Integrative translational discovery of vascular risk factors in aging and dementia

https://neurodegenerationresearch.eu/survey/integrative-translational-discovery-of-vascular-risk-factors-in-aging-and-dementia/

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Country

USA

Title of project or programme

Integrative translational discovery of vascular risk factors in aging and dementia

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 5,343,766.06

Start date of award

30/09/2015

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Cerebrovascular... Clinical Research... Clinical Research - Extramural... Dementia... Endocrine System... Estrogen... Genetics... Human Genome... Neurodegenerative... Neurosciences... Prevention... Translational Research... Vascular

Cognitive Impairment/Dementia... Women's Health for IC Use

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a progressive neurodegenerative disease characterized by the deposition of amyloid-? (A?) in the brain parenchyma as senile plaques and in the cerebrovasculature as cerebral amyloid angiopathy (CAA). CAA is also a major cause of intracranial hemorrhage in the elderly. Epidemiological studies indicate that disturbance of the vascular system contributes to the pathogenesis of both AD and CAA. In addition, the ?4 allele of the apolipoprotein E (APOE) gene is the strongest genetic risk factor for both AD and CAA. ApoE4 exacerbates A? accumulation in the brain, causes blood-brain barrier breakdown and reduction of small vessels. While APOE4 carriers have a higher risk for AD in general, APOE4 effect is significantly stronger in females compared to males. Consistently, our preliminary results indicate that APOE4 has a stronger genetic association with CAA severity in females than males. Although females have a higher risk for AD, we found that males have more severe CAA than females in AD. These data suggest the presence of sex-specific, and both apoE-dependent and independent molecular pathways in the development of CAA and AD. In this proposal, we aim to define how sex and apoE isoforms differentially affect the risk for AD and CAA, and to identify novel genes and pathways that contribute to cerebrovascular pathology in aging and AD. We will use interdisciplinary, systems-based approaches by leveraging existing and generating new data in neuropathology, genome/epigenome, and neuroimaging fields in richly phenotyped, large autopsy brain collections and the longitudinally followed, elderly cohort, Mayo Clinic Study of Aging (MCSA). Our comprehensive hypothesis-driven and hypothesis-generating studies will provide novel insights into the molecular mechanisms underlying CAA and other cerebrovascular pathologies in AD. Our specific aims are as follows: Aim 1. Define the effects of sex and apoE isoforms on the pathological distribution and severity of CAA and parenchymal amyloid plaques; Aim 2. Identify novel pathways that contribute to the development of CAA and AD; Aim 3. Discover the impact of novel pathways on vascular risk in aging and dementia; Aim 4. Investigate the molecular mechanisms mediating the impact of apoE isoforms and estrogen on brain A? clearance and the formation of CAA and amyloid plaques. Collectively, these studies are expected to both uncover mechanisms underlying apoE and sex effects for AD/CAA and discover novel genes and pathways that will be candidate diagnostic and therapeutic targets.

Lay Summary

PUBLIC HEALTH RELEVANCE: The majority of AD patients have a variety of cerebrovascular lesions in addition to the hallmark amyloid and tau pathologies. The goal of our proposed project is to assess known and discover new genetic, epigenetic and environmental risk factors, pathways and functional networks that contribute to cerebrovascular pathology in aging and AD. Our comprehensive methodologies and integrative team will use multidisciplinary approaches to uncover novel targets for diagnosis and treatment of AD and related dementias.

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