

## INTRODUCTION

APOE is the strongest risk factor for Alzheimer's Disease. Most APOE studies are focused on APOE2,3,4 alleles. Yet, there is no therapeutic intervention to reduce the risk of APOE4 carriers. The goal of this project is to identify additional biological effects involving mechanisms beyond APOE4 function by leveraging human postmortem brain multi-omics data from European and African ancestry individuals.

## RESULTS

Figure 1. Overview of APOE study in human postmortem brain (A) and novel AD risk factors (genetic, transcriptomic, and epigenetic elements) and their relative position at the APOE locus (B).

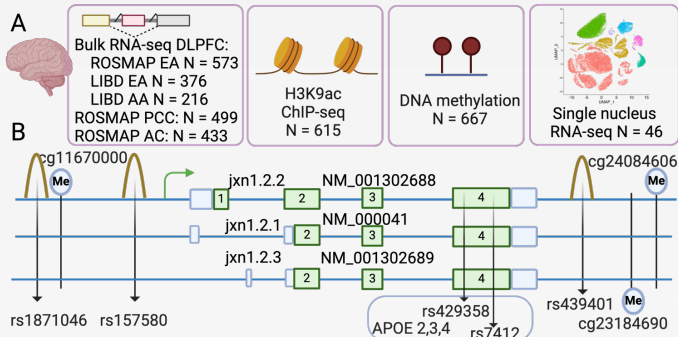


Figure 1. Overview of APOE study in human postmortem brain (A) and novel AD risk factors (genetic, transcriptomic, and epigenetic elements) and their relative position at the APOE locus (B).

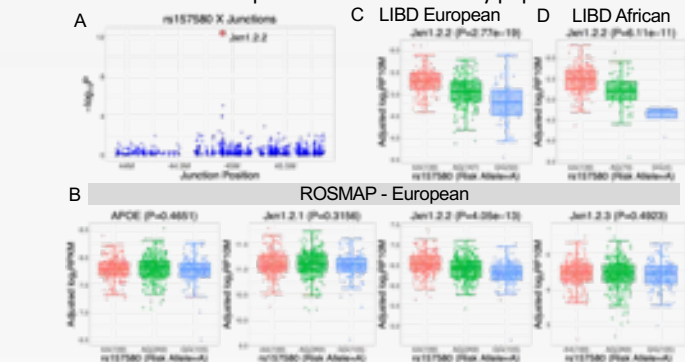
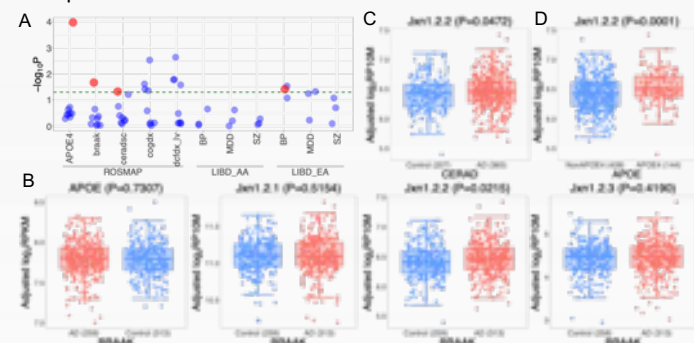


Figure 2. Gene expression of APOE jxn 1.2.2 transcript is uniquely associated with AD risk alleles in European and African ancestry populations. (A) rs157580 X Junctions. (B) ROSMAP - European. (C) LIBD European. (D) LIBD African. (E) APOE (P=0.4881), Jxn1.2.1 (P=0.3118), Jxn1.2.2 (P=0.05e-13), Jxn1.2.3 (P=0.4802).



## SUMMARY

Based on the GWAS-identified AD risk alleles, we identified a novel regulatory mechanism independent of the well-studied APOE4 allele: 1) AD risk alleles are associated with APOE jxn1.2.2 mRNA. And the associations are shared by European and African populations. 2) Two SNPs are functional indicated by epigenetic data. 3) APOE plays a role in microglia and neurons in AD.

