

PRIMES Research Conference
10.18.25

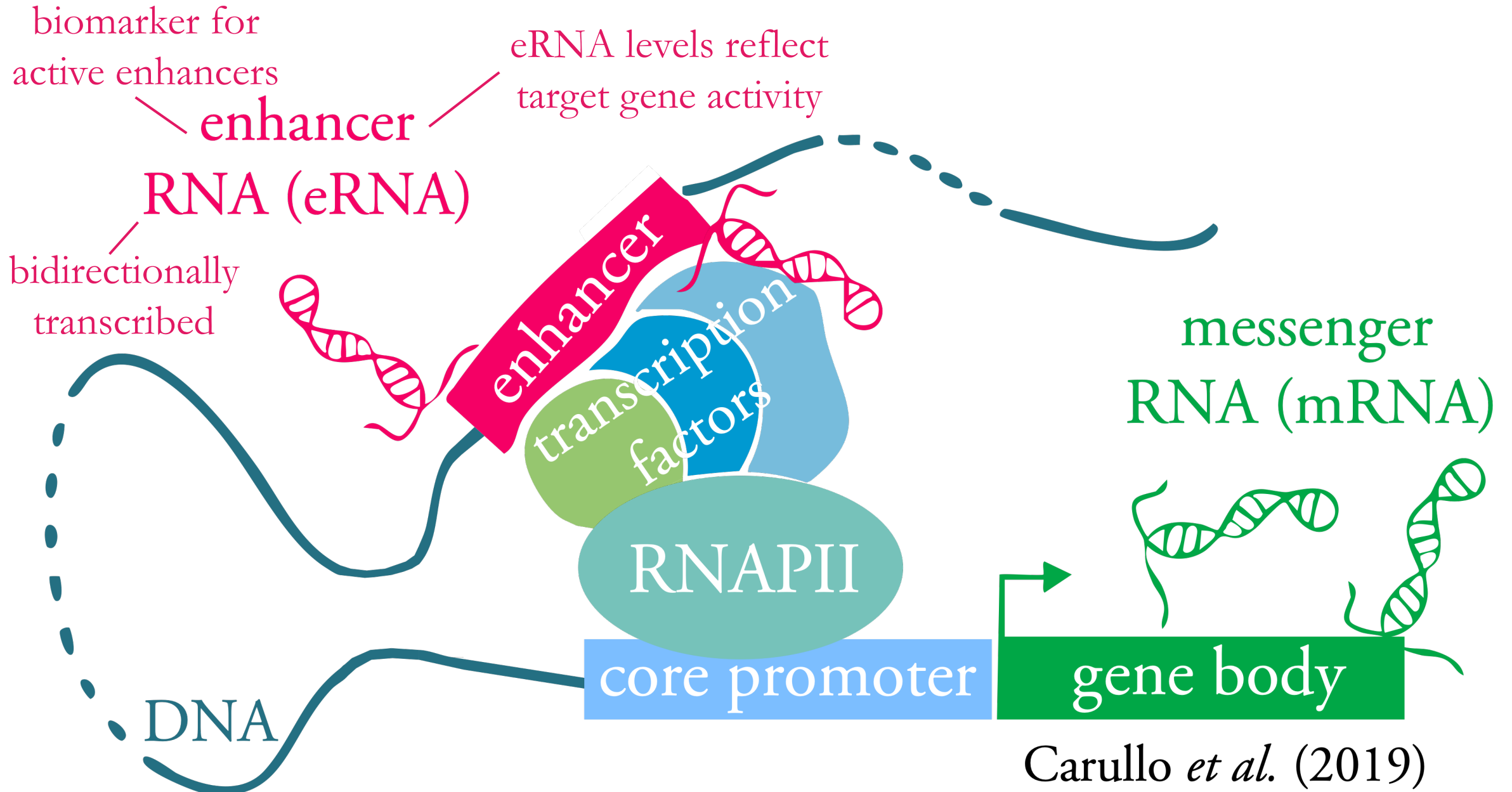
Mapping enhancer-gene interactions in the human brain reveals reduced use of enhancers for synaptic genes in schizophrenia

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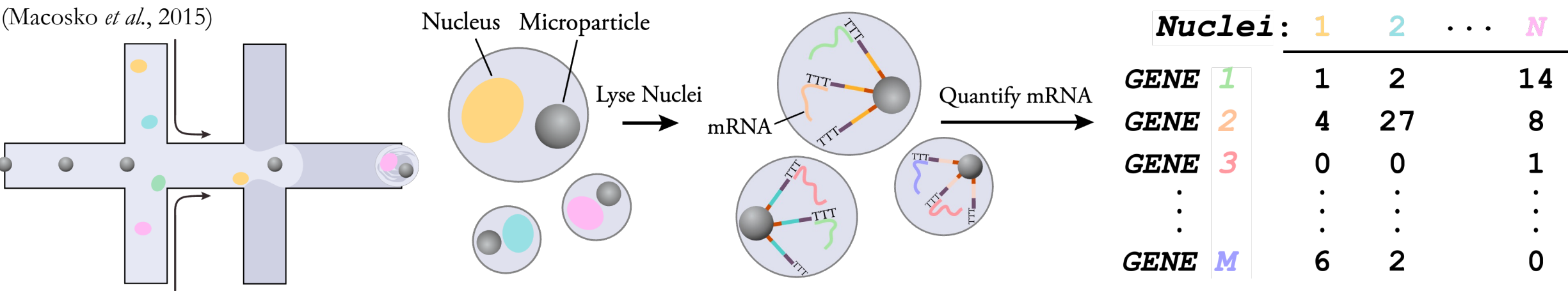
(AI Generated Image)

What is Enhancer-driven Gene Regulation?

