DOI: 10.1002/alz.093055

BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

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GENETICS

Comprehensive Analysis of Genetic Contributions to Alzheimer's Disease and Frontotemporal Dementia in Admixed Latin American Populations

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Abstract

Background: Most research initiatives have emerged from high-income countries (HIC), leaving a gap in understanding the disease's genetic basis in diverse populations like those in Latin American countries (LAC). ReDLat tackles this gap, focusing on LAC's unique genetics and socioeconomic factors to identify specific Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD) risk factors in Mexico, Colombia, Peru, Chile, Argentina, and Brazil.

Method: We employed a comprehensive genetic analysis approach, integrating Whole Genome Sequencing (WGS), Exome Sequencing, and SNP arrays to understand the cohort's unique genetic architecture. We conducted ancestry analysis and searched for disease-causing variants with mendelian inheritance, genome-wide association studies (GWAS), rare variant enrichment, and evaluation of Polygenic Risk Scores (PRS).

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Results: We recruited and genotyped an initial cohort of 1046 participants with AD, 423 with FTD, and 855 healthy controls (HC) between 2020 and 2023. Analysis is ongoing, and we expect to sequence ~600 additional samples in the coming months. Ancestry analysis revealed tri-continental admixture, except for Brazil, which showed an additional Asian component (Figure 1). Top candidate gene rare variant enrichment associations (SKAT $p < 0.05$) were *TREM2* for FTD and *ABCA7* and *ABCA1* for AD. GWAS identified a robust association with the *APOE* locus on chromosome 19 in AD vs. HC.. We tested an AD PRS developed in European populations by Bellenguez et al (2020). on our cohort using 83 single-nucleotide polymorphisms.. The PRS modestly distinguishes between all patients and HC ($p = 2.4 \times 10^{-12}$), AD vs. HC ($p = 2.2 \times 10^{-12}$), and even FTD vs. HC ($p = 4.3 \times 10^{-5}$), albeit with modest separation between groups, as expected for its application in a genetically admixed population.

Conclusion: Our findings represent a pivotal step in understanding the genetic landscape of AD and FTD in admixed populations. They underscore the importance of including diverse populations in genetic research, paving the way for future studies. These findings have the potential to inform more personalized approaches to the diagnosis and treatment of neurodegenerative diseases in diverse global populations, as well as identify novel targets for therapeutic development.