Characterization of ATXN1 in APP processing and AD pathogenesis

https://neurodegenerationresearch.eu/survey/characterization-of-atxn1-in-app-processing-and-ad-pathogenesis/

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Country

USA

Title of project or programme

Characterization of ATXN1 in APP processing and AD pathogenesis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 910,940.37

Start date of award

01/12/2013

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders... Dementia... Genetics... Human Genome... Neurodegenerative... Neurosciences

Research Abstract

ABSATRACT This proposal is aimed at functionally characterizing a novel Alzheimer’s disease

(AD) candidate gene, ATXN1, identified in our recent family-based, genome-wide association study (GWAS). AD is a devastating neurodegenerative disease and the primary cause of dementia in the elderly. Considerable evidence suggests that the excessive accumulation of a small peptide, amyloid-¿ (A¿), is a primary pathological event leading to AD. A¿ is produced from the amyloid-¿ precursor protein (APP) through sequential cleavage via ¿- and ¿-secretase. By further identifying and characterizing the genes that influence APP processing we hope to elucidate the pathogenesis of AD. In our group's most recent GWAS to identify novel AD candidate genes, we screened over 1,000 AD families (5,600 subjects) and identified four novel late-onset AD candidate genes that achieved genome-wide statistical significance. This is not only the largest family-based AD GWAS performed to date, but also the first one to identify any AD novel candidate genes with genome-wide significance. One of the four novel AD candidate genes, ataxin-1 (ATXN1) is the disease gene for spinocerebellar ataxia type 1 (SCA1), a neurodegenerative disease characterized by ataxia and loss of Purkinje cells in the cerebellum. ATXN1 undergoes alternative splicing and has two primary mRNA transcript variants. A previous study shows that knock-out of ATXN1 mouse displays severe cognitive and behavioral deficits through unknown mechanisms. To identify the underlying mechanism, in an independently funded study, we characterized the roles of ATXN1 in APP processing utilizing cell-based models. Our recently published results showed that knock-down of ATXN1 significantly potentiates ¿-secretase processing of APP and increases A¿ levels. More recently, our preliminary studies reveal that in ATXN1 knock-out mice BACE1 levels are elevated together with ¿-secretase processing of APP. In summary, emerging evidence suggests that ATXN1 is a novel AD candidate gene which contributes to AD pathogenesis, most likely, through a loss-of-function mechanism. This proposal is aimed at further characterizing the molecular mechanisms by which ATXN1 modulates BACE1 levels, APP processing and AD pathogenesis employing cell-based models, mouse models, and human AD brains in three specific aims. The proposed two years of mentored support should allow enough time to complete the first sub- aim in each of the three aims and allow me to apply for an independent position; the three years of independent support will allow me to achieve all the proposed studies. Collectively, the proposed experiments aimed at functionally characterizing ATXN1 will not only further elucidate the etiology and pathogenesis of AD, but also provide valuable new insights into the development of novel therapies for treating and preventing AD.

Lay Summary
PROJECT NARRATIVE Alzheimer's disease (AD) is a devastating and progressive neurodegenerative disease with complex and strong genetic inheritance. Currently there is no cure to stop the progress of AD due to a poor understanding of AD pathogenesis. Here we propose a ""translational"" study, aimed to functionally characterize a novel AD candidate gene, which may not only provide novel insights into the pathogenesis of AD, but also assist in identifying new therapeutic targets of AD.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A