Beyond Group-Level Transcriptomics: Patient-Level Aberrant Splicing Reveals Recurrent Patterns in Alzheimer's Disease

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Background: Alzheimer's disease (AD) exhibits substantial molecular heterogeneity, with transcriptomic alterations restricted to individual patients or subsets. Conventional group-level analyses may obscure these alterations through signal averaging. Alternative splicing generates transcript diversity through exon skipping, intron retention, alternative 5' and 3' splice-site usage, and mutually exclusive exons, and may reveal disease-associated changes not reflected at the gene-expression level. We therefore investigated patient-level aberrant splicing across three AD brain RNA-seq cohorts. Method: We analyzed post-mortem bulk brain RNA-seq data from 644 AD patients across the Mount Sinai Brain Bank (MSBB), Mayo Clinic, and ROSMAP cohorts using an outlier-based framework for detecting aberrant splicing in patients relative to controls. Event- and gene-level recurrence was assessed within and across cohorts. In MSBB, patient-level aberrant splicing was compared with group-level differential splicing and patient-level differential expression, followed by patient-level gene set enrichment analysis. Results: In MSBB, DGCR5 was the most recurrent aberrantly spliced gene, detected in 63 of 158 AD patients. FCER1G was the most recurrent gene in the literature-curated AD-related gene list, detected in 21 patients. We also identified a recurrent unannotated acceptor-site event in UMAD1. Patient-level aberrant splicing only partially overlapped with group-level differential splicing and patient-level differential expression, indicating complementary transcriptomic signals. Gene set enrichment analysis identified recurrent enrichment of terms related to mitochondrial function, neurodegenerative diseases, translation, and synaptic processes. Cross-cohort comparisons revealed shared and cohort-specific patterns, including recurrent genes and unannotated events across all three cohorts. Notably, DGCR5 was detected in at least 15% of AD patients in each cohort, occurring in 63 MSBB, 18 Mayo, and 121 ROSMAP patients. Conclusion: Aberrant splicing in AD was highly individualized yet recurrent at gene, event, and pathway levels. Patient-level aberrant splicing analysis moves beyond group-level averaging and gene-expression-centered approaches, revealing transcriptlevel alterations in AD that conventional analyses may miss or underrepresent