

Defining subgroups in Suspected non-Alzheimer’s disease pathology (SNAP) by using blood-based biomarkers and standard diagnostic process data

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Aims

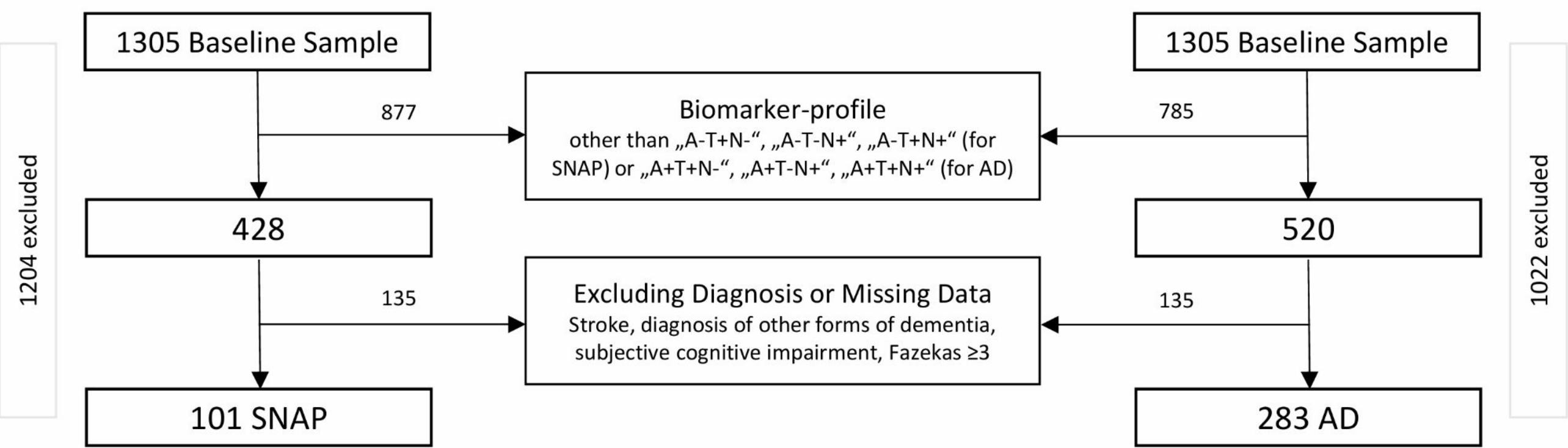
- **Characterize** the **biological heterogeneity underlying SNAP**
- **Identify distinct clusters** within the SNAP cohort **based on biomarker** and diagnostic data

Background

Suspected non-Alzheimer’s disease pathology (SNAP) is a biomarker-based concept that describes individuals without amyloid pathology (A-), but with abnormal tau and/ or neurodegeneration (ND) biomarker status, which clinically present like Alzheimer’s disease (AD) [1]. The underlying heterogenic etiologies of SNAP remain largely undefined.

Methods I

Participants



Biomarker

In Plasma:

- **GFAP** glial fibrillary acidic protein*
- **NfL** neurofilament light chain*
- **p-tau181/p-tau217** phosphorylated tau*
- **TDP-43** TAR DNA-binding protein-43**

*Lumipulse G600II platform with Lumipulse G assays (Fujirebio) ; **Simoa TDP-43 advantage assay (Quanterix);

***alpha-synuclein seed amplification assay

Amyloid ratio (Aβ42/40)

