Comparison of 3D genome structure between neuronal and clinically accessible tissues

FUNGEN functional genomics lab at Ghent University

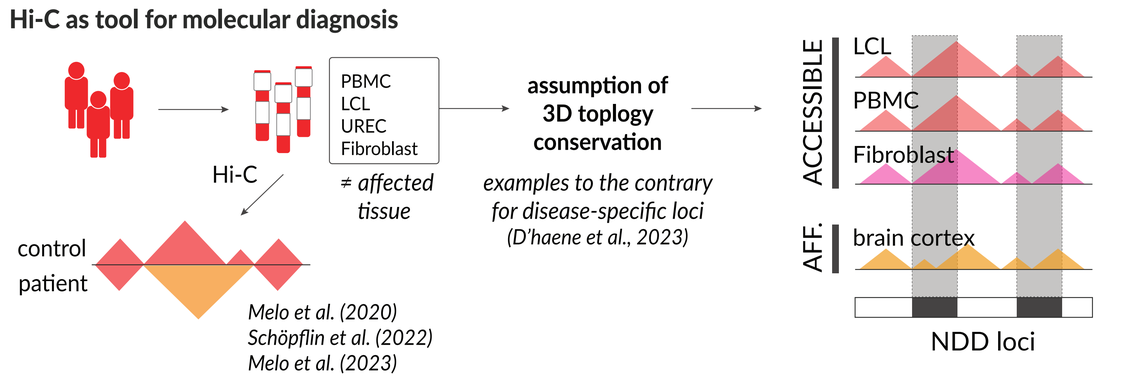
Colombo, L., Vaughan, M.B., Van Loon, N., Leimbacher, S., Daal, E., D'haene, E. & Vergult, S.

1. Department of Biomolecular Medicine, Ghent University, Belgium, 2. Center for Medical Genetics (CMGG), Ghent University Hospital, Belgium

Lara.Colombo@ugent.be | Eva.Dhaene@ugent.be | Sarah.Vergult@ugent.be @eedhaene.bsky.social | @svergult.bsky.social

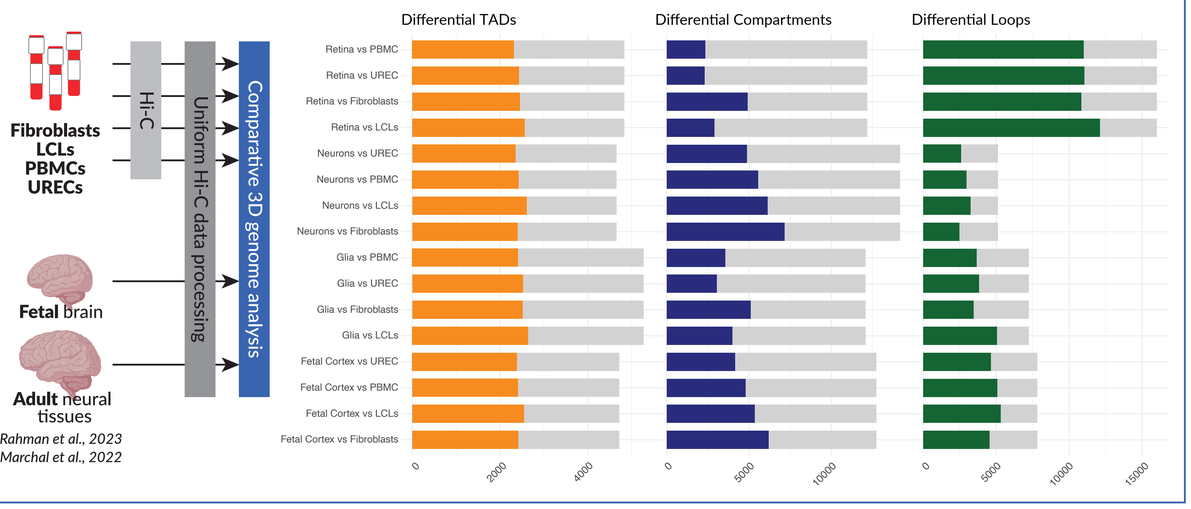
INTRODUCTION

3D genome mapping of patient samples has been leveraged to better understand the impact of structural variants (SVs) in disease. Yet, when it comes to applying **Hi-C** as an SV assessment strategy in a **clinical context**, a major obstacle is the inaccessibility of the affected tissues. This is especially true in the case of **neurodevelopmental disorders** (NDDs). Therefore, there is a need to investigate the utility of Hi-C assessment on **clinically accessible tissues** (CATs) such as blood cell lines (PBMCs, LCLs), fibroblasts and urine-derived renal epithelial cells (UREC) for the interpretation of neuro-pathogenic SVs.



