

# Comparative gene regulatory networks modulating *APOE* expression in microglia and astrocytes

## Supplementary Information

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## Supplementary Figures

### **Supplementary Figure 1 Expression profile shifts following virtual KO of APOE, CX3CR1, and P2RY12 regulating TFs in mic-resting.**

Plots boxed in red indicate those that shift expression away from the resting state. Principle component analysis was performed on the TF-by-target gene matrix. The top five principal components were used to calculate the UMAP coordinates. Gene clusters were calculated from a shared-nearest-neighbor graph using the Louvain algorithm. Linear models were used to identify TFs that significantly regulated the gene clusters. TFs for the clusters containing APOE, CX3CR1, and P2RY12 were then individually knocked out (virtually) and visualized using the SCENIC+ algorithm.

### **Supplementary Figure 2 Expression profile shifts following virtual KO of APOE, CX3CR1, and P2RY12 regulating TFs in mic-activated.**

Plots boxed in red indicate those that shift expression away from the resting state. Principle component analysis was performed on the TF-by-target gene matrix. The top five principal components were used to calculate the UMAP coordinates. Gene clusters were calculated from a shared-nearest-neighbor graph using the Louvain algorithm. Linear models were used to identify TFs that significantly regulated the gene clusters. TFs for the clusters containing APOE, CX3CR1, and P2RY12 were then individually knocked out (virtually) and visualized using the SCENIC+ algorithm.

### **Supplementary Figure 3 Full astro-resting co-regulatory network UMAP representation.**

This pairs with Figure 3D and Supplementary Figure 4.

### **Supplementary Figure 4 Detailed UMAP representation of gene regulatory networks and APOE gene cluster GO enrichment**

A-E) A UMAP visualization of each cell states' regulome that includes all pySCENIC TFs (connected to Figure 3). APOE is underlined. The TFs in red directly regulate APOE. TFs in bold black significantly upregulate the APOE gene cluster. TFs in blue are the TFs that were replicated in the ROSMAP dataset. D) Astro-resting is zoomed. The full figure can be found in Supplementary Figure 3. F) Heatmap of the GO biological process terms associated with the genes in the APOE gene clusters for each cell state. Tiles with (.) indicated an adjusted p-value < 0.05.

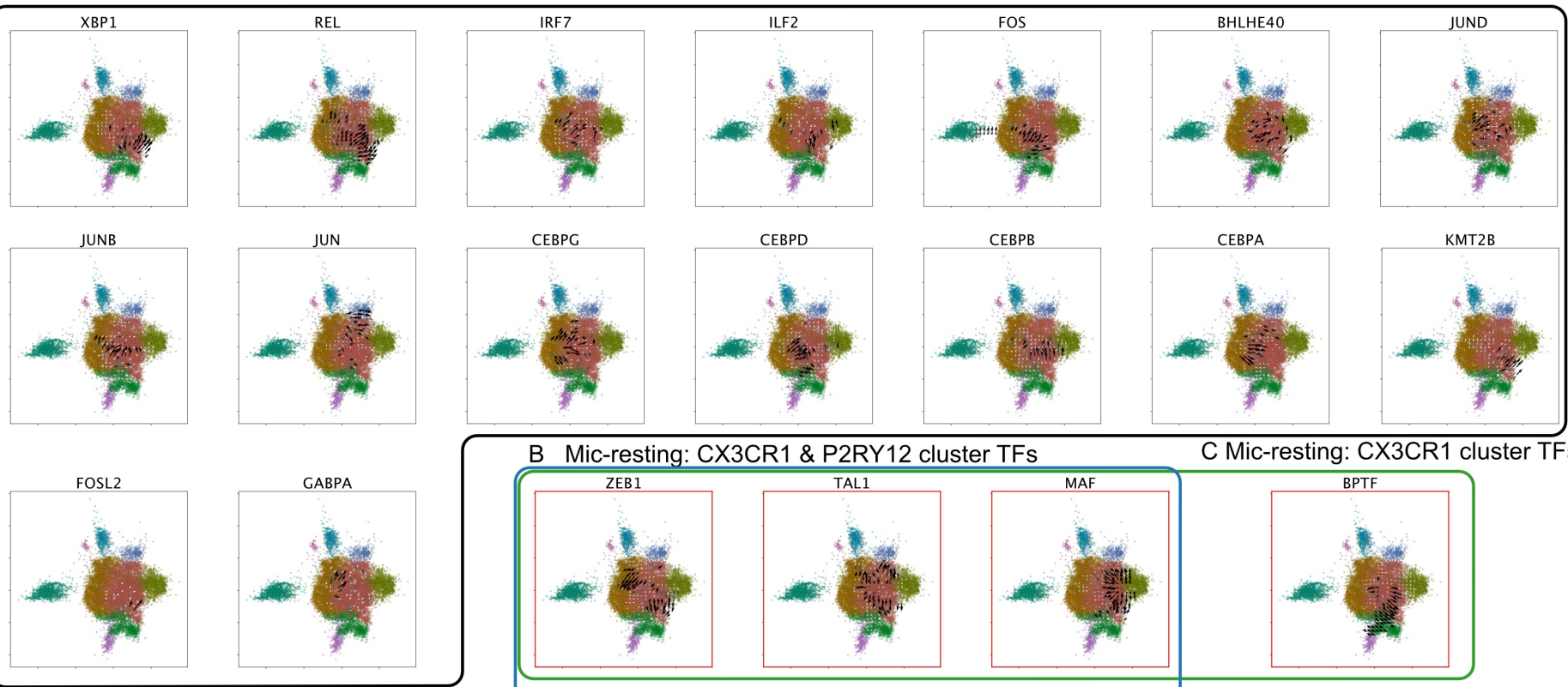
### **Supplementary Figure 5 AD GWAS genes in the co-regulatory networks.**

