

Plasma ApoE4/ApoE protein ratio and brain-derived p-tau217 improve prediction of amyloid PET positivity in cognitively unimpaired adults

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INTRODUCTION

Background

- P-tau217 is a strong indicator of Alzheimer's disease (AD) pathology in symptomatic and asymptomatic disease¹. P-tau217 reflects amyloid beta pathology in early disease and neurofibrillary tangle formation in later disease^{1,2}
- The ε4 allele of the APOE gene is the strongest genetic risk factor linked to impaired amyloid-β clearance in AD³
- Possessing two copies of the ε4 allele (homozygous) is associated with a higher risk of cognitive decline than possessing one copy of the allele (heterozygous)⁴
- Both markers offer a powerful approach for assessing risk, detecting early disease processes (p-tau217), and assessing potential ARIA from anti-amyloid therapies (ApoE4)
- In recent years, measuring blood-based p-tau217 has fully transitioned from complex, research-only workflows to fully automated, high-throughput immunoassays
- The measurement of ptau-217 and ApoE4 from one blood sample can be simultaneously evaluated in a single assay
- Plasma markers can potentially offer greater resolution and additional biological insight into amyloid pathology and AD risk

Study aims

- Quantify plasma ApoE and ApoE4 proteins from a novel immunoassay to estimate APOE genotype.
- Assess the combined performance of plasma ApoE4 protein and p-tau217 for predicting amyloid pathology in cognitively unimpaired individuals.

