Epitranscriptomic Signatures in Frontotemporal Dementia

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Background: Frontotemporal Dementia (FTD) is a devastating neurodegenerative disorder and one of the leading causes of dementia in individuals under 65 years of age. FTD is characterized by progressive degeneration of the frontal and/or temporal cortical lobes, leading to a diverse range of symptoms that can include social, emotional, behavioral, and language changes, as well as motor disorders. These symptoms severely impact the quality of life of individuals and their caretakers. The etiology of FTD is complex, often linked to mutations in C9orf72, MAPT, and GRN, which trigger pathological processes that are not yet fully understood. Currently, no effective treatments or reliable biomarkers exist for early diagnosis. Method: To investigate these molecular mechanisms, we employed a comprehensive multiomics approach integrating RNA sequencing, methylated RNA immunoprecipitation sequencing (meRIP-seq), and long-read nanopore sequencing, with a focus on m6A RNA modifications. Post-mortem medial temporal lobe tissue from 47 individuals with genetic or sporadic FTD with TDP-43 or tau pathology, as well as from controls, was analyzed. This approach enabled characterization of transcriptional and m6Aassociated changes across distinct genetic and pathological forms of FTD. Results: We identified disease-associated changes in the expression of key m6A regulatory machinery, consistent with a shift toward increased m6A deposition and enhanced stability and translation of m6Amodified transcripts. m6A-modified genes in FTD were enriched in cellular stress-response pathways and modules associated with mitophagy, lysosomal dysfunction, and aggresome formation. These findings suggest that altered m6A RNA regulation may contribute to impaired protein homeostasis in FTD. Conclusion: Our findings identify dysregulated m6A RNA modification as a potential molecular mechanism underlying FTD across distinct genetic and pathological subtypes. Altered m6A regulation may contribute to cellular stress and disrupted proteostasis by modulating transcripts involved in energy metabolism, lysosomal function, and translation, potentially reflecting a compensatory response to disease-associated cellular stress