

Atlas of human plasma proteome reveals biomarkers and potential therapeutic targets for Alzheimer’s Disease

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Key Takeaways

□ The largest human plasma proteome–phenome atlas provides a comprehensive resource for biomarker discovery.

□ CEND1 is a highly AD-specific biomarker with favorable risk predictive performance, and potential causality.

□ Plasma proteomics bridges disease prediction and therapeutic target discovery, advancing precision medicine for AD.

Contact



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Introduction

Background:

Large-scale plasma proteomics enables improved understanding of human disease biology and supports precision medicine. Existing studies have identified disease-associated proteins, but a comprehensive human proteome–phenome atlas is still lacking.

Key unresolved questions include:

Are protein associations disease-specific or shared across conditions and traits?

Can plasma proteomic profiles support biological classification of human diseases?

Can circulating proteins enable minimally invasive disease diagnosis and longitudinal monitoring?

Which associations are causal, and do they represent actionable therapeutic targets?

In this study, using data from 53,026 UK Biobank participants (median follow-up: 14.8 years), we constructed a comprehensive plasma proteome–phenome atlas. We systematically investigated associations between plasma proteins, disease outcomes, and health-related traits, with a focus on: **Alzheimer’s disease (AD)-specific biomarkers and potential therapeutic targets.**

Study overview

Data

Plasma proteomics
N= 2,920 proteins

Traits N= 986

Diseases
Prevalent N= 406
Incident N= 660

Longitudinal cohort

Association analysis

Cross-sectional analysis

2006 - 2010

Longitudinal analysis

Nov. 2023

Biological insights

Prediction & Diagnosis

Drug target assessment

Enrichment analysis

Disease clusters

Characteristic biological pathways

Protein

Demographic

Protein+Demographic

Machine learning

Sensitivity

Specificity

Mendelian randomization

Genetic instrument

Protein level

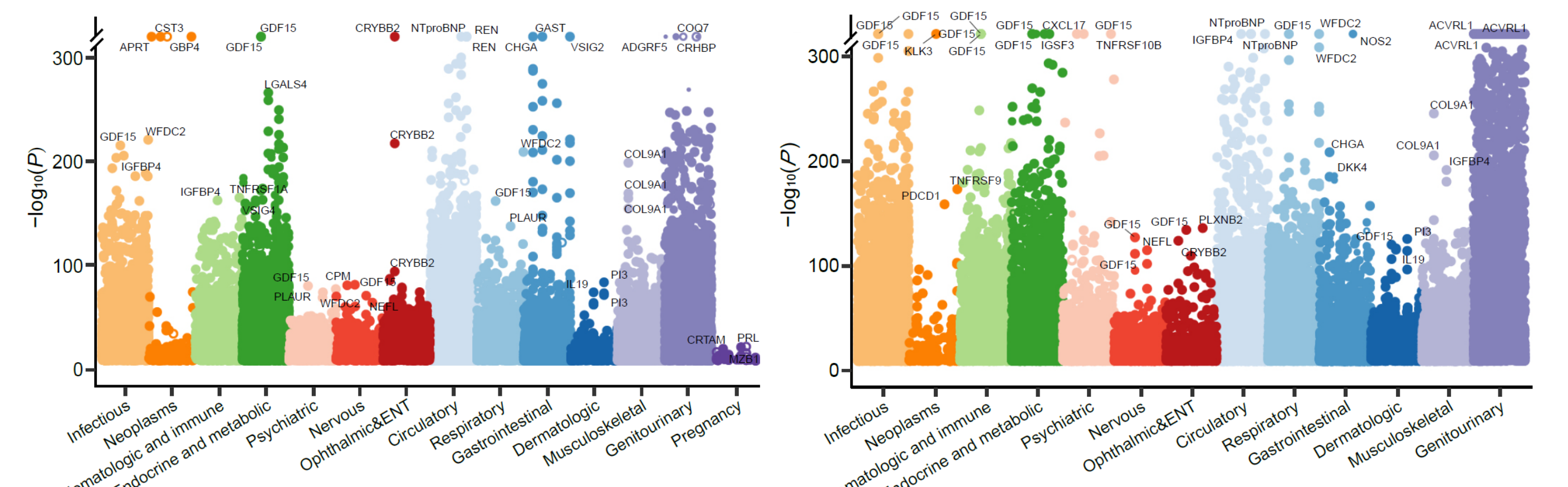
Disease

Confounders

Drug target validation & repositioning

Atlas of protein-disease associations

A total of 168,100 protein-disease associations and 554,488 protein-health trait associations were identified.

