Molecular Phenotyping in Alzheimers Disease

https://www.neurodegenerationresearch.eu/survey/molecular-phenotyping-in-alzheimers-disease/

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Country

USA

Title of project or programme

Molecular Phenotyping in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,607,836.70

Start date of award

15/08/2016

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... Neurodegenerative... Neurosciences... Precision Medicine

Research Abstract

ABSTRACT Genetic risk for AD now clearly highlights the potential for multiple molecular drivers and perhaps multiple pathogenic pathways, including forms of AD that derive from disease causing mutations in PSEN1 or PSEN2, increased risk from APOE ?4, and sporadic

disease that does not have identified genetic risk. Regardless of genetic risk, AD is a chronic illness whose ultimate clinical expression as dementia follows years if not decades of injury, response to injury, consumption of reserve, and compensation. Moreover, as highlighted at the 2013 AD Related Dementias summit, longitudinal population-based cohort studies have repeatedly observed that AD most commonly is co-morbid with vascular brain injury (VBI) and less commonly with Lewy body disease (LBD). Finally, these same longitudinal cohort studies have revealed individuals who had high levels of AD neuropathologic change but no significant clinical expression – a state of apparent resilience to AD. Here we propose to enable progress in precision medicine for AD by vastly improving the molecular characterization of disease and sharing this unique resource with the community of scientists. Indeed, much of our knowledge about injury/response to injury in AD is based on histopathologic assessments rooted in technology that is about 140 years old. Emerging technologies now permit a depth of molecular phenotyping that until recently was difficult even to imagine. We hypothesize that determining quantitative, high dimensional protein phenotypes from carefully clinically characterized individuals from longitudinal cohorts who have donated their brains for research will illuminate components of AD that currently are obscured by limited standard neuropathologic assessments. We will use this novel approach to test our hypothesis through three Specific Aims. In Aim 1, we will collect proteomics data on post-mortem brain samples from the University of Washington Alzheimer's Disease Research Center and the Adult Changes in Thought Study using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) strategy known as data independent acquisition (DIA). DIA enables the comprehensive and systematic sampling of protein digests. This data acquisition will create a permanent digital molecular archive of this unique and highly valuable sample collection. In Aim 2, we will analyze the molecular phenotype of three groups that will be critical to precision medicine for AD: (i) different genetic risk, (ii) common co-morbidities, and (iii) resilience to AD neuropathologic change. We anticipate identifying a molecular signature that is predictive of cognitive impairment as a replacement for traditional histopathological assessment. In Aim 3, we will make our data available through a novel cloud based solution, called the Chorus Project (http://chorusproject.org), engineered to enable big data reanalysis by the community of scientists. We will develop a novel query engine that will enable informatics experts without knowledge of the complexities of mass spectrometry signal processing to perform reanalysis of our data.

Lay Summary
PROJECT NARRATIVE Alzheimer's disease (AD) is a chronic illness whose ultimate clinical expression as dementia follows years if not decades of injury, response to injury, consumption of reserve, and compensation. Genetic risk for AD now clearly highlights the potential for multiple molecular drivers and perhaps multiple pathogenic pathways. By improving the molecular resolution of AD, this project will contribute to the goal of prevention of and better treatment for 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