

Cohort-scale Subcellular Proteomics Reveals Protein Mis-localisation in Alzheimer's Disease and Cognitive Resilience P-0308

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Flash talk:



Alzheimer's Disease (AD) is defined by aggregation and mislocalisation of β -amyloid and tau, yet the extent of intracellular reorganisation across the proteome remains poorly characterised. We applied subcellular proteomics to post-mortem dorsolateral pre-frontal cortex from 75 ROSMAP individuals spanning the AD-resilience spectrum, enabling inference of protein localisation, independent of abundance. 217 proteins exhibit disease associated localisation shifts, enriched for endolysosomal function, intracellular trafficking, and RNA processing. Peptide-level analysis also resolves pathological tau proteoforms associated with insoluble aggregates. Critically, this spatial dimension surfaces candidates that abundance-based studies have missed, including SCAI, a cancer-associated protein not previously linked to neurodegeneration, highlighting the discovery potential of this approach.

