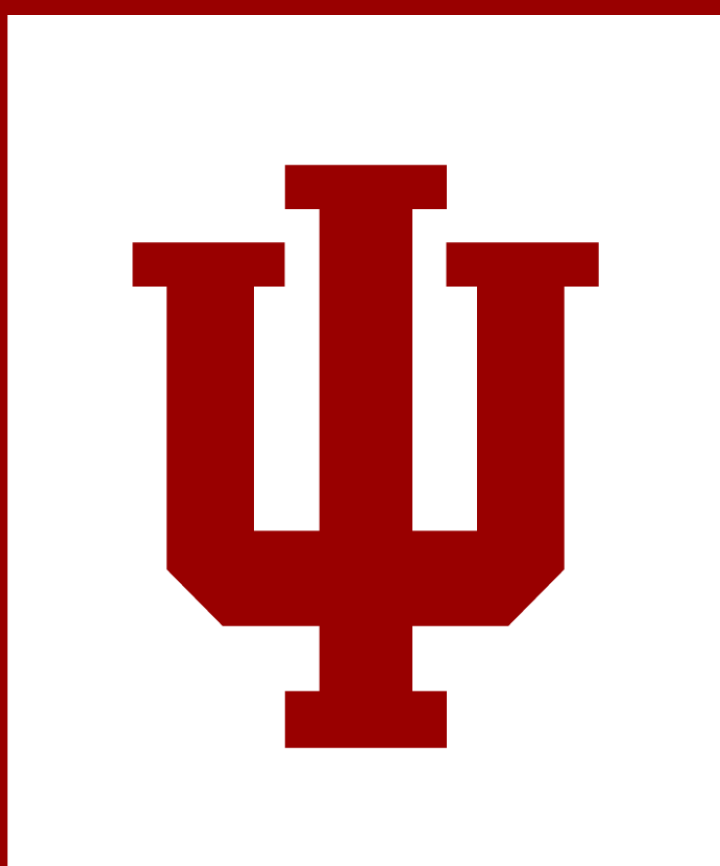




Plasma Proteomic Analysis Identifies Novel Proteins And Pathways Related To Alzheimer's Disease Risk And Progression

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Abstract

BACKGROUND: Plasma proteomics reveals peripheral proteins associated with AD A/T/N/I profiles and cognitive decline, highlighting novel blood biomarkers for disease risk and progression.

METHODS: Using longitudinal plasma proteomics (SomaScan 7K) from the Indiana ADRC, we applied mixed-effects models, network/pathway analyses, machine learning, and proteomic aging clocks to identify AD blood biomarkers associated with diagnosis, progression, cognition, and A/T/N/I profiles, followed by independent replication.

RESULTS: Dysregulated plasma proteins, network modules, and proteomic aging signatures are significantly linked to AD progression and A/T/N/I biomarkers.

Machine learning classifiers utilizing these selected protein panels achieved high accuracy in classifying AD (AUC=0.93) and predicting incident AD (AUC=0.85).

CONCLUSION: The findings from our comprehensive cross-sectional and longitudinal proteomics analysis suggest dysregulated plasma proteins and pathways in AD. Integrating proteomics signatures with organ-specific aging clocks, pseudotime trajectories, and longitudinal protein dynamics, enhances our understanding of molecular mechanisms and diagnostic strategies for AD and disease progression.

