A040 · A single nucleus multiome QTL atlas of the aging human brain maps regulatory variation underlying Alzheimer's disease risk

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Despite extensive efforts to map the genetic loci underlying AD risk, complete mechanistic mapping of variants to epigenomic and transcriptomic function remains elusive. We analyzed a 10x multiome (snRNA-seq + snATAC-seq) dataset of postmortem dorsolateral prefrontal cortex samples from ROSMAP (N = 232 individuals, 458K cells post QC) and annotated them into seven major cell types and 71 subtypes. For each major cell type, we mapped and fine-mapped cis eQTLs and cis caQTLs across 8,861 - 21,734 genes and 19,282 - 147,769 peaks, plus trans motifQTLs for 785 TF chromVAR activity phenotypes. These constitute the most comprehensive QTL map of aging human brain to date. We recovered 8,846 independent eQTL, 8,616 independent caQTL and 789 independent motif-QTL signals. In stratified LD-score regression across 57 GWAS traits, all three annotations were jointly significant for complex-trait heritability, with caQTL variants carrying the largest per-SNP effect (joint τ^* = 0.69, rising to 0.90 across 18 brain traits). 257 fine-mapped variants colocalize between a caQTL and an eQTL credible set in at least one cell type (269 variant-by-cell-type colocalizations), and 90% of these show a concordant direction of effect - the allele that opens chromatin also raises expression. We next performed enhancer-to-gene linking analysis using SCARlink, ranking gene-peak pairs by their link strength enriched colocalized pairs 3.8-6.5-fold over baseline prevalence across cell types. In Microglia, rs17783630 was picked up as a fine-mapped caQTL (PIP 1.00, P = 6.7e-37) and a fine-mapped eQTL for RIN3 (PIP 0.57, P = 1.3e-11), and SCARlink independently links the caQTL peak to AD risk gene RIN3 (z = 14.6, FDR = 1.9e-24). Additionally, rs7648145 was picked up in inhibitory neurons as a fine-mapped trans-QTL for MEF2C motif activity (PIP 0.95, P = 2.2e-8), naming an AD risk gene as the effector transcription factor. Overall, this atlas provides insights of cell-type-specific regulatory mechanisms underlying Alzheimer's disease risk.

Abstract Title:

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Abstract

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