



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

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## Background

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) and fibroblasts for the interpretation of pathogenic SVs.

## Sample Collection

NEURAL TISSUES  
Retina, Neural Organoids, Fetal Frontal Cortex, Adult Frontal Cortex

CLINICALLY ACCESSIBLE TISSUES  
LCLs, PBMCs, Fibroblasts

## Hi-C Processing Pipeline Development

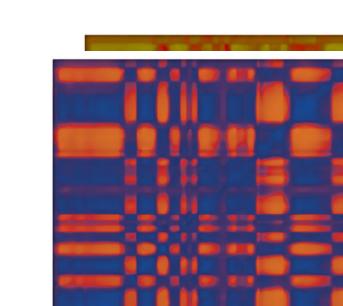


4DN

$$p = 1 - \sum_{i=0}^{k-1} \frac{\binom{M}{i} \binom{N-M}{n-i}}{\binom{N}{n}}$$

NDD Genes Over Representation

## Chromatin Maps Comparison



COMPARTMENTS



LOOPS

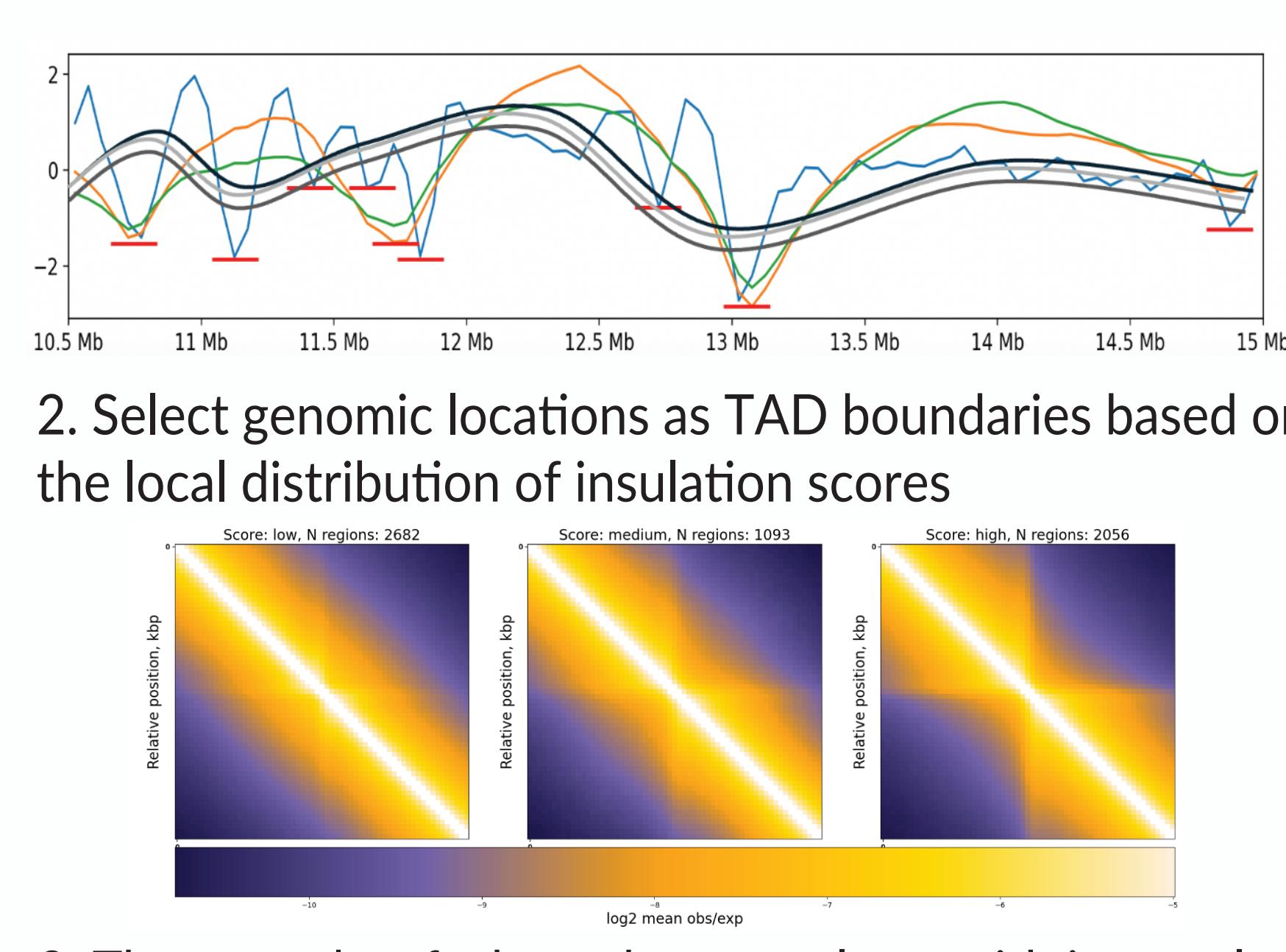
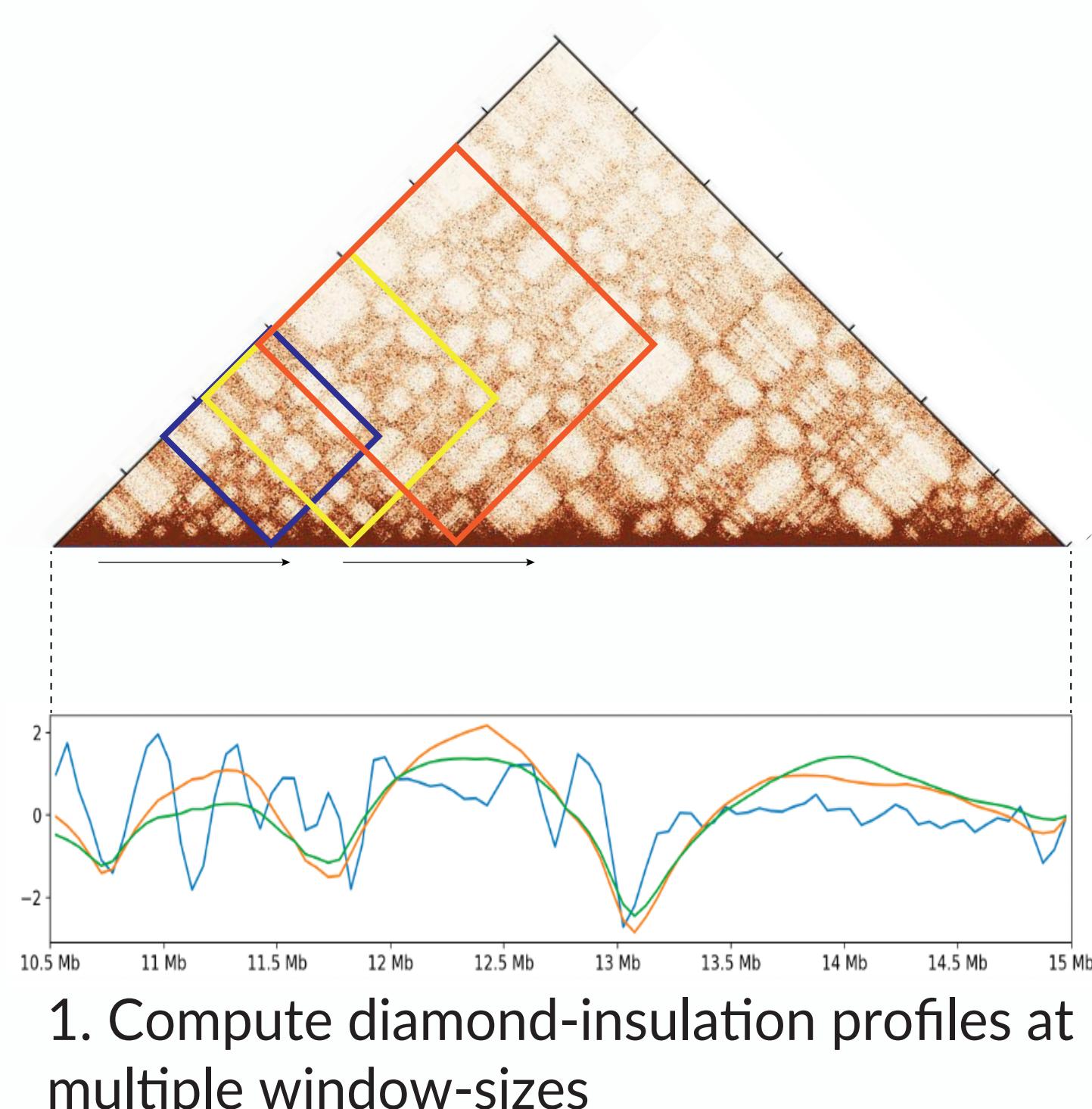


