

# EPIGENETIC AND MRNA PROFILING OF STRIATOPALLIDAL NEURONS IN HUNTINGTONS DISEASE

<https://neurodegenerationresearch.eu/survey/epigenetic-and-mrna-profiling-of-striatopallidal-neurons-in-huntingtons-disease-2/>

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### **Country**

USA

## **Title of project or programme**

EPIGENETIC AND MRNA PROFILING OF STRIATOPALLIDAL NEURONS IN HUNTINGTONS DISEASE

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NIH (NINDS)

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### **Research Abstract**

Project Abstract Huntington's disease (HD) is a devastating and fatal neurodegenerative disease with no effective treatments to date. Progressive striatal atrophy caused by the selective loss of GABAergic medium spiny neurons (MSNs) is a hallmark of HD. Transcriptional dysregulation occurs early in the course of HD progression and is thought to play a central role in this disease. Emerging evidence suggests that epigenetic mechanisms, including

posttranslational modification of histones, play important roles in the transcriptional dysregulation observed in HD. A significant gap in our current understanding of this disease is the lack of an integrated epigenetic and transcriptional landscape in the at-risk neuronal subpopulation, the striatopallidal MSN. The long-term goal of this proposal is to discover therapeutic strategies that target early epigenetic and transcriptional abnormalities in a specific, disease-relevant neuronal subpopulation to prevent neurodegeneration. The fundamental objective of this proposal is to identify and integrate the epigenome and transcriptome specifically in striatopallidal MSNs in HD model mice in vivo. The two specific aims are as follows: 1) To identify key HD- associated mRNA changes in striatopallidal MSNs; and 2) To identify key HD-associated epigenetic changes in striatopallidal MSNs in HD. The proposed research overcomes current limitations of gene expression and chromatin analysis in normal and diseased neurons in vivo by using a combination of a recently developed translating ribosome affinity purification (TRAP) technique and next-generation sequencing. Unique HD mouse models, which express genetically-tagged ribosomes specifically in striatopallidal MSNs, will be utilized for the isolation of cell type-specific mRNA and chromatin from brain for RNA-sequencing (seq) and ChIP-seq analysis. Furthermore, among the differentially regulated genes discovered in the first aim, critical genes and upstream regulatory mechanisms that contribute to cellular phenotypes caused by the mutant HD protein will be identified using physiologically relevant and complementary mouse and human neuronal culture systems. Identification of key alterations in the epigenetic and transcriptional landscape in the at-risk neuronal subpopulation in HD will provide fundamental insights into important epigenetic mechanisms that drive transcriptional dysregulation and subsequent neurodegeneration. Such findings are expected to have an important positive impact in the field of neurodegenerative disease since identified molecular changes will likely provide novel therapeutic targets for HD.

**Further information available at:**

**Types:**

Investments < €500k

**Member States:**

United States of America

**Diseases:**

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