Modeling the effects of reducing huntingtin and Hdh alternative splicing in mice

https://neurodegenerationresearch.eu/survey/modeling-the-effects-of-reducing-huntingtin-and-hdh-alternative-splicing-in-mice/

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Country

USA

Title of project or programme

Modeling the effects of reducing huntingtin and Hdh alternative splicing in mice

Source of funding information

NIH (NINDS)

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Start date of award

01/04/2015

Total duration of award in years

3

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, Alternative Splicing, beta Actin, Huntington Disease, Age-Months

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder that is caused by the expansion of a CAG triplet repeat encoding a

stretch of polyglutamine (polyQ) within Huntingtin (HTT), the protein product of the HD gene. The HD mutation confers a deleterious gain-of-function and potential loss-of- function on mutant HTT that affects a variety of cellular pathways. Gene-silencing is a promising therapeutic strategy for HD which can circumvent the challenge of finding treatments targeting all the cellular pathways that are affected by mutant HTT. To determine the optimal time for reducing mutant HTT expression for achieving maximal therapeutic benefit, and to evaluate the consequences if selective targeting of the mutant HTT allele cannot be achieved, we propose using novel HD knock-in mouse models (HdhLacO-140Q and HdhLacO- 20Qhu mice) in which Lac operators have been inserted into the mouse HD locus (Hdh). After crossing these mice with a strain of transgenic mice ubiquitously expressing the Lac repressor (ß-actin-LacIR-tg), we can globally de-repress or repress mouse mutant huntingtin (Htt) expression, or both mutant and normal Htt expression at different ages by administering or withdrawing Isopropyl-ß-D-1-thiogalactopyranoside (IPTG) in their drinking water. In Aim 1, we will characterize the effect of repressing either mutant Htt or or both mutant and wild-type Htt expression at weaning, 3-, 6-, and 9-months of age in HdhLacO-140Q/+; ß-actin-LacIR tg, HdhLacO-140Q/LacO-20Qhu; ß-actin-LacIR tg, and control mice by characterizing their behavior, neuropathology, and htt expression levels at 2- to 24- months of age. In addition, to examine the effect of de-repressing mutant htt expression in an aged mouse (modeling discontinuation of a gene therapy in an older patient), IPTG will be administered to 12-month old HdhLacO-140Q/+; ß-actin-LacIR tg mice. Their phenotypes will be characterized at 12- to 24-months of age and compared to controls. In Aim 2, in order to identify potential biomarkers for evaluating the efficacy of a gene-silencing therapy, we propose to characterize by RNA-seq the proximal gene expression changes that occur in the cortex and striatum following repression of mutant htt or both mutant and wild-type htt expression at 3-, 6-, and 9- months of age. Validation of candidate genes will be performed first with brain tissue and cultured primary neurons. Validated genes will then be further examined using blood samples obtained from mice prior to and following mutant htt repression. Together, the results of these analyses should contribute to the design of future gene-silencing therapies for HD, and to our understanding of HD pathogenesis.

Lay Summary
PUBLIC HEALTH RELEVANCE: Gene-silencing is a promising therapeutic strategy for the treatment of Huntington’s disease (HD), and other dominant hereditary disorders. We have developed new mouse models for HD in which the expression of the mouse HD gene can be turned up or down by adding or removing IPTG (a lactose analog) to their drinking water. We will use these mice to determine the optimal time for beginning a gene-silencing therapy, to examine the effects of turning on HD gene expression in an aged mouse for modeling discontinuation of a gene- silencing therapy in an older patient, and to identify potential gene expression changes that correlate with silencing of the HD gene.

Further information available at:

Types:
Investments > €500k

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United States of America

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Huntington's disease

Years:
2016

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