

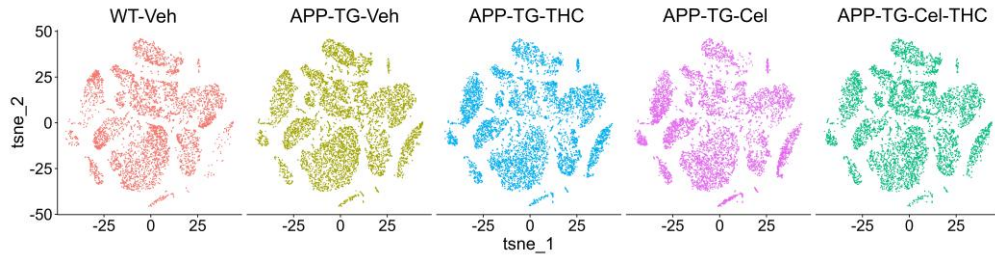
SUPPLEMENTARY DATA

**A Combination of Low-Dose  $\Delta^9$ -THC and Celecoxib as a  
Therapeutic Strategy for Alzheimer's Disease**

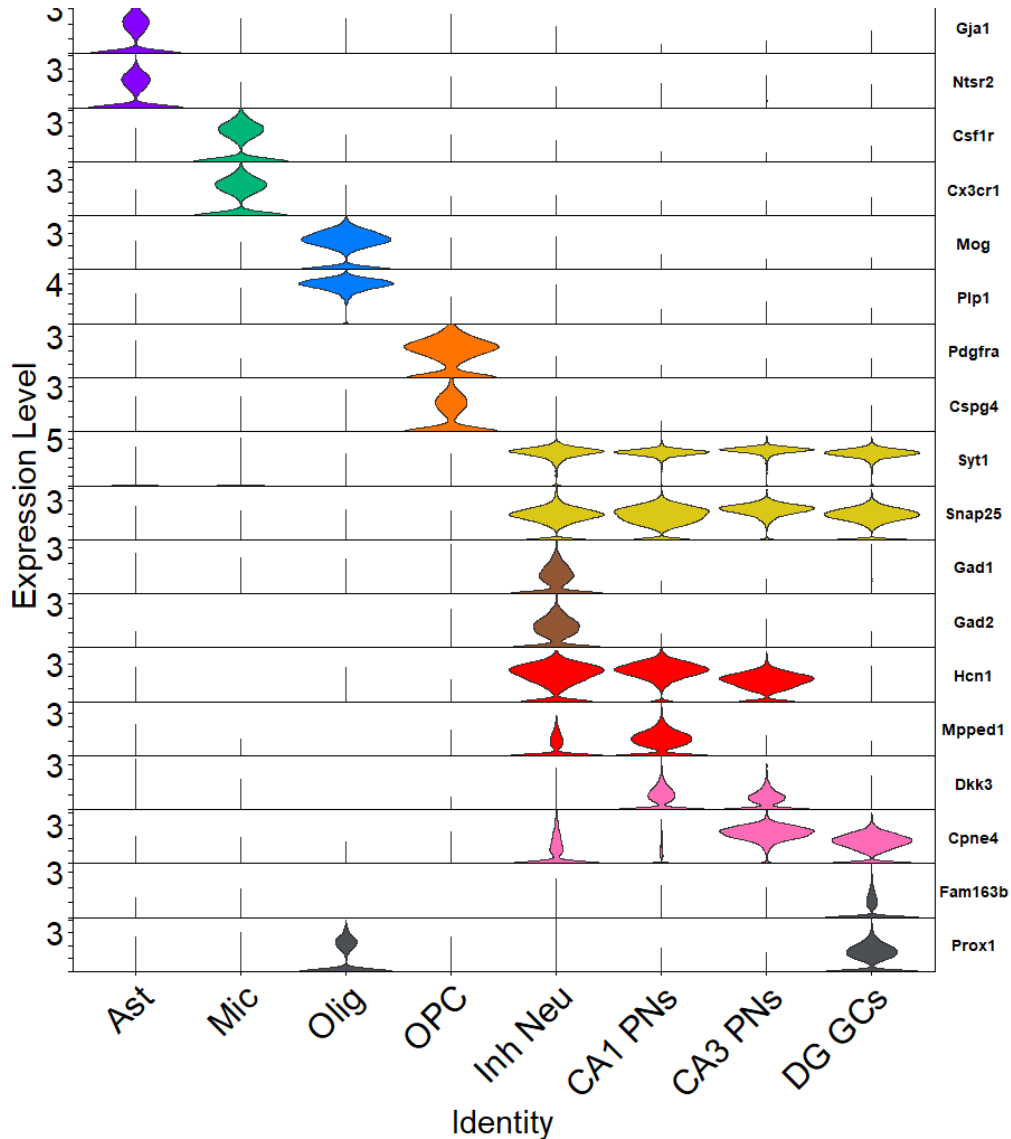
**Jian Zhang, Dexiao Zhu, Mei Hu, Mingzhe Pan, Chu Chen**

