Bioinformatics Research Starter Program by Omics Lite

Week 1 Assignment: Paper Summary (Transcriptomics)

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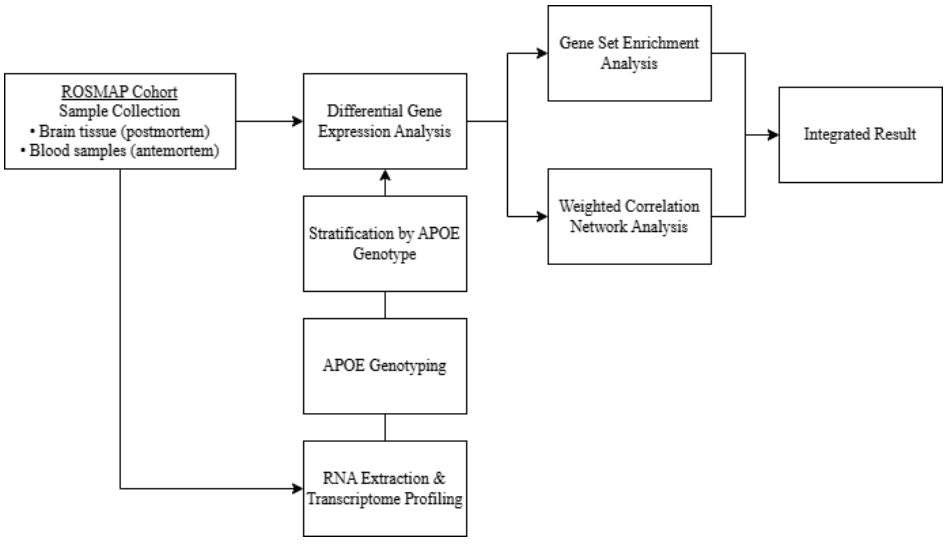
Article Title	Blood and brain transcriptome analysis reveals *APOE* genotype-mediated and immune-related pathways involved in Alzheimer disease
Introduction	
Background	**What is Alzheimer Disease?** Alzheimer's disease (AD) is a neurodegenerative disorder marked by the presence of amyloid plaques and neurofibrillary tau tangles in the brain. These pathological proteins can even be detected in the blood before clinical symptoms appear. **Mechanism** The pathogenesis of AD is mainly related to the accumulation of amyloid-β (Aβ) in the brain. Aβ accumulation triggers neuroinflammation, oxidative stress, and synaptic dysfunction. Aβ deposition can also occur in the walls of cerebral blood vessels and cause cerebral amyloid angiopathy (CAA), which contributes to blood–brain barrier (BBB) dysfunction. BBB dysfunction further exacerbates Aβ accumulation and tau protein hyperphosphorylation, accelerating the neurodegenerative process. **Contributing Genetic Factors** The main genetic factor influencing these mechanisms is the APOE gene. The ε4 allele plays a role in decreasing Aβ clearance efficiency, disrupting BBB stability, and increasing inflammatory responses, thereby accelerating the Alzheimer's pathophysiological cascade compared to the ε3 genotype. In contrast, the ε2 allele is relatively protective against disease progression. In addition, cerebrovascular pathology associated with AD shows a pattern dependent on the APOE genotype, with ε2 and ε4 reported to be associated with an increased risk of CAA.
Context	Previous transcriptomic studies have shown that the classical complement cascade and tau phosphorylation are specifically associated with Alzheimer's disease based on APOE genotype, but the expression profiles associated with Alzheimer's disease from blood and brain samples from the same individuals have not been studied, especially when stratified by APOE genotype.
Research Purposes	Identify genes and biological pathways related to Alzheimer's disease (AD) that show differences in expression between case and control groups in blood and brain tissue samples. Analysis was performed after stratification based on APOE genotype

