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Effect of Mistranslating tRNA Alanine on Polyglutamine Aggregation

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Abstract : Polyglutamine (polyQ) diseases are a group of diseases related to neurodegeneration caused by repeats of the amino acid glutamine (Q) in the DNA, which translates into an elongated polyQ tract in the protein. The pathological explanation is that the polyQ tract forms cytotoxic aggregates in the neurons, leading to their degeneration. There are no cures or preventative efforts established for these diseases as of today, although the symptoms of these diseases can be relieved. This study specifically focuses on Huntington's disease, which is a type of polyQ disease in which aggregation is caused by the extended cytosine, adenine, guanine (CUG) codon repeats in the huntingtin (HTT) gene, which encodes for the huntingtin protein. Using this principle, we attempted to create six models, which included mutating wildtype tRNA alanine variant tRNA-AGC-8-1 to have glutamine anticodons CUG and UUG so serine is incorporated at glutamine sites in poly Q tracts. In the process, we were successful in obtaining tAla-8-1 CUG mutant clones in the HTTexon1 plasmids with a polyQ tract of 23Q (non-pathogenic model) and 74Q (disease model). These plasmids were transfected into mouse neuroblastoma cells to characterize protein synthesis and aggregation in normal and mistranslating cells and to investigate the effects of glutamines replaced with alanines on the disease phenotype. Notably, we observed no noteworthy differences in mean fluorescence between the CUG mutants for 23Q or 74Q; however, the Triton X-100 assay revealed a significant reduction in insoluble 74Q aggregates. We were unable to create a tAla-8-1 UUG mutant clone, and determining the difference in the effects of the two glutamine anticodons may enrich our understanding of the disease phenotype. In conclusion, by generating structural disruption with the amino acid alanine, it may be possible to find ways to minimize the toxicity of Huntington's disease caused by these polyQ aggregates. Further research is needed to advance knowledge in this field by identifying the cellular and biochemical impact of specific tRNA variants found naturally in human genomes.

Keywords : Huntington's disease, polyQ, tRNA, anticodon, clone, overlap PCR
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