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Original Research

Genotypic Effects of the TOMM40'523 Variant and APOE on Longitudinal Cognitive Change over 4 Years: The TOMMORROW Study

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Abstract

BACKGROUND: The 523 poly-T length polymorphism (rs10524523) in TOMM40 has been reported to influence longitudinal cognitive test performance within APOE ε3/3 carriers. The results from prior studies are inconsistent. It is also unclear whether specific APOE and TOMM40 genotypes contribute to heterogeneity in longitudinal cognitive performance during the preclinical stages of AD.

OBJECTIVES: To determine the effects of these genes on longitudinal cognitive change in early preclinical stages of AD, we used the clinical trial data from the recently concluded TOMMORROW study to examine the effects of APOE and TOMM40 genotypes on neuropsychological test performance.

DESIGN: A phase 3, double-blind, placebo-controlled, randomized clinical trial.

SETTING: Academic affiliated and private research clinics in Australia, Germany, Switzerland, the UK, and the USA.

PARTICIPANTS: Cognitively normal older adults aged 65 to 83.

INTERVENTION: Pioglitazone tablet.

MEASUREMENTS: Participants from the TOMMORROW trial were stratified based on APOE genotype (APOE ε3/3, APOE ε3/4, APOE ε4/4). APOE ε3/3 carriers were further stratified by TOMM40'523 genotype. The final analysis dataset consists of 1,330 APOE ε3/3 carriers and 7,001 visits. Linear mixed models were used to compare the rates of decline in cognition across APOE groups and the APOE ε3/3 carriers with different TOMM40'523 genotypes.

RESULTS: APOE ε3/4 and APOE ε4/4 genotypes compared with the APOE ε3/3 genotype were associated with worse performance on measures of global cognition, episodic memory, and expressive language. Further, over the four years of observation, the APOE ε3/3 carriers with the TOMM40'523-S/S genotype showed better global cognition and accelerated rates of cognitive decline on tests of global cognition, executive function, and attentional processing compared to APOE ε3/3 carriers with TOMM40'523-S/VL and VL/VL genotypes and compared to the APOE ε3/4 and APOE ε4/4 carriers.

CONCLUSIONS: We suggest that both APOE and TOMM40 genotypes may independently contribute to cognitive heterogeneity in the pre-MCI stages of AD. Controlling for this genetic variability will be important in clinical trials designed to slow the rate of cognitive decline and/or prevent symptom onset in preclinical AD.

Key words: Alzheimer's disease, TOMM40, APOE, cognitive change, TOMMORROW.

Introduction

Late onset Alzheimer's disease (LOAD) is a complex neurodegenerative disease caused by the interaction of multiple factors associated with aging (1, 2). About 70% of risk for LOAD is estimated as due to genetic factors (1). Genetic susceptibility studies identified multiple genes that contribute to the development of LOAD (3, 4). The apolipoprotein E (APOE) gene on chromosome 19 has by far the largest effect size in relationship to AD risk. The protein encoded by APOE is involved in lipid transport, binding to cell surface receptors to mediate lipoprotein uptake. There are two non-synonymous APOE SNPs (rs429358 and rs7412), which define the three most common APOE isoforms (i.e., ε2, ε3, and ε4) (5). Of them, APOE ε4 has the strongest genetic risk for LOAD, conferring an earlier disease onset, more rapid cognitive decline, and the accumulation of Aβ42 peptides, compared to the most-common APOE ε3 allele. The ε2 allele is associated with a decreased risk of AD, later onset, and slower cognitive decline (6-10). Importantly, carriage of an APOE ε4 allele does not necessarily lead to clinical AD expression. Rather, as a polygenic heterogeneous disease, the risk of AD and the expression of clinical symptoms are influenced by a complex interplay of different genes (11, 12) and modifiable risk factors.

The TOMM40 gene is located upstream of the APOE gene on chromosome 19. Previous studies provided evidence for the roles of APOE-TOMM40 haplotypes in AD risk, hippocampal volume, and cognitive phenotypes (12-16). Roses et al. reported a poly-thymine (poly-T) polymorphism at the rs10524523 ('523 thereafter) locus and found that a specific length of this polymorphism is associated with an earlier onset age of AD among APOE ε3 carriers (17). There are three categories of the '523 poly-T repeat length: a "short" '523 allele (S) of ≤19 poly-T's, a "long" allele (L) of 20–29 poly-T's, and a "very long" allele (VL) of ≥ 30 poly-T's. Genetic analysis revealed that the S and VL alleles are tightly linked with the APOE ε3 allele, whereas the L allele is linked with APOE ε4 allele in white populations of primarily