# SUPPLEMENTARY DATA

**A**

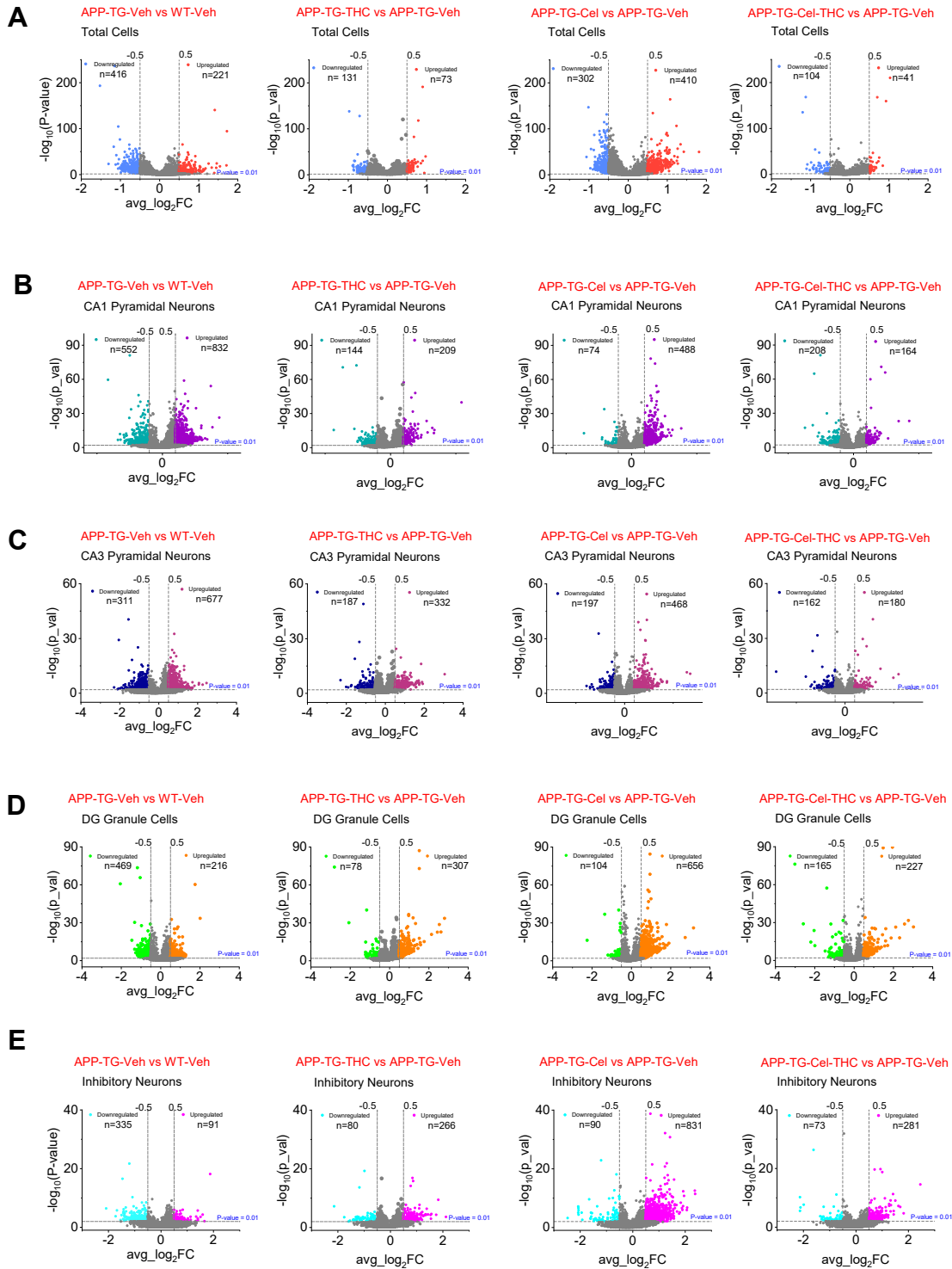


**B**



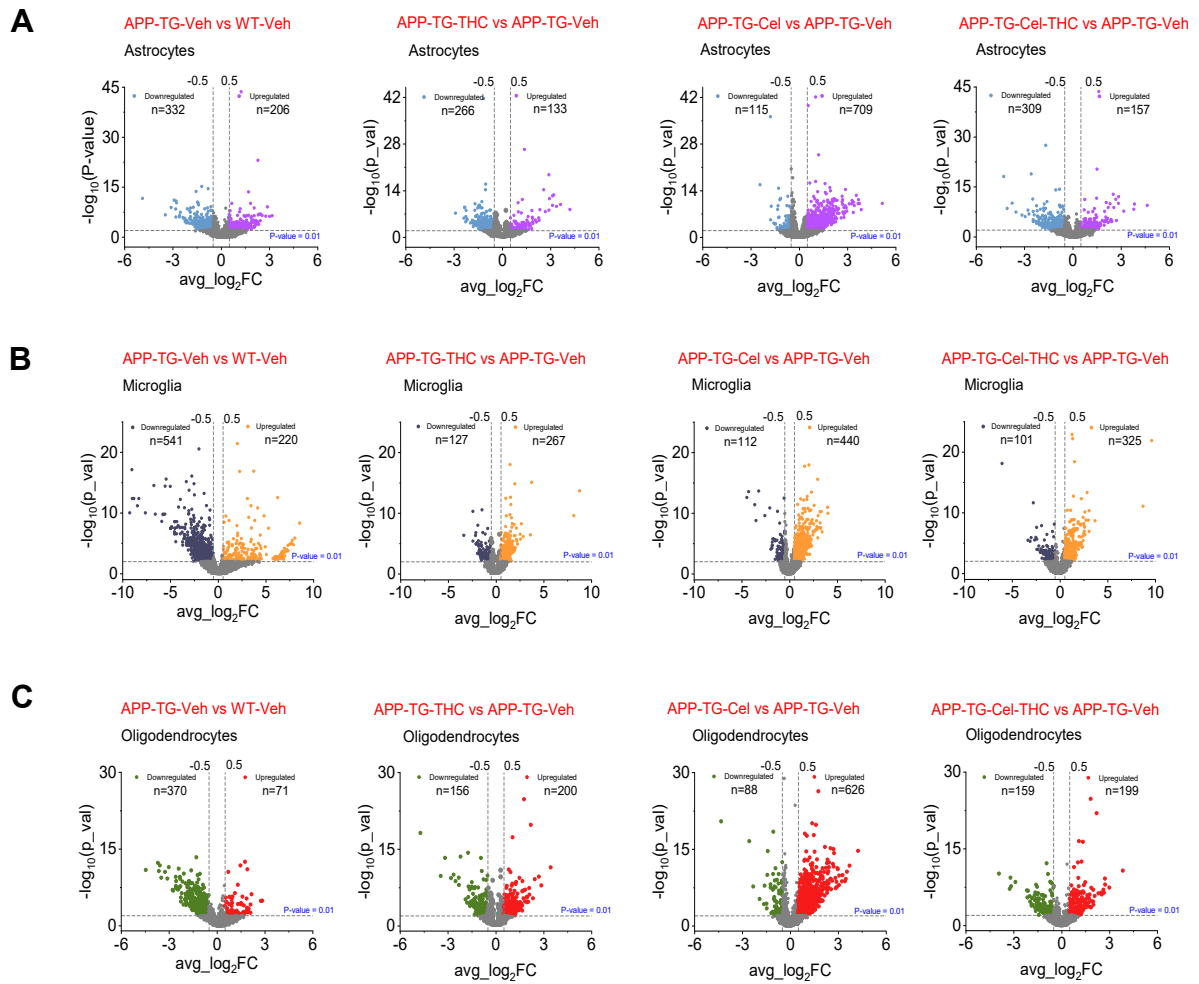
**Supplementary Figure 1. Cell type annotation.** **A**) t-Distributed stochastic neighbor embedding (tSNE) plots showing integrated nucleus from different groups. **B**) Canonical gene markers used to identify cells. *Gja1* and *nstr2* for astrocytes (Ast); *Csf1r* and *cx3cr1* for microglia (Mic); *mog* and *plp1* for oligodendrocytes (Olig); *pdgfra* and *cspg4* for OPC; *syt1* and *snap25* for neurons; *gad1* and *gad2* for inhibitory neurons; *hcn1* and *meped1* for CA1 pyramidal neurons (CA1 PNs); *dkk3* and *cpne4* for CA3 pyramidal neurons (CA3 PNs); *fam163b* and *prox1* for DG granule cells (DG GCs).

