EXTRACELLULAR VESICLE LIPID ALTERATIONS DEFINE SYSTEMIC BIOMARKERS OF DISEASE BIOLOGY IN ALS, AD, AND PD

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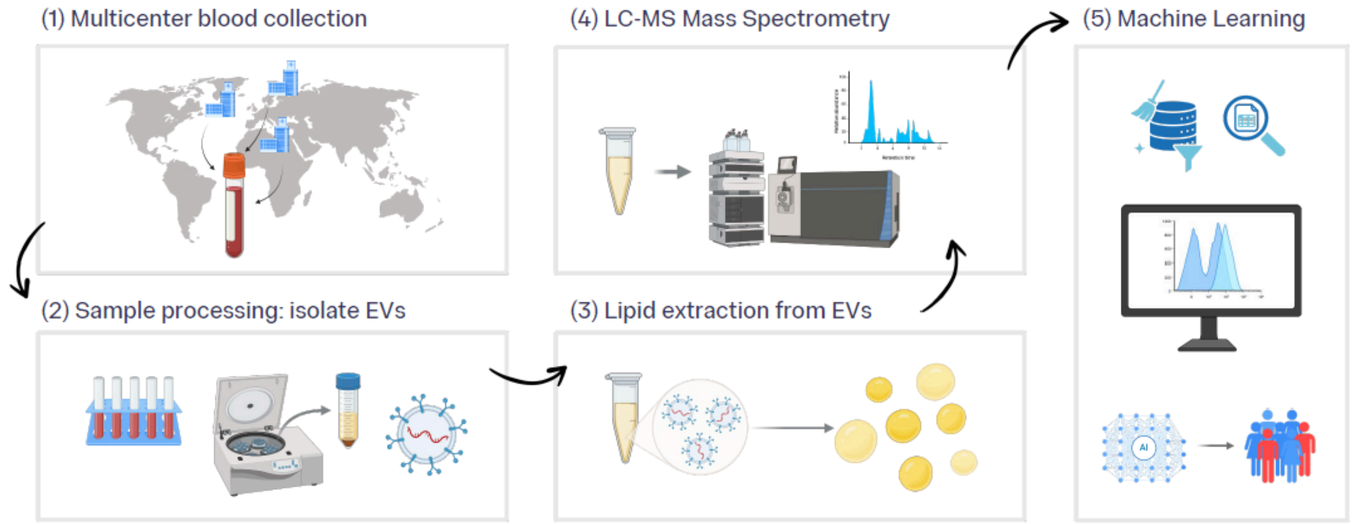
INTRODUCTION

Neurodegenerative diseases including Alzheimer's (AD), amyotrophic lateral sclerosis (ALS), and Parkinson's (PD) remain limited by **delayed diagnosis and a lack of biomarkers** that capture disease biology across heterogeneous presentations.

Growing evidence implicates **systemic metabolic dysfunction** in neurodegeneration, suggesting disease processes extend beyond the central nervous system. Yet robust circulating signatures reflecting these changes are still lacking.

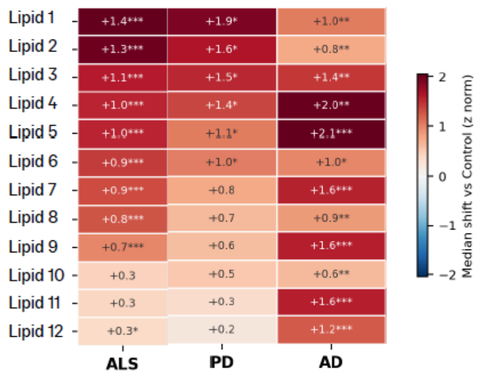
Extracellular vesicles (EVs) carry systemic molecular cargo and offer a route to a blood-based readout of this biology. We profiled the EV lipidome to test whether a coordinated signature can discriminate disease and generalise across neurodegenerative conditions. Blood samples were collected from multiple international centres, including samples from cognitively normal controls (n=149),
as well as people living with ALS (n=77), AD (n=30), and PD (n=23).

METHODOLOGY

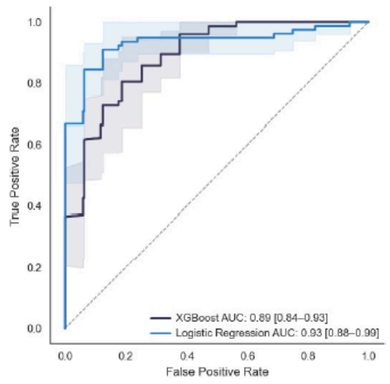


RESULTS

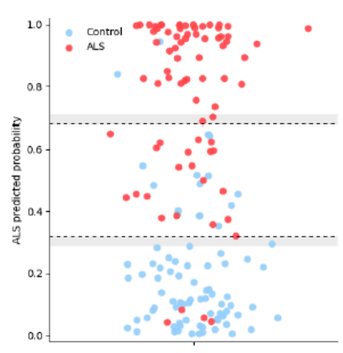
Lipid alterations are pronounced in ALS, AD, and PD
Median shift in lipid abundance relative to controls. Mann-Whitney U test with BH-FDR correction for multiple comparisons.
*** p < .001, ** p < .01, * p < .05.



EV lipids discriminate ALS from controls
Sens: 0.83 (0.69-0.98)), Spec: 0.92 (0.77, 1.00)
AUROC 0.93 (95%CI: 0.88-0.99



Risk stratification improves disc.
Sens: 0.92 (0.81-1.00), Spec: 0.97 (0.92, 1.00)
While confidently classifying 74% of samples



CONCLUSIONS

A coordinated EV lipid signature discriminates ALS from controls (AUROC 0.93 (95% CI: 0.88–0.99)), driven by opposing shifts in phosphatidylcholine and sphingomyelin species rather than uniform abundance changes.

The signal reflects membrane remodelling: disease-associated lipids are longer and more unsaturated, consistent with altered membrane fluidity under chronic cellular stress.

The same platform reveals structured lipid patterns in AD and PD, with evidence of a shared but disease-specific systemic framework.

This establishes EV lipidomics as a foundation for circulating biomarkers of systemic disease biology, supporting future stratification and therapeutic monitoring.

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