Blood and brain transcriptome analysis reveals APOE genotype-mediated and immune-related pathways involved in Alzheimer disease

Background

Alzheimer disease (AD) is a neurodegenerative disease caused by amyloid plaques and neurofibrillary tau tangles in the brain. A multi-omics approach used in this research to identify disease in blood and brain based on genotype APOE. The research aims to facilitate the detection of this disease preclinically with deep understanding of genetic factors, blood-brain barrier (BBB) dysfunction, and gene expression.

Methods

This research utilizes RNA-seq data analysis from blood (614 participants) and brain (639 participants) via the ROSMAP study. Gene expression was quantified using STAR and RSEM, followed by differential expression analysis between Alzheimer's cases and controls using VOOM/LIMMA. Blood-brain data integration was performed through O'Brien's method and meta-analysis. Additionally, WGCNA was employed to identify conserved gene networks across both tissues, complemented by biological pathway validation and measurements of vascular injury proteins (ICAM-1, VCAM-1, SAA) in brain tissue lysates.

Results

In analyses stratified by APOE genotype, only a small number of genes showed strong differential expression between Alzheimer's disease (AD) cases and controls. In individuals with the ε2/ε3 genotype, PIGHP1 was significantly upregulated at the transcriptome-wide level in the combined blood and brain data, with the effect mainly driven by brain expression but also observable in blood. In contrast, among ε3/ε4 individuals, FRAS1 was significantly downregulated in AD cases, but this effect was detected only in blood samples. No transcriptome-wide significant differentially expressed genes were identified in brain tissue alone across any APOE genotype group.

Discussion

This discussion highlights that Alzheimer's disease–related gene expression changes occur in both blood and brain and are strongly influenced by APOE genotype. Key immune-related genes, especially INPP5D and HLA-DQA1, were consistently upregulated and linked to neuroinflammation and blood–brain barrier (BBB) dysfunction, particularly in ε4 carriers. Several APOE ε3/ε4–specific pathways were enriched, many involving inflammatory and vascular processes. Genes within the shared brain–blood co-expression networks were also associated with vascular injury markers, suggesting BBB involvement. Overall, the findings support a model where APOE genotype shapes immune, vascular, and BBB-related molecular mechanisms contributing to AD.

Conclusion

This study demonstrates that integrating brain and blood gene expression data with genetic information from the same individuals is important for identifying biologically meaningful links

between blood biomarkers and Alzheimer's disease–related brain proteins. By considering APOE genotype, the results show that gene expression patterns and pathways associated with AD may differ across genetic backgrounds and are closely related to vascular and blood–brain barrier (BBB) processes. These findings highlight the value of multi-tissue and genotype-specific approaches. Future research is needed to clarify how the identified genes and pathways affect BBB function and how they contribute to the development and progression of Alzheimer's disease.