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European ancestry (18). Considering this, haplotype analysis is often used to investigate the effects of '523 alleles in addition to APOE genotype for phenotypes relevant for the study of LOAD. The TOMM40 S and VL alleles differentially influence AD risk, cognitive test performance, and changes in brain volumes (13, 14, 17, 19-23). The study of cognitively healthy populations at high genetic risk for developing AD as was the design for the TOMMORROW trial, allows an opportunity to further explore this and to determine the role of these genes in the expression of the earliest stages of the clinical disease. There have been prior studies doing this and the results are inconsistent. A longitudinal study by Yu et al. reported that among cognitively normal older adults, the global cognition for participants with APOE ε3/3 homozygotes and TOMM40 S/S homozygotes declined faster than participants with '523- S/VL or VL/VL (21), while a cross-sectional study by Laczo et al. reported that TOMM40 S/S homozygotes with amnestic mild cognitive impairment showed better cognitive performance and larger brain volumes (18). Watts et al. reported that among APOE ε3 carriers, the TOMM40 '523 S allele was associated with worse baseline cognitive performance but was not associated with longitudinal cognitive changes (22). Bussies et al. showed that TOMM40-523' length did not modify risk for late onset AD (LOAD) in APOE ε4 haplotypes with European or African local genetic ancestry, however, increasing length of TOMM40-523' was associated with a significantly reduced risk for load in European ancestry APOE ε3 haplotypes (20).

Methods

Study population

Our analysis dataset was from a phase 3, double-blind, placebo-controlled, randomized clinical trial (TOMMORROW) study (https://clinicaltrials.gov/ct2/show/NCT01931566). The purpose of the TOMMORROW study was to qualify the biomarker risk algorithm and to assess the safety and efficacy of pioglitazone to reduce the onset of MCI due to AD in cognitively normal subjects. The detail of the TOMMORROW study can be found in the literatures (24-26). Eligible participants were all clinically confirmed to be cognitively healthy at study start (education adjusted MMSE>=25) and were genotyped for TOMM40 rs1054523 (TOMM40'523) and apolipoprotein E (APOE) to determine overall risk status for developing symptomatic disease over the next five-year period. Randomized participants completed a cognitive assessment battery comprised of neuropsychological tests commonly administered in clinical practice. The measures were repeated every 6 months to detect emerging symptoms of MCI over the four years of observations (details in the cognitive assessments Section).

For the current secondary analysis of the TOMMORROW data, we included participants from both the low and high genetic risk groups in the trial. Consistent with the linkage disequilibrium structure for the APOE-TOMM40 region (14, 17, 21), analysis was restricted to participants with the APOE ε3/3 genotype with "S/S" or "S/VL" or "VL/VL" genotypes in the TOMM40'523 gene. The APOE ε3/4 genotype included participants with "S/L" or "VL/L" genotypes in the TOMM40'523 gene and the APOE ε4/4 genotype included participants with "L/L" genotype in the TOMM40'523 gene. The full analysis dataset consisted of 2,830 participants (1,330 APOE ε3/3 carriers, 1,358 APOE ε3/4 carriers, and 142 APOE ε4/4 carriers) and 15,189 visits, with a mean follow-up length of 2.24 years and SD of 1.09 years. The APOE and TOMM40'523 haplotypes were included as interaction terms in the analysis (refer to Section Statistical analysis). The main analysis dataset consists of 1,330 APOE ε3/3 carriers and 7,001 visits, with a mean follow-up length of 2.19 years and SD of 1.14 years.

Cognitive assessments

The neuropsychological test battery used in the TOMMORROW trial contained a total of 12 cognitive endpoints that assessed five principle cognitive domains affected in the early clinical expression of Alzheimer's disease. The TOMMORROW trial utilized these measures to inform clinical judgement. The prespecified cognitive domains and the measures included in each were as follows. Episodic memory was comprised of short & long delay recall from the California Verbal Learning Test-II [CVLT-II] and the delayed recall measure from the Brief Visuospatial Memory Test -Revised [BVMT-R]; executive function included the scores from the Trail Making Test Part B and the WAIS-R Digit Span backwards span; expressive language included two measures of fluency (lexical fluency, "animal" fluency test) and a measure of visual naming, Multilingual Naming Test [MiNT]; attentional processing included performance on the Trail Making Test- Part A and on WAIS-R Digit Span forward span; and visuospatial function included the Clock drawing test and constructional copy of BVMT-R figures.

Because the various cognitive scales have a differing range of values, the total raw score for each test was converted to a common metric (z scores) based on the mean and standard deviation for that test measure within the baseline trial population. Z score is a standard metric that reflects the deviation of the score in SD units from the population mean such that a z-score = 1.0 indicates that the obtained score is one SD from the population mean, and vice versa for a z-score = -1.0. The Trail Making Test scores are directionally scaled such that high scores reflect poorer performance (longer time to complete the task); whereas, all the other cognitive measures in the battery

are scaled in the opposite manner such that high scores reflect better performance. To correct for this difference in scaling across the cognitive endpoints, the Trail Making z scores were multiplied by -1. By doing so, all high scores across the test endpoints are scaled in a consistent manner, with high z scores reflecting better performance than low z scores.