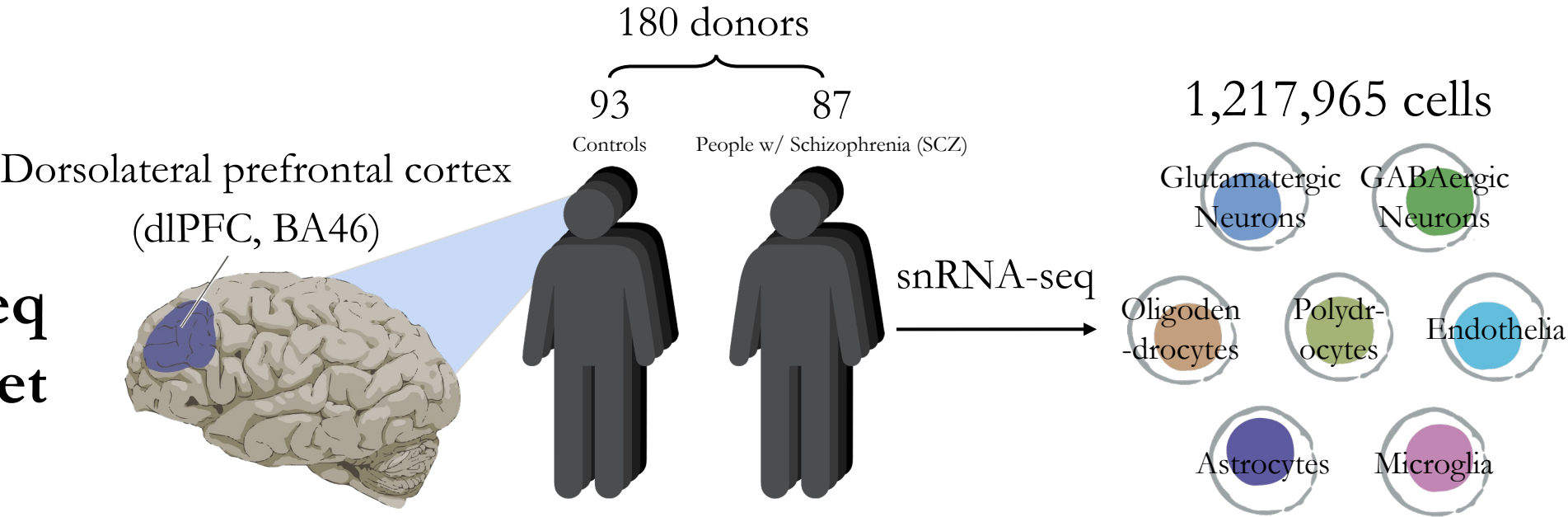


What is single nucleus RNA sequencing (snRNA-seq)?

(Macosko *et al.*, 2015)



Our snRNA-seq Dataset



Talk Outline

Motivating Question

1. Can snRNA-seq detect eRNA? (yes)

Challenges

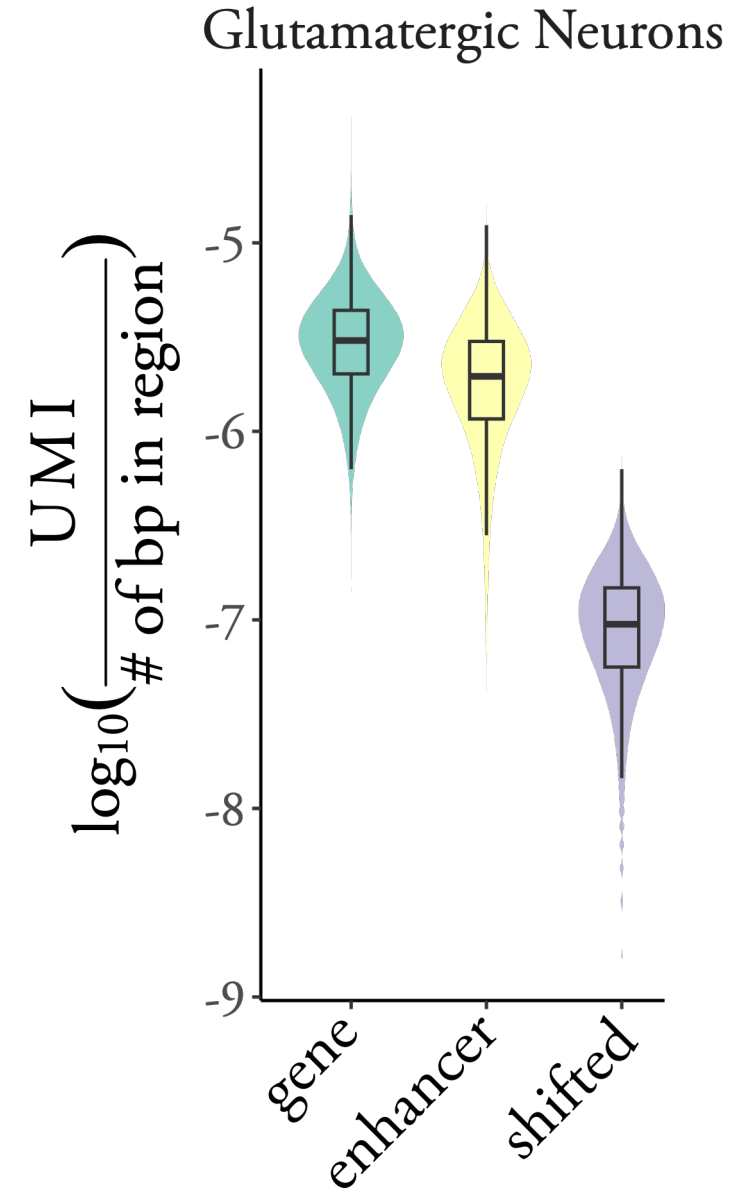
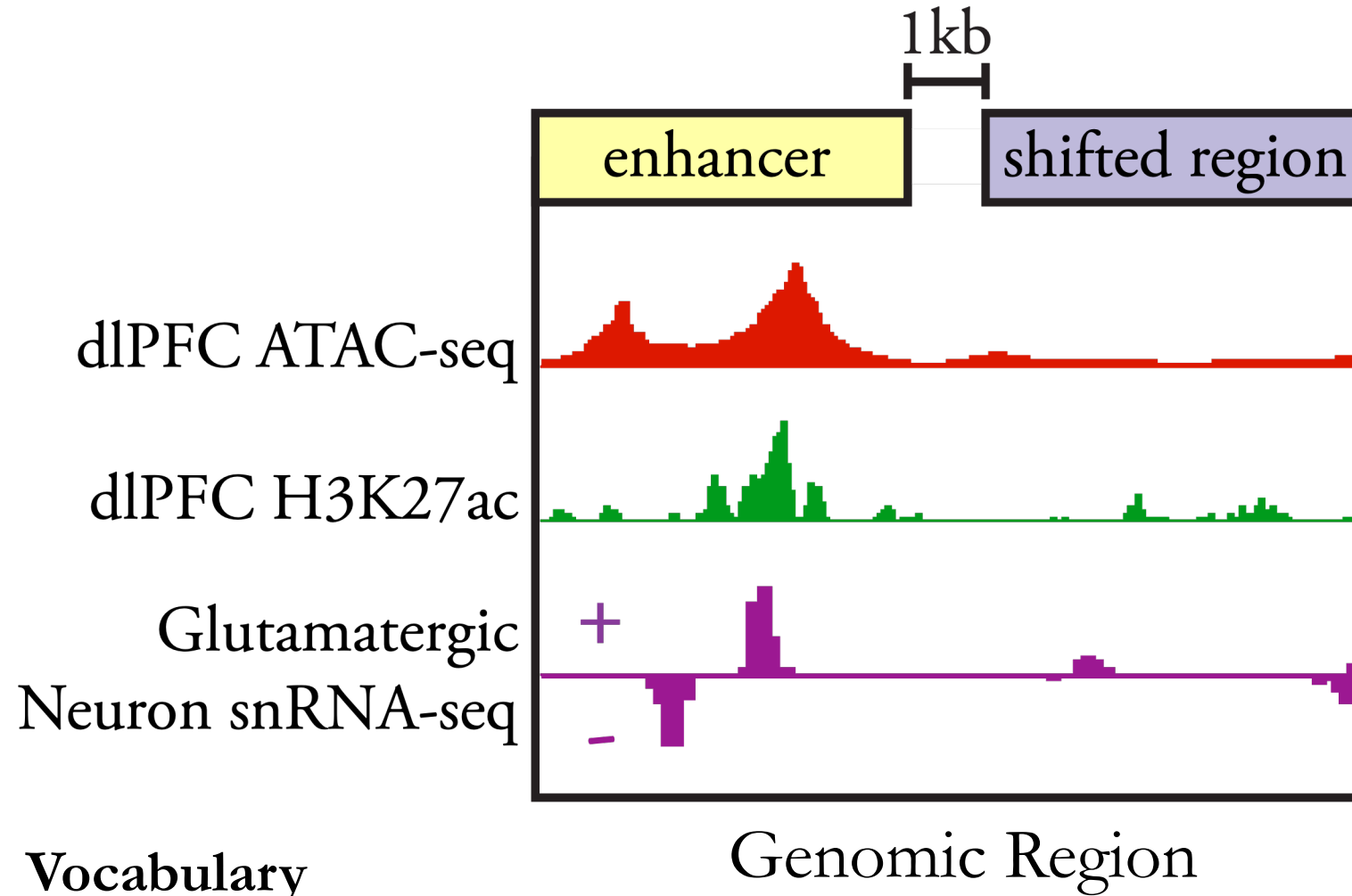
1. eRNA is unstable
2. snRNA-seq is not optimized to target eRNA

