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RESEARCH ARTICLE

Associations between *APOE-TOMM40 '523* haplotypes and limbic system white matter microstructure

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Abstract

INTRODUCTION: We assessed associations between apolipoprotein E Translocase of Outer Mitochondrial Membrane 40 (*APOE-TOMM40*)-'523 haplotypes and white matter microstructure (WMM) across limbic tracts important for memory and cognition in non-Hispanic Black and White individuals.

METHODS: Linear regression models, stratified by *APOE* and racialized groups, assessed associations between *TOMM40*-'523-S and limbic tract WMM free-water (FW) and free-water-corrected fractional anisotropy (FAFWcorr).

RESULTS: Black-ε4+-one-'523-S carriers had lower FW in the cingulum and inferior longitudinal fasciculus compared to Black-ε4+-no-'523-S carriers. Additionally, Black-ε4+-one-'523-S carriers had lower FW in the cingulum, uncinate, and fornix, and higher FA_{FWcorr} in the uncinate compared to Black-ε4+-'523-S/S carriers. White-ε3/ε3-'523-S/S carriers had lower FAFWcorr in the cingulum and inferior temporal gyrus compared to White-ε3/ε3-no-'523-S carriers, and lower FAFWcorr in the cingulum compared to White-ε3/ε3-one-'523-S carriers.

DISCUSSION: This supports prior work that '523-S is associated with abnormal aging in White-ε3/ε3 carriers, but is potentially risk-mitigating in Black-ε4+ carriers, while suggesting a differential effect by racialized background of *APOE* on WMM.

KEYWORDS
aging, Alzheimer's disease (AD), APOE, diffusion magnetic resonance imaging (dMRI), free water corrected metrics, genetic risk factors, limbic system tracts, Minority Aging Research Study, Rush Memory and Aging Project, TOMM40, white matter microstructure (WMM)

Highlights

- White matter microstructure (WMM) across limbic tracts important for cognition was measured by diffusion MRI.
- Black apolipoprotein E (APOE) ε4+ carriers with one copy of TOMM40-'523-S had normal aging WMM metrics across several tracts, including the cingulum bundle, uncinate fasciculus, fornix, and inferior longitudinal fasciculus.
- White APOE ε3/ε3 carriers with two copies of TOMM40-'523-S had abnormal aging WMM metrics in the cingulum bundle and inferior temporal gyrus.
- APOE associations with aging may differ in racialized groups due to TOMM40-'523-S copy number.

1 | BACKGROUND

Black Americans are more likely to develop cognitive impairment (CI) and Alzheimer's disease and related dementias (ADRD) relative to White Americans.[1,2] Furthermore, predictors of CI and AD may have different effects across race. Despite this knowledge, most research studies are done primarily in White individuals. For instance, the ε4 allele of the apolipoprotein E (*APOE*) gene is the largest genetic risk factor for sporadic AD, but research suggests the allele is less predictive of AD in Black individuals.[3,4] *APOE* is in linkage disequilibrium with its upstream neighbor, the Translocase of Outer Mitochondrial Membrane 40 (*TOMM40*) gene. The rs10524523 ('523) locus in *TOMM40* consists of variable length poly-T repeats: short with ≤19 repeats (S), long with 20-29 repeats (L), or very long with ≥30 repeats (VL).[5] The *APOE*-ε3 allele, associated with normal brain aging, is in linkage disequilibrium with '523-S and '523-VL in both White and Black individuals.[5–7] The *APOE*-ε4 allele, associated with abnormal brain aging, is in linkage disequilibrium with '523-L in White individuals.[5–7] Interestingly, the *APOE*-ε4 allele is in linkage disequilibrium with '523-S, '523-L, and '523-VL in Black individuals.[8–10] This heterogeneity in *APOE-TOMM40 '523* haplotypes has been shown to contribute differentially to cognitive decline and AD risk profiles.[10] Black ε3/ε3 and White ε3/ε3 individuals homozygous for *TOMM40* '523-S ('523-S/S) have faster rates of cognitive decline than Black ε3/ε3 and White ε3/ε3 individuals without '523-S/S, respectively.[10] Black ε4+ individuals who carry a '523-S have slower rates of cognitive decline than Black ε4+ '523-S non-carriers.[10] This *APOE-TOMM40 '523* haplotype variability may explain why *APOE* independently does not predict AD or cognitive decline as strongly in Black individuals. To expand the field's current understanding of how *APOE-TOMM40 '523* is associated with phenotypes of aging in Black individuals, we investigated how these haplotype variants are associated with metrics representative of the structural microstructure of the brain's white matter.

White matter microstructure (WMM) is a well-characterized marker assessed through diffusion magnetic resonance imaging (dMRI) and can act as a reliable predictor of brain health and aging.[11–17] WMM in the limbic system, which is composed of tracts that are important for memory and cognition, is highly vulnerable to decline in cases of abnormal aging.[17–33] Despite its importance in aging and brain health, WMM in Black individuals remains very understudied.

There currently exists a large gap in our understanding of how genetic risk factors contribute to CI and AD in Black individuals. For this reason, our study aimed to further understand how *TOMM40* '523 poly-T repeat lengths act as a genetic risk factor by elucidating whether *APOE-TOMM40 '523* variants are correlated with limbic system WMM, in a cohort largely comprised of cognitively normal (CN) Black individuals. Studying the effects of genetic risk factors on these quantifiable brain metrics prior to CI/AD symptomology offers the opportunity for our work to identify those at risk who may benefit from more targeted therapies designed to potentially slow or prevent onset of CI/AD. Consistent with prior studies of cognition,[10] we hypothesized that in non-Hispanic Black and non-Hispanic White ε3/ε3 individuals, '523-S/S would have limbic tract WMM metrics indicative of abnormal aging when compared to non-Hispanic Black and non-Hispanic White ε3/ε3 individuals without '523-S/S, respectively. Additionally, we hypothesized that non-Hispanic Black ε4+ individuals with one-'523-S or '523-S/S would have limbic tract WMM metrics indicative of normal aging, when compared to non-Hispanic Black ε4+ individuals with no-'523-S.

