

Supervised machine learning demonstrates peripheral inflammation precedes brain pathology in carriers of APOE4

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BACKGROUND

The **APOE4 allele** confers an elevated neurodegenerative risk, so protein profiles may be distinct in biofluids years before symptom onset.

Proteomic technologies can quantify thousands of proteins in numerous biofluids.

METHODS

Plasma and CSF collected from patients +/- APOE4 allele and +/- neuro disease.

Iterative linear discriminant analysis (iLDA) used as a dimensionality reduction tool.

Enrichment analysis to elucidate possible early-stage pathophysiology of APOE4 allele function.

RESULTS & DISCUSSION

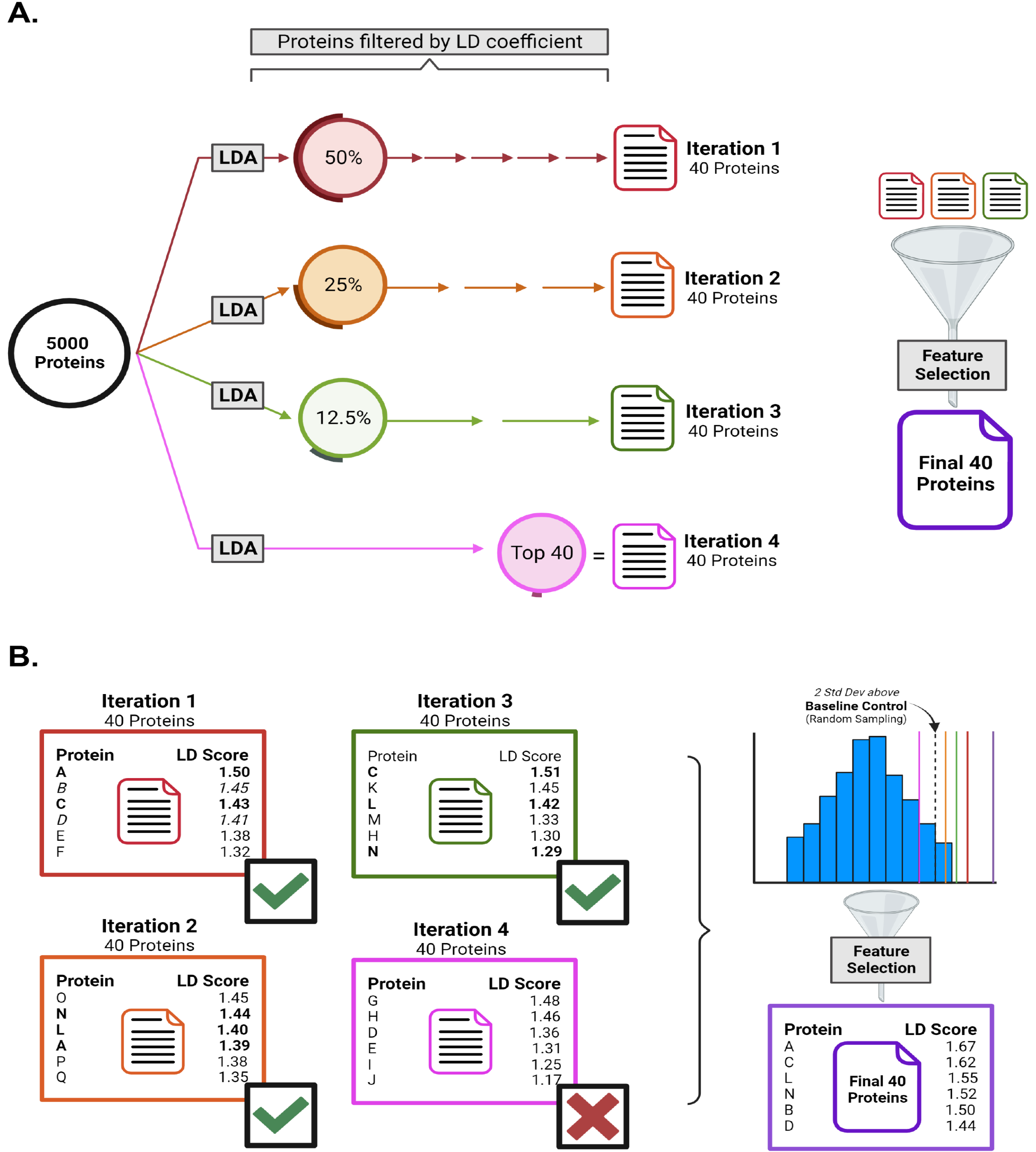
The iLDA successfully **identified a panel of proteins able to distinguish APOE4(+/-) status** in both healthy and diseased subjects.

