Structural Disruptions of the 3D Genome Architecture in Human Brain Cancer

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Introduction

- Human cancers frequently exhibit genomic rearrangements, such as deletions, inversions, translocations, and duplications[1].
- These structural variations drastically alter the three-dimensional chromatin organization in cancer cells[2].
- Emerging studies in the field aim to uncover the functional consequences of the disrupted 3D genome architecture in tumors.
- One of the key impacts of the disruption in the chromatin organization involves the formation of new chromatin loops, called neoloops[3].
- In this study, we conducted a comprehensive analysis of neoloop occurrence across 86 brain tumor samples.

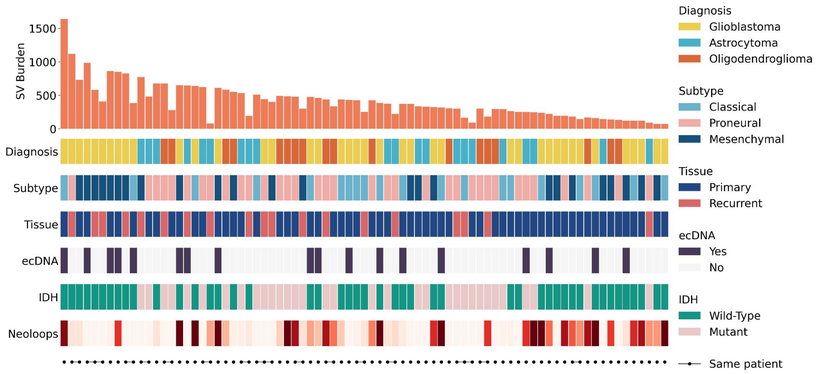
Hypotheses

- Neoloop occurrence in brain tumors will vary based on sample properties.
- Oncogenes associated with neoloops will exhibit altered expression levels.

Methods

- Hi-C sequencing technique was employed for capturing the three-dimensional chromatin conformation of tumor samples.
- ATAC sequencing data was used to detect open chromatin regions for epigenetic insights.
- RNA sequencing data was utilized for gene expression analysis.
- Whole-genome sequencing (WGS) from tumors and matched normal tissue was used for detecting somatic copy number alteration information.
- Neoloops were identified and visualized from Hi-C data with NeoLoopFinder[4].
- The IDH mutant status was analyzed using somatic mutation calls generated by Mutect2 and Strelka from the WGS data.
- Glioma subtypes were classified using the gene dataset derived from previous studies[5].
- Dimensionality reduction techniques and hierarchical clustering methods were applied to the gene expression dataset to validate our subtype classification.

Fig. 1 | Summary of 86 brain tumor samples investigated in this study[6]



A total of 86 brain cancer patient samples were included in the study, representing different glioma types such as Glioblastoma, Astrocytoma, and Oligodendroglioma.

Fig. 2 | Structural variant burden identified from WGS and Hi-C data

The analysis of structural variant burden, obtained through bioinformatic analysis on WGS and Hi-C sequencing data, offered valuable insights into the composition and count of chromosomal rearrangements across our samples.[7]

Fig. 3 | Neoloop and SV count based on IDH mutant status and tissue type

a IDH mutant status

b Primary and recurrent

a | Higher numbers of neoloops were observed in IDH wild-type gliomas compared to IDH mutant, although the association was not found to be statistically significant (p = 0.0987).

b | Between the primary tumor tissue samples and locoregional recurrent samples, there was no substantial difference in SV burden. While primary tumors exhibited an overall higher number of neoloops, it failed to reach statistical significance (p = 0.0538).

Fig. 4 | Clinical subtype classification

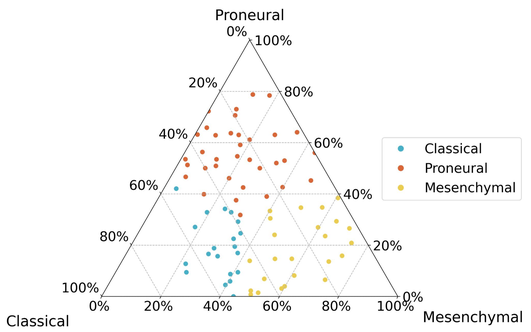


Fig. 5 | Neoloop count by subtype

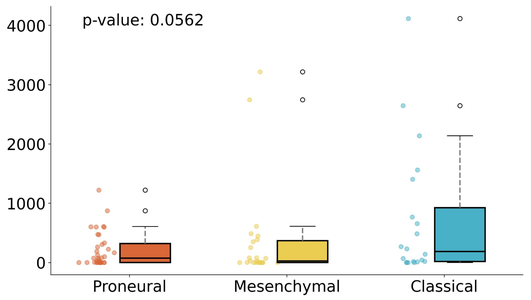


Fig. 6 | Identification of oncogenes in neoloops

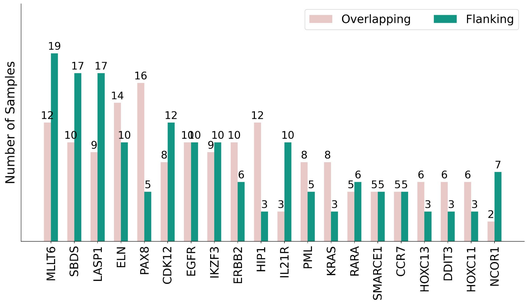
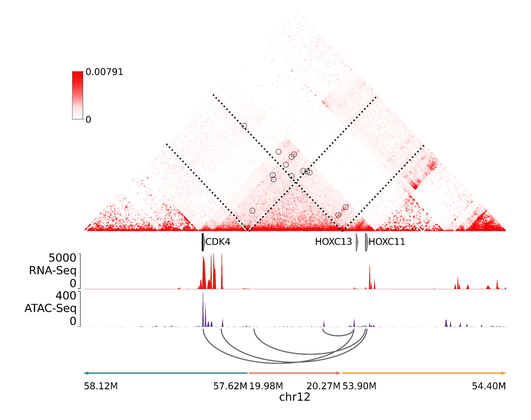


Fig. 7 | Neoloop and 3D structure alteration[4]



Results

- Based on gene expression data, the molecular subtyping of glioma samples led to the classification of 35 samples as proneural, 20 samples as classical, and 24 samples as mesenchymal.
- Among the subtypes, classical tumor samples exhibited a higher number of neoloops (t = 3.0305, p = 0.0562).
- A set of 20 oncogenes were found to recurrently overlap or flank neoloops across multiple samples.
- Further analysis revealed that among these 20 neoloop-associated genes, five genes (EGFR, IL21R, HOXC11, HOXC13, and RARA) were expressed significantly higher when involved in neoloops.
- An enhancer hijacking event was identified in genes HOXC11, HOXC13, and CDK4 within a glioblastoma sample, accompanied by significantly elevated gene expression levels (p < 0.05). This is likely influenced concurrently by alterations in gene copy number.

Conclusions

Our study sheds light on the significant impact of disrupted 3D genomic architecture in human brain tumors, particularly through the formation of neoloops. The identification of neoloop-associated genes with altered expression suggests potential oncogenic roles and offers opportunities for further investigations. Overall, these findings provide crucial insights and may guide future therapeutic interventions.

References

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