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Association of *APOE* Genotype With Heterogeneity of Cognitive Decline Rate in Alzheimer Disease

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Study Question

Is the *APOE* genotype associated with the heterogeneity in the progression of cognitive decline in patients with Alzheimer disease (AD)?

What Is Known and What This Paper Adds

APOE genotype is an important determinant of AD risk, age at symptom onset, and AD-related neuropathologic changes. This investigation's results show that the *APOE* genotype also contributes to the heterogeneity in the rate of AD clinical progression.

Methods

For these longitudinal analyses, the investigators analyzed data from 1,102 decedents with autopsy-proven AD (4.0% ε2-carriers, 39.9% ε3/ε3-carriers, and 56.1% ε4-carriers) enrolled in the National Alzheimer's Coordinating Center Neuropathology database. Participants had baseline and annual follow-up visits with demographics and standard motor, behavioral, functional, and neuropsychological evaluations (including Clinical Dementia Rating Sum of Boxes [CDR-SOB] and the Mini-Mental State Examination [MMSE]) collected in a Uniform Data Set (UDS). This analysis includes patients who died <2 years after their most recent visits at ages ≥50 years and had a Braak neurofibrillary tangle (NFT) stage III or higher, and moderate or frequent neuritic plaques by CERAD score. To investigate the associations between *APOE* genotype and rate of global cognitive decline in the CDR-SOB and MMSE, reverse-time longitudinal models were used that treated the neuropathologic abnormalities as baseline covariates and modeled the longitudinal cognitive trajectories in reverse time. A joint latent class model was used to account for time-to-events and unmeasured confounders. Adjustments were made for floor and ceiling effects and right truncation of "time to last visit" by "time to death."

Results and Study Limitations

The CDR-SOB scores increased ~1.5 times faster in *APOE* ε4-carriers than in ε3/ε3-carriers (2.12 points/year vs 1.44 points/year), and ~1.3 times faster than in ε2-carriers (1.65 points/year). The *APOE* ε2 vs *APOE* ε3/ε3 difference was not statistically significant. The MMSE scores declined ~1.1 times faster in ε4-carriers than in ε3/ε3-carriers (−3.45 points/year vs −3.03 points/year) and ~1.4 times faster than in ε2-carriers (−2.43 points/year). *APOE* ε2 carriers had ~1.2 times slower decline than *APOE* ε3/ε3 subjects (−2.43 points/year vs −3.03 points/year) (table). These findings remained largely unchanged after corrections for the presence and severity of comorbid pathologies and for the effects of AD-related neuropathologic changes on cognitive decline rate. A limitation of the study is its focus on patients with mild-to-moderate AD dementia, who do not resemble those enrolled in current therapeutic clinical trials targeting subjective or very mild cognitive impairment, nor in secondary prevention trials (i.e., cognitively intact subjects with positive AD biomarkers). Other limitations include the small sample of ε2-carriers with substantial AD pathology and the need to exclude some interaction terms from the longitudinal models to avoid overfitting.

Table Cognitive Changes for Specific *APOE* Genotypes

Genotype	Mean rate of change in CDR-SOB scores	Mean rate of change in MMSE scores
ε4	2.12 points/y	−3.45 points/y
ε3/ε3	1.44 points/y	−3.03 points/y
ε2	1.65 points/y	−2.43 points/y

CDR-SOB and MMSE score trajectories for patients with specific *APOE* genotypes.

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

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