Plasma beta-amyloid in long lived families: genetics and risk of AD

https://neurodegenerationresearch.eu/survey/plasma-beta-amyloid-in-long-lived-families-genetics-and-risk-of-ad/

Principal Investigators

COSENTINO, STEPHANIE ANN

Institution

COLUMBIA UNIVERSITY HEALTH SCIENCES

Contact information of lead PI
Country

USA

Title of project or programme

Plasma beta-amyloid in long lived families: genetics and risk of AD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 4,359,322.02

Start date of award

15/09/2004

Total duration of award in years

11

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)... Brain Disorders... Dementia... Epidemiology And Longitudinal Studies... Genetics... Human Genome... Neurodegenerative... Prevention

Research Abstract

DESCRIPTION (provided by applicant): The Long Life Family Study (LLFS), established in 2005 in response to an NIA RFA, enrolled families enriched for exceptional longevity (EL), to discover factors that contribute to healthy aging and survival. From 2006 to 2009, LLFS enrolled 539 sibships (G1), their offspring (G2) and spouses (total 4,953). Comparison with a referent cohort reveals that LLFS families have strong exceptional clustering of EL. The G2 offspring have a variety of Healthy Aging Phenotypes (HAPs), defined as an unusually low age-specific prevalence of one or more specific conditions or risk factors, compared to population-based cohorts suggesting enrichment of shared (possibly genetic) protective effects in LLFS families. In the second funding period (2010-2013), we conducted a 2.5 million SNP GWAS (dbGaP phs000397); developed a high-throughput technique and sequenced ~450 candidate genes and replicated many variants and found additional ones associated with Healthy Aging Phenotypes (HAP) and longevity. 54% of LLFS G1 and 92% of G2 remain alive. Participant retention has been 94%. We now propose a third funding period to conduct a second in-person examination (V2) to prospectively study rates of change in HAPs with age and identify genetic and other factors contributing to HAPs and longevity. We hypothesize that EL and HAPs entail common and rare variants that individually have modest effects, but which in combinations strongly influence longevity and specific HAPs, and may only be detectable in family studies enriched for HAPs, such as LLFS. HAPs evaluated at the initial in-person visit show strong linkage peaks which are not explained by common haplotypes interrogated by GWAS (HLODs ranging from 6.0-45.1). These are likely driven by rare, lineage-private alleles that will only be found by sequencing specific families, and may point to important new biology. Specific Aim 1 is to conduct a second in-home examination on all surviving LLFS participants. Specific Aim 2 is to analyze cross-sectional and longitudinal phenotypes. The goal is to identify pathways for EL and HAPs by characterizing the shared and distinct LLFS phenotypes and environmental factors. We will characterize individual longitudinal patterns of HAPs to identify subgroups showing similar patterns and exceptional phenotypes. We will test whether these HAPs are heritable, and test for differences with internal and external referent groups. Specific Aim 3 is to find genes/variants associated with cross-sectional and longitudinal phenotypes using a) Whole Exome Sequencing to comprehensively search for coding variants associated with HAPs and EL and b) Targeted Regulatory Sequencing of regions under linkage peaks for HAPs in selected families showing the strongest linkage evidence. Specific Aim 4 is to replicate our genetic and epidemiological findings in other aging study cohorts. This study could lead to the discovery of pathways and potential therapeutic/prevention targets affecting HAPs and EL. A Data Management and Coordinating Center and 4 Field Centers comprise the major components of the LLFS. This renewal application is submitted by the Duke Uni./Uni. of Southern Denmark Field Center.

Lay Summary

PUBLIC HEALTH RELEVANCE: The Long Life Family Study (LLFS) proposes a second examination of families enriched for exceptional longevity (EL), to discover genetic and environmental factors that contribute to healthy aging. These studies could lead to the discovery of new pathways and potential therapeutic/prevention targets affecting healthy aging and longevity.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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