

Washington University in St. Louis

Washington University Open Scholarship

Volume 13

Washington University
Undergraduate Research Digest

Spring 2018

Exploring the Role of Mutant-Huntingtin in Early Transcription Dysregulation of Huntington's Disease

John Palucki

Washington University in St. Louis

Follow this and additional works at: https://openscholarship.wustl.edu/wuurd_vol13

Recommended Citation

Palucki, John, "Exploring the Role of Mutant-Huntingtin in Early Transcription Dysregulation of Huntington's Disease" (2018). *Volume 13*. 158.

https://openscholarship.wustl.edu/wuurd_vol13/158

This Abstracts J-R is brought to you for free and open access by the Washington University Undergraduate Research Digest at Washington University Open Scholarship. It has been accepted for inclusion in Volume 13 by an authorized administrator of Washington University Open Scholarship. For more information, please contact digital@wumail.wustl.edu.

EXPLORING THE ROLE OF MUTANT-HUNTINGTIN IN THE EARLY TRANSCRIPTIONAL DYSREGULATION OF HUNTINGTON'S DISEASE

John Palucki

Mentor: Hiroko Yano

Huntington's disease (HD) is a progressive and invariably fatal, autosomal-dominant neurodegenerative disorder caused by an abnormal expansion of CAG repeats in the huntingtin gene (*HTT*), which encodes an abnormally long polyglutamine repeat in the HTT protein. Transcriptional dysregulation is an early anomaly in the course of HD progression and has been proposed as an underlying pathogenic mechanism. Accumulating evidence suggests that epigenetic mechanisms including DNA methylation, which control chromatin structure, play an important role in transcriptional dysregulation in HD. A recent genome-wide studies in a cell model of HD and human brain tissues demonstrated that mutant HTT extensively perturbs DNA methylation. Importantly, earlier studies conducted by the Yano Lab demonstrated a requirement for DNA methyltransferases (DNMTs) in mutant Htt-induced transcriptional alterations and neuronal death, which suggests a neurodegeneration mechanism based on DNA methylation-mediated transcriptional repression. However, how mutant Htt causes aberrant DNA methylation and subsequent neuronal dysfunction remains undefined. Our preliminary co-immunoprecipitation experiments revealed an enhanced interaction between DNMT3A and mutant Htt when compared to wild-type. Based on these data and recent published results from Yano Lab, I hypothesize that the mutant HTT activates DNMT3A through interaction with DNMT3A, thereby increasing DNA methylation on specific gene promoters. To map the domain of DNMT3A required for interaction with mutant HTT, I generated a series of DNMT3A deletion mutant constructs. Subsequent binding domain mapping using GST-HTT fusion proteins and DNMT3A deletion mutants, however, provided inconclusive results. Defining the HTT binding domain within DNMT3A may provide the mechanism of how mutant HTT induces aberrant DNA methylation in HD.