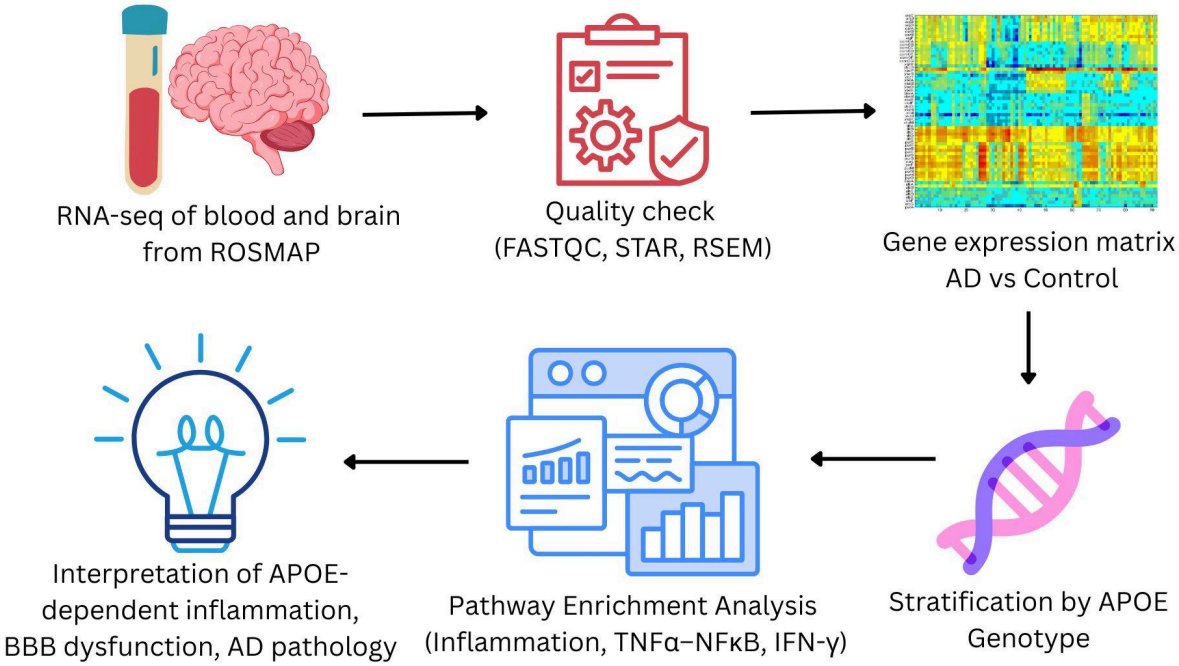

Figure 1. Diagram of methods and results

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Pendahuluan

Penyakit Alzheimer (AD) merupakan penyakit neurodegeneratif yang ditandai oleh plak amiloid dan kekusutan *neurofibrillary tau* pada otak. Penelitian ini menggunakan pendekatan multi-omik untuk mengidentifikasi tanda-tanda penyakit pada darah dan otak berdasarkan genotip APOE. Tujuannya adalah mendeteksi Alzheimer secara dini (pre klinis) dengan memahami hubungan antara faktor genetik, disfungsi *blood-brain barrier* (BBB), dan ekspresi gen.

Metode

Metode penelitian ini menggunakan analisis data RNA-seq dari darah (614 peserta) dan otak (639 peserta) melalui studi ROSMAP. Ekspresi gen dihitung menggunakan STAR dan RSEM, kemudian dilakukan analisis ekspresi diferensial antara kasus Alzheimer dan kontrol menggunakan VOOM/LIMMA. Integrasi data darah-otak dilakukan melalui metode O'Brien dan meta-analisis. Selain itu, digunakan teknik WGCNA untuk mengidentifikasi jaringan gen yang terkonservasi di kedua jaringan, serta dilakukan validasi jalur biologis melalui analisis lanjutan dan pengukuran protein cedera vaskular (ICAM-1, VCAM-1, SAA) pada lisat jaringan otak.

Hasil

Pada analisis yang dibagi berdasarkan genotip APOE, hanya sedikit gen yang menunjukkan perbedaan ekspresi yang kuat antara kasus Alzheimer dan kontrol. Pada individu dengan genotipe ε2/ε3, gen PIGHP1 mengalami peningkatan ekspresi yang signifikan secara transkriptom, terutama didorong oleh data dari otak, namun juga terlihat pada darah. Sementara itu, pada kelompok ε3/ε4, gen FRAS1 menunjukkan penurunan ekspresi yang signifikan pada penderita Alzheimer, tetapi hanya terdeteksi pada sampel darah. Tidak ditemukan gen yang berbeda secara signifikan pada tingkat transkriptom di jaringan otak saja pada semua kelompok genotip APOE.

