Preclinical AD: Correlates of Amyloid, Tau PET and fcMRI in Framingham Gen 3 Young Adults

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USA

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Preclinical AD: Correlates of Amyloid, Tau PET and fcMRI in Framingham Gen 3 Young Adults

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NIH (NIA)

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2

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... Diagnostic Radiology... Genetics... Human Genome... Neurodegenerative... Neurosciences... Prevention

Research Abstract

? DESCRIPTION (provided by applicant): The pathology of Alzheimer's disease (AD) starts >2-4 decades prior to onset of clinical dementia. Therefore it is critical to identify persons with preclinical AD, who may be most responsive to preventive interventions, and also risk factors and biomarkers for preclinical AD which may lead to new, effective AD prevention strategies. We propose to study, in a community-based cohort, heterogeneity of cognitive change at mean age 45, and (in a subset) 3 markers of preclinical AD: amyloid (PIB)-PET, resting state functional connectivity MRI, and tau (F18T807) PET at age 45-65. Such data are not currently available. Framingham Gen 3 participants are grandchildren of the Original cohort (followed since 1948) and children of the Offspring (Gen 2, followed since 1971). Omni 1 & 2 are multiethnic cohorts corresponding to Gen 2 & 3. All cohorts have genetic/epigenetic (GWAS, exome chip and sequencing, blood expression, methylome), lifestyle (diet, mood, hip accelerometry, etc.), vascular/metabolic risk factor and circulating biomarker (e.g., beta-amyloid, clusterin, inflammatory, lipids, adipokines, growth factors) data, verified clinical dementia statu, structural brain MRI (including diffusion tensor imaging [DTI]) and detailed cognitive assessments. Gen 3/Omni 2 (n=4200) participants have already been examined twice (2002-2005 and 2008-2011). These exams included 2 brief cognitive tests (of memory [CERAD word list], and of executive function [Victoria Stroop]) and a brain MRI. We have previously shown that hypertension and diabetes have a greater adverse impact in younger Gen 3 than in Gen 2 participants (2 & 6 years of brain aging in Gen 2, versus 7 & 23 years in Gen 3, respectively). We now propose the following Specific Aims: Aim 1: Obtain a brief subjective (AD8) and objective (Montreal Cognitive Assessment [MOCA], repeat Stroop and CERAD word list) cognitive assessment in all Gen 3/Omni 2 (N~3800) at exam 3 (2015-2018) and assess each person's change from 6-7 years earlier. We hypothesize that persons with a high vascular burden and/or high genetic burden of AD will experience the greatest decline in cognition. Aim 2: Obtain amyloid & tau PET and brain structural and fcMRI in 200 persons, aged 45-65 years, with prior MRI, and carefully selected to represent the entire spectrum of vascular risk. We will: assess (2-i) prevalence of amyloid, tau and fcMRI abnormalities at this age and their correlation with cognition, both directly and via an interaction with vascular brain injury; (2-ii) risk factorand circulating biomarker associations with these preclinical imaging markers of AD; also extend/validate the risk factor & biomarker associations with PET/ fcMRI (noted in Gen 3) in subjects >65 yrs with PET/ fcMRI via 4 international collaborations (N~2500). Aim 3: Examine genes, risk factors and biomarkers that we find are associated with PET/ fcMRI for additional association with: (3-i) structural MRI and cognitive measures already available in Gen 1, 2 & 3, e.g., hippocampal volumes, cortical thickness, logical memory (N=4,700); and (3-ii) with risk of developing clinical AD in Gen 1 & 2 participants (up to 1300 AD cases, 750 incident in >7500 persons).

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease pathology likely begins 20-40 years before clinical symptoms but so far this has not been systematically studied in persons below age 65 years. We propose to study cognitive change, amyloid and tau burden (using positron emission tomography [PET] scans) and brain shrinkage, vascular injury and functional connections (using brain magnetic resonance imaging [MRI]) in the young to middle-aged Framingham Gen 3 participants, and to use data on risk factors, genetics and biomarkers collected over the past 12 years on these persons to look for new ways to predict and prevent Alzheimer dementia.

Further information available at:

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