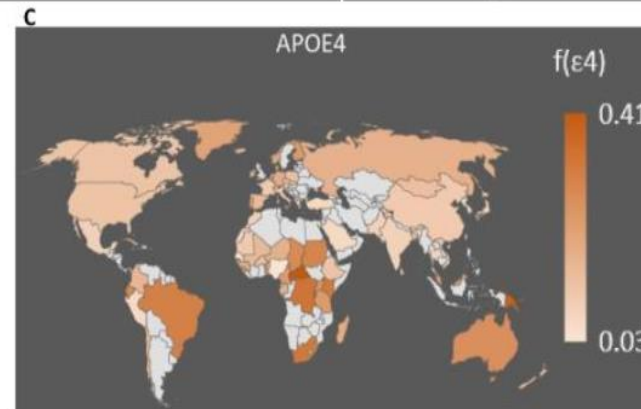
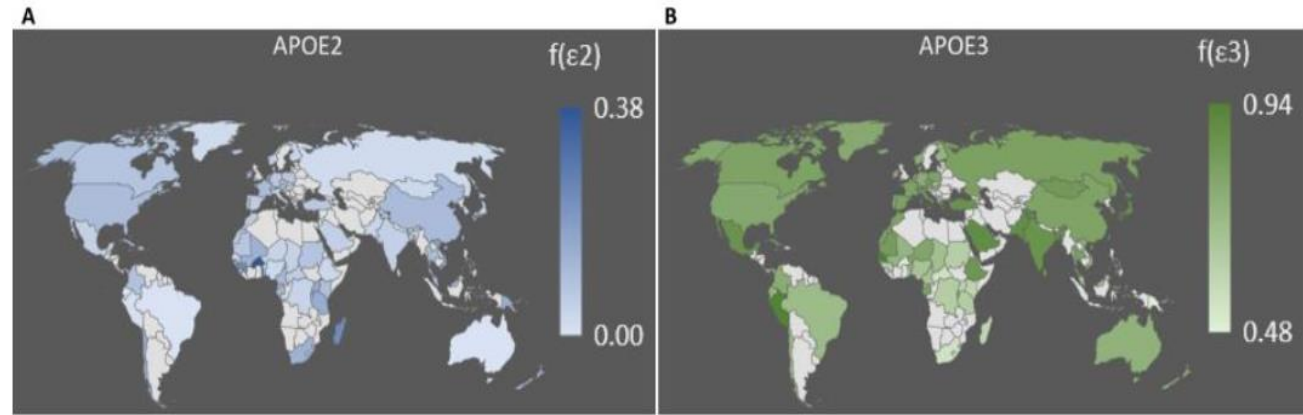


ApoE Allele Frequency Varies Across Populations



Abondio et al., CC by 4.0²

Population ¹	ApoE4 frequency: Overall population	ApoE4 frequency: AD population
Asian	9%	28%
Hispanic	12%	24%
White	14%	38%
African descent	19%	35%
Other/admixed	23%	45%

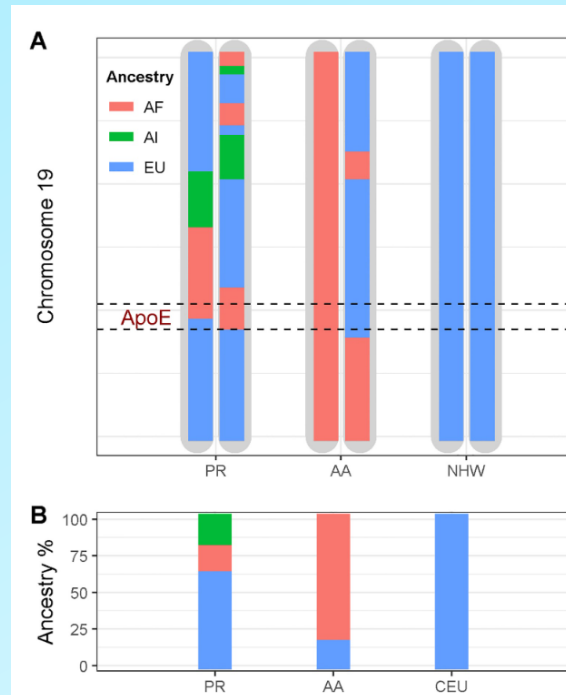
The Ancestry-Specific Region Around the ApoE Gene Determines ApoE4 Allele LOAD Risk—Lower in African, Higher in European Ancestry

Global ancestry:¹

- An individual's average ancestry across their genome
- Associated with ethnic, cultural, and environmental factors that may interact with the ApoE gene

Local ancestry:

- Ancestral background of a pertinent chromosomal region in a genome
- Ancestry-specific genetic factors located near a specific part of the genome

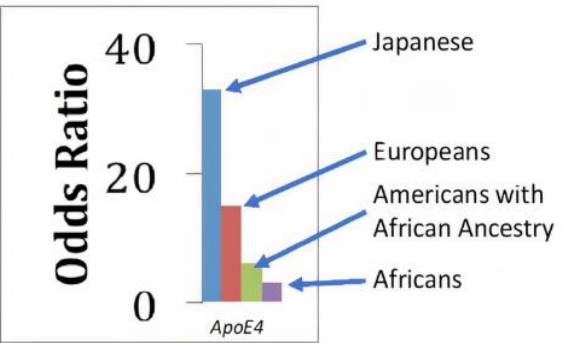


This figure represents chromosome 19 from Puerto Rican, African American, and European ancestry individuals. (A) The colored chromosomal segments represent the admixture blocks “local” to each genomic region, with each ancestry coded by a different color (red: African (AF), blue: European (EU), green: American Indian (AI)). (B) The global ancestry estimated by the average ancestry across the whole genome.²

Cohort ²	Genetic ancestry	Number of haplotypes (gene blocks)	AD risk, odds ratio (ApoE4 compared to ApoE3)
Puerto Rican	European	307	4.49
	African	67	1.26
African American	European	1341	3.05
	African	5387	2.34

Most populations are admixed with genetic contributions from multiple ancestries. The ancestry of the chromosomal region around the ApoE gene impacts risk.²

The ApoE4 Variant Confers a Different Degree of Risk Across Ethnic/Racial Populations, but the Disease Mechanisms and Pathways Overlap Across Ethnicities

ApoE4 allele effect	The ApoE4 allele represents a major risk factor for AD in all ethnic groups studied, across all ages between 40 and 90 years, and in both men and women ¹
Native immune response, intracellular trafficking, lipid metabolism, nervous system development, and synaptic plasticity	Molecular mechanisms and pathways implicated in LOAD largely overlap across ethnicities. However, the disease-associated loci within these pathways may differ ²
Effect of ApoE4 allele on AD risk in racial/ethnic groups ApoE4 odds ratio relative to ApoE3E3 carriers ³ 	<ul style="list-style-type: none">• People with African ancestry may inherit gene regions around the ApoE allele that reduce ApoE4 expression and decrease their risk of AD by approximately 75%³• R145C variant found only in people of African descent can be found on the ApoE3 allele and triples LOAD risk only in combination with an ApoE4 allele⁴• ApoE4 effect is higher in Japanese populations than those with European ancestry³

LOAD, late-onset Alzheimer's disease.

1. Farrer LA et al. *JAMA*. 1997;278:1349-1356; 2. Kunkle BW et al. *JAMA Neurol*. 2021;78:102-113; 3. Rajabli F et al. *PLoS Genet*. 2022;18:e1009977 (CC by 4.0); 4. Le Guen Y. et al. *JAMA*. 2023;329:551.