

Proteomic Signatures of *APOE*- ϵ 4 Resilience Reveal Causal Pathways That Delay Alzheimer's Disease Onset

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BACKGROUND

- *APOE*- ϵ 4 is the strongest common genetic risk factor for late-onset Alzheimer's disease, but many carriers remain cognitively unimpaired into late life.
- Identifying the biology of protected *APOE*- ϵ 4 carriers may reveal pathways that delay clinical onset.
- Plasma proteomics enables scalable biomarker discovery in living humans.
- Integrating proteomic signals with orthogonal human genetic evidence can help prioritize causal mechanisms and therapeutic targets.

OBJECTIVE

- To identify plasma proteins associated with delayed clinical onset among older protected *APOE*- ϵ 4 carriers.
- To prioritize protective pathways by integrating GNPC proteomics with rare-variant burden testing and Mendelian randomization

STUDY DESIGN

Figure 1. Protected- ϵ 4-first plasma proteomics and genetic triangulation framework

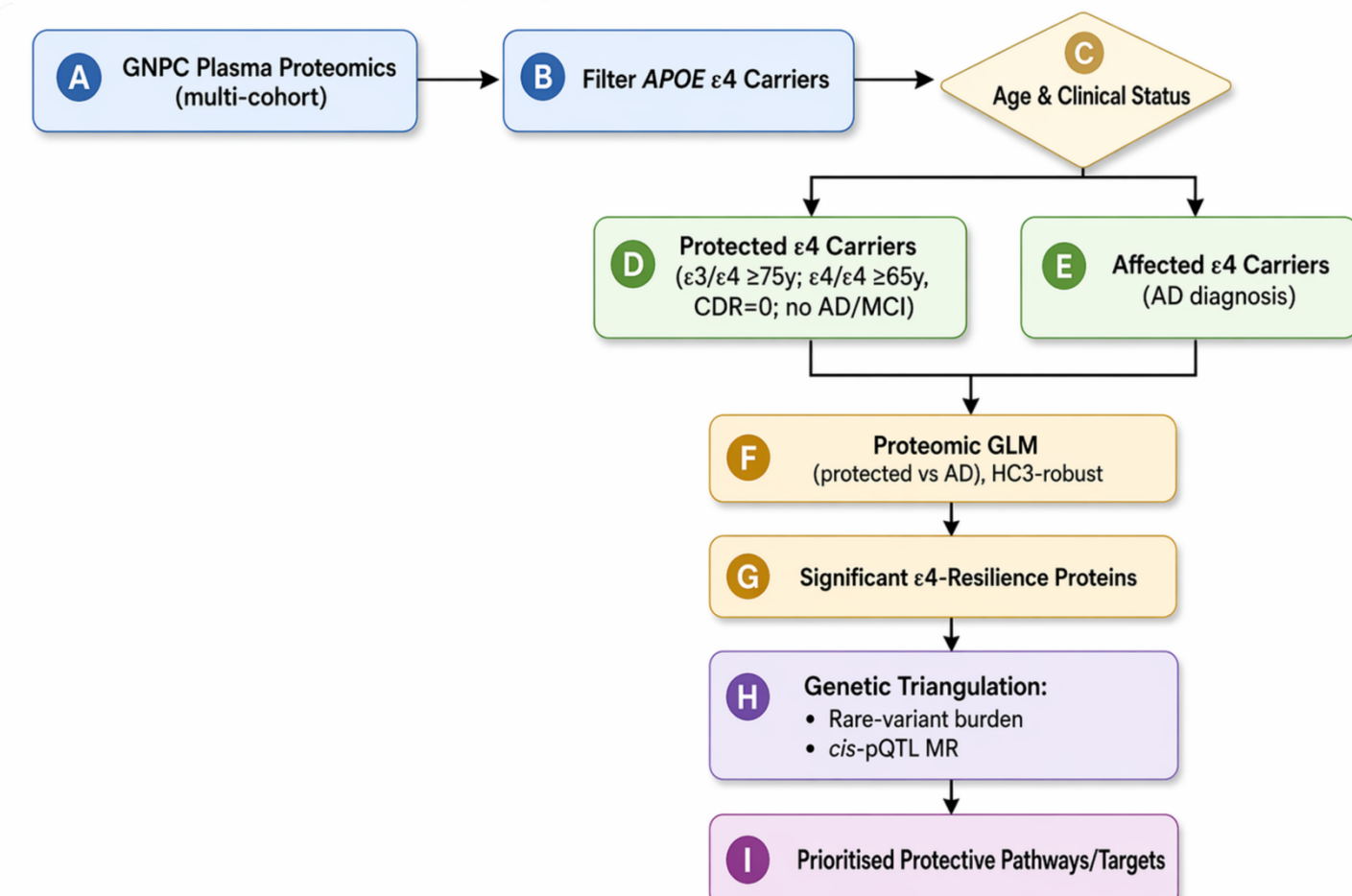
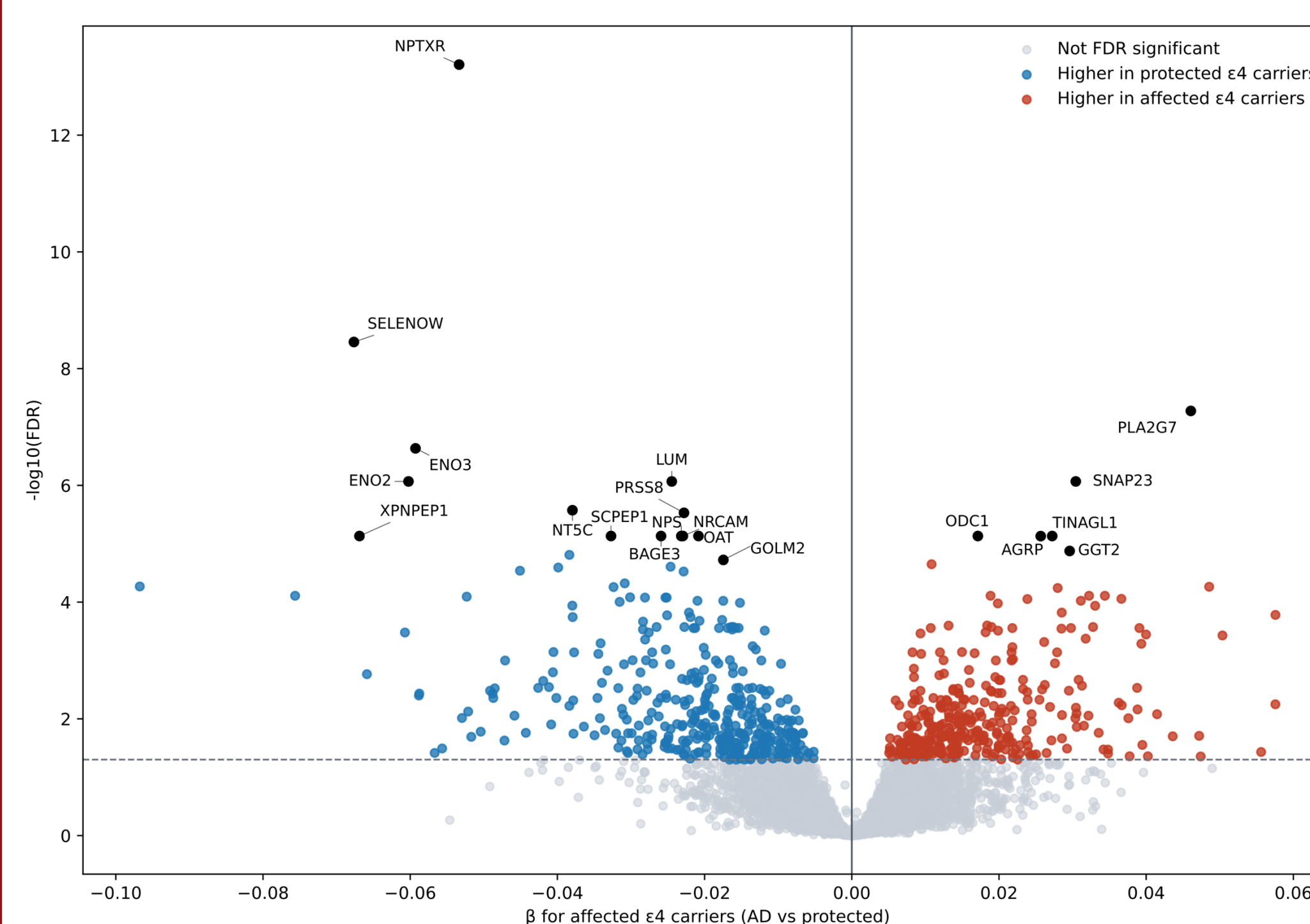


Figure 2. Proteome-wide landscape of protected versus affected *APOE*- ϵ 4 carriers