TOPOLOGICALLY ASSOCIATING DOMAINS

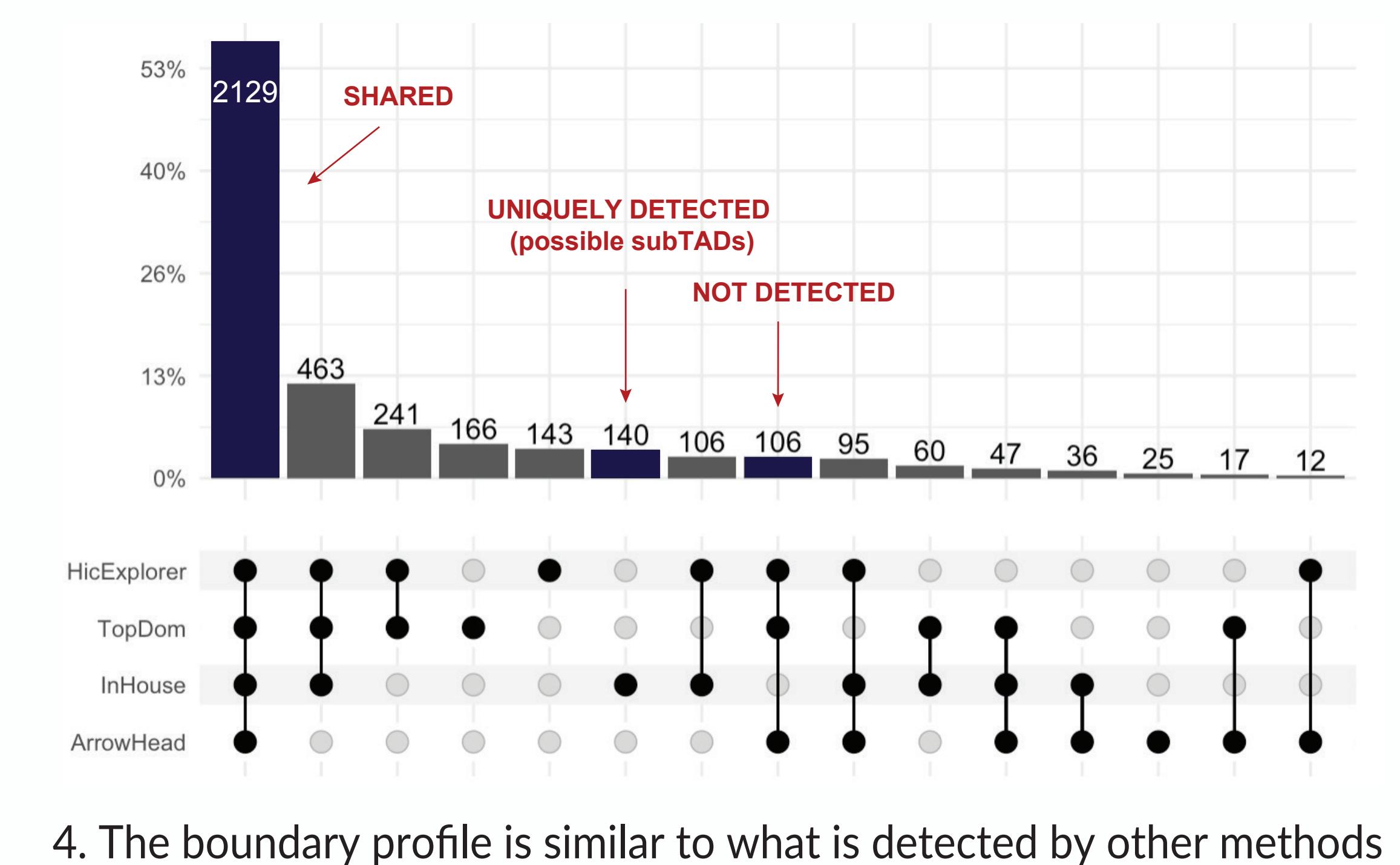
## 1. In-house TAD-calling approach accurately detects the position of boundaries

We developed an unbiased approach for TAD boundary calling, based on the cooltools framework, which detects boundaries by computing diamond-insulation profiles at increasing window sizes,

until redundancy is reached. This allows us to score boundaries based on their consistency at different scales. The results are concordant with popular existing tools.

