

Plasma Proteomic Signatures of Domain-specific Alzheimer’s Disease Polygenic Risk

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BACKGROUND

Alzheimer’s disease (AD) is genetically heterogeneous, with risk variants implicating various biological pathways, including immune response, lipid metabolism, synaptic function, mitochondrial metabolism, proteostasis, and structural stabilization.

Conventional genome-wide AD polygenic risk scores (PRS) aggregate genetic effects across distinct biological pathways. While useful for risk prediction, collapsing across pathways may dilute or obscure pathway-specific biological signals

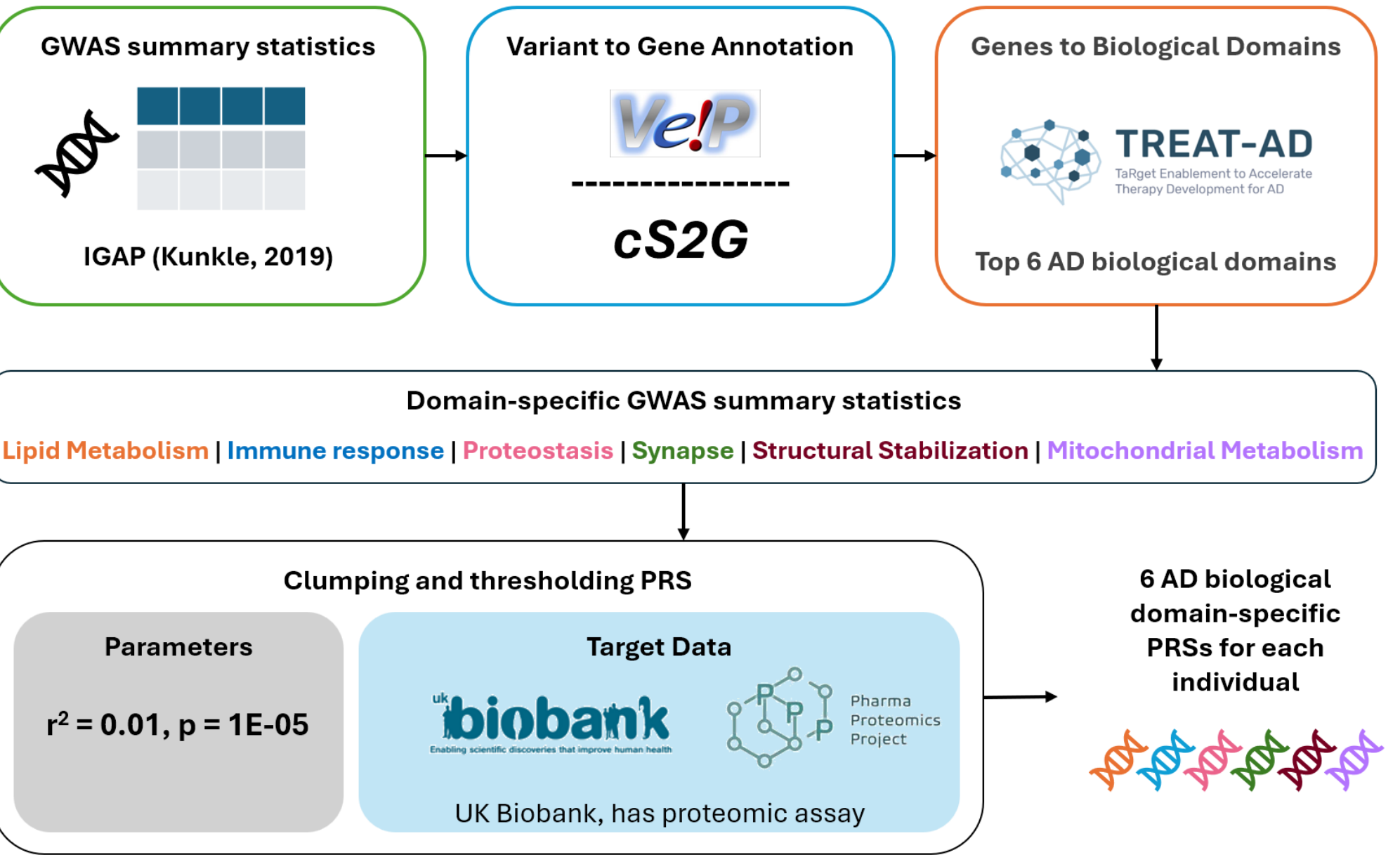
Plasma proteins can capture downstream biological signatures associated with pathway-specific AD genetic risk.

