Genome Wide Analysis LXR Binding-Metabolic and Epigenetic Regulation in AD

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Country

USA

Title of project or programme

Genome Wide Analysis LXR Binding-Metabolic and Epigenetic Regulation in AD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,219,938.53

Start date of award

15/03/2016

Total duration of award in years

4

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)... Basic Behavioral and Social Science... Behavioral and Social Science... Brain Disorders... Dementia... Genetics... Human Genome... Neurodegenerative... Neurosciences... Nutrition

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common form of dementia with more than 5.5 million patients in the USA, a number that will quadruple by 2047. The disease can be characterized as an accelerated loss of cognitive functioning to such an extent that it interferes drastically with a person’s daily life and activities. AD is a complex trait in that underlying quantitative variation in susceptibility is controlled by multiple genes and environmental factors. Importantly, some of these environmental and metabolic stimuli, like hypercholesterolemia, obesity, hyperinsulinemia and insulin resistance, which follow certain dietary patterns and lifestyle, are associated with increased risk of dementia and AD at advanced age, only if confronted in midlife. In this respect the epigenetic reprogramming by dietary agents, which change histone modifications and are retained throughout the life, should be considered highly relevant to AD pathogenesis, supporting the idea of age dependent gene-environment interactions as critical for the development and progression of late onset AD (LOAD). The metabolic pathways of cholesterol and phospholipid transport in the periphery and CNS, as well as some rate limiting steps of insulin secretion, are controlled by oxysterol-sensing transcription factors nuclear liver X receptors (LXRs) – LXR1 and LXR2, through the expression level of their responsive genes. We hypothesize that in the context of AD the response to high fat diet (HFD) is mediated by epigenetic chromatin modification and LXR binding to DNA and is ultimately realized by tissue and organ-selective transcriptional activity. The goal of this proposal has two major aspects: Aim 1. Using second generation high throughput sequencing to assess changes in chromatin modifications induced by nutritional signals and their role in the development and progression of cognitive performance and AD pathology. Aim 2. To reveal genome-wide changes in LXR binding caused by HFD and thus to identify LXR targets whose transcriptional up- or down-regulation has a role in the development and progression of AD-like phenotype in model mice.

Lay Summary

PUBLIC HEALTH RELEVANCE: This study will address questions that are important for continuing research in a field highly relevant to human health – Alzheimer’s disease and changes in chromatin modifications induced by nutritional signals and their role in the development and progression of this disease. The result from this study will help us to understand the interplay between important genes and proteins involved in cholesterol transport in brain, and how the knowledge about disturbed function of those proteins can help in developing new therapeutic strategies for slowing AD progression.

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

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