# SUPPLEMENTARY DATA



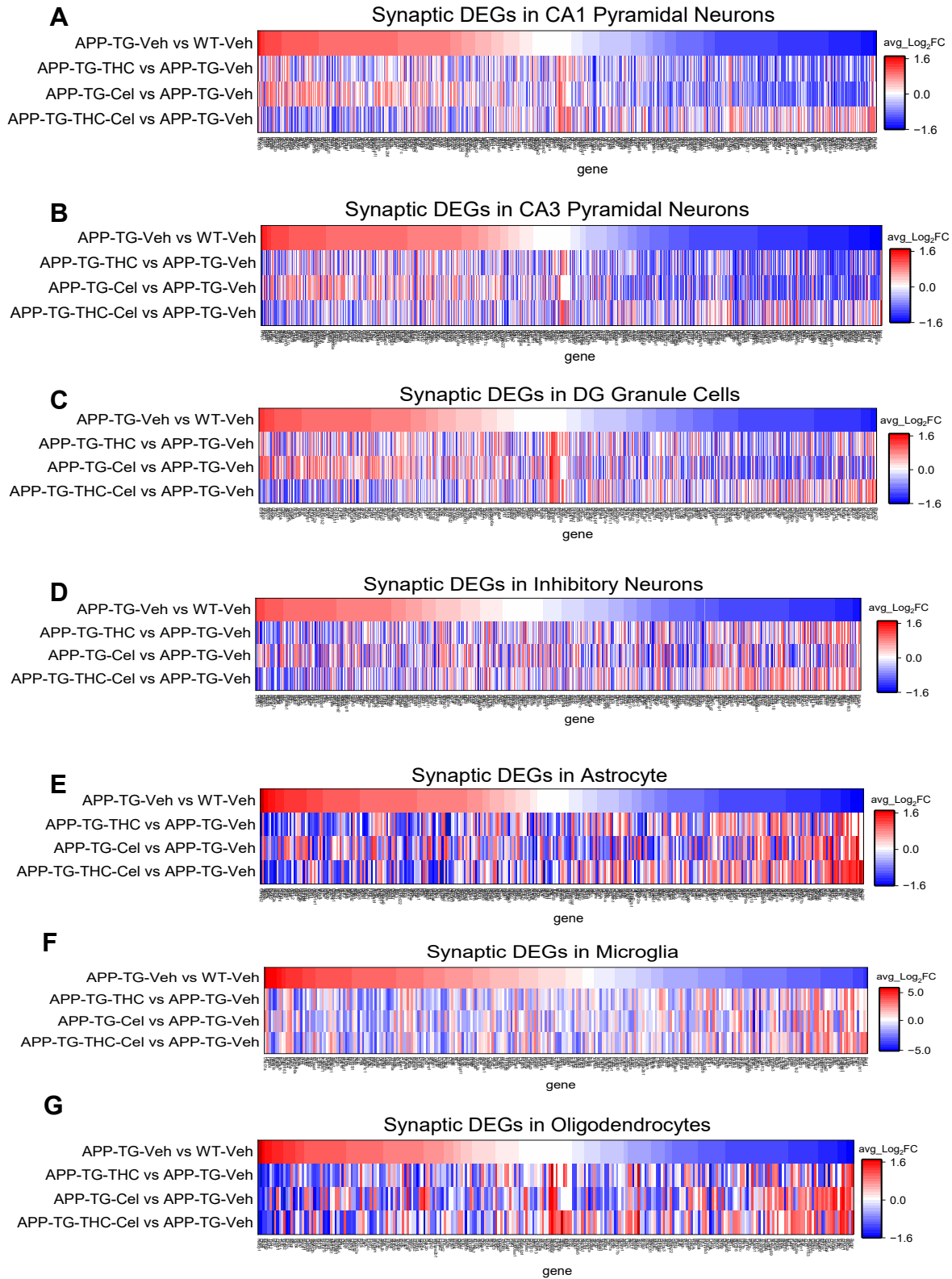
**Supplementary Figure 2. Summary of cell type-specific differential gene expression in total cells, CA1 pyramidal neurons, CA3 pyramidal neurons, DG granule cells, and inhibitory neurons across TG-Veh, TG-THC, TG-Ce, and TG-Ce-THC groups relative to WT-Veh/TG-Veh controls. A) Volcano plot displays DEGs from total cells. B) Volcano plot shows DEGs for CA1 pyramidal neurons. C) CA3 pyramidal neuron-specific DEGs are visualized in the volcano plot. D) DEGs in DG granule cells are shown. E) DEGs in inhibitory neurons are displayed. Upregulated and downregulated genes are marked, with statistical significance and fold change thresholds indicated.**

