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Large-scale proteomics analysis of Alzheimer's Disease plasma blood reveals sex and APOE specific signatures

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Abstract

Background: Age, sex, and APOE4 genotype are key non-modifiable risk factors for Alzheimer's disease (AD), with APOE4 significantly increasing risk, especially in women. The APOE-sex (APOE-SX) interaction underscores the need for personalized AD treatments. We analyzed plasma blood proteomic data from the UK Biobank to identify sex and APOE-specific protein and pathway signatures.

Method: Plasma samples were analyzed for AD-diagnosed participants and controls. After propensity-score matching on age and education level, 199 AD cases (133 F) and 199 controls (104 F) from APOE3/3, 3/4 and 4/4 individuals were retained. Protein levels were normalized using z-scores and a two-step approach of within-batch and across-batches intensity normalization. For each APOE-SX condition, differentially expressed proteins (DEPs, p-value < 0.05) between AD and controls were identified using linear regression with empirical Bayes estimators to calibrate per-protein variance using information from all proteins. Gene Set Enrichment Analysis (GSEA) was subsequently conducted using Gene Ontology Biological Processes (GO-BP) accounting for DEP fold change. Redundant GO-BP terms (adjusted p-values<0.05) were removed (GO-BP semantic similarity cut-off of 0.6). Comparison analyses were then conducted to identify common and unique DEPs and enriched GO-BPs across APOE-SX conditions. To achieve this, heatmaps were generated to visualize the overlap and differences in protein expression and pathway enrichment across groups, enabling systematic between-group comparisons.

Result: Differential expression analysis identified 95 common DEPs in females and 7 DEPs among APOE4 carriers, while no GO-BPs were shared across all sex-genotype subgroups. Female APOE4 carriers exhibited the highest number of DEPs (F4/4: $n = 759$; F3/4: $n = 698$) while male APOE3 carriers had the lowest ($n = 102$), but the number of enriched GO-BPs was comparable to across APOE-SX conditions, suggesting that a greater number of dysregulated proteins are involved in a limited set of biological processes. GO-BPs were predominantly downregulated

in females and upregulated in males. Notably, humoral immune response mediated by circulating immunoglobulin was uniquely upregulated in F4/4, whereas interferon-gamma response was a shared pathway in males across APOE genotypes.

Conclusion: These findings suggest APOE-SX specific proteomic signatures and altered biological processes in AD, highlight strong sex differences in AD plasma proteomics and support the development of personalized therapeutics considering APOE-SX interaction.