More Than *APOE*: Genetic Predictors in Alzheimer Disease in *APOE*ε3 Carriers

Peters, Nils; Unschuld, Paul

How to cite

PETERS, Nils, UNSCHULD, Paul. More Than *APOE*: Genetic Predictors in Alzheimer Disease in *APOE*ε3 Carriers. In: Neurology. Genetics, 2025, vol. 11, n° 4, p. e200284. doi: 10.1212/NXG.0000000000200284

This publication URL: https://archive-ouverte.unige.ch/unige:186864

Publication DOI: 10.1212/NXG.0000000000200284

EDITORIAL OPEN ACCESS

More Than *APOE*: Genetic Predictors in Alzheimer Disease in *APOE*ε3 Carriers

Nils Peters[1,2] and Paul G. Unschuld[3,4]

Neurol Genet 2025;11:e200284. doi:10.1212/NXG.0000000000200284

Correspondence
Dr. Peters
nils.peters@unibas.ch

RELATED ARTICLE

Research Article
Combating Genetic Heterogeneity for Polygenic Prediction of Susceptibility to Brain β-Amyloid Deposition: Beyond *APOE*
Page e200266

Alzheimer disease (AD) is the most common underlying condition of dementia, imposing a substantial medical and psychosocial burden on affected individuals as well as their caregivers. AD is characterized by neurodegeneration in the context of deposition of cerebral amyloid-beta (Aβ), which can be captured by PET. Early diagnosis of AD, e.g., based on amyloid-PET, is the basis for timely initiation of the recently developed anti-Aβ antibody-treatment approaches in AD. Various risk factors are known to be related to AD, including both modifiable and nonmodifiable factors, the latter especially comprising genetic factors. Genetic variants in the presenilins and the amyloid precursor protein cause inherited familial forms of AD.[1] Other genetic variants, such as the Triggering receptor expressed on myeloid cells 2 and especially apolipoprotein (*APOE*) allele ε4, are important genetic risk factors in sporadic AD.[2,3] However, the frequency of *APOE*ε4 in the general population is rather low, and AD may develop in the absence of the allele, raising the issue of potential other genetic risk factors of AD and amyloid deposition in non–*APOE*ε4-carriers, including polygenic effects on AD biomarkers.[4]

In this issue of *Neurology® Genetics*, Ramanan et al.[5] present their findings on potential genetic predictors of amyloid deposition in "pure" cohorts of *APOE* ε3/ε3 carriers, representing a large group of participants in the general population and thus excluding confounding by ε4 as well as ε2 carriers, the latter having a protective effect.[6] In cohorts derived from different studies, the authors performed a genome-wide association study and genetic risk score (GRS) analyses, based on the biologic diagnosis of amyloid deposition in approximately 1,500 *APOE* ε3/ε3 carriers studied by amyloid PET as well as cohorts with available plasma p-tau and postmortem neuropathologic data. They identified both previously described and novel genetic variants associated with amyloid burden on PET, and GRS top variants also showed association in some of the studied cohorts. Furthermore, the authors found an association of non-*APOE* GRS with AD-related postmortem neuropathologic changes as well as plasma p-tau181 concentrations. Based on their observations, the authors discuss the potential implications, including individualized risk prediction of amyloid deposition beyond *APOE*ε4, thus in an overall large proportion of participants.

All good things come in threes: by including *APOE* ε3/ε3 carriers, the study intriguingly examines a large group of individuals potentially affected by AD not related to *APOE*ε4. The findings were strengthened by a multistep approach with 3 measures assessing biologically defined AD: PET, p-tau, and postmortem studies. The authors acknowledge potential limitations of their study, such as the overall sample size, heterogeneous genetic methodology, as well as distinct clinical and demographic compositions of their cohorts. Yet, despite the limitations, the findings were generally consistent, emphasizing the potential value of individual GRS for better understanding amyloid deposition and the potential effect on both the design of future clinical trials and personalized, biomarker-based treatment decisions. Given that in some parts of the world, eligibility for AD-antibody treatment is based on *APOE* status, genetic factors beyond *APOE* as presented in the current article by Ramanan et al. may further influence research and clinical practice with individualized approaches in the future.

Study Funding

The authors report no targeted funding.

[1]Department of Neurology and Stroke Center, Klinik Hirslanden, Zürich, Switzerland; [2]University of Basel, Switzerland; [3]Division of Geriatric Psychiatry, University Hospitals of Geneva (HUG), Thônex, Switzerland; and [4]Department of Psychiatry, University of Geneva (UniGE), Switzerland.

Disclosure

N. Peters is a member of the executive board of the Swiss Society of Hypertension, the dementia task force of the Swiss Neurological Society, and the dementia committee of the European Stroke Organisation. P.G. Unschuld is a member of the executive board of the Swiss Society of Geriatric Psychiatry and of the Swiss Society of Neurology. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

Publication History

Received by *Neurology® Genetics* April 17, 2025. Accepted in final form May 29, 2025.

References

1. Shen J, Kelleher RJ 3rd. The presenilin hypothesis of Alzheimer's disease: evidence for a loss-of-function pathogenic mechanism. *Proc Natl Acad Sci USA*. 2007;104(2):403-409. doi:10.1073/pnas.0608332104
2. Guerreiro R, Wojtas A, Bras J, et al.; Alzheimer Genetic Analysis Group. TREM2 variants in Alzheimer's disease. *N Engl J Med*. 2013;368(2):117-127. doi:10.1056/NEJMoa1211851
3. Mattsson N, Groot C, Jansen WJ, et al. Prevalence of the apolipoprotein E ε4 allele in amyloid β positive subjects across the spectrum of Alzheimer's disease. *Alzheimers Dement*. 2018;14(7):913-924. doi:10.1016/j.jalz.2018.02.009
4. Kagerer SM, Awasthi S, Ripke S, et al. Polygenic risk for Alzheimer's disease is associated with neuroaxonal damage before onset of clinical symptoms. *Alzheimers Dement*. 2024;16(1):e12504. doi:10.1002/dad2.12504
5. Ramanan V, Heckman M, Hofrenning E, et al. Beyond *APOE*: combating genetic heterogeneity for polygenic prediction of susceptibility to brain amyloid-β deposition. *Neurol Genet*. 2025;11(4):e200266. doi:10.1212/NXG.0000000000200266
6. Castellano JM, Kim J, Stewart FR, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Sci Transl Med*. 2011;3(89):89ra57. doi:10.1126/scitranslmed.3002156