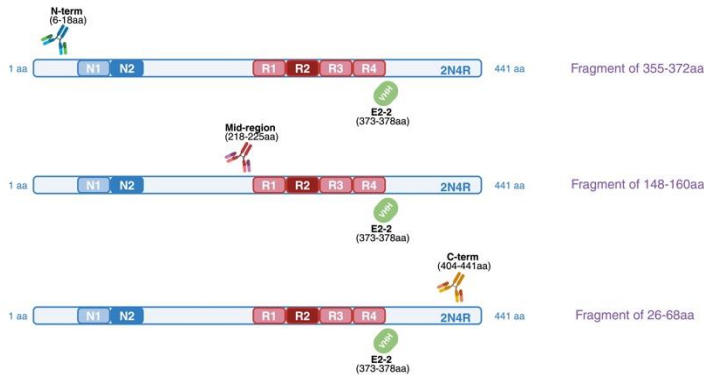


# ANTI-TAU SINGLE-DOMAIN ANTIBODY (VHH)–BASED DETECTION OF TAU FRAGMENTS DISTINGUISHES SOLUBLE AND SARKOSYL-INSOLUBLE PATHOLOGY ACROSS TAUOPATHIES

Luisa Sophie Braun-Wohlfahrt, Marine Nguyen, Justine Mortelet, Elena Camporesi, Juan Lantero-Rodriguez, Tammaryn Lashley, Gunnar Brinkmalm, Henrik Zetterberg, Isabelle Landrieu & Laia Montoliu-Gaya

## Background

Tauopathies exhibit disease-specific patterns of tau aggregation and truncation, yet existing assays often lack sufficient sensitivity to resolve low-abundance, fragment-specific tau species.<sup>1,2</sup> Single molecule array (Simoa) technology enables ultrasensitive quantification of defined tau epitopes. Here, we applied anti-tau single-domain antibody (VHH)–based Simoa assays to characterize N-, mid-, and C-terminal tau fragment profiles in soluble and sarkosyl-insoluble (SI) fractions from human brain across different tauopathies.<sup>3</sup>

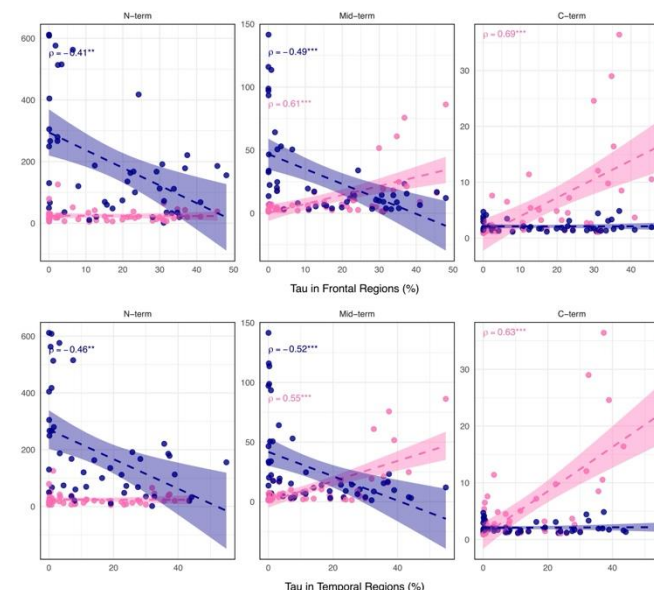
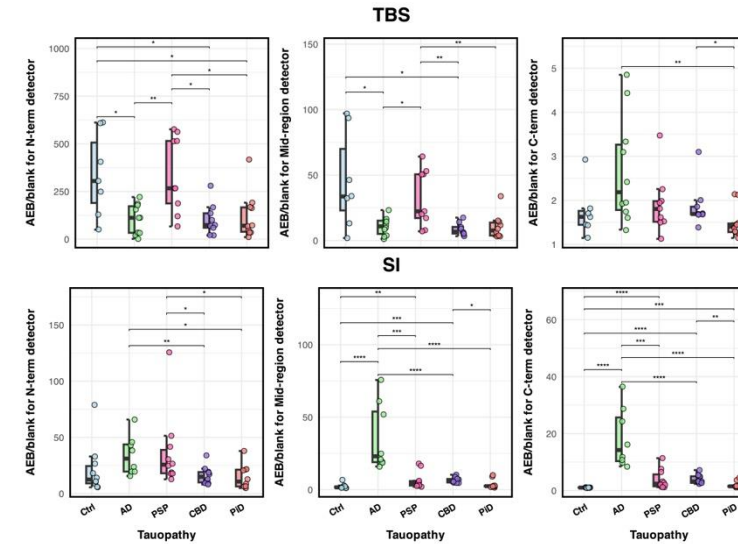