# SUPPLEMENTARY DATA



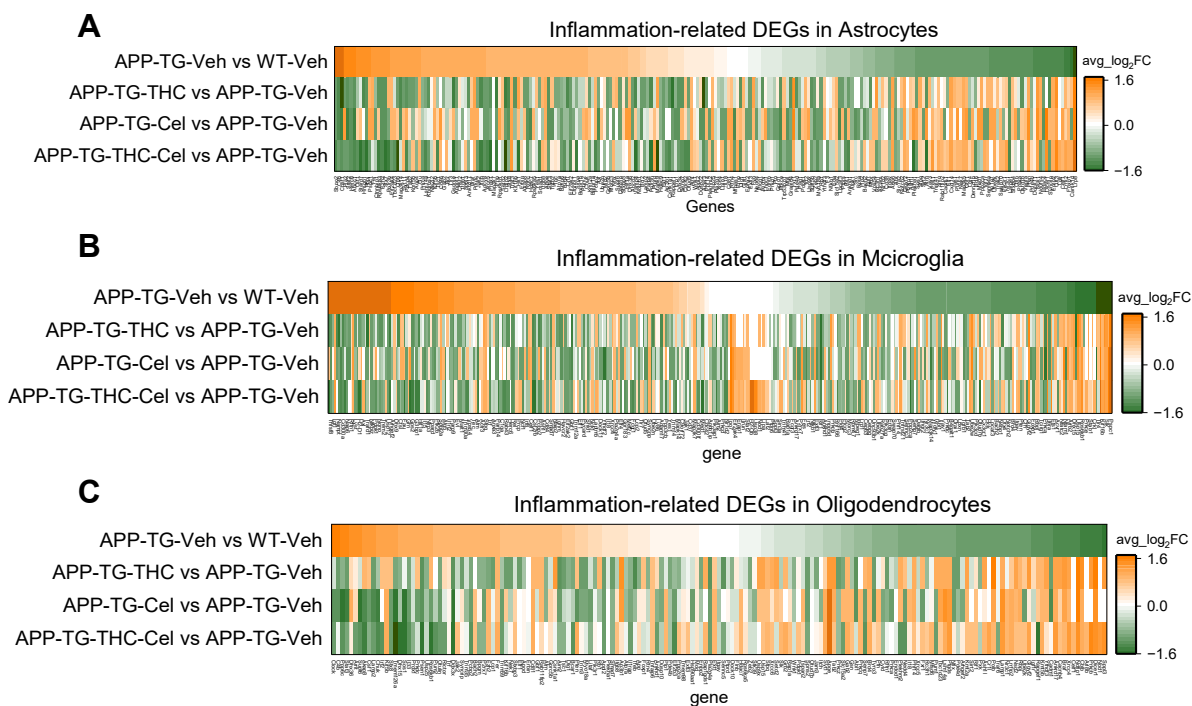
**Supplementary Figure 3. Summary of cell type-specific differential gene expression in astrocytes, microglia, and oligodendrocytes across TG-Veh, TG-THC, TG-Cel, and TG-Cel-THC groups, compared to the WT/APPTG group. A) Volcano plot shows DEGs in astrocytes. B) Volcano plot illustrates DEGs in microglia. C) Volcano plot presents DEGs in oligodendrocytes. Upregulated and downregulated genes are marked, with statistical significance and fold change thresholds indicated.**

