Early identification of Alzheimer’s disease: dynamic biomarkers for enrichment of trials

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Name of Fellow

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Institution
Funder

MRC

Contact information of fellow
Country

United Kingdom

Title of project/programme

Early identification of Alzheimer's disease: dynamic biomarkers for enrichment of trials

Source of funding information

MRC

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€ 343,722

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3.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Alzheimer Disease | Amyloid beta-Protein | Biomarkers | Dementia | Neuroimaging | Plasma | Prodromal Symptoms | Proteomics

Research Abstract

Aim: To use integrated biostatistics and bioinformatics to relate genetic, peripheral and cognitive biomarkers to central Alzhiemer’s disease (AD) pathology, in order to reduce barriers to clinical trials in the prodromal phase of the disease. Objectives 1. Characterise genetic and environmental influences on candidate protein markers. 2. Identify tasks from cognitive tests that reflect amyloid pathology. 3. Relate markers to central pathology using a systems biology approach applied to post-mortem brains. 4. Build a causal model of genetic factors, brain Abeta, cognitive test items and candidate protein markers. Methods Objective 1 Sample: 106 twin pairs (for main analysis) Analyses: An established quantitative-genetic model to test for genetic and environmental control of plasma protein levels and cognitive ability. Analysis of association of protein levels with other AD-related phenotypes, and with genetic data. Objective 2 Sample: 144 + 273 + 56 = 473 subjects combined (across cohorts) Analyses: Meta-analysis of association of cognitive task scores with brain amyloid beta levels. Multivariate regression and machine learning to find optimal combination of cognitive task scores. Objective 3 Sample: ~200 case and ~200 control brains (for main analysis) Analyses: Candidate markers will be assessed for differential expression in AD brains, taking into account genetic differences that affect their levels. Common genetic control of these traits will be further explored using ‘co-localisation’ analysis. Finally, genome-wide analyses on multiple genomic levels will be performed in an integrated fashion. Objective 4 Sample: 116 + 273 + 170 = 559 combined subjects (across cohorts) Analyses: The most promising markers from Objectives 1-3 will be studied further, with the causal relationship between genetics, brain amyloid levels and these markers investigated using Structural Equation Modelling.

Types:
Fellowships

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