Alzheimers disease risk analyzed using population imaging genomics

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USA

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Alzheimers disease risk analyzed using population imaging genomics

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NIH (NIA)

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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)... Biotechnology... Brain Disorders... Dementia... Diagnostic Radiology... Epidemiology And Longitudinal Studies... Genetics... Human Genome... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): The recent discovery of new Alzheimer's disease (AD) risk genes has re-ignited efforts to understand how genes interact to impact brain vulnerability to AD. Deeper genetic analysis of AD risk using sophisticated imaging biomarkers will enable us to (1) predict risk for AD in younger adults to initiate prevention strategies in those at risk and (2) boost power in drug trials by selecting those at greatest risk of decline. Our goal is to assess genetic control over two measures that show deficits in AD patients: (1) functional ""connectivity"" (synchronicity) between the posterior cingulate cortex (PCC) and medial frontal cortex (MFC) at rest and (2) white matter integrity in the associated cingulum tract and splenium of the corpus callosum. Our project advances the study of AD genetic risk by investigating how multiple risk genes interact to disrupt brain connectivity. In this first-ever genomic analysis of structural and functional connectivity, we use both genome-wide association scanning (GWAS) and a candidate gene analyses of two large healthy cohorts: (1) 1150 young adult Queensland twins (QTwin; age: 20-29), and (2) 273 older healthy and cognitively impaired adults in the Alzheimer's Disease Neuroimaging Initiative cohort (ADNI; age: 55-90). Carriers of a common AD risk gene (CLU) have deficits in white matter integrity even as young adults and AD pathology may later exploit this vulnerability. We now expand our investigation of DTI genetics to assess structural connectivity. We also study how risk genes may impair functional synchronicity between PCC and MFC using resting state fMRI (rs-fMRI). We will: 3/4 Use a candidate gene approach to reveal how (1) known risk genes impair connectivity and fiber integrity in the splenium and cingulum in the young and elderly (QTwin and ADNI) and how (2) PCC-MFC synchronicity is influenced in both cohorts by top identified AD risk SNPs and SNPs that affect white matter integrity in the splenium and cingulum. 3/4 Use GWAS to identify new risk genes, whose carriers have impaired brain connectivity. We previously used GWAS to identify genes related to deficits in gray and white matter. We extend these findings to determine SNPs associated with (1) reduced FA and structural connectivity in the splenium and cingulum and (2) reduced synchronicity of PCC-MFC fMRI signal in the QTwin and ADNI samples. Promising hits will be proposed for verification and meta-analysis in Enigma (http://enigma.loni.ucla.edu) (N=10,000). 3/4 Use new multi-locus genetic models (ridge regression, PC regression, vGeneWAS) to evaluate how multiple common risk SNPs and multiple genes interact to impair brain connectivity. The product of these efforts will be (1) new assessments of genetic risk for brain dysconnectivity in healthy adults, (2) a means to boost clinical trial power, based on imaging and multi-SNP modeling of liability.

Lay Summary

The strength of brain connections is reduced in people with Alzheimer's disease (AD), a disease whose onset and progression are influenced by many known risk genes as well as lifestyle and environmental factors. We will use MRI measurements of this connectivity as an AD risk proxy to better characterize how known AD risk genes affect the brain, helping researchers to improve treatment focus. We will also use this proxy to identify new possible AD risk genes, allowing researchers to assess more homogeneous samples of people. Covarying for individual genetic risk will empower the evaluation of treatments and preventative measures, and identify subjects early in life who are vulnerable to impaired brain connectivity.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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