2 | METHODS

2.1 | Participants

This study included participants from two community-based cohorts, the Rush Memory and Aging Project (MAP) and the Minority Aging Research Study (MARS),[34–36] The MAP cohort is a longitudinal clinical study of chronic conditions associated with aging, with an emphasis on cognitive decline and AD.[36] The MARS cohort is a longitudinal clinical study of cognitive decline and risk for AD in older African Americans.[34] Both cohorts recruited participants who were 65 years or older without dementia at time of enrollment.[34–36] Participants were included in the present study if they had dMRI scans ($N = 853$), self-identified as non-Hispanic Black (henceforth referred to as Black) or non-Hispanic White (henceforth referred to as White) (Black = 209; White = 644), had *APOE* and *TOMM40 '523* poly-T repeat genotype information available (Black = 144; White = 500), and had demographic data including age (years), sex/gender, education (years), and a clinical diagnosis [no CI, mild CI (MCI), AD]. Our final analytic sample focused within Black *APOE* ε3/ε3 ($N = 83$), Black *APOE* ε4+ ($N = 35$), and White *APOE* ε3/ε3 ($N = 327$) carriers. All studies were approved by an Institutional Review Board at the Rush University Medical Center and written informed consent was acquired for each participant.

2.2 | Clinical diagnosis

Clinical evaluation of cognitive status was conducted using a three-stage process, including computer scoring of 19 cognitive assessments, clinical judgment by a neuropsychologist, and diagnostic classification made by a clinician. The 19 neuropsychological assessments of cognition are used to capture each individual's episodic memory (seven test scores), semantic memory (three test scores), working memory (three test scores), perceptual speed (four test scores), visuospatial ability (two test scores), and global cognition (average of standardized individual test scores). Alzheimer's dementia required a history of cognitive decline, impairment in memory, and at least one other cognitive domain. Diagnosis of MCI was rendered for persons who were judged to have CI by a neuropsychologist but did not meet criteria for dementia by the clinician. Persons diagnosed with MCI may also have been diagnosed with another condition that contributed to CI. Persons without dementia or MCI were considered CN.[34,36]

2.3 | Genotyping

APOE alleles were genotyped using polymorphisms at the rs429358 and rs7412 loci at exon 4 of the *APOE* gene, while *TOMM40 '523* poly-T repeat variants were genotyped at the rs10524523 locus at intron 6 of the *TOMM40* gene.[37,38] DNA was obtained from peripheral blood samples or from frozen postmortem brain tissue.[37,38] Black participants were classified as ε4 carriers (ε4+) if at least one ε4 allele was present (ε3/ε4, ε4/ ε4) ($N = 35$). ε2/ε4 participants were excluded from the present analysis, as the effects of this group remain unclear (Black = 8; White = 11). ε2/ε2 (Black = 1; White = 3) and ε2/ε3 (Black = 17; White = 59) participants were excluded from the study because of small sample sizes and unknown haplotype association between ε2 and '523 variants. White ε4+ individuals, ε3/ε4 ($N = 91$) and ε4/ε4 ($N = 9$), were also not included in this study, due to a lack of *APOE*-ε4-*TOMM40*-'523 haplotype heterogeneity in this population. *TOMM40 '523* poly-T repeat length was defined as: ≤19 repeats = Short (S), 20-29 repeats = Long (L), ≥30 repeats = Very Long (VL) as previously defined.[5] *TOMM40 '523* variants were further grouped by the number of copies of the '523-S variant: no S-variant = no-'523-S, one '523-S = one-'523-S, and homozygous for '523-S = '523-S/S.

2.4 | dMRI acquisition, preprocessing, tract fitting, harmonization, and metrics

Only baseline MRI data was used for this study. Diffusion MRI data were acquired using three distinct site × scanner × protocol combinations: a 1.5T GE Signa system with 12 b-vectors at a b-value of 900 s/mm^2, and a 3T Siemens MAGNETOM TrioTim system with 45 b-vectors at a b-value of 1000 s/mm^2, used at two separate sites. All dMRI data were preprocessed using the *PreQual* pipeline, a freely available containerized pipeline (https://github.com/MASILab/PreQual), which combined integrated preprocessing methods with quality control assurance for diffusion-weighted MRI (DWI).[39] *PreQual* processes and corrects DWI images and then produces summary statistics, including volume trends as well as qualitative and quantitative quality assurance that are ready for secondary analysis in a culminated PDF report.[39] All quality control PDFs from *PreQual* were manually inspected by researchers at Vanderbilt University Medical Center, and any participants with poor image quality were excluded from our current analyses. Once preprocessed through *PreQual* and manually inspected, all data were then input into DTIFIT in FSL (version 6.0.1.) to calculate conventional diffusion MRI metrics,[40] including fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. The preprocessed data were further processed in custom written MATLAB (*version R2019a*) scripts to calculate free-water (FW) corrected metrics, including FW-corrected fractional anisotropy (FA_{FWcorr}), FW-corrected mean diffusivity (MD_{FWcorr}), FW-corrected axial diffusivity (AxD_{FWcorr}), and FW-corrected radial diffusivity (RD_{FWcorr}).[41] The present study focused on FW and FA_{FWcorr} metrics to assess WMM, as both have demonstrated high sensitivity in previous research which compared normal and abnormal aging brains, with FW metrics being particularly sensitive to detecting decline in cases of abnormal aging.[17,41] Additional analyses with MD_{FWcorr}, RD_{FWcorr}, AxD_{FWcorr}, and conventional uncorrected MD, RD, AD, and FA metrics were also included.

Conventional FA values as well as FA_{FWcorr} range from 0 to 1, where higher FA_{FWcorr} values are indicative of directionally constrained fluid whose flow is oriented preferentially rather than randomly in

space.[17,29,41] Higher FA_{FWcorr} within a voxel is typically associated with normal aging. FW values range from 0 to 1, where high FW within a voxel indicates heightened levels of random fluid movement in the extracellular space, possibly indicative of disruption to the brain tissue at a microstructural level, inflammation, or neurodegenerative processes . Lower FW within a voxel is indicative of less random fluid movement and is generally associated with normal aging. Although similar, high FW is distinct from low FA_{FWcorr}. High FW reflects increased extracellular, unrestricted fluid diffusion, often associated with neuroinflammation or tissue damage, while low FA_{FWcorr} measures reduced intracellular directional organization of fluid diffusion, indicative of compromised structural integrity in axonal tracts. Overall, these two metrics capture distinct aspects of tissue microstructure.

