Association Of Apolipoprotein E Genotype And Blood-based Biomarkers In The Cog-aging Cohort Study

Maurício Lemos Bueno Fontes[1,2], Joice Coutinho Alvarenga[2,3], Rafaela D'Angelo Machado[2,4], Giovanna Correia Pereira Moro[1,2], João Arthur Rodrigues Barbosa[5], Gabriela Tomé Oliveira Engelmann[2,3], Jonas Jardim de Paula[3,6], Marco Aurélio Fagundes Angelo[7], Anja Schneider[8], Pamela Martino Adami[9], Maria Carolina DALMASSO, PhD[10], Débora Marques de Miranda[11,3], Marco Aurélio Romano-Silva[3,11], Luiz Armando Cunha de Marco[3,11], Bernardo de Mattos Viana[3,6], Alfredo Ramírez Zuniga[9,8], MARIA APARECIDA BICALHO, PhD[3,12].

[1]Undergraduate Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil, [2]Cog-Aging Research Group, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [3]Molecular Medicine Postgraduate Program, School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil, [4]Undergraduate Psychology, Faculty of Health Sciences of Minas Gerais, Belo Horizonte, Brazil, [5]Older Adult's Psychiatry and Psychology Extension Program (PROEPSI), School of Medicine, Universade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil, [6]Department of Psychiatry, School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil, [7]Federal University of Minas Gerais, Belo Horizonte, Brazil, [8]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany, [9]Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, [10]Neuroscience and Complex Systems Unit - CONICET, Florencio Varela, Argentina, [11]Neurotec R National Institute of Science and Technology (INCT-Neurotec R), Faculty of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil, [12]Department of Internal Medicine, School of Medicine, Federal University of Minas gerais, Belo Horizonte, Brazil.

#7446

BACKGROUND

- Variations in blood-based biomarkers (BBM) have been reported across different apolipoprotein E (APOE) genotypes along the Alzheimer's disease (AD) continuum.
- These alterations remain understudied in populations with low educational attainment.
- **Objectives:** To investigate the association between BBM and APOE genotype across the clinical continuum of AD.

METHODS

- **Sample:** 316 individual from Brazilian Cog-Aging cohort
- **Clinical groups:** Cognitively unimpaired (CU = 29.8%), Mild cognitive impairment (MCI = 43.7%), dementia of the Alzheimer's type (DAT = 23.9%), and other dementias (2.5%)
- **Genetics:** APOE genotyping via real-time PCR, by ε4 allele presence (ε4+ and ε4-).
- **Blood biomarkers:** pTau-217, Aβ42, Aβ40, GFAP, and NfL were quantified using Simoa® technology.
- **Statistical Analysis:** The Mann-Whitney U test was employed for hypothesis testing (JASP software).
- **Data Visualization:** Clustermaps and hierarchical clustering were performed using Python (Seaborn), grouped by median and standardized by z=score. Genotypes ε2/ε2 and ε2/ε4 were excluded due to small sample size.

CONCLUSIONS

- In this cohort from a low- and middle-income country, characterized by low educational attainment, ε4 allele was associated with a distinct BBM expression pattern that is consistent with findings previously reported in high-income populations.
- In the MCI group, these differences suggest that ε4 carriers exhibit a higher reactive astrogliosis, amyloid and Tau disease burden. The NfL results may reflect the limited specificity of this BBM, highlighting the need for further investigation.

The ε4 allele was associated with a distinct BBM expression pattern in a sample with low educational attainment.

RESULTS

Mean age 76.77 years (SD=6.562); median 4 years of schooling (IQR=3); Women (76%); ε4+ (37.1%). In CU groups, no significant differences were found between ε4+ and ε4- groups. In MCI groups, pTau-217 levels (p<0.001), pTau-217/Aβ42 ratio (p<0.001), and GFAP levels (p=0.030) were higher in ε4+ and the Aβ42/Aβ40 ratio (p=0.006) was lower. In DAT groups, NfL (p=0.026) and Aβ42 (p=0.048) levels in ε4+ were lower. (table 1) (figure 1). Cluster analysis showed that ε4 carriers across genotypes exhibited higher pTau-217, pTau-217/Aβ42 and GFAP, with lower Aβ42 and Aβ42/Aβ40 ratio, whereas NfL exhibits a distinct pattern (figure 2).

