

Research Plan Summary

Huntington's disease (HD) is a fatal neurodegenerative disease caused by an expanded CAG repeat in the huntingtin gene. Chronic expression of mutant huntingtin protein (mHTT) causes cellular dysfunction, including early and reproducible transcriptomic dysregulation of mRNAs and miRNAs. The development of disease-modifying therapies has been challenged by a lack of biomarkers to track disease progression. Recently, it has been elucidated that expression levels of certain miRNAs are altered under different disease states. This proposal is focused on identifying potential miRNA biomarkers for HD. Potential modes for the selective incorporation of miRNAs into exosomes have been proposed. One of them is through a heterogenous nuclear ribonucleoprotein (hnRNP) dependent pathway, in which hnRNPA2B1 recognizes a GGAG motif at the 3' end of miRNA sequences. We hypothesize that altered hnRNPA2B1 activity contributes to an altered exosomal miRNA profile in HD patients. Our preliminary data show decreased hnRNPA2B1 protein levels in HD patient-derived iPSC-neurons and exosomes isolated from post-mortem CSF, and exosomal miRNA dysregulation in HD CSF exosomes isolated from living patients. We propose to define exosome release and RNP dysregulation using differentiated HD iPSCs and CSF biopsy assays to elucidate potential miRNA-based biomarkers and novel therapeutic targets.