Follow-up Questions

1. How similar is enhancer-gene regulation across cell-types?
2. Are enhancers of SCZ genes enriched for SCZ variants?
3. What functions do enhancer-gene pairs have in controls? SCZ?

snRNA-seq Can Detect eRNA

Ascertainment rates of eRNA are comparable to mRNA, higher than intergenic RNA



Vocabulary

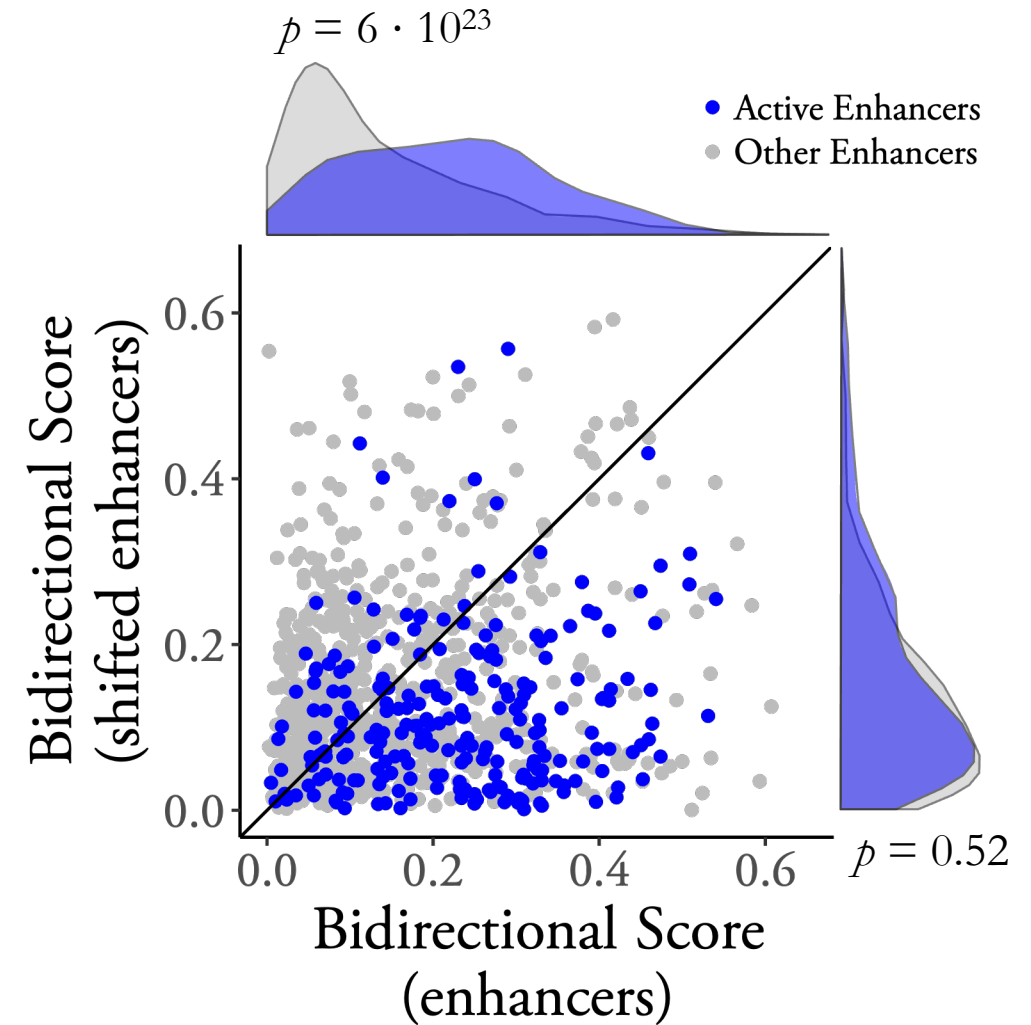
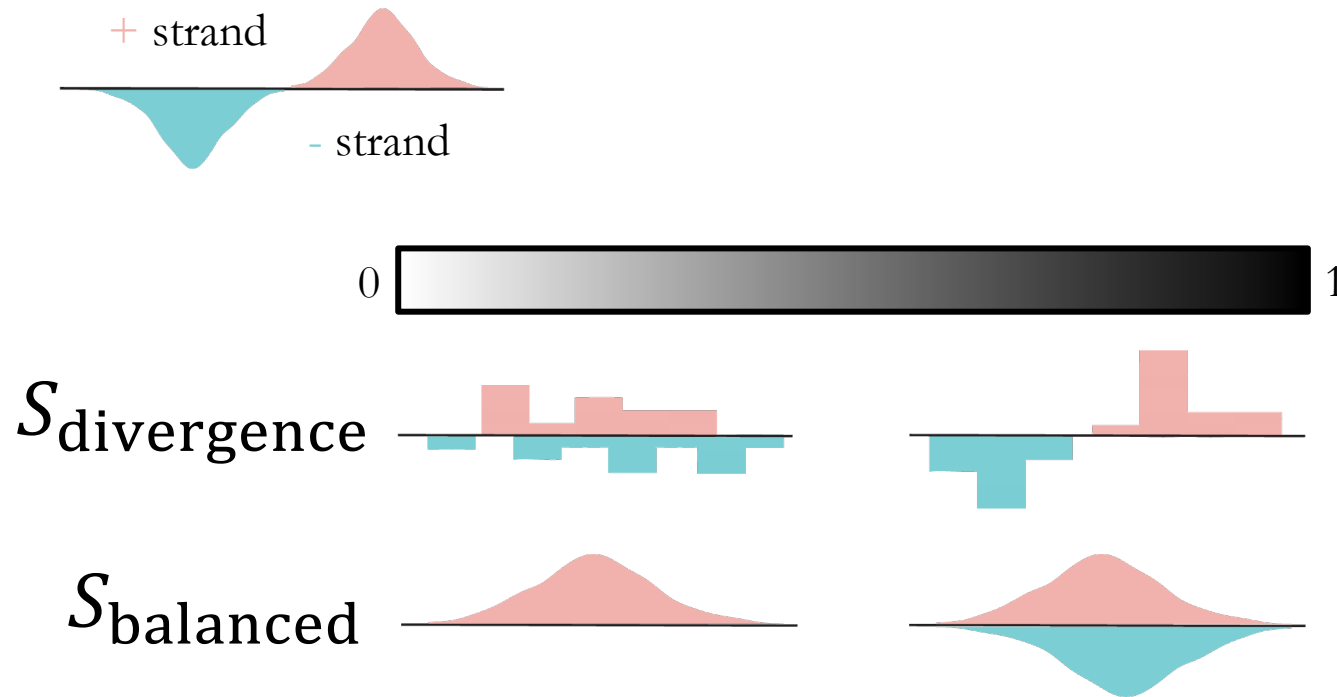
ATAC-seq: Measures region's chromatin accessibility