ROC of ApoE4/APOE for ε4 genotype

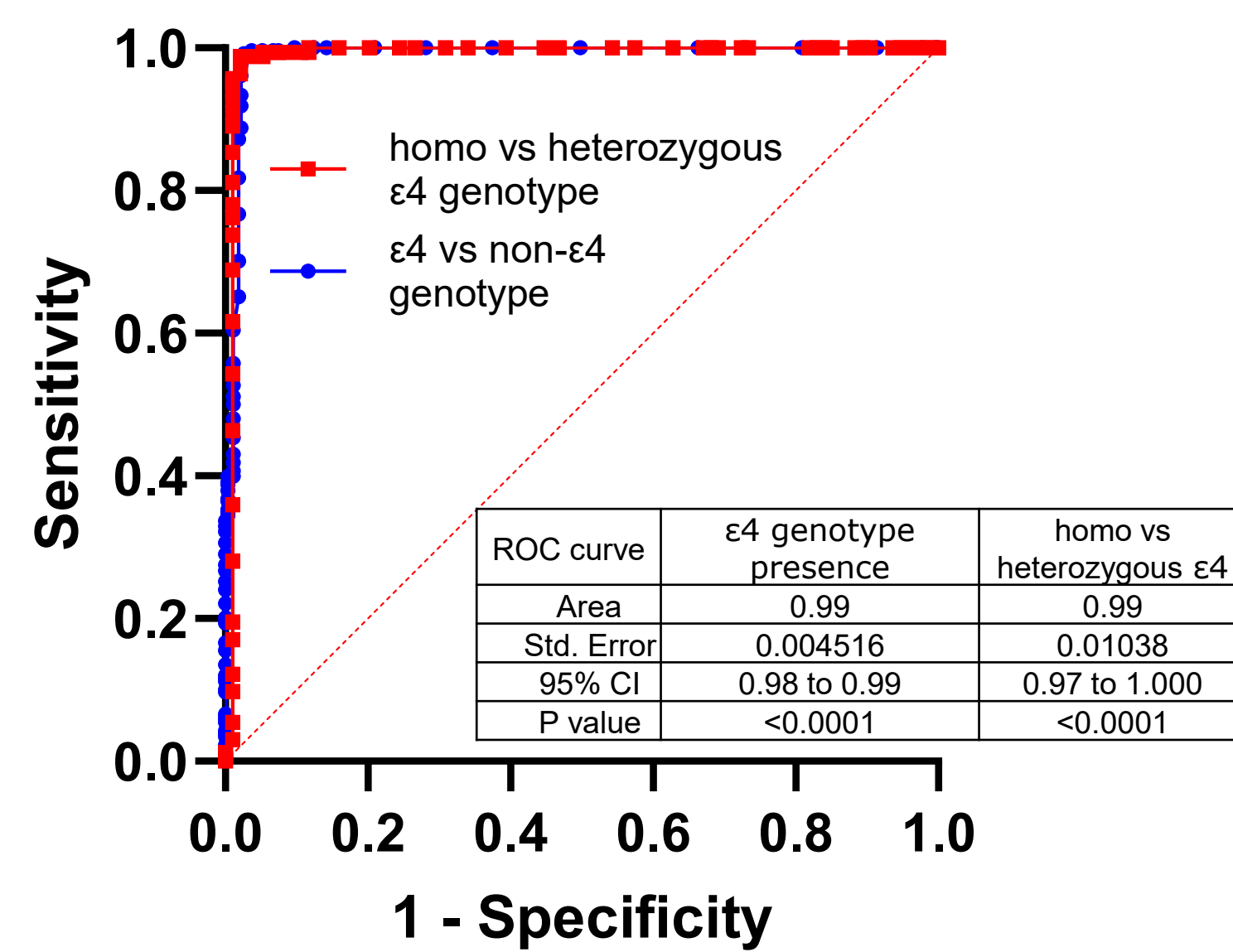


Figure 1. ROC curve for ApoE4/ApoE. Classification was based on genetically determined absence or presence of ε4 genotype (red), and number of ε4 copies (blue).

ROC of brain ptau-217, ApoE4/ApoE vs brain ptau-217 + ApoE4/ApoE

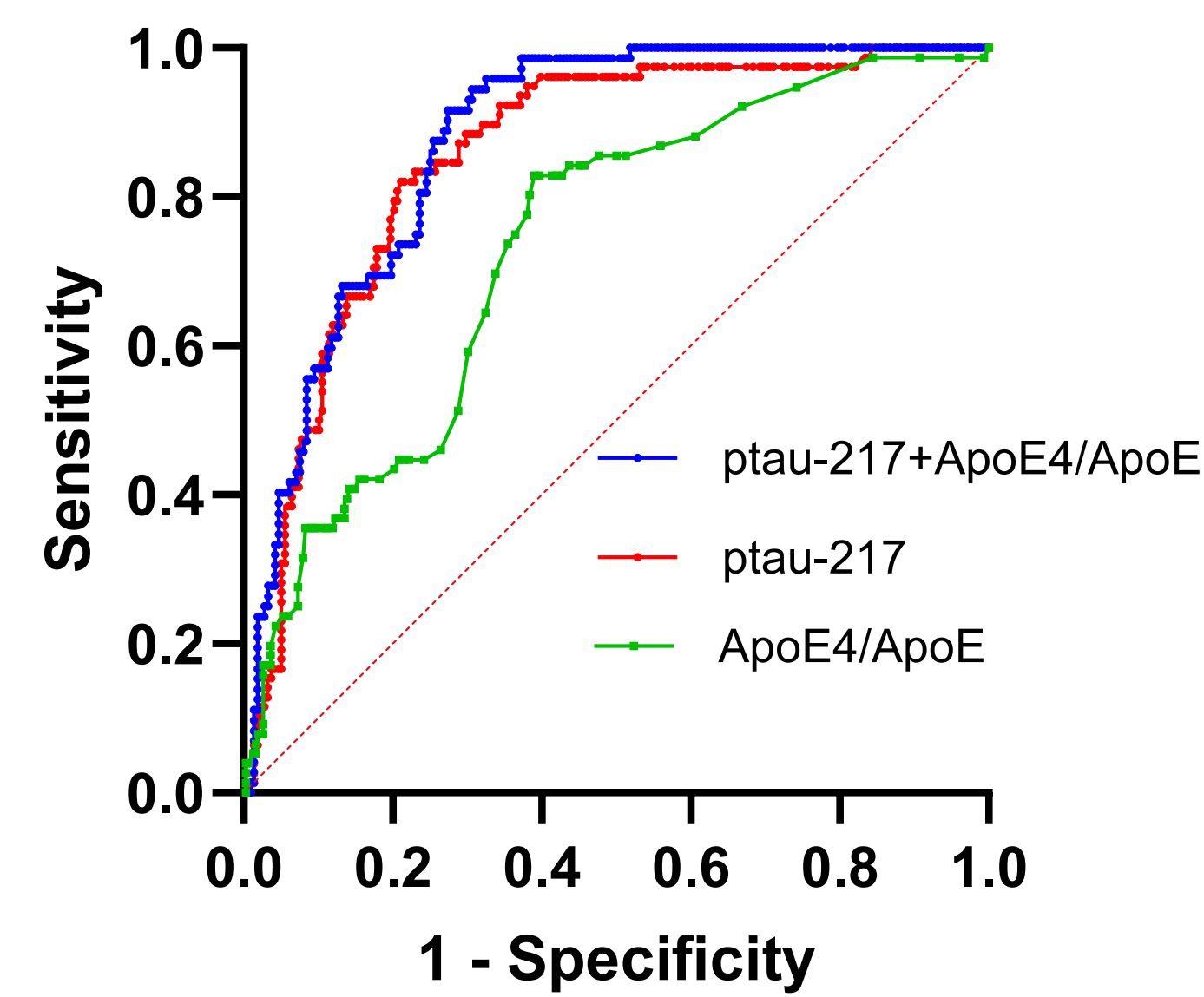


Figure 2. ROC curves for brain-derived p-tau217 and ApoE4/ApoE alone and brain-derived p-tau217 combined with ApoE4/ApoE. Classification was based on amyloid PET imaging with Centiloid scale cutoff of 24.1 in cognitively normal individuals.