Pathway analysis of plasma proteins in healthy APOE4+ individuals highlighted associations consistent with a **heightened immune response** while CSF proteins in diseased APOE4+ carriers were indicative of **BBB leakage**.

CONCLUSIONS

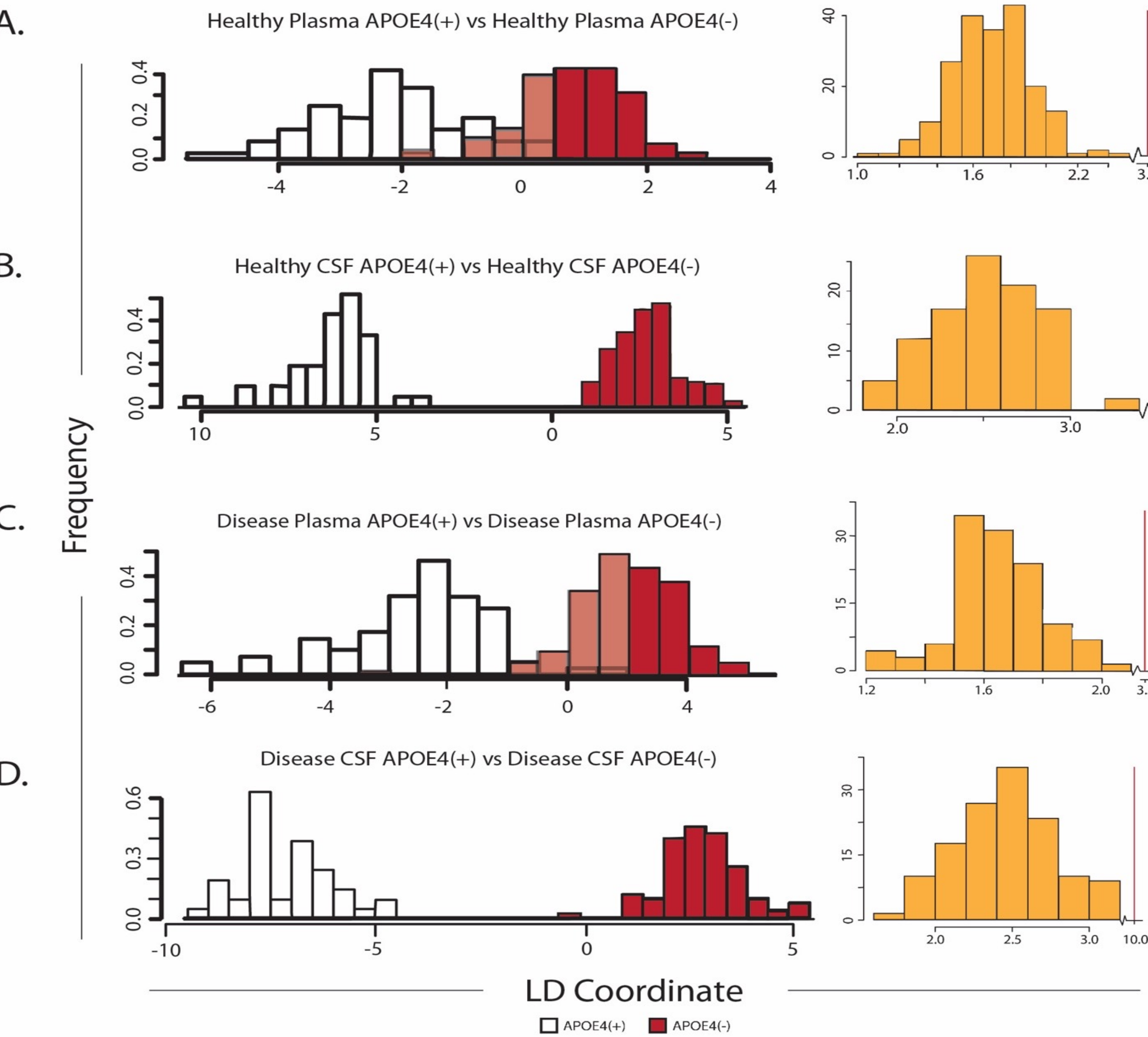
APOE4 carriers have unique protein signatures, and results of pathway analysis suggest that **peripheral inflammation may precede brain barrier dysfunction** and subsequent brain degeneration.

