**Integrating single-cell and whole-brain transcriptomes to study the progression of Alzheimer’s disease**

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Alzheimer’s disease (AD) affects one in nine people of age 65 or older, and one in three above the age of 85. However, therapeutic development has been limited by an incomplete understanding of AD progression. To detect early markers of AD development, we measured gene expression profiles of whole brains from wild type (C57BL/6J) or AD-prone mouse models at multiple ages between two and six months. The AD-prone transgenic mouse model carries the human mutant APP and PSEN1 genes, and show evidence of Aβ deposits at four months of age. A total of 108 age-specific, transgene-specific, or age-transgene-interacting genes were identified, which were potential gene markers for the relevant sample groups. While meaningful in inferring biological dysfunction related to AD development, marker genes provide little information of their cell type origins. Meanwhile, single cell transcriptome measurements have advanced rapidly, which can facilitate identifying cell types that characterize AD development. To infer these cell-specific signals in our bulk RNA-seq samples, we developed a novel method, permutation-based maximum covariance analysis (PMCA). PMCA uses the covariance of gene expression profiles from bulk and single-cell samples to detect the bulk-cell pairs that significantly covary. By integrating gene expression profiles of 48 major cell types from mouse brain data, we found that oligodendrocyte and microglia transcript signatures are absent in the AD mice relative to the wild type. This suggests a loss-of-function of oligodendrocytes and microglia during AD progression.