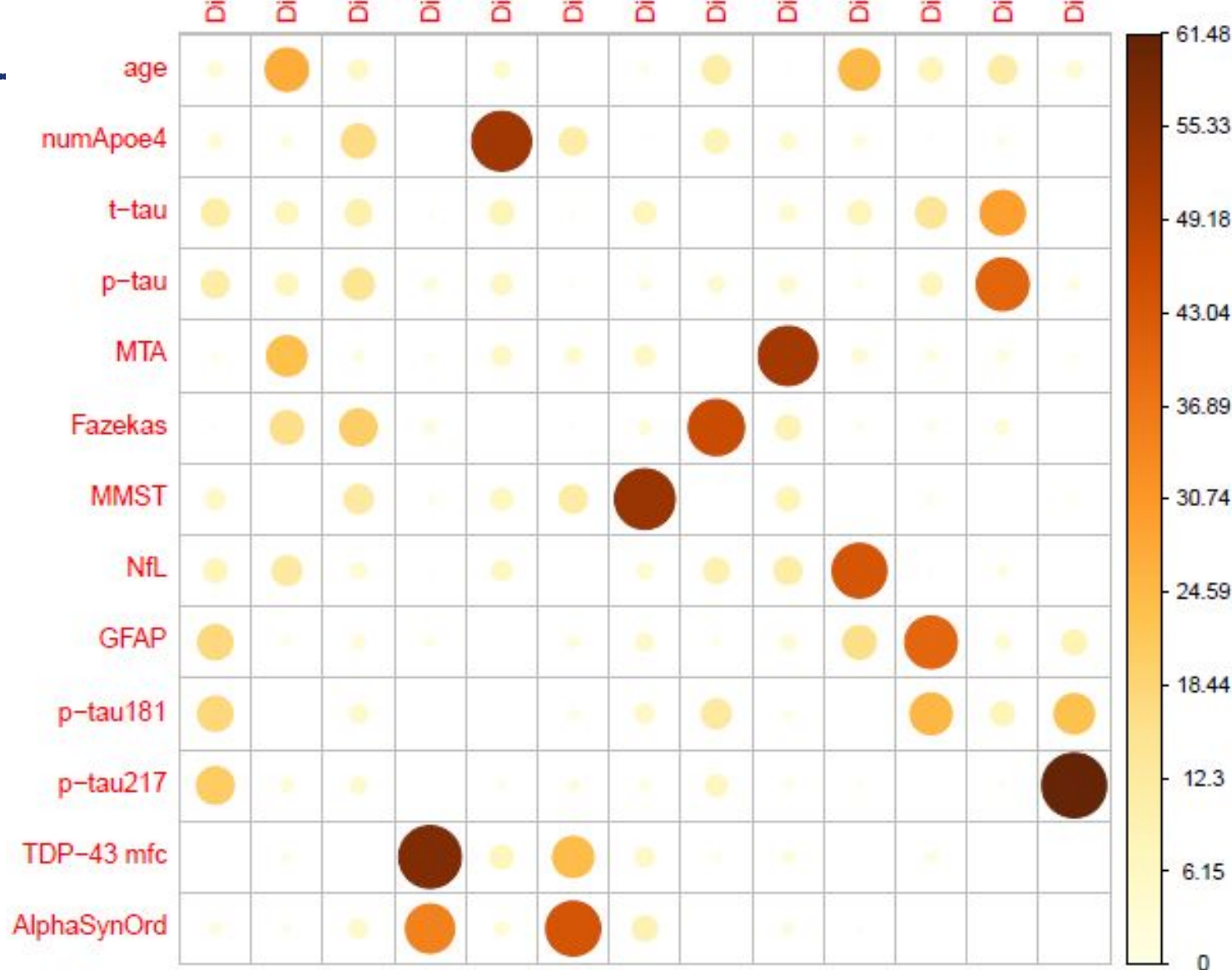
- measured on LUMIPULSE G600II automated platform (Fujirebio)
- cut-off value 0.62 [2]

Statistics

The statistical analyses were performed using R version 4.5.1. Prior to PCA and hierarchical clustering, all variables were standardized using z-transformation. Hierarchical cluster analysis was performed using Euclidean distance and Ward D2 linkage. Therefore, the following parameters are analyzed on logarithmic scale: Aβ42/40, t-tau, p-tau, NfL, GFAP, p-tau181, p-tau217, TDP-43.

Results I

Figure 1. Principal Component Analysis (PCA) of complete cohort using shown parameters and contribution of variables to the PCA principal components.



