Molecular Characterization and Validation of Gender Differences in Alzheimers Disease Pathogenesis

https://neurodegenerationresearch.eu/survey/molecular-characterization-and-validation-of-gender-differences-in-alzheimers-disease-pathogenesis/

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Country

USA

Title of project or programme

Molecular Characterization and Validation of Gender Differences in Alzheimers Disease Pathogenesis

Source of funding information

NIH (NIA)

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€ 3,863,410.09

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15/09/2016

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 including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders...

Dementia... Genetics... Neurodegenerative... Neurosciences... Women's Health for IC Use

Research Abstract
Alzheimer’s disease (AD) is a neurodegenerative disease that affects approximately one-half of the U.S. population greater than 85 years old. The burden of AD at the patient level falls disproportionately on females, as many studies find that age-matched females have a higher proportion of AD cases. Indeed, evidence suggests that the APOE ?4 allele (ApoE4), which is the strongest risk factor for AD, may have an especially large effect in females compared to males. Surprisingly, although many studies have focused on genetic and gene expression risk factors for AD, and many studies have focused on clinical, neuropathologic, and neuroimaging differences in AD between females and males, few if any studies have focused on the genetic and gene expression mechanisms that mediate the apparent gender differences in AD presentation. In order to address this gap in our understanding of AD pathogenesis, we will employ what is to the best of our knowledge the largest gene expression study of postmortem human brains in AD, which includes currently 1400+ postmortem human brain samples, and will grow as more data is generated over the course of this project. We will perform an extensive quality control and covariate correction of the assembled data to ensure that gender status is annotated correctly and that covariates such as age do not confound our analyses. This cleaned and aggregated human postmortem brain gene expression data set will be made available to the research community to improve standards among the field of AD research and accelerate AD research by avoiding duplication of work. Next, we will systematically search for genes and pathways that differentiate AD progression between females and males, as well as ApoE4 carriers and non-carriers, and we will validate the differences in gene and protein expression levels using additional postmortem human brain samples to confirm the biological relevance of the findings. Then, we will generalize the analysis of human postmortem brain gene expression data to the network level, which will allow us to detect higher-order trends and identify target genes that drive major differences in AD progression between females and males. We will validate several key targets that are likely to play a mechanistic role in AD via genetic analysis of AD risk in females and males with and without APOE ?4 carriers. Finally, we will corroborate the findings at the gene expression and network level via targeted validation studies in AD animal models, such as female and male ApoE4 KI mice without and with 3xTg AD background. We expect that this proposed research program will lead to a dramatic improvement in our understanding of AD biology, because instead of attempting to adjust away sex differences in AD progression, we will explicitly study them and work towards a comprehensive understanding of the molecular mechanisms underlying sex differences in AD pathogenesis. It will also pave a path towards distinct targeted drug discovery efforts for AD in females and males, which will be crucial to help decrease the burden of this devastating disease.

Lay Summary
We will construct gender- and ApoE-specific multiscale gene networks of AD by integrating large-scale molecular data and known gene regulatory relationships and use genome sequence data to identify variants within these gene networks and drivers that influence risk AD. We will validate these results using male and female AD mouse models, and postmortem human brain tissues. We will investigate functional roles of identified key drivers using gene manipulation in AD mice.

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