

Systemic and brain immune dysregulation defines APOE ε4

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INTRODUCTION

APOE ε4 is the strongest genetic risk factor for late-onset Alzheimer's disease (AD), yet the biological pathways connecting genotype to disease risk remain incompletely defined. Emerging evidence implicates APOE ε4 in immune regulation, however, it remains unclear whether this is a primary, systemic biological state or arise secondarily in response to established AD pathology. To resolve this, we tested whether APOE ε4 defines a conserved immune phenotype across peripheral and central tissues, independent of clinical AD.

METHOD

We performed large-scale proteomic profiling across plasma (n = 9,028), cerebrospinal fluid (CSF; n = 1,099), dorsolateral prefrontal cortex (dlPFC; n = 720), and superior temporal gyrus (STG; n = 105) to identify immune signatures associated with APOE ε4 carriage across tissues. APOE ε4 associated proteins were identified using mutual information integrated with supervised machine learning modelling. Pathway and cell-type enrichment analyses were applied to identify systemic and brain-specific immune processes.

RESULTS

Across all tissues, APOE ε4 carriage was associated with a conserved, allele dose-dependent immune proteomic signature that was independent of AD. Supervised classification models reliably discriminated APOE ε4 carriers from non-carriers in plasma, CSF, dlPFC, and STG (AUC > 0.90).

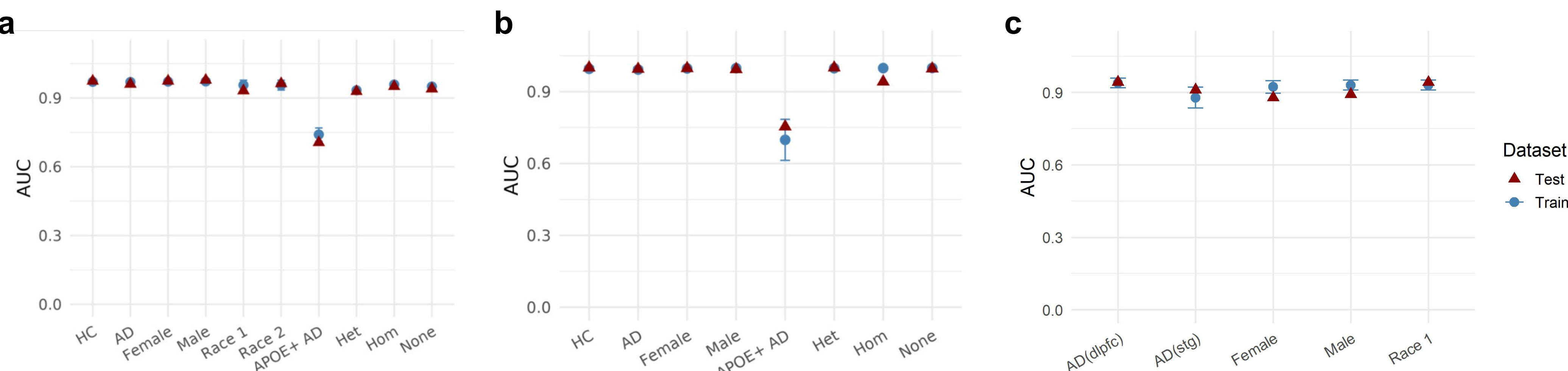


Fig. 1. Classification and regression tree modelling of APOE ε4 proteins across (a) plasma, (b) CSF, and (c) dlPFC and STG.

Across predictive APOE ε4 proteins, six proteins overlapped across the CSF and plasma (Fig. 2).