# SUPPLEMENTARY DATA



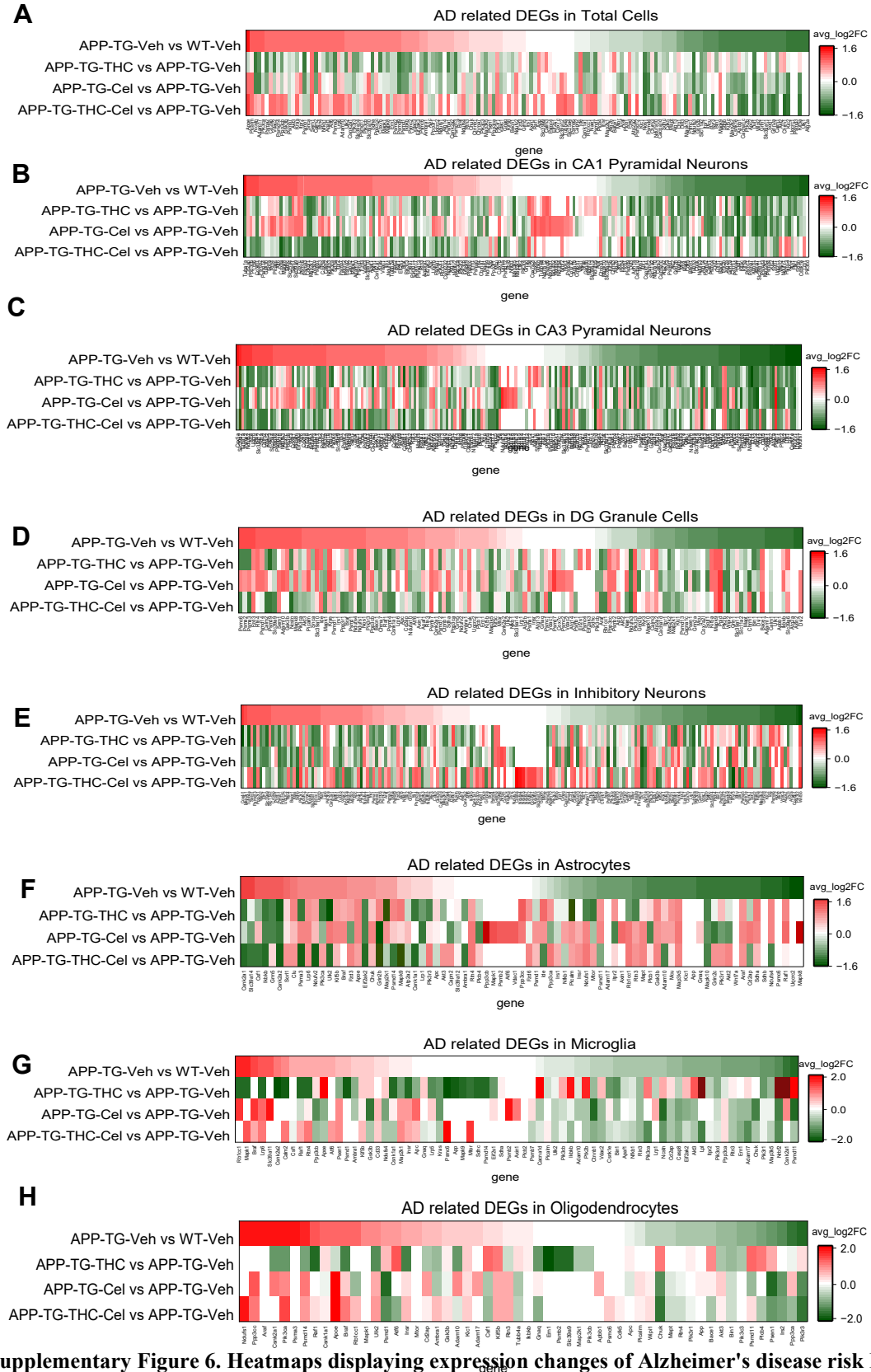
**Supplementary Figure 4. Heatmaps display fold-change expression patterns of differentially expressed synapse-related genes (DEGs) identified in: A) CA1 pyramidal neurons (PNs), B) CA3 PNs, C) Dentate gyrus granule cells (DG GCs), D) Inhibitory neurons, E) Astrocytes, F) Microglia, G) Oligodendrocytes, . Each column represents a synaptic gene; rows represent experimental groups compared to WT-Veh or TG-Veh. Color intensity indicates log<sub>2</sub> fold-change (scale shown).**