Method: Study samples

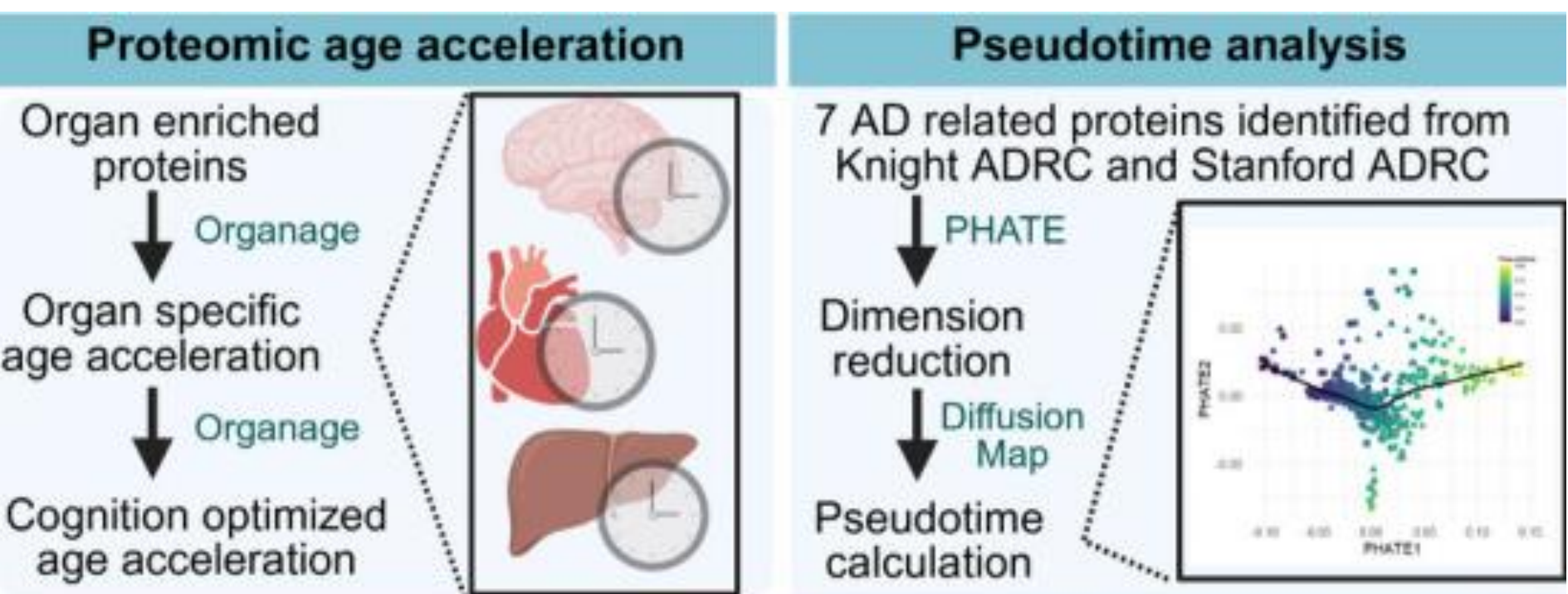
- Plasma proteomics profiling:** Plasma proteins were measured using the SomaScan 7K assay, a high-throughput proteomics platform based on modified aptamer technology.
- Study participants:** The longitudinal data for plasma proteins (Year 1: N=277; Year 2: N=198; Year 3: N=157; > Year 4: N=70), cognition, diagnosis, and AD biomarkers were obtained from the Indiana AD Research Center (IADRC) (Baseline N=498).

Table 1. Participant characteristics.

Baseline	CN (N=273)	MCI (N=122)	AD (N=103)
Age (mean±SD)	69.1±8.6	71.4±8.7	68.6±11.7
Sex (F:M)	93:180	59:63	49:54
APOE ε4 (0:1)	167:106	51:71	35:68
Education (years, mean±SD)	218:51	86:52	29:55
CDR-SB (mean±SD)	0.21±0.4	1.42±1.0	5.88±3.6

Methods: Proteomics aging clocks and pseudotime trajectory calculation

- Organ-specific proteomics aging clocks:** LASSO regression models trained using GTEx-verified organ-enriched proteins (≥ 4 -fold enrichment) to predict biological age, defining age acceleration via LOWESS-adjusted z-scores.
- Pseudotime trajectory:** Diffusion Maps applied to a 7-protein AD panel from cross-sectional data, extracting the first diffusion component as a latent progression metric (scaled 0-1).



