

Exploratory evaluation of plasma TDP-43 in LATE and other TDP-43 proteinopathies using a SIMOA assay

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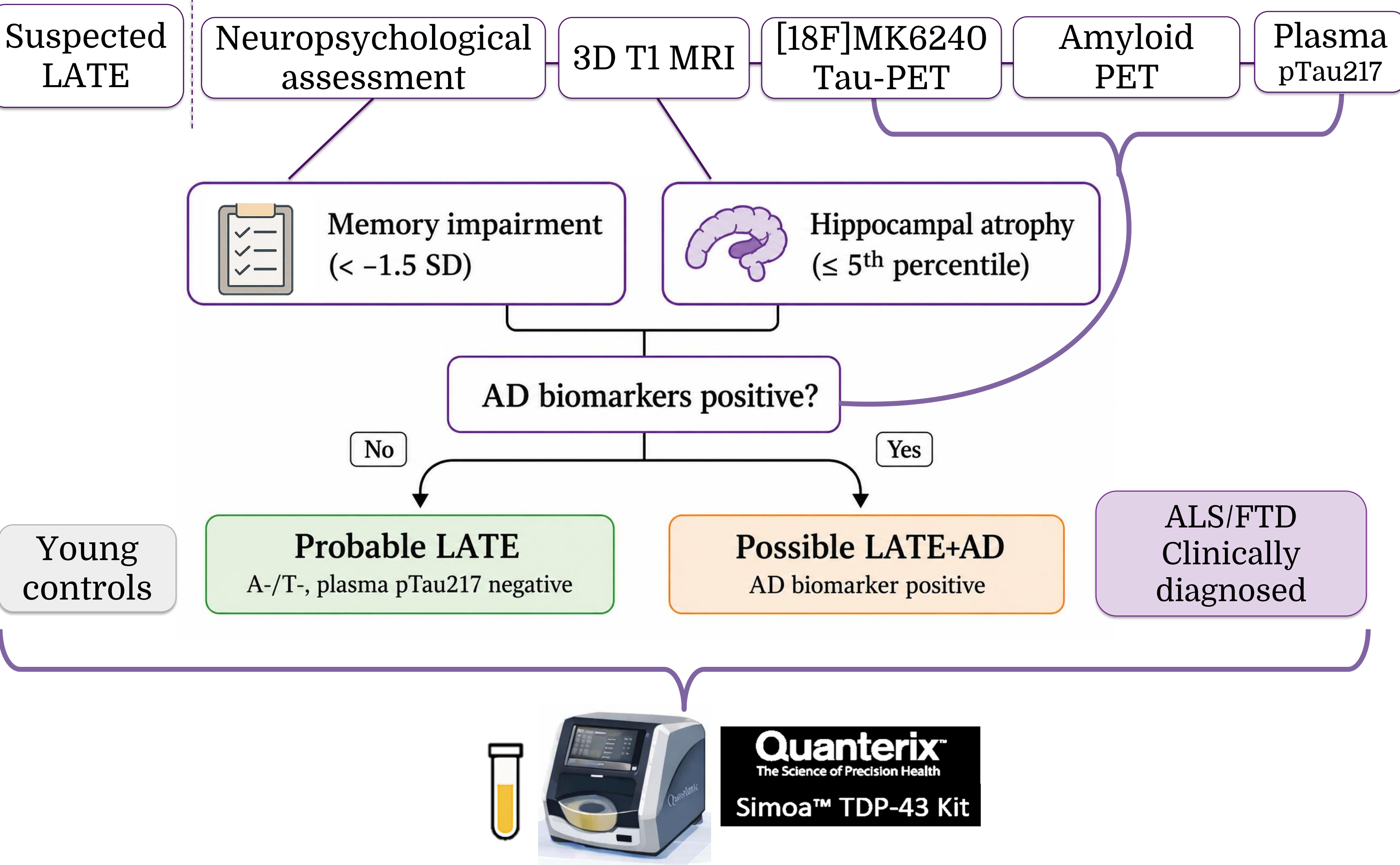
Background

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is characterized by TDP-43 pathology predominantly affecting medial temporal structures and associated with episodic memory impairment in adults over 75 years. Currently, no validated in vivo biomarker exists for LATE. Plasma TDP-43 represents a minimally invasive candidate biomarker, however, its behavior in LATE and other TDP-43-related disorders remains poorly understood.

We aimed to evaluate plasma TDP-43 concentrations in clinically defined probable and possible LATE + Alzheimer’s disease (AD) according to the clinical framework proposed by Wolk et al. (2025), as well as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), using the Simoa™ TDP-43 assay.

