

LIPID, DOPAMINE, AND AMINO ACID DERIVATIVES IDENTIFIED AS EARLY URINARY BIOMARKERS IN ALZHEIMER'S DISEASE VERSUS LEWY BODY DEMENTIA

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BACKGROUND

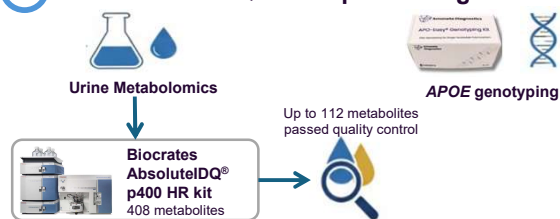
- Early and accurate differential diagnosis of **Alzheimer's disease (AD)** and **dementia with Lewy bodies (DLB)** is clinically challenging due to overlapping symptoms and limited biomarker specificity.
- Blood-based metabolomics shows promise, but **urine** offers a more accessible, non-invasive biofluid for clinical translation.
- This study aims to identify **urinary metabolite signatures** reflecting disease-specific pathophysiology and evaluate their diagnostic utility when combined with **APOE** genotype.

MATERIAL & METHODS

ADDIA Cohort (NCT03030586), N=78 participants

- 35 Healthy Control (HC)
- 30 Mild AD (miAD)
- 13 DLB

1 PHASE I: Data QC & Preprocessing



2 PHASE II: Statistical Analysis and Exploration

- Cohort Characteristics
- Covariate Assessment & Adjustment
 - Multivariate ANOVA model to quantify effects of covariates.
 - Data adjusted for Age & Sex effects via linear modeling to isolate disease-specific signals.
- Differential expression analysis (Volcano plots)

3 PHASE III: Statistical Modelling and Evaluation

- Multinomial LASSO regression with Leave-One-Out Cross-Validation (LOOCV)
- Models:
 - Metabolites Alone
 - APOE Genotype Alone
 - Metabolites + APOE
- One-vs-rest classification strategy
- Performance Metrics:
 - Area Under ROC Curve (AUC)
 - Confusion matrices
 - Variable importance from standardized coefficients

I. Demographic and Clinical Characteristics

Table 1. Participant Characteristics by Diagnosis

Variable	HC (n=35)	miAD (n=30)	DLB (n=13)	P-value
Female, n (%)	16 (46)	16 (53)	6 (46)	0.81
Age, mean ± SD (year)	76 ± 4.2	77 ± 5.2	75 ± 9.4	0.64
APOE ε4 carrier, n (%)	2 (6)	20 (67)	2 (15)	<0.001

Notes: Values are n (%) unless stated. *p* from χ^2 tests (categorical) and ANOVA (age).

III. Machine Learning analysis

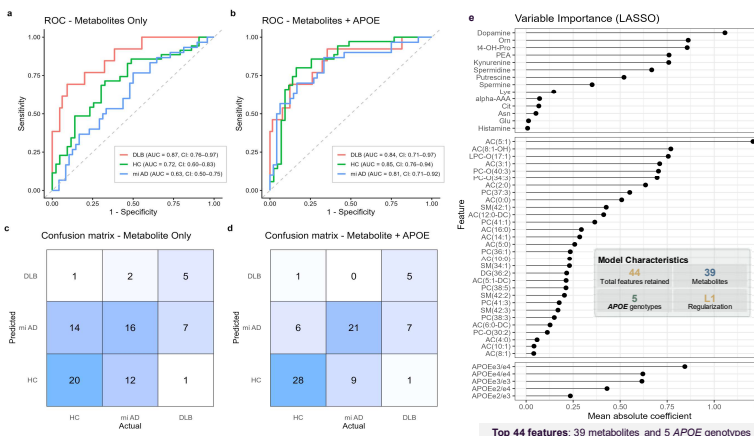


Figure 3. Classification performance (AUCs, confusion matrices, variable importance) for the differentiation of diagnostic groups.

II. Differentiation expression analysis

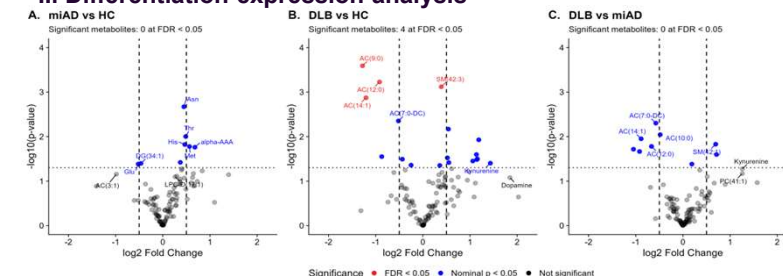


Figure 2. Volcano plots of differential metabolite abundance in urine.

CONCLUSION

- A novel **multi-pathway urinary metabolite panel** (energy, lipid, neurotransmitter, vascular) distinguishes early AD, DLB, and healthy aging.
- Combining **urine metabolomics with APOE** enhances diagnostic accuracy beyond either modality alone, offering a **clinically viable, non-invasive strategy**.
- Rigorous QC and covariate adjustment** underpin the robustness of the identified biomarkers. And **addresses a key unmet need** in early differential dementia diagnosis.

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Acknowledgement

This work was done thanks to the contribution of the following program:



The ADDIA cohort has been established thanks to the funding by the Horizon 2020 Research and Innovation program of the European Union, under the GA: 674474 (www.addia-project-h2020.eu/)