A global UMAP visualization of each cell states' regulome (same as Figure 3) that highlights the GWAS genes in the same cluster with APOE (black labels) and all other GWAS genes (blue labels). Point color indicates cluster membership. The background shade of green depicts the density of AD GWAS genes in that location, where the darker the green the greater colocalization of GWAS genes in the network. Principle component analysis was performed on the TF-by-target gene matrix. The top five principal components were used to calculate the UMAP coordinates.

### **Supplementary Figure 6 Other AD GWAS genes are coregulated with APOE Genes in AD GWAS loci full figures.**

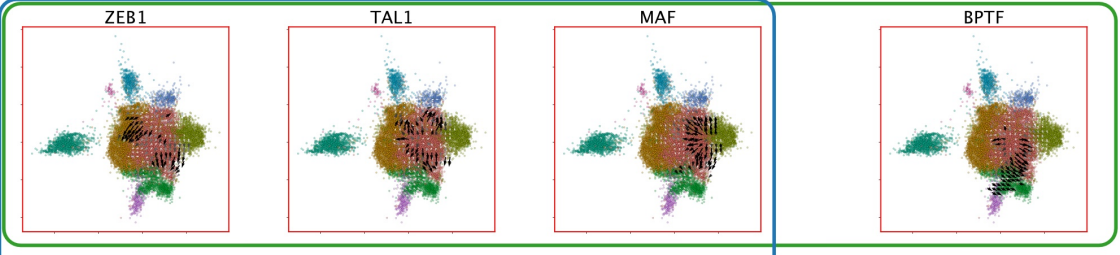
(A,B) co-regulated by APOE-associated TFs and (C,D) co-clustered with APOE in co-regulation networks. Rows are colored by loci. Some genes are within two loci and therefore have two colors. These plots are the non-truncated versions of plots in Figure 5.