Statistical analysis

Factor analysis

To validate the previous findings (21), we performed an exploratory factor analysis (EFA) to verify the fit of the 12 cognitive tests into the five pre-specified cognitive domains: episodic memory, executive function, expressive language, attentional processing, and visuospatial function. We included 1,330 participants with APOE ε3/3 genotype and used their baseline standardized cognitive scores as the outcome. We used five factors in the factor analysis. Factor loading matrix and the proportion of variance accounted were computed in Table S1 in the Supplemental Material.

Table S1 suggests that for 12 cognitive tests, Factor 1 (episodic memory) consists of CVLT-II short & long delay recall and BVMT delayed recall tests. Factor 2 (executive function & attentional processing) consists of Trail Making Test Part B and Part A. Factor 3 (executive function & attentional processing) consists of WAIS-III Digit Span Test – backward span, Lexical/phonemic fluency, WAIS-III Digit Span Test – forward span. Factor 4 (visuospatial function) consists of BVMT delayed recall, Multilingual Naming Test (MiNT), Clock-drawing test, and Copy of BVMT figures. Factor 5 (expressive language) consists of Multilingual Naming Test (MiNT), Sematic fluency (animals), Lexical/phonemic fluency, Trail Making Test (Part A). Most results agreed with the split of 12 cognitive tests along conceptual domains used in the trial and described in the Methods Section. BVMT-R delayed recall loaded on both a memory and visuospatial factor; digit span tests (forward and backward) loaded together on the executive function and attentional processing; and lexical/phonemic fluency loaded on this same factor and on a factor with language measures. Given the rather close correspondence between the empirical and conceptual domains, we use the conceptual domains described in the Cognitive assessments section.

Linear mixed model analysis

Linear mixed models (LMM) were fit to test the hypothesis that the number of APOE 4 alleles influenced cognitive decline. We used longitudinal global cognition as the primary response variable. In secondary analyses, we repeated the model for each of the 5 cognitive domains separately. In each of the LMM, we used as the reference group APOE ε3/3 and included the following covariates as main effects: time in years since the baseline, age, sex, education, APOE ε3/4, APOE ε4/4, and two interaction terms of these genotypes with time, in addition to random effects (random intercepts and random slopes).

Among APOE ε3/3 carriers, we fit LMM to test the hypothesis that the rate of linear decline in cognition differs by TOMM40'523 genotype. In each of the LMM, we included the following covariates as main effects: time in years since the baseline, age, sex, education, TOMM40'523 S/S (presence of this genotype), and the interaction term of TOMM40'523 S/S and time (assuming recessive model so that we combined "S/VL" and "VL/VL" genotypes and used these as the reference group), in addition to random effects (random intercepts and random slopes).

To investigate the effect of various haplotypes of APOE and TOMM40'523 on cognitive decline, we fit six linear mixed models (LMM) with the response variable being the longitudinal global cognition and each of the 5 cognitive domains. We considered two haplotypes of APOE and TOMM40'523 (TOMM40'523 S/S and APOE ε3/3, TOMM40'523 S/VL or VL/VL and APOE ε3/3) and two APOE genotypes: APOE ε3/4, and APOE ε4/4. We used as the reference group the haplotype of TOMM40'523 S/VL or VL/VL and APOE ε3/3. In each of the LMM model, we included the following covariates as main effects: time in years since the baseline, age, sex, education, haplotype of TOMM40'523 S/S and APOE ε3/3, genotypes of APOE ε3/4 and APOE ε4/4, and three interaction terms of these haplotype and genotypes with time, in addition to random effects (random intercepts and random slopes).

Results

The baseline characteristics of the final analysis dataset (2,830 participants with APOE ε3/3, ε3/4, and ε4/4 genotypes) and the main analysis dataset (1,330 APOE ε3/3 carriers) are displayed in Table 1. For all full analysis dataset of 2,830 participants, APOE ε3/3 carriers were 4.8 years older and had worse baseline cognitive scores in the global and the five cognitive domains as compared to APOE ε3/4 carriers and APOE ε4/4 carriers. These differences were likely a consequence of the biomarker risk algorithm used to select trial participants for the high risk group. The highest risk APOE ε3/3 participants would be selected at older ages to map to the high risk group. Among 1,330 APOE ε3/3 carriers, participants with TOMM40'523 S/S genotypes were older as compared to TOMM40'523 VL/VL carriers, and they had a better baseline cognitive scores in global and five cognitive domains as compared to TOMM40'523 S/VL carriers. The Locally Weighted Scatterplot Smoothing (LOWESS) curves of the main analysis dataset (1,330 APOE ε3/3 carriers, Figure 1) show an improving trend of the global cognition before 2 years and a deterioration