Tractography templates used were drawn from existing resources and are publicly available through a GitHub repository (https://github.com/VUMC-VMAC/Tractography_Templates). In this present study, we analyze the microstructure of five white matter tracts projecting from the limbic system due to their susceptibility for exacerbated WMM decline in abnormal agers, shown in prior work.[17] Specific tracts within the limbic system included in our analysis were the inferior longitudinal fasciculus (ILF), cingulum bundle, fornix, inferior temporal gyrus transcallosal tract, and uncinate fasciculus (UF). FW and FA_{FWcorr} WMM metrics for all five of the above tracts were calculated, resulting in 10 unique values for each participant included in our present analyses. These values were then harmonized using *Longitudinal ComBat* in R v4.1.0.[42] In the harmonization, a batch variable controlled for any possible combination of *site x scanner x protocol* used.[17,42] To control for heterogeneity in diffusion MRI acquisitions, *Longitudinal ComBat* was conducted in a large-scale dataset which included 5144 participants across 10,346 longitudinal sessions. In this harmonization approach, we controlled for 34 unique batches, which represent unique scanner × site × protocol combinations, and we harmonized across 432 different imaging features. Following harmonization, we subset our dataset to include our participants of interest. This approach allows us to harmonize our dataset with the most statistical power. Additionally, our study design minimized scanner variability, as the MARS cohort (Black participants) and MAP cohort (primarily White participants) used different scanners, and analyses were stratified by racialized group, eliminating scanner heterogeneity as a confounder.

2.5 | Covariates

Age at time of MRI scan was used. Education was measured by the number of years of formal schooling one reported receiving. Sex/gender (male, female) and ethnicity (Latino, yes/no) were both self-reported. Female and CN participants served as our reference groups. Only Black and White participants who selected "No" for ethnicity "Latino" were included in the present study. Clinical diagnosis was dichotomized, such that CN participants were assigned a value of 0 and acted as our reference group, while participants with MCI or AD were assigned a value of 1.

2.6 | Statistical analysis

Demographic differences were assessed using one-way analyses of variance (ANOVAs) for continuous variables and chi-squared tests for categorical variables. Linear regression models were used to determine the effect of '523-S copy number on FW and FA_{FWcorr} metrics in five limbic system tracts of interest, stratified by *APOE* status (ε3/ε3 or ε4+) and self-identified racialized group (Black or White), where those with no-'523-S were the reference group using the following model:

Limbic Tract FW or FA_{FWcorr} Metrics (5 Limbic Tracts) ~ '523-S Copy Number + centered age + sex + centered education + clinical diagnosis

Additional analyses were run with MD_{FWcorr}, RD_{FWcorr}, AxD_{FWcorr}, and conventional uncorrected MD, RD, AD, and FA metrics as the outcome variables. All models included covariates for centered age (Black = 71.74 years; White = 77.79 years), centered education (Black = 15.16 years; White = 15.74 years), sex/gender, and clinical diagnosis, and performed using R v4.2.3.

3 | RESULTS

3.1 | Demographics

Participant demographics are summarized in Table 1. Although no significant differences were found within stratified groups, Black ε4+ no-'523-S carriers on average were younger and had higher education than Black ε4+ one-'523-S and Black ε4+ '523-S/S carriers. Black ε3/ε3 one-'523-S carriers on average were younger and were more likely to be CN than Black ε3/ε3 no-'523-S and ε3/ε3 '523-S/S. White ε3/ε3 one-'523-S carriers on average were more likely to be female than White ε3/ε3 no-'523-S and ε3/ε3 '523-S/S carriers.

3.2 | '523-S associations with WMM metrics in limbic tracts of interest

Black ε4+ carriers with one-'523-S had lower cingulum bundle FW ($\beta = -0.027$, SE = 0.009, $p = 0.007$) and lower ILF FW ($\beta = -0.033$, SE = 0.013, $p = 0.017$), compared to Black ε4+ carriers with no-'523-S (Table 2, Figure 1). Black ε4+ carriers with '523-S/S had higher UF FW ($\beta = 0.030$, SE = 0.012, $p = 0.019$), higher fornix FW ($\beta = 0.040$, SE = 0.015, $p = 0.013$), and higher cingulum bundle FW ($\beta = 0.014$, SE = 0.006, $p = 0.043$), compared to Black ε4+ carriers with one-'523-S (Figure 1). Finally, Black ε4+ carriers with '523-S/S had lower UF FAFWcorr ($\beta = -0.015$, SE = 0.007, $p = 0.042$), compared to Black ε4+ carriers with one-'523-S (Figure 1).

White ε3/ε3 carriers with '523-S/S had lower cingulum FAFWcorr ($\beta = -0.006$, SE = 0.003, $p = 0.027$) and lower inferior temporal gyrus FAFWcorr ($\beta = -0.007$, SE = 0.003, $p = 0.042$), compared to White ε3/ε3 carriers with no- '523-S (*Table 3*, Figure 2). White ε3/ε3 carriers with one-'523-S had lower cingulum bundle FAFWcorr ($\beta = 0.005$, SE = 0.002, $p = 0.035$), compared to White ε3/ε3 carriers with '523-S/S

TABLE 1 Participant demographics.

