

Transcriptomic Insights of Enrupatinib Administration in Alzheimer's Disease Mouse Models

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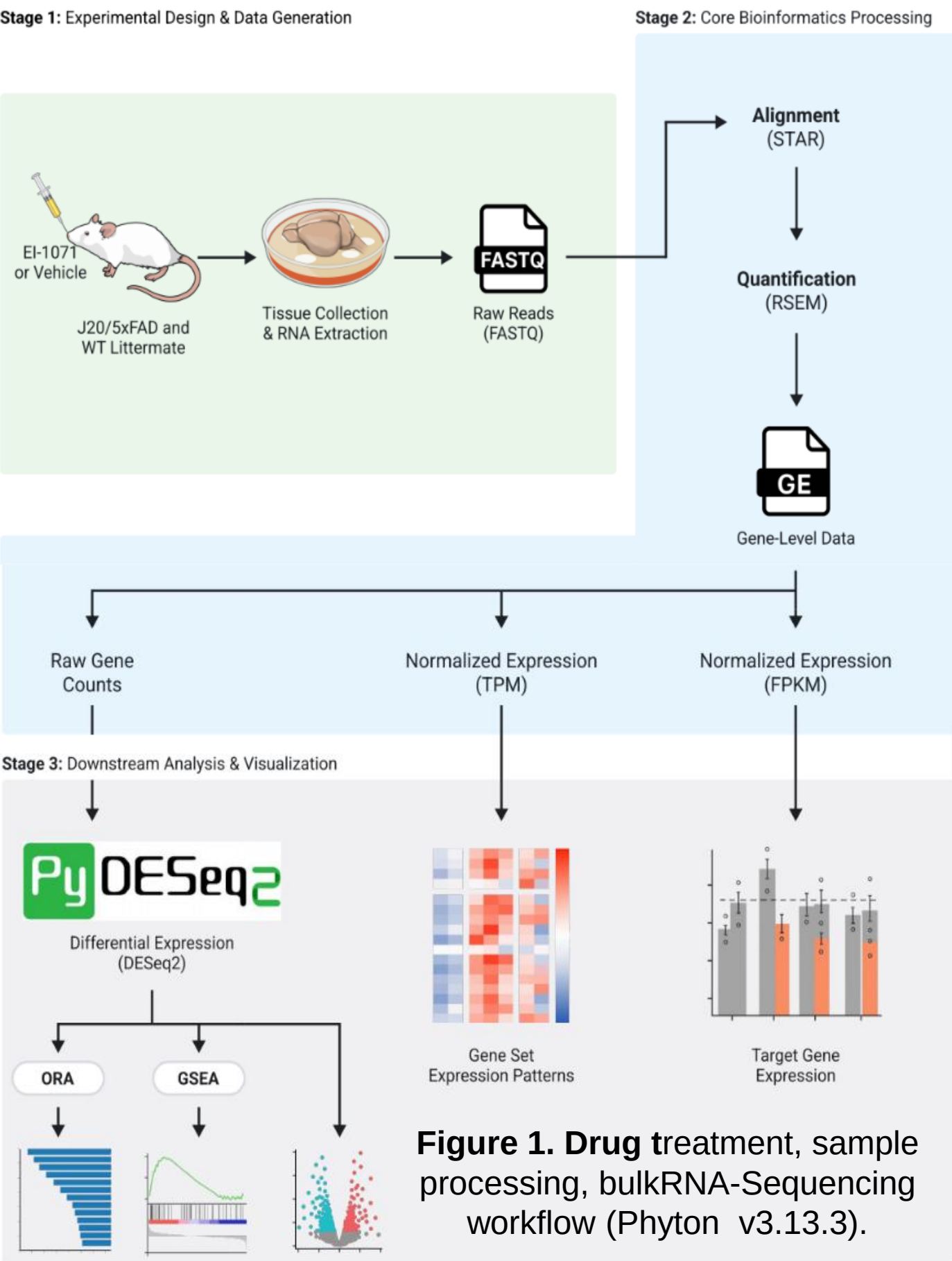


KEY TAKE AWAY: TRANSCRIPTOMIC ANALYSIS REVEALS THAT ENRUPATINIB TREATMENT DAMPENS NEUROINFLAMMATION IN BOTH 5XFAD AND J20 MODELS

Backgrounds

Alzheimer's disease pathology triggers chronic microglial activation and neuroinflammation, driving synaptic loss and cognitive decline. Consequently, therapeutic strategies aimed at modulating microglial activity are of significant interest. Enrupatinib is a potent, brain-penetrant inhibitor of the Colony Stimulating Factor 1 Receptor (CSF1R) designed to regulate microglial phenotypes. In this study, we investigated the therapeutic efficacy of enrupatinib by evaluating its impact on the neuroinflammatory transcriptomic profiles of two distinct transgenic amyloidosis models: the 5xFAD and J20.