Table 1. Baseline characteristics of all patients (upper panel) and APOE ε3/3 carriers (lower panel)

All patients	**APOE E3/E3 (1330, 47.0%)**	**APOE E3/E4 (1358, 48.0%)**	**APOE E4/E4 (142, 5.0%)**
Age (years)	77.1 (4.4)	72.3 (4.9)	70.4 (4.1)
Female (%)	724 (54.4%)	738 (54.3%)	74 (52.1%)
Education (years)	14.6 (3.0)	14.8 (3.0)	14.9 (2.8)
Max follow-up (years)	2.2 (1.1)	2.3 (1.0)	2.3 (1.0)
Baseline MMSE score	28.6 (1.4)	28.8 (1.3)	28.8 (1.2)
Baseline global cognition	-0.08 (0.54)	0.07 (0.53)	0.07 (0.49)
Baseline episodic memory	-0.08 (0.83)	0.07 (0.83)	0.07 (0.77)
Baseline working memory	-0.06 (0.83)	0.06 (0.80)	0.03 (0.80)
Baseline semantic memory	-0.10 (0.76)	0.09 (0.72)	0.12 (0.68)
Baseline perceptual speed	-0.07 (0.76)	0.06 (0.72)	0.08 (0.79)
Baseline visuospatial ability	-0.05 (0.79)	0.04 (0.77)	0.03 (0.79)
APOE E3/E3 carriers	**TOMM40 S/S (n=399, 30.0%)**	**TOMM40 S/VL (n=879, 66.1%)**	**TOMM40 VL/VL (n=52, 3.9%)**
Age (years)	77.2 (4.6)	77.4 (4.1)	71.3 (4.5)
Female (%)	223 (55.9%)	471 (53.6%)	30 (57.7%)
Education (years)	14.5 (3.1)	14.6 (3)	14.9 (3.1)
Max follow-up (years)	2.2 (1.1)	2.2 (1.1)	2.2 (1.3)
Baseline MMSE score	28.7 (1.3)	28.6 (1.5)	28.8 (1.4)
Baseline global cognition	0.04 (0.54)	-0.02 (0.52)	0.07 (0.51)
Baseline episodic memory	0.05 (0.82)	-0.02 (0.82)	-0.02 (0.83)
Baseline working memory	0.05 (0.84)	-0.03 (0.81)	0.09 (0.77)
Baseline semantic memory	0.02 (0.77)	-0.01 (0.73)	0.09 (0.74)
Baseline perceptual speed	0.02 (0.74)	-0.02 (0.74)	0.12 (0.82)
Baseline visuospatial ability	0.05 (0.79)	-0.03 (0.77)	0.16 (0.69)

* All patients: 2,830 patients with APOE ε3/3 or ε3/4 or ε4/4 genotypes; APOE ε3/3 carriers: 1,330 patients, lower panel. Bold numbers indicate the global cognition scores among groups are different.

pattern after 2 years for TOMM40'523 S/S carriers and S/VL carriers. For TOMM40'523 VL/VL carriers, they continued to show an improving trend of the global cognition after 2 years.

Effect of number of APOE 4 alleles on cognitive decline

Table 2 displays the summary statistics of six linear mixed models for 2,830 participants with APOE ε3/3, ε3/4, or ε4/4 genotypes. As it shown, both APOE ε3/4 and APOE ε4/4 genotype were associated with worse cognitive scores in episodic memory and executive function domains compared with APOE ε3/3 carriers. The APOE ε4/4 genotype was also associated with worse global cognition compared with APOE ε3/3 carriers. Older ages and fewer education years were associated with significantly worse global cognition and five individual cognitive domains (episodic memory, executive function, expressive language, attentional processing, and visuospatial function). Male sex was associated with worse global cognition, episodic memory, and visuospatial function.

Figure S1 displays the spaghetti plot of global cognition from randomly selected 50 participants with APOE ε3/3, ε3/4, or ε4/4 genotypes and the predicted mean trajectory estimated from the linear mixed model. Figure S1 suggests that participants with APOE ε4/4 genotype (green color) had a worse baseline global cognition as compared with participants with APOE ε3/3 or APOE ε3/4 genotypes (blue color and red color, respectively).

TOMM40'523 variant and cognitive decline in older persons with APOE 3/3 genotype

Table 3 displays the summary statistics of six linear mixed models for 1,330 APOE ε3/3 carriers. Table 3 suggests that among APOE ε3/3 carriers, TOMM40'523-S/S genotype was associated with better global cognition and episodic memory, and faster deterioration rate in global cognition, executive function, and attentional processing domains as compared with TOMM40'523-S/VL and VL/VL genotypes. Older age and fewer education years were associated with worse global cognition and

five cognitive domains. Figure S2 displays the spaghetti plot of global cognition from randomly selected 50 participants with APOE ε3/3 genotype and the predicted mean trajectory estimated from the linear mixed model. Figure S2 suggests that TOMM40'523 S/S carriers (grey color) had a slower/worse progression rate as compared with TOMM40'523 carriers (blue color).

