Gene expression changes in Lewy body disease driven by alpha-synuclein pathology and independent of co-pathologies.

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Lewy body disease (LBD) is a neurodegenerative disorder marked by cognitive impairments and parkinsonian motor symptoms, which are closely associated with the accumulation of pathological alpha-synuclein in key brain regions. Phosphorylation of alpha-synuclein at serine 129 (pS129) is strongly implicated in disease pathology, with over 90% of alpha-synuclein in Lewy bodies phosphorylated at this site compared to just 4% of alpha-synuclein healthy brains. While co-pathologies such as tau, amyloid-β, and TDP-43 are frequently observed in LBD, they confound efforts to identify alpha-synuclein–specific molecular changes. Therefore, to better isolate molecular pathways specific to alpha-synuclein pathology, we analyzed brains from LBD cases without significant co-pathologies. We obtained amygdala tissue from neuropathologically confirmed LBD cases (N=41) and matched controls (N=26), evaluating each case for tau, amyloid-β, and TDP-43 pathology. RNA was extracted and sequenced to profile gene expression, and an immunoassay was developed to quantify pS129 alpha-synuclein burden. The LBD cohort included brainstem-predominant (N=5), transitional (N=18), and diffuse (N=18) subtypes. Histopathological evaluation confirmed low Braak and Thal stages, indicating minimal tau and amyloid-β pathology. Importantly, there was no evidence of TDP-43 dysfunction, as assessed by both immunoassay for insoluble phosphorylated TDP-43 and RNA-level analysis of cryptic exon inclusion in TDP-43 target genes. Quantification of pS129 burden is ongoing, and we aim to correlate these levels with differential gene expression to identify alpha-synuclein–specific molecular alterations. This approach will help uncover mechanisms intrinsic to LBD and may inform the development of targeted therapeutic strategies.

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