Gene-Neurotoxicant Interactions in Huntington Disease

https://neurodegenerationresearch.eu/survey/gene-neurotoxicant-interactions-in-huntington-disease/

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Country

USA

Title of project or programme

Gene-Neurotoxicant Interactions in Huntington Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,622,777.06

Start date of award

15/08/2008

Total duration of award in years

1

The project/programme is most relevant to:

Huntington's disease

Keywords

Neurotoxins, Huntington Disease, Manganese, toxicant interaction, Huntington gene

Research Abstract
DESCRIPTION (provided by applicant): Huntington Disease (HD) is a neurodegenerative disorder pathologically characterized by selective degeneration of neurons within the striatum, cortex and hypothalamus. HD is caused by a CAG repeat expansion within the HTT gene, with

longer repeats being strongly associated with earlier age-of-onset. Although repeat length explains over half of the variability in age of onset, a landmark genetic study attributed the majority of residual variability to unknown environmental factors. Metal ions with neurotoxic properties are strong candidates for environmental agents that may modulate selective neurodegenerative process like HD because, (1) the differential accumulation of various metals across neuronal subtypes, (2) the similarities between metal ion cytotoxicity and cellular pathways of neurodegeneration, and (3) our research in the previous funding cycle demonstrating altered vulnerability in mouse models of HD to both manganese and cadmium. The long-term goal of this research program is to reveal the pathogenic mechanisms underlying gene-environment interactions in neurodegenerative disease, focusing on HD given its clearly defined genetic etiology, to inform environmental health strategies to delay disease onset or slow the progression of disease. Our highly innovative approach combines (a) a novel high-throughput method to quantify cellular Mn status, (b) a state-of-the-art high throughput screen (HTS) facility at the Vanderbilt Institute of Chemical Biology (VICB), and (c) the clinical relevance of a patient-specific neuronal model system based on human induced pluripotent stem cell (hiPSC) technology. Aim 1 will test the hypothesis that an HD striatal Mn handling deficit discovered in the previous funding cycle will enable a HTS to find small molecules that mitigate the actions of HD environmental risk factors. Aim 2 will test the hypothesis that human striatal neuroprogenitors (NPs) from HD patients have increased sensitivity to non-cytotoxic levels of metal toxicants impinging upon specific stress response pathways. Aim 3 will test the clinical potential of small molecule modifiers of environmental risk factors in HD and whether the magnitude of HD-specific toxicant vulnerability will correlate by patient with established disease-modifiers such as neural lineage specificity, CAG-repeat length and clinical variation in age-of-onset. These specific aims will reveal disease-relevant environmental stress responses and identify small molecules to mitigate vulnerabilities and restore neuronal homeostasis in HD. Furthermore, discovery of toxicant interactions and patient-specific responses may inform environmental health strategies to delay disease onset or slow the progression of HD using a personalized medicine approach.

Lay Summary
PUBLIC HEALTH RELEVANCE: The proposed studies will (1) evaluate p53 and AKT/mTOR cell stress signaling pathways as mediators of gene-environment interactions in Huntington disease (HD), (2) test whether human striatal neuroprogenitors derived from HD patients will exhibit selective vulnerability to Mn and other neurotoxicants that impinge upon these specific stress response pathways, (3) validate the pathogenic relevance of these pathways in an in vivo HD mouse model, and (4) determine if patient variation in HD age-of-onset correlates with sensitivity to HD- relevant neurotoxicants. Our multidisciplinary approach seeks to define the functional domains that underlie modulation of HD by environmental risk factors and identify the clinical correlates of the stress response pathways that underlie this neurodegenerative disease.

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