Genetic Colocalization of Expression Quantitative Trait Loci (eQTL) Mapping and GWAS in MU-BRAINS: An Insight into ancestry-specific Regulatory Architecture in AD

Abstract ID #107199

Vivek Ruhela, PhD[1], Basilio Cieza, PhD[1], Richard Mayeux, MD[2], Dolly Reyes-Dumeyer[3], Andrew F. Teich, MD, PhD[1] and Giuseppe Tosto, M.D., Ph.D.[4],

1. Columbia University, New York, NY, USA, 2. Departments of Neurology, Psychiatry, and Epidemiology, Gertrude H. Sergievsky Center, The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA, 3. Gertrude H. Sergievsky Center, Vagelos College of Physicians & Surgeons, Columbia University, New York, NY, USA, 4. Department of Neurology, College of Physicians and Surgeons, Columbia University, and the New York Presbyterian Hospital, New York, NY, USA

ABSTRACT

We performed ancestry-stratified cis- and trans-eQTL analyses and colocalization of gene expression and GWAS signals in prefrontal cortex samples from Hispanic and Non-Hispanic White individuals, identifying ancestry-specific regulatory variants linked to Alzheimer's disease.

BACKGROUND

Expression quantitative trait loci (eQTL) have been identified using tissue or cell samples from diverse human populations.

These discoveries have enhanced our understanding of gene expression regulation in the context of complex diseases, including Alzheimer's disease (AD).

However, few studies have examined eQTL across multiple ethnic groups, limiting insights into ancestry-specific regulatory mechanisms.

To address this gap, we analyzed prefrontal cortical brain samples from the New York Brain Bank at Columbia University.

METHODS

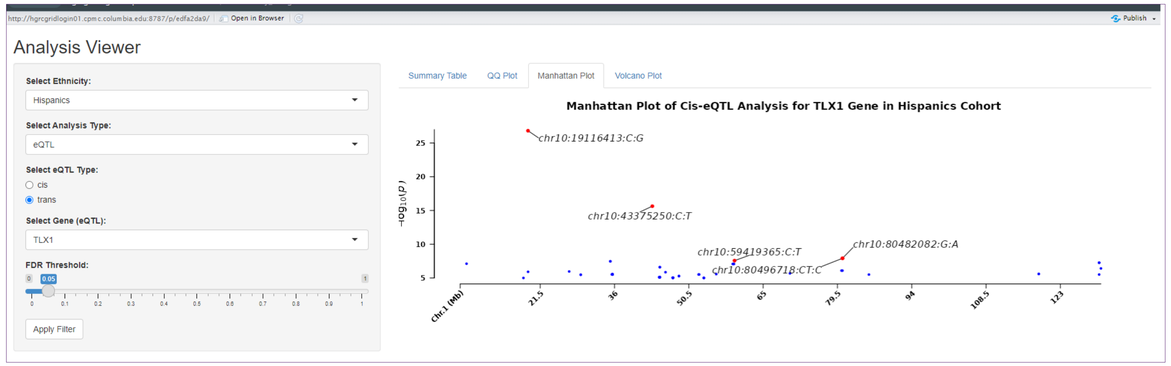
We analyzed RNA-Seq data from prefrontal cortical brain samples of 32 Hispanic and 263 Non-Hispanic White (NHW) individuals.

Stratified cis- and trans-eQTL analyses were conducted using TensorQTL to identify regulatory variants within and across chromosomes.

GWAS analysis of common variants (MAF > 5%) was performed using a linear mixed model to account for population structure and relatedness.

To evaluate genetic colocalization in Hispanic and NHW brains, we applied eCAVIAR, estimating the probability that the same variants are causal for both eQTL and GWAS signals.

RESULTS



In the colocalization of cis-eQTL and GWAS signals for Hispanics, we observed a high colocalization posterior probability (CLPP = 0.99) for rs4503558 on chromosome 11, which locally regulates *RAD9A and TBC1D10C* gene (GWAS p-value = 0.01, cis-eQTL p-value = 2.5E-07). Similarly, in NHW brains, we identified strong colocalization for rs11883596 on chromosome 2 (GWAS p-value = 0.001, cis-eQTL p-value = 0.0099) colocalized with SLC35F6 (CLPP=0.99) and rs199972720 on chromosome 12 (GWAS p-value = 0.04, cis-eQTL p-value = 0.0086) colocalized with TMEM116 (CLPP=0.84) expression in NHW brains.

CONCLUSIONS

This study highlights the importance of population-stratified eQTL and colocalization analyses in uncovering genetic regulatory mechanisms underlying complex diseases such as Alzheimer's disease (AD). We identified strong colocalization for *rs4503558* regulating *RAD9A* and *TBC1D10C* expression in Hispanics (CLPP ~0.99), as well as rs11883596 on chromosome 2 colocalized with *SLC35F6* (CLPP=0.99) and *rs199972720* on chromosome 12 colocalized with *TMEM116* (CLPP=0.84) expression in Non-Hispanic White brains. The implicated genes are functionally relevant to AD biology and may reflect ancestry-specific contributions to disease risk. These insights contribute to a deeper understanding of the genetic architecture of AD, with potential implications for precision medicine approaches across diverse populations. Results can be explored using BRAINscape, an interactive Shiny-based platform for integrative multi-omics data visualization.

Acknowledgement

This research was supported by NIH/NIA grants U01AG081817; R01AG082009; R01AG062517;R01AG67501; P30AG072972; P30AG062429; P30 AG062677; P01 AG003949; P30 AG062429 & AG066530;. Florida Department of Health, Ed and Ethel Moore Alzheimer's Disease Research Program (20A22, 8AZ06).