

## **Supplementary Materials**

Fig. S1. Single nucleus transcriptomics quality control of human brain prefrontal cortex in PD.

Fig. S2. Single cell RNA velocity field describes transcriptional dynamics of neuronal and glial cell types in PD brain.

Fig. S3. RNAscope in situ hybridization validation of differentially expressed genes in PD and healthy control brains.

Table S1. Postmortem Brain Cases.

Table S2. Differentially Expressed Genes.

Table S3. CellPhoneDB Analysis.

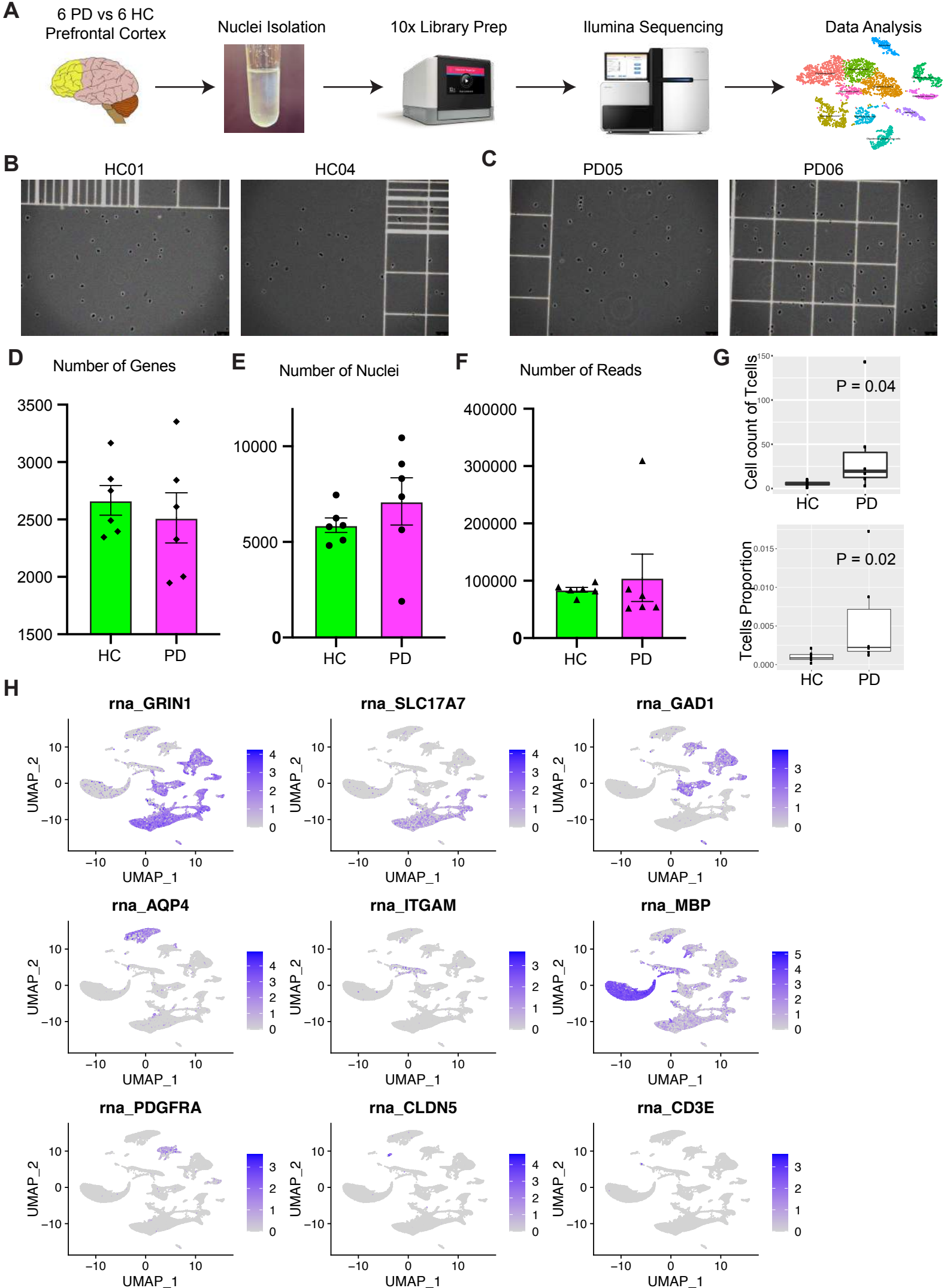


Figure S1

**Fig. S1. Single nucleus transcriptomics quality control of human brain prefrontal cortex in PD.** (A) Single nucleus RNA sequencing workflow of Parkinson's disease (PD) human postmortem brain prefrontal cortex. (B-C) Bright field images of single nucleus suspension (sucrose gradient ultracentrifugation isolated human brain nuclei) in healthy controls (HC) (B) and PD (C). (D-F) Single nucleus RNA sequencing quality controls of number of genes per nucleus in each individual (D), number of nuclei per individual (E), and number of reads per nucleus in each individual (F) (n = 6 PD and 6 HC). (G) Box plots of cell counts of brain-resident T cells (top panel, P = 0.04) and T cells proportion (bottom panel, P = 0.02) in PD or healthy controls (HC) with Wilcoxon Rank-Sum test. (H) UMAP plotting of brain cell type marker gene expression in the postmortem human brains of PD and HC (n = 77,384 nuclei, 6 PD and 6 HC). *GRINI*, neurons; *SLC17A7*, excitatory neurons; *GADI*, inhibitory neurons; *AQP4*, astrocytes; *ITGAM*, microglia; *MBP*, oligodendrocytes; *PDGFRA*, oligodendrocyte precursor cells; *CLDN5*, endothelial cells; *CD3E*, brain-resident T cells.

