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Deep Analysis of Transcriptome Identifies Molecular Mediators of Substance Use Disorders in Rats

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Transcriptomic data is commonly used to identify the molecular mechanisms driving GWAS signals through colocalization analysis and transcriptome-wide association studies (TWAS). While RNAseq has the potential to assay many modalities of transcriptional regulation, such studies are often limited to gene expression due to the complexity of extracting and analyzing multiple RNA phenotypes. We present Pantry (Pan-transcriptomic phenotyping), a framework to efficiently generate diverse RNA phenotypes from RNAseq data and perform integrative analyses with genetic data. Pantry currently generates phenotypes from six modalities of transcriptional regulation (gene expression, isoform ratios, splice junction usage, alternative TSS/polyA usage, and RNA stability) and integrates them with genetic data via QTL mapping, TWAS, and colocalization testing. We show that generalizing TWAS to multiple RNA modalities (xTWAS) approximately doubles the discovery of unique gene-trait associations and enhances the identification of regulatory mechanisms underlying GWAS signal in many previously associated gene-trait pairs. We use Pantry to extend RatGTEx, a resource of expression, splicing, eQTL, and sQTL data for 10 rat brain regions and other tissues, provided as downloadable data and interactive visualizations. Along with expanding these data to six RNA modalities, we apply Pantry's xTWAS to all RatGTEx tissues and to GWAS data for 120 physiological and behavioral traits from 14 studies of outbred rats, identifying 3,110 gene-trait associations. We provide the Pantry code, RatGTEx portal (ratgtex.org), and Rat TWAS Hub (twas.ratgtex.org) on the web. These results facilitate understanding of the biological basis of complex trait genetic associations observed in rats.

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