	Black ε3/ε3 participants				Black ε4+ participants				White ε3/ε3 participants			
Parameter	**no-'523-S**	**one-'523-S**	**'523-S/S**	***p*-value**	**no-'523-S**	**one-'523-S**	**'523-S/S**	***p*-value**	**no-'523-S**	**one-'523-S**	**'523-S/S**	***p*-value**
N	12	31	40		6	16	13		82	149	96	
Years of age (SD)	72.55 (5.08)	70.42 (3.20)	72.91 (6.61)	0.146	68.95 (3.23)	72.21 (4.90)	71.26 (5.06)	0.368	78.18 (6.61)	77.70 (7.28)	77.58 (7.44)	0.837
Years of education (SD)	14.75 (3.02)	15.03 (2.56)	14.98 (3.63)	0.966	17.67 (3.01)	15.56 (2.76)	14.77 (1.92)	0.081	15.32 (3.12)	15.80 (3.40)	16.02 (3.04)	0.338
Female (%)	11 (91.7)	23 (74.2)	34 (85)	0.32	5 (83.3)	14 (87.5)	10 (76.9)	0.754	61 (74.4)	119 (79.9)	64 (66.7)	0.068
CN (%)	9 (75)	28 (90.3)	34 (85)	0.436	5 (83.3)	12 (75)	10 (76.9)	0.917	65 (79.3)	124 (83.2)	81 (84.4)	0.643
Limbic system WMM (SD)												
Cingulum FW	0.24 (0.03)	0.24 (0.02)	0.25 (0.03)	0.194	0.26 (0.02)	0.24 (0.02)	0.25 (0.03)	0.129	0.25 (0.02)	0.25 (0.03)	0.26 (0.03)	0.815
Cingulum FA_{FWcorr}	0.49 (0.02)	0.49 (0.02)	0.49 (0.02)	0.637	0.49 (0.02)	0.50 (0.02)	0.49 (0.03)	0.334	0.49 (0.02)	0.49 (0.02)	0.49 (0.02)	0.16
Inferior temporal gyrus FW	0.26 (0.04)	0.24 (0.03)	0.25 (0.03)	0.309	0.24 (0.02)	0.23 (0.02)	0.25 (0.03)	0.357	0.25 (0.03)	0.25 (0.03)	0.25 (0.03)	0.378
Inferior temporal gyrus FA_{FWcorr}	0.61 (0.02)	0.61 (0.02)	0.61 (0.02)	0.709	0.61 (0.02)	0.61 (0.03)	0.60 (0.03)	0.762	0.61 (0.02)	0.60 (0.02)	0.60 (0.03)	0.238
Uncinate fasciculus FW	0.28 (0.03)	0.27 (0.04)	0.28 (0.04)	0.724	0.28 (0.03)	0.27 (0.03)	0.30 (0.05)	0.108	0.29 (0.04)	0.29 (0.03)	0.28 (0.04)	0.733
Uncinate fasciculus FA_{FWcorr}	0.42 (0.02)	0.43 (0.02)	0.42 (0.02)	0.376	0.42 (0.01)	0.43 (0.02)	0.42 (0.03)	0.135	0.42 (0.02)	0.42 (0.02)	0.42 (0.02)	0.959
Fornix FW	0.47 (0.06)	0.45 (0.05)	0.46 (0.04)	0.302	0.45 (0.04)	0.43 (0.04)	0.46 (0.06)	0.155	0.48 (0.05)	0.48 (0.05)	0.48 (0.05)	0.683
Fornix FA_{FWcorr}	0.45 (0.02)	0.45 (0.02)	0.44 (0.02)	0.307	0.43 (0.01)	0.45 (0.02)	0.44 (0.03)	0.213	0.44 (0.02)	0.44 (0.03)	0.44 (0.03)	0.908
Inferior longitudinal fasciculus FW	0.24 (0.03)	0.24 (0.03)	0.25 (0.04)	0.215	0.26 (0.03)	0.24 (0.03)	0.25 (0.04)	0.249	0.25 (0.03)	0.25 (0.04)	0.26 (0.04)	0.794
Inferior longitudinal fasciculus FA_{FWcorr}	0.46 (0.02)	0.46 (0.02)	0.46 (0.02)	0.469	0.46 (0.02)	0.47 (0.02)	0.46 (0.03)	0.494	0.46 (0.02)	0.46 (0.02)	0.46 (0.02)	0.357

Note: Data given as mean (SD).

Abbreviations: CN, cognitively normal; SD, standard deviation; WMM, white matter microstructure.

TABLE 2 Associations between '523-S copy number and WMM metrics in limbic system tracts in non-Hispanic Black ε4+ participants.

Parameter	Cingulum	Inferior temporal gyrus	Uncinate fasciculus	Fornix	Inferior longitudinal fasciculus
Free water (FW)					
Intercept	0.2570 (0.0082) 31.19, *< 0.001*	0.2437 (0.0104) 23.44, *< 0.001*	0.2712 (0.0144) 18.80, *< 0.001*	0.4548 (0.0180) 25.25, *< 0.001*	0.2616 (0.0114) 22.97, *< 0.001*
One-'523-S	−0.0272 (0.0093) -2.93, *0.007*	−0.0190 (0.0117) −1.62, 0.1155	−0.0117 (0.0163) −0.72, 0.4766	−0.0350 (0.0203) −1.72, 0.0958	−0.0327 (0.0128) −2.55, *0.017*
'523-S/S	−0.0136 (0.0097) −;1.39, 0.175	−0.0027 (0.0123) −0.22, 0.830	0.0183 (0.0170) 1.07, 0.294	0.0050 (0.0213) 0.23, 0.817	−0.0180 (0.0135) −1.34, 0.192
Years of education	0.0007 (0.0013) 0.57, 0.575	0.0005 (0.0017) 0.33, 0.748	0.0007 (0.0023) 0.30, 0.765	−0.0008 (0.0029) −;0.28, 0.782	0.0004 (0.0018) 0.24, 0.812
Years of age	0.0023 (0.0007) 3.30, *0.003*	0.0029 (0.0009) 3.25, *0.003*	0.0032 (0.0012) 2.62, *0.014*	0.0035 (0.0015) 2.27, *0.031*	0.0034 (0.0010) 3.52, *0.002*
Sex (male)	0.0133 (0.0088) 1.51, 0.142	0.0154 (0.0111) 1.38, 0.178	0.0391 (0.0154) 2.53, *0.017*	−0.0293 (0.0193) −;1.52, 0.1407	0.0314 (0.0122) 2.58, *0.016*
Clinical diagnosis	0.0181 (0.0078) 2.33, *0.027*	0.0197 (0.0098) 2.00, 0.055	0.0284 (0.0136) 2.08, *0.047*	0.0433 (0.0170) 2.54, *0.017*	0.0147 (0.0108) 1.37, 0.182
Free water corrected fractional anisotropy (FA FW-Corr)					
Intercept	0.4816 (0.0085) 56.88, *< 0.001*	0.6006 (0.0114) 52.74, *< 0.001*	0.4171 (0.0094) 44.30, *< 0.001*	0.4308 (0.0093) 46.45, *< 0.001*	0.4536 (0.0092) 49.54, *< 0.001*
One-'523-S	0.0148 (0.0095) 1.55, 0.131	0.0085 (0.0128) 0.66, 0.515	0.0108 (0.0106) 1.02, 0.318	0.0193 (0.0105) 1.85, *0.076*	0.0128 (0.0103) 1.24, 0.226
'523-S/S	0.0033 (0.0100) 0.33, 0.741	−0.0016 (0.0135) −0.12, 0.904	−0.0052 (0.0111) −0.47, 0.644	0.0081 (0.0110) 0.74, 0.468	0.0061 (0.0108) 0.56, 0.580
Years of education	0.0006 (0.0014) 0.45, 0.658	−0.0009 (0.0018) −0.51, 0.611	−0.0003 (0.0015) −0.22, 0.825	−0.0001 (0.0015) −0.04, 0.973	0.000001 (0.0015) 0.001, 0.999
Years of age	−0.0005 (0.0007) −;0.69, 0.498	−0.0014 (0.0010) −1.41, 0.169	−0.0001 (0.0008) −0.08, 0.939	−0.0003 (0.0008) −;0.41, 0.686	−0.0011 (0.0008) −1.35, 0.188
Sex (male)	0.0205 (0.0091) 2.26, *0.032*	0.0139 (0.0122) 1.14, 0.264	0.0086 (0.0101) 0.85, 0.401	0.0175 (0.0099) 1.76, 0.089	−0.0046 (0.0098) −0.47, 0.645
Clinical diagnosis	0.0049 (0.0080) 0.62, 0.543	0.0018 (0.0108) 0.16, 0.871	0.0073 (0.0089) 0.82, 0.419	−0.0116 (0.0088) −;1.32, 0.198	0.0083 (0.0086) 0.96, 0.344

Note: Beta coefficients (SE) *T*−values, *p*−values.
p−Values < 0.05 are italicized.
Abbreviations: SE, standard error; WMM, white matter microstructure.

