

CSF Proteomics Identifies Distinct Markers For *TREM2* Risk Variant Carriers of Alzheimer's Disease

Jigyasha Timsina^{1,2}, Menghan Liu^{1,2}, Yike Chen^{1,2}, John Budde^{1,2}, Carlos Cruchaga^{1,2,3}

¹Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA

²NeuroGenomics and Informatics Center, Washington University School of Medicine, St. Louis, MO 63110, USA

³Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO 63110, USA

- Findings from CSF proteomic networks suggest a contact system induced coagulation-inflammatory crosstalk.
- This ultimately results into a weakened brain barrier in *TREM2* variant carriers.
- Proteomic signature differ between *TREM2* variant type.

INTRODUCTION

- Triggering receptor expressed on myeloid cells 2 (*TREM2*) is considered the second strongest genetic risk factor for LOAD, with rare coding variants in the gene increasing the risk of AD by up to three-fold^{1,2}.
- Altered *TREM2* homeostasis in presence of rare coding variants are likely to produce a distinct disease signature beyond the established hallmark of AD disease^{3,4}.
- It is thus necessary to identify *TREM2* variant carrier specific disease mechanism.

Table 1: Table showing sample characteristics of participants

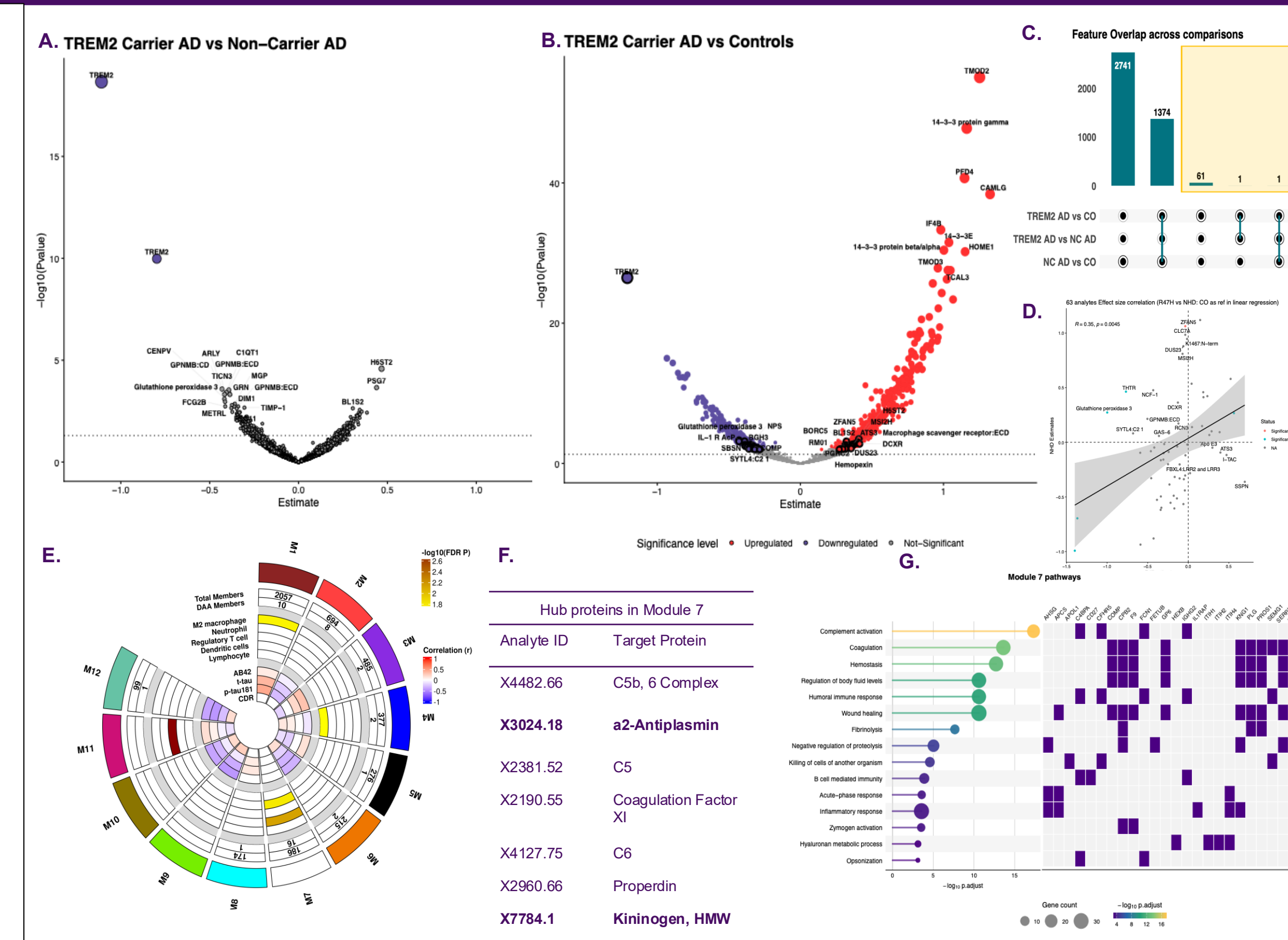
Group	N	Average Age (±SD)	%Female
Non-Carrier AD	1058	73.8 (±7.55)	50.85
Controls	616	74.6 (±8.75)	54.22
<i>TREM2</i> variant carrier AD			
R47H	15	73.5 (±8.32)	13.33
R62H	26	75.3 (±7.11)	46.15
NHD associated Variants	7	72.6 (±7.41)	57.14
Others	17	75.3 (±8.69)	58.82

