Single-Cell Network Medicine for Psychiatric Disorders

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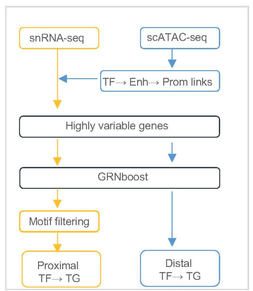
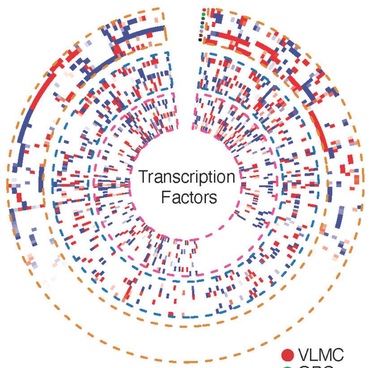
Introduction

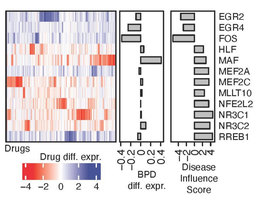
Background: Psychiatric disorders, including schizophrenia (SCZ), bipolar disorder (BPD), and autism spectrum disorder (ASD) are complex conditions lacking effective treatments due to complex gene regulation and cellular heterogeneity. Single-cell multi-omics offer a promising avenue for analyzing dysregulated epigenomic and transcriptional states and identifying specific cell types affected by disease. Analysis of cell type gene regulatory networks and dysregulated pathways that underpin disease can lead to identification of novel therapeutic targets for specific cell types. This resolution enables drug repurposing efforts to focus on modulating abnormalities in gene regulation within specific cell types, thereby facilitating the discovery of effective treatments that are tailored to the underlying etiology of each disease. However, post-genomic drug repurposing efforts for cell types perturbed in neuropsychiatric disorders remain poorly characterized, mainly due to the lack of uniformly processed datasets that allow investigation interrogation across disorders using control and disease groups.

Abstract: Neuropsychiatric disorders lack effective treatments due to limited understanding of underlying cellular and molecular mechanisms. To address this, we integrated population single-cell genomics data and analyzed cell-type-level gene regulatory networks across schizophrenia, bipolar disorder, and autism (23 cell classes/subclasses). Our analysis first revealed potential druggable transcription factors co-regulating known targets and converged disease genes into several cell-type-specific co-regulated modules. We then applied graph neural networks on those modules to prioritize additional risk genes and leveraged network-based drug repurposing to identify 220 drug molecules with potential for targeting specific cell types, with 37 reversing disorder-associated transcriptional phenotypes. Additionally, we discovered 335 Drug-Cell QTLs, revealing genetic variation's influence on drug response at the cell-type level. Our results provide a single-cell network medicine resource that provides mechanistic insights for advancing treatment options for neuropsychiatric disorders.

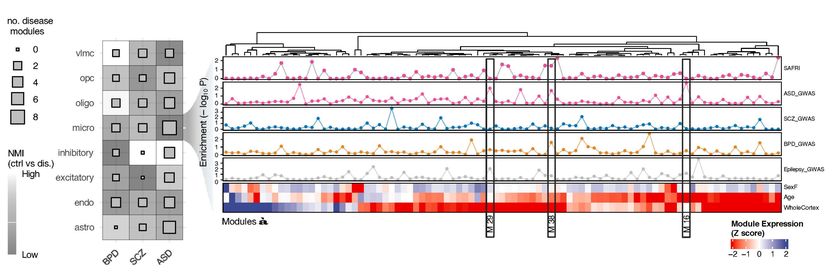
Druggable Cell-Type Regulons for Psychiatric Disorders



