Temporal Trends, Novel Imaging and Molecular Characterization of Preclinical and Clinical Alzheimers Disease in the Framingham Cohorts

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Temporal Trends, Novel Imaging and Molecular Characterization of Preclinical and Clinical Alzheimers Disease in the Framingham Cohorts

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NIH (NIA)

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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)... Biotechnology... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Diagnostic Radiology... Epidemiology And Longitudinal Studies... Genetics... Human Genome... Neurodegenerative... Neurosciences... Precision Medicine... Prevention

Research Abstract
The Framingham Heart Study (FHS) is a prospective, community-based 3-generational study that enrolled participants between ages 20-50 and has examined them every 2-4 years to collect extensive lifestyle, vascular, biomarker data; 9300 have GWAS. Embedded in this cohort are 1036 multigenerational families. Surveillance for AD dementia (and MCI) has been ongoing for over 4 decades. We have identified 1421 incident AD, 1767 MCI, enrolled 800+ in a brain donation program, obtained 7000+ 1.5T brain MRI, and repeated, detailed neuropsychological assessments. We have recently obtained extensive omics in ~6000 (gene expression, methylation, miRNA, metabolomics and proteomics) and genomics (50X whole genome sequences [WGS] in 4197 with pedigree-based imputation to 6554) through the NHLBI funded SABRe CVD (omics) and TOPMed (WGS) programs. We seek to leverage these rich resources (>$25 million). We propose these specific aims: AIM 1 is to examine and explain temporal trends in clinical AD dementia in the FHS cohorts. The age-specific incidence of dementia has declined over the past 4 decades among FHS participants (in press). However, the reasons for this decline remain unclear. We thus propose to continue tracking temporal trends in AD dementia and MCI through intensive surveillance, and verifying diagnoses at autopsy. We hypothesize that better education, treatment of some vascular factors and protective lifestyle changes (diet, activity, social engagement) may partially explain these trends. AIM 2 is to identify the patterns and predictors of preclinical AD within FHS families by obtaining (i) a novel circulating biomarker (plasma tau on 8000+ persons, using samples collected 5-15 years ago and repeat assay in 450) to supplement 1000+ biomarkers already available, and (ii) brain imaging with tau- and amyloid- PET, 3TMRI, including assessment of functional connectivity, tractography and blood flow, in 450 dementia- and stroke-free, FHS participants age 35-75 on whom we have (a) directly verified familial cognition and AD dementia status (both parents and all 4 grandparents were FHS participants), and also (b) have WGS and omics data. AIM 3 is to utilize the available WGS and extensive `omics' data for deep molecular phenotyping of AD. We will undertake conventional family-based WGS analyses of AD dementia and preclinical AD endophenotypes and novel high dimensional (co-expression, network, systems-based) analyses in collaboration with Drs. DeJager (PI of Accelerated Medicine Partnerships-AD, with omics data in 1200 brains), Witten (award-winning mathematician in applying graphical analysis to omics) and Levy (PI of SABRe-CVD at FHS). We will validate our findings in unrelated and multi-ethnic (Omni) FHS participants, through collaborations with other cohorts, and share all data through dbGaP and BioLINCC for analyses by others. We expect to identify new biologic pathways, drug targets and biomarkers for AD, especially those applicable to the preclinical stage of AD and those explaining promising trends in AD risk; such pathways should prove most useful for AD prevention.

Lay Summary
Whereas the total number of persons with Alzheimer disease (AD) is increasing as the population ages, we have 4 decades of Framingham data suggesting that the risk at any given age is declining. We plan to study the reasons for this hopeful trend in detail through continuing

our surveillance for dementia and cognitive impairment, collecting cutting edge brain imaging (amyloid and tau-PET, volumes, connectivity and perfusion on MRI) in the dementia-free (preclinical AD), and using sophisticated analysis of very extensive genetic and omic data already collected on Framingham subjects. This could help us better understand AD trends and biology and identify new biomarkers and treatment targets.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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2016

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