Methods



Enrupatinib treatment modulates DAM phenotypes

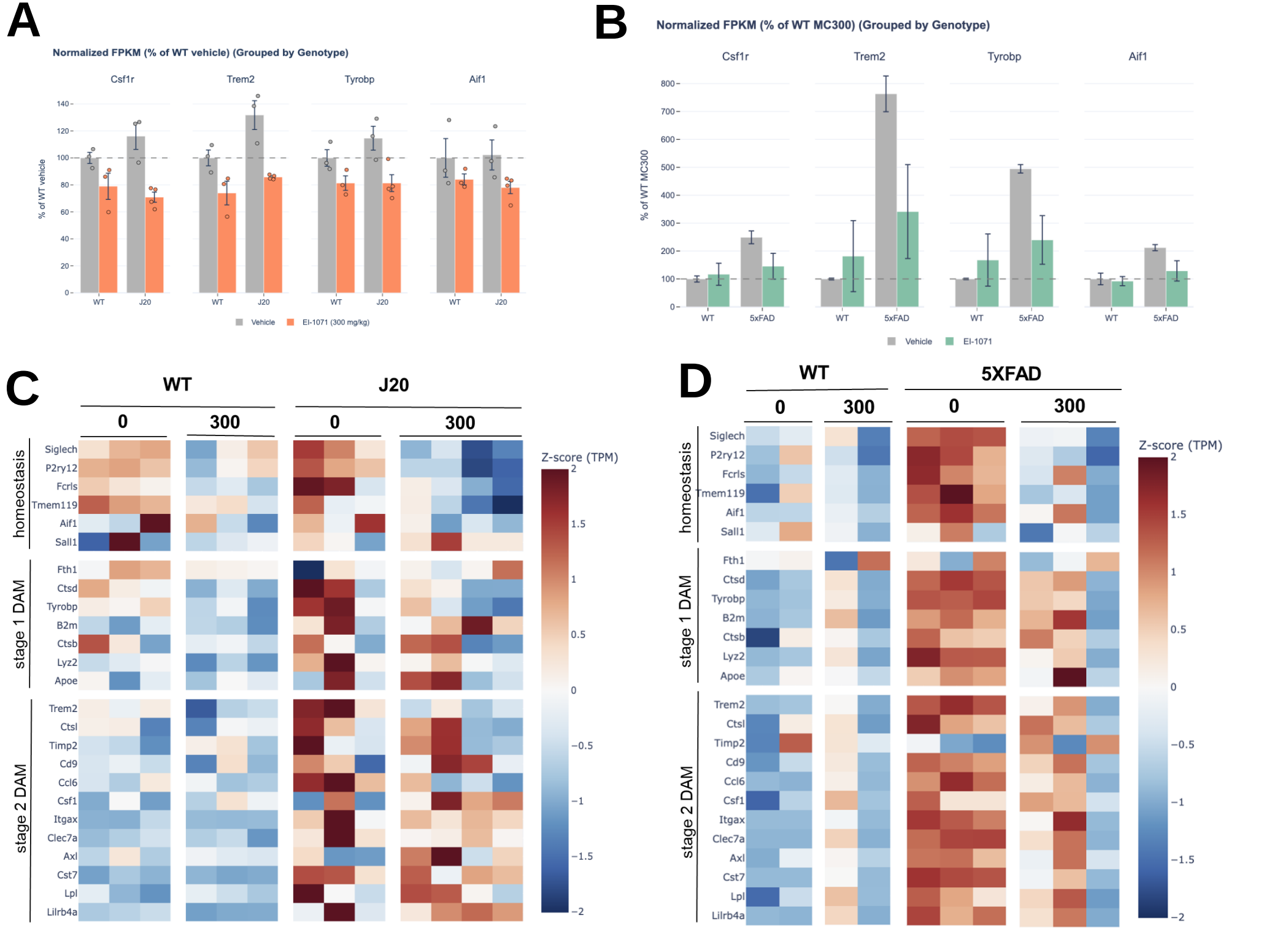


Figure 2. (A, B) Normalized FPKM values (as % of WT) for microglial genes (*Csf1r*, *Trem2*, *Tyrobp*, *Aif1*) in (A) J20 and (B) 5xFAD mice treated with 150 or 300 mg/kg EI-1071. Data analyzed by Python v3.13.3. (C, D) Heatmaps comparing homeostatic, stage 1, and stage 2 DAM states in (C) J20 and (D) 5xFAD cortex.

