Multivariate analysis of longitudinal cerebrospinal fluid biomarkers of pathophysiology in preclinical Alzheimer's disease

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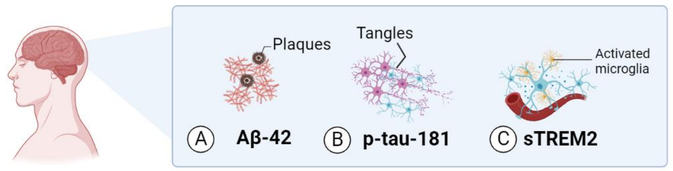
BACKGROUND

Cerebrospinal Fluid (CSF) Biomarkers

- Distinct pathological features of Alzheimer's disease (AD) [1]:

1. Senile plaques composed of amyloid β -protein (Aβ)
2. Neurofibrillary tangles composed of phosphorylated tau (p-tau)
3. Reactive microglia producing soluble trigger receptors expressed on myeloid cells 2 (sTREM2) [2]



***APOE* e4 allele**

- The greatest genetic risk factor encoding apolipoprotein E protein (ApoE) [3]

Similarity Network Fusion (SNF)

- Studies evaluating CSF biomarkers have been using univariate and cross-sectional analyses, which fail to capture the dynamic biomarker interactions and trajectories [4]
- SNF—a novel data integration technique—presents a balanced analysis of multimodal data while accounting for patient heterogeneity [5]

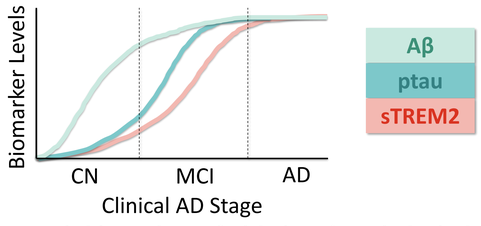


Figure 1. Dynamic biomarkers of Alzheimer's pathological cascade. CN = Cognitively Normal. MCI = Mild Cognitive Impairment.

OBJECTIVES

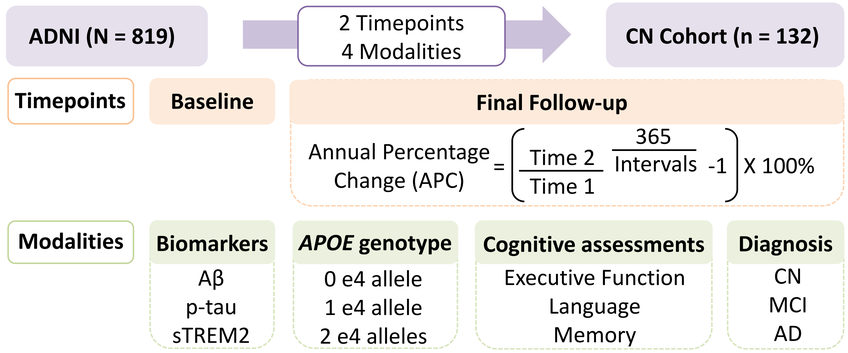
1. Detect distinct AD phenotypes based on CSF biomarkers using the patient similarity networks constructed by SNF
2. Determine whether the CSF biomarker profiles can identify patients in the preclinical stages of AD
3. Examine whether the *APOE* genotype is associated with the distinct CSF biomarker profiles detected by SNF

HYPOTHESIS

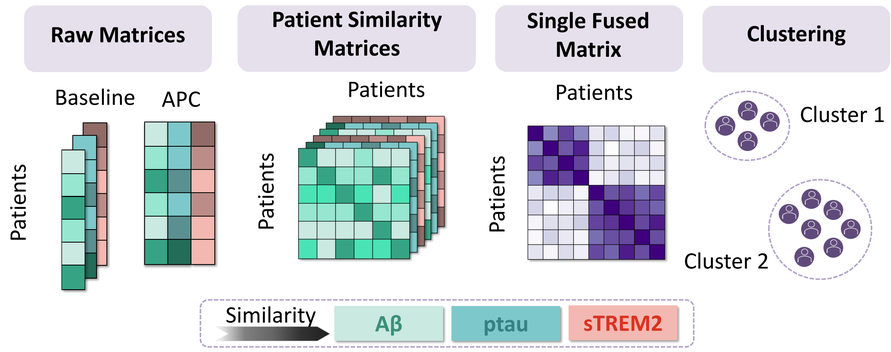
Longitudinal multivariate analysis of CSF biomarkers will reveal clusters of patients associated with the *APOE* genotype and predict AD disease progression

METHODS

Alzheimer's Disease Neuroimaging Initiative (ADNI)



Similarity Network Fusion (SNF)



RESULTS — *APOE* e4 Alleles & Final AD Diagnosis

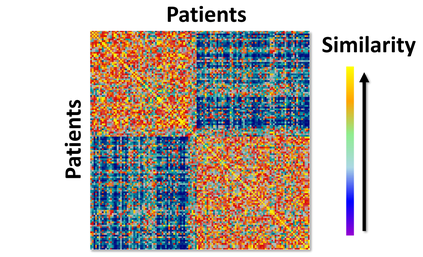


Figure 2. Fused patient similarity network matrix derived from. Cluster one, *n*=63; Cluster two, *n*=69.

