Genomic Network Analysis of Three Key Genes In Neuropsychiatric Disorders

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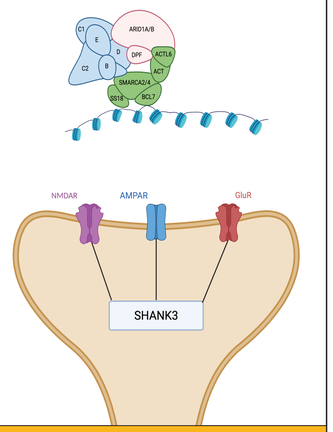
1 Abstract

The SSPsyGene Initiative, launched by the NIMH, aims to functionally characterize ~100 genes associated with autism and schizophrenia. As part of this effort, we generated ~700 clonal knockout human stem cell lines via CRISPR/Cas9. To contribute to the consortium's goals, here we perform an in-depth analysis of 3 genes critical to neuropsychiatric disorders (NPDs): **SHANK3, ARID1B**, **and SMARCC2**. These genes play key roles in synaptic density and chromatin remodeling. Despite their importance, the biological pathways that converge downstream of gene perturbations, particularly those affecting seemingly unrelated functions but leading to similar phenotypes, remain poorly understood. Using R, we applied genomic functional analysis tools, including Gene Ontology (GO), Gene Set Enrichment Analysis (GSEA), and Weighted Gene Co-expression Network Analysis (WGCNA), to identify shared molecular functions and biological processes. Our findings aim to provide insight into the convergent mechanisms of gene regulation in the developing nervous system and the etiology of NPDs.

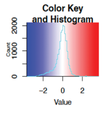
2 Background

Gene Name	Molecular Function	Specific Function
SMARCC2	Chromatin Remodeler	**Structural subunit of the SWI/SNF complex;** facilitates ATP-dependent **chromatin remodeling** to regulate transcription by modifying chromatin accessibility for transcription factors and other regulatory proteins.
ARID1B	Chromatin Remodeler	**DNA-binding subunit that directs the SWI/SNF/cBAF complex to** specific genomic loci, particularly **enhancers**; regulates gene expression by modulating chromatin structure, particularly during **neural development** and differentiation.
SHANK3	Scaffolding Protein	Key **structural protein at synapses**; organizes and **stabilizes postsynaptic density** (PSD) by linking neurotransmitter receptors with the cytoskeleton. **Critical for excitatory synaptic transmission** and plasticity.



3 Bulk-RNA Sequencing

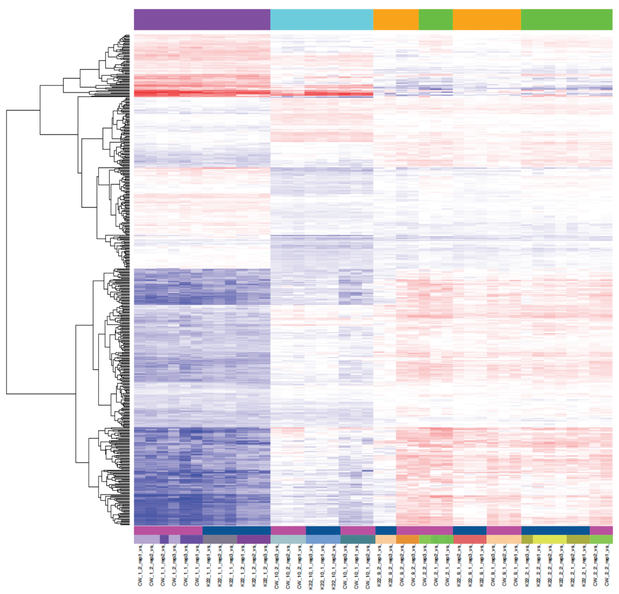
Preliminary Data



ARID1B
SMARCC2
SHANK3
ASXL3

Female
Male

P adj-value < 0.005



4 GSEA, GO-term, & WGCNA Analysis

A)

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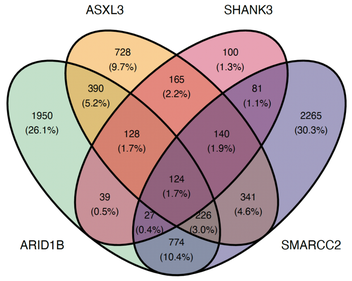