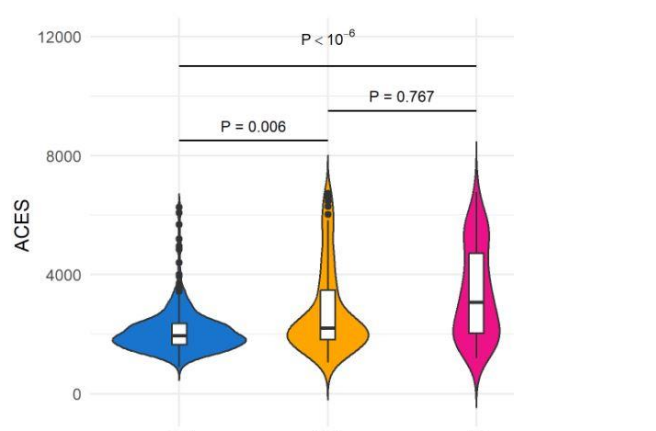
Methods: Association/classification analysis

Cross-sectional analysis

- Plasma proteins~ Phenotypes
- Age acceleration~ Phenotypes
- Pseudotime~ Phenotypes

Phenotypes:

- AD diagnosis
- Plasma A/T/N/I biomarkers
- Neuroimaging A/T/N biomarkers

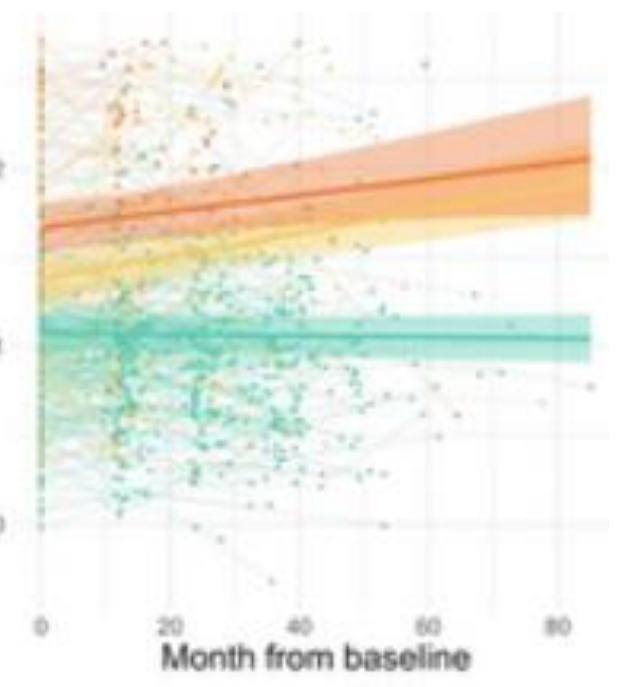


Longitudinal analysis

- Longitudinal plasma proteins~ Phenotypes

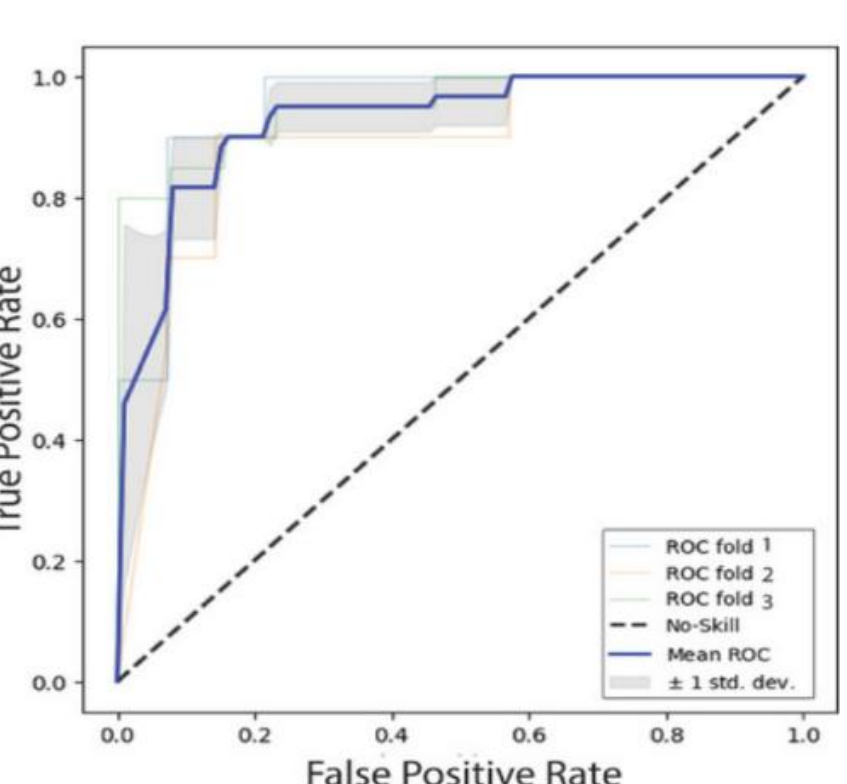
Phenotypes:

- AD diagnosis
- AD conversion
- Cognitive decline



Machine learning classification

- ML classifier: plasma proteins added value for CN/AD, A/T positivity and incident AD classification



Cross-sectional analysis: Age acceleration/pseudotime ~ AD phenotypes

- Fig. 1A:** Cognition-optimized brain age acceleration was significantly associated with AD diagnosis, plasma A/T/N/I and neuroimaging A/T/N biomarkers.
- Fig. 1B:** Subjects were mapped along a pseudotime trajectory in the two-dimensional PHATE space, derived from 7 differentially abundant proteins.
- Fig. 1C:** Pseudotime was significantly associated with AD diagnosis, plasma A/T/N/I and neuroimaging A/T/N biomarkers.

