Integrative Biology Approach to Complexity of Alzheimers Disease

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Country

USA

Title of project or programme

Integrative Biology Approach to Complexity of Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 11,657,365.14

Start date of award

20/09/2013

Total duration of award in years

3

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): Alzheimer’s disease (AD) affects half of the US

population over the age of 85 and causes destruction of select networks and cell groups within the brain. AD manifests initially as mild cognitive decline, but gets progressively worse and is always fatal. Despite significant progress identifying susceptibility loci for AD in genome-wide association and whole exome sequencing studies, to date, a predictive risk score for AD that achieves clinical utility on an individual basis given DNA variation information alone has been elusive. This proposal aims to develop a multiscale-network approach to elucidating the complexity of AD. Multiscale network models causally linked to AD will be developed based on existing AD-related large scale molecular data and the high-impact, high-resolution complementary datasets generated through this application. Using brain slice cultures, iPS-cell-derived mixed cultures of human neuronal, oligodendroglial, and astrocytic cell systems, and fly models of AD, we seek to reconstitute the AD-related networks discovered in the multiscale analysis in these living systems and then employ high-throughput molecular and cellular screening assays to not only validate the actions of individual genes on molecular and cellular AD-associated processes, but also validate the molecular networks we implicated in the disease. Our initial multiscale studies have implicated the microglial protein TYROBP as one key driver of AD pathogenesis, a “”hit”” we have partially validated, but that we will further validae along with other hits using iPSC-derived mixed cultures of different brain cell types, murine brain slices and AD fly models. We will analyze the potential ability for network-derived hits like TYROBP to modulate standard AD pathology involving A? and tau as well as its ability to shift networks in those same systems in such a way as to reflect the behavior of networks discovered in the multi-scale analysis. Importantly, the model building and validation will be iterated to produce updated/refined models based on validation results that, in turn, will be mined to generate updated lists of prioritized targets for validation. In this way, through the course of th grant, as new knowledge accumulates externally and as we generate increased amounts of data including validation data, our models will take into account the most up to date information to produce the most predictive models of AD. As a service to the AD research community, we will provide dramatically improved general access to large-scale, multidimensional datasets, together with systems level analyses of these datasets.

Lay Summary

PUBLIC HEALTH RELEVANCE: We will develop and apply a multiscale-network approach to elucidate the complexity of Alzheimer’s disease (AD) via the unbiased integration of large-scale molecular, cellular, and clinical data. Using murine brain slices, mixed human cell cultures of relevant brain cell types, and fly models of AD, we will reconstitute the AD-related networks discovered in the multi-scale analysis in these living systems and then employ high-throughput molecular and cellular screening assays to not only validate the actions of individual genes on molecular and cellular AD-associated processes, but also to validate the molecular networks predicted to drive 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