Table 2. Summary statistics of six linear mixed models in older persons

Cognitive domains	Predictors	Estimates (SE, p-value)
Global cognition	Age	-0.035 (0.002, <0.001)
	Male	-0.114 (0.018, <0.001)
	Education	0.043 (0.003, <0.001)
	APOE e3/4	-0.024 (0.021, 0.245)
	APOE e4/4	-0.115 (0.044, 0.009)
	APOE e3/4 * Time	0.007 (0.005, 0.122)
	APOE e4/4 * Time	0.008 (0.011, 0.436)
Episodic memory	Age	-0.048 (0.003, <0.001)
	Male	-0.405 (0.028, <0.001)
	Education	0.043 (0.005, <0.001)
	APOE e3/4	-0.074 (0.031, 0.018)
	APOE e4/4	-0.209 (0.067, 0.002)
	APOE e3/4 * Time	0.000 (0.009, 0.997)
	APOE e4/4 * Time	-0.012 (0.021, 0.556)
Executive function	Age	-0.038 (0.003, <0.001)
	Male	-0.030 (0.027, 0.264)
	Education	0.058 (0.004, <0.001)
	APOE e3/4	-0.068 (0.031, 0.030)
	APOE e4/4	-0.199 (0.067, 0.003)
	APOE e3/4 * Time	0.022 (0.009, 0.012)
	APOE e4/4 * Time	0.023 (0.020, 0.248)
Expressive language	Age	-0.031 (0.003, <0.001)
	Male	-0.010 (0.025, 0.694)
	Education	0.053 (0.004, <0.001)
	APOE e3/4	0.039 (0.029, 0.184)
	APOE e4/4	-0.023 (0.062, 0.712)
	APOE e3/4 * Time	0.011 (0.007, 0.111)
	APOE e4/4 * Time	0.001 (0.016, 0.929)
Attentional processing	Age	-0.033 (0.002, <0.001)
	Male	0.026 (0.023, 0.259)
	Education	0.035 (0.004, <0.001)
	APOE e3/4	-0.038 (0.028, 0.165)
	APOE e4/4	-0.092 (0.059, 0.120)
	APOE e3/4 * Time	0.019 (0.008, 0.025)
	APOE e4/4 * Time	-0.010 (0.019, 0.581)
Visuospatial function	Age	-0.020 (0.002, <0.001)
	Male	-0.073 (0.020, <0.001)
	Education	0.015 (0.003, <0.001)
	APOE e3/4	-0.017 (0.028, 0.550)
	APOE e4/4	-0.043 (0.060, 0.474)
	APOE e3/4 * Time	-0.008 (0.010, 0.424)
	APOE e4/4 * Time	0.022 (0.023, 0.329)

* Linear mixed models assessed the association between APOE 4 alleles and cognitive decline. Bold numbers are significant effects.

Effect of various haplotypes of APOE and TOMM40'523 on cognitive decline

Table 4 displays the summary statistics of six linear mixed models for haplotypes of APOE and TOMM40'523. Table 4 suggests that haplotype of TOMM40'523 S/S & APOE ε3/3 was associated with better global cognition and episodic memory and faster deterioration rate in global cognition, executive function, and attentional processing domains as compared with other haplotypes. Haplotype of TOMM40'523 L/L and APOE ε4/4 was associated with worse global cognition, episodic memory, and executive function scores. Older age and fewer education years were associated with worse global cognition and five cognitive domains.

Table 3. Summary statistics of six linear mixed models for older persons with APOE 3/3 genotype

Cognitive Domains	Predictors	Estimates (SE, p-value)
Global cognition	Age	-0.031 (0.003, <0.001)
	Male	-0.087 (0.027, 0.001)
	Education	0.040 (0.004, <0.001)
	TOMM40 S/S	0.068 (0.029, 0.018)
	TOMM40 S/S*Time	-0.021 (0.008, 0.006)
Episodic memory	Age	-0.036 (0.005, <0.001)
	Male	-0.414 (0.040, <0.001)
	Education	0.042 (0.007, <0.001)
	TOMM40 S/S	0.086 (0.044, 0.049)
	TOMM40 S/S*Time	-0.010 (0.014, 0.490)
Executive function	Age	-0.036 (0.004, <0.001)
	Male	-0.022 (0.039, 0.585)
	Education	0.059 (0.006, <0.001)
	TOMM40 S/S	0.082 (0.043, 0.058)
	TOMM40 S/S*Time	-0.038 (0.014, 0.006)
Expressive language	Age	-0.029 (0.004, <0.001)
	Male	0.021 (0.037, 0.571)
	Education	0.046 (0.006, <0.001)
	TOMM40 S/S	0.040 (0.041, 0.326)
	TOMM40 S/S*Time	-0.01 (0.011, 0.331)
Attentional processing	Age	-0.029 (0.004, <0.001)
	Male	0.054 (0.034, 0.110)
	Education	0.035 (0.006, <0.001)
	TOMM40 S/S	0.054 (0.039, 0.165)
	TOMM40 S/S*Time	-0.034 (0.013, 0.011)
Visuospatial function	Age	-0.023 (0.003, <0.001)
	Male	-0.025 (0.030, 0.395)
	Education	0.010 (0.005, 0.032)
	TOMM40 S/S	0.077 (0.040, 0.053)
	TOMM40 S/S*Time	-0.017 (0.015, 0.270)