We hypothesized that biologically partitioned (domain-specific) AD polygenic risk scores would reveal proteomic signatures not detected by a genome-wide PRS.

METHODS

We constructed six domain-specific AD PRS corresponding to the primary TREAT-AD biological domains. We excluded the APOE region.

Figure 1. Pipeline for domain-specific PRS construction



In **UK Biobank**, we tested associations between each domain-specific AD PRS and plasma protein abundance using linear regression.

We compared domain-specific PRS results with a genome-wide AD PRS. We repeated PRS-protein association tests within age strata to evaluate whether pathway-specific proteomic signatures differ across midlife and later life.

We annotated associated proteins for relevance to AD biology using the AGORA database, which aggregates brain eQTL evidence and differential RNA and protein expression in AD brains versus controls.

Proteins identified in the discovery cohort with independent biological support were carried forward for longitudinal follow-up in **MESA**. We used linear mixed-effects models to test whether domain-specific AD PRS were associated with protein trajectories.

CONCLUSIONS

- Domain-specific AD PRS uncover plasma proteomic signatures not detected by a genome-wide score
- Immune response and lipid metabolism pathways dominate proteomic associations at age 64+; structural stabilization and mitochondrial metabolism pathway associations are enriched earlier (age 39–50).
- Longitudinal changes in ANXA1, SERPINE2, and PLXDC2 were associated with domain-specific AD PRS in MESA, with directions concordant with UKB cross-sectional discovery results.

RESULTS

Cross-sectional PRS–protein association analysis (UKB)

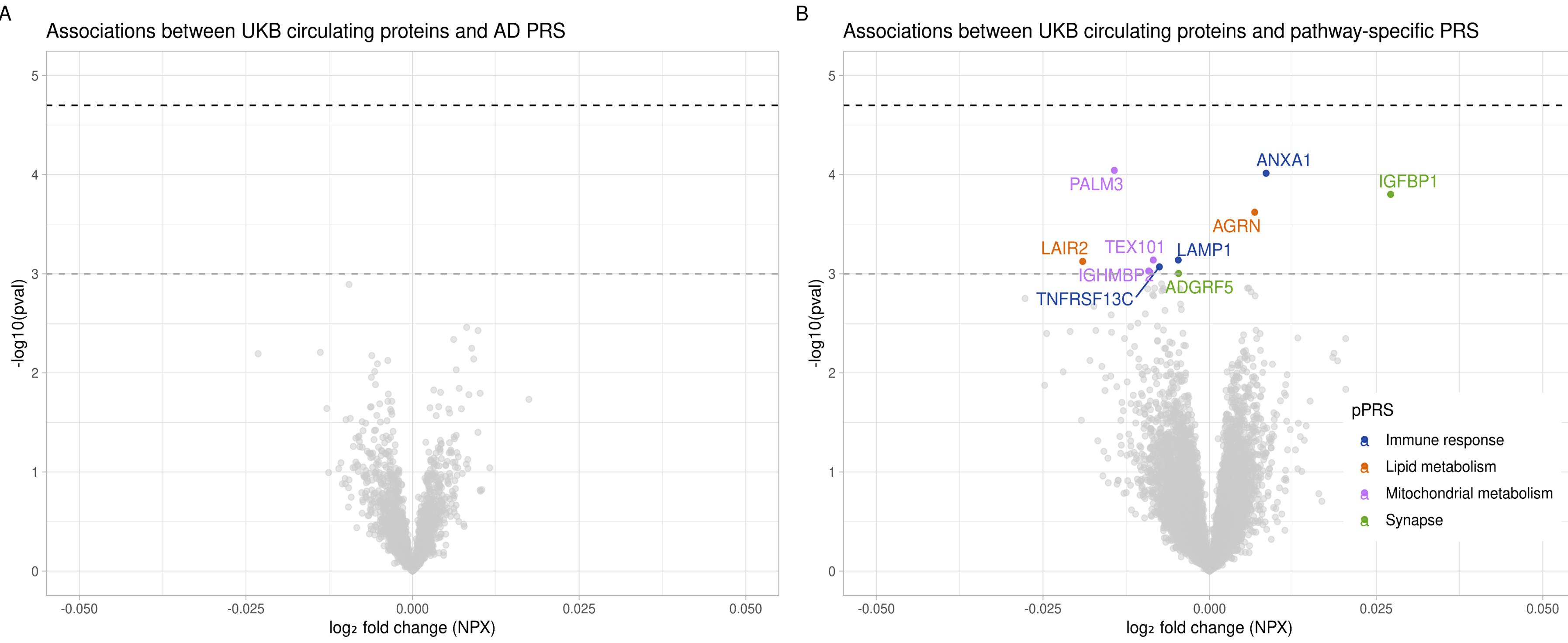
Table 1: Each PRS was tested for association with clinical AD using ADSP data

