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PgmNr 344: Single-cell co-expression network demonstrated superior biological signal in tissue-specific network analyses.

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Single-cell RNA sequencing (scRNA-seq) technologies have emerged as a powerful tool to dissect cellular heterogeneity in a variety of tissues. Despite recent interests in co-expression networks based on scRNA-seq data, there is limited evidence showing direct utility of scRNA-seq co-expression networks in understanding biological circuitry. Here we obtained thalamic reticular nucleus (TRN) tissues enriched for neurons from six adult mice (99-113 days), and sequenced single-nucleus full-length transcriptomes using optimized Smart-Seq2 and Nextera protocols (N = 694 cells). Using a modified WGCNA pipeline, we constructed a TRN co-expression network with 229,205 interactions spanning 11,934 genes (TRNNet). We then applied a random forest classifier ("Quack" algorithm) trained on 306 neurodevelopmental pathways curated from the Molecular Signature Database (MSigDB). TRNNet exhibited superior performance in recapitulating neuronal pathway architecture (AUC = 0.80) compared to generic co-expression network constructed using bulk RNA-Seq (from GEO Database, AUC = 0.78), and as negative controls, cancer dependency and cell-perturbation-based networks (AUC < 0.70). To further demonstrate the ability of TRNNet to perform tissue-specific network analyses, we applied TRNNet-specific Quack model to predict novel genes implicated in autism spectrum disorders (ASDs), using 65 well-established ASD risk genes. TRNNet recapitulated ASD candidate genes from recent sequencing studies including *FAM47A*, *DOCK8* and *SETBP1*. By integrating frontal-cortex-specific eQTL data based on GTEx V7, TRNNet also nominated *TDO2* (Quack probability = 0.90), suggesting thalamocortical regulation as a potential mechanism for its association with ASD as previously established. Overall, we have established a computational pipeline to

leverage the unique potential of scRNA-seq data for high-resolution tissue-specific network analyses.