H3K27ac: An active enhancer marker

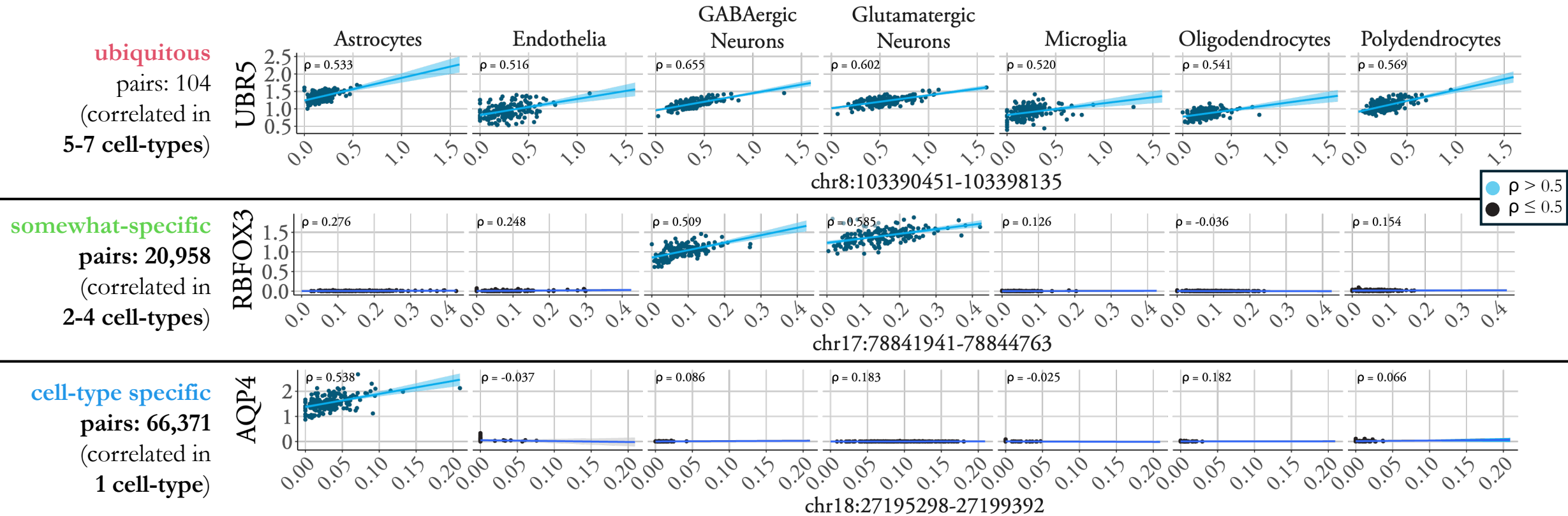
snRNA-seq Can Detect eRNA

Active enhancers show higher bidirectional transcription behavior than non-active & shifted enhancers