Figure 2: Genome-wide and domain-specific AD PRS were tested for association with circulating protein abundance

PRS	OR (95% CI)
Lipid Metabolism	1.11 (1.06, 1.17)
Immune Response	1.16 (1.10, 1.22)
Proteostasis	1.10 (1.04, 1.16)
Synapse	1.11 (1.05, 1.17)
Structural Stabilization	1.09 (1.03, 1.14)
Mitochondrial Metabolism	1.05 (1.00, 1.11)
Overall (genome-wide)	1.14 (1.08, 1.20)

Figure 2.

Linear regression: $NPX \sim PRS + age + sex + batch + PC1-10$



Age-stratified analysis of PRS–protein associations (UKB)

Table 2: Counts of PRS-associated proteins by age stratum and biological domain

Figure 3: Hierarchical heatmap of PRS–protein associations across domain-specific PRS and age-stratified analyses

Table 3: AGORA annotation of PRS-associated proteins using AD therapeutic target, brain eQTL, differential RNA, and differential protein evidence.

	39-50	51-58	59-63	64-70
Lipid Metabolism	1	4	0	7
Immune Response	1	3	0	14
Proteostasis	0	2	1	7
Synapse	1	2	0	2
Structural Stabilization	3	4	1	0
Mitochondrial Metabolism	3	3	1	0

Figure 3.

