Unraveling the cell type-specific regulatory mechanisms underlying neuropsychiatric and neurodegenerative disease risk

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Introduction

- Most GWAS variants associated with neurodegenerative and neuropsychiatric disease are in non-coding regions of the genome, making it difficult to decipher their impact on disease. Expression quantitative trait locus (eQTL) mapping can link GWAS variants to disease; however, many variants remain unexplained by current bulk brain tissue eQTLs, as bulk primarily captures shared effects across cell types.
- Single-nucleus RNA-seq (snRNA-seq) studies show greater success linking cell type-specific eQTLs with GWAS variants, but many context-specific eQTLs remain undiscovered due to low power from small cell counts, limited definitions of cell-type specificity, and the intra-individual correlation inherent to snRNA-seq studies.
- This project addressed these gaps by applying FastGxC,[1] a powerful context-dependent cis-eQTL mapping method, to snRNA-seq data from the dorsolateral prefrontal cortex (DLPFC) of 440 individuals in the ROSMAP cohort.
- We integrated FastGxC eQTLs with neurodegenerative/neuropsychiatric GWAS summary statistics using cell type-specific stratified linkage equilibrium score regression (LDSC) to quantify and compare the proportion of trait heritability due to shared versus specific eQTLs.[2]

Methods

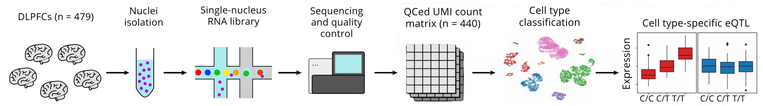


Figure 1. Overview of pre-processing workflow. Figure modified from Fujita et al., 2024.[3] After genotype and expression QC, we retained 440 individuals for genetic analysis. Following FastGxC cell type-specific and shared eQTL mapping, we performed LDSC to quantify cell type-specific trait heritability.

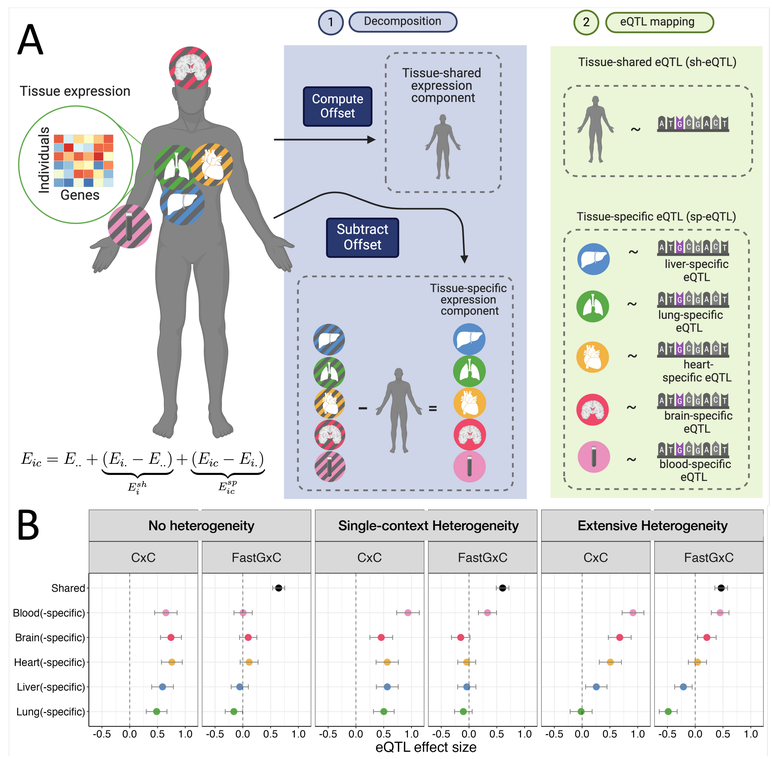


Figure 2. Overview of FastGxC eQTL mapping and examples of specific eQTLs.
A. FastGxC was applied to our snRNA-seq ROSMAP data to estimate cell type-specific and cell type-shared eQTL effect sizes.

B. Examples of eQTLs mapped by FastGxC and comparison of FastGxC eQTL effect sizes versus the context-by-context approach. The first panel shows an eQTL with a shared-only effect. The next two panels show an eQTL with a shared and a context-specific effect, one in which specificity is driven by a single context (blood) and one in which heterogeneity is extensive across contexts.

Results

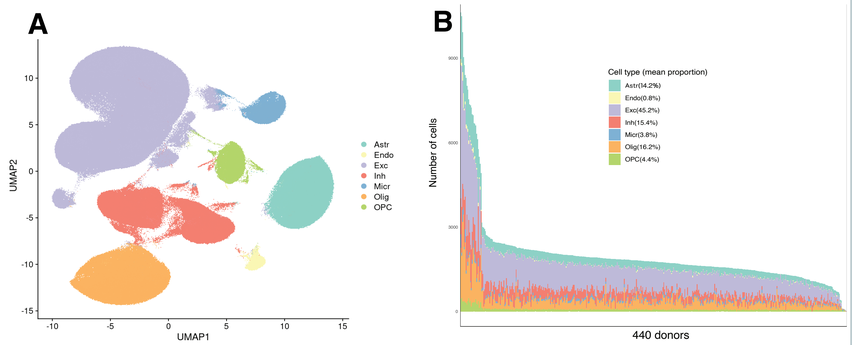


Figure 3. UMAP and Cell Type Proportions. **A.** UMAP visualization of 887,971 nuclei from 440 donors in the ROSMAP cohort illustrating the cell type clustering. **B.** Number of cells of each type in 440 donors.

