



CSF Proteomic Signatures Reveal the Molecular Transition from Preclinical Alzheimer's Disease to Symptom Onset

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Introduction

- Symptom onset marks a decisive inflection point in Alzheimer's disease (AD), separating silent pathology from irreversible clinical decline and exhibiting striking inter-individual variability.
- Identifying cognitively-unimpaired individuals poised for clinical conversion is central to secondary prevention and deployment of emerging disease-modifying therapies (A4, AHEAD 3-45)^{1,2}.
- We test whether CSF proteomics capture the earliest molecular transitions that foreshadow clinical disease.

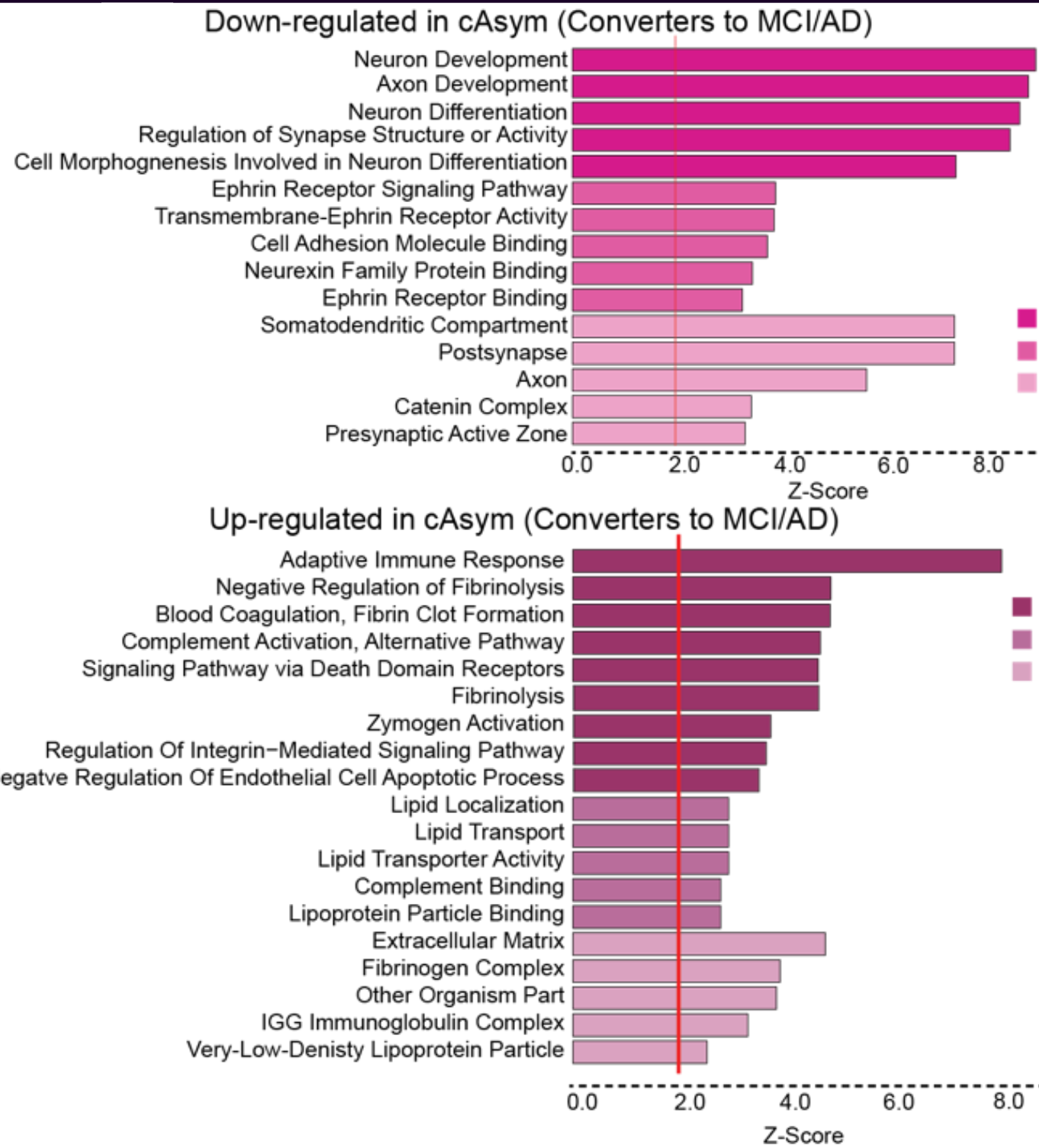
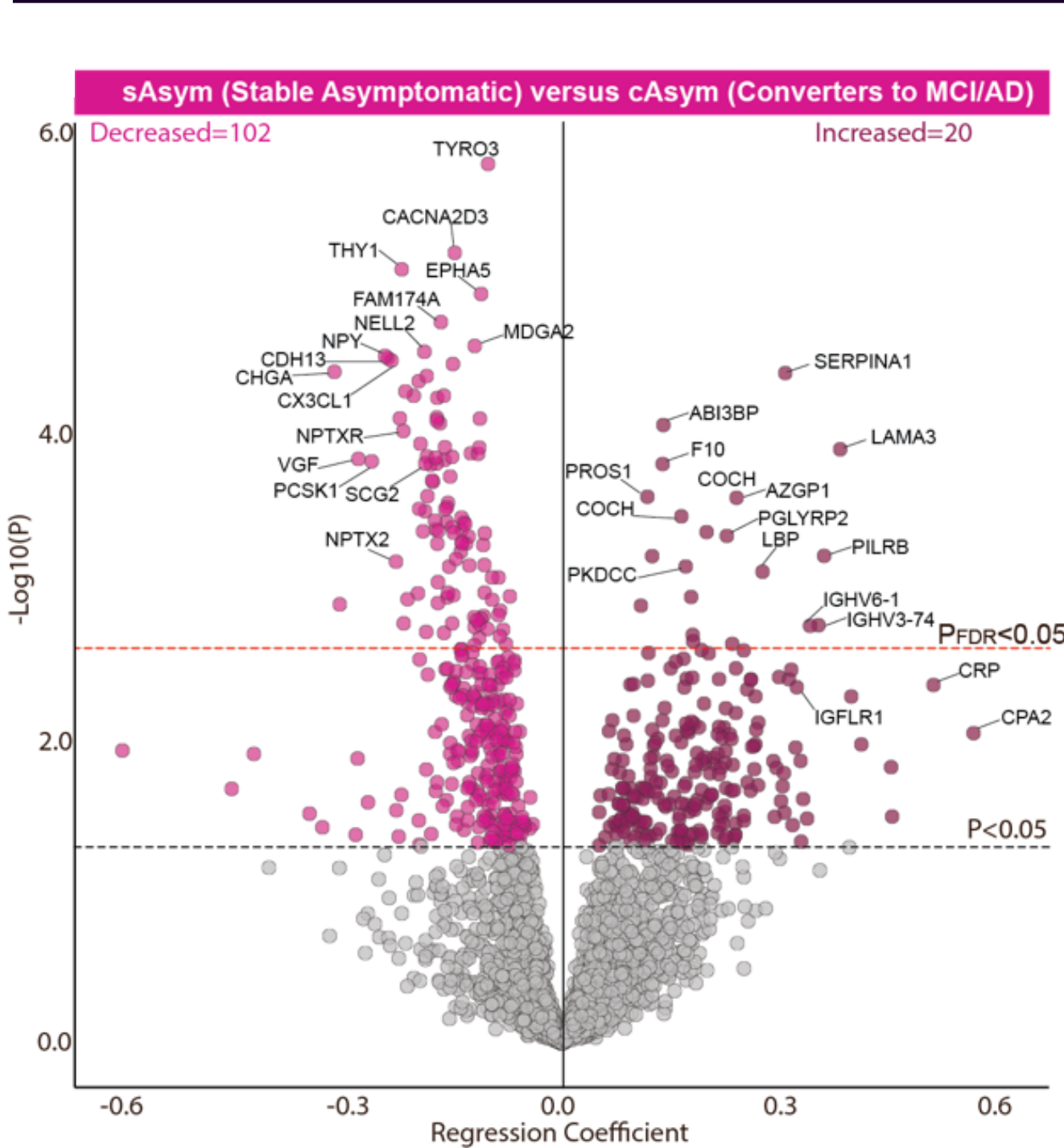
Methods