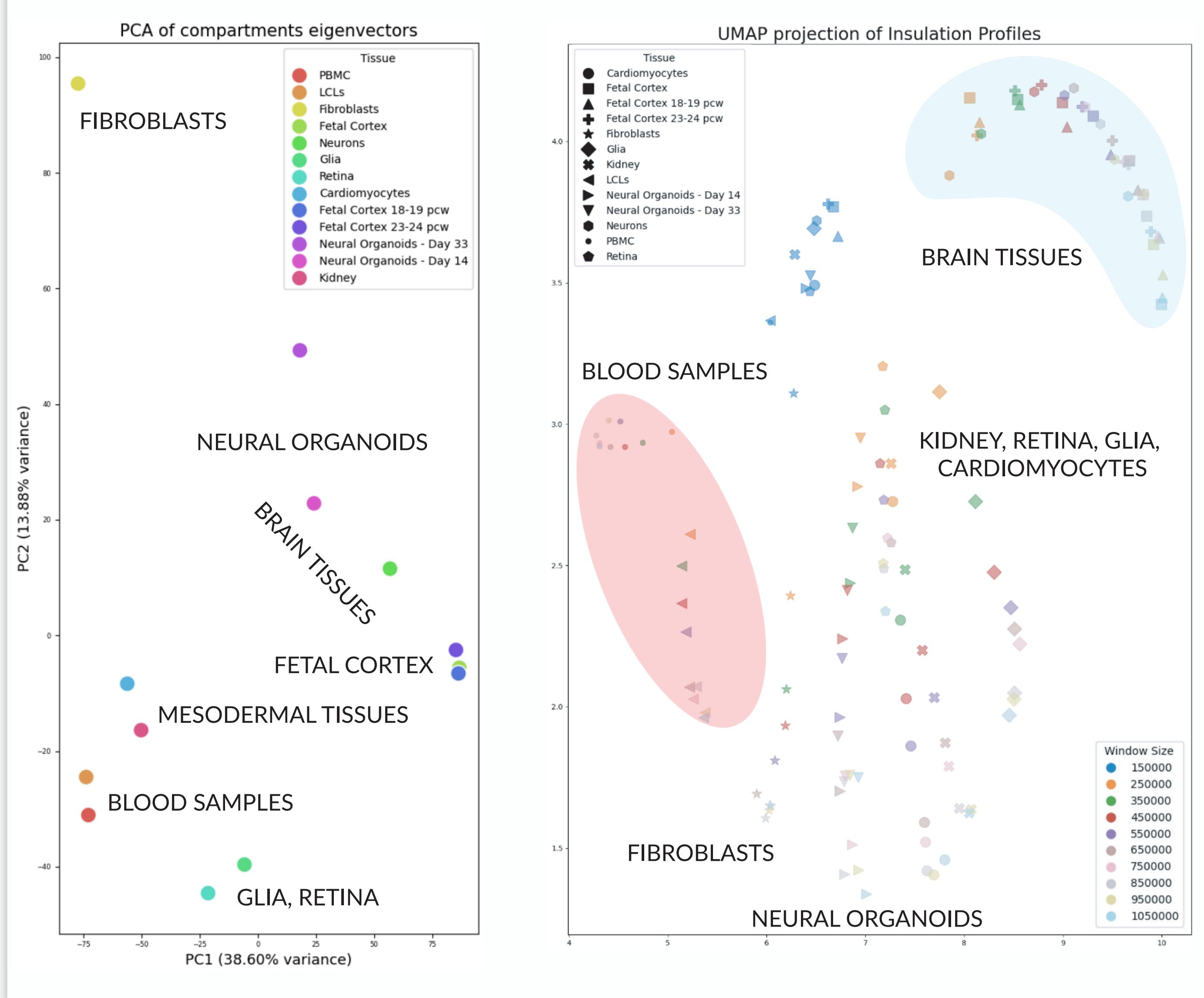


3. The strength of a boundary correlates with its overlap across window sizes (Overlap Score)



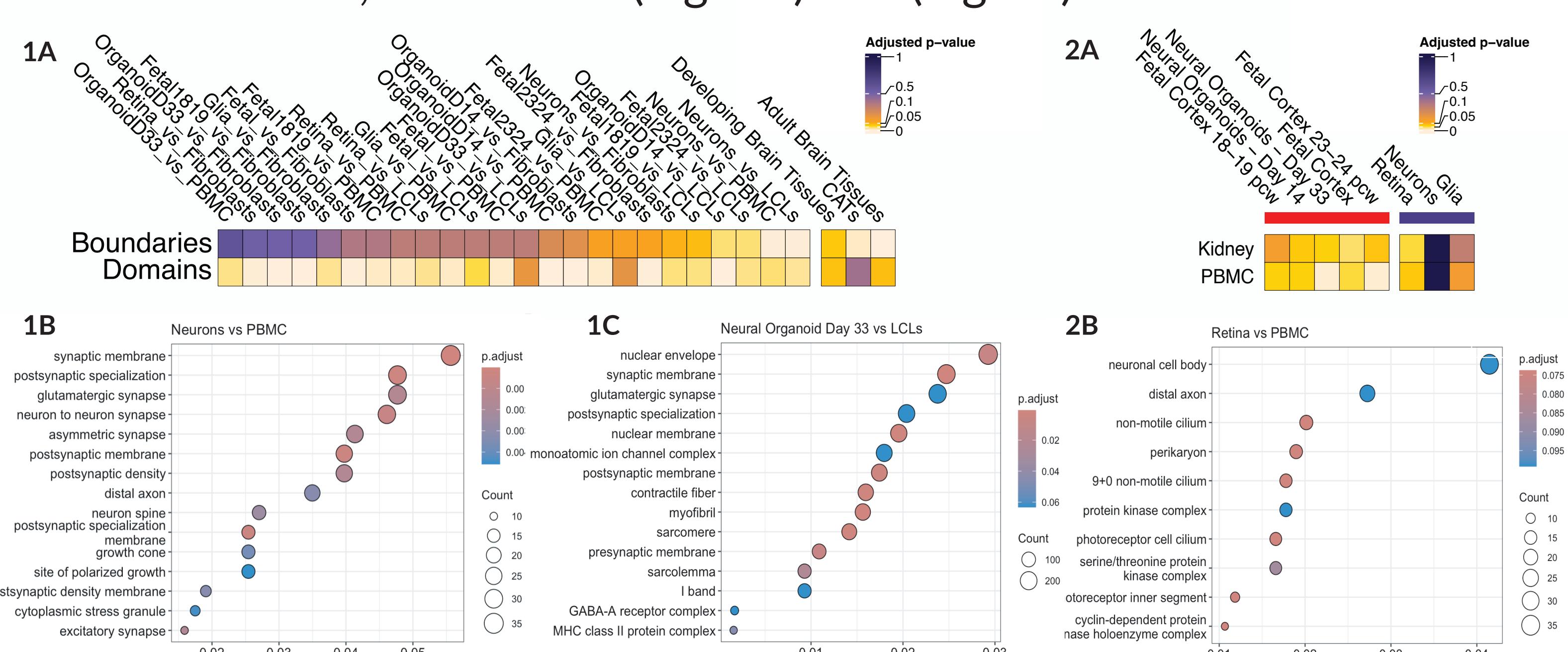
## 2. Chromatin features reflect tissue (dis)similarity

We correlated the **insulation profiles** and the **chromatin compartments** computed by eigendecomposition of the matrices to assess whether they clustered by technical (experimental) or biological variability. We determined that both TADs and A/B patterns reflected **biological similarity** across tissues. Clustering patterns reflected absolute values of correlation ( $>0.9$ ) between sparsely-close samples (not shown here).



## 3. Differential 3D organization reflects gene specificity

By comparing chromatin structures in neuronal tissues versus CATs, we found that genes at differential TADs (Fig. 1B), domains (Fig. 1C) and loops (Fig. 2B) were enriched for **brain-related gene ontology** terms. Also, we found that genes associated with **NDDs** were enriched both across differential TADs, boundaries (Fig. 1A) and (Fig 2A) in neuronal tissues.



## 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.