

APOE genotyping enhances Urine-based metabolomics for early Differentiation of Alzheimer's Disease and Lewy Body Dementia

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1. Introduction

- Early and accurate differentiation between Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) is difficult due to overlapping symptoms and a lack of non-invasive biomarkers (Goldman et al., 2020; Liang et al., 2025).
- While blood-based metabolomics combined with APOE genotype has shown promise (Mukesha et al., *J Alzheimers Dis*, 2025), the diagnostic potential of urine-based metabolomics for early AD vs. DLB remains largely unexplored...

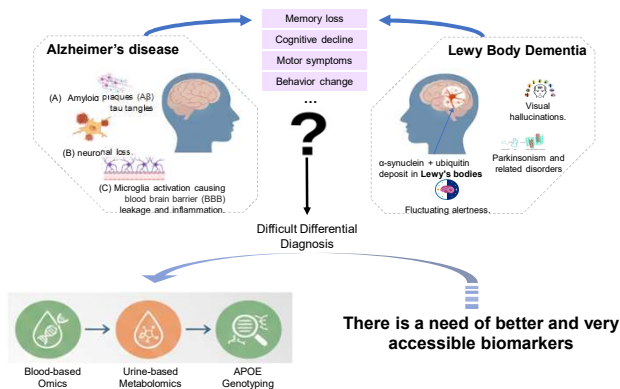


Figure 1

Our Hypothesis:

Integrated APOE genotyping + urine-based metabolomics improves the early differentiation between mild AD (miAD) and DLB

2. Material and Method

ADDIA Cohort (NCT03030586), N=78 participants

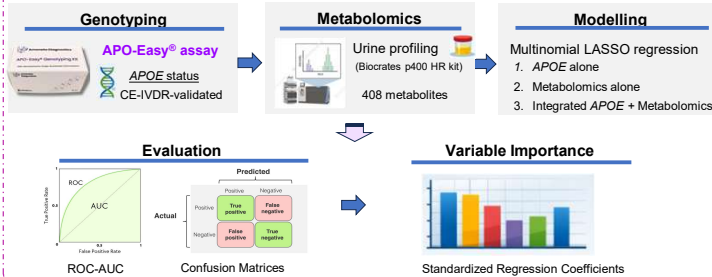


Figure 2 | Study Design Integrating APOE Genotyping and Urinary Metabolomics for AD and DLB Classification
Seventy-eight ADDIA participants (35 HC, 30 miAD, 13 DLB) underwent APOE genotyping (APOE-Ready) and urine metabolomics profiling (Biotarcs p400 HR, 408 metabolites). Multinomial LASSO models (APOE, metabolomics, integrated) were evaluated using ROC-AUC, confusion matrices, and feature importance.

3. Demographic and Clinical Characteristics

Table 1. Participant Characteristics by Diagnostic Group

Characteristic	HC (n = 35)	miAD (n = 30)	DLB (n = 13)	P Value
Age, mean (SD), year	76 (4.2)	77 (5.2)	75 (9.4)	.64
Female sex, No. (%)	16 (46)	16 (53)	6 (46)	.81
APOE ε4 carrier, No. (%)	2 (6)	20 (67)	3 (23)	<.001

Groups were comparable in age and sex, but APOE ε4 carrier status differed significantly across groups ($p < .001$).

4. Machine Learning Analysis

Table 2. Classification Performance (ROC-AUC)

Class	APOE Only	Metabolomics	Metabolomics + APOE
DLB	(AUC = 0.67, CI: 0.52–0.81)	(AUC = 0.87, CI: 0.76–0.97)	(AUC = 0.84, CI: 0.71–0.97)
miAD	(AUC = 0.69, CI: 0.55–0.84)	(AUC = 0.63, CI: 0.50–0.75)	(AUC = 0.81, CI: 0.71–0.92)
HC	(AUC = 0.53, CI: 0.38–0.68)	(AUC = 0.72, CI: 0.60–0.83)	(AUC = 0.85, CI: 0.76–0.94)

The combined model outperformed single-modality models, specifically improving the discrimination of AD cases.

Differential Metabolomic Signatures in DLB, AD, and HC: Integration of APOE Genotype Enhances Predictive Accuracy

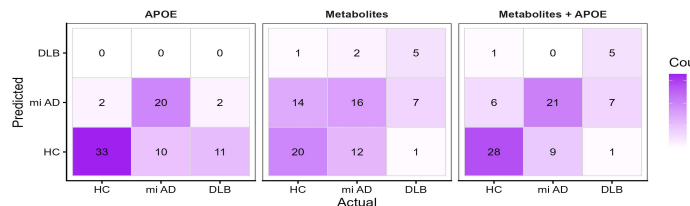


Figure 3 | Predictive performance of metabolite panels with and without APOE ε4 status for discriminating dementia subtypes.

The confusion matrices compare the number of correctly predicted metabolites across diagnostic groups: Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), and healthy controls (HC), under two model conditions; metabolites alone and metabolites combined with APOE ε4 carrier status. Integration of APOE genotype improves predictive accuracy across all groups, with notable enhancement in DLB and AD differentiation. HC = healthy controls; AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; APOE = apolipoprotein E.

- References**
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5. Variable Importance

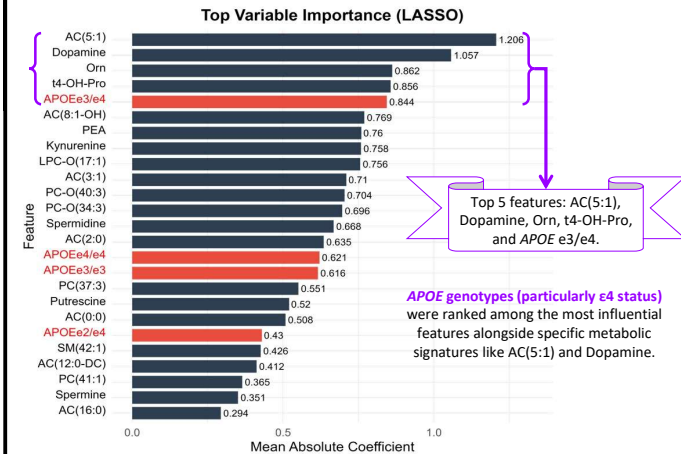


Figure 4 | Variable importance derived from LASSO multinomial regression coefficients.

Features are ranked by mean absolute standardized LASSO coefficients across outcome classes. Feature importance reflects the strength and consistency of each predictor in the combined model.

6. Conclusion

- Integrating APOE with urine-based metabolomics provides a robust, non-invasive strategy for the early differentiation of AD and DLB.
- The multimodal approach addresses a critical diagnostic gap and supports improved patient stratification, outperforming single-biomarker models.
- Future Work: Validation in larger, longitudinal cohorts to assess clinical utility in diagnostic pathways.

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