

APOE ε4 Status and Clinical Debut in Latino Patients with Alzheimer's Disease: Associations with Age at Onset and Initial Cognitive Domain

Authors and Affiliations

Carolina Ospina, MD¹; Daniel Vasquez, MD¹; Victoria Zubiri, MD¹; Alejandro Guerrero, MD¹; Claudia Ramos, MD¹; Natalia Londoño Sotomayor, MA¹; Yamile Bocanegra, PhD¹; Laura Osorio, MA¹; Sarita Firstman, MA¹; Claudia Muñoz, MA¹; Laura Serna, BSc¹; David Aguillon, PhD¹.

1. Grupo de Neurociencias de Antioquia, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia.



Background //

Alzheimer's disease (AD) presents substantial clinical heterogeneity. The APOE ε4 allele is the strongest genetic risk factor identified to date, yet most studies have focused on non-Latino populations. Evidence remains limited regarding its association with age of onset (AOO) and the initial cognitive domain in Latino cohorts.

Objective //

To examine whether APOE ε4 status is associated with age at onset and the clinical profile at debut in Latino patients with AD.

Methods //

We conducted a cross-sectional study based on clinical records of patients with clinically diagnosed AD evaluated at the Grupo de Neurociencias de Antioquia (GNA). Participants with sufficient sociodemographic/clinical data and DNA for APOE genotyping were included. APOE alleles (ε2, ε3, ε4) were classified as APOE4 carriers (APOE4+) or non-carriers (APOE4-). Group comparisons used chi-square or Wilcoxon tests. Logistic regression assessed first symptom (memory vs. other) and generalized linear models (gamma family) estimated age at onset.

Results //

A total of 254 AD patients were included (72.4% female; median education 8 years). APOE4+ status was significantly associated with AOO ($p = 0.001$) and first symptom domain ($p = 0.007$), but not with sex, education, or diagnostic certainty. Mean AOO was 72.4 years (95%CI: 71.3-73.6). APOE4+ had a 4% earlier onset (95%CI: 1.0-7.0%), independent of sex and education. Each additional 10 years of education reduced AOO by 6.2% (95%CI: 3.2- 9.4%). Women had over threefold higher odds (OR_{adj} = 3.3, 95%CI: 1.48-7.28) and APOE4+ had more than double odds (OR_{adj} = 2.53, 95%CI: 1.14-5.98) of debuting with memory complaints, respectively.

References //

- Acosta-Urbe J, Piña Escudero SD, Cochran JN, Taylor JW, Castruita PA, Jonson C, et al. Genetic Contributions to Alzheimer's Disease and Frontotemporal Dementia in Admixed Latin American Populations. 2024.
- . Whitwell JL, Tosakulwong N, Weigand SD, Graff-Radford J, Ertekin-Taner N, Machulda MM, et al. Relationship of APOE, age at onset, amyloid and clinical phenotype in Alzheimer disease. *Neurobiol Aging*. 2021 Dec;108:90–8.
- Ryan, N. S., Nicholas, J. M., Weston, P. S. J., Liang, Y., Lashley, T., Guerreiro, R., Adamson, G., Kenny, J., Beck, J., Chavez-Gutierrez, L., de Strooper, B., Revesz, T., Holton, J., Mead, S., Rossor, M. N., & Fox, N. C. (2016). Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. *The Lancet. Neurology*, 15(13), 1326–1335.
- Llibre-Guerra, J. J., Li, J., Qian, Y., Llibre-Rodriguez, J. J., Jiménez-Velázquez, I. Z., Acosta, D., Salas, A., Llibre-Guerra, J. C., Valvuerdi, A., Harrati, A., Weiss, J., Liu, M. M., & Dow, W. H. (2023). Apolipoprotein E (APOE) genotype, dementia, and memory performance among Caribbean Hispanic versus US populations. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 19(2), 602–610.