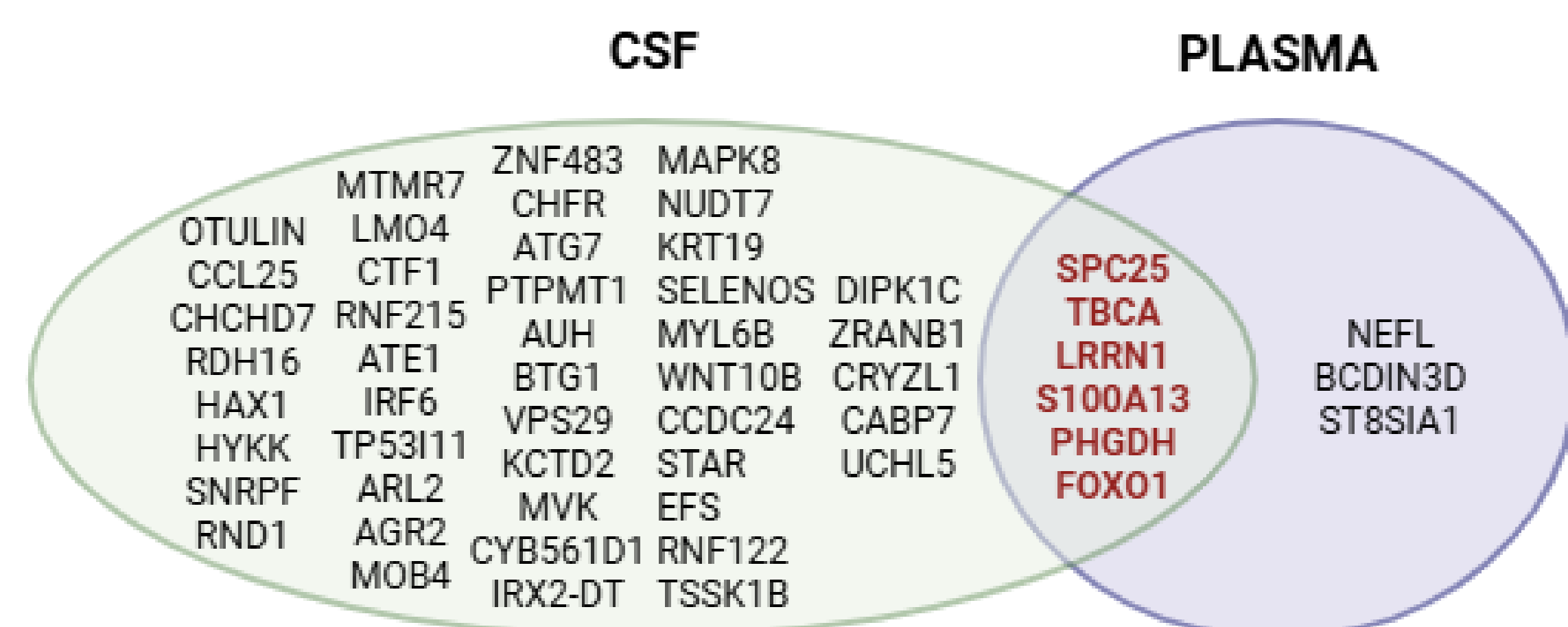


Fig. 2. Predictive APOE ε4 across the CSF and plasma.

Functional enrichment analyses demonstrated dominant involvement of innate and adaptive immune pathways, with consistent overrepresentation of antiviral, interferon, cytokine, and antigen-presentation signalling (Fig. 2a-b). Although a core set of immune pathways was shared across CSF and plasma (Fig. 3a), cortical regions exhibited distinct immune states characterized by region-specific pathway enrichment and directionality (Fig. 3b).

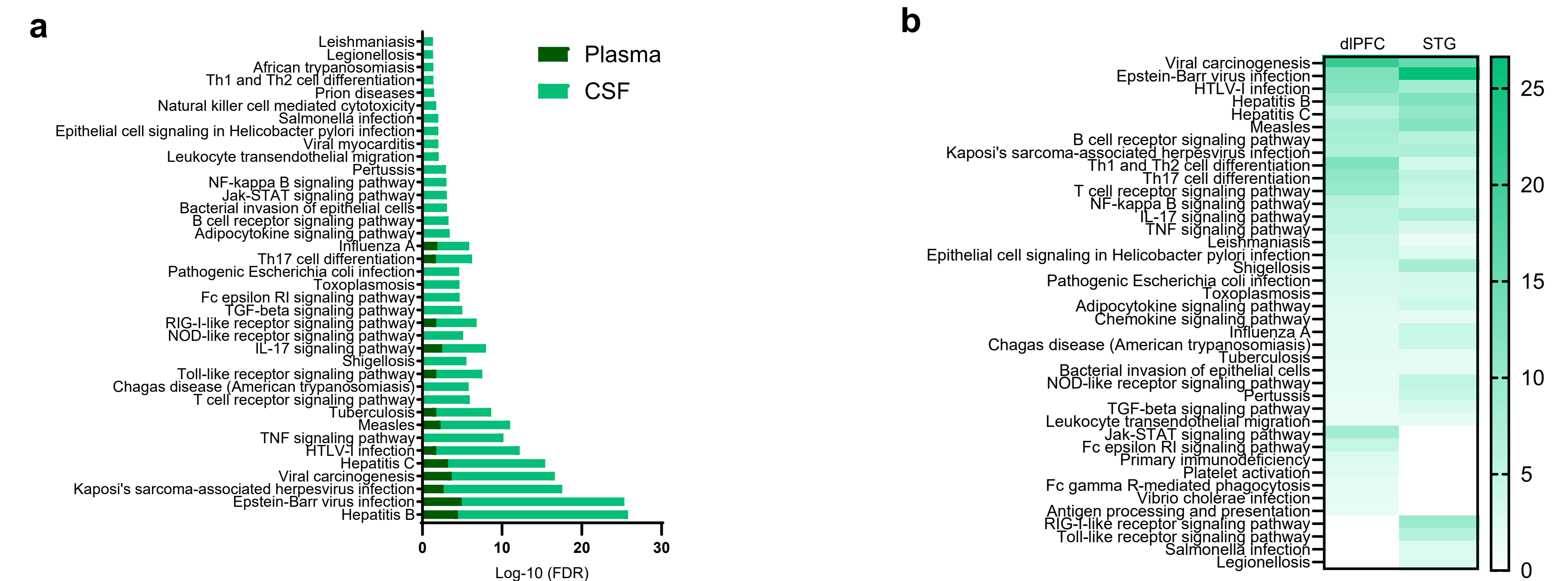


Fig. 3. KEGG immune pathway enrichment across (a) plasma and CSF (b) dlPFC and STG.

