Disease-Modifying Genes in Huntingtons Diseae

https://www.neurodegenerationresearch.eu/survey/disease-modifying-genes-in-huntingtons-diseae/

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Country

USA

Title of project or programme

Disease-Modifying Genes in Huntingtons Diseae

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,750,835.78

Start date of award

01/04/2015

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

Gene-Modified, Huntington Disease, Huntington gene, Ulysses Contracts, Motor

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a devastating neurodegenerative disorder involving motor, psychiatric and cognitive disturbances present in more than 1 in 10,000 persons but, as a family disorder with a long, costly, debilitating course,

with an indirect impact on a far greater proportion of the population at great cost to the individul and society. While some palliative treatments are used, there is currently no effective treatment for preventing clinical onset of the disorder or for delaying its inevitable progression toward premature death, ~15 years after diagnosis. In past decades, genetics provided the tools to map the HD gene to chromosome 4 and ultimately to identify its mutation as an expanded CAG trinucleotide repeat in the coding sequence of a large protein, dubbed huntingtin. The length of the expanded HD CAG repeat is negatively correlated with the appearance of diagnostic motor signs but does not explain all of the variance in this phenotype, as other genetic factors also influence the disease process. We have used genome-wide association analysis to identify regions of the human genome which harbor disease-modifying genetic variation that acts to alter age at motor onset in human patients of European ancestry. Identification of the actual modifier genes at these locations will highlight processes occurring before clinical diagnosis to alter the course of HD and therefore to provide new, human-validated targets for traditional drug development. Our aims are to capitalize on existing genetic data and carry out focused additional genotyping of subjects to determine whether 1) these modifiers also modify cognitive and psychiatric onsets; 2) overlap with genetic factors in other disorders; and 3) show enrichment for pathways/processes that could provide targets for intervention. These findings, combined in each associated region with dense haplotyping, sequencing and expression analysis of the loci involved and testing of candidate genes in established disease-relevant assays in human induced pluripotent stem cells and precise genetic HD mouse models will converge to identification of the gene responsible for disease modification and its functional variation. The product of this work will be a knowledge of specific genes and pathways that can delay HD pathogenesis in human patients, of the degree to which they broadly affect both HD motor and other phenotypes and of the potential mechanisms by which they act. We will also provide critical cellular and mouse model resources necessary to rapidly drive the findings toward translation for the HD community. It is our belief that the identification of novel targets, implicated by the natural variation in biological processes ongoing in HD patients themselves, will provide a firm foundation for developing effective pharmaceutical interventions to push those processes toward a strong therapeutic benefit in HD patients. Thus, the promise of this grant is a new and powerful route to fulfilling the greatest need of HD patients and families: an effective treatment to delay of prevent onset of the disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD), with its single genetic cause, expanded CAG tracts in the HTT gene, is an inherited neurodegenerative disorder that devastates entire families. This project uses genetic and genomic approaches to uncover other genes that significantly alter the timing with which diagnosable symptoms become manifest in Huntington’s disease patients. We have discovered definitive chromosomal locations of several such modifier genes and have suggestive evidence for the locations of many more. Using a combination of human HD disease patient sample collections, induced pluripotent stem cell lines and neuronal cells derived from them, and lines of mice that precisely replicate the human mutation, we will home in on the precise genes and DNA variants and, therefore, the biological pathways that influence the HTT CAG-initiated disease process that leads to onset of motor symptoms, cognitive impairment and psychiatric symptoms and will evaluate their effects in accurate model systems. We will thereby generate the knowledge and experimental resources to support therapeutic development for the first time based upon targets already validated to alter the rate of HD in humans.

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