Contact //

Name: David Aguillon
Email: david.aguillon@gna.org.co



GNA research
capabilites summary



Results //

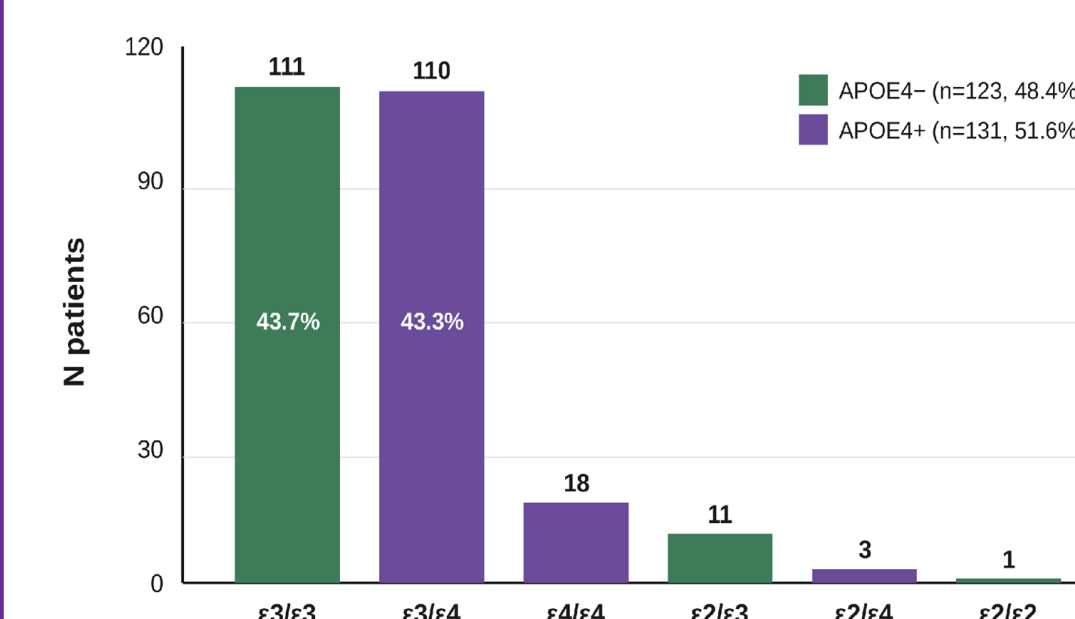


FIGURE 1. Distribution of APOE genotypes
Number and percentage of patients by APOE genotype (N=254), colored by APOE4 carrier status (APOE4-, n=123; APOE4+, n=131).

