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BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

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GENETICS

Influence of APOEε4 on Blood Transcriptomics in Cognitively Impaired Individuals

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Abstract

Background: The APOEε4 allele is a well-known genetic risk factor for sporadic Alzheimer's disease (AD). However, its influence on gene expression in peripheral blood remains underexplored. This study aimed to investigate the influence of the ε4 allele on blood gene expression in cognitively unimpaired (CU) and impaired (CI) individuals.

Method: We selected 423 individuals from the ADNI database with available APOE status, clinical diagnosis, and blood microarray data. CU and CI individuals were divided into ε4 carriers ($n = 184$) and non-carriers ($n = 239$) (Table.1). Differentially expressed genes (DEGs) between CU and CI individuals stratified by APOEε4 carriership were analyzed in R using the Limma package. Linear models were performed to associate DEGs with CSF Aβ42, pTau181, total-Tau, and FDG-PET ($p < 0.05$). In addition, pathway enrichment analysis using Gene Ontology (GO) and KEGG was performed for up and downregulated genes across groups.

Results: The CU vs. CI comparison identified 607 upregulated and 593 downregulated genes in carriers, while non-carriers showed 501 upregulated and 390 downregulated genes (Figure 1A-B). In the enrichment analyses, carriers revealed upregulated pathways related to innate immunity, neutrophil degranulation, MAPK cascade, and GTPase signaling, while downregulated pathways were associated with ribosome biogenesis, mitochondrial function, cell cycle regulation, and RNA metabolism. For non-carriers, only upregulated pathways showed significant enrichment, primarily in ubiquitin-related processes and Golgi vesicle transport and organization (Figure 1B-C). Linear regressions identified 106 upregulated genes (70 carriers, 36 non-carriers) and 79 downregulated genes (55 carriers, 24 non-carriers) influencing at least one biomarker (CSF Aβ42, pTau181, total-Tau, or FDG-PET). Among carriers, FDG-PET emerged as a notable biomarker, showing a negative association with most upregulated

genes (60) and a positive association with most downregulated genes (39). Conversely, Aβ42 was the most altered biomarker in non-carriers, following a similar pattern to FDG-PET in carriers, being negatively associated with 31 upregulated genes and positively associated with 15 downregulated genes (Figure 2A-B).

Conclusion: Our findings suggest the APOEε4 allele influences blood gene expression in CI individuals, leading to distinct transcriptomic signatures and pathophysiological pathways. Additionally, distinct gene expression patterns in carriers and non-carriers impact biomarker variability, notably FDG-PET and Aβ42.

Table.1 - Demographic overview of the study population

	ε4 CARRIERS				NON-CARRIERS			
	CU	MCI	CI	TOTAL	CU	MCI	CI	TOTAL
Sample size	37	100	47	184	97	124	18	239
Female, n (%)	23 (62 %)	45 (45 %)	21 (44 %)	89 (48 %)	49 (50.5 %)	52 (42 %)	8 (44.5 %)	109 (45.6 %)
Age, mean ± SD	72.8 (± 5.9)	70.3 (± 7.1)	72.2 (± 6.7)	71.3 (± 6.8)	73.7 (± 5.8)	72.1 (± 7.3)	77.9 (± 7.5)	73.2 (± 6.9)
MMSE, mean ± SD	28.9 (± 1.2)	27.8 (± 1.8)	21.8 (± 3.8)	26.5 (± 3.6)	29.2 (± 1)	28.2 (± 1.5)	20.6 (± 3.6)	28 (± 2.7)
CSF Aβ+*	17 (65 %)	55 (73.4 %)	27 (96.4 %)	95 (77 %)	12 (21 %)	34 (34.4 %)	5 (62.5 %)	51 (31 %)

*Not all of the population had data available.