Figure 4. Genotypic impact of candidate SNPs on DNA methylation levels in ROSMAP DLPFC. (A) Association of the candidate AD risk SNPs with CpG sites. (B) The association of the AD-linked CpGs is not affected by the APOE 2&4 allele by conditional analysis.

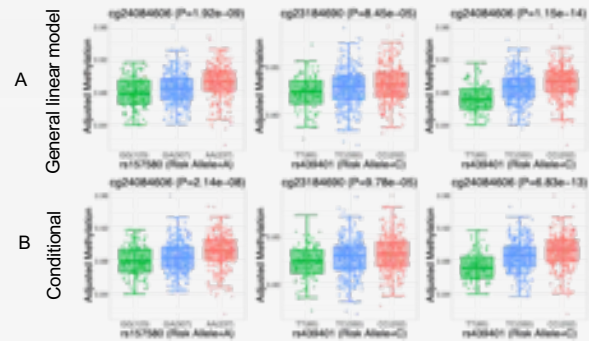


Figure 5. Candidate SNP at the APOE locus located within active chromatin affects transcriptional factors (TFs) binding affinity.

(A) Left panel: rs157580 are co-localized with H3K9ac ChIP-seq peak from human postmortem brains. Right panel: Recognition sites of TFs involved in Alzheimer's disease are influenced. The red dash box indicates the binding site. (B) rs157580 is relatively independent of other SNPs spanning APOE, including the two APOE2,3,4-determining SNPs.

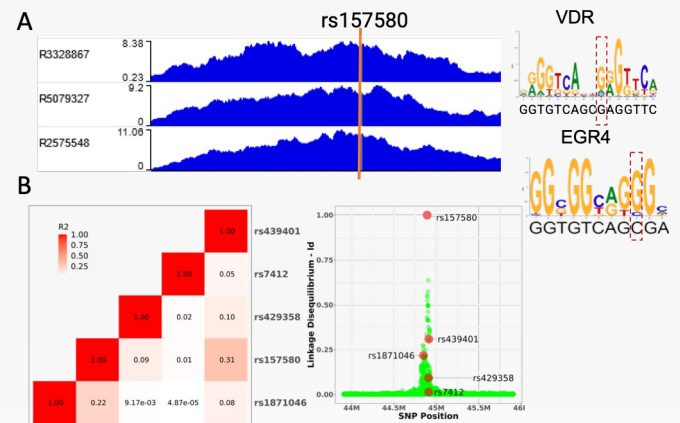
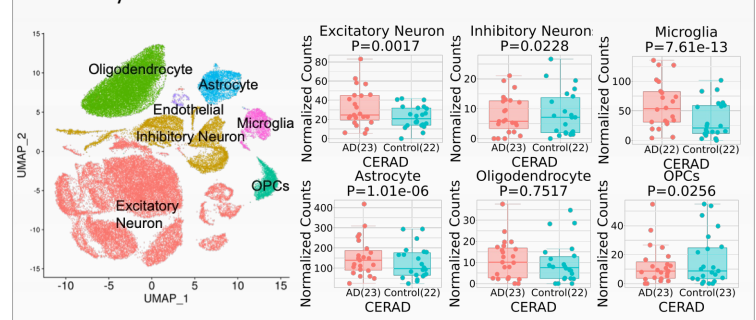


Figure 6. APOE upregulation in microglia is associated with AD pathology (i.e., amyloid plaques, neurofibrillary tangles) and cognitive impairment in DLPFC determined by single nuclei sequencing (63,781 cells). We also observed that APOE gene expression is associated with APOE4 allele in excitatory neurons.



Liang Ma, [mal1@uthscsa.edu](mailto:mal1@uthscsa.edu); Lab website: <https://labs.uthscsa.edu/ma/>

Chen Q, Aguirre L, Liang G, Zhao H, Dong T, Borrego F, Rojas Id, Hu Q, Reyes C, Su L-Y, Zhang B, Lechleiter J, Goring H, Jager PD, Kleinman J, Hyde T, Li PP, Ruiz A, Weinberger D, Seshadri S, Ma L\* (2024) Identification of a specific APOE transcript and functional elements associated with Alzheimer's disease. Mol Neurodegeneration. PMID: 39210471