Novel Differentially Expressed Genes in Alzheimer's Disease, LATE, and Their Co-Occurrence

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This project investigates the genetic mechanisms underlying Alzheimer's Disease (AD) and Limbic-Predominant Age-Related TDP-43 Encephalopathy (LATE) and their co-occurrence by analyzing differential gene expression in specific cell types within the Dorsolateral Prefrontal Cortex (DLPFC) using the SEA-AD (Seattle Alzheimer's Disease) Single-Cell RNA(scRNAseq) sequencing dataset. The study is divided into three key steps: (1) sorting subjects into four groups based on their disease status —control, LATE-NC, ADNC, and mixed AD-LATE, (2) performing statistical analysis using multinomial logistic regression to evaluate demographic and genetic factors such as age, sex, education, cognitive scores, and APOE4 genotype, and (3) analyzing gene expression profiles of microglial and astrocyte cells to identify genes that are significantly upregulated or downregulated in relation to the different disease groups. This research provides the first comprehensive single-cell RNA sequencing analysis of LATE and mixed AD-LATE pathology, uncovering novel genetic signatures. UBE2B and SYT1 were upregulated in AD, implicating synaptic and proteasomal dysfunction. Most notably, the upregulation of ARL17B in LATE suggests a previously unidentified mechanism where impaired protein trafficking may exacerbate TDP-43 accumulation—a hallmark of LATE pathology. Additionally, ABCC1 upregulation in the mixed pathology group may indicate a compensatory mechanism mitigating AD pathology. Furthermore, the downregulation of mitochondrial genes such as MT-ATP8 and MT-ND2 in LATE and mixed groups indicates disrupted energy metabolism, a key contributor to neurodegenerative progression. This novel research establishes new biomarkers and therapeutic targets for these understudied neurodegenerative diseases

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