A Reproducible MCI-Centered Ubiquitin-Proteasome Transcriptional Signature in Peripheral Blood Across Alzheimer's Disease Datasets

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The ubiquitin-proteasome system (UPS) is central to cellular proteostasis, yet it remains unclear whether UPS-related transcriptional alterations vary systematically across clinically defined stages of cognitive impairment. We tested whether peripheral blood expression of genes involved in proteasome-mediated ubiquitin-dependent protein catabolism shows a reproducible, non-monotonic pattern across cognitively healthy controls, mild cognitive impairment (MCI), and Alzheimer's disease (AD).

We analyzed three public blood transcriptomic datasets (GSE63060, GSE63061, and GSE140829). Age- and sex-adjusted linear regression models were used to calculate a standardized MCI-centered contrast for each gene, representing MCI expression relative to the control-AD midpoint. Among genes exhibiting non-monotonic patterns, pathway-level effects were quantified using the median absolute deviation and compared with those of expression-matched non-UPS genes, using 100,000-permutation Monte Carlo null distributions.

UPS genes showed significantly larger MCI-centered deviations than matched non-UPS genes in all three datasets: GSE63060 (UPS/null ratio 1.1001, difference 0.0284, p=0.0217), GSE63061 (1.1392, 0.0236, p=0.0008), and the independently generated GSE140829 cohort (1.1428, 0.0194, p=0.0008). The effect was driven primarily by MCI-centered reductions ("valleys") rather than increases ("peaks"). Valley UPS/null ratios were 1.1125, 1.1585, and 1.2026, compared with peak ratios of 0.9784, 1.1027, and 1.0135, respectively. Valley enrichment was significant in GSE63061 and GSE140829 and directionally concordant in GSE63060. Signed UPS deviations were strongly concordant across datasets (pairwise r=0.61-0.71).

To assess pathway specificity, 876 size-filtered Gene Ontology Biological Process gene sets were analyzed with the same analytical framework. Only three comparator pathways remained FDR-significant in all three datasets; two contained more than 58% of UPS genes. By cross-dataset median rank, UPS placed in the 95.8th percentile for observed/null ratio and the 95.0th percentile for absolute effect difference.

These findings identify a reproducible, stage-specific peripheral UPS transcriptional signature centered on MCI rather than a monotonic shift from control to AD. The predominance of MCI-centered reductions and the unusually strong effect relative to the broader GO landscape support longitudinal investigation of peripheral proteostasis-related transcription as a potential indicator of disease-stage biology.

Special Request

Designate the presenting author as a high school or undergraduate student.

Theme: C.02.b. Alzheimer's disease - Transcriptomics and genomics

Keywords: Ubiquitin-proteasome system; Alzheimer's disease; Mild cognitive impairment