a. Title

Blood and Brain Transcriptome Analysis Reveals *APOE* Genotype-Mediated and Immune-Related Pathways Involved in Alzheimer Disease

b. Introduction

Alzheimer disease (AD) is typically viewed as a brain disorder, yet blood-based biomarkers may help diagnose or predict AD-related brain pathology. The *APOE* ε4 allele is noted for cerebrovascular effects, including acceleration of blood-brain barrier (BBB) breakdown. The study aimed to analyze blood and brain transcriptomes (stratified by *APOE* genotype) to identify AD-related differential expression, pathways, and gene networks shared across tissues.

c. Main Content

Methods

Differential expression of established AD genes in brains from 344 pathologically confirmed AD cases and 232 controls and in blood from 112 pathologically confirmed AD cases and 67 controls (ROSMAP) was evaluated. Blood and brain differential expression were analyzed jointly using a multivariate approach in the total sample and within *APOE* genotype groups. Gene set enrichment analysis (within *APOE* groups) and WGCNA co-expression network analyses were conducted in brain and blood. Top-ranked genes from pathways and networks were further evaluated against vascular injury traits.

Results

In both brain and blood, two established AD genes showed nominal differential expression ($P < 0.05$): INPP5D (upregulated) and HLA-DQA1 (downregulated). Two genes reached transcriptome-wide significance within specific *APOE* groups: PIGHP1 (ε2/ε3; $P < 3.3 \times 10^{-6}$) and FRAS1 (ε3/ε4; $P < 3.3 \times 10^{-6}$). Gene set enrichment identified 21 significant pathways (FDR $P < 0.05$) in at least one *APOE* group. 10 pathways were enriched in the ε3/ε4 group, with six unique to that group. Four pathways (allograft rejection, interferon gamma response, peroxisome, and TNFA signaling via NFKB) were enriched for AD upregulated genes in ε3/ε4 but for AD downregulated genes in subjects lacking ε4. A co-expressed gene network in brain reproduced in blood and showed higher average expression in ε4 carriers. 23 genes from pathway/network analyses were significantly associated with at least one vascular injury trait.

Discussion

Overall, findings indicate *APOE* genotype-dependent transcriptomic profiles shared across blood and brain. Several implicated genes and networks were associated with vascular injury measures, supporting a potential link to ε4-related BBB effects.

d. Conclusion

The study concludes that jointly evaluating blood and brain transcriptome data together with genetic information helps identify meaningful correlations between blood gene expression and AD-related brain measures, and highlights the need for further studies on *APOE* genotype-contextual genes and pathways in relation to BBB dysfunction and AD pathology.

e. References

Panitch, R., Hu, J., Xia, W., Bennett, D. A., Stein, T. D., Farrer, L. A., & Jun, G. R. (2022). Blood and brain transcriptome analysis reveals *APOE* genotype-mediated and immune-related pathways involved in Alzheimer disease. *Alzheimer's Research & Therapy, 14*, 30. https://doi.org/10.1186/s13195-022-00975-z