KEY FINDINGS



Protected ϵ 4 status was associated with many significant protein differences



Negative β values indicate proteins relatively higher in protected carriers

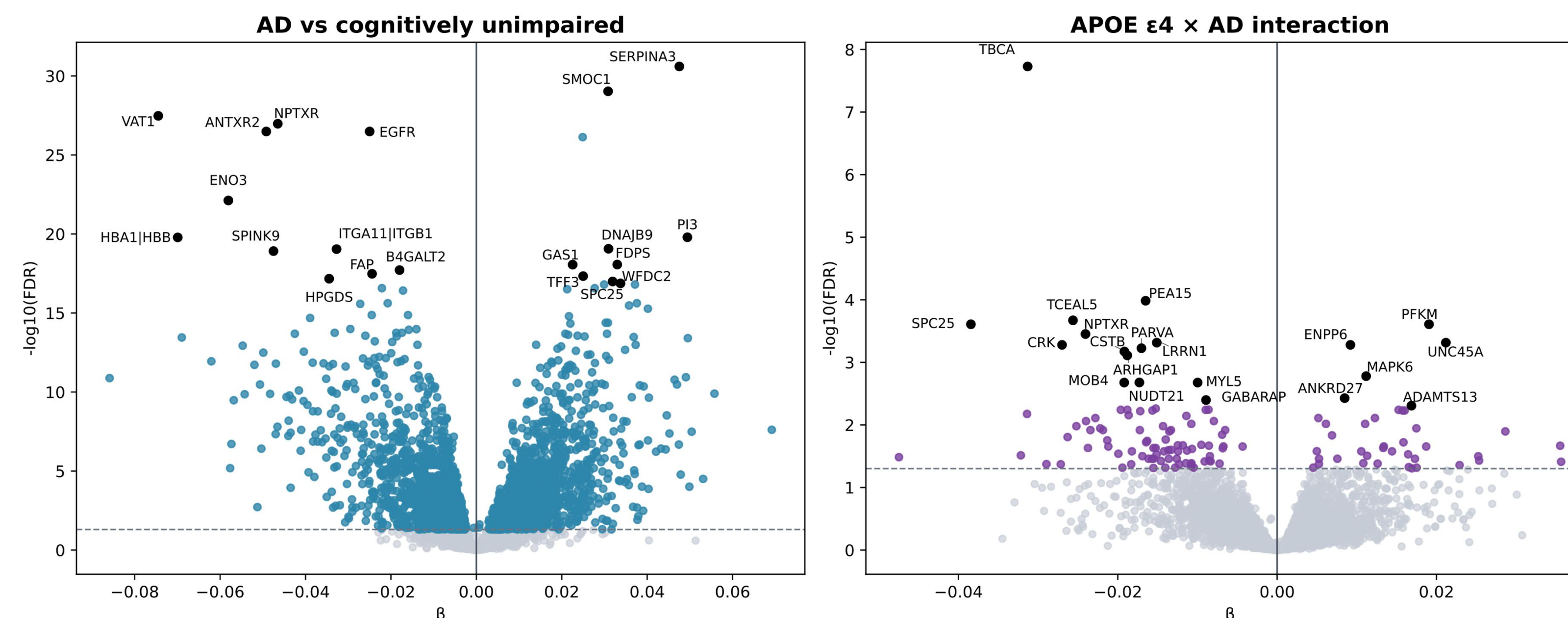


Positive β values indicate proteins relatively higher in affected carriers



Representative highlighted signals include NPTXR and SELENOW on the protected side and PLA2G7 and SNAP23 on the affected side

Figure 3. Population-wide AD association and *APOE* ϵ 4 $\times$ AD interaction analyses



INTERPRETATION



Population-wide AD signals and ϵ 4-modified signals partially overlap but are not identical

