Genome editing in HD iPS cells to reduce mutant and total Huntington expression

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Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a fatal neurodegenerative disease which strikes in the prime of life and progresses over 10-20 years, producing movement abnormalities, cognitive dysfunction, and psychiatric manifestations. HD is caused by a dominant expansion of a CAG trinucleotide repeat tract within the protein-coding region of the Huntingtin (Htt) gene and corresponding cortical dysfunction and striatal degeneration. As mutant HTT is the disease causing agent, one current strategy for disease

intervention is to reduce the production of the HTT protein. In fact, inhibitory RNA strategies which knock down both mutant and wild-type Htt alleles have shown effectiveness in cell and mouse models at reducing HD-related phenotypes. However, the balance between efficacy in reducing Htt levels and side effects from lowering Htt must be considered given the important roles for normal HTT in neurodevelopment and other cellular functions. For this reason, alternative strategies have also focused on selectively reducing mHtt levels to diminish potential side effects. Recently, we and others have developed HD patient-derived induced pluripotent stem cells (iPSCs). These lines can be differentiated to mature neurons specified for striatal development and differentiated cells display HD- related phenotypes, thereby providing a system in which to examine the progression of “”symptoms”” in HD iPS cells and the degree to which these phenotypes are reversible by HTT reduction. Here we propose to use genome editing of existing HD iPSC lines to constitutively or inducibly express RNAi’s that target either total HTT or preferentially target the mutant allele. This approach is distinct from isogenic lines where the expanded repeat is corrected to wild type range repeats through genome editing or homologous recombination in order to validate CAG-dependent phenotypes in the same genetic background. In the isogenic context, no disease phenotypes occur as the corrected iPS cell no longer expresses mHTT. In contrast, when considering RNAi or ASO approaches for treatment of HD, patients continuously express the expanded repeat mutation beginning in early development and the ability to modify the impact of that chronic mHTT expression is what is required of that RNAi or ASO. Questions that emerge are 1) whether CAG repeat dependent changes are modifiable in a mHTT background through reduction of HTT, 2) whether specific mHTT phenotypes can be ameliorated by total or mHTT reduction once disease phenotypes are manifest and 3) whether reducing HTT in general has consequences as even mHTT is likely to have functions that could be lost following knockdown strategies. The proposed aims are: Aim 1. To generate HD iPS Lines with constitutive or inducible silencing of Htt. Aim 2. To evaluate the consequence of lowering total versus mutant HTT in HD iPS cells.

Further information available at:

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