Differential gene expression and pathway analysis following enrupatinib treatment

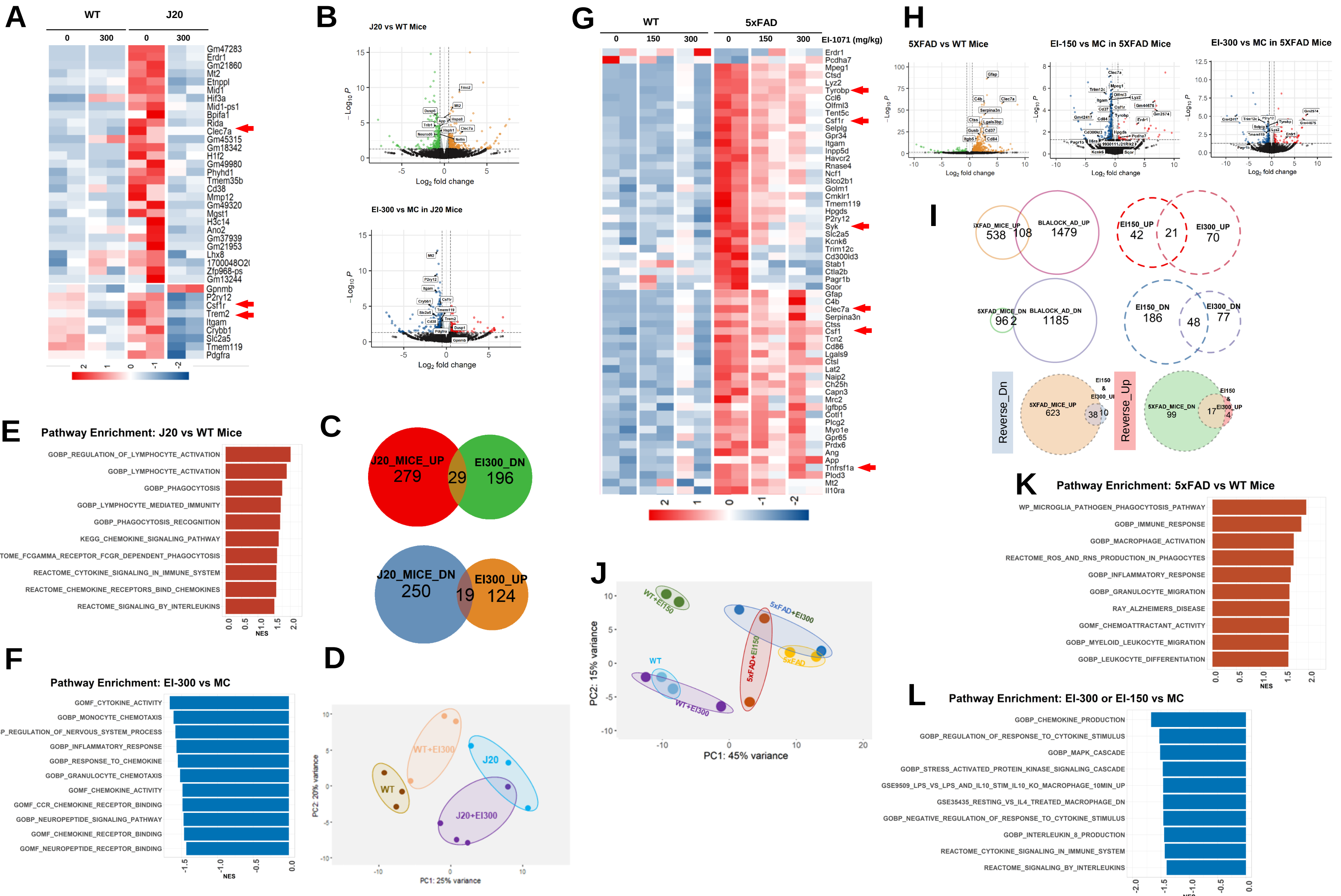


Figure 3. (A,G) Heatmaps of signed log10 (p-value) for cortical DEGs (adjusted $p < 0.05$) in (B,H) Volcano plots comparing WT vs. transgenic models and the effects of enrupatinib doses (150 mg/kg) and 300 mg/kg). Upregulated genes are in red log2 (FC)>0, downregulated genes are in blue (log2 (FC)<0), and non-significant genes are in grey (adjusted $p > 0.05$; $n = 2$ per group) (C,I) Venn diagram showing overlapping downregulated genes (adjusted $p < 0.05$) between the two EI-1071 dosage groups (D,J) PCA plot of cortical RNA-seq data, showing separation by genotype (PC1) and treatment effect (PC2) ($n = 2$ per group). (E-F, K-L) Top ten enriched (E,K) upregulated and (F,L) downregulated inflammatory pathways following EI-1071 treatment. (A-F) for J20 (G-L) for 5xFAD.

