

APOE Genotype Modulates the Longitudinal Association between Plasma GFAP and Cognition in Cognitively Unimpaired Older Adults

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INTRODUCTION

- Elevations in glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivity and neuroinflammation, have been linked to increased AD-risk.
- In preclinical and prodromal AD, higher brain GFAP levels are associated with cognitive decline, amyloid beta (Aβ) deposition, tau spread, and neurodegeneration associated with AD.
- Studies have reported that APOE ε4 may strengthen the association between astrocyte reactivity and AD pathology.

PURPOSE

- 1) Are there APOE-related genotype differences in plasma GFAP in cognitively unimpaired older adults?
- 2) What is the association between plasma GFAP and cognition in this group? What is its association with other AD biomarkers?

METHODS

- Participants were enrolled in the Memory Education and Research Initiative (MERI) program.
- The MERI Evaluation

Medical History
Medication Review
Lab Results Review

Blood Draw for Plasma
AD Biomarkers

Behavioral Surveys
Cognitive Testing

Clinical Evaluation
Psychiatric Interview

 - Participants were classified into APOE groups: APOEε2 carriers, APOEε3/3 or APOEε4 carriers.
 - Blood-based AD biomarker concentrations (BBMs) were measured using single-molecule array platform.
 - Cognitive evaluation included a global cognitive function test (MMSE) and tests of episodic memory and executive function.
 - Analysis of covariance was conducted to compare APOE groups. Linear mix models were run for each APOE group to examine longitudinal associations with BBMs and cognition.
 - We also examined the interaction of genotype and GFAP on BBMs and cognition.
- PARTICIPANTS
- MERI Cohort Characteristics (a) and Demographics (b) at Baseline, by APOE groups
 - Baseline = first blood sample/plasma biomarker determination
 - MMSE ≥ 24 at Baseline

(a) Total participants enrolled in the MERI N = 1385

Participants with plasma biomarkers N = 725

Participants with APOE genotype N = 675

Participants with MMSE assessment N = 671

Participants with MMSE ≥ 24 at baseline N = 584 Included in cross-sectional analyses

(b)

	E2 Carrier	E3 Homozygous	E4 Carrier	p
n	57	329	188	
Age (mean (SD))	71.63 (8.47)	72.39 (8.92)	71.52 (8.00)	0.579
Sex = Male (%)	18 (31.6)	141 (42.9)	83 (44.1)	0.225
Race (%)				0.114
Black or African-American	4 (7.0)	9 (2.7)	10 (5.3)	
Caucasian	52 (91.2)	289 (87.8)	165 (87.8)	
Other	1 (1.8)	31 (9.4)	13 (6.9)	
Education (years) (mean (SD))	15.88 (2.99)	15.98 (2.92)	15.51 (2.77)	0.203
MMSE (mean (SD))	28.61 (1.74)	28.67 (1.52)	28.24 (1.93)	0.02
Aβ40 (pg/mL) (mean (SD))	97.51 (26.10)	102.62 (40.95)	99.57 (37.35)	0.523
Aβ42 (pg/mL) (mean (SD))	6.22 (1.61)	6.44 (2.38)	5.67 (1.96)	0.001
Aβ42/40 Ratio (mean (SD))	0.0640 (0.0115)	0.0623 (0.0118)	0.0569 (0.0119)	<0.00
Log10 p-Tau231 (pg/mL) (mean (SD))	0.89 (0.18)	0.93 (0.23)	1.00 (0.21)	<0.00
Log10 NfL (pg/mL) (mean (SD))	1.38 (0.26)	1.41 (0.26)	1.40 (0.25)	0.762
Log10 GFAP (pg/mL) (mean (SD))	2.08 (0.21)	2.10 (0.25)	2.14 (0.25)	0.191
APOE Genotype (%)				<0.00
E2/E2	17 (29.8)	0 (0.0)	0 (0.0)	
E2/E3	40 (70.2)	0 (0.0)	0 (0.0)	
E3/E3	0 (0.0)	329 (100.0)	0 (0.0)	
E3/E4	0 (0.0)	0 (0.0)	161 (85.6)	
E4/E4	0 (0.0)	0 (0.0)	27 (14.4)	
- Elevations in GFAP in ε2 and ε4 are related to lower amyloid over time
- GFAP levels did not significantly differ across APOE groups (p=0.20) at baseline (Figure 1b).
 - However, higher baseline GFAP was associated with lower Aβ42/40 over time within ε2 (p=0.021) and ε4 carriers (p=0.040), but not ε3/ε3 (Fig 2).
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- GFAP and longitudinal inverse associations with cognition
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- CONCLUSION
- There were no differences in baseline levels of plasma GFAP across APOE groups
 - APOEε2 carriers with elevated GFAP had lower longitudinal Aβ42/40 but not greater cognitive decline. Whereas, in APOEε3/3 and APOEε4 carriers, elevated GFAP levels were associated with higher pTau231 and cognitive decline, and greater reductions in Aβ42/40.
 - The incongruous findings with regards to the lack of interactions of APOE genotype X GFAP on either BBMs or cognitions may be related to the uneven group sizes, particularly for the ε2 and ε4 carriers.
 - These findings suggest that association between increased baseline astrocytic reactivity and longitudinal cognitive decline, depend on APOE status.
 - APOEε2 genotype confers cognitive resilience against detrimental AD biomarkers, but more studies are needed to understand how this genotype influences astrocyte response.
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