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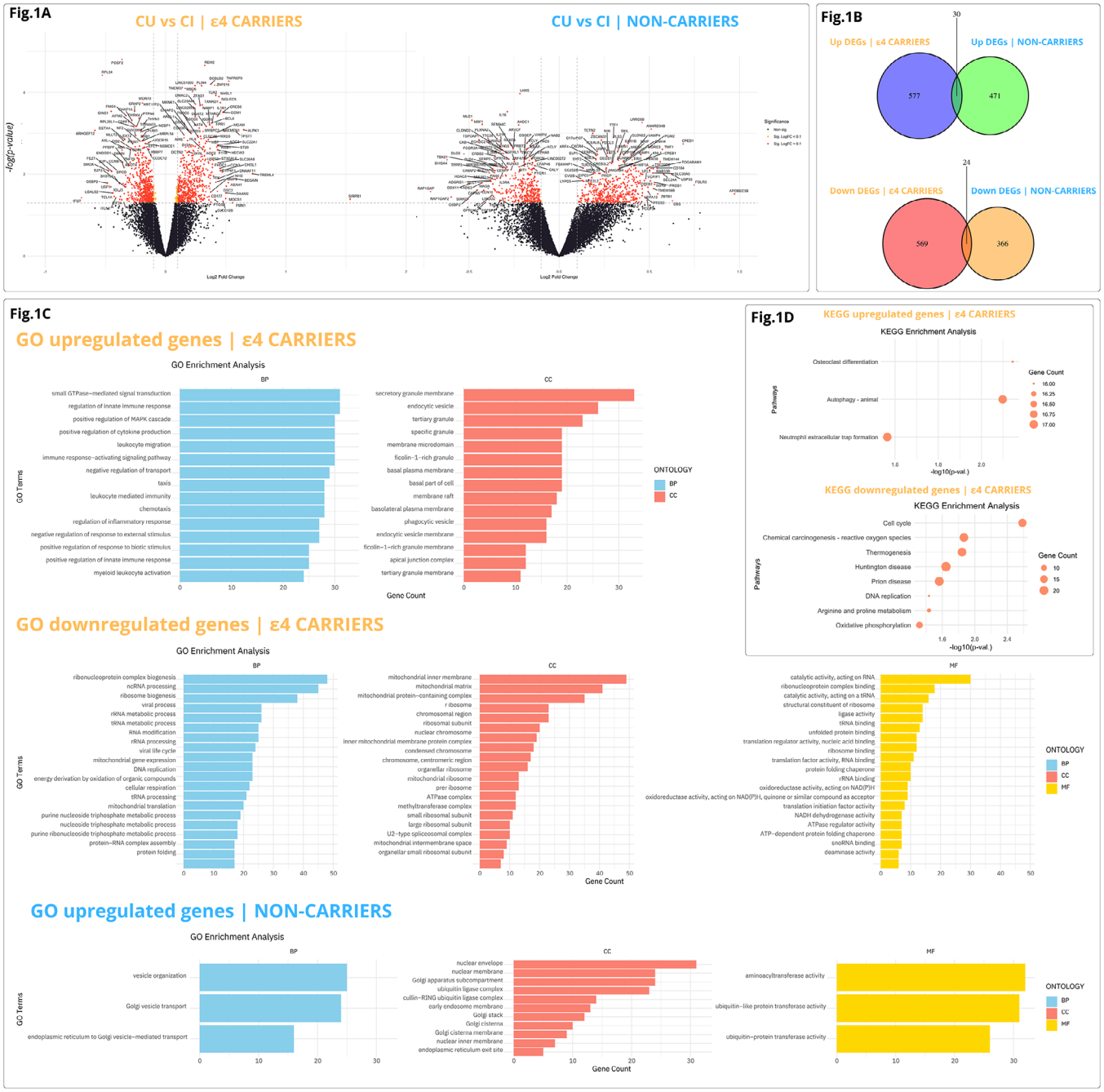

Figure 1: Volcano plot, Gene Ontology (GO) andKEGG results of differentially expressed genes (DEGs). (A) Volcano plot of differentially expressed genes (DEGs) between cognitively unimpaired (CU) and cognitively impaired (CI) individuals and ε4 carriers and non-carriers. Black dots represent non-significant genes and red dots represent significant ones. **(B)** Shared DEGs among ε4 carriers and non-carriers for upregulated genes (30 genes) and downregulated genes (24 genes) **(C)** Gene Ontology (GO) enrichment was performed for upregulated and downregulated genes in ε4 carriers, as well as for upregulated genes in non-carriers. Blue color represents Biological processes, red represents Celular Component, and yellow represents Molecular Function. **(D)** KEGGs of upregulated and downregulated genes in ε4 carriers. The size of the circles represents the number of genes sharing the term, while "-log10(p-val)" represents the number of zeros following the decimal point. **Acronyms:** CU: cognitively unimpaired; CI: cognitively impaired; DEGs: differentially expressed genes; GO: gene ontology; BP: biological process; CC: cellular component; MF: molecular function;

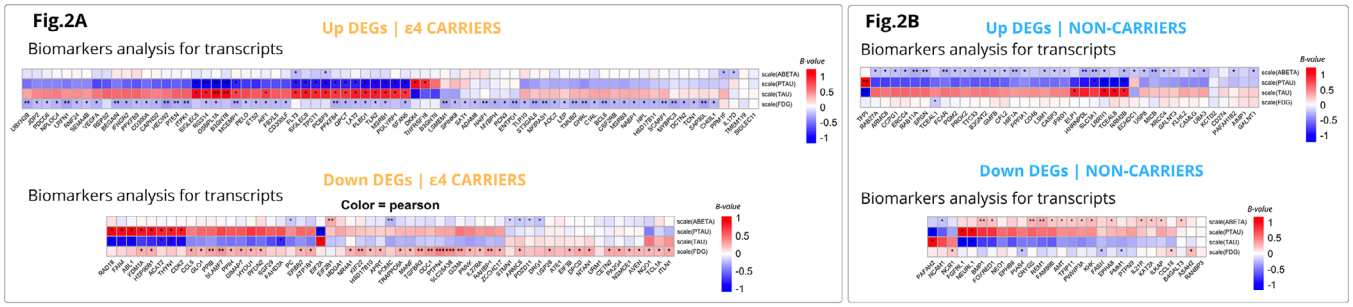

Figure 2: Linear regression analysis of differentially expressed genes (DEGs). (A) Linear regression associating up and downregulated ε4 carriers DEGs with Alzheimer's Disease biomarkers. **(B)** Linear regression associating up and downregulated non-carriers DEGs with Alzheimer's Disease biomarkers. Red squares represent positive associations and blue squares represent negative associations. Also, colors represent beta values. Each "*" represent a significant association (FDR-p-val. < 0.05). **Acronyms:** DEGs: differentially expressed genes;