(Figure 2). Finally, '523-S copy number was not associated with any limbic tract WMM metrics in Black ε3/ε3 participants (Table 4). '523 associations with RD, MD, AD, FA, MD_{FWcorr}, RD_{FWcorr}, and AxD_{FWcorr} can be found in Table S1 (Black ε4+), Table S2 (White ε3/ε3), and Table S3 (Black ε3/ε3).

4 | DISCUSSION

To our knowledge, this is the first study examining the associations between *APOE-TOMM40 '523* haplotype variants and WMM in Black individuals using FW-corrected metrics. Results from the present analysis point to an association between '523-S copy number and limbic system tract WMM. We found that '523-S is associated with limbic tract WMM metrics indicative of abnormal aging in White ε3/ε3 individuals and limbic tract WMM metrics indicative of normal aging in Black ε4+ individuals, reinforcing prior findings that '523-S may have adverse effects when inherited with *APOE*−ε3 for White individuals, but have protective effects when inherited with *APOE*−ε4 for Black individuals.[10,38]

In White ε3/ε3 carriers, we saw that '523-S/S was associated with lower cingulum bundle and inferior temporal gyrus FA_{FWcorr}, compared to those White ε3/ε3 no-'523-S carriers. Additionally, we saw differences between White ε3/ε3-one-'523-S and White ε3/ε3-'523-S/S, where '523-S/S carriers had lower cingulum bundle FA_{FWcorr}. The cingulum bundle's role in cognition is well established in diffusion imaging studies.[15,18,20,21,43,44] The cingulum is important for memory performance, executive functioning, language, and attention, with abnormal cingulum bundle microstructure observed in individuals with MCI or AD.[15,18,26] Additionally, the inferior temporal gyrus is known for its involvement in higher cognitive functioning and visual processing, with atrophy shown to predict future risk of AD in CN individuals.[45] Lower

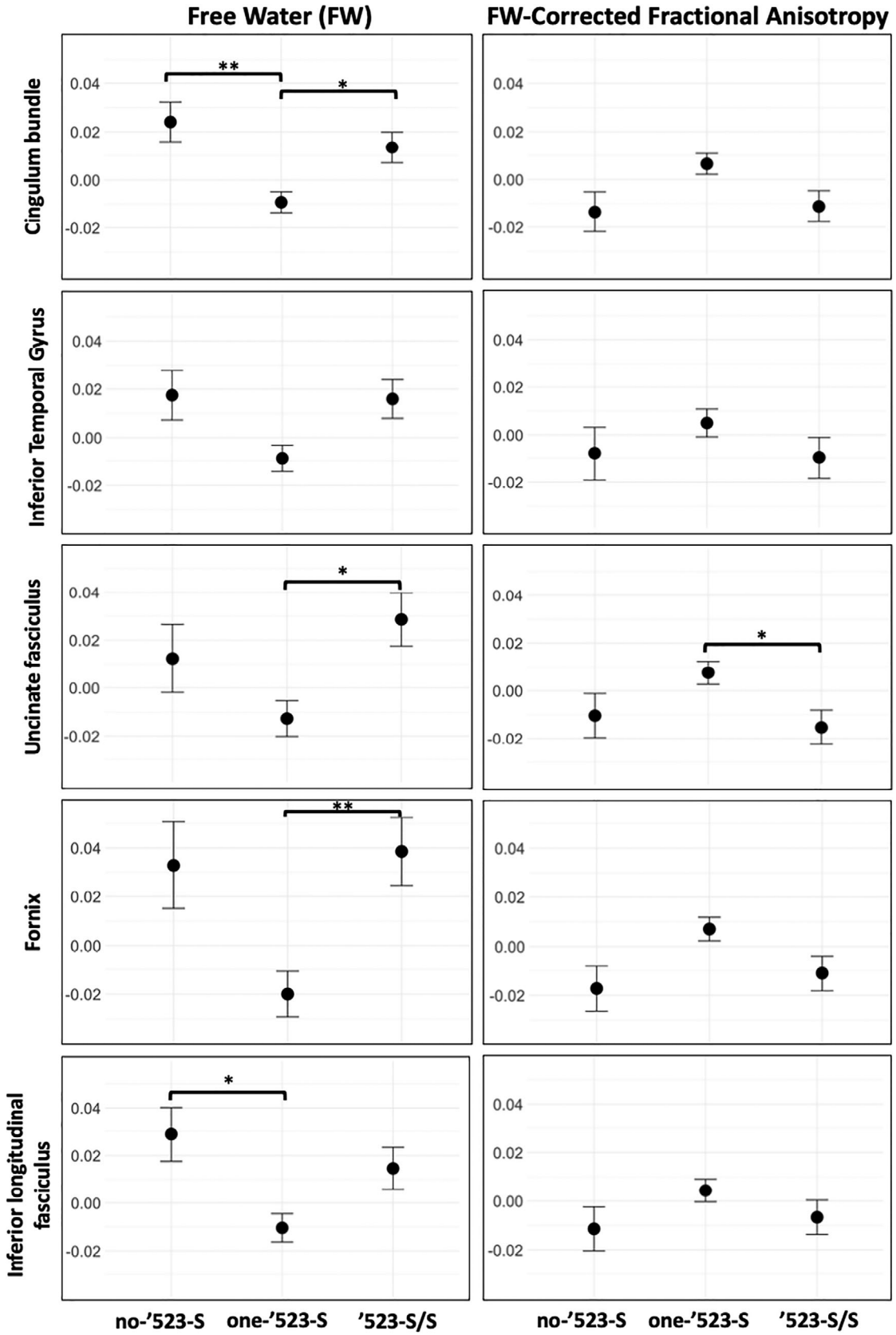

FIGURE 1 Residualized beta estimates of '523-S copy number and WMM metrics across limbic system tracts in non-Hispanic Black ε4+ participants, adjusted by age, sex, education, and clinical diagnosis. *p*–values < 0.05 are shown with *, *p*–values < 0.01 are shown with **. WMM, white matter microstructure.