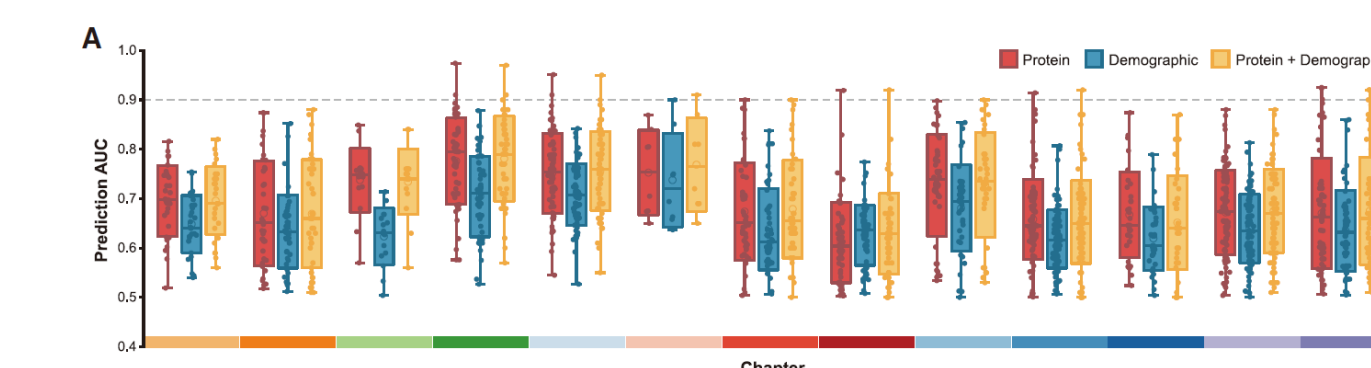


Comparisons with other diseases revealed **CEND1** as a highly neuro-specific protein, with its association to AD being the most significant.

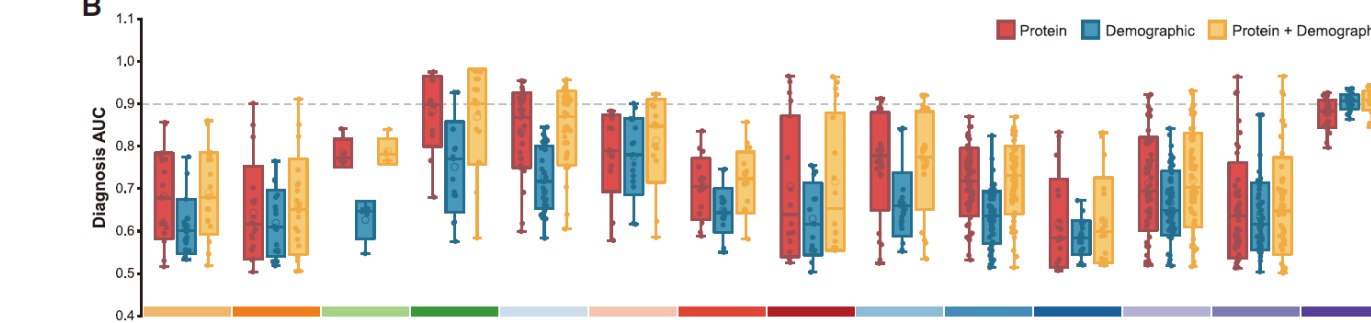
Protein	Outcome	HR	HR_lowerCI	HR_upperCI	pval_raw
CEND1	G6_ALZHEIMER	1.35921	1.24522	1.48363	6.53709E-12
CEND1	F5_ALZHEMENT	1.39468	1.26762	1.53449	8.78144E-12
CEND1	G6_NEURODEGENERATIVE	1.35573	1.24221	1.47962	9.03062E-12
CEND1	N14_CHRONKIDNEYDIS	1.17755	1.11632	1.24213	1.98344E-09

