

Proteomic Signatures Predict Beneficial and Adverse Response to Amyloid Targeting Therapy

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Background

- Proteomic analyses have identified many pathways impacted in Alzheimer's disease
- Little is known about how amyloid targeting therapies (ATTs) impact broader biological pathways
- Alterations in specific pathways may provide insight into key biologic mechanisms involved in beneficial and adverse therapeutic response
- Goal: Investigate alterations in protein abundance after 3 months of ATT compared to pre-treatment baseline and evaluate proteomic signatures predicting rate of cognitive decline and ARIA-E risk**

Study Design and Participant Characteristics

Penn Alzheimer's Therapeutic Monitoring (ATM) study design:

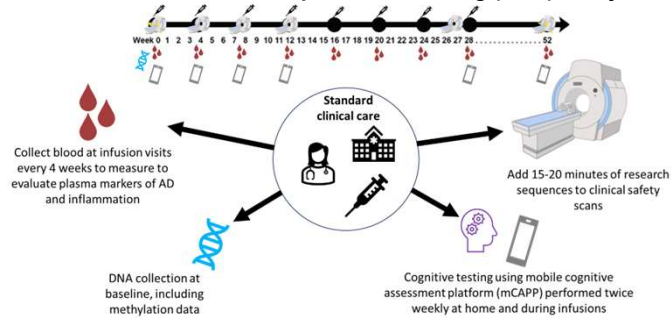


Figure 1. Participant Characteristics

Characteristic	Overall (N = 119)	No ARIA-E (n = 94)	ARIA-E (n = 25)
Age, years	73.2 (7.2)	73.3 (7.1)	72.5 (7.4)
Sex			
Female	58 (48.7%)	41 (43.6%)	17 (68.0%)
Male	61 (51.3%)	53 (56.4%)	8 (32.0%)
Race			
Asian	1 (0.8%)	1 (1.1%)	
Black or African American	3 (2.5%)	2 (2.1%)	1 (4.0%)
Unknown or Not Reported	4 (3.4%)	2 (2.1%)	2 (8.0%)
White	111 (93.3%)	89 (94.7%)	22 (88.0%)
Diagnosis			
MCI	81 (68.1%)	62 (66.0%)	19 (76.0%)
Mild Dementia	38 (31.9%)	32 (34.0%)	6 (24.0%)
Education, years	16.6 (2.6)	16.5 (2.5)	16.9 (2.9)
MMSE	24.2 (3.5)	24.2 (3.6)	24.5 (2.9)
Baseline BD-pTau-217, pg/mL	12.8 (0.7)	12.8 (0.7)	12.9 (0.7)
ApoE Genotype			
Non-Carrier	40 (33.6%)	36 (38.3%)	4 (16.0%)
Heterozygote	72 (60.5%)	54 (57.4%)	18 (72.0%)
Homozygote	7 (5.9%)	4 (4.3%)	3 (12.0%)
Amyloid Targeting Therapy			
Donanemab	51 (42.9%)	35 (37.2%)	16 (64.0%)
Lecanemab	68 (57.1%)	59 (62.8%)	9 (36.0%)

Values are mean (SD) for continuous variables and n (%) for categorical variables.

- Samples collected in EDTA tubes, centrifuged and stored at -80°C
- Pre-treatment and 3 months post-ATT plasma analyzed using Nulisa CNS 120 panel
- ARIA-E identified on clinical surveillance MRIs
- For participants with at least 6 months of longitudinal MMSE data available post-treatment, slope of MMSE change during treatment was calculated using linear regression

- Linear mixed-models used to compare effects of interest on relative abundance of each target protein while controlling for age, sex, and random effect of participant
- Minimum log2-fold change of 0.25 and FDR-corrected $p < 0.05$ were considered significant

Tau-MaX and Clinical Impairment by Stage

- Linear mixed-models evaluated the interaction between treatment × MMSE slope on relative abundance of each target protein while controlling for age, sex, education, and baseline BD-pTau-217
- Identified proteins were used to create multivariable signature of treatment response and then baseline and follow-up abundance were used to predict MMSE slope and compared to actual MMSE slope