## Methods

- Post-mortem Broadmann area 9 tissue
- Alzheimer's Disease (AD, n = 10), Corticobasal Degeneration (CBD, n = 10), Pick's Disease (PiD, n = 10), Progressive Supranuclear Palsy (PSP, n = 11), Controls (n = 10)
- Tissue was homogenized in Tris-buffered saline (TBS) to obtain soluble fractions
- Pellets were extracted with sarkosyl to generate SI fractions
- Immunoassays were developed using the VHH E2-2 (aa 373-378) as capture
- Detectors used were IgGs recognizing N-terminal (aa 6-18), mid-region (aa 218-225) and C-terminal (aa 401-441) tau
- Frontal and temporal tau burden (% area) was used for correlation analyses

## Results

**Tau fragment abundance differed across tauopathies and between biochemical fractions.** SI fractions showed pronounced enrichment of mid- and C-terminal tau fragments in AD compared with PSP, CBD, PiD, and controls, whereas TBS fractions displayed more modest disease-associated differences.



**Tau fragment concentrations correlated with frontal tau burden in a fragment- and fraction-dependent manner.**

Significant positive correlations were observed for SI-derived mid- and C-terminal fragments, whereas TBS-derived N- and mid-terminal fragments showed inverse associations with frontal pathology.

**Similar relationships were observed in temporal regions.** SI-derived mid- and C-terminal tau fragments positively correlated with temporal tau pathology, while TBS-derived N- and mid-terminal fragments exhibited significant negative correlations.

## Conclusions

- This VHH-based immunoassay differentiated tauopathies based on fragment-specific and solubility-dependent tau profiles
- AD exhibited the greatest accumulation of SI-enriched tau fragments
- PSP and PiD displayed selective fragment increases; CBD showed uniformly low levels
- PSP and CBD exhibited distinct fragment profiles despite both being 4R tauopathies, highlighting the potential of fragment-resolved assays for differential diagnosis
- Opposing correlations between soluble and insoluble tau species suggest differential partitioning of truncated tau across biochemical fractions

## References

- Kametaani F, Yoshida M, Matsubara T, Murayama S, Saito Y, Kawakami I, Onaya M, Tanaka H, Kakita A, Robinson AC, Mann DMA, Hasegawa M. Comparison of Common and Disease-Specific Post-translational Modifications of Pathological Tau Associated With a Wide Range of Tauopathies. *Front Neurosci*. 2020 Nov 4;14:581936. <https://doi.org/10.3389/fnins.2020.581936>
- Lantero-Rodriguez J, Camporesi E, Montoliu-Gaya L, et al. Tau protein profiling in tauopathies: a human brain study. *Mol Neurodegeneration* 19, 54 (2024). <https://doi.org/10.1186/s13024-024-00741-9>
- Danis, C., Dupré, E., Bouillet, T. et al. Inhibition of tau neuronal internalization using anti-tau single domain antibodies. *Nat Commun* 16, 3162 (2025). <https://doi.org/10.1038/s41467-025-58383-4>

Contact: [luisa.braun-wohlfahrt@gu.se](mailto:luisa.braun-wohlfahrt@gu.se)



Funded by  
the European Union

