Integrate single cell RNA-seq and bulk RNA-seq to study the progression of Alzheimer’s disease

Xulong Wang1, Robyn Ball2, Harriet Jackson1, Gareth Howell1, and Gregory Carter1

The Jackson Laboratory1

Quantitative Sciences Unit, Stanford University2

Alzheimer’s disease (AD) affects 1 in 9 age 65 or older, and 1 in 3 age 85 or older. However, no effective therapeutic targets are available because of the limited understanding of the mechanisms. To detect early markers of AD progression, we measured gene expression profiles of the brain from normal or AD-prone mouse models at multiple ages (2 to 6 months). We detected 108 genes that are specifically associated with certain age or the AD-prone mouse strain. On the other hand, single cell RNA sequencing (scRNAseq) has proven powerful in measuring the single cell transcriptomes. This promises to identify AD markers in terms of cell types by integrating the bulk RNA sequencing (bulkRNAseq) and scRNAseq. To detect the marker cells of our bulkRNAseq samples during AD progression, we developed a novel method, permutation-based maximal covariance analysis (pMCA). pMCA measured the covariance of gene expression profiles from a bulk RNAseq sample and a certain cell type, and detect the bulk-cell pairs that covariate significantly in a statistically rigorously manner. By integrating gene expression profiles of 48 major cell types of mouse brain, we found oligodendrocyte and microglia as significant marker cells of the 5 and 6 months wild type mice, but not the AD-prone mice. This suggests a malfunction of oligodendrocytes and microglia during AD progression. In summary, (1) we developed a novel method, pMCA, to extract cell-type specific information from bulkRNAseq; (2) we suggested oligodendrocytes and microglia important players of AD progression.