# Huntingtin proline-rich region modulation of Huntingtons disease pathogenesis

https://neurodegenerationresearch.eu/survey/huntingtin-proline-rich-region-modulation-of-huntingtons-disease-pathogenesis/

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**Country**

USA

**Title of project or programme**

Huntingtin proline-rich region modulation of Huntingtons disease pathogenesis

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NIH (NINDS)

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22/09/2014

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3

**The project/programme is most relevant to:**

Huntington's disease

**Keywords**

Proline-Rich Domain, Huntington gene, Huntington Disease, polyglutamine, Stretching

**Research Abstract**

? DESCRIPTION (provided by applicant): In Huntington’s disease (HD), flanking protein domains modulate the toxicity of mutant Huntingtin’s (HTT”s) expanded polyQ stretch. In

mammals, a proline-rich region (PRR) is located at the C-terminal end of the polyQ stretch, and it has co-evolved with the polyQ stretch, increasing in size as the normal HTT polyQ stretch has lengthened during evolution. In yeast model systems, deletion of the HTT PRR in the context of an expanded polyQ stretch interferes with aggresome formation and increases toxicity of an N-terminal fragment of mutant HTT. To determine the role of the HTT PRR in modulating mutant HTT pathogenesis in mouse models for HD, we have generated three knock-in alleles of the mouse HD gene (Hdh) that express normal or mutant huntingtin (htt ) with deletions of the PRR – Hdh?P, Hdh140Q?P, and Hdh3xFlag140Q?P. We have found, in contrast to the results of the yeast studies, that deletion of the mutant htt PRR ameliorates several phenotypes exhibited by the CAG140 knock-in mouse model for HD, resulting in a significant delay in aggregate formation, alterations in aggregate conformation, normalization of striatal Darpp-32 expression, and the rescue of activity deficits. Using these new mouse models, we propose three complementary aims to determine the mechanisms by which deletion of the htt PRR affects HD mouse model pathogenesis. In Aim 1, we will test the hypothesis that deletion of the PRR modulates mutant htt's toxicity by altering the association of htt-interacting proteins. We propose using anti-FLAG immunoaffinity purification to enrich for proteins associating with 3xFlag140Q?P- tt and 3xFlag140Q-htt in the striatum and cortex, and characterize their identity using mass spectrometry. In addition, we will characterize the protein composition of htt aggregates purified from the Hdh140Q/+ and Hdh140Q?P/+ brain to determine if differential sequestration of cellular proteins by 140Q-htt and 140Q?P-htt aggregates contributes to pathogenesis. In Aim 2, we will test the hypothesis that deletion of the mutant htt PRR alleviates mutant htt's perturbation of gene expression by performing RNA-seq analysis of wild-type, Hdh140Q/+, and Hdh140Q?P/+ striatal gene expression to identify those genes whose expression is altered in the Hdh140Q/+ brain but restored by the mutant htt PRR deletion in the Hdh140Q?P/+ brain. In Aim 3, we will genetically test the role of the htt PRR on aggresome formation (in cis or in trans), and the potential difference between the murine and human PRR in HD pathogenesis by characterizing behavior and neuropathology in Hdh140Q?P/?P, Hdh140Q?P/+, Hdh140Q?P/7QhuPRR and Hdh140Q?P/20QhuPRR mice as they age. In addition, we will characterize microtubule-based transport and autophagy (two pathways involved in aggresome formation and protein degradation) in early postnatal (P5) primary cortical and striatal neuronal cultures generated from wild-type, Hdh?P/?P, Hdh140Q/140Q and Hdh140Q?P/140Q?P mice.

**Lay Summary**
PUBLIC HEALTH RELEVANCE: Huntington's disease is caused by the expansion of a polyglutamine stretch within the protein Huntingtin. Neighboring protein domains influence the toxicity of Huntingtin's polyglutamine stretch, and we propose to determine how removing one of these domains, the proline-rich region (PRR), can rescue HD mouse model phenotypes. What we learn from this project will help us to devise new therapies for HD that target the Huntingtin PRR.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**

Huntington's disease

**Years:**
2016

**Database Categories:**
N/A

**Database Tags:**
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