Role of the TOMM40 poly-T variant in the pathogenesis of Alzheimers disease

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Country

USA

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Role of the TOMM40 poly-T variant in the pathogenesis of Alzheimers disease

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4

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)... Biotechnology... Brain Disorders... Dementia... Genetics... Human Genome... Neurodegenerative... Neurosciences... Prevention... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): We have demonstrated that there is a strong association between polymorphic poly-T variant of TOMM40 and the age of onset of late-onset Alzheimer’s disease (AD). For APOE e3/4 patients who develop AD, those with long poly-T repeats linked to APOE e3 developed AD on average 7 years earlier than those with shorter poly-T polymorphisms linked to APOE e3. We have replicated this finding in a distinct population. In APOE e3/e3 homozygotes there is also a significant correlation between the length of the poly-T variant and grey matter density, which is independent of APOE e4. TOMM40 is in linkage disequilibrium with APOE and encodes the protein Translocase of the Outer Mitochondrial Membrane. Our central hypothesis is that the poly-T tract controls expression of TOMM40 and APOE in brain, and thus regulates the pathways in which these proteins participate. We will test this hypothesis at the genomic, genetic and biochemical levels. We will precisely identify the long, short and the ancestral poly-T tracts, and correlate the age o onset of AD and AD risk to these alleles. We will test our working model that the poly-T tract regulates TOMM40 and APOE expression by measuring APOE and TOMM40 mRNA and protein levels in rapidly autopsied human brain samples, and correlate these changes with susceptibility to AD-related damage across different brain regions. We will also construct two humanized mouse models of the TOMM40-APOE linkage disequilibrium region, that will permit more detailed, mechanism-based studies of the regulation of expression of these genes. We will exchange the mouse TOMM4-APOE linkage disequilibrium region with the homologous human region. Both models will be made homozygous for human APOE e3, thus eliminating possible confounding effects of APOE e4, and we will make one homozygous for the short poly-T polymorphism while we will make the other homozygous for the long poly-T variant. Successfully fulfilling these aims will advance our understanding of the molecular mechanisms underlying the genetic risk factors in AD and will provide valuable pathways for developing an effective preventive therapy for late-onset Alzheimer’s disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease is a critical unmet medical need. Currently more than five million Americans have AD and they cost Medicare $91 billion annually, and their caregivers provide billions in “”free”” care and cost their employers billions more in lost productivity. These trends will worsen because there are no disease-modifying therapies that improve dementia or the cognitive decline associated with it. Our studies build on a new genetics discovery to understand genetic factors affecting the rate of change in disease risk for AD with age that will lead to the discovery of preventive therapies for Alzheimer’s disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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