$$S_{\text{bidirectional}} = S_{\text{divergence}} \cdot S_{\text{balanced}}$$

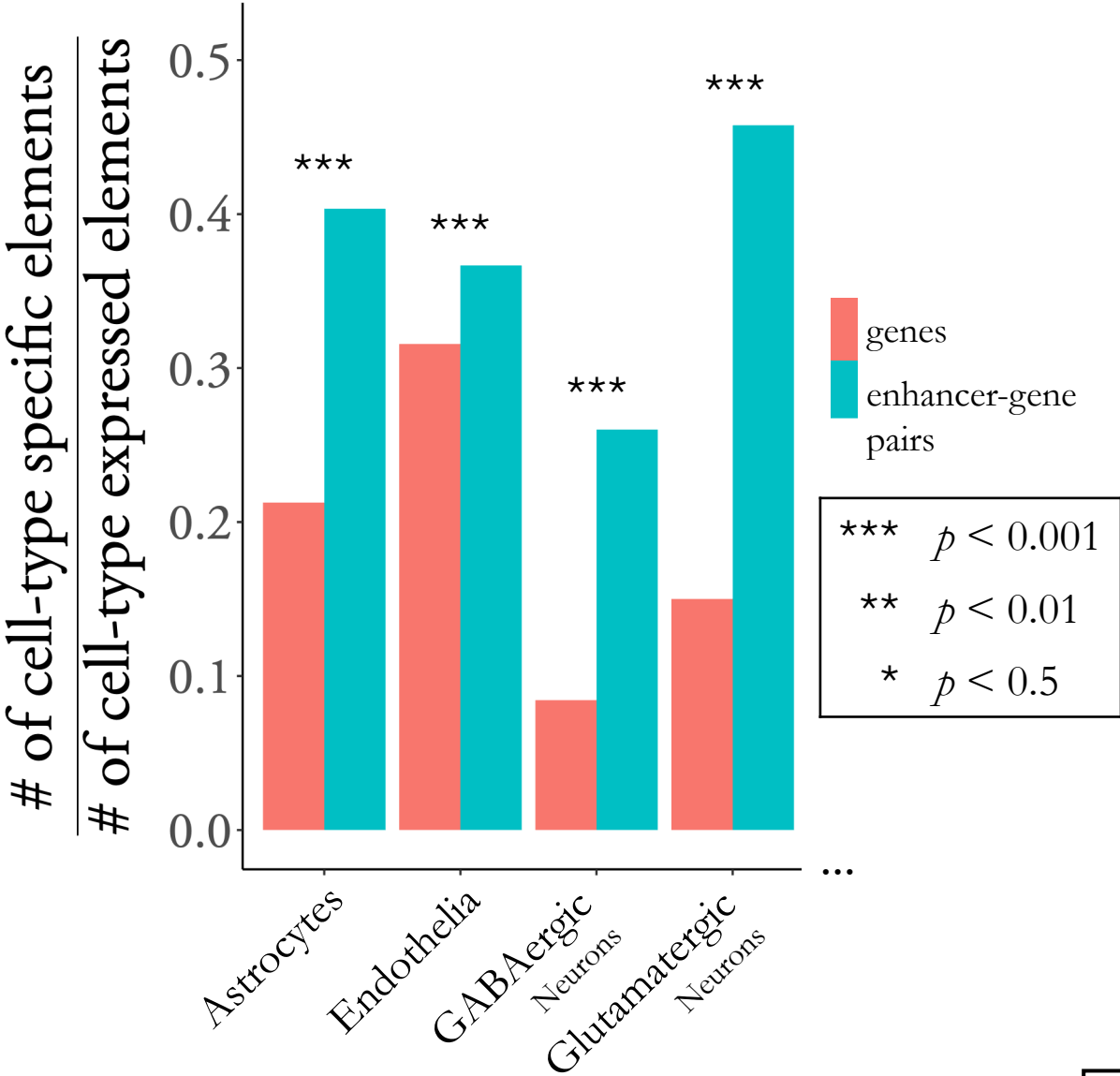
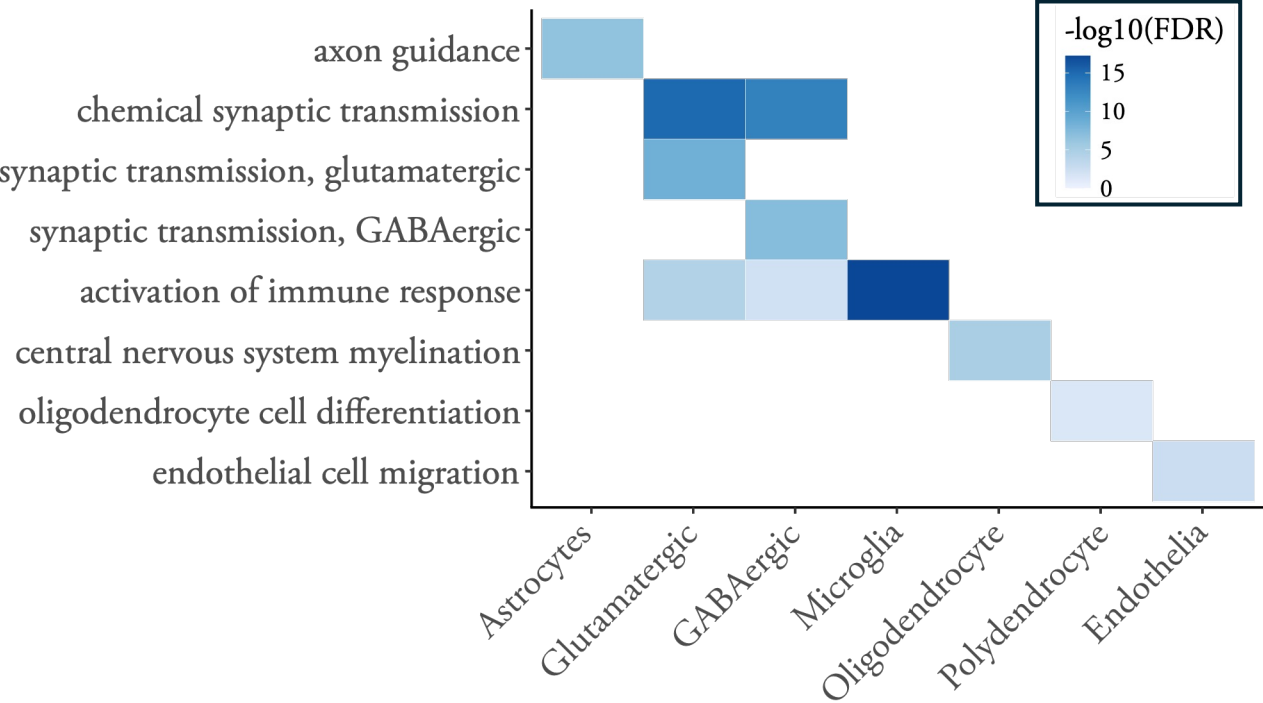