- We analyzed mass-spectrometry CSF proteomes from 100 asymptomatic Aβ+ individuals (CSF Aβ42/pTau181 ≤ 39.20³, cognitively-unimpaired) from ADNI.
- **64 stable** (sAsym; mean follow-up=5.28Y); **36 converted** to MCI/Dementia (cAsym; mean time-to-conversion=4.59Y).
- Performed differential abundance analyses to identify proteins associated with conversion.
- Anchored CSF signatures within brain proteomic network⁴.
- Machine-learning using random forest⁵ and LASSO⁶ across 100 runs was used to derive a predictive panel for onset.

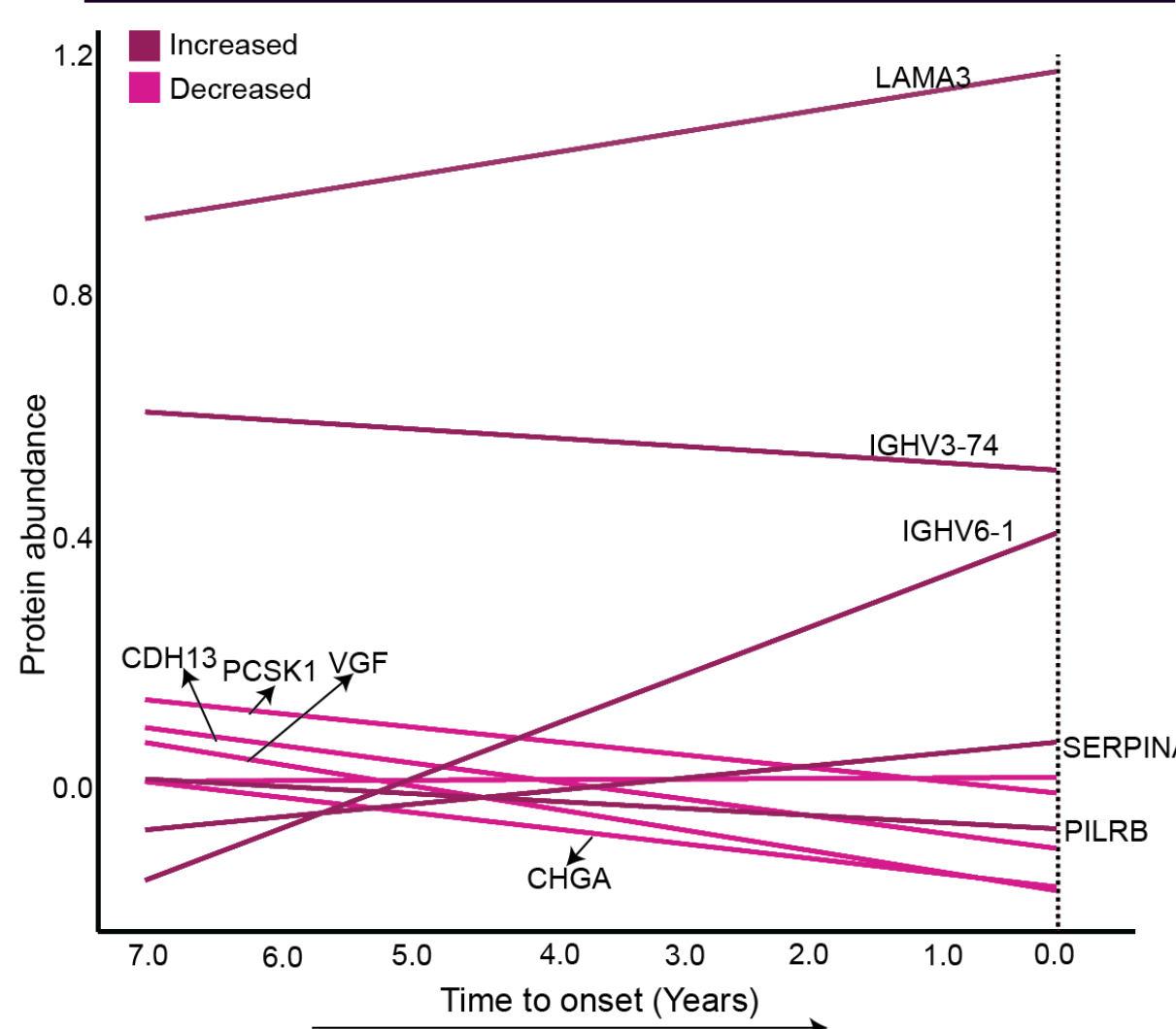
Summary demographics and clinical characteristics of asymptotic AD participants who either remained stable (sAsym) or converted to MCI/Dementia (cAsym).

	Asym AD	cAsym	sAsym
No participants, n (%)	100	36 (36.00%)	64 (64.00%)
Age: Mean (SD)	75.34 (5.88)	76.37 (4.54)	74.76 (6.47)
CSF Biomarkers			
pTau181: Mean (SD)	29.58 (10.18)	29.34 (9.99)	29.72(10.36)
Aβ42: Mean (SD)	720.42 (227.35)	700.97(210.40)	731.35 (237.26)
Sex			
Female, n (%)	61 (61.00%)	18 (50.00%)	43 (67.19%)
Male, n (%)	39 (39.00%)	18 (50.00%)	21 (32.81%)
Race			
Black, n (%)	4 (4.00%)	2 (5.56%)	2 (3.12%)
White, n (%)	96 (96.00%)	34 (94.44%)	62 (96.88%)
APOE Genotype			
Non-carriers, n (%)	42 (42.00%)	16 (44.44%)	26 (40.62%)
Heterozygous, n (%)	51 (51.00%)	18 (50.00%)	33 (51.56%)
Homozygous, n (%)	7 (7.00%)	2 (5.56%)	5 (7.81%)
Cognitive measures			
ADAS-Cog13: Mean (SD)	9.59 (4.78)	8.46 (4.36)	11.58 (4.89)
MMSE: Mean (SD)	29.00 (1.19)	28.86 (1.36)	29.08 (1.09)
CDR-SB: Mean (SD)	0.04 (0.15)	0.04 (0.14)	0.04 (0.16)