A Mic-resting: APOE cluster TFs

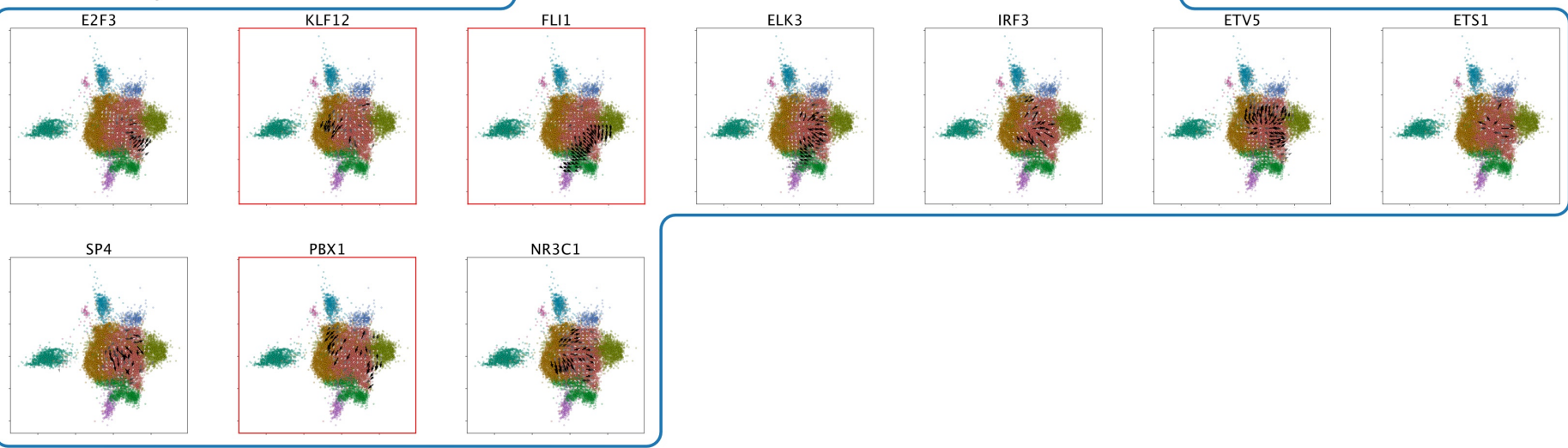


B Mic-resting: CX3CR1 & P2RY12 cluster TFs

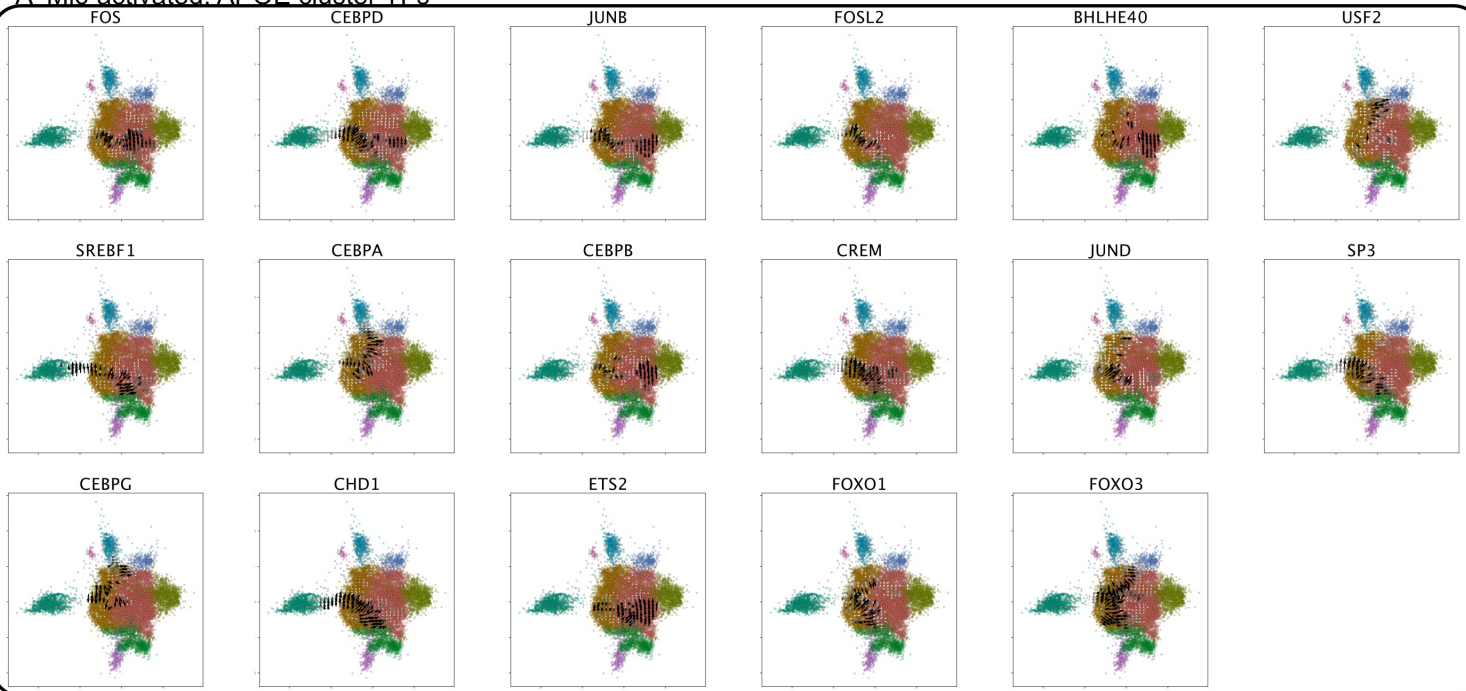
