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Genetic Basis of Pleiotropy

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A meta-genome-wide association study (GWAS) of eight psychiatric disorders has shed light on the genetic architecture of pleiotropy in major psychiatric disorders. However, the mechanisms underlying pleiotropic effects of the associated variants remain to be investigated. We conducted a massively parallel reporter assay (MPRA) to decipher the regulatory logic of variants with disorder-specific and pleiotropic effects. Pleiotropic variants differ from disorder-specific variants by manifesting chromatin accessibility that extends across diverse cell types in the neuronal lineage and altering motifs for transcription factors with higher connectivity in protein-protein interaction (PPI) networks. Comparison between statistical and empirical fine-mapping suggests that statistical fine-mapping is effective for loci with small credible sets and simple linkage disequilibrium (LD) patterns, but may struggle with loci that have complex LD and larger credible sets. We plan to apply a similar approach to substance use disorder (SUD) GWAS to uncover the regulatory principles underlying SUD genetic etiology.

Relevant publications
https://pubmed.ncbi.nlm.nih.gov/37868037/
https://pubmed.ncbi.nlm.nih.gov/36085003/
https://pubmed.ncbi.nlm.nih.gov/32747698/