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Single-nucleus and spatial transcriptomic analysis identified molecular features of neuronal heterogeneity and distinct glial responses in Parkinson's disease.

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The heterogeneity of Parkinson's disease (PD) is increasingly recognized as crucial for understanding the disorder. Ethnic differences are primary factors influencing the likelihood of PD development and the nature of its initial symptoms. Despite numerous reports related to PD in East Asia, there has been a lack of single-cell (or nucleus) transcriptome studies, which are vital for understanding PD. In this study, 33,293 nuclei from the substantia nigra (SN) of confirmed pathological PD and control patients in South Korea were profiled, revealing 8 different cell types through cluster analysis. Monocle-based pseudotime analysis identified two disease-associated trajectories for each astrocyte and microglia and identified genes that differentiate them. Interestingly, we uncovered the inflammatory intervention in the early PD-associated transition in microglia and identified the molecular features of this intermediate state of microglia. Additionally, gene regulatory networks (GRNs) based on TENET analysis revealed the detrimental effect of an HSPA5-led module in microglia and MSRB3- and HDAC8-led modules specifying the two different astrocyte trajectories. In SN neurons, we observed population changes, a decrease in dopaminergic and glutamatergic neurons, and a proportional increase in GABAergic neurons. By deconvolution in spatial transcriptome obtained from the PD sample, we confirmed spatiotemporal heterogeneity of neuronal subpopulations and PD-associated progressive gliosis specific to dopaminergic nuclei, SN, and ventral tegmental areas (VTAs). In conclusion, our approach enabled the identification of genetic

and spatial characterization of neurons and demonstrated different glial fates in PD. These findings advance our molecular understanding of cell type-specific changes in the progression of Korean PD, providing a foundation for predicting and validating interventions or drug effects for future treatments.