Enhancer-Gene Regulation is Highly Cell-Type Specific



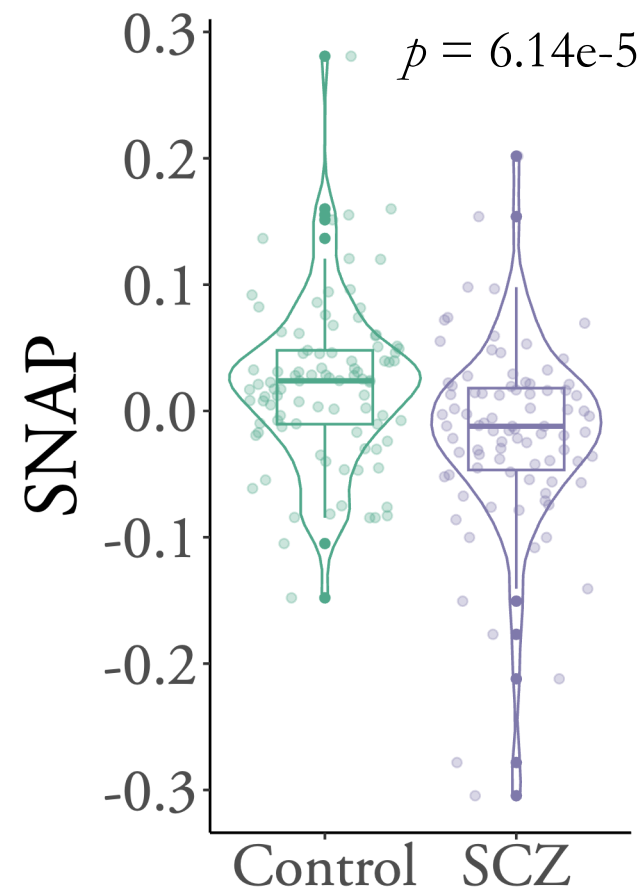
Gene Regulation More Cell-Type Specific Than Gene Expression

Genes of **Cell-type Specific** Pairs



Introduction to SNAP (Synaptic Neuronal Astrocyte Program)

(Ling *et al.*, 2024)



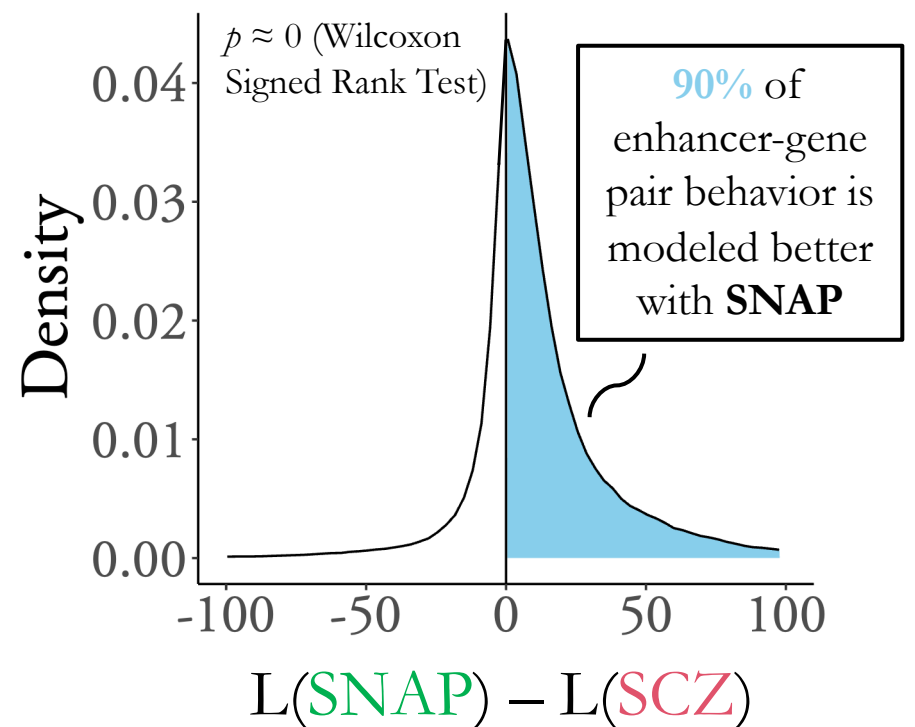
Controls $\approx$ High SNAP
SCZ $\approx$ Low SNAP

SCZ Mixed Effects Model

$$Y_{\text{gene.expr}} \sim \beta_{\text{enhancer.expr}} \cdot X_{\text{enhancer.expr}} + \beta_{\text{cell-type}} \cdot X_{\text{cell-type}} + \beta_{\text{age}} \cdot X_{\text{age}} + \beta_{\text{sex}} \cdot X_{\text{sex}} + \beta_{\text{scz}} \cdot X_{\text{scz}} + \beta_{\text{enhancer.expr:scz}} \cdot X_{\text{enhancer.expr}} \cdot X_{\text{scz}} + (1 \mid \text{donor}) + \text{Intercept}$$

SNAP Mixed Effects Model

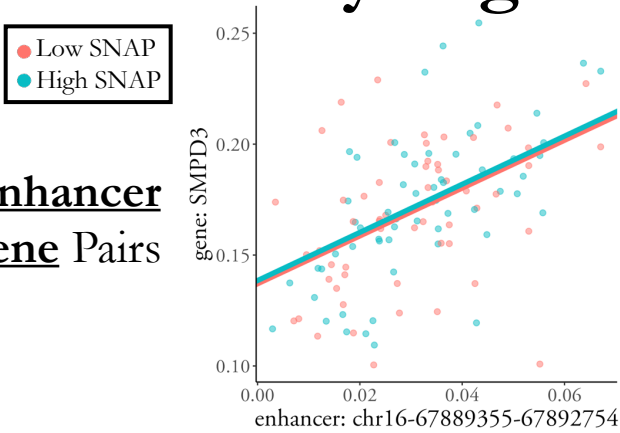
$$Y_{\text{gene.expr}} \sim \beta_{\text{enhancer.expr}} \cdot X_{\text{enhancer.expr}} + \beta_{\text{cell-type}} \cdot X_{\text{cell-type}} + \beta_{\text{age}} \cdot X_{\text{age}} + \beta_{\text{sex}} \cdot X_{\text{sex}} + \beta_{\text{snap}} \cdot X_{\text{snap}} + \beta_{\text{enhancer.expr:snap}} \cdot X_{\text{enhancer.expr}} \cdot X_{\text{snap}} + (1 \mid \text{donor}) + \text{Intercept}$$



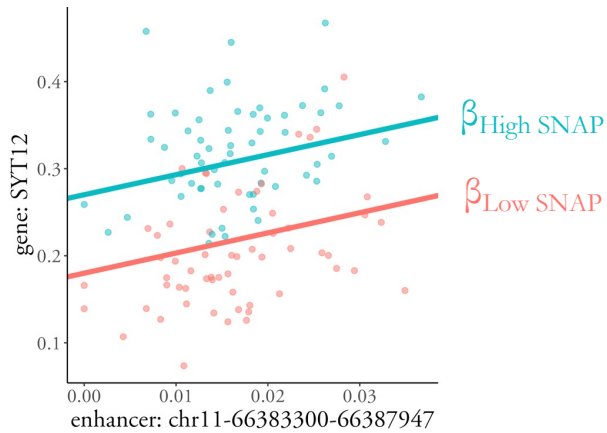
$L(\text{model}) = \text{log-likelihood}$
(how well model explains the observed data)

