Integrating Quality Control: Studies of UBQLN2 in Age-Related Neurodegeneration

https://www.neurodegenerationresearch.eu/survey/integrating-quality-control-studies-of-ubqln2-in-age-related-neurodegeneration-2/

Principal Investigators

PAULSON, HENRY L

Institution

UNIVERSITY OF MICHIGAN

Contact information of lead PI
Country

USA

Title of project or programme

Integrating Quality Control: Studies of UBQLN2 in Age-Related Neurodegeneration

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,857,325.69

Start date of award

15/09/2009

Total duration of award in years

5

The project/programme is most relevant to:

Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

age related neurodegeneration, Controlled Study, Frontotemporal Dementia, ubiquilin, Amyotrophic Lateral Sclerosis

Research Abstract
? DESCRIPTION (provided by applicant): Mutations in Ubiquilin2 (UBQLN2) were recently

identified as a cause of Frontotemporal Dementia and Amyotrophic Lateral Sclerosis (FTD/ALS) associated with TDP43 deposition, and UBQLN2 itself has emerged as a sensitive marker of pathology in a substantial portion of sporadic and familial FTD/ALS. UBQLN2 is also one of four closely related ubiquilins, a family of ubiquitin adaptor proteins implicated in ubiquitin-dependen protein quality control in the nervous system. Although mounting evidence implicates UBQLN2 and other ubiquilins in numerous age-related neurodegenerative diseases defined by protein accumulation, their functions in brain health and disease remain poorly understood. Moreover, the mechanisms by which mutations in UBQLN2 cause FTD/ALS are unknown. The current proposal investigates these critical gaps in knowledge. Our primary goals are to define pathogenic mechanisms in UBQLN2-mediated FTD/ALS and to gain insight into the cellular pathways driving TDP43 deposition and neurodegeneration in FTD/ALS. In three specific aims employing complementary approaches (biochemistry, animal models, and automated microscopy), our investigative team will seek to 1) define the molecular properties driving aggregation of mutant UBQLN2, 2) explore the functional consequences of UBQLN2 aggregation in mouse models, and 3) investigate how mutant UBQLN2 alters TDP43 homeostasis in neurons. The proposed studies build on: novel biochemical insights into the distinct properties of wild type and mutant UBQLN2; newly generated mouse models expressing wild type or mutant UBQLN2 that show robust aggregate pathology selectively in mutant UBQLN2 mice; a completed proteomics screen demonstrating that wild-type UBQLN2 interacts with the two other brain-expressed ubiquilins, UBQLN1 and UBQLN4; and evidence that TDP43-positive cytoplasmic puncta accumulate in neurons of mutant UBQLN2 mice, offering a pathway to explore functional links between UBQLN2 and TDP43. The proposed multi-system approach greatly increases the probability of uncovering disease mechanisms in FTD/ALS and achieving our long-term objective of finding routes to therapy for this spectrum of fatal, age-related neurodegenerative diseases.

Lay Summary
PUBLIC HEALTH RELEVANCE: This study will explore the basis of neurodegenerative disease caused by mutations in UBQLN2.These studies will provide insight into the role that UBQLN2, one of a family of ubiquitin receptor proteins, normally plays in neuronal protein quality control and how mutant UBQLN2 precipitates neurodegenerative disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias, Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A