Single-cell transcriptional hallmarks and individual subtyping for Alzheimer's Disease across 430 participants

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Abstract:

Alzheimer's Disease (AD) is multifaceted, with many implicated biological pathways, across diverse cell types. The heterogeneous phenotypic manifestation, beyond the common characteristic signature of Amyloid beta plaque, across cognition, pathology, and treatment response is well recognized, but the molecular and cellular heterogeneity of AD remains uncharacterized at genomic and cellular resolution.

Here, we use single-cell RNA-seq profiling of 1.9 million cells from 430 human dorsolateral prefrontal cortex post-mortem brain samples across age-matched AD and non-AD individuals spanning all stages of AD progression. To assess heterogeneous molecular manifestation of the key biological processes, we develop a regularized multivariate differential expression analysis framework and identify 1621 gene expression patterns across 6 major cell types (implicating 1391 unique genes) associated with AD, which we cluster into 30 transcriptional hallmarks (Tx1-Tx30).

Our 30 transcriptional hallmarks capture several known cellular and pathological signatures in AD, pinpointing their candidate driver genes and cell types of action, and are associated with distinct phenotypic enrichments. For example, cytoplasmic translation in oligodendrocytes (Tx12) was most associated with early AD (p-value=5.3x10-7) but not late AD (p>0.9) changes; cytoplasmic translation in oligodendrocyte precursor cells (Tx23) instead showed the strongest association (p=1.0x10-9) with amyloid level in the cortex; and response to zinc ion in astrocytes (Tx16) was most associated with neuritic plaque burden (p=2.6x10-9).

Using combinations of hallmark burdens, we classify our 430 donors into 12 AD and non-AD subtypes. Four and three of those groups were enriched in AD cases and non-AD individuals, respectively, and the other five were balanced between AD cases and controls. One of the AD groups driven by oligodendrocyte-associated hallmarks was preferentially enriched in neuritic plaque burden, which is more directly indicative of neuronal damage.

Focusing on genetic variants associated with single-cell gene expression (sc-eQTLs) across our 430 samples, we found the genetic basis for some hallmarks (heritability ~= 2%), indicating the ability to predict dysregulated AD hallmarks, risk groups, and subtypes across individuals decades before symptoms occur.

Overall, our results pave the way towards pathway-level therapeutic development, personalized prognosis and treatment tuning in AD, and more generally towards genetics-based prognosis, transcriptional subtyping, and clinical trial design in complex and heterogeneous traits even in inaccessible tissues.