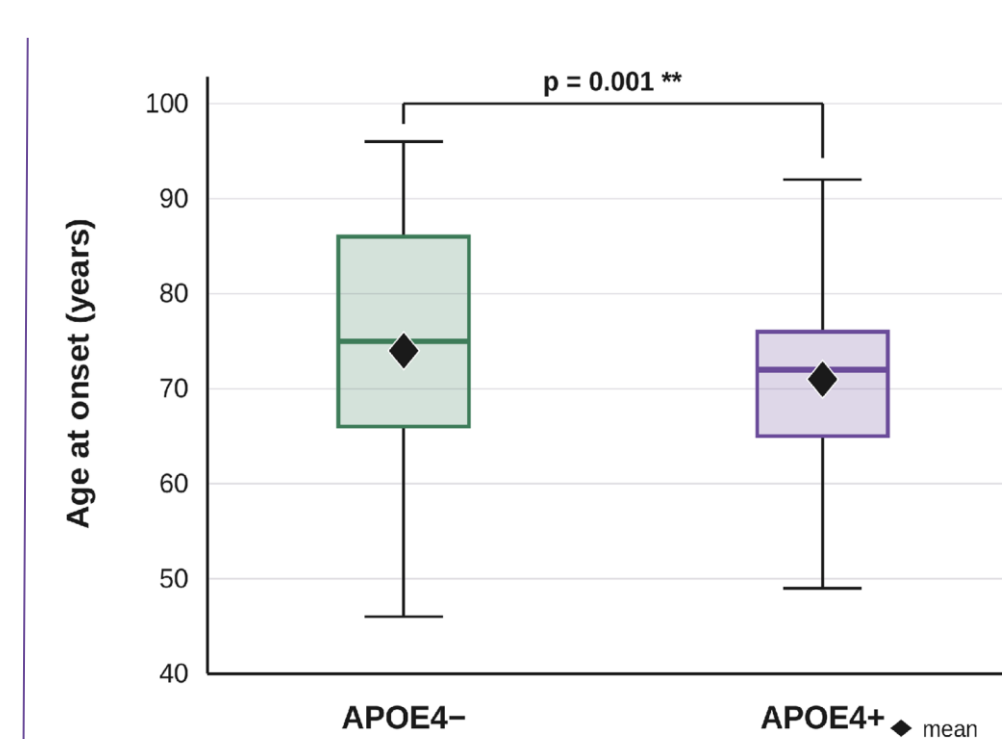


FIGURE 2. Age at onset by APOE4 status
Box plots of age at onset (years) in APOE4- (n=123) and APOE4+ (n=131) patients. Boxes show the interquartile range; horizontal line, median; diamond, mean; whiskers, minimum–maximum. Group difference assessed by Wilcoxon test ($p=0.001$).

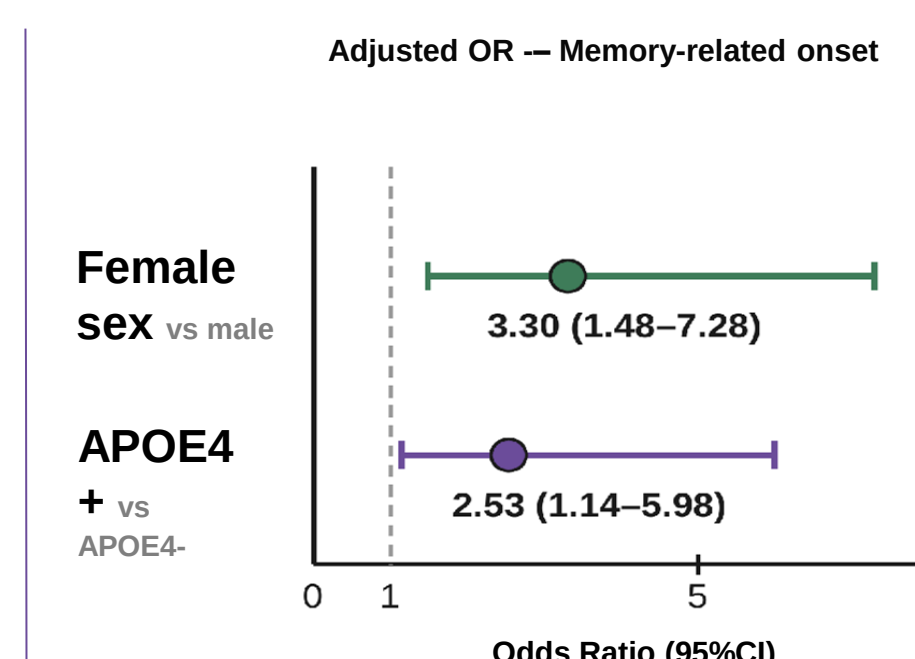


FIGURE 3. Adjusted odds ratios and percent change in age at onset
Adjusted odds ratio for memory-related symptom onset by sex and APOE4 status. Estimates from multivariable models controlling for sex and education; points, estimate; horizontal lines, 95% confidence interval; dashed line, null value (OR=1 or 0% change).

Conclusions //

In this Latino cohort with AD, APOE4 status was linked to earlier onset and increased odds of memory-related debut, independent of sex and education. These findings highlight APOE ε4 as an early phenotypic marker and suggest that genetic and sociodemographic factors shape the initial clinical profile in AD.

Acknowledgments

The authors respectfully acknowledge that Dr. Francisco Lopera passed away prior to the publication of this manuscript and honor his lifelong dedication to advancing the study of Alzheimer's disease and related dementias, without which this work would not have been posible.