Results

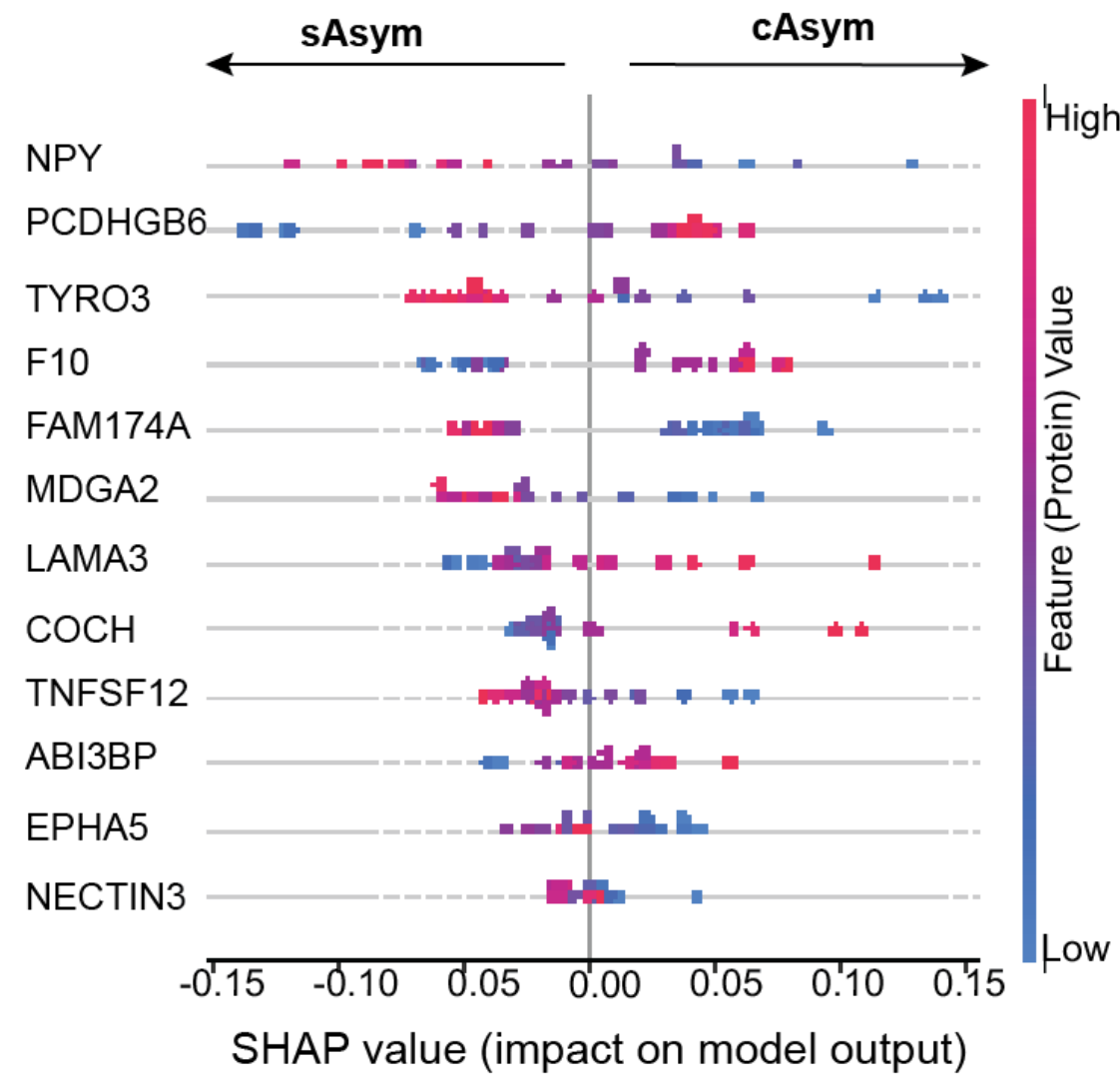


Protein abundance levels start changing years before symptom onset.



A machine learning panel of 12 proteins could predict converters in advance.

CSF protein panel predictive of onset



AUC: Median 0.89 (95% CI: 0.74-1.00)

Acknowledgements/Contacts



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We identified a mass spectrometry CSF proteomic signature that flags cognitively-unimpaired Aβ+ individuals poised to convert, offering a scalable tool to enrich secondary-prevention and disease-modifying therapy trials.

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