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Family history and TOMM40 '523 interactive associations with memory in middle-aged and AD cohorts

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Abstract

INTRODUCTION—Family history (FH) of Alzheimer's disease (AD) affects mitochondrial function, and may modulate effects of Translocase of Outer Mitochondrial Membrane–40kD (*TOMM40*) rs10524523 ('523) poly-T length on memory decline.

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METHODS—For 912 non-Apolipoprotein $\epsilon 4$ (non-*APOE4*) middle-aged adults, and 365 aged adults across the AD spectrum, linear mixed models gauged FH and *TOMM40* ‘523 interactions on memory and global cognition between baseline and up to 10 years later. A CSF mitochondrial function biomarker was also assessed.

RESULTS—For FH negative participants, gene-dose preservation of memory and global cognition was seen for “very long” (VL) vs. “short” (S) carriers. For FH positive, an opposite gene-dose decline was seen for VL vs. S carriers. Maternal FH was a stronger predictor in aged, but not middle-aged, participants. Similar gene-dose effects were seen for the mitochondrial biomarker aspartate aminotransferase.

DISCUSSION—These results may clarify conflicting findings on *TOMM40* poly-T length and AD-related decline.

Keywords

Alzheimer’s disease; mitochondrial function; memory; global function; TOMM40; aspartate aminotransferase

1. Introduction

The Apolipoprotein E (*APOE*) gene is the most replicated genetic risk factor for late-onset Alzheimer’s disease (LOAD)[1]. Subjects without the $\epsilon 4$ allele (non-*APOE4*s) are considered at neutral risk but show substantial variability for developing AD, where there is tremendous interest in finding genetic risk factors for non-*APOE4*s that strongly predict memory, global decline, and cognitive impairment risk. As mitochondrial dysfunction is associated with LOAD[2], several groups have investigated gene loci that impact mitochondrial bioenergetics, such as Translocase of Outer Mitochondrial Membrane-40kD (*TOMM40*).

TOMM40 shares strong linkage disequilibrium (LD) with *APOE* on chromosome 19[3]. *TOMM40* constitutes the central channel of the outer mitochondrial membrane, through which mitochondria-specific ribosomal pre-proteins enter for post-translational modification in the inner matrix[4]. Genome-wide association studies (GWAS) have implicated several *TOMM40* single nucleotide polymorphisms (SNPs) in increased LOAD risk, cognitive decline, and brain atrophy, particularly SNP rs2075650 that has consistently shown such associations [4–7]. In addition, a *TOMM40* variable length deoxythymidine-homopolymer (poly-T) at rs10524523 (‘523) within intron 6 has sometimes been shown to associate with LOAD risk. Among non-*APOE4*s, the phase-in haplotypes are *APOE* $\epsilon 3$ -linked to either a *TOMM40* ‘523 “short” (S) or “very long” (VL) poly-T length[8]. Some studies find that subjects with the VL allele have worse memory and executive function scores in middle-aged[6] and aged[9] cohorts. To date, several studies have also found that *TOMM40* VL in non-*APOE4*s or *APOE* $\epsilon 3/\epsilon 4$ s predicts memory deficits or earlier age of AD onset[6, 8–12]. However, other reports with large samples have found no effect or a benefit of *TOMM40* VL on age of onset and memory decline[13–15].

It may be important to account for other factors that can modulate mitochondrial function, such as AD family history (FH). AD FH is typically defined as maternal or paternal LOAD

onset between ages 65 to 80[16]. Both FH and *TOMM40* influence mitochondrial bioenergetic processes needed for adenosine triphosphate (ATP) synthesis. For example, maternal FH (FHM) is related to reduced cytochrome oxidase activity[17], leading to electron transport chain dysfunction, lower ATP production, and neuronal damage. Like *TOMM40*, FH can increase AD risk independent of *APOE*[18]. To link FH and *TOMM40* with AD, the mitochondrial cascade hypothesis posits that multiple factors determine baseline and age-related decline in mitochondrial function[19]. As neurons in hippocampus and other medial temporal lobe (MTL) areas have high ATP requirements[16], FH and *TOMM40* might interact to affect mitochondrial dysfunction and contribute to memory and global cognitive decline, as well as cognitive impairment risk.