Enrupatinib suppresses neuroinflammatory pathways in 5xFAD and J20 models

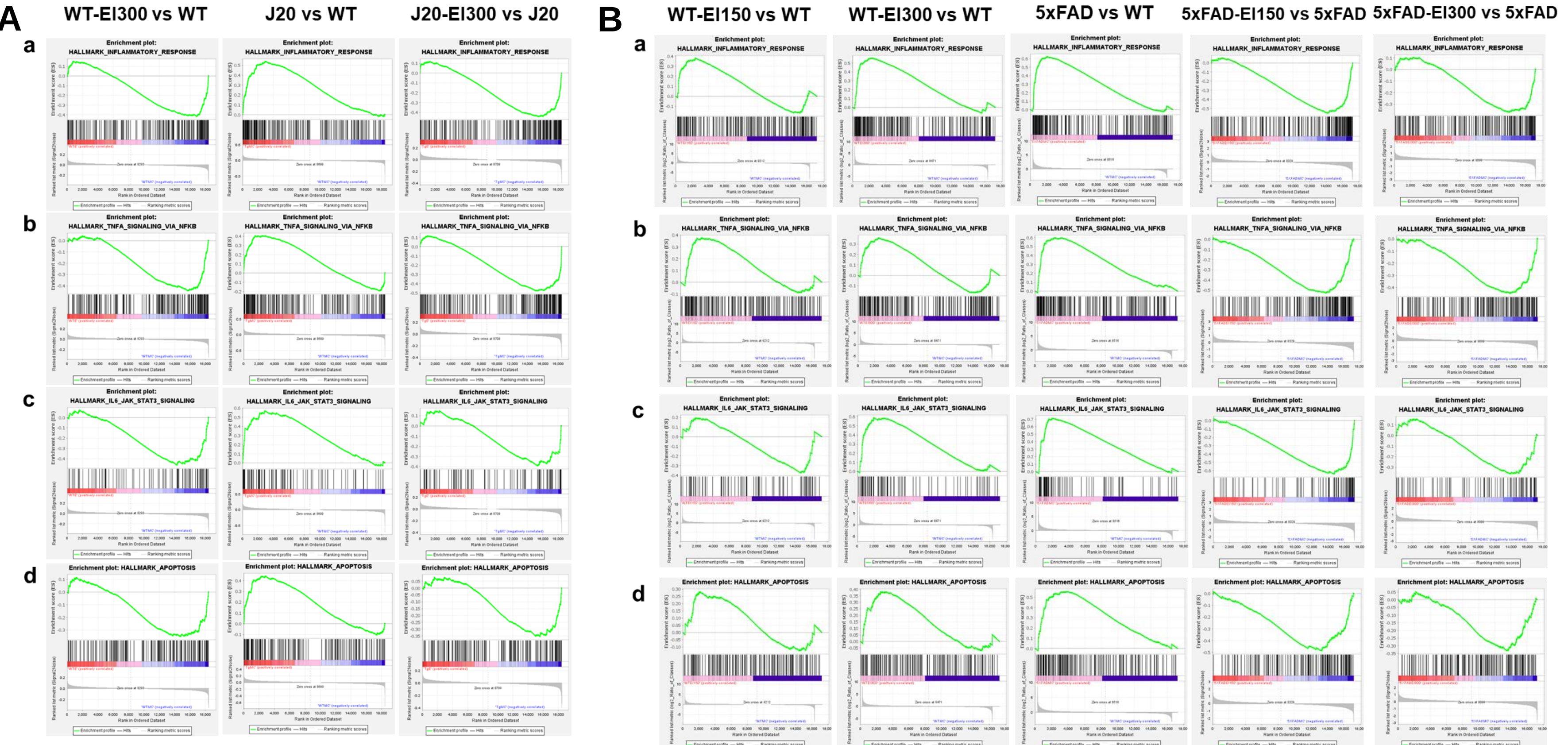


Figure 4. GSEA plots showing significant downregulation of key inflammatory pathways (in a. Hallmark of inflammatory response; b. Hallmark of TNF-A signaling via NFkB; c. Hallmark of IL-6/JAK/STAT3 signaling; and d. Hallmark apoptosis) in the cortex of J20 and 5xFAD mice following enrupatinib treatment compared to vehicle controls ($n = 2-4$ mouse per group; NES: Normalized Enrichment Score, FDR < 0.05).

Enrupatinib reduced diseased activated microglia markers in mice models

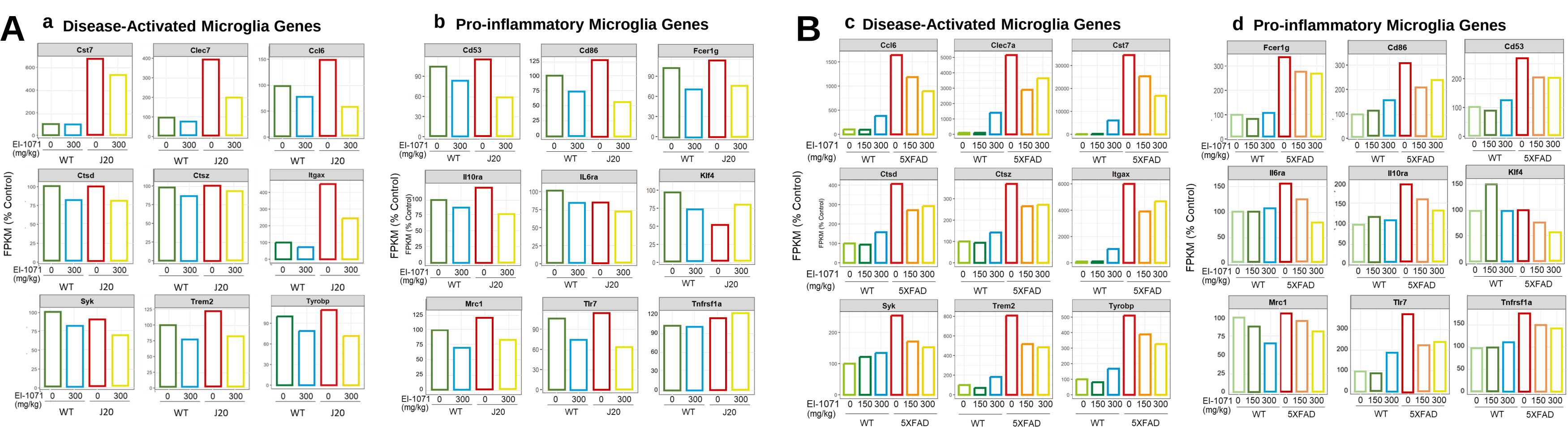


Figure 5. Cortical expression of microglial markers derived from bulk RNA-sequencing. FPKM values reveal lower expression of (A) J20 cortical markers, including (a) disease-activated and (b) pro-inflammatory microglia genes, and (B) 5xFAD cortical markers, including (c) disease-activated and (d) pro-inflammatory microglia genes.

Conclusions

These findings demonstrate that enrupatinib successfully reverses the neuroinflammatory transcriptomic profile in both 5xFAD and J20 models, offering a promising clinical avenue for targeting microglia in Alzheimer's disease.

Contact



Acknowledgements

We thank the **Genomics Research Center, NYCU (Yang Ming Campus)** for their valuable discussions on the RNA-sequencing data. Special thanks to the **Alzheimer's Association** for the **travel grant** supporting the presentation of this project at this major global event. We hope this work successfully contributes to future alternative treatments for AD patients as we proceed with publication steps.