



# Genetic Architecture of Cortical and Hippocampal Atrophy in a dementia case-control study of Admixed Latin American Population

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## Introduction

- Neurodegenerative dementia, are characterized by progressive cortical and hippocampal atrophy.
- Genome-wide association studies (GWAS) have identified multiple loci influencing brain structure and dementia risk, but these findings have been derived predominantly from European ancestry populations.
- The genetic architecture of neurodegeneration in admixed Latin American populations remains poorly characterized.
- Investigating ancestry-specific and regulatory genetic variation in underrepresented populations is essential to better understand the biological mechanisms underlying brain structural changes in dementia.

## Methods

336 participants from the ReDLat multi-site case-control study

Derivation of volumes of 40 cortical and hippocampal subregions. (T1- and T2-weighted structural MRI at 1.5T or 3T)

Genetic data: whole-genome sequencing or the Neurobooster genotyping array (Illumina).

Ancestry Inference based on 1kGP reference ancestry groups

GWAS on volumes of 40 cortical and hippocampal subregions. Covariates: Sex, age, sampling protocol, site (country) diagnosis, first 5 genetic PC's

Obtention of gene expression of identified genes from the Human Protein Atlas (HPA).

## Results

- Population structure:** 64% women, with 141 AD and 105 FTD cases, and 90 cognitively healthy controls. Ancestry predominantly Admixed American.
- Sixteen non previously reported significant variants were identified:** thirteen genome-wide ( $p < 5 \cdot 10^{-8}$ , *Figure 1*) mapping to PTPRD, CAMK2D, SERPINI2 and EPG5, and three suggestive signals ( $p < 1 \cdot 10^{-7}$ ) annotated to CELSR1, NR2F2-AS1 and PANK4.
- High expression of genes PTPRD and CAMK2D across multiple brain regions (Figure 2)**, which have been previously linked to neurodegeneration, including synaptic signaling and neuronal plasticity. Additionally, thirty non-coding regulatory variants were identified, supporting a predominantly regulatory genetic architecture.

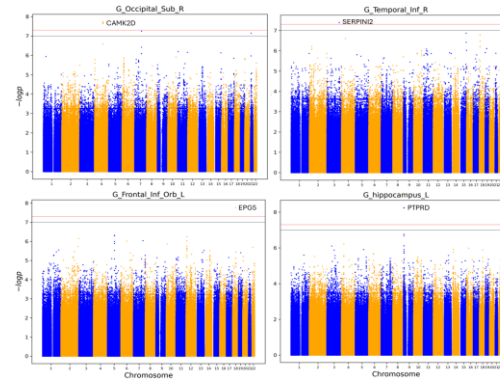


Figure 1: Manhattan plots of GWAS results for selected cortical and hippocampal brain regions. Panels show association signals for G\_Occipital\_Sub\_R, G\_Temporal\_Inf\_R, G\_Frontal\_Inf\_Orb\_L and G\_Hippocampus\_L. Horizontal red line indicates the Bonferroni-corrected genome-wide significance threshold ( $p < 5 \cdot 10^{-8}$ ). Top associated genes are highlighted for each region (CAMK2D, SERPINI2, EPG5 and PTPRD, respectively). Horizontal black line indicates suggestive significance threshold ( $p < 1 \cdot 10^{-7}$ ).

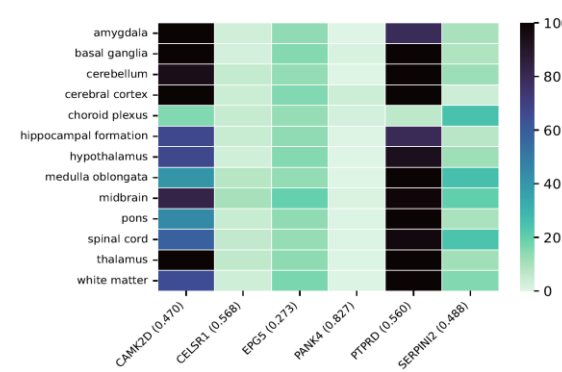


Figure 2: Heatmap of gene expression across brain regions. Rows represent major brain regions and columns show genes identified in the association analyses (CAMK2D, CELSR1, EPG5, PANK4, PTPRD and SERPINI2). Color intensity indicates normalized transcripts per million (nTPM) expression levels. Values in parentheses next to each gene correspond to tissue-specific differential expression scores ranging from 0 to 1, with higher values indicating greater relative expression specificity in brain tissues.

## Conclusion

We identified genetic associations influencing hippocampal and cortical brain volumes in an admixed Latin American population. These findings highlight neurobiological pathways implicated in AD and other dementia and support the relevance of regulatory and neuronal processes in brain atrophy. Our results provided a strong rationale for extending this study to a larger Latin American sample.

## References

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