Multidimensional Iterative LDA Workflow



Our novel workflow to obtain 40 proteins of interest from our initial list of 5000 proteins when comparing two groups using iterative LDAs. After obtaining our list, the mean difference of LD1 scores was calculated and compared to sample-matched control values.

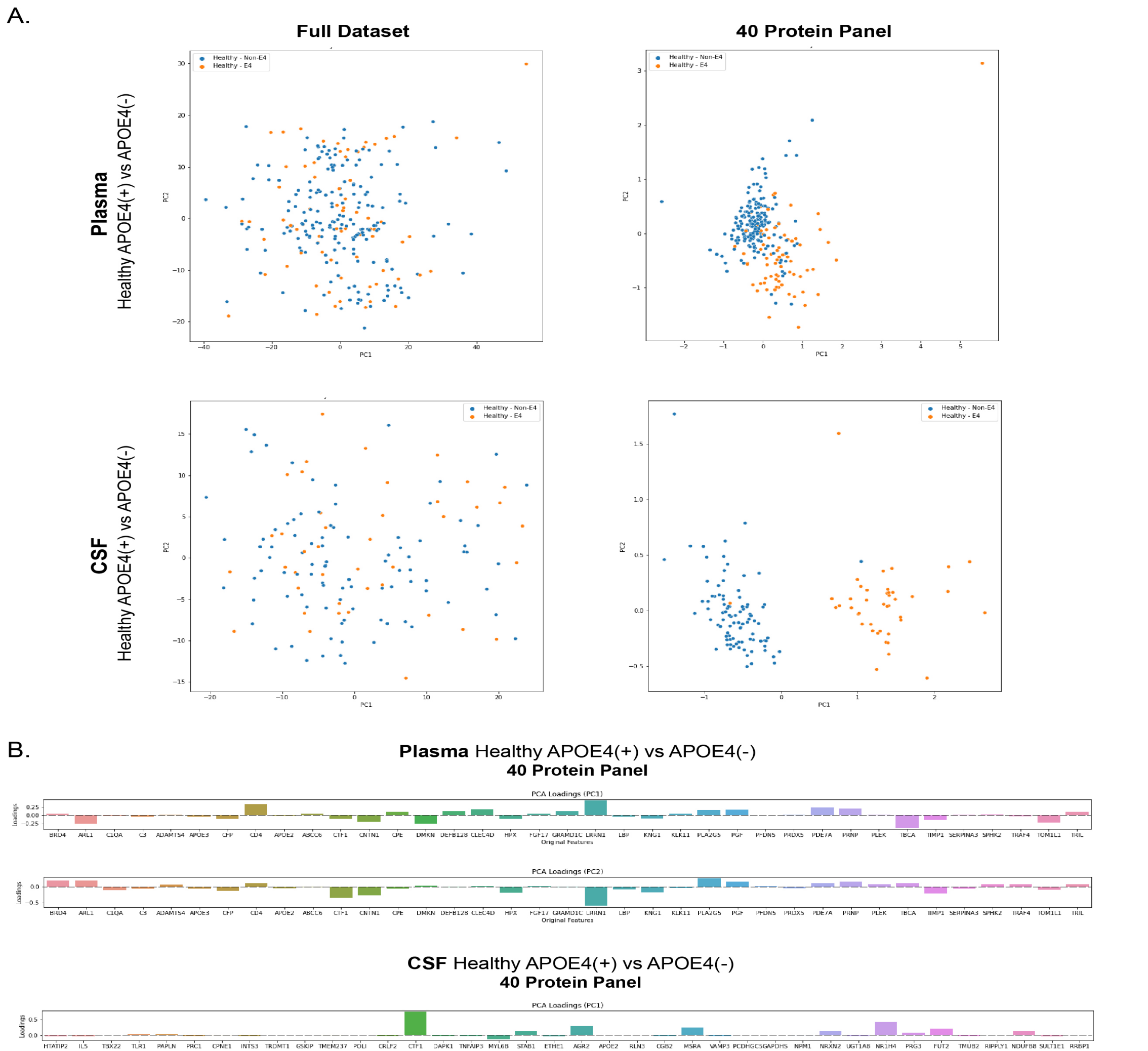
LDA Separation of Plasma Proteins



LDA separation by APOE4 status of healthy individuals in plasma (A) and CSF (B) as well as for diseased individuals in plasma (C) and CSF (D) from list of top 40 proteins.

Sample-matched controls were generated for each comparison, and the mean from the APOE4 comparison was plotted versus controls. A mean percentile was then calculated (All results 100th percentile).