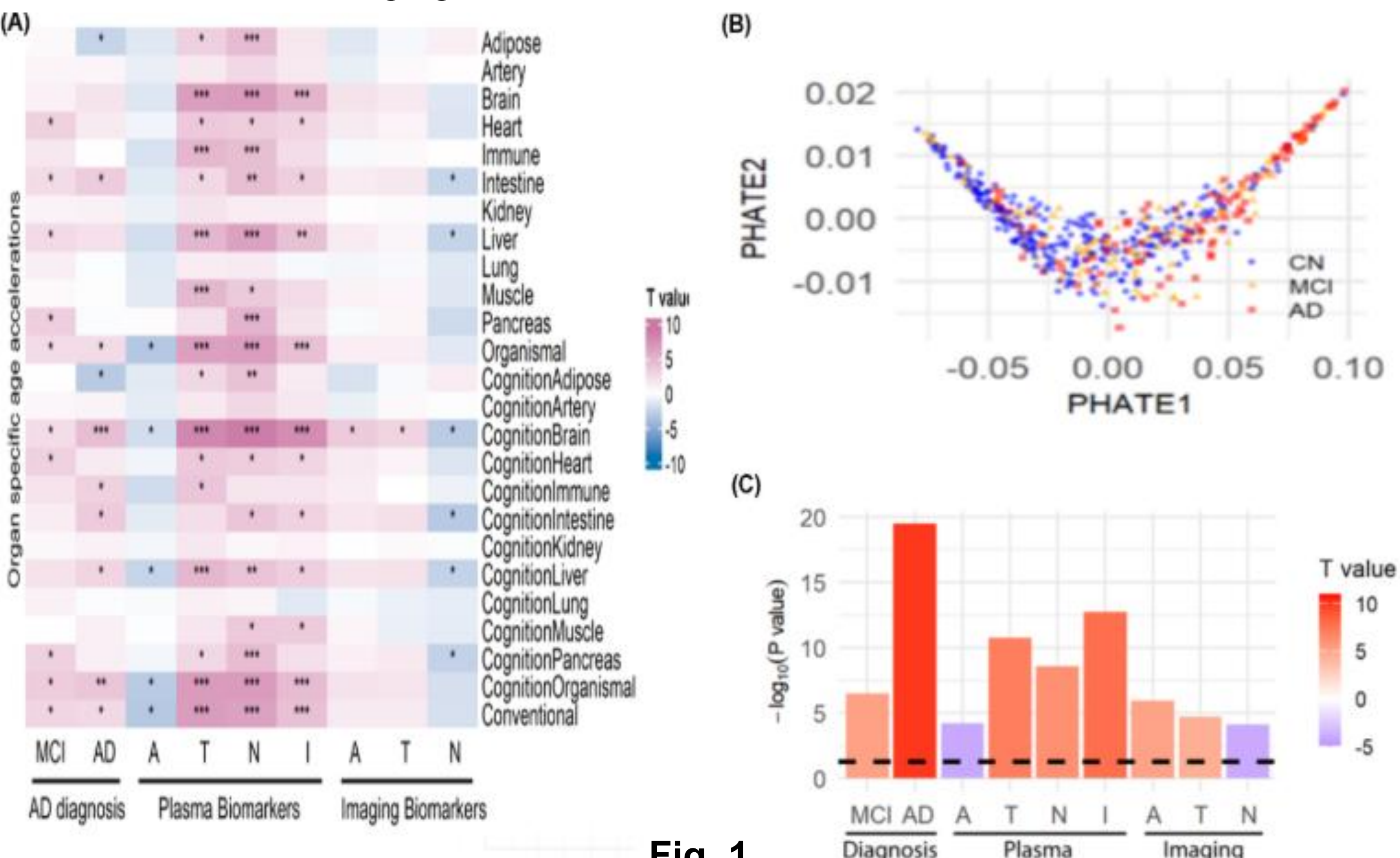


Fig. 1

- Notably, pseudotime outperformed established plasma biomarkers for CN/AD classification

References

- Huang Y-N et al. Plasma proteomic analysis identifies proteins and pathways related to Alzheimer's risk. Alzheimer's Dement. 2025.
- Liu S, et al. Plasma proteomic Alzheimer's risk score: Biological age clock and pseudotime trajectory. Alzheimer's Dement. 2025.
- Lee EH, et al. Longitudinal plasma proteomics: relation to incident Alzheimer's disease dementia and biomarkers. Alzheimer's Dement. 2025.

Cross-sectional analysis: Baseline plasma proteins~ plasma A/T/N/I and neuroimaging A/T/N biomarkers

- Fig. 2A:** Plasma proteins were significantly associated with AD.
- Fig. 2B-2D:** Plasma proteins were significantly associated with plasma T/N/I biomarkers.
- Fig. 2E:** Plasma proteins were significantly associated with neuroimaging A/T/N biomarkers.

