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Spatially resolved single-nucleus transcriptomic profiling reveals regional and cellular vulnerability in Parkinson's disease midbrain

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Parkinson's disease (PD) is clinically and biologically heterogeneous, and ethnic differences may influence its pathogenesis. However, single-nucleus transcriptomic data from East Asian populations remain limited. Here, we present the spatially resolved single-nucleus transcriptomic atlas of the human substantia nigra (SN) across the PD continuum, control, incidental Lewy body disease (iLBD), and advanced PD, in pathologically confirmed Korean individuals. Our integrative analysis revealed early α-synuclein aggregation localized to the ventrolateral SN, subtype-selective vulnerability of dopaminergic neurons, and relative preservation of the dorsomedial SN and ventral tegmental area. Trajectory and gene regulatory network analyses of astrocytes and microglia revealed spatiotemporally distinct, disease-associated glial responses, each driven by divergent molecular programs. We also identified two transcriptionally distinct vascular spatial clusters that exhibited differential vulnerability and remodeling. Ligand-receptor analysis in α-synuclein-positive regions revealed early intercellular signaling events, including extracellular matrix remodeling, synaptic adhesion, and microglial activation, which were prominent in iLBD but absent in advanced PD. MAGMA analysis using PD GWAS data identified SV2C and CNTNAP2 as α-synuclein-associated

genetic risk loci specific to East Asians, while also showing that microglial trajectory genes and vascular-associated spatial differential genes were significantly enriched at PD susceptibility loci shared between East Asian and European populations. This study provides the first high-resolution, spatially mapped single-nucleus transcriptomic resource from an East Asian PD cohort, illuminating early perturbations in the midbrain intercellular and microenvironment that may underlie selective dopaminergic vulnerability and guide for ancestry-informed therapeutic strategies.