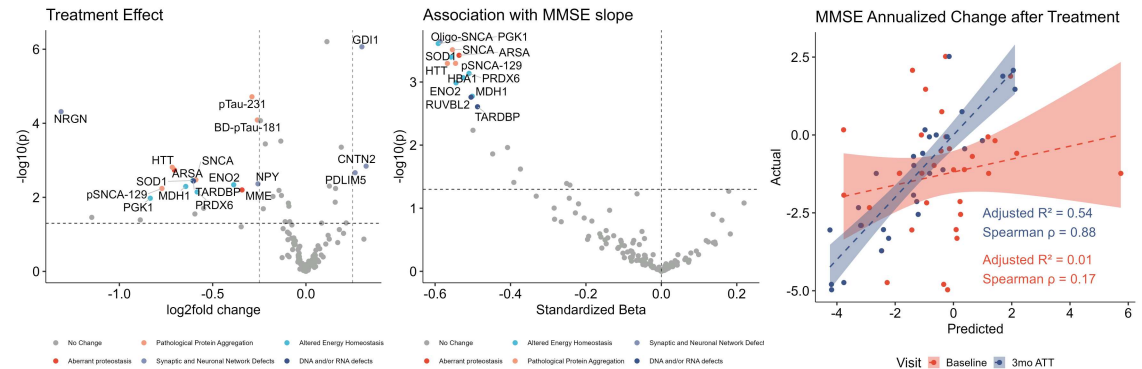


Figure 1. Differential abundance analyses before and after treatment (left) and association of changes with MMSE slope during treatment (middle). Proteins surviving FDR correction are labeled and vertical dashed lines represent minimal fold-change considered significant. Right: Association between MMSE predicted by a proteomic signature made up of all significant proteins from the middle panel and actual MMSE using baseline and follow-up protein abundance

Regional Tau Burden by Stage

- Baseline abundance of proteins was compared between those who developed ARIA-E and those who did not while controlling for age, sex, ATT agent, and ApoE genotype
- ARIA risk signature created by combining these proteins and ApoE genotype and compared in those who did and did not develop ARIA-E

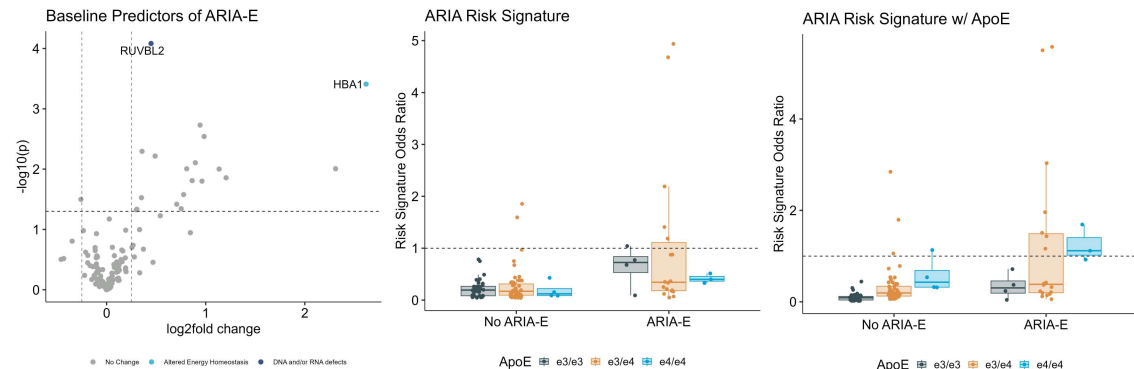


Figure 2. Left: Differential abundance analysis comparing baseline levels in those who develop ARIA-E versus those who do not. Proteins surviving FDR correction are labeled. Comparison of those developing ARIA-E and those without ARIA-E using the proteomic signature without (middle) and with (right) ApoE genotype included in the risk score with color indicating ApoE genotype

Conclusions

- Alterations in protein levels within the first 3 months of ATT predict both cognitive outcomes and ARIA risk
- These proteins are largely unique from traditional AD molecular markers of pathology

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