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Investigation of disease-associated spatial molecular signatures in the neurodegenerative human brain at single-cell resolution

Seyoung Jin[1], Baekgyu Choi[1], and Inkyung Jung[1,*]

[1]*Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST)*
**Corresponding author: ijung@kaist.ac.kr*

Neurodegenerative diseases exhibit complex causes due to their genetic and cellular heterogeneity. Recently, multi-omics approaches have been introduced to investigate cellular characteristics at single-cell resolution, revealing the unique molecular properties and disease contribution of individual cell-types. However, the absence of spatial information limits our understanding of intercellular interactions and disease-specific spatial molecular signatures in disease contexts. In this study, we uncover spatial organization of disease-specific gene expression patterns in both Alzheimer's disease (AD) and Parkinson's disease (PD), previously undetectable by single-cell omics. Specifically, we utilized Multiplexed Error-Robust Fluorescence In Situ Hybridization (MERFISH) to profile the spatial distribution of disease-specific gene expression and uncover the complex cellular networks in the human prefrontal cortex and hippocampal tissues from both neurotypical individuals and neurodegenerative disease patients. We revealed that disease-specific genes are highly expressed near well-known disease marker genes, such as APP and MAPT. With five representative genes related to AD, we observed that the cells are spatially divided into two groups: high and low expression levels of representative disease marker genes given the disease specimens regardless of the cellular composition. Interestingly, over 95% of oligodendrocytes are predominantly found in disease-specific spatial sub-regions, and these disease-associated oligodendrocytes present activation of ERK1/2 signaling and MAPK signaling pathways. In conclusion, our approach suggests the existence of brain sub-regions characterized by distinct disease-specific molecular signatures.