AD: Alzheimer's Disease; NHD: Nasu Hakola Disease; SD: Standard deviation. Age represents Age at sample draw. NHD variants include p.D87N and p.H157Y. Others include p.W191*, p.A197V, p.G166E, p.L133, p.L195, p.L211P, p.R98Q, p.R98W, p.S162R, p.T36K and p.T223L.

METHODS

- 65 variant carrier AD cases (VC AD) were compared against 1058 non-carrier AD (NC AD) and 616 non-carrier controls (CO).
- Protein levels were measured using SomaScan platform (v4.1). 7008 unique aptamers that mapped to 6361 unique proteins were available for analysis.
- Differential protein abundance (DAA). was assessed using linear regression, adjusting for age, sex, and plate effects. (FDR-corrected $p < 0.05$).
- Features of interest were identified as proteins significantly different between VC AD and NC AD or uniquely altered in VC AD compared to the Controls.
- Protein co-expression networks were constructed using Weighted Gene Coexpression Network Analysis (WGCNA).
- Pathway analysis performed for module of interest.

RESULTS



- 63 proteins** of interest identified by DAA (2 unique to VC AD vs NC AD; 62 unique to VC AD vs CO, with 1 shared). s*TREM2* was the strongest signal.
- p.R47H** and **NHD** variant carrier showed **weak correlation of effect size** for the 63 features ($r = 0.35$). p.R62H was moderately correlated with both subgroups ($r_{p.R47H} = 0.67$, $r_{NHD} = 0.62$).
- WGCNA** identified **12 modules**; **Module 7** was significantly enriched for DAA proteins and uniquely associated with **VC AD**.
- KNG1** and **$\alpha 2$ -antiplasmin** were the among the hub proteins within the module with altered levels in cases, with higher effect size in VC AD.
- Pathway analysis highlighted **immune, hemostasis and injury response related** pathways as most enriched in *TREM2* specific module. Module 7 was enriched for **peripheral immune cells**.

Conclusion

Our findings identify a distinct VC AD proteomic network that differentiates this subtype and highlights candidate biomarkers and pathways for future validation.

REFERENCES

- Deming Y, Li Z, Benitez BA, Cruchaga C. Triggering receptor expressed on myeloid cells 2 (*TREM2*): a potential therapeutic target for Alzheimer disease? Expert Opin Ther Targets. Jul 2018;22(7):587-598. doi:10.1080/14728222.2018.1486823
- Wang L, Nykanen NP, Western D, et al. Proteo-genomics of soluble *TREM2* in cerebrospinal fluid provides novel insights and identifies novel modulators for Alzheimer's disease. Mol Neurodegener. Jan 3 2024;19(1):1. doi:10.1186/s13024-023-00687-4
- Ulrich JD, Ulland TK, Colonna M, Holtzman DM. Elucidating the Role of *TREM2* in Alzheimer's Disease. Neuron. Apr 19 2017;94(2):237-248. doi:10.1016/j.neuron.2017.02.042

CONTACT

timsinai@wustl.edu
cruchagac@wustl.edu