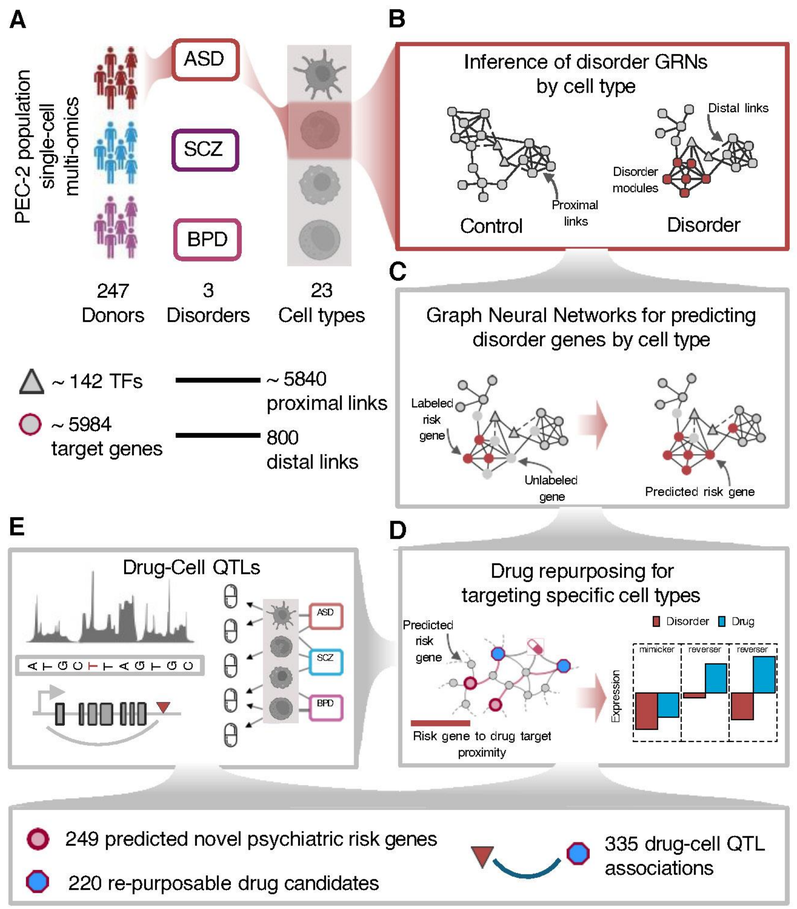




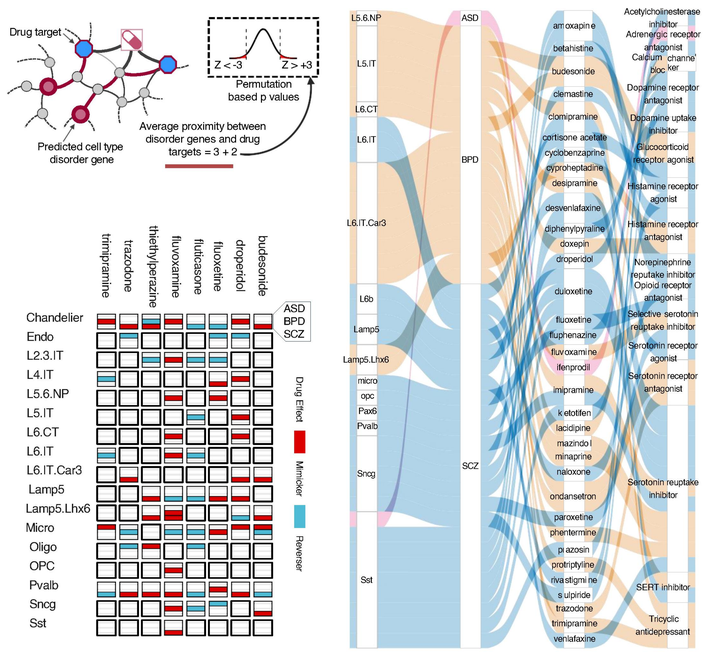
Disorder Risk Genes Converge on Coregulated Modules



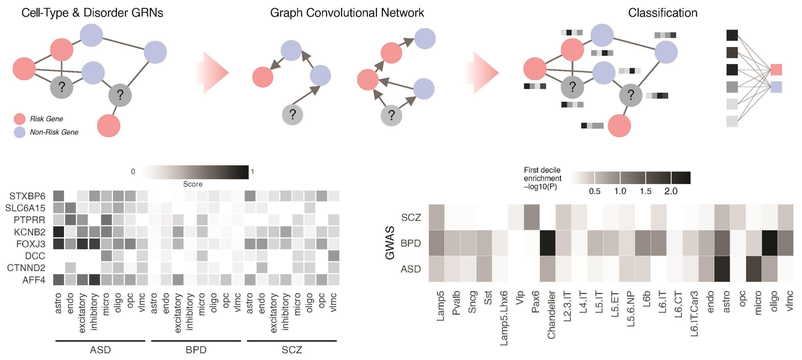
Disorder Gene Prediction and Drug Repurposing



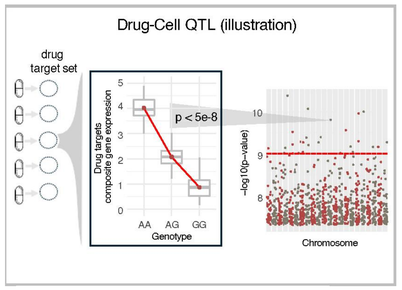
Coregulatory Networks Allow Drug Repurposing for Psychiatric Disorders

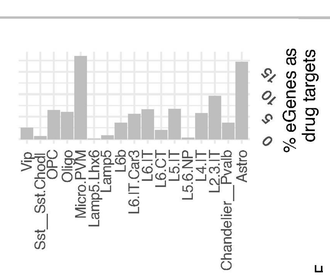


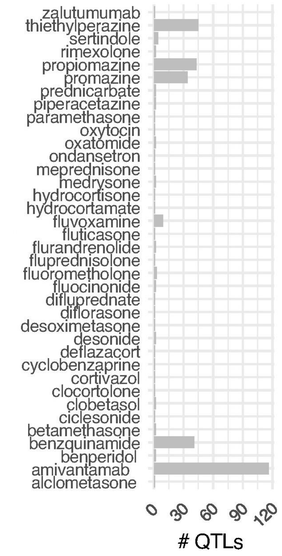
Cell-Type Graph Neural Networks Predict Novel Candidate Genes



Drug-Cell QTLs







Conclusions

- GRNs effectively predicted cell-type specific risk genes
- Predicted >200 psychiatric risk genes and corresponding drug candidates
- Analysis was repeated for several psychiatric disorders, including autism, schizophrenia, and bipolar disorder.

Acknowledgements

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