Methodology

Assessment workflow & group classification

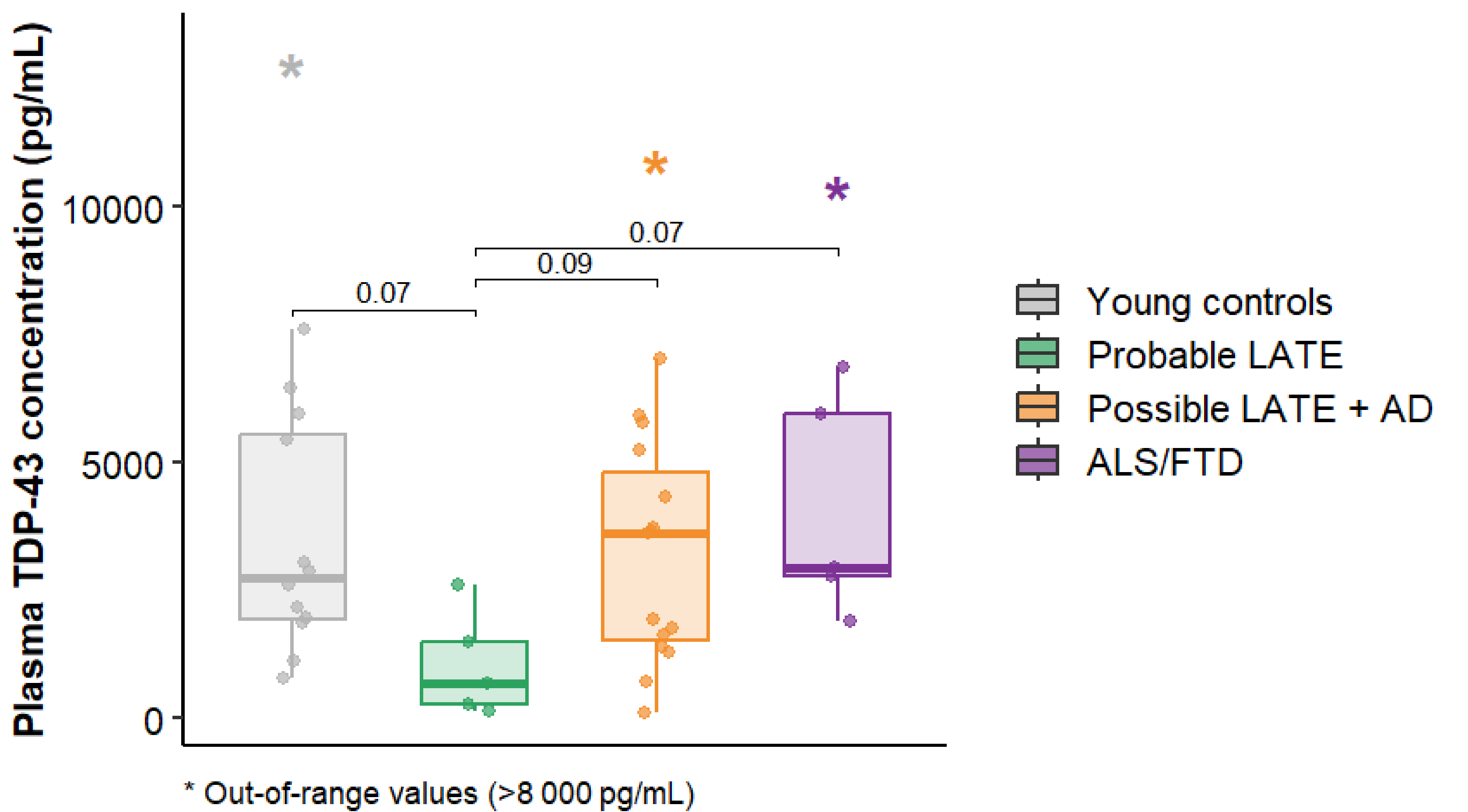


Controls underwent MMSE screening and blood sampling only. **Probable LATE** was defined by memory impairment (Free and Cued Selective Reminding Test <-1.5 SD), hippocampal atrophy ≤5th percentile, absence of amyloid and tau and negative plasma pTau217 (<0.193pg/mL). **Possible LATE + AD** met similar criteria but showed AD biomarker positivity. **ALS and FTD** diagnoses were established clinically. 3 behavioral FTD, 1 primary progressive aphasia FTD, 1 FTD/ALS, 1 ALS. Plasma TDP-43 was measured in duplicate using a Simoa™ assay. Assay precision was acceptable (coefficient of variation: 5.81%).

Results

Plasma TDP-43 appeared reduced in **probable LATE**

Diagnosis Group	N	Age (years)	Sex (F%)	Mean plasma TDP-43 (pg/mL)	Mean plasma pTau 217 (pg/mL)
Young Controls	13	25.4 ± 3.6	69.2%	4190.2 ± 3320.4	0.099 ± 0.036
Probable LATE	5	78.7 ±9.0	40%	1039.9 ±1024.7	0.124 ± 0.034
Possible LATE + AD	16	73.4 ±9.0	56.2%	3675.2 ±2774.7	0.607 ± 0.411
ALS/FTD	6	62.2 ± 4.4	66.7%	5096.9±3143.7	0.142 ± 0.071



Group differences were assessed using the Kruskal–Wallis test followed by pairwise Wilcoxon rank-sum tests with Benjamini–Hochberg correction.

Conclusion

- Plasma TDP-43 appeared reduced in probable LATE, possibly reflecting reduced physiological TDP-43, pointing to the loss of nuclear TDP-43.
- Divergence from higher ALS/FTD levels remains unclear.
- Given the small sample, findings require cautious interpretation and further study
- Comparisons of these plasma assays with post-mortem diagnoses are important for clinical validation