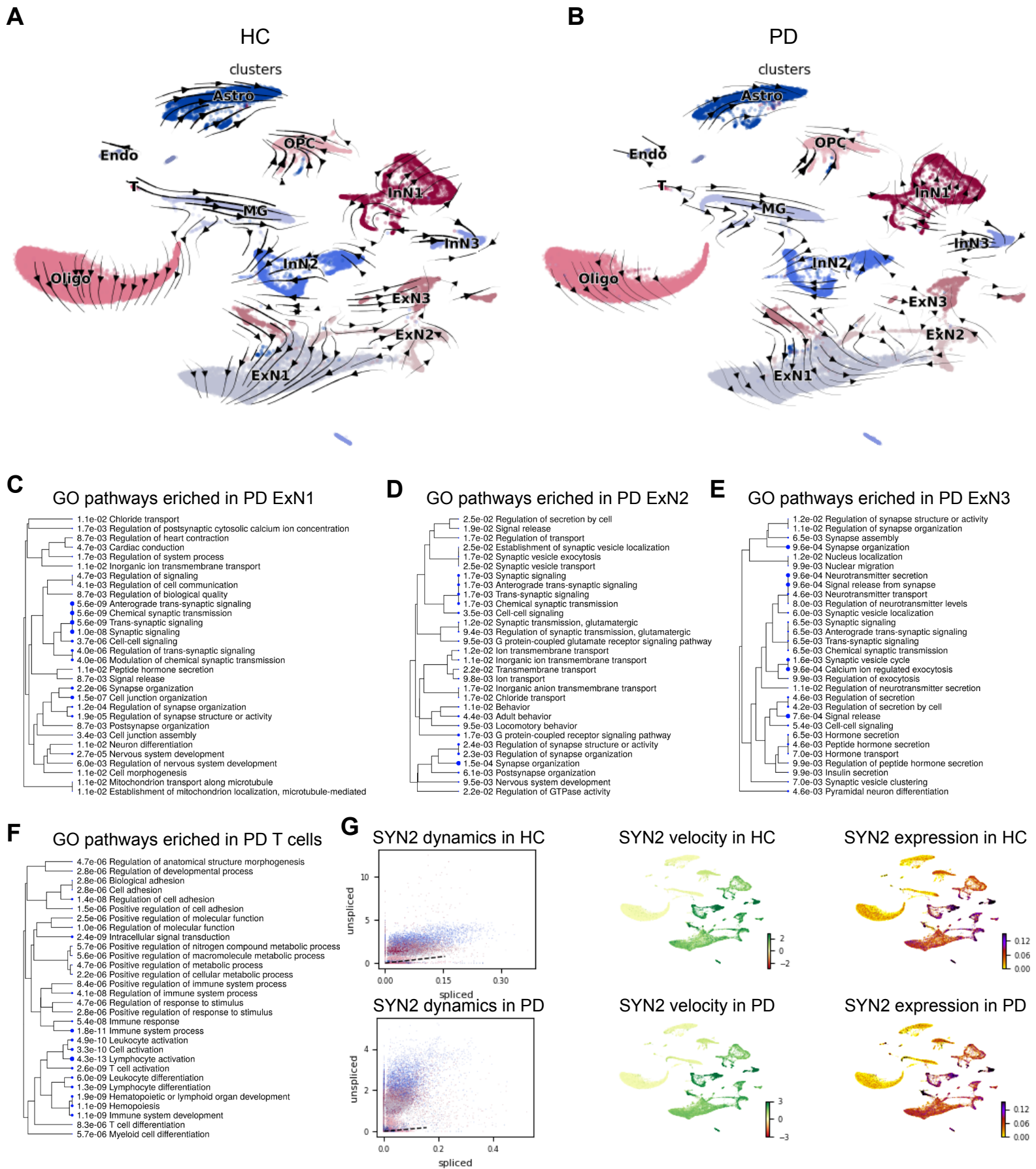


Figure S2



**Fig. S2. Single cell RNA velocity field describes transcriptional dynamics of neuronal and glial cell types in PD brain.** (A-B) Single cell RNA velocity field projected on to UMAP plot of either healthy control (HC) (A) or Parkinson's disease (PD) (B) human brains. Arrows show the local average velocity evaluated on a regular grid. (C-F) Gene ontology (GO) pathway analysis of PD enriched genes identified by RNA velocity analysis in excitatory neuron subcluster 1 (ExN1) (C), excitatory neuron subcluster 2 (ExN2) (D), excitatory neuron subcluster 3 (ExN3) (E) and brain-resident T cells (F). (G) Transcriptional dynamics, velocity and expression of *SYN2* in HC or PD.