APOE ε4-associated proteins were preferentially expressed in adaptive immune cell populations (Fig. 4a), microglia, and cerebrovascular-associated cell types (Fig. 4b), implicating white-matter and neurovascular immune processes as central features of the APOE ε4 phenotype.

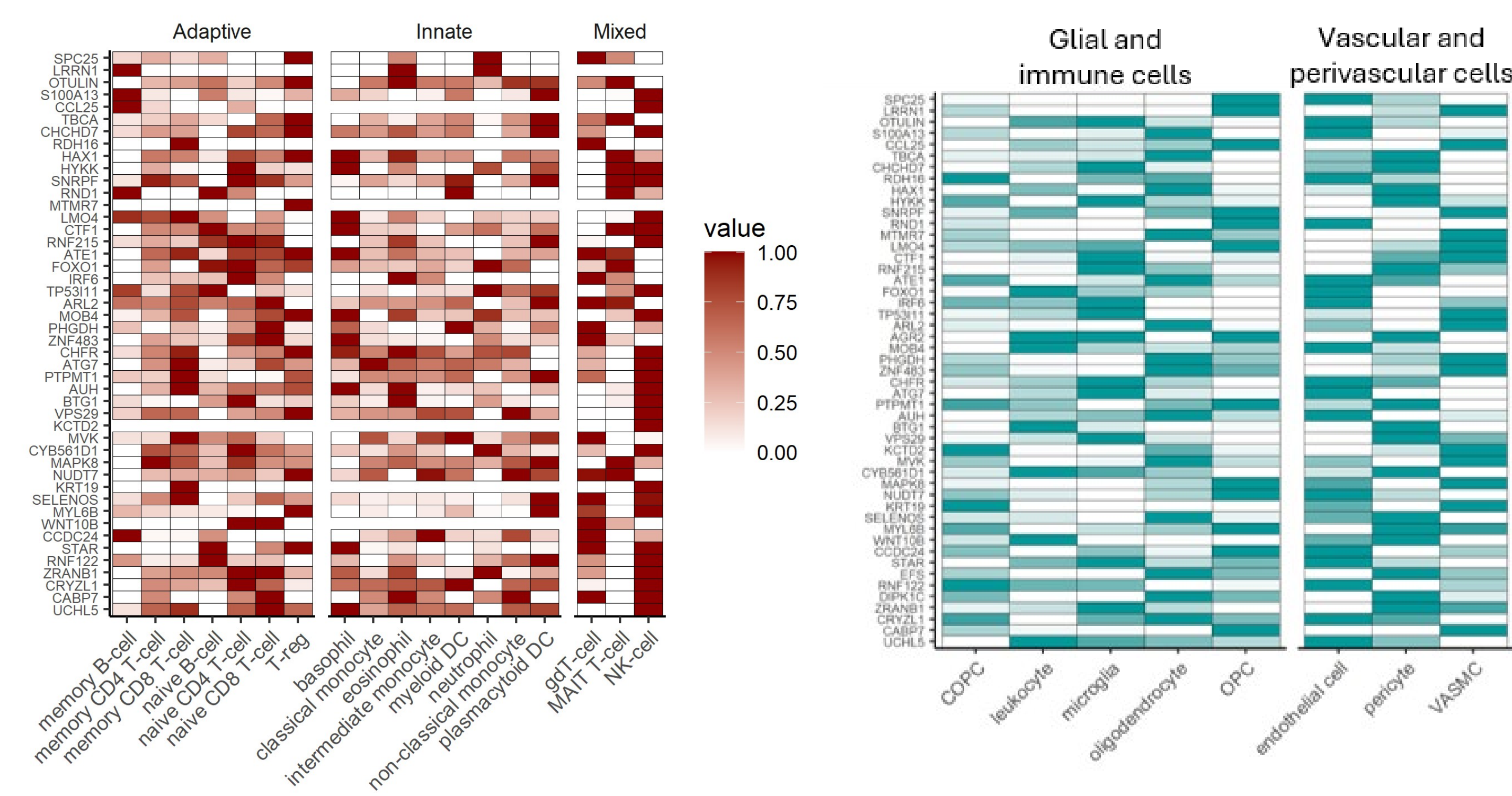


Fig. 4. Heatmap of cell-type enrichment of APOE ε4-associated (a) immune cell and (b) brain cell populations.

CONCLUSION

POE ε4 is associated with a robust, systemic pro-inflammatory immune phenotype that is detectable across the periphery and brain and independent of AD. Together, these findings support immune dysregulation as a defining biological feature of APOE ε4 carriage rather than a secondary consequence of neurodegeneration, with important implications for biomarker development, genetic risk stratification, and the prioritization of immune pathways for precision medicine approaches in AD.

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