Our objective was to explore FH and *TOMM40* interactions separately in non-*APOE4* late middle-aged or aged subjects from the Wisconsin Registry for Alzheimer's Prevention (WRAP) study or Alzheimer's Disease Neuroimaging Initiative (ADNI) respectively, to see if FH or FHM modulated *TOMM40* effects in middle-age and along the AD spectrum in old age. The primary outcomes were longitudinal memory decline in both cohorts and global decline in the aged cohort. Previous WRAP and ADNI reports either focused on cross-sectional cognition with fewer subjects[6] or age of onset but not cognitive or mitochondrial outcomes[13].

To establish that FH and *TOMM40* meaningfully interacted to affect mitochondrial processes, CSF levels of a cytosolic aspartate aminotransferase (AST) peptide were gauged. Cytosol AST is an enzyme that facilitates catabolism of glucogenic amino acids through the malate-aspartate shuttle by a final conversion step of aspartate to oxaloacetate, helping to maximize ATP production through glycolysis[20, 21]. AST, also called glutamic oxaloacetate transaminase, differs in CSF levels among AD patients and related dementias[22], and shows higher concentrations in AD frontal and parietal cortices[23]. *APOE4* subjects were not considered for this report, as their in-phase *TOMM40* genotype ("Long", or L) is different and could confound effects of S and VL genotypes in *APOE* ϵ 3/ ϵ 4 subjects.

2. METHODS

2.1. Participants

Late middle-aged subjects (91.3% Caucasian, non-Hispanic) were recruited from the WRAP study[24]. Participants were originally recruited from 40–65 years of age. There were 912 non-*APOE4* (129 *APOE* ϵ 2/ ϵ 2 or ϵ 2/ ϵ 3; 783 *APOE* ϵ 3/ ϵ 3) participants with *TOMM40* '523 and neuropsychological data. Cognitive performance was assessed once every roughly 2 years over 4 Waves, from baseline to approximately 7–10 years later for a given participant.

Data on aged subjects (92.7% Caucasian, non-Hispanic) was obtained from the ADNI database (adni.loni.usc.edu). The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Among 365 non-*APOE4* s (60 *APOE* ϵ 2/ ϵ 2 or ϵ 2/ ϵ 3; 305 *APOE* ϵ 3/ ϵ 3), *TOMM40* '523 data was available for 146

cognitively normal (CN), 163 MCI, and 56 AD participants. Data was downloaded from baseline and months 6, 12, 24, and 36. All subjects had: 1) demographic measures; 2) *TOMM40* '523 poly-T genotype; 3) *APOE* genotype; and 4) neuropsychological performance. We also examined clinical diagnosis at baseline and month 36.

2.2 AD Family History

For WRAP, a parental history of AD—defined by clinical diagnosis or autopsy before ages 70 and 75 for paternal FH (FHP) and FHM respectively—was determined as described[25]. For ADNI, presence of FHM and FHP was determined for AD by the participant, informant, or both.

2.3. Protocol Approvals, Registrations, and Patient Consents

For WRAP, the University of Wisconsin–Madison Health Sciences Institutional Review Board approved the study, and all participants provided written informed consent. For ADNI, written informed consent was obtained from all ADNI participants at their respective ADNI sites. Site-specific Institutional Review Boards approved the ADNI protocol.

2.4. *APOE* Genotyping

For ADNI, the Biomarker Core at the University of Pennsylvania conducted *APOE* genotyping[26] as described in white papers (<http://adni.loni.usc.edu/>). For WRAP, extraction and isoform classification of *APOE* alleles has been described previously[6]. Participants who were non-*APOE4* were analyzed. Ancillary analyses were also conducted on *APOE3,3* carriers only or *APOE2* carriers (Supplemental Text 1), where the pattern of results was similar for *APOE3,3* subjects.

