# Understanding the role of TDP-43 in Alzheimers disease and FTLD

https://neurodegenerationresearch.eu/survey/understanding-the-role-of-tdp-43-in-alzheimers-disease-and-ftld/

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**Country**

USA

**Title of project or programme**

Understanding the role of TDP-43 in Alzheimers disease and FTLD

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 1,504,013.76

**Start date of award**

01/07/2010

**Total duration of award in years**

7

**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)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

**Research Abstract**

? DESCRIPTION (provided by applicant): In the first cycle of our R01 we demonstrated that the

transactive response DNA binding protein of 43 kDa (TDP-43) influences memory loss and hippocampal atrophy in Alzheimer's disease (AD). This showed that TDP-43 plays a key role in neurodegeneration in AD and represents an important new treatment target for AD. This work, however, was limited to subjects with advanced neuropathological stages of AD. If treating AD is going to be successful, there needs to be advancement in our understanding of how TDP-43 interacts with the other AD associated proteins of tau and beta-amyloid (Aß) to affect neurodegeneration across the entire spectrum of AD neuropathologic changes. The primary goal of our second cycle is therefore to determine how TDP-43, tau and Aß interact to account for neurodegeneration across all levels of AD neuropathologic changes. We aim to investigate the relationship between the frequency, burden and topographic distribution of TDP-43 and the topographic distributions of tau and Aß, and assess how these three proteins interact and influence clinical, neuropsychological and neuroimaging outcomes. We also aim to investigate whether neurodegeneration in AD is dependent on the ratio of C to N terminal TDP-43 specie, or TDP-43 subtype (A- D). To accomplish our aims we will perform pathological analyses on a cohort of 768 cases that have been prospectively recruited and autopsied between 1/1/2000 and 12/31/2013 at Mayo Clinic, Rochester, Minnesota. All 768 cases have already undergone a standard neuropathological assessment and been assigned a Braak neurofibrillary tangle stage measuring the distribution of tau deposition. For the renewal, we will perform Thal staging to assess Aß distribution on all 768 cases. TDP-43 immunohistochemistry was already performed on 342 cases in the first cycle, and so for this cycle we will perform TDP-43 immunohistochemistry on the remaining 426 cases to assess for 1) the presence of TDP-43, 2) TDP-43 distribution and assign each case a TDP-43 in AD stage, 3) TDP-43 burden in the hippocampus, 4) TDP-43 specie and 5) TDP-43 subtype. Clinical data will be abstracted for each case and tensor-based morphometry will be utilized to calculate volumes of the hippocampus and neocortex on all available MRI scans for each case. Statistical models will be utilized to assess the relationships between TDP-43, tau and Aß, accounting for other potentially confounding pathologies such as Lewy bodies, vascular disease and hippocampal sclerosis, and their relationship to cognitive impairment and brain atrophy across the AD neuropathologic spectrum. Ultimately, we aim to generate a model demonstrating how TDP-43, tau and Aß influence hippocampal and neocortical atrophy with disease duration. Findings from this R01 will significantly improve understanding of how these three potential molecular targets interact to influence the AD neurodegenerative process. Given that these proteins currently have the greatest potential as therapeutic targets for the treatment of AD, our R01 has potential for significant public health impact.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: We recently showed that a protein called TDP-43 is partially responsible for memory loss and brain atrophy in advanced Alzheimer's disease, and hence could be a target for the treatment of Alzheimer's disease. Two other proteins, beta-amyloid and tau, also appear to be contributing to memory loss and brain atrophy in Alzheimer' disease. In this R01 we will study how all three proteins interact to cause memory loss and brain atrophy in early stages, as well as advanced stages, of Alzheimer's disease.

**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:**
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