Genomic and functional analysis of transcriptome changes in Huntingtons Disease

https://neurodegenerationresearch.eu/survey/genomic-and-functional-analysis-of-transcriptome-changes-in-huntingtons-disease/

Principal Investigators

DAVIDSON, BEVERLY L

Institution

CHILDREN'S HOSP OF PHILADELPHIA

Contact information of lead PI
Country

USA

Title of project or programme

Genomic and functional analysis of transcriptome changes in Huntingtons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,940,595.41

Start date of award

30/09/2013

Total duration of award in years

2

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, transcriptome, functional genomics, Huntington gene, RNA Splicing

Research Abstract

DESCRIPTION (provided by applicant): A CAG repeat expansion in exon 1 of the HD gene product, huntingtin, causes Huntington’s disease (HD), a fatal neurodegenerative disease for

which there is no cure or neuroprotective treatment. Dysregulation of transcription is a major feature of HD pathogenesis, as indicated by a large body of work using RNA array techniques, and work on specific transcription factors and their targets. More recent studies have also suggested a role for huntingtin in RNA processing. Prior work on gene expression alterations in HD brain tissues used 3? biased gene expression arrays. Of increasing importance in many human diseases, particularly neurodegenerative diseases, is the occurrence of aberrant alternative pre-mRNA splicing. However, conventional gene expression techniques are not well suited to quantitative analysis of alternative splicing patterns, and do not sample rare transcript well. Several lines of evidence from our preliminary work suggest global splicing abnormalities in HD. For example, we reported earlier that microRNA miR-124 was significantly reduced in HD brains. Work by Maniatis and colleagues showed that miR-124 promotes neuronal-specific alternative splicing events by down- regulating an important tissue-specific splicing regulator, polypyrimidine tract-binding protein (PTBP1). Consistent with the decrease in miR-124, we have preliminary evidence for significantly increased PTBP1 mRNA levels in HD patient samples. Moreover, preliminary data suggest that several exons in genes regulated by PTBP1 show corresponding changes in exon inclusion/exclusion in HD brain. Inclusion or exclusion of non-constitutive exons can have dramatic effects on transcript stability and protein activity. Thus transcriptome alterations in HD may extend beyond up- and down-regulated genes to include changes in gene and protein isoforms. Assessing these events on a global scale for HD will aid efforts to unravel disease pathophysiology, and may identify new drug targets for therapy. In our work, which encompasses 3 aims, we will move from identification of the altered HD transcriptome, to validation, to in vitro and in vivo studies to test their relevance on HD phenotypes. These studies combine the genomics and bioinformatics expertise of the Xing lab and the HD expertise of the Ross and Davidson labs. The functional relevance of those changes will be elucidated using gain and loss of function studies in the Davidson and Ross labs, where both groups have substantial experience with HD models.

Lay Summary
PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is a fatal neurodegenerative disease for which there is no cure. This project will provide a systematic assessment and functional analysis of transcriptome changes in HD. These studies will lead to a better understanding of HD pathophysiology, and reveal novel molecular targets and pathways for therapeutic development.

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:
N/A