CALIFORNIA STATE SCIENCE FAIR
2008 PROJECT SUMMARY

Name(s)

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Project Number

S0421

Project Title

The Role of Histone Modifications in Transcriptional Dysregulation of Neuronal Genes in Huntington's Disease

Abstract

Objectives/Goals

In patients with Huntington's Disease (HD), the transcription of several genes is altered. One emerging notion is that the down-regulation of genes may be due to the formation of heterochromatin that progressively affects larger portions of the genome. Heterochromatin is known to have certain histone modifications such as the trimethylation of the Lysine 9 (K9me3) residue on histone H3.

Data based on a ChIP-on-chip analysis suggested that there were altered levels of K9me3 at several loci in the striatum from an R6/2 mouse model of HD. The goal of this experiment was to determine whether there is a correlation between transcriptional dysregulation and the presence of the K9me3 mark on histone H3. The genes studied, which were chosen based on their proximity to K9me3 as well as their expression in high levels within the mouse brain, included Slc9a6, Slc25a5, Pctk1, Mcrs1, Lin7c, CENPB, PIAS2, Clpp, Gprasp1, and Spred2.

Methods/Materials

In order to compare the expression of these genes, RNA from the striatal tissues of 2 Wild Type (WT) and 2 Transgenic (TG) mice was obtained. The RNA was then reverse transcribed and the expression of each of the genes was quantified using Real-time PCR of the cDNA samples. The level of expression was calculated using the difference in Crossing Threshold C(t) values between actin (which was used as a control) and the gene of interest.

Results

Genes associated with lower levels of K9me3 in transgenic mice (Lin7C, Pias2, CENPB, Clpp, and Spred2) were clearly downregulated in the transgenic mice. The most statistically significant result was the change in expression of Lin7c, whose ratio-to-actin level changed from 0.048 to 0.072 between wild type and transgenic mice.

Conclusions/Discussion

Results showed a general correlation between fewer K9me3 modifications and transcriptional upregulation. Thus, K9me3 modifications may be one of the factors behind the dysregulation of these genes. Lin7c, which was clearly upregulated due to the lack of K9me3, is known to play a role in olfactory epithelium and in neuronal junctions. It is possible that the increase in Lin7c seen in WT mice could be altering neurotransmission and thus contributing to the onset of HD.

One of the mechanisms behind the onset of HD may be the histone H3K9 modification. A potential cure for HD would be to inhibit enzymes such as histone demethylases, which catalyze the removal of the K9me3 modification.

Summary Statement

This experiment used a mouse model of Huntington's Disease to determine whether or not a correlation exists between the H3K9me3 mark and transcriptional dysregulation of neuronal genes.

Help Received

Used lab equipment at UCI under supervision of Dr. Leslie M. Thompson; Mother helped complete board; Father helped develop presentation.