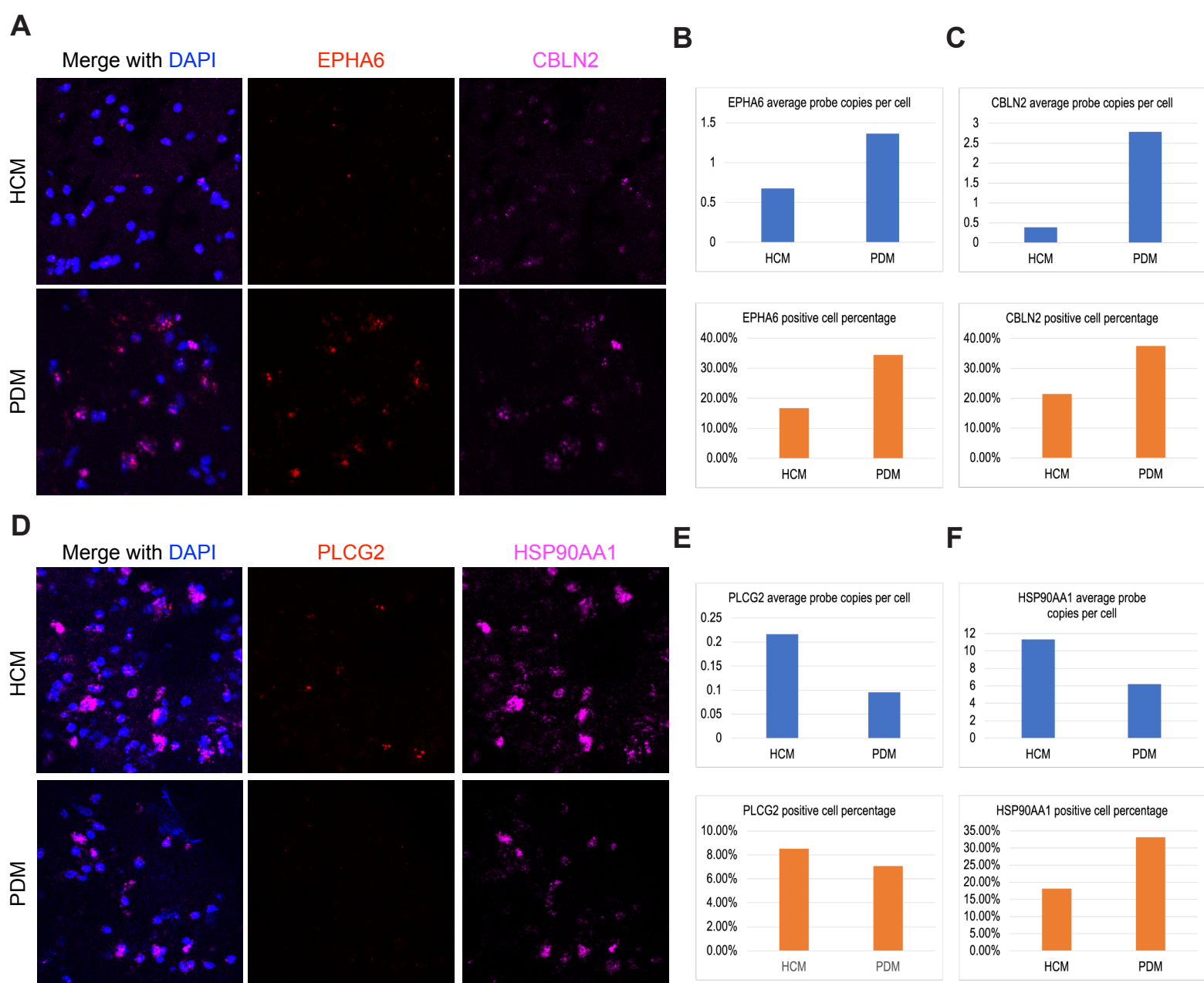


Figure S3

**Fig. S3. RNAscope *in situ* hybridization validation of differentially expressed genes in PD and healthy control brains.** (A) RNAscope images of *EPHA6* and *CBLN2* in male Parkinson's disease (PDM) or male healthy control (HCM) brains. Blue: DAPI; Red: *EPHA6*; Magenta: *CBLN2*. (B-C) QuPath quantification of RNAscope images for *EPHA6* (B) and *CBLN2* (C) (HCM, n = 13,219 cells; PDM, n = 8,963 cells). Upper panels: average probe copies per cell; Lower panels: positive cell percentage in all cells. (D) RNAscope images of *PLCG2* and *HSP90AA1* in male Parkinson's disease (PDM) or male healthy control (HCM) brains. Blue: DAPI; Red: *PLCG2*; Magenta: *HSP90AA1*. (E-F) QuPath quantification of RNAscope images for *PLCG2* (E) and *HSP90AA1* (F) (HCM, n = 16,071 cells; PDM, n = 11,543 cells). Upper panels: average probe copies per cell; Lower panels: positive cell percentage in all cells.