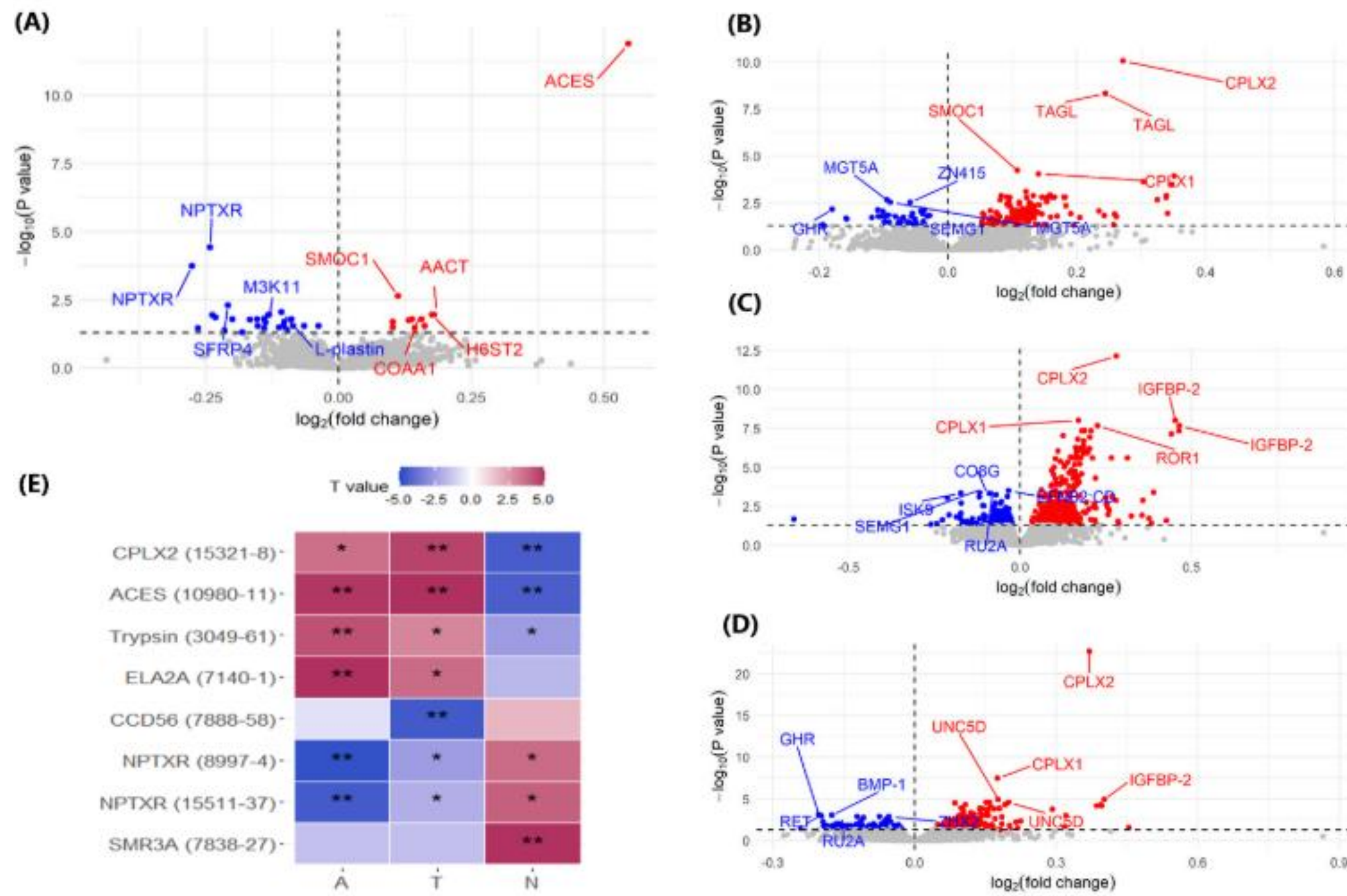


Fig. 2

Longitudinal analysis: Associations between longitudinal changes in plasma proteins and incident AD

- Fig. 3A:** Six plasma proteins showed significantly different change rates between the non-incident AD group and the incident AD group.
- Fig. 3B:** The plots display observed data points and estimated trajectories of plasma proteins, showing significantly faster increases over time in the incident AD group compared to the non-incident AD group.
- Furthermore, estimated slopes of proteins showed significantly improved classification performance for incident AD beyond plasma A/T biomarkers.**