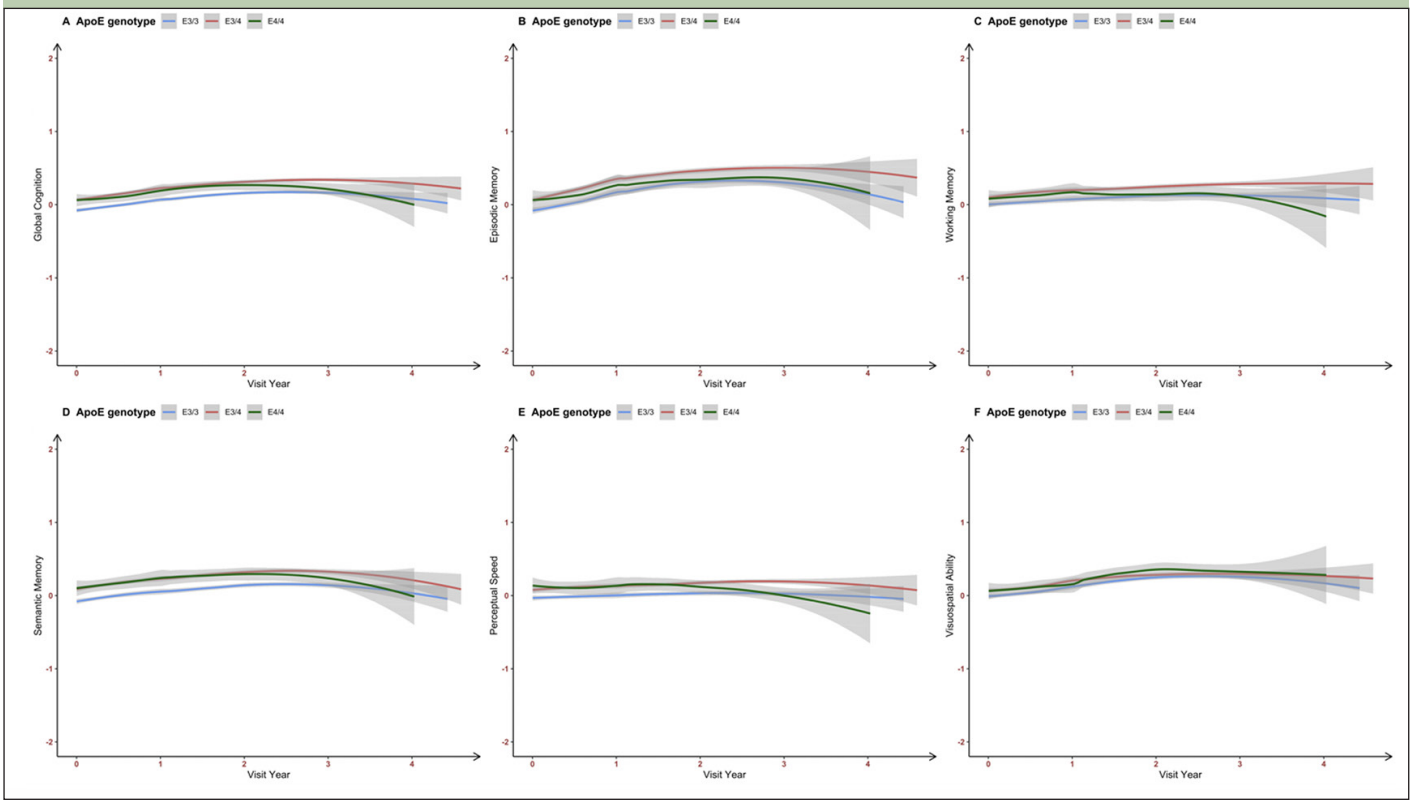
* Linear mixed models assessed the association between TOMM40'523 variant and cognitive decline. Bold numbers are significant effects.