C Mic-resting: CX3CR1 cluster TFs



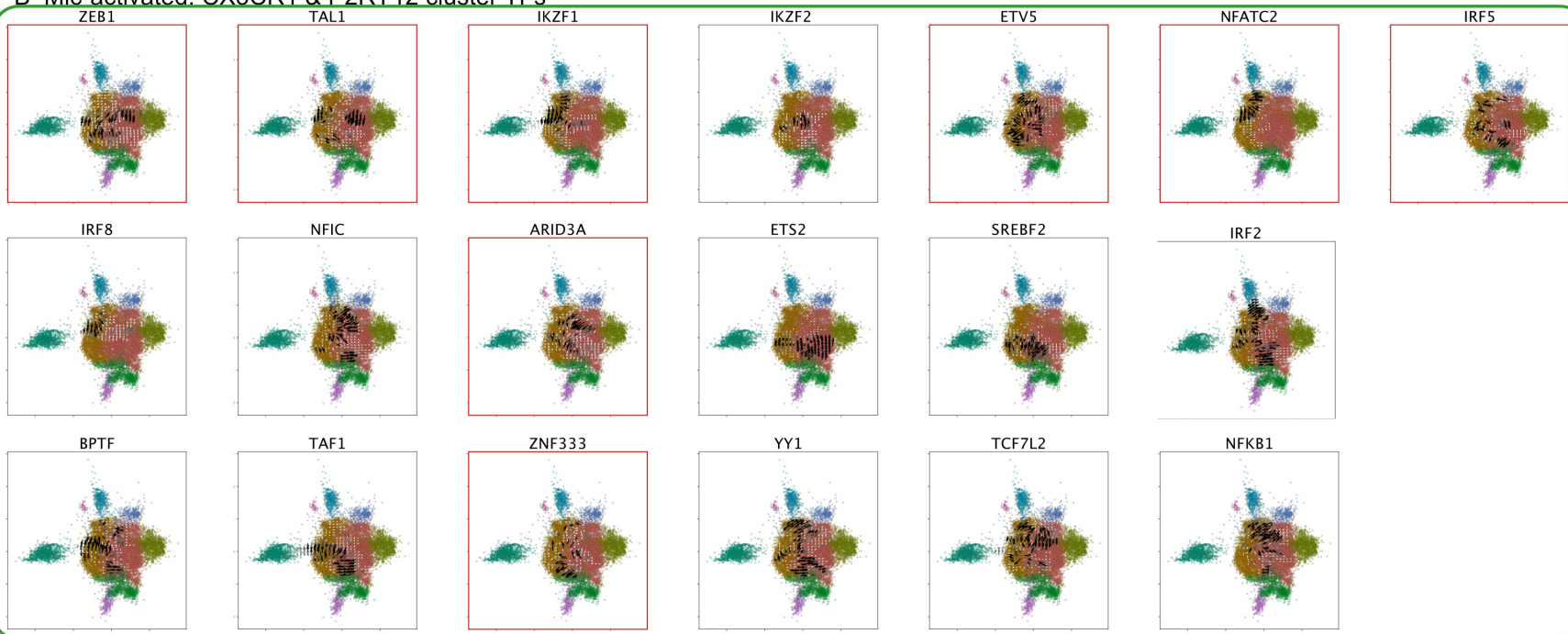
D Mic-resting: P2RY12 cluster TFs



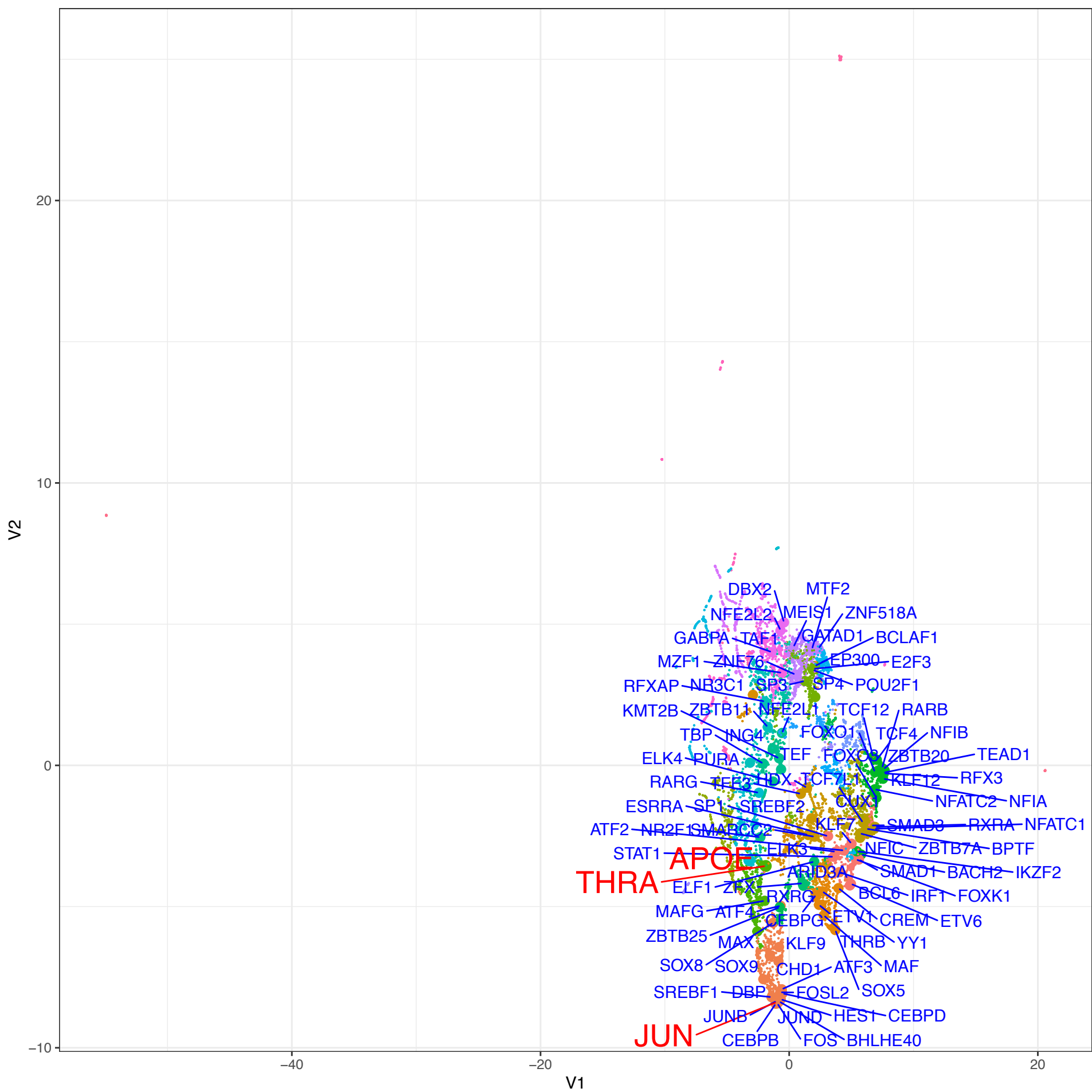