# SUPPLEMENTARY DATA



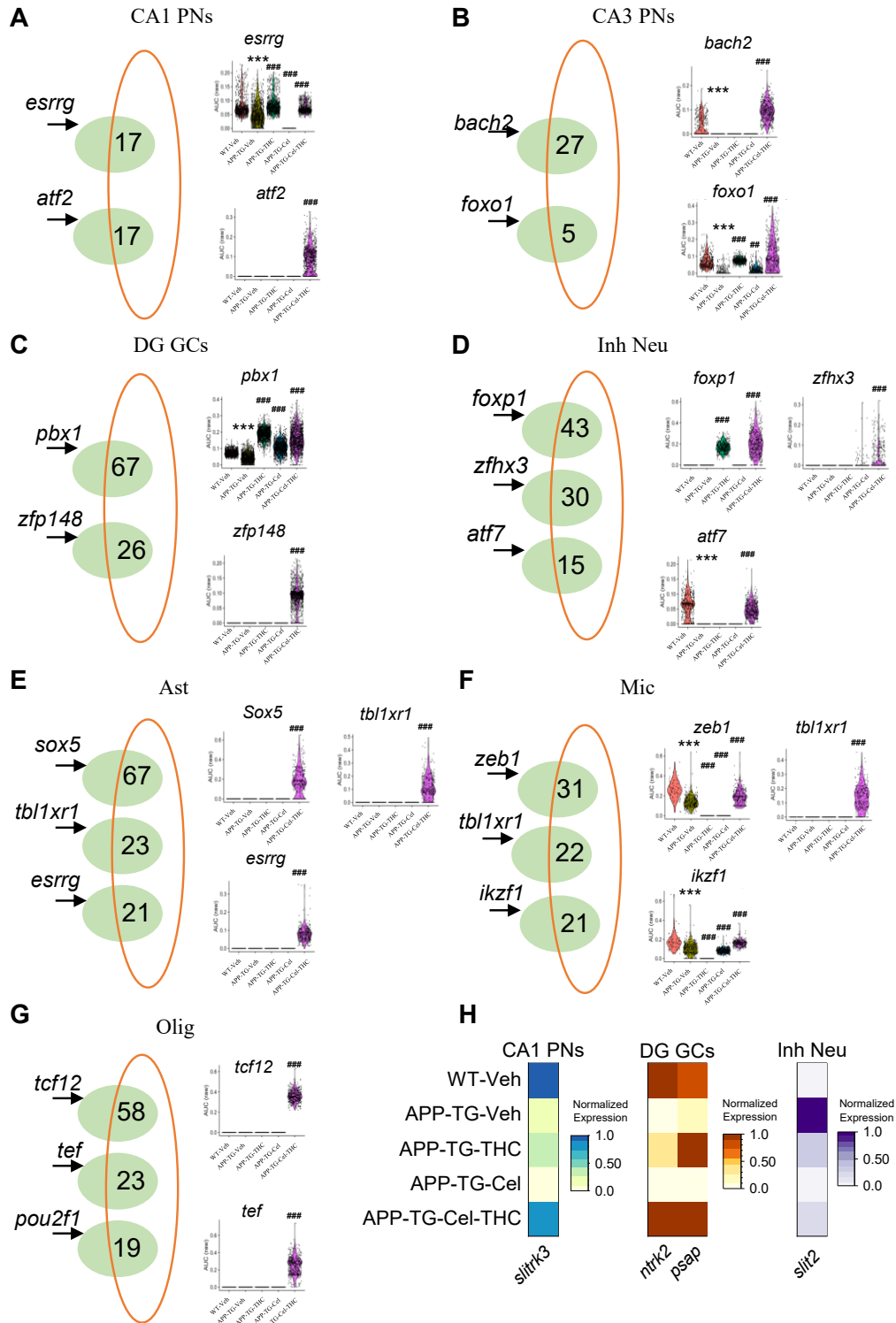
**Supplementary Figure 5. Inflammation-associated DEG heatmaps in glial cells. A) Astrocytes, B) Microglia, and C) Oligodendrocytes. Columns: experimental groups vs WT-Veh/TG-Veh.**

# SUPPLEMENTARY DATA



**Supplementary Figure 6. Heatmaps displaying expression changes of Alzheimer's disease risk DEGs across seven major brain cell types.** Each panel represents total or a distinct cell population: **A)** total cells, **B)** CA1 pyramidal neurons (CA1 PNs), **C)** CA3 pyramidal neurons (CA3 PNs), **D)** dentate gyrus granule cells (DG GCs), **E)** inhibitory neurons, **F)** astrocytes, **G)** microglia, and **H)** oligodendrocytes. The color intensity indicates relative gene fold changes.

# SUPPLEMENTARY DATA



**Supplementary Figure 7. Number of overlapping genes shared between cell type-specific differentially expressed genes (DEGs) and transcription factor (TF) target genes (predicted using the SCENIC package), along with TF activity in the hippocampus of APP-TG mice under different treatment conditions. Shown as violin plots for: A) CA1 pyramidal neurons (CA1 PNs), B) CA3 pyramidal neurons (CA3 PNs), C) dentate gyrus granule cells (DG GCs), D) inhibitory neurons (Inh Neu), E) astrocytes (Ast), F) microglia (Mic), and G) oligodendrocytes (Olig). \*\*\*:  $P < 0.001$ ; ###:  $P < 0.001$ . H) Normalized expression levels of ligands and receptors in CA1 PNs, DG GCs, and Inh Neu from hippocampus of APP-TG mice treated with  $\Delta 9$ -THC or in combination with Celecoxib.**