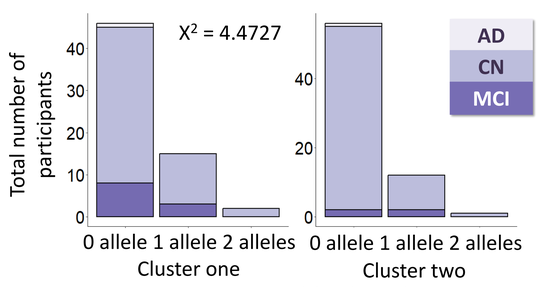


Figure 3. APOE e4 and final AD diagnosis

RESULTS — Cerebrospinal Fluid Biomarkers

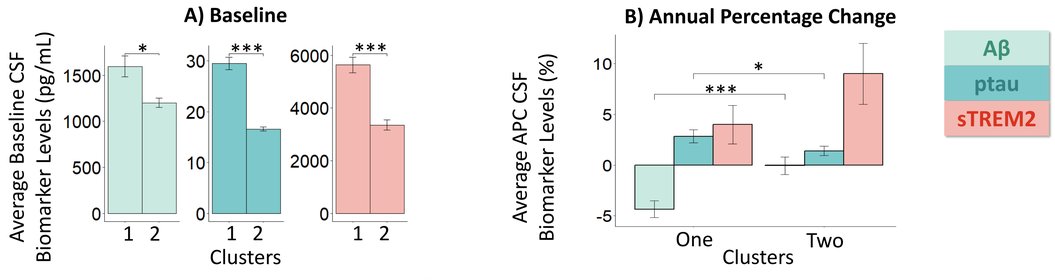


Figure 4. Average CSF biomarker levels at baseline (A) and APC time points (B). *p<0.05, **p<0.01, ***p<0.001.

RESULTS — Cognitive Assessments

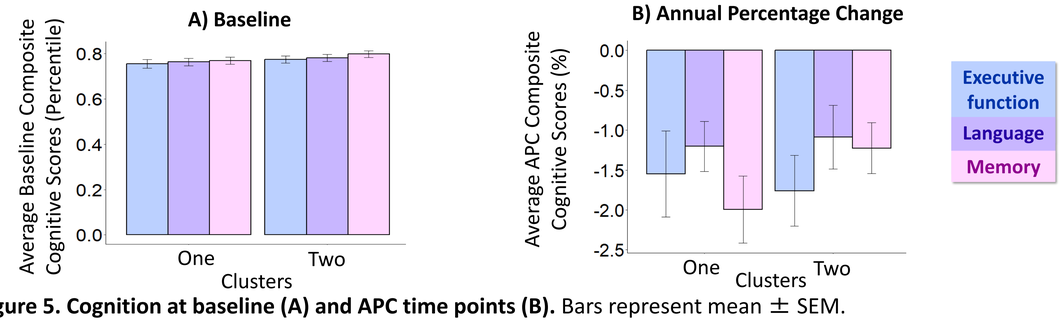


Figure 5. Cognition at baseline (A) and APC time points (B). Bars represent mean ± SEM.

DISCUSSION

- SNF detected two clusters of participants with unique CSF biomarker profiles exhibiting distinct baseline levels of Aβ, p-tau, and sTREM2 as well as distinct trajectories of Aβ and p-tau over the course of the study (Fig. 2 & Fig. 4)
- Cognition in all three domains declined in both clusters, suggesting strong age-related effects (Fig. 5)
- None of the participants with two e4 alleles transitioned to the AD group by the end of the study. The two participants that transitioned from NC to AD had zero e4 alleles. This suggests that the *APOE* genotype is not sensitive or specific to the clinical diagnosis of AD (Fig. 3).
- Ultimately, the findings from this study demonstrate that longitudinal multivariate analysis of CSF biomarkers do not predict the *APOE* e4 allele status or identify patients in the preclinical stages of AD
- Future studies will investigate whether the integration of imaging biomarkers with CSF biomarkers will detect the asymptomatic trajectories of AD pathology with greater confidence

REFERENCES

1. Anoop A, Singh PK, Jacob RS, and Maji SK (2010) CSF Biomarkers for Alzheimer's Disease Diagnosis. *Int J Alzheimers Dis* **2010**:606802.
2. Zhong L, Chen X-F, Wang T, Wang Zhe, Liao C, Wang Zongqi, Huang R, Wang D, Li X, Wu L, Jia L, Zheng H, Painter M, Atagi Y, Liu C-C, Zhang Y-W, Fryer JD, Xu H, and Bu G (2017) Soluble TREM2 induces inflammatory responses and enhances microglial survival. *J Exp Med* **214**:597–607.
3. Liu C-C, Kanekiyo T, Xu H, and Bu) Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. *Nat Rev Neurol* **9**:106–118. G (2013
4. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, and Trojanowski JQ (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* **9**:119.
5. Wang B, Mezlini AM, Demir F, Fiume M, Tu Z, Brudno M, Haibe-Kains B, and Goldenberg A (2014) Similarity network fusion for aggregating data types on a genomic scale. *Nat Methods* **11**:333–337, Nature Publishing Group.

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