Research Content	
Method	I. Specimens Samples were obtained from the Religious Orders Study and the Rush Memory and Aging Project. A. AD cases (pathologically confirmed): - Brain tissue: 344 samples - Blood: 112 samples B. Controls: - Brain tissue: 232 samples - Blood: 67 samples II. Analysis A. Differential Gene Expression Analysis Differences in gene expression between AD cases and controls in blood and brain samples were analyzed using multivariate methods 1. In the overall sample 2. After stratification based on APOE genotype B. Gene Set Enrichment Analysis Performed in each APOE genotype group based on the results of combined blood and brain analysis to identify significant biological pathways C. Weighted Correlation Network Analysis To analyze gene co-expression networks in blood and brain samples. The highest-ranked genes from these networks and biological pathways were then further evaluated for vascular injury characteristics.
Method Visualization	
Result	A. Differential Gene Expression Analysis Previously known AD genes show differential expression in blood and brain - INPP5D → increased (upregulated) - HLA-DQA1 → decreased (downregulated)

	Transcriptome-wide analysis identified: - PIGHP1 → significant in the ε2/ε3 genotype group - FRAS1 → significant in the ε3/ε4 genotype group after stratification based on the APOE gene. B. Gene Set Enrichment Analysis - A total of 21 biological pathways showed statistical significance (FDR < 0.05) in at least one APOE genotype group. - Ten significant pathways were identified in the ε3/ε4 group, and six of them showed exclusive significance in that group. - Four pathways (allograft rejection, interferon gamma response, peroxisome, and TNFA signalling via NFKB) showed increased gene expression in AD cases in the ε3/ε4 group, but showed a pattern of decreased expression in subjects without the ε4 allele. C. Weighted Correlation Network Analysis - Co-expression gene networks were identified in brain tissue that could be replicated in blood samples. - These networks showed higher average expression in ε4 allele carriers. - A total of 23 genes from pathway and network analyses were significantly associated with at least one characteristic of vascular injury.
Discussion	This study aims to identify genes and biological pathways associated with Alzheimer's disease (AD) that show differences in expression between cases and controls in blood and brain, particularly in a genotype-specific manner towards APOE. Two known AD genes, INPP5D and HLA-DQA1, were found to exhibit consistent changes in expression in both tissues. Of the 21 major biological pathways identified, 10 were specific to individuals with the ε3/ε4 genotype. Several major inflammatory pathways (allograft rejection, interferon gamma response, peroxisome, and TNFA signalling via NFKB) showed increased expression patterns in ε4 carriers and decreased patterns in non-ε4 carriers, indicating different molecular mechanisms depending on APOE genotype. These pathways are known to play a role in inflammatory processes, lipid metabolism, and blood-brain barrier (BBB) dysfunction. BBB dysfunction has been associated with early cognitive decline and neuroinflammation, and is known to be more prominent in ε4 carriers. Several identified genes (including INPP5D, HLA-DQA1, FRAS1, FOSL1, TRIP10, VASP, and C4B) are associated with immune processes, microglial activation, and vascular integrity regulation.

	Furthermore, genes in co-expression pathways and networks maintained between the brain and blood showed significant associations with vascular injury proteins such as ICAM-1, VCAM-1, and SAA, which are markers of BBB disruption and systemic inflammation. **These findings reinforce the hypothesis that in ε4 carriers, the pathogenesis of AD involves interactions between inflammation, the immune system, and vascular damage.** However, this study has limitations, including a relatively small blood sample size, the presence of batch effects, limitations in blood cell type analysis, and the correlational rather than causal nature of co-expression network analysis. Therefore, **further experimental studies are needed to confirm the proposed biological mechanisms**.
Conclusion	- This study shows the importance of evaluating brain and blood transcriptomic data together with genetic information obtained from the same individuals to identify significant correlation between biomarker and AD related protein. - Further studies are needed to investigate how the genes and biological pathways identified in this study in the context of the APOE genotype affect the blood-brain barrier (BBB) and contribute to and/or exacerbate AD-related pathology.