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Functional genomics resources for the human brain elucidates the neurobiological basis of schizophrenia.

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Strong genetic relationships between substance abuse and psychiatric conditions have emerged. A recent study using Mendelian randomization has reported a causal effect of schizophrenia on cannabis use (Pasman et al., 2018). Therefore, we hypothesized that understanding the molecular mechanism of schizophrenia may help identify the neurobiological basis of substance abuse.

To achieve this goal, we have built a comprehensive regulatory network of adult prefrontal cortex (PFC) by combining Hi-C, expression quantitative trait loci (eQTLs), and transcription factor (TF) binding sites (Wang et al., 2018). For 142 schizophrenia GWAS loci, we identified a set of 1,111 putative schizophrenia risk genes, covering 119 loci (Pardinas et al., 2018). The majority of schizophrenia risk genes were not in linkage disequilibrium (LD) with the index SNPs, consistent with the fact that regulatory relationships often do not follow linear genome organization (Won et al., 2016).

Schizophrenia risk genes were enriched for translational regulators, cholinergic receptors, calcium channels, synaptic genes, and genes dysregulated in schizophrenia postmortem brains. Developmental expression trajectories of schizophrenia risk genes suggested mid-gestation as a critical period. Integration with single-cell transcriptomic profiles pinpointed excitatory neurons as a central cell type for schizophrenia.

Collectively, we leveraged our regulatory network in PFC to link schizophrenia GWAS loci to the risk genes, which revealed the neurobiological mechanisms of schizophrenia. We want to apply the same framework for GWAS loci for cannabis use and examine the crosstalk between schizophrenia and cannabis use at a mechanistic level.