TABLE 3 Associations between '523-S copy number and WMM metrics in limbic system tracts in non-Hispanic White ε3/ε3 participants.

Parameter	Cingulum	Inferior temporal gyrus	Uncinate fasciculus	Fornix	Inferior longitudinal fasciculus
Free water (FW)					
Intercept	0.2460 (0.0029) 84.64, *< 0.001*	0.2477 (0.0031) 80.32, *< 0.001*	0.2847 (0.0039) 72.59, *< 0.001*	0.4754 (0.0046) 103.41, *< 0.001*	0.2503 (0.0036) 69.49, *< 0.001*
One-'523-S	0.0021 (0.0033) 0.63, 0.532	−0.0022 (0.0036) −0.61, 0.540	0.0016 (0.0045) 0.36, 0.716	−0.0028 (0.0053) −0.52, 0.602	−0.0004 (0.0042) −0.09, 0.925
'523-S/S	0.0038 (0.0037) 1.03, 0.304	0.0028 (0.0039) 0.73, 0.466	−0.0014 (0.0050) −0.28, 0.779	−0.0015 (0.0058) −0.26, 0.793	0.0024 (0.0045) 0.52, 0.606
Years of education	0.0002 (0.0004) 0.40, 0.690	0.00001 (0.0005) 0.01, 0.989	−0.0012 (0.0006) −2.08, *0.038*	−0.0001 (0.0007) −0.21, 0.833	−0.0002 (0.0005) −0.46, 0.649
Years of age	0.0017 (0.0002) 8.49, *< 0.001*	0.0019 (0.0002) 8.79, *< 0.001*	0.0017 (0.0003) 6.23, *< 0.001*	0.0035 (0.0003) 10.88, *< 0.001*	0.0022 (0.0002) 8.99, *< 0.001*
Sex (male)	0.0010 (0.0031) 0.33, 0.741	0.0028 (0.0033) 0.85, 0.396	0.0016 (0.0042) 0.37, 0.712	0.0112 (0.0050) 2.26, *0.025*	0.0044 (0.0039) 1.14, 0.256
Clinical diagnosis	0.0070 (0.0037) 1.91, 0.057	0.0031 (0.0039) 0.79, 0.429	0.0061 (0.0050) 1.22, 0.222	0.0127 (0.0058) 2.17, *0.031*	0.0093 (0.0046) 2.04, *0.043*
Free water corrected fractional anisotropy (FA FW-Corr)					
Intercept	0.4888 (0.0021) 233.33, *< 0.001*	0.6080 (0.0025) 239.68, *< 0.001*	0.4196 (0.0022) 188.61, *< 0.001*	0.4378 (0.0026) 165.74, *< 0.001*	0.4619 (0.0022) 205.51, *< 0.001*
One-'523-S	−0.0010 (0.0024) -0.42, 0.677	−0.0038 (0.0029) −1.31, 0.193	−0.0005 (0.0026) −0.21, 0.837	−0.0001 (0.0030) −0.03, 0.979	−0.0021 (0.0026) −0.80, 0.422
'523-S/S	−0.0059 (0.0026) -2.23, *0.027*	−0.0065 (0.0032) −2.04, *0.042*	−0.0014 (0.0028) −0.51, 0.609	−0.0011 (0.0033) −0.34, 0.737	−0.0051 (0.0028) −1.80, 0.072
Years of education	0.0005 (0.0003) 1.60, 0.110	0.0004 (0.0004) 1.03, 0.305	0.0006 (0.0003) 1.84, 0.067	0.0005 (0.0004) 1.32, 0.189	0.0004 (0.0003) 1.32, 0.188
Years of age	−0.0003 (0.0001) -2.33, *0.020*	−0.0011 (0.0002) −6.05, *< 0.001*	−0.0003 (0.0002) −1.74, 0.082	−0.0015 (0.0002) −8.30, *< 0.001*	−0.0006 (0.0002) −3.77, *0.0002*
Sex (male)	0.0063 (0.0023) 2.78, *0.006*	−0.0015 (0.0027) −0.55, 0.583	0.0104 (0.0024) 4.35, *< 0.001*	−0.0031 (0.0028) −1.10, 0.275	0.0029 (0.0024) 1.21, 0.229
Clinical diagnosis	−0.0039 (0.0027) -1.47, 0.143	0.0004 (0.0032) 0.13, 0.898	−0.0044 (0.0028) −1.55, 0.123	−0.0079 (0.0034) −2.37, *0.019*	−0.0023 (0.0029) -0.82, 0.412

Note: Beta coefficients (SE) *T*−values, *p*−values.
p−Values < 0.05 are italicized.
Abbreviations: SE, standard error; WMM, white matter microstructure.

FA_{FWcorr} values in the cingulum bundle and inferior temporal gyrus among White ε3/ε3 '523-S/S carriers align with prior studies highlighting '523-S/S as a risk factor.[10,38] Together, these results showcase *APOE* ε3/ε3 '523-S/S haplotype's association with quantifiable neuroimaging metrics of abnormal aging in White ε3/ε3 individuals and point to '523-S playing a potential role as another genetic risk factor when inherited with *APOE*−ε3.