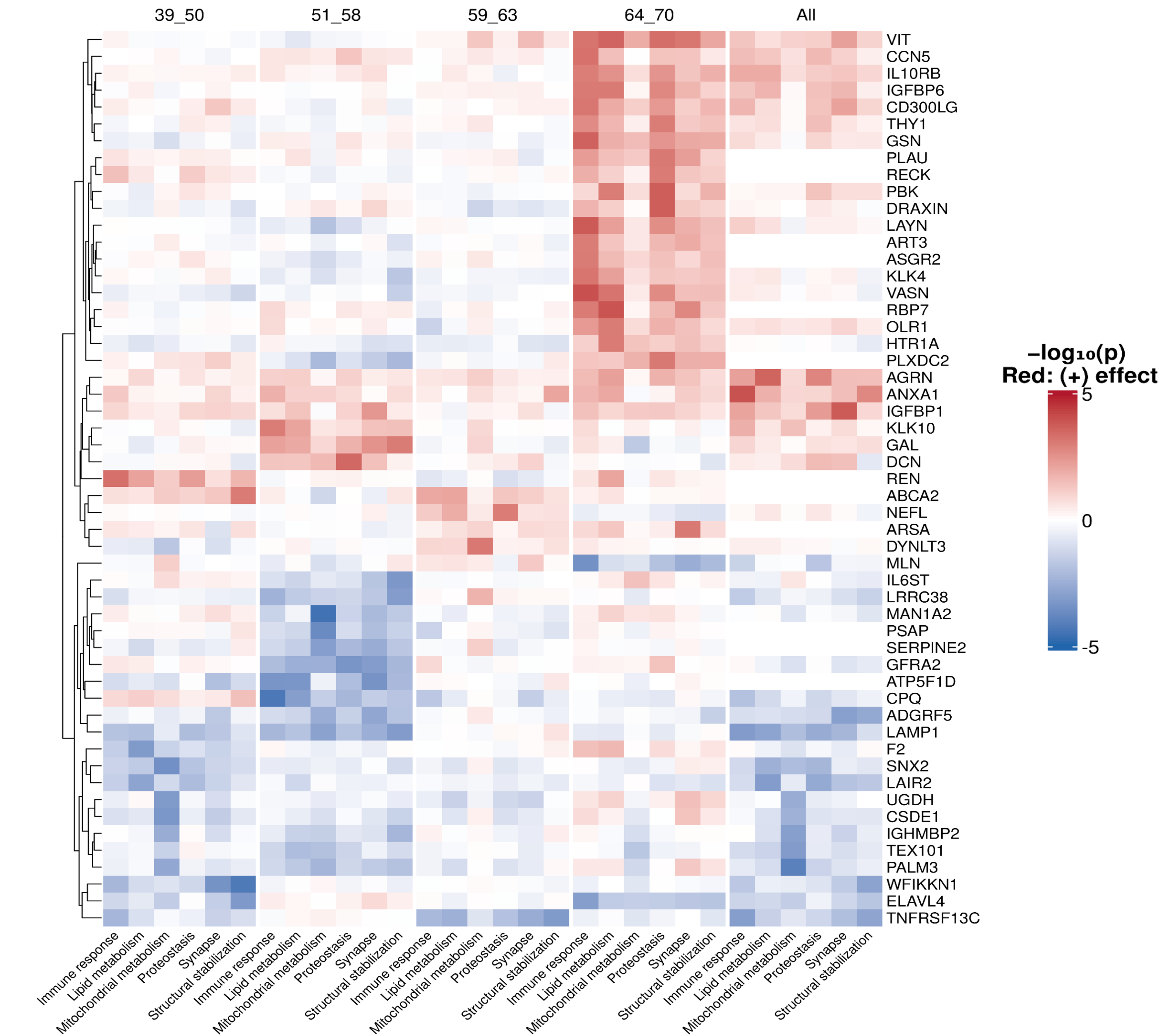


Table 3.

	eQTL	RNA	Protein
ANXA1*			
DCN*			
ELAVL4*			
GSN*			
IL6ST*			
NEFL*			
PLXDC2*			
PSAP*			
AGRN			
GFRA2			
HTR1A			
PALM3			
SERPINE2			
THY1			
TNFRSF13C			

*previously nominated AGORA target

eQTL: gene has eQTL evidence in AD-relevant brain tissue

RNA: differential RNA expression in AD brain vs control

Protein: differential protein expression in AD brain vs control

Longitudinal PRS–protein trajectory analysis (MESA)

Figure 4: Proteins with both UKB PRS–protein association evidence and AGORA AD biological support were tested using repeated MESA plasma proteomic measurements across Exams 1, 5, and 6.

Linear mixed-effects models evaluated whether genome-wide domain-specific AD PRS were associated with protein trajectories over approximately 16 years.

Proteins with significant PRS-by-time trajectory associations are shown. No significant longitudinal associations were observed for the genome-wide AD PRS.

Figure 4.

Change in plasma protein abundance from baseline by AD PRS tertile

Points show mean +/- 95% CI at each exam