2.5. *TOMM40* Genotyping

For both WRAP[6] and ADNI[8, 11], genotyping of *TOMM40* '523 poly-T was conducted as described (Polymorphic DNA Technologies, Inc., Alameda, CA)[6]. Briefly, the '523 poly-T polymorphism was determined using PCR amplification of each region's variant site, followed by corresponding A-peaks to the N values (poly-T length) of each component, relative to the C-peak reference base upstream of the poly-T intron site. Manual electrogram review was also conducted to avoid errors. This process obviated the concern of PCR slippage.

2.6. Cognition, Clinical, and Mitochondrial Biomarker Measures

For WRAP, participants underwent a full neuropsychological battery. While factor analysis derived 6 cognitive factors[27, 28], the focus of this report is on memory--to maintain overlap with ADNI data and reduce type 1 error. Latent memory factors were derived as described[27], which encapsulated immediate and delayed memory. Composite scores based on the latent factor structure were largely derived from Z-scores of longitudinal measures of the immediate memory and delayed recall portions of the Rey Auditory Verbal Learning Test (RAVLT)[29]. RAVLT sub-components were not considered because they have been investigated elsewhere[6].

For ADNI, as described[30], a Z-score general memory composite was derived from longitudinal immediate and delayed RAVLT scores, AD Assessment Schedule-Cognition (ADAS-Cog)[31], Mini-Mental State Examination (MMSE), and the Wechsler Memory Scale-Revised Logical Memory II. Total RAVLT for immediate memory and delayed recall were separately assessed to establish which aspect of memory function drove the factor result. Global cognition and function were assessed by MMSE and clinical dementia rating-sum of boxes (CDR-sob). Finally, as described[32], a peptide of CSF cytosol AST (IVASTLSNPFLFEEWTGNVK) was available in 119 ADNI subjects only at baseline, as acquired by the ADNI Biomarker Core using mass spectrometry[32]. No other direct mitochondrial biomarkers were present in existing assays. Values are in arbitrary log units derived from signal intensity.

2.7. Statistical Analysis

SPSS 23 (Chicago, IL) was used for analyses. Data were analyzed using mixed-effects regression models. Model equations and both fixed and random terms are described in Supplemental Text 2. Aikake's Information Criterion was used to determine the optimal covariance matrix. In each cohort separately (WRAP or ADNI), for a given Z-score memory factor, we tested all main effects and interactions for FH, *TOMM40*, and Time as predictors in a single model. A similar approach was used for testing global cognition outcomes in ADNI participants. This approach assessed if FH modified *TOMM40* genotype associations, and if these effects on memory decline were the same over time or dynamically changed based on FH and genotype. To explore which memory components drove significant findings for the single ADNI memory factor, immediate and delayed RAVLT scores were assessed. Exploratory analyses were also conducted with FHM, due to FHM's influence on mitochondrial function[17]. We controlled for sex, age, and education. A similar mixed model approach was used to predict baseline CSF AST in ADNI. Logistic regression was used in ADNI data to identify if FH and *TOMM40* predicted a greater likelihood of being MCI or AD at baseline versus the CN reference group. Importantly, we did not investigate if *TOMM40* and FH modified clinical diagnosis effects on memory, due to small sample sizes among sub-groups stratified by *TOMM40*, FH, and *APOE*.

To minimize type 1 error, as described elsewhere[25], Holm-Bonferroni correction was used to maintain a family-wise error rate of $p < .05$. Briefly, for WRAP, family-wise adjusted p values were .025 and .05 for testing 1 model among 2 latent memory factors, and similarly .025 and .05 for ADNI MMSE and CDR-sob. If a *TOMM40* * FH or *TOMM40* * FH * Time interaction was not significant, we separately examined 2 additional models in FH- and FH+ to tests main effects of *TOMM40* and its interaction with Time. This required family-wise adjustment of .017, .025, and .050 to yield significance. No statistical violations were found for colinearity, normality, outliers, or model overfitting.

