Genome-wide Profiling of Brain DNA Hydroxymethylome in Alzheimer’s Disease

https://www.neurodegenerationresearch.eu/survey/genome-wide-profiling-of-brain-dna-hydroxymethylome-in-alzheimer%c2%92s-disease/

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Country

USA

Title of project or programme

Genome-wide Profiling of Brain DNA Hydroxymethylome in Alzheimer’s Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,421,529.36

Start date of award

15/06/2016

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

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is a devastating neurodegenerative disorder for which there is no cure or effective treatment. A thorough understanding of its molecular mechanisms is a prerequisite for discovering novel diagnostic and therapeutic strategies against AD. DNA methylation at the fifth position of cytosine (5mC) is a well-studied epigenetic mark that is implicated in AD. The newly discovered 5-hydroxymethylcytosine (5hmC) is an oxidative product of 5mC that is essential for DNA demethylation. 5hmC is particularly enriched in the brain, accumulates with aging process, and is dynamically regulated by life experiences. 5hmC exhibits distinctive genomic distribution as compared to 5mC, and altered 5hmC influences gene expression. These findings suggest that 5hmC represents a new dimension of epigenetic regulation for brain function and neurodegeneration. However, there is little research examining the genome-wide pattern of 5hmC in human brain and its role in AD in human populations. Building on our prior work in human brain and animal models, we hypothesize that aberrant 5hmC modification is causally associated with AD pathology. Our goal is to identify causative 5hmC alterations associated with quantitative neuropathological measures for early features of AD pathology (e.g., amyloid plaques, neurofibrillary tangles). To achieve this, we propose four specific aims: (1) Identify differentially hydroxymethylated regions associated with AD pathology by genome-wide profiling of 5hmC in 740 postmortem brains collected by two large, community-based population studies of aging and dementia: the Religious Order Study (discovery sample) and the Rush Memory and Aging Project (replication sample). As traditional methods cannot discriminate between 5mC and 5hmC, we will perform 5hmC-capture sequencing, followed by TET-assisted bisulfite sequencing using novel techniques developed by our group and collaborators. (2) Conduct targeted methylation sequencing to identify additional AD-associated 5mC alterations that may have been missed by our previous EWAS as a result of the limited resolution and genome coverage of the Illumina platform. (3) Functionally validate the putative genes identified in Aims 1 and 2 using existing RNA-seq data from the same brain cortex and a fly model for AD. (4) Perform integrative `omics' analyses to test the joint and interactive effects of multi-layer `omic' markers on AD pathology. This innovative project leverages the wealth of deep clinical and neuropathological phenotypes and multi-level `omics' datasets generated in the same brain tissue, and provides unprecedented opportunities to uncover novel molecular mechanisms underlying AD pathology. Our proposal brings together an exceptionally strong and unique multi- disciplinary team with complementary expertise needed to achieve our goal. The work proposed represents the frontier in the interface between AD and `omics' research. Findings of this study will provide important mechanistic insights into disease etiology, and are highly likely to lead to the discovery of novel strategies for early detection, prevention and therapeutic intervention of AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is a fatal neurodegenerative disorder that affects over 5 million Americans. Despite substantial effort, the mechanisms underlying AD remains elusive. This project leverages the wealth of unique resources collected by two large, community-based longitudinal cohorts of aging and dementia with brain donation at the time of death to identify novel causative epigenetic determinants for AD pathology. Findings of this study will provide important mechanistic insights into disease etiology, and are highly likely to lead to the discovery of novel diagnostic and therapeutic tools against AD.

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