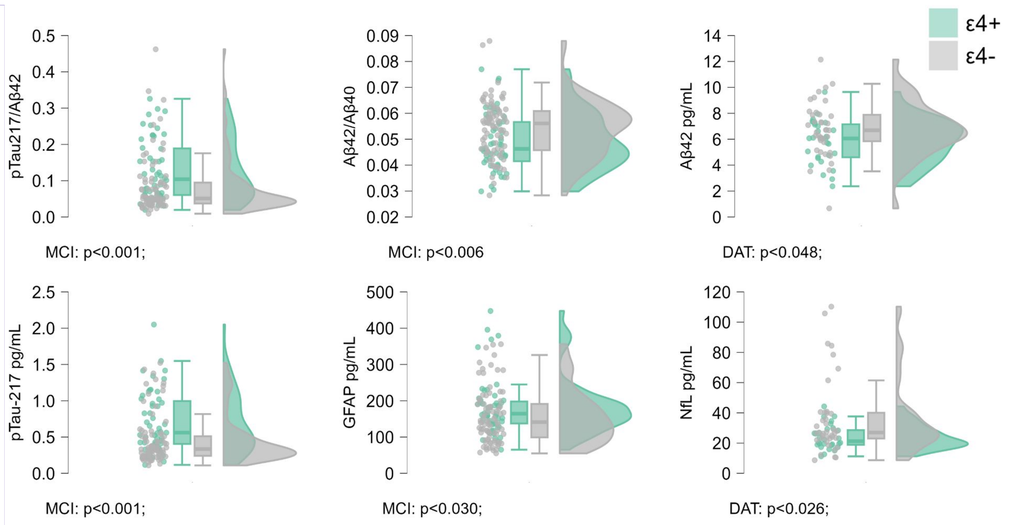


Figure 1.

Table 1.

	CU			MCI			DAT		
	ε4+	ε4-	p-Value	ε4+	ε4-	p-Value	ε4+	ε4-	p-Value
pTau-217 pg/mL (mean±SD)	0.59±0.57	0.36±0.26	0.083	0.70±0.42	0.47±0.34	<0.001**	1.26±0.58	1.11±0.64	0.225
pTau-217/Aβ42 (mean±SD)	0.10±0.09	0.06±0.04	0.067	0.13±0.08	0.08±0.08	<0.001**	0.26±0.02	0.21±0.21	0.083
Aβ42 pg/mL (mean±SD)	6.33±2.07	6.61±2.66	0.819	5.95±1.93	6.54±2.41	0.107	5.78±1.72	6.75±2.12	0.048*
Aβ40 pg/mL (mean±SD)	121.75±24.40	119.55±44.23	0.364	122.65±26.85	119.84±35.70	0.199	126.76±37.58	134.58±38.79	0.222
Aβ42/Aβ40 (mean±SD)	0.05±0.01	0.06±0.01	0.214	0.05±0.01	0.05±0.01	0.006*	0.05±0.01	0.05±0.01	0.114
GFAP pg/mL (mean±SD)	189.04±137.66	136.46±64.47	0.087	182.73±79.84	158.02±76.18	0.030*	250.02±90.56	259.63±107.17	0.565
NfL pg/mL (mean±SD)	20.02±12.14	18.45±9.46	0.636	21.88±10.07	23.78±18.14	0.859	23.87±8.09	36.57±25.42	0.026*

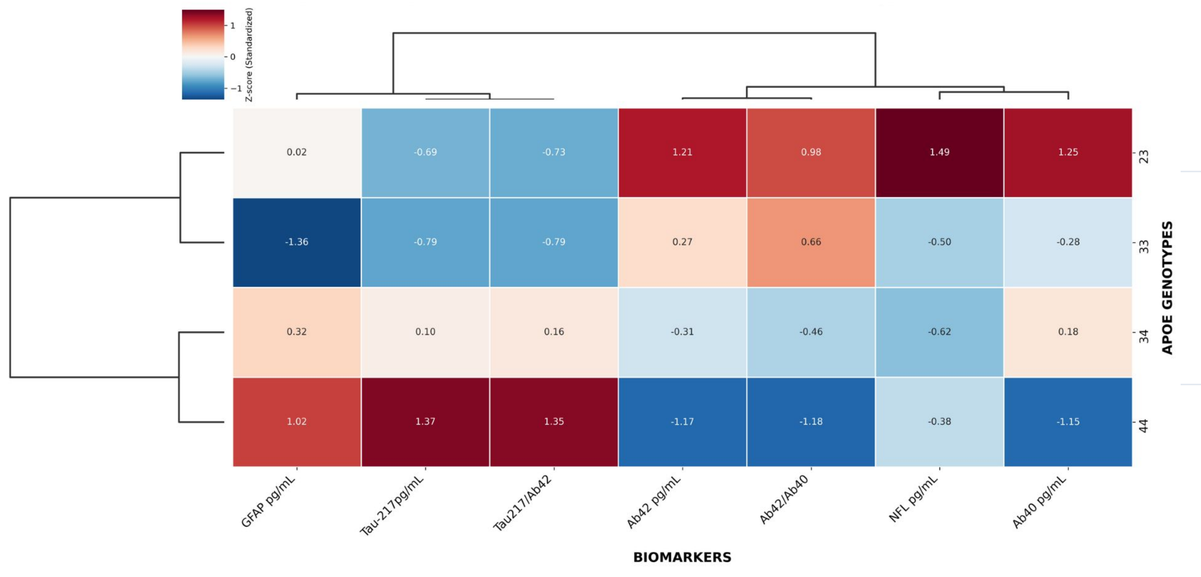


Figure 2.

REFERENCES

1. Agnello L, et al. Exploring the effect of APOE ε4 on biomarkers of neurodegeneration in Alzheimer's disease. Clin Chim Acta. 2024;562:119876. doi:10.1016/j.cca.2024.119876.
2. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708-3821. doi:10.1002/alz.13809.

CONTACT

Maurício Lemos Bueno Fontes
UFMG| Cog-Aging Research Group
mauricio.l.b.fontes@gmail.com