Large-scale proteomics to enable precision medicine for Alzheimer's disease

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Background

Precision neuroscience is emerging as a transformative approach that aims to identify the **right treatment for the right patient at the right time**.

Heterogeneous population receiving same **"one size fits all therapy"**

Trial and error health care
Poor drug response rates
Adverse events

Homogeneous subgroups receiving **specific targeted therapies**

Optimized risk/benefit ratio
Early detection and intervention
Faster & smaller clinical trials

Precision neuroscience:

- Recognizes that **each patient is unique** and that individual differences in their genes, environment, and lifestyles must be considered in the treatments they receive,
- Requires **understanding of molecular drivers of disease,**
- Leverages **biomarkers** linked to these mechanisms to detect disease, even before clinical symptoms, and to monitor treatment response.

For **Alzheimer's disease** great progress has been made with the development of the **A/T/N framework** that provides a **biological definition of disease.** Further precision is needed to optimize the risk/benefit profile of treatments for patients:

- The A/T/(N) framework does **not capture all biological mechanisms** that are involved in Alzheimer's disease and might further evolve into **A/T/N/X**
- Disease **mechanisms overlap across neurodegenerative diseases** and **pathologies often co-occur**.

Methods

Proteomic profiles from body fluids reflect the pathological processes that are ongoing in the brain and support the identification of biomarkers for **patient stratification and staging along the disease trajectory**.
Johnson & Johnson is collaborating in two of the world's largest proteomics consortia: **UK Biobank Pharma Proteomics Project and Global Neurodegeneration Proteomics Consortium.**

UKB-PPP: n=62k • all common diseases & healthy controls • Olink (3k proteins, plasma) • linked to genomics, imaging & detailed health data • 13 pharmaceutical companies
GNPC: n=40K+ • multiple well-characterized neurodegeneration cohorts • Somalogic (7k proteins, plasma & CSF) • linked to genetics, cognitive assessments, fluid biomarkers, imaging & health data • funding partners: Gates Ventures & Johnson & Johnson

Here, we present analyses of CSF proteomics data from the Spanish ACE Alzheimer's disease cohort (n = 1321). Proteomic profiles were generated using the Somalogic SomaScan™ 7k aptamer-based proteomics assay. A/T/N classification is based on CSF biomarker measurements for Abeta42, PTau-181 and total Tau.

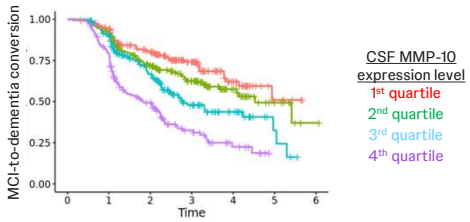
Analyses leverage Cox proportional-hazards regressions to identify biomarkers of disease progression and, hypothesis-driven (GSVA[1]) and hypothesis-free approaches (WGCNA[2], consensus clustering[3]) to characterize pathological processes and disease subtypes.

Results: Augmenting the A/T/N framework with additional prognostic biomarkers

Cox proportional-hazards regression analysis confirms that A/T/N status is a strong predictor of MCI-to-dementia progression.

Factor	P-value univariate Cox Prop-Hazards regression	P-value multivariate Cox Prop-Hazards regression
Age	<2e-16 (***)	0.000151 (***)
MMSE	<2e-16 (***)	3.41e-09 (***)
Years School	0.0209 (*)	0.238
APOE4 carrier	1.5e-06 (***)	0.330
A/T/N	<2e-16 (***)	<2e-16 (***)

CSF proteomic data enable identification of **biomarkers that further improve prediction of disease progression**, e.g. MMP-10.

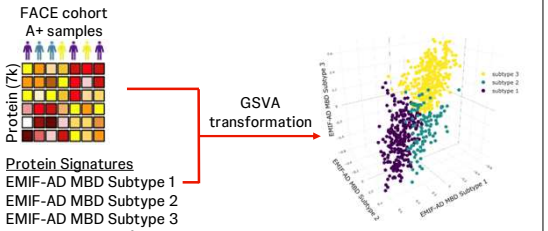


P-value multivariate Cox prop.-hazards for MMP-10 expression: 4.04 e-05 ***; adjusted for Age, MMSE & A/T/N status

In line with the study from Adami *et. al.*, 2022[4], this result nominates **MMP-10** as a **candidate biomarker to augment the A/T/N framework**.

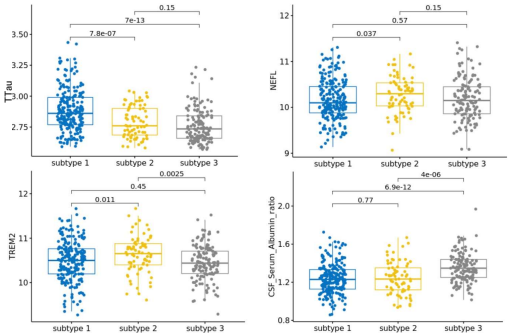
Results: Identification and validation of Alzheimer's disease subtypes

GSVA[1] transformation using the Alzheimer's disease subtype protein signatures identified by Tijms *et. al.*, 2020[2] was applied to the FACE CSF proteomics data to stratify the FACE cohort into subtypes.



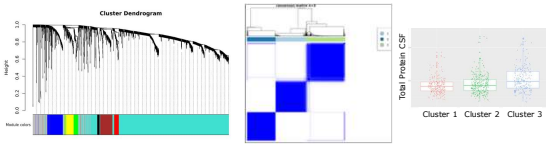
Sample subtype = subtype signature that has highest activity in sample

The subtypes **stratify patients beyond the A/T/N staging system** and display **different molecular characteristics.** E.g.: CSF TTau, NEFL, sTREM2 and CSF/serum albumin ratio of A+/T+/N+ individuals stratified by subtype.



Unsupervised analysis using **WGCNA[2] and consensus clustering[3]** identifies two strong **protein signatures that drive heterogeneity** in the FACE **Alzheimer's disease** cohort:

- **Neuronal Plasticity** - Turquoise module/cluster 1: proteins associated with nervous system development, axogenesis; increased PTau & TTau levels; enriched for proteins associated with EMIF-AD MBD subtype 1 (FDR adj. Pvalue = 1.65 e-08)
- **Blood-brain-barrier Dysfunction** - Blue module/cluster 3: proteins associated with complement signaling and blood coagulation; increased levels of total proteins in CSF and CSF/serum albumin ratio; enriched for proteins associated with EMIF-AD MBD subtype 3 (FDR adj. Pvalue = 9.20 e-31)



Preliminary results (not shown) also show strong convergence with the Alzheimer's disease subtypes described in Tijms *et al.*, 2024[5].

Taken together, these results support the hypothesis that **different molecular subtypes of Alzheimer's disease** exist. Stratification of patients based on these subtypes might further **increase precision**.

Conclusion

Large-scale **proteomics** are an invaluable tool to **accelerate the development of novel precision treatments for Alzheimer's disease**, enabling the identification of novel fluid biomarkers for patient identification, stratification and disease progression, the characterization of molecularly defined disease subtypes, and the discovery of novel drug targets that are linked to specific patient populations. .

References

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