A Mic-activated: APOE cluster TFs



B Mic-activated: CX3CR1 & P2RY12 cluster TFs

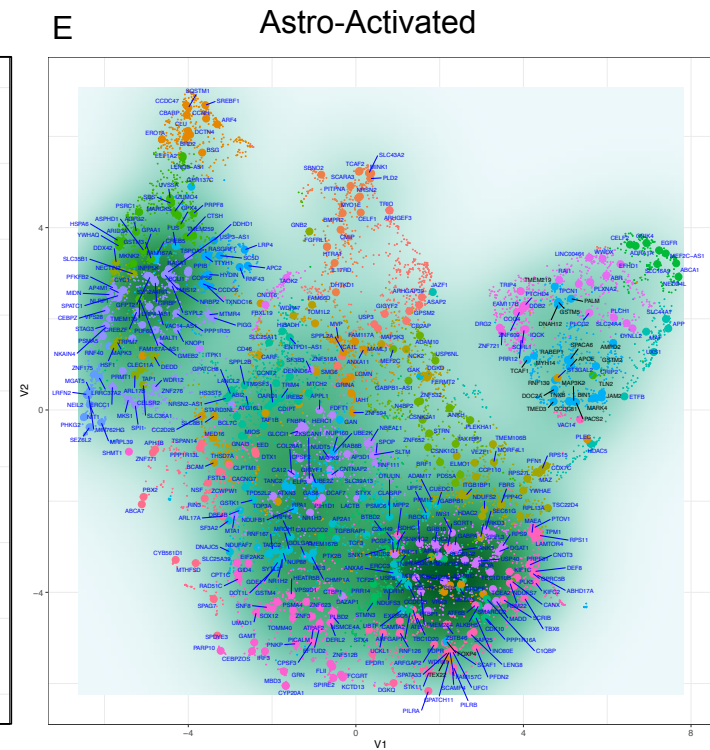
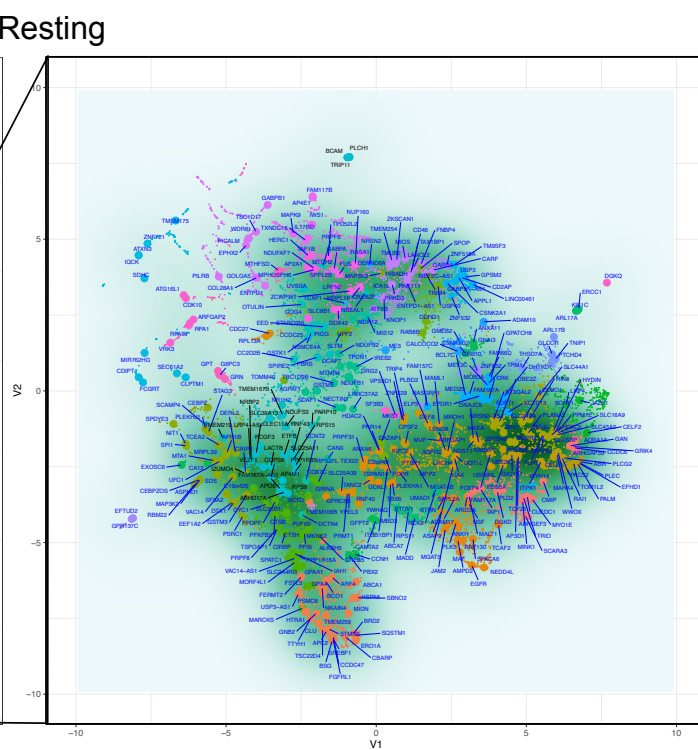
