Characterization of Alzheimers Mutations in ADAM10.

https://neurodegenerationresearch.eu/survey/characterization-of-alzheimers-mutations-in-adam10/

Principal Investigators

TANZI, RUDOLPH EMILE

Institution

MASSACHUSETTS GENERAL HOSPITAL

Contact information of lead PI
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USA

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Characterization of Alzheimers Mutations in ADAM10.

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

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

Research Abstract
DESCRIPTION (provided by applicant): Abundant clinical, genetic, and biochemical data

support the hypothesis that abnormal processing of the amyloid precursor protein (APP) and the cerebral accumulation of its metabolite, A?, play key roles in the etiology and pathogenesis of Alzheimer's disease (AD). A? is generated via serial cleavage of APP by ?- and ?- secretase. In contrast, cleavage of APP by ?-secretase precludes A? production; the major ?-secretase in the brain is ADAM10. We recently reported two rare missense mutations in ADAM10 that strongly co- segregates with late-onset AD (LOAD). Both are prodomain mutations that were found in 7 of 1000 NIMH and NIA LOAD families tested (average age of onset, ~70 years). We have also previously reported that both mutations significantly attenuated ?-secretase activity and elevated A? levels in vitro. To further validate and expand upon these novel findings, we propose to 1. Search for additional novel familial LOAD mutations in ADAM10; 2. Validate the pathogenicity of these two missense mutations in vivo; and 3. Determine the molecular mechanism by which these two mutations impair ?-secretase activity. For Aim 1, we will search for additional novel familial LOAD mutations in ADAM10, through targeted re-sequencing (and genotyping) of 2454 additional AD families (N=6516 subjects) from the NIMH and NIA AD family collections. Our family-based GWAS on >900 NIMH and NIA AD families suggest the existence of additional AD-associated SNPs in ADAM10. With regard to Aim 2, we will attempt to validate the pathogenicity of these two mutations in vivo in transgenic mice (already generated) overexpressing either wild-type (WT) or mutant (Q170H, R181G, artificial dominant-negative) forms of ADAM10. These mice have already been crossed with Tg2576 (APPswe) AD mice so that we can also test for effects of these mutations on neuropathological and cognitive phenotypes of AD. Our preliminary in vivo results reveal that the ADAM10 prodomain mutations attenuate non-amyloidogenic processing of APP, and that senile plaque counts and A? levels were significantly increased in the brains of APPswe/ADAM10 double transgenic mice expressing mutant forms of ADAM10, as compared to those expressing WT forms. Moreover, to test the impact of the prodomain mutations under more physiologically relevant conditions, we have added a plan to generate and characterize ADAM10 mutant knock-in mice. Finally, in Aim 3, we will investigate the molecular mechanism by which the prodomain mutations down-regulate ADAM10 ?-secretase activity. Briefly, we will test for effects of these mutations on three prodomain functions: regulation of enzyme activity, intracellular trafficking, and intramolecular chaperoning. At the completion of this project, we hope to provide genetic, biochemical, and mechanistic evidence validating the pathogenicity of late-onset familial AD mutations in ADAM10. Moreover, the data emerging from the proposed study would serve as a firm foundation for the discovery and development of new therapies targeting ADAM10 for the treatment and prevention of this devastating disease.

Lay Summary

We will attempt to establish in vivo validation for the pathogenicity and to elucidate the molecular mechanism of two ADAM10 prodomain mutations, which we have already confirmed in several late-onset Alzheimer's disease (AD) families. We will also search for additional AD mutations in the ADAM10 gene.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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