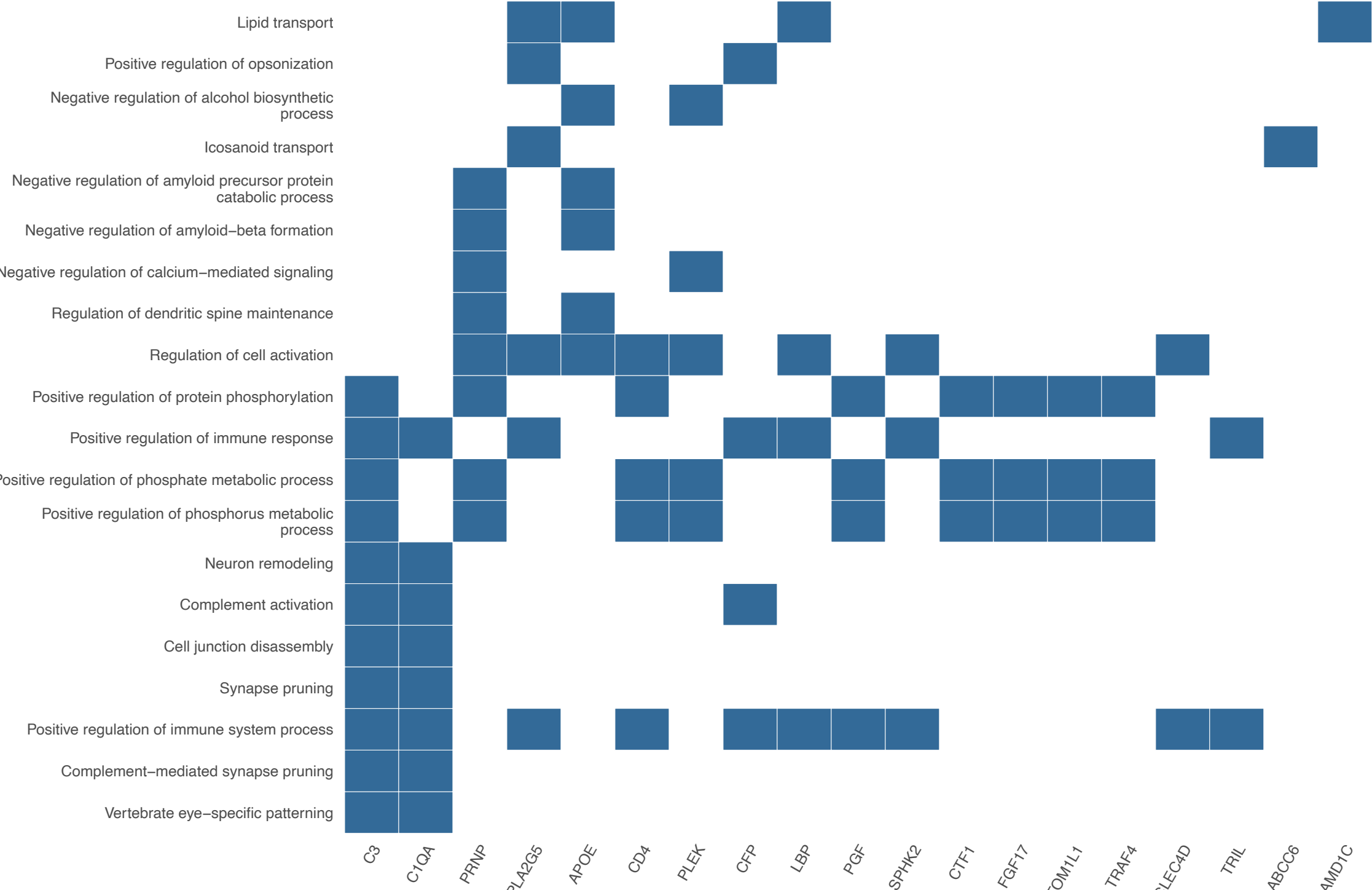
APOE4 Proteins of Interest



PCA for all proteins grouped by APOE status in plasma (top left) and CSF (bottom left). A subsequent PCA was then performed from the 40 proteins from our LDA analysis for plasma (top right) and CSF (bottom right).

Pathway Analysis

APOE4 Plasma – Early Inflammation



Our analysis highlighted heightened activation patterns of potentially pathological immune states and synaptic restructuring in the periphery (plasma) of healthy APOE4+ subjects prior to any clinical indications of disease. This finding may suggest that the neurodegenerative and APOE4+-mediated changes in protein expression may begin, at least in part, in the periphery.

ACKNOWLEDGEMENTS

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