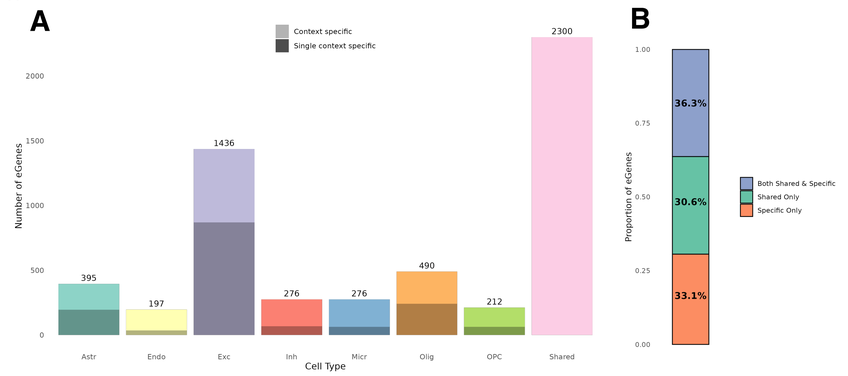
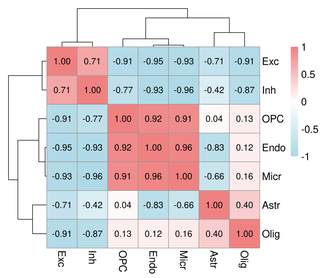


Figure 4. Context-specificity of eGenes, i.e., a gene with at least one significant eQTL
A. Number of eGenes with shared and context-specific eQTLs per context. For eGenes with context-specific eQTLs, the darkest opacity indicates the number of eGenes unique to that cell type. Excitatory neurons contributed the largest proportion of context-specific eQTLs.

B. Percent of eGenes with shared-only, specific-only, and both shared and specific eQTLs across cell types. There is an unusually high proportion of specific-only eGenes, which indicates increased specificity of brain cell types, but is also concurrent with the disproportionately large number of excitatory neuron-specific eGenes.

Figure 5. Correlation of effect sizes for cell-type-specific eQTLs.

- Pearson correlation of β effect sizes in context-specific eQTLs shared between two cell types. Only eQTLs significant in both cell types were considered in the correlation analysis.
- The order of the rows and columns display hierarchical clustering of cell types.



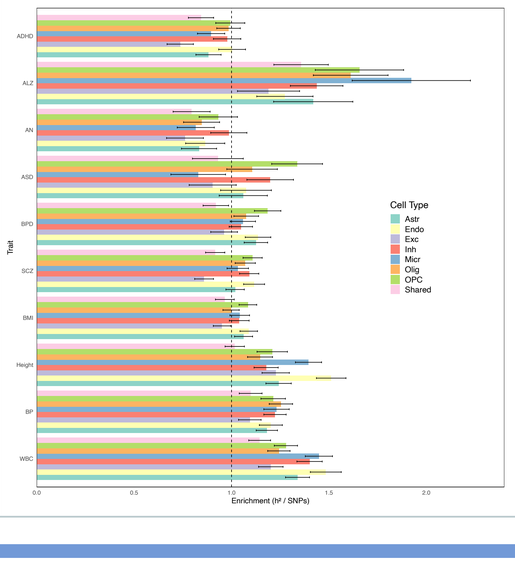


Figure 6. Enrichment of shared and specific eQTLs among GWAS associations

- Enrichment measures how much more heritability is present in a specific annotation category than expected by chance, given the proportion of SNPs in that category.
- For every trait (both neuropsychiatric/neurodegenerative and non-neurological traits), a majority of the cell type-specific annotations had higher enrichment than the cell-type shared annotation.

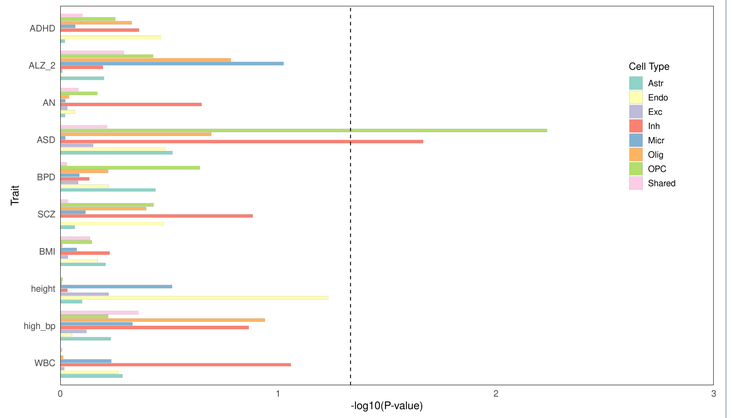


Figure 7. Significant trait-relevant cell type(s)

- The black dotted line indicates the significant threshold (FDR < 0.05).
- Autism was the only trait with significant cell type enrichment. The most significant enrichment in autism was in OPC and Inh, which is consistent with previous findings.[4]
- Lack of significance for other traits is likely due to limited power and improper case/control classification in the GWAS summary statistics rather than the absence of biological relevance.

Summary

- Applying FastGxC to single-nucleus RNA-seq data from 440 ROSMAP donors enabled robust detection of both shared and cell type-specific eQTLs, overcoming limitations of traditional eQTL mapping and bulk brain tissue analyses.
- Context-specific eQTL effect sizes are correlated within groups of biologically related cell types.
- For all traits, cell type-specific annotations were more enriched than the shared annotations.
- Autism spectrum disorder was the only trait with statistically significant cell type enrichment (OPC and Inh).
- Overall, this work reveals powerful insights into the cell type–specific regulatory mechanisms underlying neuropsychiatric and neurodegenerative diseases.

References

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