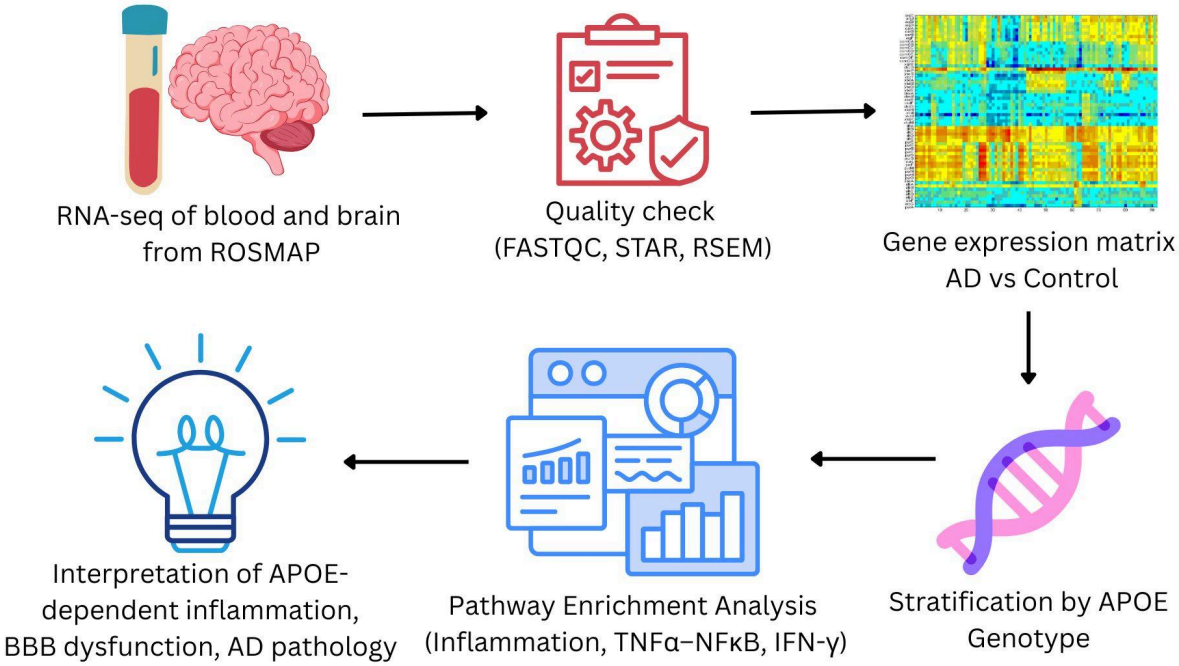
Pembahasan

Pembahasan ini menunjukkan bahwa perubahan ekspresi gen terkait Alzheimer terjadi baik di darah maupun otak dan sangat dipengaruhi oleh genotipe APOE. Gen imun utama seperti INPP5D dan HLA-DQA1 meningkat konsisten dan berkaitan dengan peradangan saraf serta gangguan blood–brain barrier (BBB), terutama pada pembawa alel ε4. Beberapa jalur biologis spesifik ε3/ε4 yang berkaitan dengan inflamasi dan vaskular juga teridentifikasi. Selain itu, gen dalam jaringan ko-ekspresi yang sama di otak dan darah berhubungan dengan penanda kerusakan vaskular. Secara umum, hasil ini menegaskan peran APOE dalam mengatur mekanisme imun, vaskular, dan BBB pada Alzheimer.

Kesimpulan

Studi ini menunjukkan bahwa penggabungan data ekspresi gen dari otak dan darah dengan informasi genetik dari individu yang sama sangat penting untuk mengidentifikasi hubungan biologis yang berarti antara biomarker darah dan protein terkait Alzheimer di otak. Dengan mempertimbangkan genotip APOE, hasil penelitian menunjukkan bahwa pola ekspresi gen dan

jalur biologis terkait Alzheimer berbeda antar latar belakang genetik dan berkaitan erat dengan proses vaskular serta fungsi blood–brain barrier (BBB). Dengan demikian penting untuk melakukan pendekatan multi-jaringan dan spesifik genotipe. Penelitian lanjutan diperlukan untuk memahami peran gen dan jalur ini dalam gangguan BBB dan perkembangan penyakit Alzheimer.



Gambar 1. Diagram metodologi dan hasil