Proteins contribute to disease diagnosis and prediction

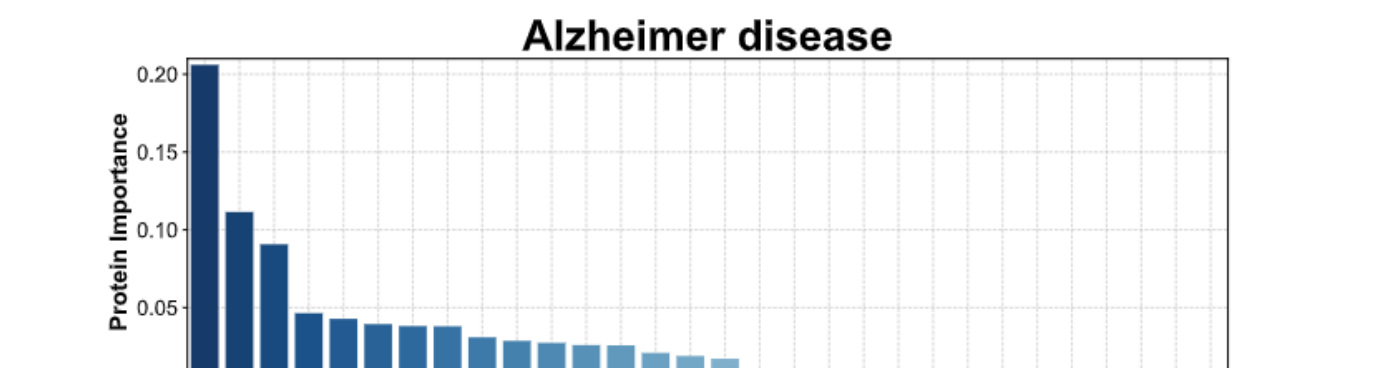
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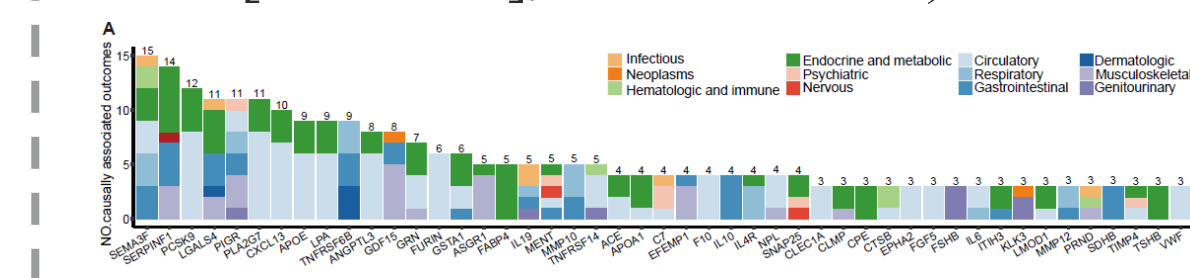
Alzheimer disease



Plasma proteomic models demonstrated excellent disease discrimination (AUC > 0.80 for 183 diseases), with **CEND1** ranking among the top 10 predictors of Alzheimer's disease (AD) risk.

Potential causal proteins

MR analysis identified **474 causal proteins**, with increased expression of **CEND1** showing a potential causal relationship with elevated AD risk (OR = 1.04 [1.02-1.07], $P = 1.10 \times 10^{-4}$).



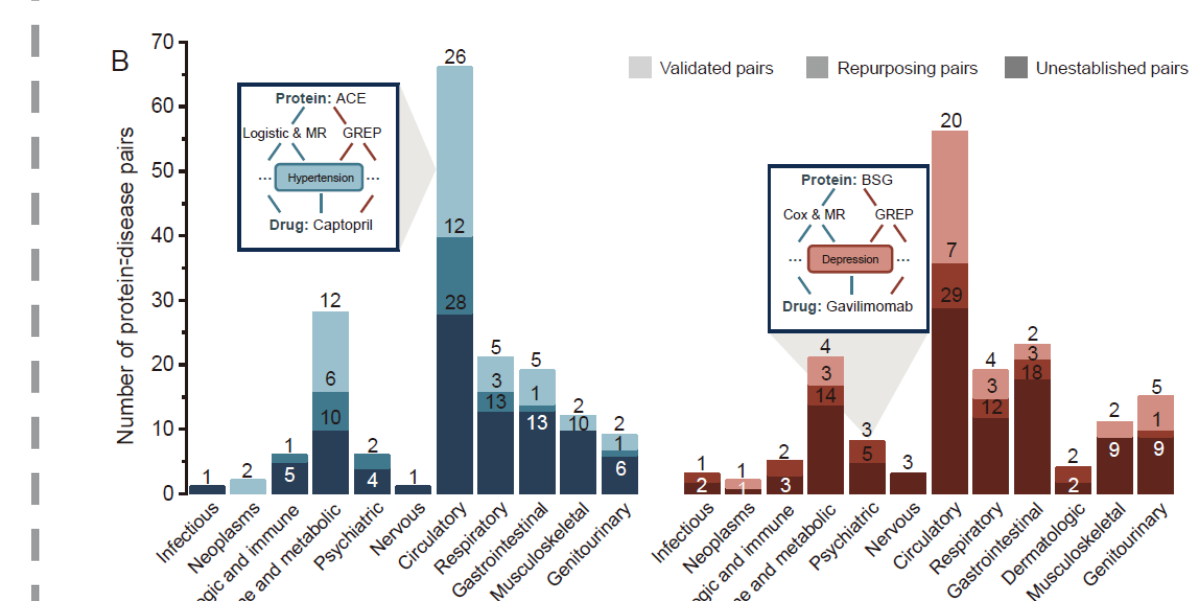
Drug target identification

Drug target analysis uncovered **37 known drug targets with repositioning potential**, alongside **26 novel targets** with favorable safety profiles.

Protein: ACE

Logic: & MR, & GP

Drug: Captopril



Protein: BSG

Logic: & MR, & GP

Drug: Glimepiride