Our structural imaging findings partially reinforce prior work in Black ε4+ individuals, where '523-S carriers (one-'523-S and '523-S/S) have slower rates of cognitive decline compared to those Black ε4+ no-'523-S carriers.[10] In our present analysis, Black ε4+ carriers with one-'523-S had lower FW in the cingulum bundle and ILF compared to those Black ε4+ carriers with no-'523-S. Black ε4+ one-'523-S carriers also had lower FW in the cingulum bundle, lower FW in the UF, lower FW in the fornix, and higher FA_{FWcorr} in the UF compared to those Black ε4+ carriers with '523-S/S. All four aforementioned tracts are involved in cognitive processes including decision making, executive function, learning, memory, emotion, and object recognition, with changes in the WMM of these tracts being highly prevalent in cognitively impaired individuals or those at risk for CI.[18,23,25,43] Lower FW and higher FA_{FWcorr} in four of the five limbic system tracts evaluated emphasizes the potentially risk-mitigating nature of one-'523-S when inherited with the ε4 allele in Black individuals. Despite this work reinforcing associations between one-'523-S and phenotypes of normal aging, our structural imaging study did not reinforce prior research in which both one-'523-S and '523-S/S were associated with slower rates of cognitive decline when compared to no-'523-S in Black ε4+ carriers.[10] This disconnect may be due to high *APOE* genotype heterogeneity in the Black ε4+ '523-S/S carrier group in our sample. For example, among the Black ε4+ '523-S/S carriers, 11 were *APOE* ε3/ε4 carriers and only 2 were *APOE* ε4/ε4 carriers. As it is currently understood, '523-S promotes risk mitigation when inherited with ε4 but

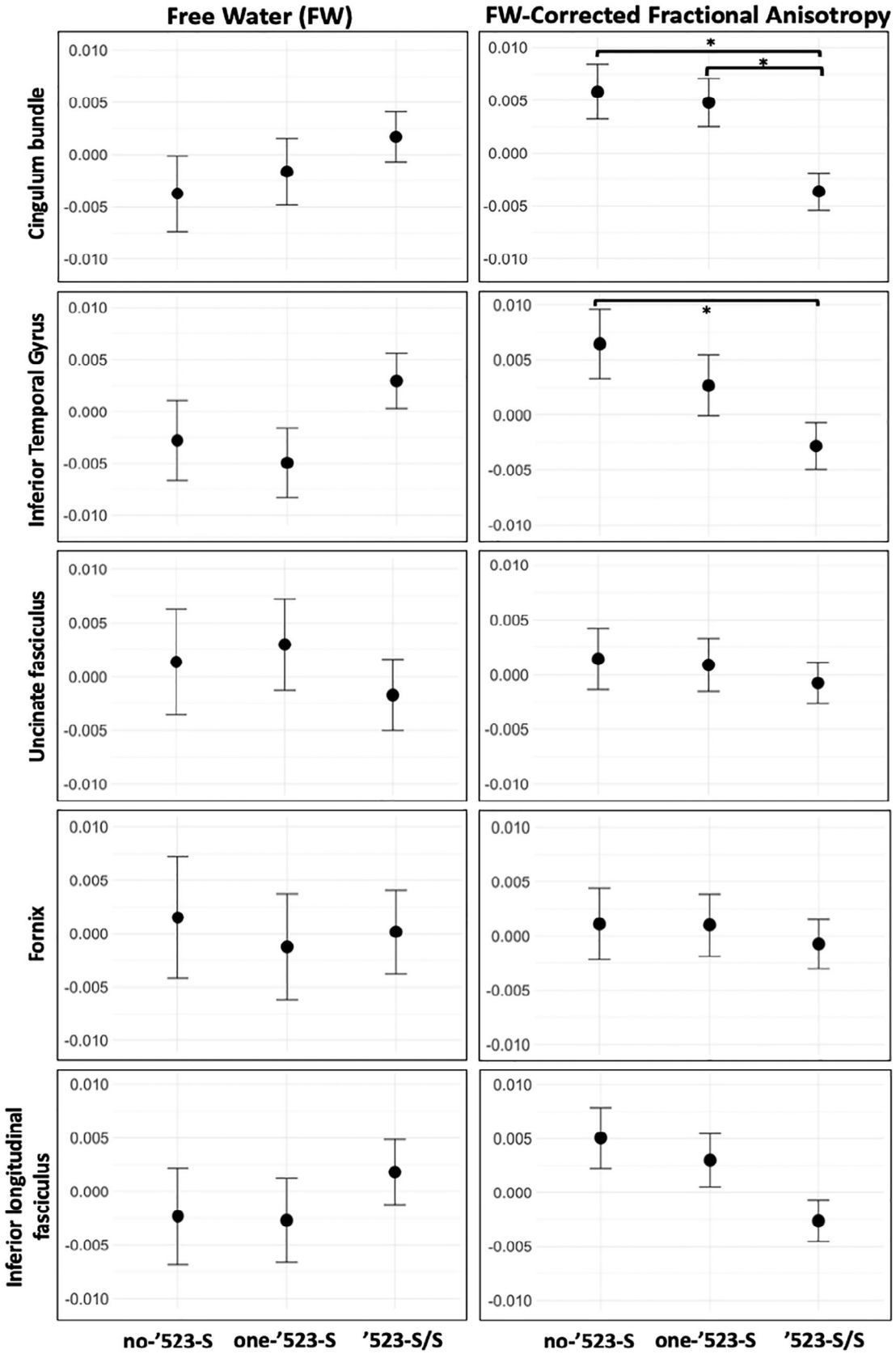

FIGURE 2 Residualized beta estimates of '523-S copy number and WMM metrics across limbic system tracts in non-Hispanic White ε3/ε3 participants, adjusted by age, sex, education, and clinical diagnosis. *p*–values < 0.05 are shown with *, *p*–values < 0.01 are shown with **. WMM, white matter microstructure.

TABLE 4 Associations between '523-S copy number and WMM metrics across limbic system tracts in non-Hispanic Black ε3/ε3 participants.

