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Integrative analyses of single-nucleus and spatial transcriptome resolve neurodegenerative molecular ecosystem in the human brain

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Neurodegenerative disorders deteriorate cognition and motor function through complex molecular alteration in brain cells, including neuroinflammation and neuronal damage. However, the combinatorial nature of cell type-specific or common transcriptional dysregulation responsible for disease pathogenesis remains elusive, limiting the scope only to the most prevalent disease feature. Here, we establish single-nucleus transcriptomic (snRNA-seq) landscapes with about two million nuclei obtained from the human brain under neurotypical controls and neurodegenerative patients to dissect diverse molecular signatures. Through the non-negative deconvolution of snRNA-seq landscapes, we have identified 60 candidates of molecular signatures that are disease-specific or shared between diseases. Those molecular signatures were further mapped to finely resolved sub-cell types, capturing combinatorial expression of sub-types and disease associated molecular patterns. To reveal out how those identified signatures are populated on disease tissue, we annotated disease-associated molecular signatures to each single cell in patient tissue based on spatial transcriptome data. Notably, these disease-specific molecular signatures exhibit proximal modular patterns, highlighting the potential contribution of combinatorial molecular signatures arising from diverse cell types. Together, our integrative approaches reveal the presence of a neurodegenerative ecosystem, enlarging the target molecular candidates for disease treatment.