Integrating spatial transcriptomics and known regulatory elements to elucidate mechanisms of Parkinson's disease

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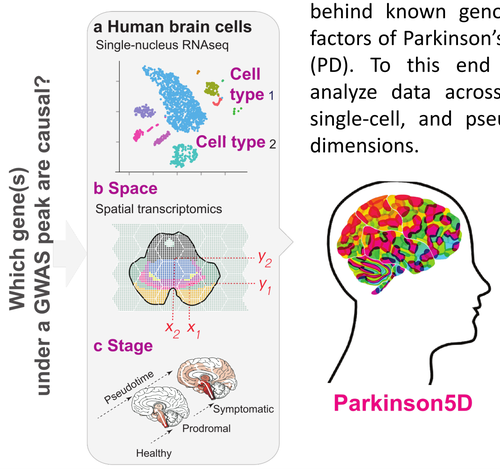
Objective

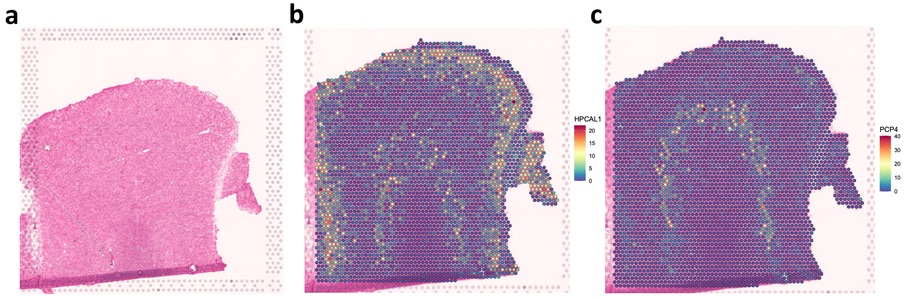
In the Parkinson5D project, we are interested in building regulatory networks describing the molecular mechanisms behind known genomic risk factors of Parkinson's Disease (PD). To this end we will analyze data across spatial, single-cell, and pseudo-time dimensions.



Methods

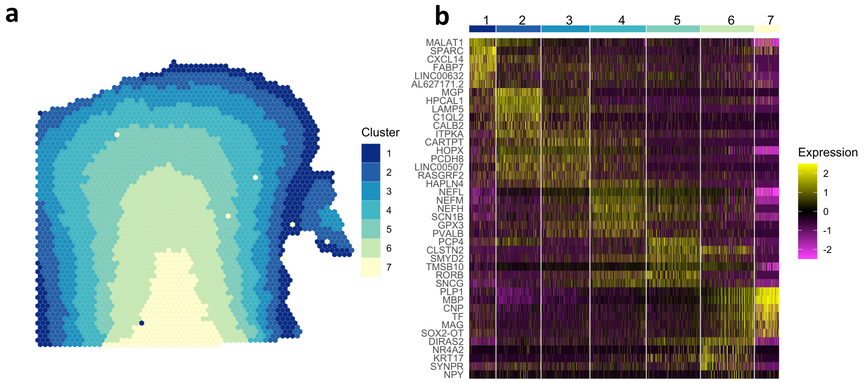
- **Spatial expression patterns:** We use the 10X Visium platform to generate spatial transcriptomics data for 52 DLPFC samples representing controls, prodromal, and clinically manifest PD, with the goal of reaching 100 samples. We segment spots according to inferred cortical layer and identify gene expression patterns unique to each layer.
- **Multi-omics integration:** In known PD-associated loci, we aggregate existing omics annotations including significant GWAS SNPs[1], proxy SNPs with high LD, cell-type specific chromatin accessibility, UCSC refSeq genes, and chromatin conformation.
- We construct the regulatory networks of enhancers → TFs → mRNA based on co-expression of transcribed non-coding elements (TNEs), TFs, and non-TF genes in 106 BRAINcode samples[2].

Spatial Transcriptomics



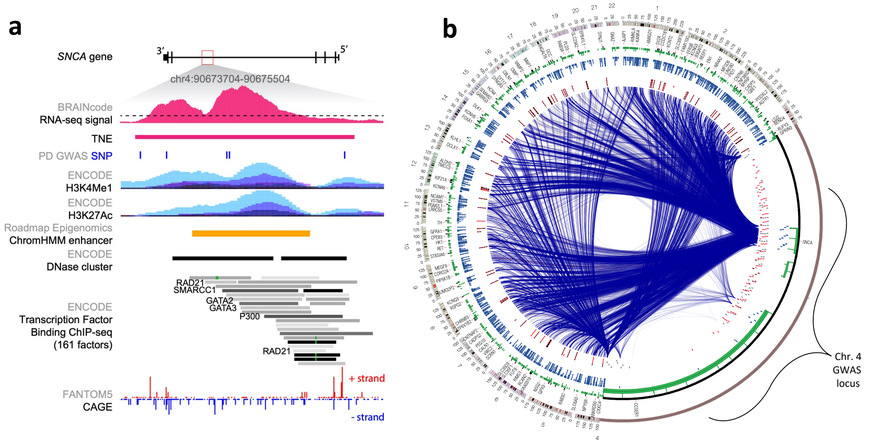
- H&E staining **(a)** for one DLPFC sample collected from an individual with PD. Read counts are estimated in each of a grid of roughly 4,000 spots. Cortical layers exhibit distinct gene expression patterns (e.g., HPCAL1 in Layers 2,6 **(b)** and PCP4 in layer 5 **(c)**).

Layer-specific expression



- We use the BayesSpace[3] algorithm to segment spots into cortical layers 1-6 and white matter **(a)**. We identify top differentially expressed genes in each layer by the Wilcoxon Rank-Sum test[4] **(b)**.
- We observe significant layer-specific localization of genes implicated in neurodegenerative diseases, such as the gamma-synuclein gene (SNCG) in Layer 4 (adj. p-val: 1.34×10^{-55}) and Layer 5 (adj. p-val: 5.71×10^{-69}).

Multi-omics Integration



- We select TNEs defined in BRAINcode to be likely enhancers as supported by genomics and epigenomics, for example in the α-synuclein gene **(a)**.
- We combine known omics features with possible regulatory relationships across 78 GWAS-significant loci. In **(b)**, spearman correlations > 0.6 between at least one member of the SNCA locus (enlarged) are shown. From the center outward: 1. GWAS significant SNPs, SNPs in LD ($r^2 > 0.8$); 2. class-I TNEs reported in BRAINcode; 3. TFs significantly correlated with SNCA TNEs.

Conclusion

- Preliminary spatial transcriptomics results show that gene expression is highly stratified across cortical layers, potentially providing more power to detect differentially expressed genes between cases and controls.
- We observe significant correlations among the expression of enhancers throughout the genome, suggesting high regulatory activity in the brain genome.
- Moving forward, we intend to apply single-cell expression and ATAC-seq data to unify these analyses using cell type. This will allow us to identify cell type-specific ATAC-seq and eRNA profiles and link them to cortical layers based on inferred cell-type mixtures in each spot.

REFERENCES

1. Nalls, et al. *The Lancet Neurology,* 2019.
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4. Hao, et al. *Cell,* 2021.

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