Table 4. Summary statistics of six linear mixed models for haplotypes of APOE and TOMM40'523

Cognitive domains	Predictors	Estimates (SE, p-value)
Global cognition	Age	-0.035 (0.002, <0.001)
	Male	-0.113 (0.018, <0.001)
	Education	0.043 (0.003, <0.001)
	TOMM40 S/S & APOE e3/3	0.069 (0.029, 0.016)
	TOMM40 S/L or VL/L & APOE e3/4	-0.003 (0.022, 0.880)
	TOMM40 L/L & APOE e4/4	-0.094 (0.045, 0.035)
	TOMM40 S/S & APOE e3/3 * Time	-0.021 (0.007, 0.005)
	TOMM40 S/L or VL/L & APOE e3/4 * Time	0.001 (0.005, 0.832)
	TOMM40 L/L & APOE e4/4 * Time	0.002 (0.011, 0.842)
Episodic memory	Age	-0.048 (0.003, <0.001)
	Male	-0.404 (0.028, <0.001)
	Education	0.043 (0.005, <0.001)
	TOMM40 S/S & APOE e3/3	0.089 (0.044, 0.042)
	TOMM40 S/L or VL/L & APOE e3/4	-0.048 (0.034, 0.156)
	TOMM40 L/L & APOE e4/4	-0.182 (0.068, 0.008)
	TOMM40 S/S & APOE e3/3 * Time	-0.010 (0.014, 0.499)
	TOMM40 S/L or VL/L & APOE e3/4 * Time	-0.003 (0.010, 0.770)
	TOMM40 L/L & APOE e4/4 * Time	-0.015 (0.021, 0.475)
Executive function	Age	-0.038 (0.003, <0.001)
	Male	-0.030 (0.027, 0.267)
	Education	0.058 (0.004, <0.001)
	TOMM40 S/S & APOE e3/3	0.084 (0.043, 0.054)
	TOMM40 S/L or VL/L & APOE e3/4	-0.043 (0.034, 0.205)
	TOMM40 L/L & APOE e4/4	-0.174 (0.068, 0.010)
	TOMM40 S/S & APOE e3/3 * Time	-0.039 (0.014, 0.004)
	TOMM40 S/L or VL/L & APOE e3/4 * Time	0.010 (0.010, 0.295)
	TOMM40 L/L & APOE e4/4 * Time	0.011 (0.020, 0.582)
Expressive language	Age	-0.032 (0.003, <0.001)
	Male	-0.010 (0.025, 0.700)
	Education	0.053 (0.004, <0.001)
	TOMM40 S/S & APOE e3/3	0.038 (0.041, 0.348)
	TOMM40 S/L or VL/L & APOE e3/4	0.050 (0.031, 0.112)
	TOMM40 L/L & APOE e4/4	-0.012 (0.064, 0.853)
	TOMM40 S/S & APOE e3/3 * Time	-0.009 (0.011, 0.387)
	TOMM40 S/L or VL/L & APOE e3/4 * Time	0.008 (0.008, 0.283)
	TOMM40 L/L & APOE e4/4 * Time	-0.001 (0.016, 0.930)
Attentional processing	Age	-0.033 (0.002, <0.001)
	Male	0.026 (0.023, 0.261)
	Education	0.035 (0.004, <0.001)
	TOMM40 S/S & APOE e3/3	0.054 (0.039, 0.159)
	TOMM40 S/L or VL/L & APOE e3/4	-0.022 (0.030, 0.462)
	TOMM40 L/L & APOE e4/4	-0.076 (0.060, 0.209)
	TOMM40 S/S & APOE e3/3 * Time	-0.034 (0.013, 0.008)
	TOMM40 S/L or VL/L & APOE e3/4 * Time	0.008 (0.009, 0.372)
	TOMM40 L/L & APOE e4/4 * Time	-0.021 (0.019, 0.279)
Visuospatial function	Age	-0.020 (0.002, <0.001)
	Male	-0.073 (0.020, <0.001)
	Education	0.015 (0.003, <0.001)
	TOMM40 S/S & APOE e3/3	0.077 (0.040, 0.052)
	TOMM40 S/L or VL/L & APOE e3/4	0.006 (0.030, 0.831)
	TOMM40 L/L & APOE e4/4	-0.020 (0.062, 0.739)
	TOMM40 S/S & APOE e3/3 * Time	-0.017 (0.015, 0.257)
	TOMM40 S/L or VL/L & APOE e3/4 * Time	-0.013 (0.011, 0.229)
	TOMM40 L/L & APOE e4/4 * Time	0.017 (0.023, 0.466)

* Bold numbers are significant effects.

Figure 1. LOWESS curves of cognitive progression for different TOMM40'523 genotypes among APOE ε3/3 carriers



A: global cognition; B: episodic memory; C: working memory; D: semantic memory; E: perceptual speed; F: visuospatial ability.

