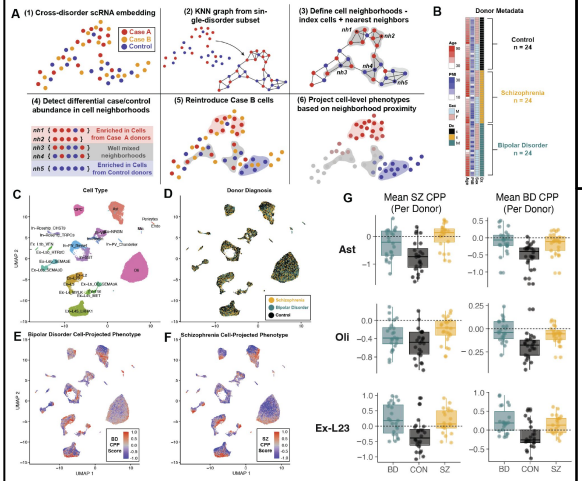
Pathway-centric personalized precision psychiatry by single-cell multiomics-genetics-EHR integration

scRNA Profiling to Define Molecular Components of Psychiatric Disorders

Relating Donor Labels to Cell-Level Phenotypes with CPP



Cross-Disorder Single-Cell Analysis of Psychiatric Disorders. (a) Multi-disorder Cell-Projected Phenotype (CPP) methodology. Cells from many donors, with diverse condition labels, are jointly embedded. A KNN graph is constructed from this embedding, and local cell transcriptional neighborhoods are defined as cells and their immediate neighbors. Differential case/control abundance in neighborhoods can be quantified, and these enrichments are used to define cell-level phenotypes. **(b)** Cohort metadata. **(c-f)** UMAP projection of sequenced cells are labeled by **(c)** cell type **(d)** donor diagnosis **(e)** bipolar disorder CPP score or **(f)** schizophrenia CPP score. **(g)** Mean CPP score per donor in 3 representative cell types. SZ and BD donors both exhibit elevated scores for either disorder across cell types, consistent with shared transcriptional disruptions across disorders.

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Overview

1 Multiple Approved Drugs for Same Condition

SSRIs
SNRIs
Depression
Bupropion
TCAs

2 Treatment Response is Highly Variable

Patient A: SSRIs ✓, SNRIs ✗
Patient B: SSRIs ✗, SNRIs ✓

3 Trial-And-Error Status Quo

Try Drug → Wait Weeks → Change Dose → Wait Weeks → Try New Drug → (Symptoms Continue) Wait Weeks

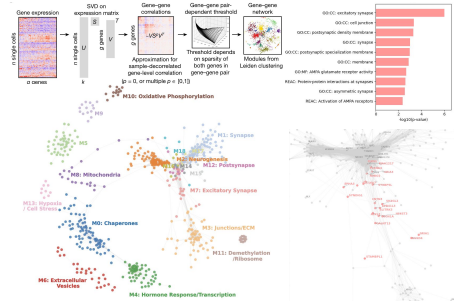
4 Predict Treatment with AI

Electronic Health Record
Medications, Procedures, Diagnoses, etc.
Drug A ✗
Drug B ✓
What's Missing? Molecular Evidence

5 Genetics-Based Prediction Frameworks

100s of postmortem brain samples
Gene Expression Measurements in Millions of Cells
Find Patient Mutations in these Genes
Identify Disrupted Genes Across Disorders
Prioritize Variants with Genomic Deep Learning
Next-Generation Treatment Response Prediction

Gene Co-expression Modules with scDemon

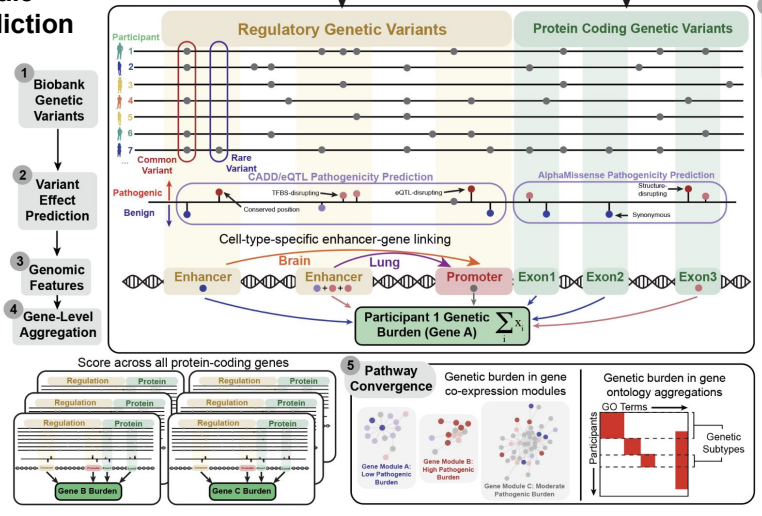


Single-cell decorrelated module networks (scDemon) workflow.
SVD on gene-by-cell matrices produces gene-gene correlation matrices, which reveal gene co-expression clusters, or modules, corresponding to functionally interpretable gene categories. A representative gene co-expression module is highly enriched in excitatory synaptic genes. These patterns are data-driven, and not dependent on manual annotation

A Gene Regulatory Network Convergence Model of Genetic Burden for Biobank-Scale Precision Psychiatric Prediction

All of Us RESEARCH PROGRAM

66,794 Biobank Participants with:
- Short Read WGS
- EHR
- Antidepressant Prescription History



* Rare and common, regulatory and protein coding genetic variants can be paired with electronic health records (EHR) for tens of thousands of patients with relevant prescription histories.
* Regulatory deep learning models can predict noncoding pathogenicity, and AlphaFold-derived pathogenicity predictions can score protein coding variants.
* Cell-type-specific enhancer-gene linkings, generated in our group, can relate noncoding variation to target genes.
* Gene level aggregation scores reduce features.
* Features are further reduced through aggregation across gene co-expression modules or gene ontology categories.
* Treatment response predictive models can be constructed from a combination of genetic features and EHR-derived variables.