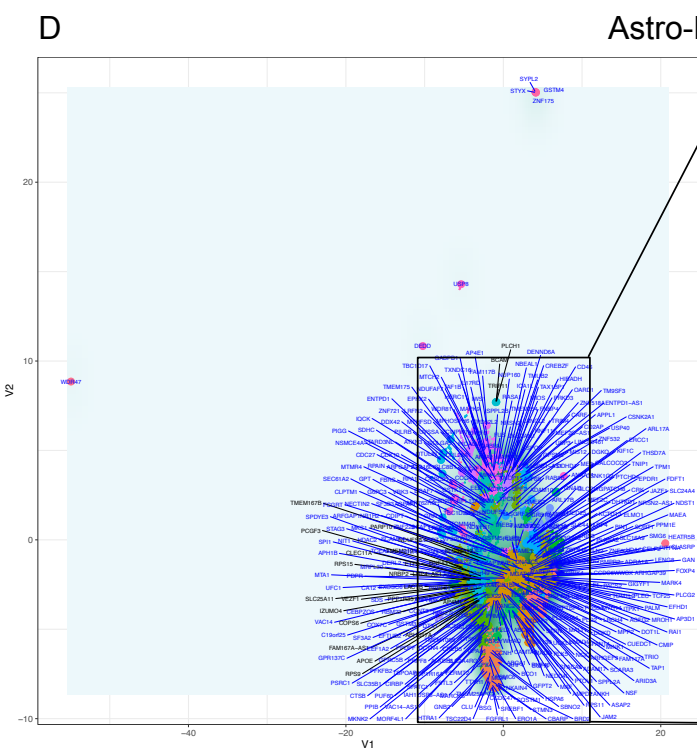
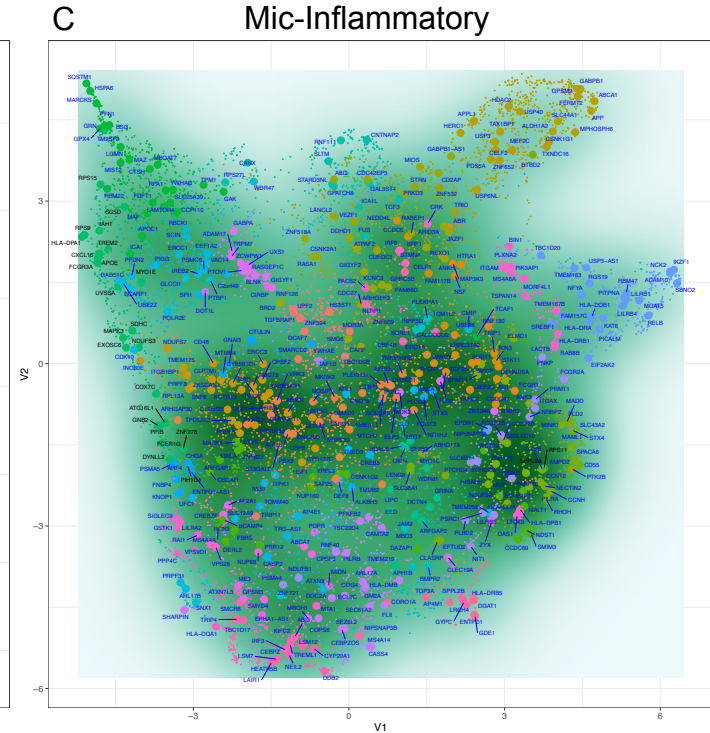
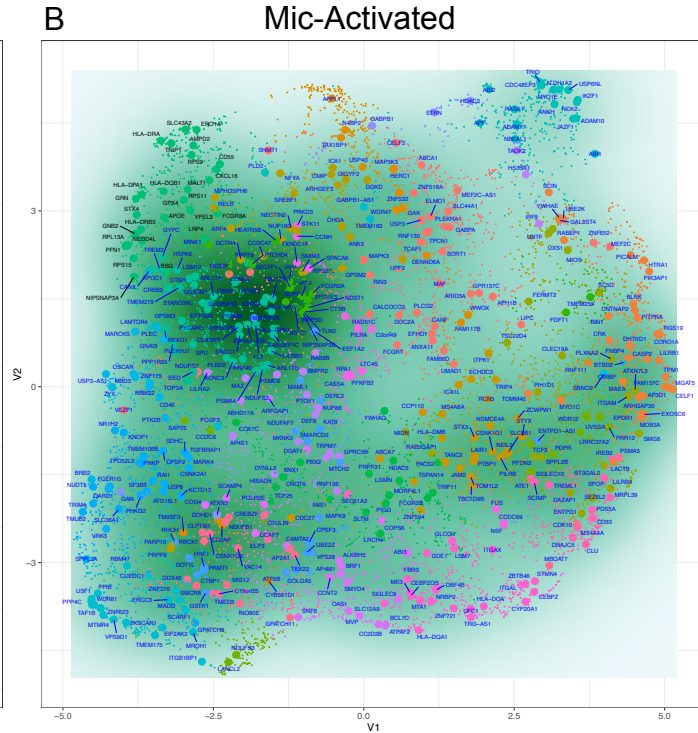
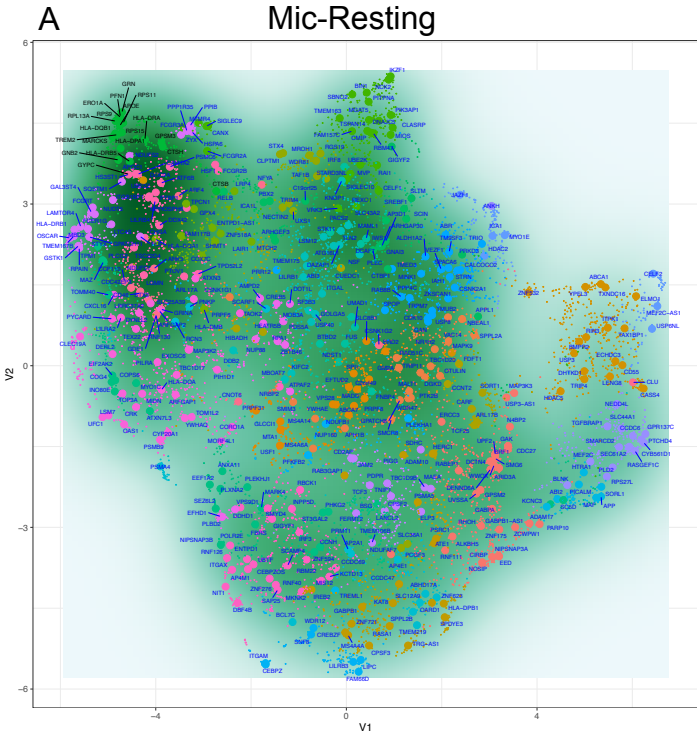