	Cingulum	Inferior temporal gyrus	Uncinate fasciculus	Fornix	Inferior longitudinal fasciculus
Free water (FW)					
Intercept	0.2379 (0.0072) 32.86, *< 0.001*	0.2412 (0.0091) 26.48, *< 0.001*	0.2765 (0.0103) 26.91, *< 0.001*	0.4595 (0.0129) 35.60, *< 0.001*	0.2353 (0.0091) 25.86, *< 0.001*
One-'523-S	0.0013 (0.0084) 0.16, 0.875	−0.0053 (0.0106) -0.51, 0.614	−0.0024 (0.0119) −0.20, 0.841	−0.0152 (0.0150) −1.02, 0.313	0.0046 (0.0106) 0.43, 0.666
'523-S/S	0.0080 (0.0080) 1.00, 0.321	0.0011 (0.0101) 0.11, 0.915	0.00002 (0.0114) 0.002, 0.999	−0.0086 (0.0143) −0.60, 0.549	0.0121 (0.0101) 1.20, 0.234
Years of education	−0.00004 (0.0009) −0.05, 0.961	−0.00003 (0.0011) −0.03, 0.975	0.0003 (0.0013) 0.21, 0.835	−0.0008 (0.0016) −0.51, 0.615	−0.0001 (0.0011) −0.12, 0.906
Years of age	0.0014 (0.0005) 2.58, *0.012*	0.0010 (0.0007) 1.49, 0.141	0.0014 (0.0008) 1.90, 0.061	0.0023 (0.0010) 2.42, *0.018*	0.0016 (0.0007) 2.36, *0.021*
Sex (male)	−0.0026 (0.0071) -0.36, 0.721	−0.0069 (0.0090) -0.76, 0.447	0.0036 (0.0101) 0.35, 0.726	0.0120 (0.0127) 0.94, 0.350	−0.0072 (0.0090) −0.80, 0.428
Clinical diagnosis	0.0216 (0.0079) 2.74, *0.008*	0.0200 (0.0099) 2.02, *0.047*	0.0121 (0.0112) 1.08, 0.285	0.0258 (0.0141) 1.84, 0.070	0.0222 (0.0099) 2.23, *0.029*
Free water corrected fractional anisotropy (FA FW-Corr)					
Intercept	0.4935 (0.0051) 97.69, *< 0.001*	0.6076 (0.0063) 96.99, *< 0.001*	0.4237 (0.0055) 76.99, *< 0.001*	0.4481 (0.0060) 74.56, *< 0.001*	0.4636 (0.0058) 79.94, *< 0.001*
One-'523-S	−0.0056 (0.0059) -0.96, 0.339	−0.0024 (0.0073) -0.33, 0.740	0.0029 (0.0064) 0.45, 0.652	−0.0019 (0.0070) −0.27, 0.790	−0.0009 (0.0067) -0.13, 0.897
'523-S/S	−0.0051 (0.0056) -0.91, 0.366	−0.0041 (0.0069) -0.59, 0.557	−0.0004 (0.0061) −0.06, 0.954	−0.0073 (0.0066) −1.09, 0.278	−0.0047 (0.0064) −0.73, 0.468
Years of education	−0.0007 (0.0006) -1.12, 0.265	0.0011 (0.0008) 1.45, 0.151	0.0004 (0.0007) 0.67, 0.505	−0.0002 (0.0007) −0.33, 0.743	−0.0005 (0.0007) −0.74, 0.460
Years of age	−0.0009 (0.0004) −2.42, *0.018*	−0.0005 (0.0005) −1.07, 0.289	−0.0005 (0.0004) -1.16, 0.250	−0.0005 (0.0004) −1.15, 0.255	−0.0006 (0.0004) −1.43, 0.156
Sex (male)	0.0090 (0.0050) 1.81, 0.074	0.0119 (0.0062) 1.92, 0.058	0.0070 (0.0054) 1.30, 0.199	−0.0029 (0.0059) −0.49, 0.623	−0.0007 (0.0057) −0.12, 0.904
Clinical diagnosis	0.0022 (0.0055) 0.40, 0.690	0.0062 (0.0068) 0.91, 0.365	−0.0097 (0.0060) −1.61, 0.112	−0.0071 (0.0066) −1.08, 0.283	−0.0016 (0.0063) −0.25, 0.805

Note: Beta coefficients (SE) *T*−values, *p*−values.
p−Values < 0.05 are italicized.
Abbreviations; SE, standard error; WMM, white matter microstructure.

exerts potentially adverse effects when inherited with ε3.[10,38] Considering the majority of our Black ε4+ '523-S/S carriers are ε3/ε4, this could explain why we do not see the expected risk-mitigating effects of '523-S, as ε3-'523-S may negate them. Future work with larger samples in which Black ε4+ models are stratified by *APOE* genotype, particularly investigating the associations between ε3/ε4 '523-S carriers and ε4/ε4 '523-S carriers with phenotypes of aging separately, is essential.

The differences we found in limbic system tracts may be attributed to vascular comorbidities. Cardiovascular risk factors such as hypertension, diabetes, and obesity have been linked to changes in WMM, particularly in the cingulum bundle, UF, fornix, and ILF, as demonstrated in previous studies.[46,47] Given the higher prevalence of these conditions among Black individuals, vascular health disparities may plausibly underlie the observed regional vulnerabilities. Furthermore, studies suggest that TOMM40 '523 poly-T variants may influence the transcription of both TOMM40 and APOE, potentially contributing to the observed associations between TOMM40 '523 and aging profiles we found. For example, studies found that longer poly-T variants were linked to increased gene expression, while others reported that shorter variants may act as transcriptional repressors.[48,49] These findings underscore the need to further explore the role of TOMM40-APOE interactions in aging and neurodegeneration.

Limitations in the present study include small sample sizes within the Black population. Re-evaluating these associations in larger cohorts may allow for a more comprehensive understanding of '523-S as a context-dependent risk factor for either normal or abnormal aging, dependent on *APOE* genotype. Additionally, we were unable to adjust for multiple comparisons due to small sample sizes. In this current study, we were unable to explore how '523-S copy number influences cognitive decline trajectories following WMM metric acquisition via dMRI scan due to limited follow-up years post-scan. As prior work has shown associations between '523-S and within-person rates

of cognitive decline in Black ε4+, Black ε3/ε3, and White ε3/ε3 individuals, future analyses to assess ways in which WMM may work to impact these associations would allow insights into the underlying mechanism of cognitive decline. As abnormal limbic tract WMM has been shown to be predictive of later cognitive decline or progression from CN to MCI/AD, these future studies will be essential to potentially identify at-risk *APOE-TOMM40* '523 groups that could benefit from early therapeutic intervention, prior to the onset of cognitive decline.

In conclusion, this study suggests that *TOMM40* '523-S has differential effects on limbic tract WMM in Black ε4+ and White ε3/ε3 individuals. These findings also emphasize the importance of research focusing on other genetic risk factors for abnormal aging for Black ε4 carriers. Future work focused on identifying the impact of *APOE-TOMM40 '523* on other markers of aging, as well as work assessing the impact of social determinants of health, such as experiences of discrimination, on these associations in the Black community is essential for understanding disease progression within this population.

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All human subjects provided informed consent. All studies were approved by an Institutional Review Board at the Rush University Medical Center and written informed consent was acquired for each participant.

CONFLICT OF INTEREST STATEMENT

Dr. Lisa Barnes (co-author) serves as the Deputy Editor of "Alzheimer's & Dementia." Dr. Timothy Hohman (co-author) serves as the Deputy Editor for "Alzheimer's & Dementia: Translational Research and Clinical Intervention," Senior Associate Editor for "Alzheimer's & Dementia," and served on the Scientific Advisory Board for "Vivid Genomics." No other competing interests were declared by the authors. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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