repeats include two large families: Alu and MIR which perform different functions in the genome and have a potential effect on transcription processes. This study aims to explore how SINEs affect the spatial organization of the genome and their subsequent impact on gene regulation in gliomas. Employing a comprehensive approach that includes Hi-C analysis to assess the 3D genome architecture, transcriptomic analysis to identify gene dysregulation, and genomic analyses to map SINE distribution, this research seeks to identify patterns and mechanisms by which SINE elements contribute to the development and progression of cancer.
Methods and Algorithms: The methodology employed in this study follows a systematic framework comprising several analytical stages to address the research objectives (Fig. 1). Initially, transcriptomic analysis is conducted to identify genes implicated in cancerogenesis, utilizing approaches such as differential gene expression analysis to discern patterns of gene dysregulation. Subsequently, the spread of SINEs within the genome is studied, with a focus on identifying SINE elements located in proximity to gene regions. This involves genomic analyses to characterize the distribution and abundance of SINEs across the human genome. Hi-C analysis investigates differences in genome organization between samples, aiming to identify correlations with the findings from transcriptomic and SINE analysis. Also in this study was performed a new method of investigation interaction between distinct chromosomal regions with high resolution. Closeness and betweenness centralities were used for detecting potential regulatory bins which could take part in chromatin reorganization. Finally, visualization to highlight key regions of the genome and explore their potential 3D structure, offering insights into the functional implications of SINE-mediated genome organization.
Results: Genomic analysis has revealed that 8.43 % of the entire genome is occupied by SINEs, with 26.2 % located within gene regions and 31.1 % in promoter regions extending from –50Kb to the transcription start site (TSS). Detailed investigations were

focused on SINEs within these promoter regions. Transcriptomic analysis of two diffuse intrinsic pontine glioma (DIPG) samples, compared to a control sample from healthy brain tissue, revealed differential expression in 297 genes. These genes are primarily involved in pathways responsible for the regulation of DNA-templated transcription and nervous system development, showing upregulation in DIPG. In contrast, when comparing glioblastoma multiforme (GBM) samples with controls, pathways associated with cell division were predominantly affected. Additionally, a downregulation of the Keratin Filament pathway (GO:0045095) was observed in both DIPG and GBM samples. Comparative Hi-C analysis across these samples yielded an average correlation coefficient of 0.39 between DIPG patients and the control, and 0.43 between GBM samples and the control. RNA-seq analysis corroborated these findings, indicating a closer genetic expression between the control and GBM than with DIPG samples. In the final stage of analysis, chromatin regions were examined for 5000 bp bins showing high contact frequency with adjacent bins and containing SINEs. For instance, a bin at 52,165,000–52,170,000 within the Intermediate Filament (IntFil) gene cluster on chromosome 12 was identified. This bin showed extensive contacts with neighboring bins in the 52–54 Mb region and contained a previously identified SINE with a high identity score. Additional regions of interest with highly conserved SINEs were identified on chromosomes 1, 5, 11, 17, and X, emphasizing the widespread impact of these elements across the genome.

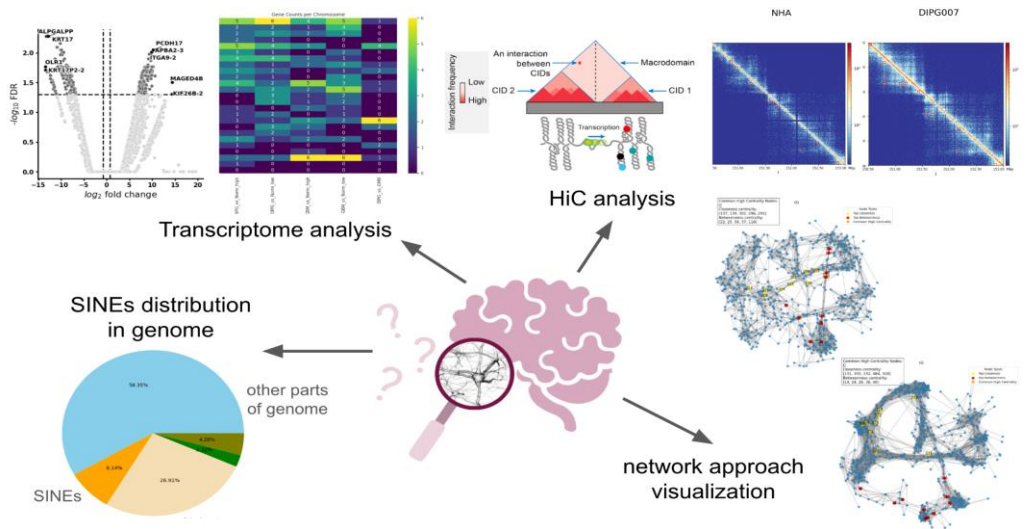

Fig. 1. Stages of research. Step1. Identification of differential gene expression between healthy and tumor cell samples. Step2. SINEs distribution in the genome. Step3. 3D chromatin organization. Step4. Visualization of the most significant chromatin regions

Conclusion: This study elucidates the role of SINEs in influencing the genomic architecture and regulatory landscapes in high-grade gliomas. By integrating Hi-C, transcriptomic, and genomic analyses, the study provides novel insights into how SINEs may drive the complex pathophysiology of these aggressive tumors. Ultimately, these findings could pave the way for developing targeted therapeutic strategies that address the genetic and epigenetic underpinnings of glioma recurrence and progression.

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