Admixture mapping in late-onset Alzheimer’s disease

https://neurodegenerationresearch.eu/survey/admixture-mapping-in-late-onset-alzheimer%c2%92s-disease/

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1

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Research Abstract

PROJET SUMMARY Prevalence and incidence of late-onset Alzheimer’s disease (LOAD) are higher in admixed population such as Caribbean Hispanics (CH) and African-Americans (AA) than in non-Hispanic Whites. Admixture occurs when isolated populations begin interbreeding

for historical or social events, and their offspring are mixtures of the genetic materials of the founding populations, resulting in mosaic chromosomes. Admixture can be a valuable source of statistical power to map disease-associated genes when the disease has different frequency across populations, such as LOAD. Investigations in other conditions (cardiovascular diseases, glaucoma, asthma) demonstrated the importance of admixture mapping and a recent study on AA showed the significant contribution of African ancestry in LOAD. This has never been performed in Hispanics. In our previous investigation, we performed a large genome-wide association study in Caribbean Hispanics: a novel locus in the FBXL7 gene was found to be associated with LOAD, along with other known-loci previously identified in large GWAS of European ancestry. This new finding implicates additional mechanisms underlying the pathophysiology of LOAD, and demonstrates the valuable asset of admixed populations in advancing the understanding of the disease. Preliminary results indicate that in our Caribbean Hispanic sample, LOAD cases have higher African ancestry as compared to healthy controls, matching previous reports in African Americans. Given these premises, we hypothesize that genetic loci with excess ancestry with respect to LOAD contribute to the observed higher frequency of LOAD in Caribbean Hispanics. This is based on the assumption that causal variants leading to increased risk occur more frequently on chromosomal segments (“ancestral blocks”) inherited from the ancestral population that has higher disease risk. Capitalizing on the large sample of individuals with extensive phenotype and genetic data, a two-layers approach of fine mapping will be carried out: first, we will conduct admixture mapping in GWAS data in order to identify genetic loci with risk profiles for LOAD that differ by ancestry (Aim 1). Secondly, we will conduct analyses in WES data (Aim 2) focusing on those loci prioritize by analyses conducted in the previous aim. Ultimately, we will seek to functionally characterize the newly discovered genetic loci by investigating their role in app processing, tau proteostasis and synaptic function (Aim 3).

Further information available at:

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