

Supplemental Figure 1. MS4A4A expression split by (A) rs1582763 and (B) rs6591561 genotypes across microglia clusters Mic.0, Mic.1, Mic.2.



Supplemental Figure 2. *MS4A4A*, *MS4A6A*, *MS4A4E* and *TREM2* expression across the microglia clusters in human brain snRNA-seq. (A) Feature plot (B) Ridge plot (C) Violin plot (D) Dot plot of *MS4A4A*, *MS4A6A*, *MS4A4E* and *TREM2* across different microglia clusters.



Supplemental Figure 3. Examples of RNA velocity in some individual samples that contains Mic3. Top row represents merged data. Individual donors represents below.





Supplemental Figure 4. Low CXCR4 and CD44 co-expression in human brain snRNAseq data. rs1582763-A minor allele carriers have less CD44+ nuclei and more CXCR4+ nuclei in microglia.



verapamil	Calcium channel blocker		taselisib	PI3K inhibitor
TAK-715	P38 MAPK inhibitor		SB-2343	MTOR inhibitor PI3K inhibitor
MK-1775	WEE1 kinase inhibitor		crizotinib	ALK inhibitor
BRD-K555755	31		PRT-062607	Syk inhibitor
edaravone	Nootropic agent		BRD-K28372487	
ORE-1001	ACE inhibitor		ZM-447439	Aurora kinase inhibitor
EX-527			LCB-03-0110	
acipimox	Cholesterol inhibitor		GDC-0068	AKT inhibitor
mepazine	Mucus protecting agent		PF-05212384	MTOR inhibitor PI3K inhibitor
GSK-461364	PLK inhibitor		GSK-2110183	AKT inhibitor
0 -0.25	-0.50 -0.75 -1.00 -1.25 Normalized Connectivity Score (norm_cs)	-1.50	0.00 0.25 0.50 No	0.75 1.00 1.25 1.50 prmalized Connectivity Score (norm cs)

Supplemental Figure 5. CMAP predicted compounds which contradict 1582763 and mimic

rs6591561 in Mic3. (Left) Compounds with effects that reverse gene expression changes associated with the protective variant rs1582763. (Right) Compounds with effects that mimic gene expression changes associated with the risk variant rs6591561.



Supplemental Figure 6. Pathways for "Cytokine-cytokine receptor interaction" and "Cholesterol metabolism" for differentially expressed genes in meta-analysis of bulk RNA-seq data in human brains. For each given box, left is rs1582763, right is rs6591561. Red and green indicate up-regulated and down-regulated DEG in LogFC.



Supplemental Figure 7. Removing Mic.3 eliminated the effect of rs6591561 on overall microglia population.



Supplemental Figure 8. Integration of human microglia and iTF-microglia data. A.

Schematic diagram of transcriptomic integration with human microglia and iTF-microglia using the Mutual Nearest Neighbors (MNN) method. (B) UMAP of Knight ADRC clusters. (C) iTF-microglia cluster clusters. Circle shows overlapping area between Mic.3 and iTF-microglia.8 (Chemokine) and iTF-microglia.9 (CCL13+ Chemokine).