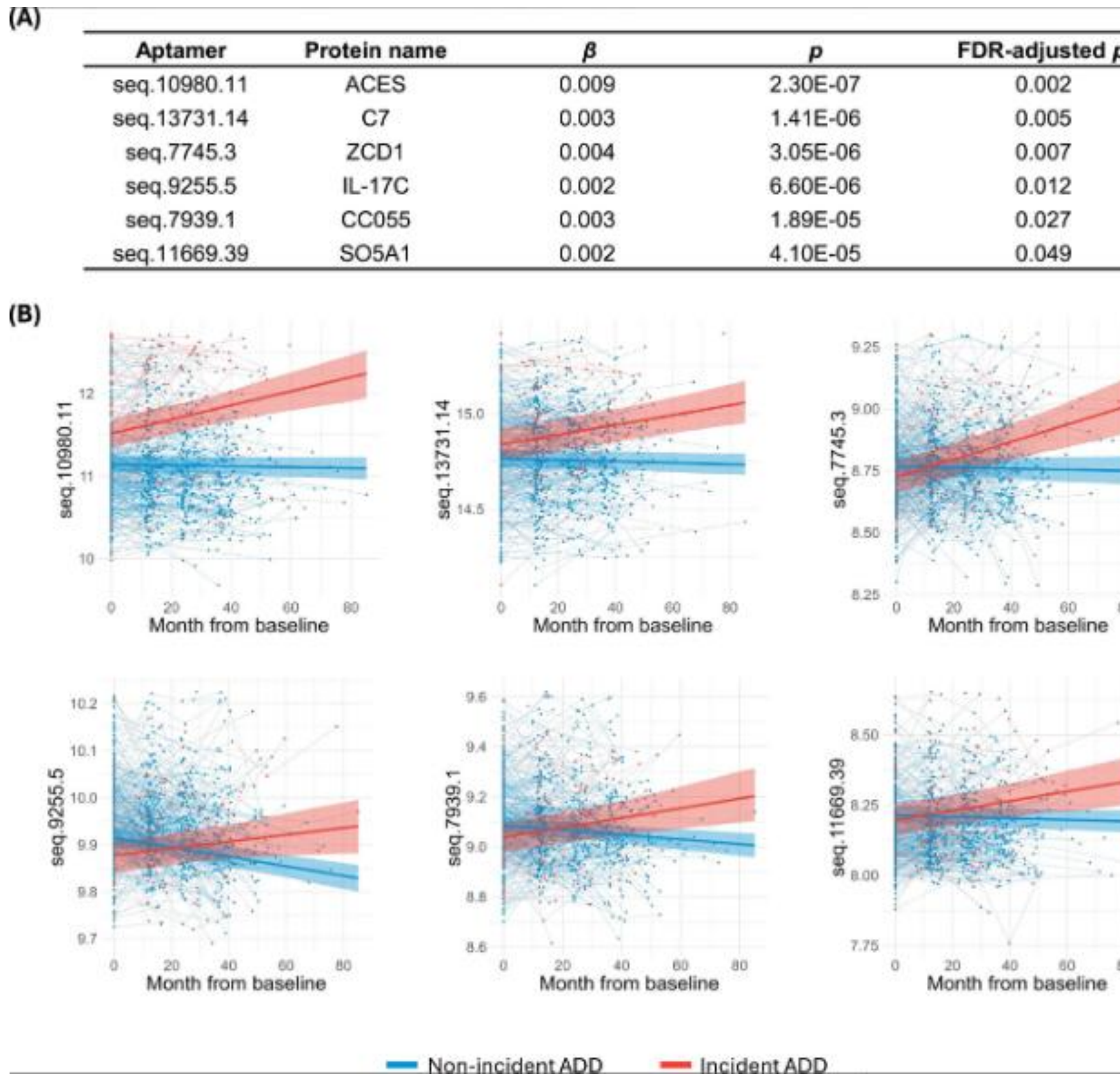


Fig. 3

Conclusions

- Dysregulated plasma proteins and pathways were identified, providing important insights into AD molecular mechanisms.
- Plasma proteomics-derived biological aging clocks and pseudotime trajectory may be a potential complementary biomarkers to current plasma A/T/N/I frameworks.
- Longitudinal changes in plasma proteins may be potential molecular signatures for tracking disease progression and predicting incident AD.