Genetic Modifiers of Alzheimer Disease in PSEN1 Mutation Carriers in Puerto Rico

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USA

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Genetic Modifiers of Alzheimer Disease in PSEN1 Mutation Carriers in Puerto Rico

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract

SUMMARY The primary goal of this project is to identify genetic modifiers of the PSEN1 mutation by studying a group of high risk PSEN1-G206A mutation carriers. If successful, we may be able to learn how these modifier variants may lower the risk of AD by delaying age at onset or slowing age-related memory decline. In 2001, we identified a founder mutation in PSEN1 (G206A) in family members from eight Caribbean Hispanic families with origins in Puerto Rico. The average age at onset with this mutation was unusually late (mean: 55.6 years) and was remarkably variable within as well as across families, ranging from 22-77 years. In this group of Puerto Rican families with multiple affected family members, this mutation is as prevalent as APOE ?4, but, unlike APOE ?4 carriers who have an increased risk of AD, most PSEN1 carriers will eventually develop Alzheimer disease (AD). To determine whether these PSEN1 mutation carrier families can be used to identify genetic modifiers, we performed a pilot whole exome sequencing (WES) study. Using 31 G206A carriers, we identified six candidate genes that may harbor variants that alter onset of AD in these families, and variants within these genes accounted for as much as 15-20 years differences in age at onset of AD [2]. We then observed that three out of six genes had SNPs that were associated with variable age at onset in individuals with late onset AD (LOAD), suggesting that these may be generalizable to LOAD, the most common form of AD. In the present study, we propose to perform state of the art whole genome sequencing (WGS) to identify genetic modifiers of age at onset or memory performance, while capitalizing on this unique high risk group with a founder mutation. To date, we have recruited and examined 75 extended EOAD families that have one or more individuals who carry the PSEN1-G206A mutation. Most of these individuals have in-depth phenotype data as well as GWAS data. In addition, we will have access to independent sets of unrelated Caribbean Hispanics as well as non-Hispanic Whites to examine how clinically relevant these variants are in the general populations. The short-term goal of this study is to identify genetic variants that modify the age at onset and/or memory performance in PSEN1-G206A carriers, but the long-term goal is to identify a potential therapeutic target(s) that might delay or prevent AD.

Lay Summary

NARRATIVE The goal of this proposal is to identify novel genetic modifiers that contribute to variable age at onset or memory performance using 75 PSEN1 (G206A) mutation carrier families. We will apply the state-of-the-art whole genome sequencing (WGS) guided by GWAS, and perform joint linkage and association analysis to identify coding, non-coding, and structural variants that are associated with age at onset or memory performance. Our preliminary exome sequencing study identified three genes that may modify of age at onset in PSEN1 carriers, and confirmed these in late onset Alzheimer disease (AD). This WGS study of genetic modifiers may identify variants that may delay or accelerate age at onset in both early and late onset AD, which may lead to potential therapeutic targets for AD.

Further information available at:

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Investments > €500k

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United States of America

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