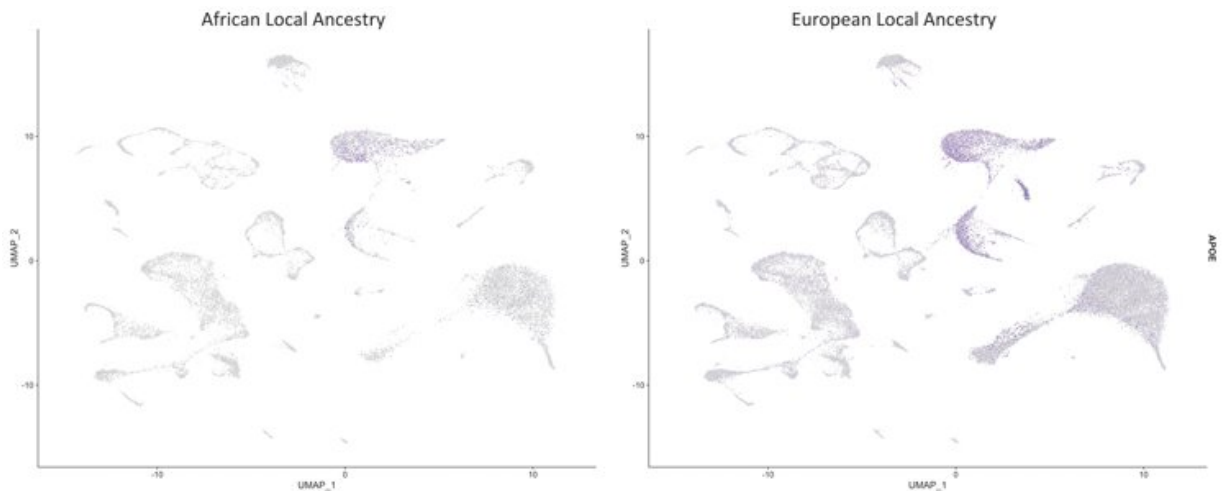


# Genetics study finds ancestral background can affect Alzheimer's disease risk

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The difference in APOE expression between African and European local ancestry carriers. University of Miami Leonard M. Miller School of Medicine

Genetics contributes to the risk of developing Alzheimer's disease, and the APOE gene is the strongest genetic risk factor, specifically the APOE4 allele. However, it has been known for a while that the risk due to the APOE4 allele differs considerably across populations, with Europeans having a greater risk from the APOE4 allele than Africans and African Americans.

"If you inherited your APOE4 allele from your African ancestor, you have a lower risk for Alzheimer disease than if you inherited your

APOE4 allele from your European ancestor," said Jeffery M. Vance, M.D., Ph.D., professor and founding chair of the Dr. John T. Macdonald Foundation Department of Human Genetics, professor of neurology, and director of the Center for Genomic Medicine at the John P. Hussman Institute for Human Genomics (HIHG).

Dr. Vance and his colleagues—co-senior author Juan Young, Ph.D., an associate professor in the Department of Human Genetics and HIHG, and lead authors Anthony J. Griswold, Ph.D., research assistant professor of human genetics and associate director of the Center for Genome Technology, and Katrina Celis, M.D., postdoctoral fellow—have led a new Miller School genetics study following up on this observation. They have found that among individuals with the same high-risk APOE4 allele, those with European local ancestry in the APOE region have a significantly higher expression of APOE in specific cell types in their brains than those with African ancestry, suggesting this contributes to the difference in risk.

The article, "Increased APOE4 Expression is Associated with the Difference in Alzheimer Disease Risk from Diverse Ancestral Backgrounds," was published February 1 in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*.

The Miller School study involved RNA sequencing of more than 60,000 individual cell nuclei taken from the brain tissues of Alzheimer's patients carrying the APOE4 with African or European local ancestry.

"The brain is an organ made up of many different cell types. To properly understand the effects of changes in gene expression you should look at each cell independently, rather than as a mixture," Dr. Griswold said. "In this study we used single cell processing and sequencing to look at brains of African and European APOE4 carriers at a higher resolution than had been done previously."

Dr. Griswold noted that the APOE gene was expressed significantly higher in the brains of the people with European ancestry. In addition, European ancestry individuals had high numbers of a cell type resembling reactive astrocytes, brain [cells](#) that are formed under stress and are toxic to neurons. "This suggests a possible linkage of APOE4 with inflammation response, which is another risk factor for AD," he said, adding that those astrocytes were not observed in any of the African ancestry individuals.

"The data from our study suggests that finding a way to block the increased expression of the APOE4 allele could have potential therapeutic benefits," said Dr. Vance. "It also supports the importance of knowing the ancestral origin of the APOE4 allele when predicting the risk of AD for any individual carrying the APOE4 [allele](#)."

**More information:** Anthony J. Griswold et al. Increased APOE  $\epsilon$ 4 expression is associated with the difference in Alzheimer's disease risk from diverse ancestral backgrounds, *Alzheimer's & Dementia* (2021). [DOI: 10.1002/alz.12287](https://doi.org/10.1002/alz.12287)

Provided by University of Miami Leonard M. Miller School of Medicine

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