Huntingtons disease repeat instability and pathogenesis

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Country

USA

Title of project or programme

Huntingtons disease repeat instability and pathogenesis

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,631,374.31

Start date of award

01/07/2004

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, MLH1 gene, Huntington gene, Mismatch Repair, CAG repeat

Research Abstract

? DESCRIPTION (provided by applicant) Huntington’s disease (HD) is a devastating and fatal neurodegenerative disorder caused by the expansion of a polymorphic CAG repeat in the HTT gene that triggers cell death with a specificity towards neurons in the striatum and cortex.

Although the underlying genetic mutation was discovered over 20 years ago, there is still no cure or effective treatment despite extensive efforts. The HTT CAG repeat mutation is highly unstable both in transmissions to subsequent generations and somatically. Notably the repeat undergoes dramatic tissue-specific somatic expansion, particularly in the brain regions affected in the disorder, strongly suggesting that somatic HTT CAG length increases in target tissues contribute to HD pathogenesis. We have shown in accurate genetic HD knock-in mouse models that genes in the mismatch repair (MMR) pathway (Msh2, Msh3, Mlh1, Mlh3) are critical for CAG expansion and enhance the pathogenic process. The relevance of these findings to HD patients is indicated by a recent genome-wide association study in which MLH1 SNPs were associated with motor onset, and more generally, in which DNA repair pathways were highlighted as a source of disease modification. In this study we will: 1) perform genetic experiments in HD knock-in mice that will provide insight into mechanism(s) of MMR-dependent instability and pathogenesis; 2) test the impact of MLH1 SNPs in HD patients on gene expression, cellular phenotypes and on somatic and intergenerational repeat instability; 3) Use gene knockdown and gene editing approaches to test the impact of additional DNA repair genes, implicated as disease modifiers in patients, as modifiers of instability and striatal pathogenesis in HD knock-in mice. Together, these experiments will provide critical insight into pathways and mechanisms by which MMR/DNA repair genes modify pathogenesis, which will directly impact on the development of therapeutics that promise to target mechanism(s) that occur very early in the disease process.

Lay Summary
PUBLIC HEALTH RELEVANCE Huntington’s disease is a devastating and fatal neurodegenerative disorder for which there is no cure or effective treatment. The combination of emotional, cognitive and motor symptoms, leading to long-term care needs results in an extremely high healthcare cost, estimated at 25 billion dollars a year. This study is aimed at identifying early modifiers of disease with the potential of discovering novel targets for early therapeutic intervention

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

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