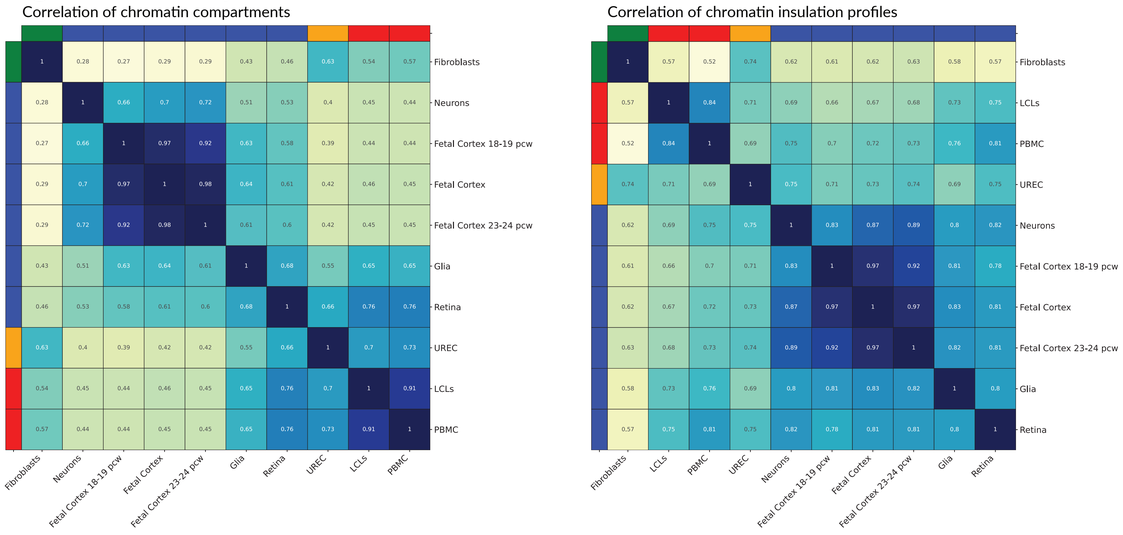
DIFFERENTIAL 3D ORGANIZATION ACROSS TISSUES

A preliminary comparison across four CATs (UREC, LCLs, PBMC and fibroblasts) and four brain tissues (fetal cortex, adult glia, adult neurons and retina) identified distinct **chromatin features** that were present in brain samples, but not CATs.



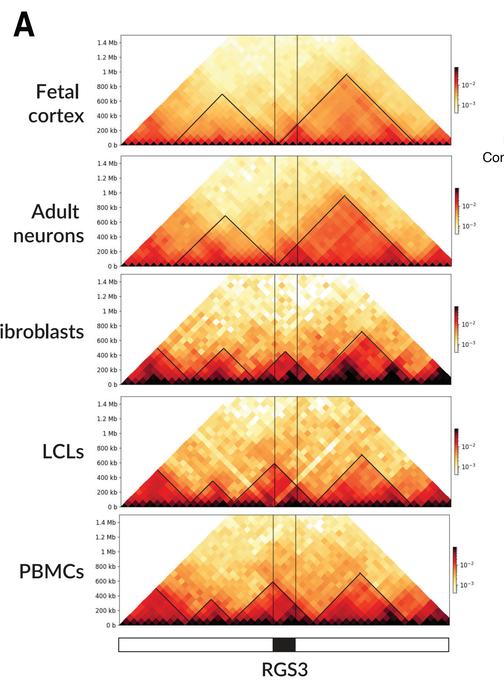
CHROMATIN FEATURES REFLECT TISSUE (DIS)SIMILARITIES

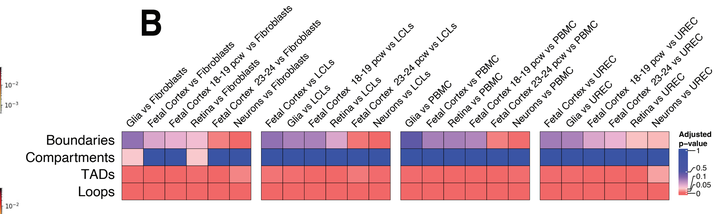
Cross-tissue correlation analysis of **chromatin compartments** and **insulation profiles** demonstrated that both TAD and A/B compartment patterns reflected **biological similarity** across tissues.

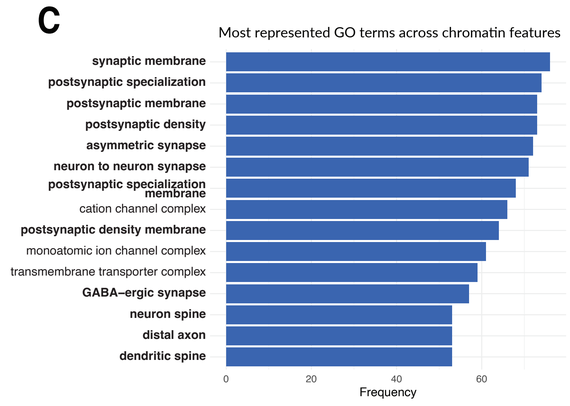


DIFFERENTIAL 3D FEATURES AT DISEASE LOCI

Our lab and others demonstrated the presence of **tissue-specific 3D genome structures** within complex tissues such as the retina and brain (Fig. A), especially at disease loci. Our comparative analysis across four CATs and four brain tissues showed the **enrichment of NDD-associated genes** (N=1188, in-house list) at diferential boundaries, TADs, compartments and loops (Fig. B; adjusted p-values from Fisher's exact test). We found that genes at differential chromatin features were enriched in **brain-related GO terms**; Fig. C shows the most frequent significant terms detected across all comparisons for each differential feature.







CONCLUSION

In sum, our study provides preliminary insights into common and tissue-specific chromatin structures in clinically accessible vs. disease-affected tissues. Initial results indicate that disease genes, such as known NDD genes, can be associated with tissue-specific TAD structures that are not shared across CATs. This represents an important consideration when selecting CATs for SV assessment in a diagnostic context.

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