Results II

	AD (n=283)	SNAP (n=101)	p-value
Age, years	70.2 ± 8.0 (51–86)	66.7 ± 8.7 (51–87)	<0,001
Female sex, n (%)	164 (58%)	48 (48%)	0,091
MMSE score	24.1 ± 4.2 (11–30)	26.5 ± 3.3 (10–30)	<0.001
APOE ε4 carriers, n (%)	175 (61.8%)	24 (23.8%)	<0,001
MTA score	1.27 ± 0.90 (0–4)	1.29 ± 0.97 (0–4)	0,862
Fazekas score	0.95 ± 0.66 (0–2)	0.89 ± 0.65 (0–2)	0,436
Aβ42/40 ratio	0.045 ± 0.008	0.095 ± 0.014	<0,001
GFAP (pg/mL)	94.15 ± 35.39	50.08 ± 24.36	<0,001
NfL (pg/mL)	26.58 ± 14.52	24.13 ± 13.99	0,015
p-tau181 (pg/mL)	2.22 ± 0.94	1.14 ± 0.86	<0,001
p-tau217 (pg/mL)	0.70 ± 0.45	0.21 ± 0.25	<0,001
TDP-43 (pg/mL)	221.68 ± 210.88	195.59 ± 116.65	0,195

Table 1. Table with baseline statistics for numeric parameters analyzed on natural scale. Continuous variables are presented as mean ± SD and categorical variables as n (%). The p-value column gives the p-values of a t-Test and X2-Test.