3. RESULTS

3.1. Data Summary

Participant data is listed in Table 1 for 912 WRAP and 365 ADNI non-*APOE4* participants. For WRAP, the sample size was 333 FH- (S/S=112; S/VL=143; VL/VL=78) vs. 579 FH+

(S/S=177; S/VL=285; VL/VL=117). For ADNI, the sample size was 238 FH– (S/S=59; S/VL=124; VL/VL=55) vs. 127 FH+ (S/S=28; S/VL=71; VL/VL=28). The roughly 1:2:1 ratio among genotypes is comparable to what has been reported in predominantly Caucasian cohorts[6, 8]. All latent factor analyses without APOE2's remained significant (Supplemental Text 1).

3.2. WRAP: *TOMM40* and FH Interaction Effects on Memory Performance over 7–10 Years

We first examined change in immediate and delayed memory factors in late middle-aged *APOE4*- WRAP subjects. For immediate memory, a *TOMM40* * FH effect [$F=4.704$, Estimate $\pm$ SE=–0.279 $\pm$ 0.192, $p=.009$] showed that *TOMM40* VL was related to better memory among FH– and worse memory among FH+ subjects, regardless of Time (Supplemental Figure A.1). For example, higher scores were seen in FH– VL/VL vs. S/S [$D_{\text{Cohen}}=0.352$] and lower scores for FH+ VL/VL vs. S/S [$D_{\text{Cohen}}=-0.787$]. It should be noted here and throughout the report that FH also modified S/S genotype effects. When exploring FHM, a FHM * *TOMM40* interaction [$F=2.935$, Estimate $\pm$ SE=–0.320 $\pm$ 0.248, $p=.050$] showed similar effects.

For the delayed memory factor, a *TOMM40* * FH * Time interaction [$F=3.695$, Estimate $\pm$ SE=0.502 $\pm$ 0.189, $p=.025$] indicated a strong effect of VL for either slowing (FH–) or exacerbating (FH+) memory decline over 7–10 years (Figure 1). FH– VL/VL had less memory decline compared to S/S ($D_{\text{Cohen}}=1.126$), whereas FH+ VL/VL had more memory decline versus S/S ($D_{\text{Cohen}}=-1.322$). Exploratory analyses with FHM revealed a *TOMM40* * FHM * Time interaction [$F=2.036$, Estimate $\pm$ SE=0.323 $\pm$ 0.230; $p=.047$] showing similar, albeit weaker effects.

3.3. ADNI: *TOMM40* and FH Interaction Effects on Mitochondrial Function

Among the subset of ADNI participants (N=119) who had baseline CSF AST measurements, we assessed if *TOMM40* and FH interacted to affect CSF AST, a biomarker of mitochondrial function. As indicated in Figure 2, a FH * *TOMM40* interaction [$F=3.418$, Estimate $\pm$ SE=–0.263 $\pm$ 0.148, $p=.036$] showed a VL effect for higher (FH–) [$D_{\text{Cohen}}=1.077$] or lower (FH+) [$D_{\text{Cohen}}=-0.449$] AST. Small sample size for VL/VL genotype precluded formal analysis among FH– (n=20) and FH+ (n=15) subjects, but trended in the expected direction (FH– VL/VL=12.71 $\pm$ 0.03 log units; FH+ VL/VL=12.92 $\pm$ 0.06 log units).