Predicted vs True Amyloid PET from brain ptau-217 + ApoE4/ApoE

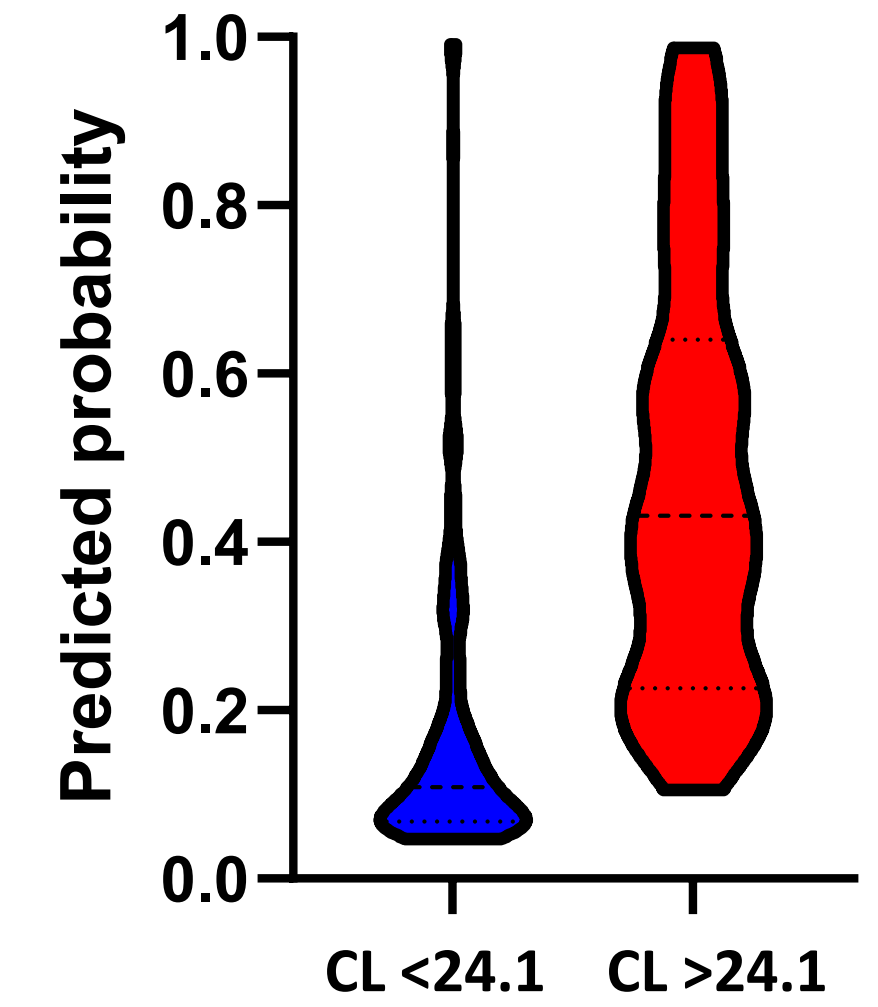


Figure 3. Predicted vs true cases of amyloid PET above and below CL cutoff (24.1) from brain-derived ptau-217 + ApoE4/ApoE.

METHODS

Study Design

Plasma samples from 477 cognitively unimpaired adults aged 47–90 years in the Arizona APOE cohort were analyzed. Participants' genotype and Amyloid PET scan Centiloid scores at the time of blood draw were included. Analysis was performed with the Siemens Healthineers research-use immunoassays. Plasma samples were analyzed using readily available immunoturbidimetric assays to measure ApoE4, total ApoE, total p-tau217, and CNS-enriched LMW (brain-derived) p-tau217 on the Atellica® CI Analyzer.

Measurements

- **Plasma ApoE4, ApoE protein** (Atellica CI analyzer)
- **Plasma total, brain-derived ptau-217** (Atellica CI analyzer)
- **Amyloid-PET scan Centiloid (CL) score**

Amyloid PET data was analyzed using FreeSurfer defined anatomical regions. Centiloid conversion was performed following recommended procedures^{5,6}. The following amyloid tracers were utilized: ¹¹C-Pittsburgh Compound B ([¹¹C]PiB), Florbetapir ([¹⁸F]AV45), and Flutafuranol F-18 ([¹⁸F]NAV4694).