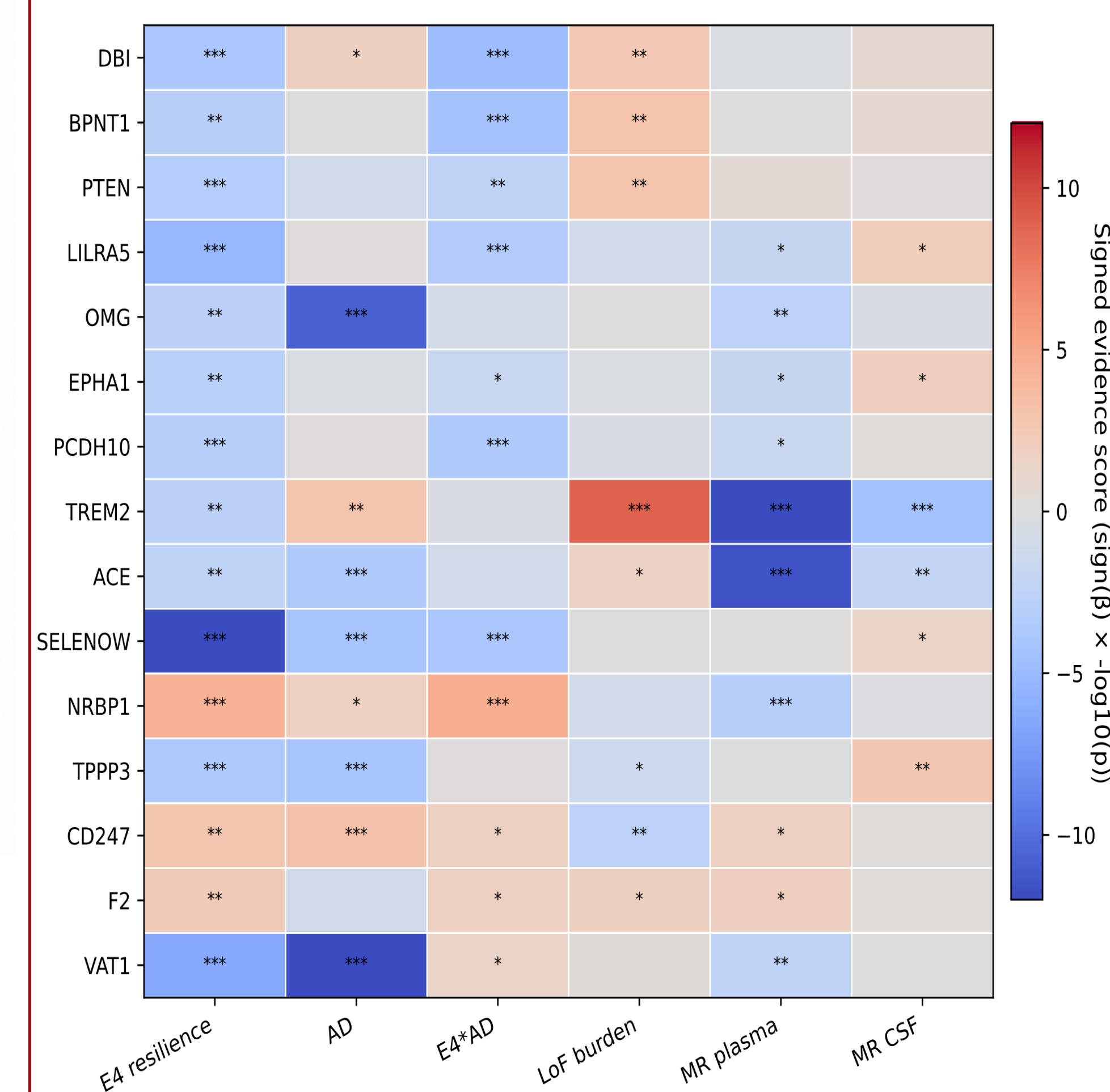


The *APOE* ϵ 4 $\times$ AD interaction analysis highlights proteins whose AD association differs by ϵ 4 carrier status



TREM2 and ACE were also supported by integrated evidence

Figure 4. Integrated evidence across proteomic and genetic analyses



PRIORITIZED PROTEINS



ϵ 4-modified candidate proteins:
LILRA5, DBI, BPNT1, PTEN, EPHA1, PCDH10



Broader AD-related signals:
OMG, SELENOW, VAT1, TPPP3



Additional supported proteins:
TREM2 and ACE

TAKE-HOME MESSAGES

- 1 A resilience-first design identifies plasma signatures associated with delayed clinical onset among *APOE*- ϵ 4 carriers 
- 2 Integrated proteomic and genetic analyses prioritize immune, synaptic, metabolic-stress, and myelin/axonal pathways 
- 3 These results highlight candidate protective mechanisms and targets relevant to delaying Alzheimer's disease onset 

FUTURE DIRECTIONS



Replicate prioritized signals across independent cohorts and platforms



Test whether prioritized proteins predict resilience, progression, or treatment response



Functionally investigate leading targets and pathways.