Results III

Hierarchical clustering of the SNAP group

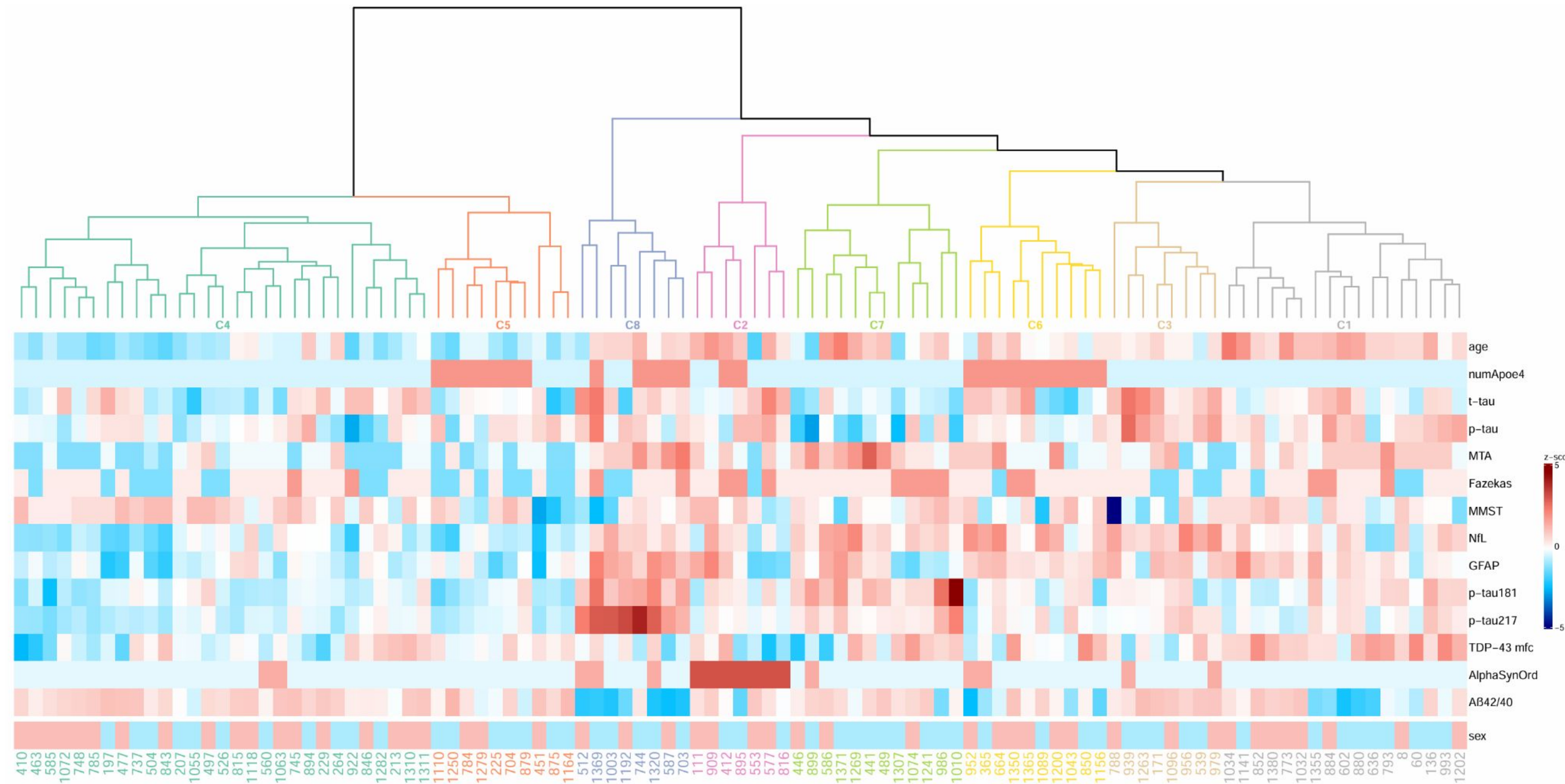


Figure 2. Left: **Dendrogram of SNAP group including heatmap of clustering.** Hierarchical clustering with Euclidean distance and Ward.D2 linkage. The tree was cut to build eight clusters. All shown parameters except sex were used for clustering, for sex red codes for females and blue for male patients. The figure shows the dendrogram including a heatmap of the clustering. Right: **Radar Charts** showing the profiles of the eight clusters derived from hierarchical clustering using Euclidean distance and Ward.D2 linkage. All values are scaled to their observed data range. For visualization of the cluster characteristics, we arranged the data so that more peripheral values consistently indicate greater impairment.

Discussion

- Hierarchical clustering and PCA revealed substantial biological heterogeneity within the SNAP group.
- Several clusters showed biomarker profiles compatible with known neurodegenerative diseases, including LATE, α-synucleinopathies, FTD, vascular dementia, and AD-like pathology, while other clusters may represent mixed or currently unclassified forms of SNAP.
- Although significant cerebrovascular pathology was an exclusion criterion of the sample, higher Fazekas scores observed in cluster 7 indicates that subthreshold vascular burden may contribute to a specific SNAP phenotype.
- Blood-based biomarkers may improve biological stratification of amyloid-negative patients with a clinical AD phenotype.
- More disease-specific biomarkers are needed to better define distinct pathophysiological processes.
- These exploratory findings require validation in larger, independent, and longitudinal cohorts.

Blood-based biomarkers reveal that SNAP is biologically heterogeneous and comprises several distinct biomarker-defined subgroups suggestive of different underlying neurodegenerative pathologies.

Literature

[1]] Jack, C. R., Jr, Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M.,...Contributors. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*, 14(4), 535-562. <https://doi.org/10.1016/j.jalz.2018.02.018>

[2] Alcolea, D., Pegueroles, J., Munoz, L., Camacho, V., Lopez-Mora, D., Fernandez-Leon, A., Le Bastard, N., Huyck, E., Nadal, A., Olmedo, V., Sampedro, F., Montal, V., Vilaplana, E., Clarimon, J., Blesa, R., Fortea, J., & Lleó, A. (2019). Agreement of amyloid PET and CSF biomarkers for Alzheimer's disease on Lumipulse. *Ann Clin Transl Neurol*, 6(9), 1815-1824. <https://doi.org/10.1002/acn3.50873>