Prediction of Psychosis in Alzheimer Disease

https://neurodegenerationresearch.eu/survey/prediction-of-psychosis-in-alzheimer-disease/

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Country

USA

Title of project or programme

Prediction of Psychosis in Alzheimer Disease

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NIH (NIA)

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01/12/2005

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10

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)... Behavioral and Social Science... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Genetics... Human Genome... Mental Health... Mental Illness... Neurodegenerative... Neurosciences... Prevention... Schizophrenia... Serious Mental Illness

Research Abstract

DESCRIPTION (provided by applicant): Psychotic symptoms, defined as the occurrence of

delusions or hallucinations, are frequent in Alzheimer Disease (AD+Psychosis, AD+P), affecting ~ 40% to 60% of individuals with AD. Psychosis is a marker for a subtype of AD associated with more rapid cognitive and functional decline, poor outcomes including premature institutionalization, and elevated caregiver distress. Current treatments for AD+P have limited efficacy and cause excess mortality. It is thus imperative to develop a translational approach to promote discovery regarding the biology of AD+P and identify opportunities to intervene to prevent its adverse trajectory. To address this goal, we have exploited our initial observation of the familial aggregation of AD+P, now replicated in two independent cohorts. During the current funding period we have completed the first Genome-Wide Association Study (GWAS) of AD+P, finding strong preliminary evidence for association with novel loci and with psychosis risk loci shared with schizophrenia. We have similarly found evidence of association of AD+P with genetic variation in the putative schizophrenia risk gene, neuregulin1 (NRG1), which we demonstrated impacts expression of mRNA transcripts of novel NRG1 exons. In contrast we have found that AD+P is not associated with several established risk genes for neurodegeneration. Finally, we have clarified that the adverse cognitive trajectory of AD+P emerges within the earliest stages of AD, and have developed innovative analytic methods to chart personal trajectories of cognitive decline and test the impact of genetic variation on them. These findings have led us to hypothesize that AD+P results from a set of risk alleles that includes common psychosis risk alleles, but is independent of those conferring risk for AD; and that these risk alleles alter the molecular milieu within the brain resulting in a more rapidly deteriorating neurodegenerative trajectory. We will test our hypotheses, capitalizing on the initia success of our GWAS to further identify common genetic variants associated with AD+P in a staged analysis of nearly 10,000 subjects (Aim 1), utilize these variants to predict the adverse cognitive and behavioral trajectory of AD+P in two well characterized cohorts (Aim 2), and leverage a high quality cerebral cortex transcriptome dataset to identify the molecular changes associated with the AD+P risk alleles (Aim 3). Upon completion, the planned studies will have identified a set of common genetic variants which predict cognitive and behavioral outcomes in AD and will have established gene transcript levels altered by these variants. Such findings could provide for generation of an AD+P “”gene chip”” to predict the poor outcomes associated with AD+P and thus target individuals for more aggressive intervention. Similarly, findings will guide studies to delineate the brain mechanisms leading to the development of psychosis in AD.

Lay Summary
Individuals who develop psychotic symptoms such as delusions or hallucinations during Alzheimer disease have a more rapid deterioration and worse outcomes. We have found that the risk for developing psychosis during Alzheimer disease is influenced by genetic factors. In this grant we will conduct a large scale genetic analysis of individuals with Alzheimer disease (both with and without psychosis), in an effort to identify the specific genetic markers that lead to psychotic symptoms in Alzheimer disease. We will further test whether these genetic markers can be used to predict more rapid deterioration and examine whether they affect the amount of their respective genes that are expressed in brain tissue.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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