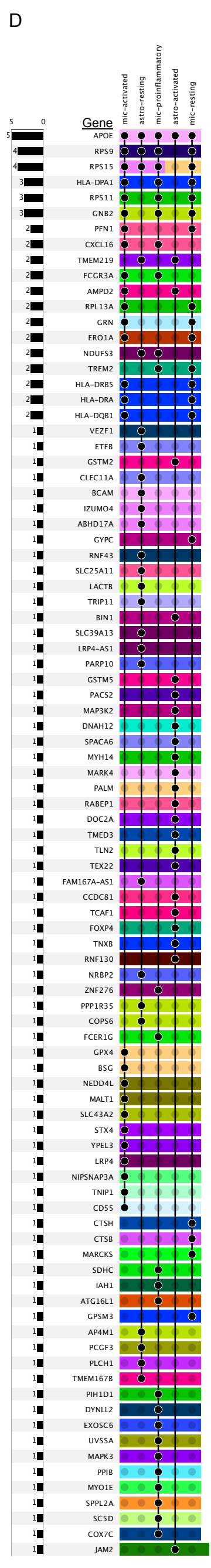
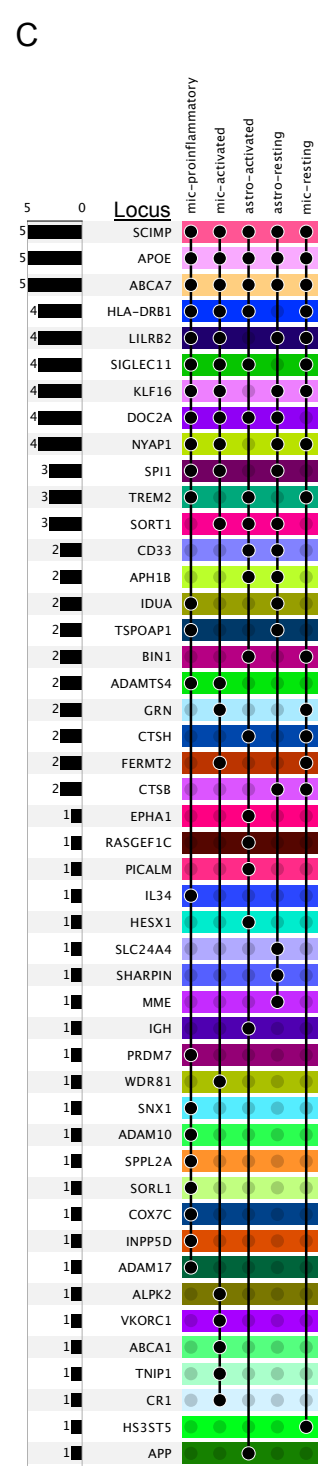
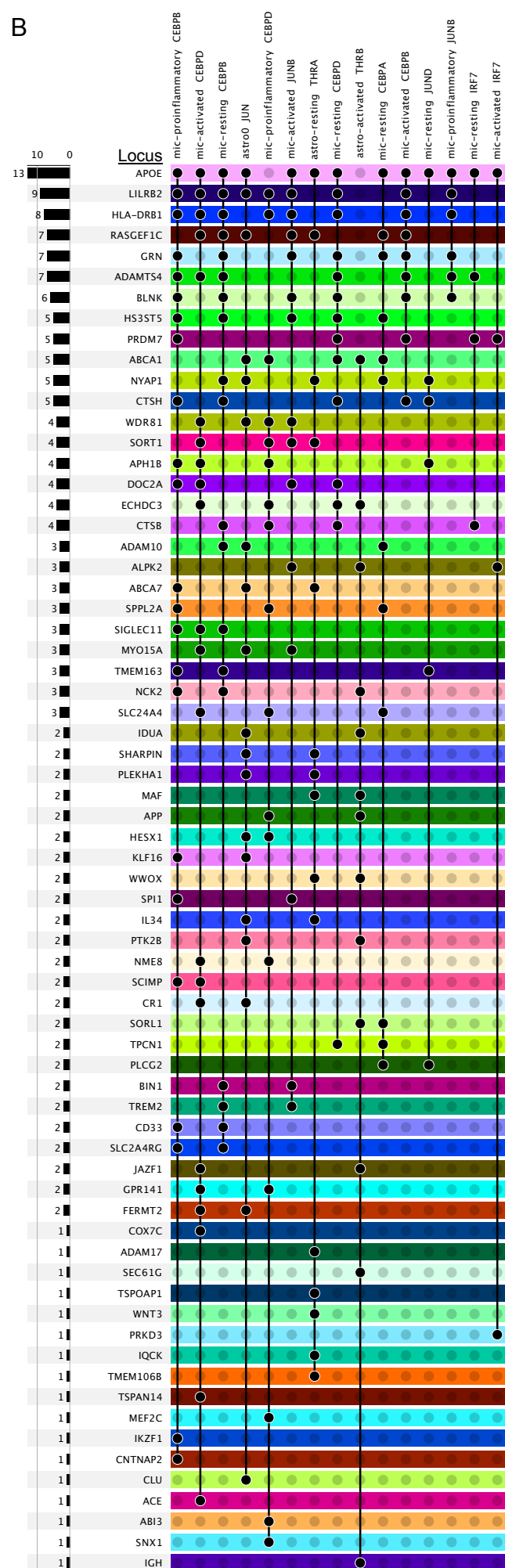
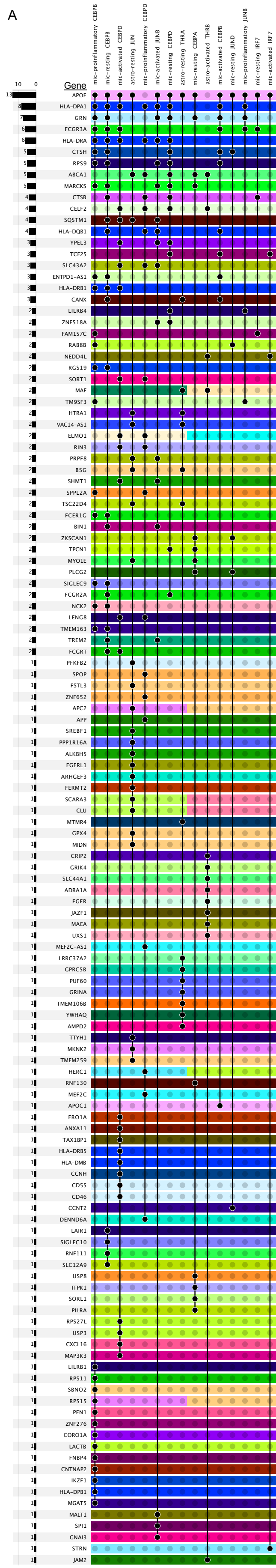