• APOE Genotype

APOE genotyping methods used for the Arizona APOE Cohort Study including the following source sites:

Mayo Clinic	TaqMan SNP Genotyping Assays. analyzed on a Quantstudio 7 Flex Real-Time PCR System		
NCRAD	Standard BioTools SNPtype allele-specific PCR assay		
GeneMatch	Eurofins: TaqMan SNP Genotyping Assays	LabCorp: Infinium iSelect HTS Custom Array (Version 2)	

Statistical Analysis

Associations with ε4 genotype and amyloid burden were assessed using ROC analysis and multiple logistic regression. Statistical analysis was performed using GraphPad Prism software (version 11.0.0). A PET Centiloid cutoff 24.1 was used to classify patients with positive and negative Amyloid pathology.

CONCLUSION / DISCUSSION

Discussion

Results

- The ratio of ApoE4/ApoE in plasma demonstrated very high sensitivity and specificity in distinguishing the absence or presence of ε4 genotype, with an AUC of 0.99 (95% CI: 0.98–0.99)

- ApoE4/ApoE ratio in plasma also demonstrated very high sensitivity and specificity for discriminating between homozygous and heterozygous ε4 genotype, with an AUC of 0.99 (95% CI: 0.97–1.0)

- Plasma brain-derived ptau-217, when combined with plasma ApoE4/ApoE protein, more effectively distinguished amyloid pathology above a 24.1 CL cutoff (AUC: 0.88; 95% CI: 0.84–0.92) than brain-derived ptau-217 and ApoE4/ApoE alone (AUC: 0.85; 95% CI: 0.81–0.90 and AUC: 0.73; 95% CI: 0.67–0.79)

- Plasma ptau-217 and ApoE4/ApoE ratio correctly predicted amyloid pathology in 80.28% instances (positive predictive power: 67.39%, negative predictive power: 82.77%)

Conclusion

- Plasma ApoE4 phenotyping demonstrated robust analytical concordance with ε4 status when performed on the same immunoassay platform as p-tau217
- Combined measurements of ptau-217 and ApoE4 protein in plasma demonstrated a modest improvement of amyloid prediction

Clinical implications and Future directions

- p-tau217 and ApoE risk can be routinely and simultaneously evaluated through blood
- These results from a cognitively unimpaired cohort support further clinical validation of integrated plasma biomarkers for early AD

REFERENCES

1. Stowe, A. M., Kahn, B., Ballesteros, A., Cortez, M., Hynan, L. S., Cantrell, V., Raman, I., Chen, G., Vidoni, E. D., Binder, E., Burns, J., Keller, J. N., Kerwin, D. R., Hall, T., Yanev, P., Vongapatanasin, W., Zhu, D. C., Scheel, N., Cullum, C. M., Zhang, R., ... German, D. C. (2026). Plasma p-tau217 and APOE genotype: Prodromal Alzheimer's disease staging. *Alzheimer's & dementia (Amsterdam, Netherlands)*, 18(1), e70279. <https://doi.org/10.1002/dad2.70279>
2. Telser, J., Risch, L., Saely, C. H., Grossmann, K., & Werner, P. (2022). P-tau217 in Alzheimer's disease. *Clinica chimica acta; international journal of clinical chemistry*, 531, 100–111. <https://doi.org/10.1016/j.cca.2022.03.018>
3. Wildsmith, K. R., Holley, M., Savage, J. C., Skerrett, R., & Landreth, G. E. (2013). Evidence for impaired amyloid β clearance in Alzheimer's disease. *Alzheimer's research & therapy*, 5(4), 33. <https://doi.org/10.1186/alzrt187x>
4. Donix, M., Small, G.W. & Bookheimer, S.Y. (2012). Family History and APOE-ε4 Genetic Risk in Alzheimer's Disease. *Neuropsychol Rev* 22, 298–309. <https://doi.org/10.1007/s11065-012-9193-2>
5. Su, Y., D'Angelo, G. M., Vlasenko, A. G., Zhou, G., Snyder, A. Z., Marcus, D. S., Blazey, T. M., Christensen, J. J., Vora, S., Morris, J. C., Mintun, M. A., & Benzinger, T. L. (2013). Quantitative analysis of PiB-PET with FreeSurfer ROIs. *PLoS one*, 8(11), e73377. <https://doi.org/10.1371/journal.pone.0073377>
6. Klunk, W. E., Koeppe, R. A., Price, J. C., Benzinger, T. L., Devous, M. D., Sr, Jagust, W. J., Johnson, K. A., Mathis, C. A., Minhas, D., Pontecorvo, M. J., Rowe, C. C., Skovronsky, D. M., & Mintun, M. A. (2015). The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 11(1), 1–15.e154. <https://doi.org/10.1016/j.jalz.2014.07.003>

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