Exploring the Role of the Brain Epigenome: Cognitive Decline and Life Experiences

https://neurodegenerationresearch.eu/survey/exploring-the-role-of-the-brain-epigenome-cognitive-decline-and-life-experiences/

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Country

USA

Title of project or programme

Exploring the Role of the Brain Epigenome: Cognitive Decline and Life Experiences

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 5,067,575.23

Start date of award

15/09/2009

Total duration of award in years

6

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

Research Abstract

? DESCRIPTION (provided by applicant) Following recent technological developments and the rapid evolution in our understanding of the epigenome, the structure of genomic DNA, studies of the role of the aging brain’s epigenome in Alzheimer’s disease (AD) have recently emerged. In our first funding cycle, we profiled DNA methylation and a histone mark (H3K9Ac) in the dorsolateral prefrontal cortex (DLPFC) of more than 700 older subjects from two prospective clinical-pathologic cohort studies. Given the depth of ante- and post-mortem phenotyping, we made important advances in our understanding of the aging brains’ epigenome: amyloid and tau pathologies, the hallmarks of AD, have profound but distinct and reproducible effects on the epigenome. These associations occur throughout the genome. Although independent of the effects of genetic variants associated with AD susceptibility, the epigenomic changes integrate into a genetically-defined AD susceptibility network and may be involved in disease susceptibility. In this application, we propose to use a new experimental approach, ATACseq, which provides a comprehensive, genome-wide profile of active chromatin, to generate cell-type specific profiles, targeting cortical neurons implicated in both amyloid and tau pathology by our earlier studies as well as microglia/macrophages whose role in AD susceptibility was highlighted by genetic studies and our methylome analyses. Our proposal leverages an extensive experimental research infrastructure, benefits from an experienced analytic team applying cutting-edge methods, and contributes to the AD research community by delivering both a more comprehensive evaluation of epigenomes in the original collection of ~700 brains and new epigenomic and transcriptomic data in an additional 500 brains. Further, application of causal inference techniques will generate network models for each cell type and identify regulator genes that we will both validate and target with compound discovery in the translational component of the application. Thus, we propose to uncover fundamental mechanisms of the epigenome that contribute to AD and to begin to identify targets that can be manipulated in drug discovery efforts.

Lay Summary

PUBLIC HEALTH RELEVANCE Following our initial successes in exploring the structure of brain DNA in relation to Alzheimer’s Disease, we extend our studies by applying novel technologies that more precisely map which segments of DNA are involved in the accumulation of pathologies that lead to cognitive decline and dementia. Further, we apply cutting-edge analytic techniques to identify broad patterns in these disease-related changes in the brains of older individuals and translate our results by identifying and validating regulator genes for therapeutic development and also testing certain candidate compounds against tau pathology, which still has few compounds in clinical development.

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:
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