

Waseequr Rahman Mohammed^{1,2}, Dr. Sivaprakasam Ramamoorthy¹

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¹Centre for Brain Research, Indian Institute of Science, Bengaluru, Karnataka, India

²Manipal Academy of Higher Education, Manipal, Karnataka, India

INTRODUCTION

- ❖ Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by amyloid- β plaques and tau neurofibrillary tangles.
- ❖ Tau accumulation shows a strong association with cognitive decline in AD patients.
- ❖ Dementia progression rates vary widely among individuals with AD, suggesting underlying molecular heterogeneity.
- ❖ The role of neurodegenerative co-pathologies in the dementia progression of AD remains unclear.
- ❖ Around 50% of AD patients display Lewy body pathology at the autopsy.
- ❖ AT8 and pS129 are pathological markers of AD and Dementia with Lewy Bodies (DLB) respectively.
- ❖ Pathological distinctions between pure Alzheimer's disease (AD) and AD with coexisting Lewy body pathology (AD-DLB) remain to be fully characterized.

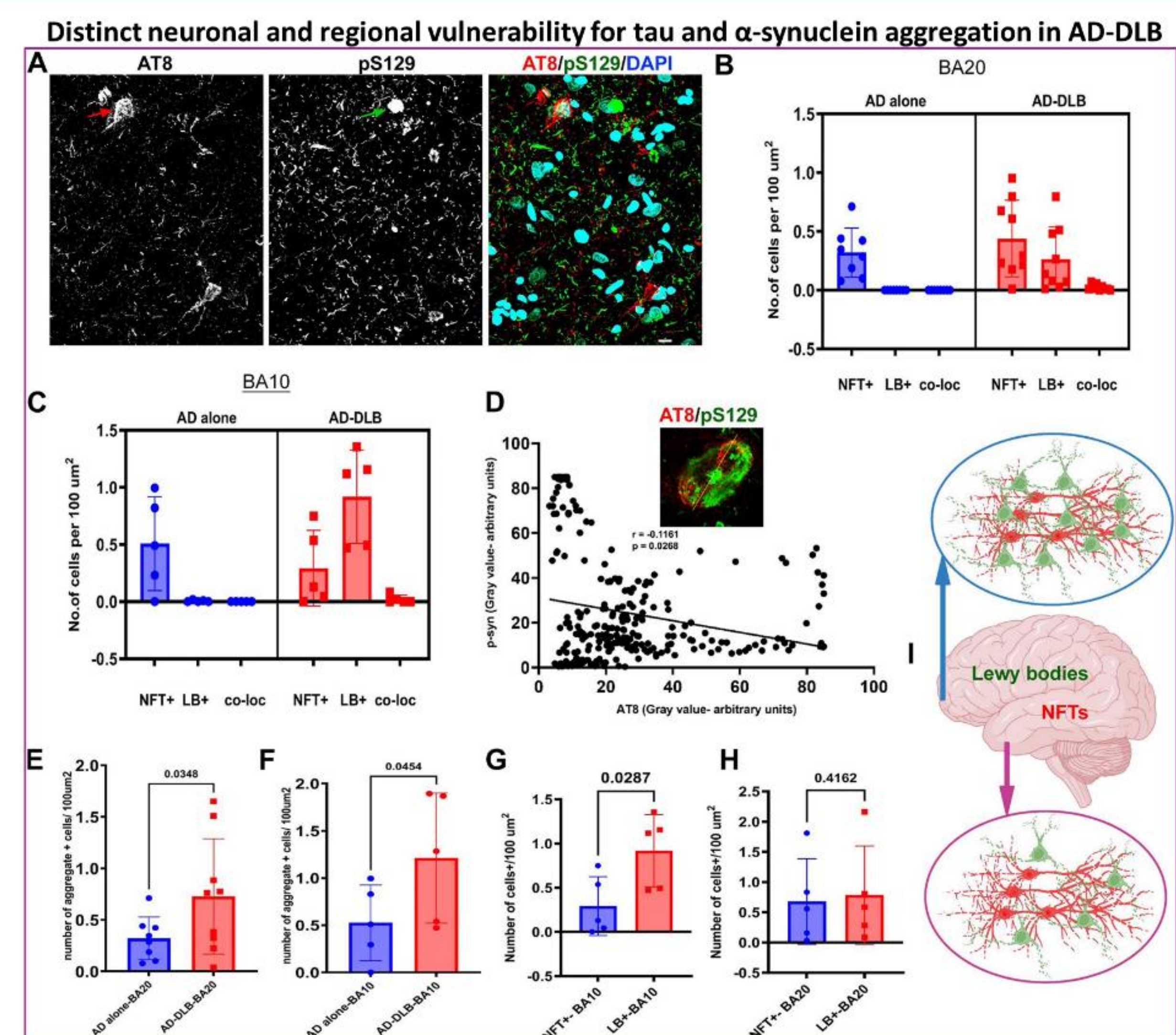
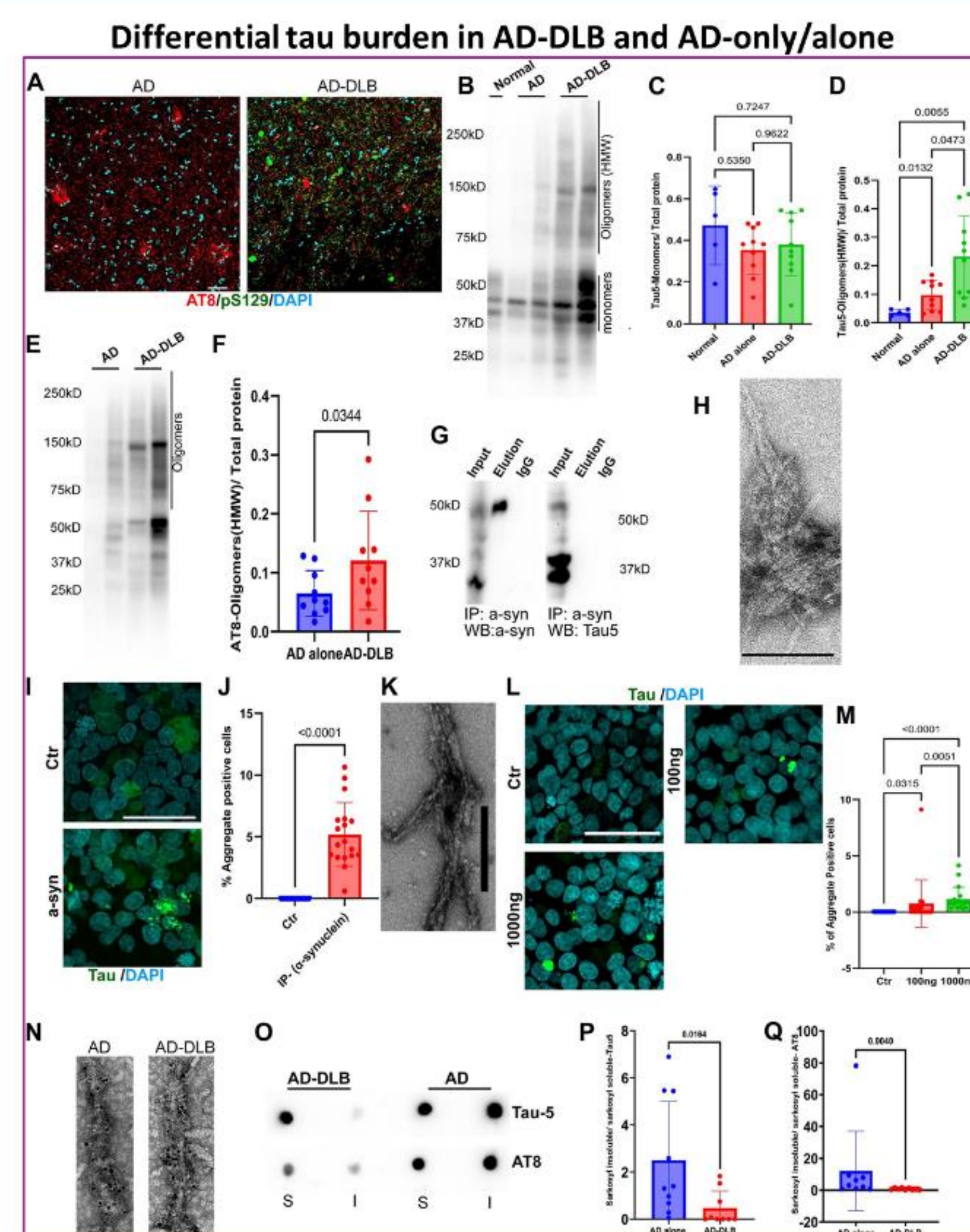
OBJECTIVE