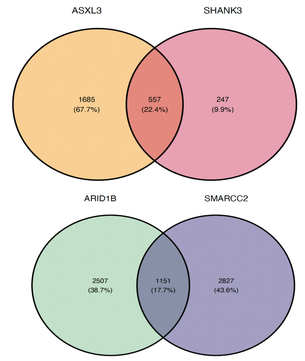

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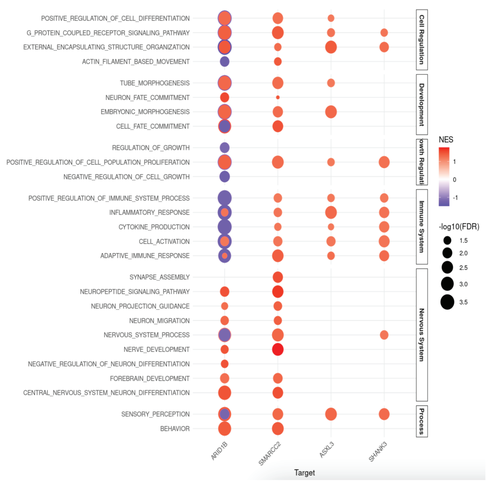

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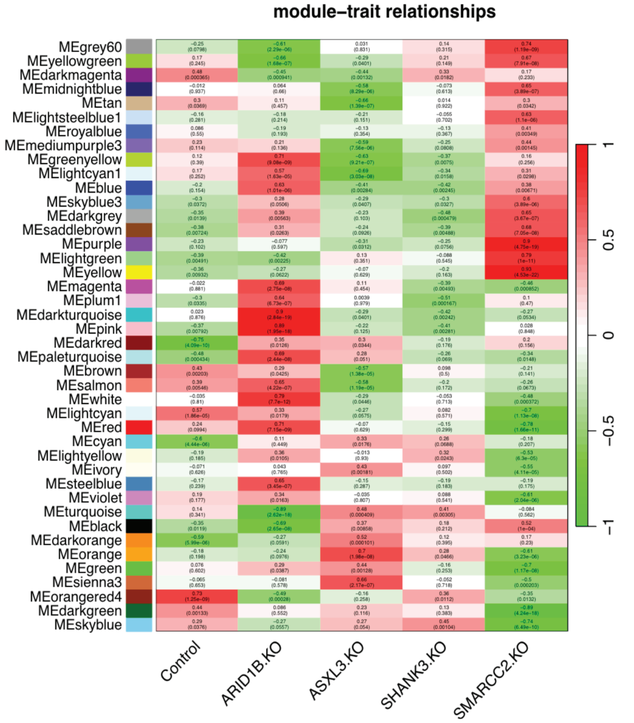
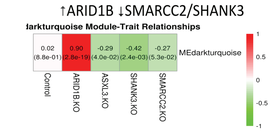
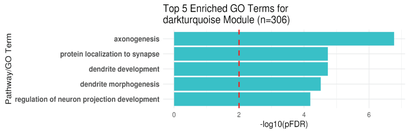


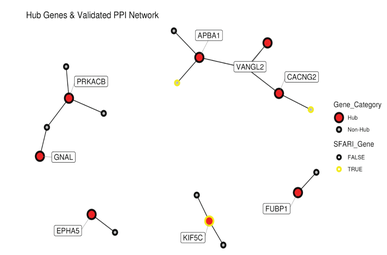
D)

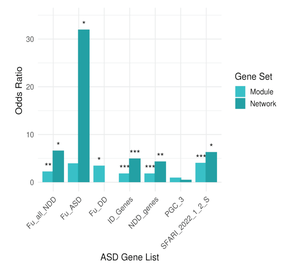
Dark Turquoise

↑ARID1B ↓SMARCC2/SHANK3



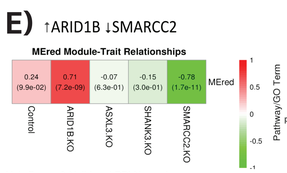


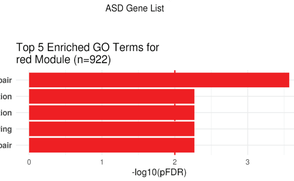


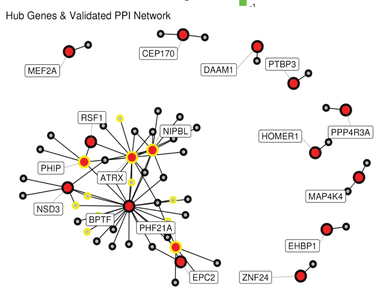


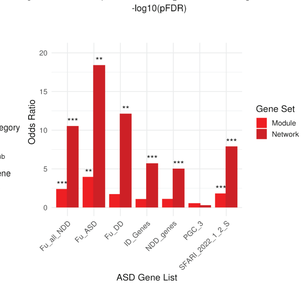
E) ↑ARID1B ↓SMARCC2

Red









5 Conclusions

- Strong relationship between SMARCC2 and ARID1B
- SHANK3 Relationship Still Complex
- Deep Learning Potential to better faciliate this work
- Future calcium imaging and organoid analysis