Discussion

The association between TOMM40'523 variant and cognitive performance is inconclusive. Bakeberg et al. found that the short '523 allele was associated with more severe cognitive decline; while Watts et al. reported that '523 short alleles in APOE ε3 homozygotes was only associated with lower baseline cognitive performance and not with the longitudinal cognitive changes (22, 27). These inconsistencies might be potentially due to population heterogeneity. A prior study by Chiba-Falek et al. examined published studies APOE-independent association of the TOMM40'523 with numerous LOAD-related phenotypes by including APOE genotypes as a covariate in the statistical models or by designing the study to include only individuals with the same APOE genotypes (e.g., analyzing the association in the APOE 33/33 stratum) (28). The study concluded that the identity of the TOMM40 poly-T risk allele depended on the phenotype being evaluated, the ages of the study subjects at the time of assessment, and the context of the APOE genotypes (29).

Our findings are broadly consistent with the previous report that the TOMM40'523-S/S genotype in APOE ε3/3 carriers was associated with accelerated rates of cognitive decline when compared to APOE ε3/3 carriers with TOMM40'523-S/VL and VL/VL genotypes (21), although the domains mostly impacted differed in that report to the present study and included episodic memory and expressive language. Methodological differences across the studies in terms of the length of overall observation in the cohorts (up to 4 years in TOMMORROW vs 20+ years in ROS-MAP dataset) and the frequency of measurement (every 6 months in TOMMORROW trial vs annual observations in ROS-MAP) as well as other sample differences (clinical trial cohort vs community cohorts) and age differences with ROS-MAP much older may explain the differences in the cognitive domains mostly affected across the genotypic groups (21, 25).

The biological mechanism underlying the association of TOMM40'523 S allele and cognitive decline is still unclear. Prior evidence suggests that the '523 variant may act as protective against the effect of APOE ε4 on the level of cerebrospinal fluid neurofilament light proteins and is associated with lower white matter integrity (30, 31). Zeitlow et al. reported that the very long allele in poly-T results in higher expression than the short allele in poly-T in luciferase expression systems, and Tom40 over-expression can enhance mitochondrial efficiency and protect cells against beta-amyloid-induced cellular damage (32). Chemical crosslinking demonstrated that the APP preprotein interacts with the Tom40, Tim44 and Tim23 and arrests in the import channels, resulting in reduced respiration and reduced membrane potential (33). The accumulation of APP across the import channels may also contribute to AD pathology by inhibiting mitochondrial import and increasing hydrogen peroxide production (34). Several studies have pointed to a role for

the TOMM40'523 allele in gene regulation and expression of both TOMM40 and APOE (29, 35-37).

The study population on average are older and more educated than the general population. Our findings need to be replicated in other studies before applying to the general population. Additionally, the current study is restricted to white populations of primarily European ancestry. Nuytemans et al. showed that there was differential regulatory control of APOE -e4 on African versus European haplotypes, including identification of genomic regions in introns 2-3 of TOMM40 that are strong candidates as factors contributing to differential APOE expression (38). Considering different APOE-TOMM40'523 linkage patterns between individuals with different genetic ancestry, it will be helpful to reveal the independent role of the TOMM40'523 variant in diverse populations studied over several years to assess cognitive change in the future. The TOMMORROW study did not evaluate amyloid evaluation in preclinical AD patients, which is an important factor that may affect the rate of cognitive decline among different genotype groups. For example, APOE genotype is related to steeper decline in memory and language functioning in individuals with abnormal amyloid-β (39). Hence, future studies that incorporate amyloid evaluation in preclinical AD patients from diverse populations are needed to better understand the role of amyloid burden and genetic factors in predicting cognitive decline and developing targeted interventions for AD.

In this study, we applied linear mixed models (LMM) to assess the effect of APOE 4 alleles on cognitive decline, the association of TOMM40'523 variant on cognitive decline among APOE ε3/3 carriers, and the effect of various haplotypes of APOE and TOMM40'523 on cognitive decline. For participants with APOE ε4/4 genotypes, we found they had worse cognitive scores in global cognition, episodic memory, and executive function domains when compared to APOE ε3/3 carriers. The APOE ε3/3 and 523 S/S haplotype was associated with better global cognition and slower/worse progression rate in global cognition, executive function, and attentional processing domains as compared to APOE ε3/3 genotype with TOMM40'523-S/VL and VL/VL genotypes and compared to the APOE ε3/4 and APOE ε4/4 genotypes. Older age and fewer years of education were associated with significantly worse global cognition and performance across the five individual cognitive domains (episodic memory, executive function, expressive language, attentional processing, and visuospatial function). Controlling for the genetic variability introduced by the APOE-TOMM40 haplotype will be important in clinical trials designed to slow the rate of cognitive decline and/or prevent symptom onset in preclinical AD.

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Ethical standards: This study used the existing and de-identified TOMMORROW study datasets. There is no patient contact and no health risk to the subjects under study. This study was approved by the Institutional Review Board of Duke University.

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