- ❖ To investigate the relationship between tau and α -synuclein pathology in AD-DLB by examining tau aggregation states, regional pathological burden, and co-localization patterns, and to evaluate their relevance to proposed α -synuclein-mediated tau cross-seeding mechanisms.

METHODOLOGY

- ❖ **Tissue Processing and Biochemical Analysis:** Frozen postmortem brain tissues (BA10, BA20) from AD-alone (Braak stage VI), AD-DLB (Braak stage VI), and Normal/control subjects (Braak stage 0), all age-matched, were obtained from Banner Sun Health and NIH NeuroBioBank. Homogenates were analyzed by SDS-PAGE and Western blotting for total and phosphorylated tau (Tau5, AT8). Sarkosyl-insoluble tau was isolated and characterized by dot blot and pronase resistance assay.
- ❖ **Tau Cross-Seeding Assay:** Phosphorylated α -synuclein was immunoprecipitated from AD-DLB brain lysates and applied to tau FRET biosensor HEK293 cells. Aggregation was analyzed using confocal microscopy.
- ❖ **Imaging:** Immunostained brain sections were imaged using confocal microscopy. Sarkosyl-insoluble and immunoprecipitated fractions were visualized by transmission electron microscopy (TEM).
- ❖ **Antibodies used:** AT8 for phosphorylated tau, pS129 for phosphorylated α -synuclein, Tau5 for total tau

RESULTS



CONCLUSIONS

In conclusion, our study identifies AD-DLB as a distinct subtype within the Alzheimer's disease continuum, characterized by higher levels of soluble tau oligomers and reduced insoluble tau aggregates. We observed distinct regional vulnerabilities, with the prefrontal cortex showing greater susceptibility to Lewy body pathology, while the temporal cortex was similarly affected by both tau and α -synuclein aggregates. The limited co-localization between neurofibrillary tangles and Lewy bodies suggests that these pathologies may propagate through distinct neuronal populations. Notably, the increased burden of soluble tau species in AD-DLB is consistent with literature suggesting that α -synuclein aggregates may promote tau misfolding and aggregation through cross-seeding mechanisms, potentially facilitated by liquid-liquid phase separation (LLPS). Together, these findings highlight the importance of co-pathologies in shaping Alzheimer's disease heterogeneity and emphasize the need for co-pathology-specific biomarkers and therapeutic strategies.

REFERENCE AND KEY WORDS

- ❖ Rahman MW, Sharma P, Chattopadhyay T, Saroja SR. Distinct neuronal vulnerability and metabolic dysfunctions are characteristic features of fast-progressing Alzheimer's patients with Lewy bodies. J Biol Chem [Internet]. 2025;301(4):108396. Available from: <http://dx.doi.org/10.1016/j.jbc.2025.108396>
- ❖ Alzheimer's Disease, Tau, α -Synuclein, AD alone, and AD-DLB, Lewy Bodies, Cross seeding

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Email:
waseequrr@cbr-iisc.ac.in
waseequr1998@gmail.com