Enhancers of Dysregulated Pairs Enriched for SCZ Risked Variants

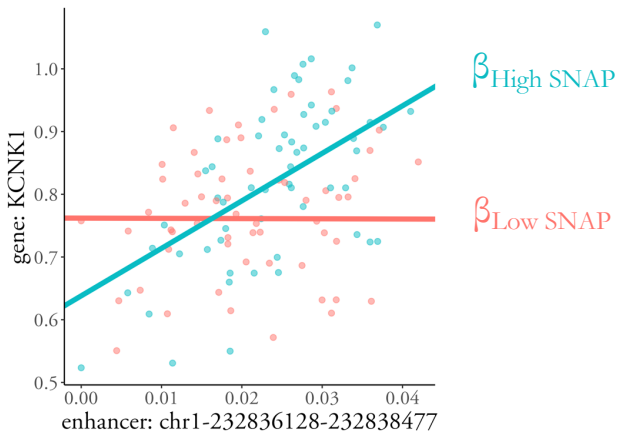
97K Enhancer
on Gene Pairs



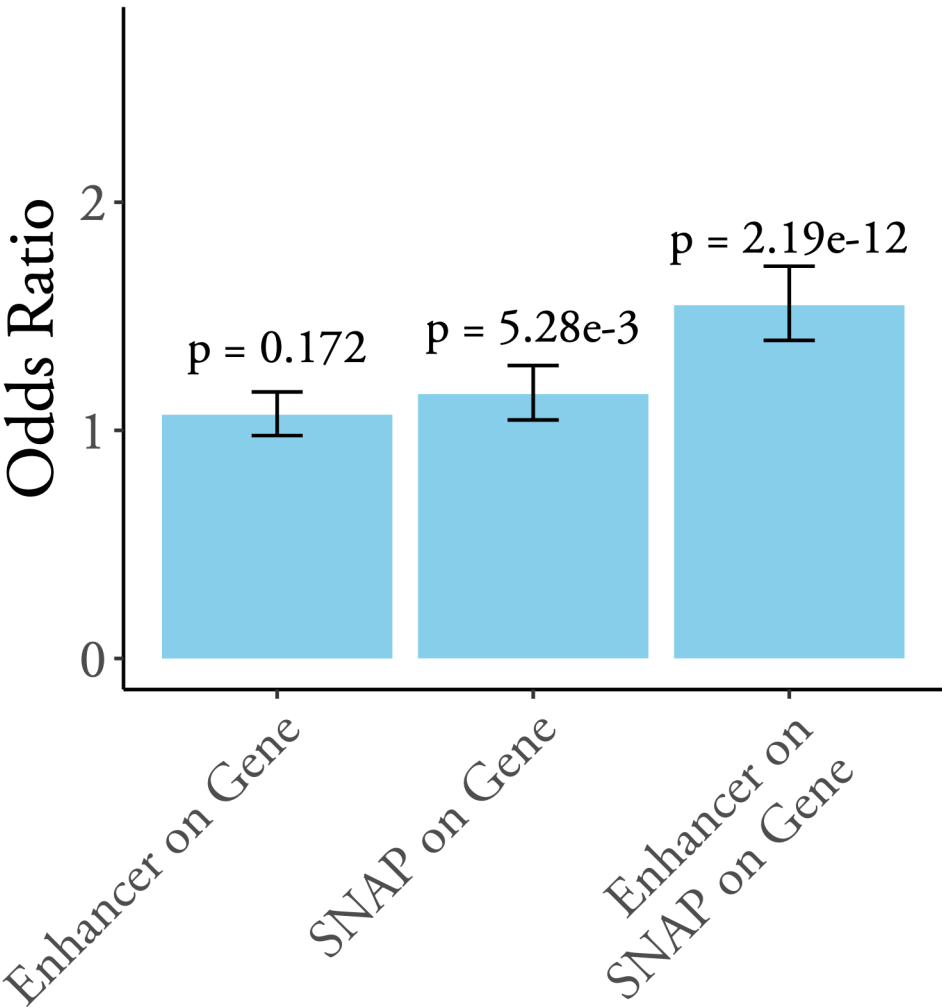
18K SNAP
on Gene Pairs



13K SNAP on Enhancer
on Gene Pairs

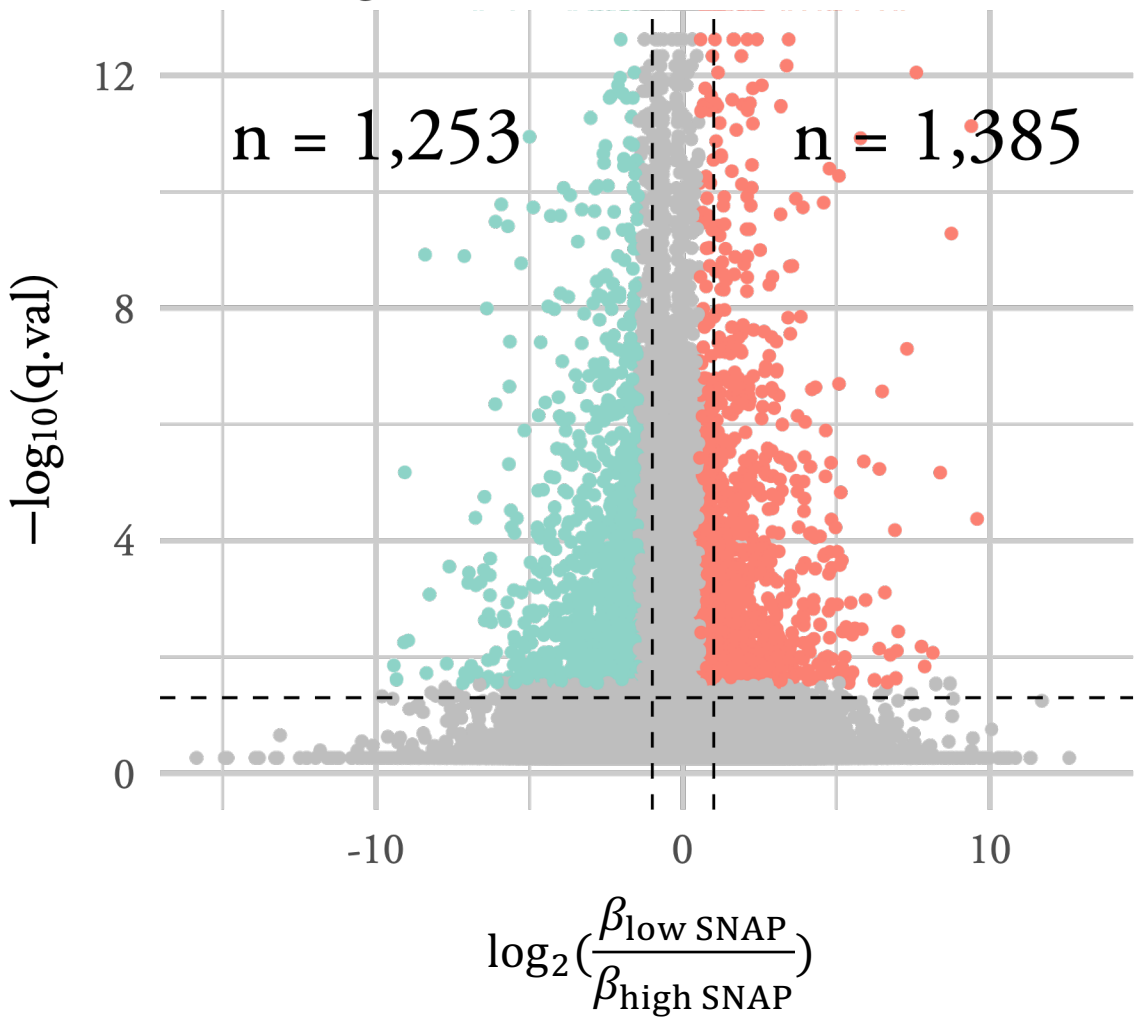


SCZ Variant Enrichment

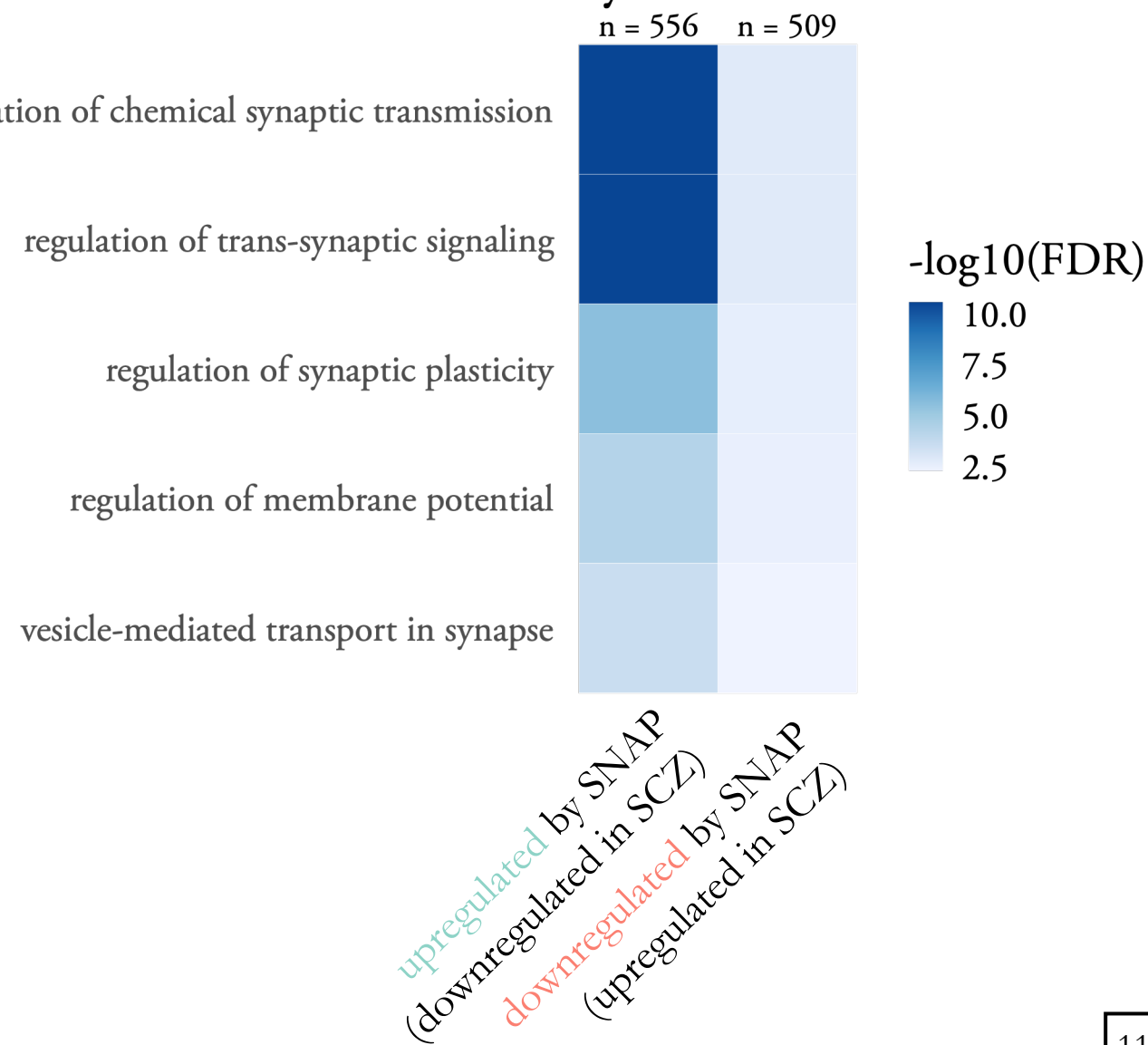


Loss of Enhancer Regulation for Synaptic Genes in SCZ

Glutamatergic Neuron Enhancer-Gene Pairs



Enriched Pathways of SNAP Pair Genes



Conclusions

1. **snRNA-seq can detect enhancer RNA (eRNA)**
 - Probably by picking up on A-rich regions in the eRNA transcript
2. **Enhancer-gene regulation is highly cell-type specific**
 - Ubiquitous enhancers are highly expressed (on average)
 - Cell-type specific enhancers are lowly expressed (on average)
3. **SNAP enhancers are enriched in non-coding SCZ risk variants**
 - Suggesting enhancer-dysregulation plays an important role in disease mechanism
 - Non-coding variants at enhancer regions could change TF binding sites
4. **Loss of synaptic gene regulation in glutamatergic neurons in SCZ**
 - Which aligns with what is known about schizophrenia: cognitive decline in people with SCZ.

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