Concordance of TDP-43 Inclusions with Cortical Atrophy and Clinical Phenotype

https://neurodegenerationresearch.eu/survey/concordance-of-tdp-43-inclusions-with-cortical-atrophy-and-clinical-phenotype/

Principal Investigators

GEULA, CHANGIZ

Institution

NORTHWESTERN UNIVERSITY AT CHICAGO

Contact information of lead PI
Country

USA

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Concordance of TDP-43 Inclusions with Cortical Atrophy and Clinical Phenotype

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NIH (NIA)

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€ 1,550,316.51

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01/08/2014

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

cerebral atrophy, Frontotemporal Lobar Degenerations, DNA-Binding Proteins, clinical phenotype, regional atrophy

Research Abstract
DESCRIPTION (provided by applicant): Aggregation of misfolded proteins in the form of

abnormal inclusions is a common feature of numerous neurodegenerative diseases. The exact relationship of these inclusions to the neurosynaptic loss is incompletely understood, particularly in frontotemporal lobar degeneration (FTLD). The major goal of this proposal is to clarify the relationship between transactivation response element DNA binding protein-43 (TDP- 43) inclusions and neuronal death in FTLD. This is important because FTLD-TDP is arguably the most frequent form of FTLD and can lead to a bewildering heterogeneity of atrophy sites and clinical phenotypes. While the past few years have witnessed dazzling advances in the genetics and cellular biology of FTLD-TDP, quantitative information on the regional distribution of TDP-43 inclusions and its relationship with disease phenotype is glaringly absent from the literature. We propose to base our investigation on the unbiased stereological quantification of abnormal TDP-43 precipitates in a unique set of autopsy specimens from patients with known patterns of regional atrophy and clinical phenotypes. The central goal will be to infer the putative causes of cell death in these specimens. The hypotheses that will emerge from this human material will then be tested in a transgenic mouse model of abnormal TDP-43 precipitates. The application comes from an Alzheimer's Disease Center (ADC) with a focus on FTLD and a brain bank that has 118 autopsied pathologically characterized cases of FTLD with detailed clinical information. We will test the following hypotheses: 1. Regional differences in densities of TDP-43 inclusions will mirror clinical phenotype, focal atrophy patterns, distribution of neuronal and synaptic loss, and concentrations of inflammatory markers. 2. Conditionally TDP-43 overexpressing mice will display age-dependent behavioral abnormalities related to accumulation of cortical TDP-43 inclusions, neuronal and synaptic loss and concentration of inflammatory markers. 3. The known circuitry of the hippocampal dentate gyrus and its predilection to TDP-43 inclusions will reveal potential anterograde axodendritic and transsynaptic spread of neuropathology in human brains with FTLD-TDP pathology and in conditionally TDP-43 overexpressing mice. Histological, immunohistochemical, unbiased stereological quantitative methods and optical density measures will be used to address these hypotheses. The proposed research will generate information relevant to the contribution of TDP-43-positive inclusions, not only to disease phenotype and atrophy, but also to the underlying neuronal and synaptic loss. In the long-run, this information will be relevant to therapeutic approaches targeting TDP-43.

Lay Summary

PUBLIC HEALTH RELEVANCE: Frontotemporal lobar degeneration (FTLD) with transactivation response element (TAR) DNA binding protein 43 (TDP-43) inclusions is arguably the most prevalent form of this dementing disorder, which presents with a bewildering heterogeneity of atrophy sites and clinical phenotypes. While the past few years have witnessed dazzling advances in the genetics and cellular biology of FTLD-TDP, quantitative information on the regional distribution of TDP-43 inclusions and its relationship with disease phenotype is glaringly absent from the literature. The proposed research will generate a great deal of information relevant to the contribution of TDP- 43-positive inclusions, not only to disease phenotype and atrophy, but also to the underlying neuronal and synaptic loss. In the long-run, this information will be relevant to therapeutic approaches targeting TDP-43.

Further information available at:

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Alzheimer's disease & other dementias

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