## Supplementary Tables

| <i>Supplementary Table 1 Cell state summaries</i> | Mic resting | Mic activated | Mic inflammatory | Astro resting | Astro activated |
|---|-------------|---------------|------------------|---------------|-----------------|
| TF regulators                                     | 114         | 114           | 109              | 119           | 127             |
| ROSMAP TF regulators                              | 109         | 112           | 106              | 107           | 113             |
| Replicated TFs                                    | 94          | 100           | 86               | 97            | 101             |
| Co-regulatory network clusters                    | 27          | 23            | 24               | 31            | 30              |
| Genes in APOE cluster                             | 199         | 365           | 352              | 310           | 409             |
| TFs regulating APOE cluster                       | 16          | 17            | 18               | 6             | 9               |

*Supplementary Table 2 TFs for each cell state*

<https://wustl.box.com/v/pySCENIC-TF-intersect-upset>

*Supplementary Table 3 APOE gene cluster gene set enrichment analysis results*

<https://wustl.box.com/v/APOE-gene-cluster-enrichment>

*Supplementary Table 4 State-specific TF gene set enrichment analysis results*

<https://wustl.box.com/v/TF-enrichr-results>

*Supplementary Table 5 Genes co-regulated with APOE*

<https://wustl.box.com/v/genes-coregulated-with-APOE>

*Supplementary Table 6 Genes in AD GWAS loci*

<https://wustl.box.com/v/genes-in-AD-GWAS-loci>