3.4. ADNI: *TOMM40* and FH Interactions for MCI and AD Diagnosis Odds Ratios

For FH and *TOMM40*, no main effects or interactions for risk of MCI or AD versus CN diagnosis were noted. In exploratory analyses for FHM, a *TOMM40* * FHM interaction [$\text{Wald}=6.154$, $p=.046$] showed that for FHM–, S/S and S/VL compared to VL/VL participants had a 4.67 higher odds ratio of being MCI or AD at baseline, whereas for FHM+ the S/S and S/VL genotypes had a 0.215 lower odds ratio. As there were only 102 non-*APOE4* MCI converters to AD by month 36, there was not sufficient sample size to stratify by FH and *TOMM40* to conduct age of onset or logistic regression analyses for stable versus progressive MCI.

3.5. ADNI: *TOMM40* and FH Interactions on Memory Performance over 3 Years

Unlike WRAP, the *TOMM40* * FH * Time interaction was non-significant among ADNI participants, perhaps due to lower power. When stratified by FH status, FH- subjects showed a *TOMM40* * Time effect [$F=2.465$, Estimate $\pm$ SE=-0.349 $\pm$ 0.096, $p=.012$] while FH+ subjects had a *TOMM40* main effect [$F=3.453$, Estimate $\pm$ SE=0.228 $\pm$ 0.070, $p=.008$]. FH- *TOMM40* genotypes did not vary at baseline, whereas 3 years later S/S carriers showed a decline of over 0.3SD, with no decline evident in S/VL or VL/VL [$D_{\text{Korr}}=0.497$]. FH+ *TOMM40* VL/VL carriers, meanwhile, showed a gene-dose decrease in memory performance relative to S/S or S/VL that did not vary over time [$D_{\text{Cohen}}=0.430$].

Analyses with FHM had similar, stronger effects. FHM- showed a *TOMM40* * Time effect [$F=2.352$, Estimate $\pm$ SE=-0.318 $\pm$ 0.094, $p=.017$], where for example S/S but not VL/VL carriers evinced decline [$D_{\text{Korr}}=0.378$] (Figure 3, left panels). Among FHM+, a main effect of *TOMM40* [$F=4.284$, Estimate $\pm$ SE=0.350 $\pm$ 0.139, $p=.014$] illustrated a clear gene-dose effect on overall memory performance that did not change over 3 years (Figure 3, right panel). For example, VL/VL vs. S/S carriers had lower memory scores [$D_{\text{Cohen}}=0.607$].

3.6. ADNI: *TOMM40* and FH Interaction Effects on RAVLT Over 3 Years

As ADNI has one memory factor including immediate and delayed components, we did follow-up analyses to see if the RAVLT encoding or retention portions explained results for the factor. For RAVLT immediate memory (i.e., Trials 1–5 Total), a *TOMM40* * FH * Time [$F=2.203$, Estimate $\pm$ SE=9.124 $\pm$ 2.942, $p=.027$] pattern similar to the general memory factor emerged. VL's of both FH groups did not differ at baseline. However, over 3 years, FH- S/S showed progressive decline while VL/VL showed little to no decline [$D_{\text{Korr}}=0.378$]. The opposite pattern was observed for FH+ VL/VL versus S/S, where VL/VL showed greater decline over time [$D_{\text{Korr}}=-0.248$].

For FHM, a similar *TOMM40* * FHM * Time [$F=2.008$, Estimate $\pm$ SE=8.412 $\pm$ 3.558, $p=.042$] interaction showed no FHM differences at baseline, but VL gene-dose preservation (FH-) or decline (FH+) over 3 years (Supplemental Figure A.2). For example, FH- VL/VL vs. S/S had progressively better scores [$D_{\text{Korr}}=0.601$] but FH+ VL/VL vs. S/S had progressively worse scores [$D_{\text{Korr}}=0.271$].

RAVLT delayed memory was not affected by FH or FHM, *TOMM40*, or their interaction with or without Time. These results suggest that immediate verbal memory encoding rather than delayed retention may underlie the statistical effect on the ADNI memory factor.

3.7. ADNI: *TOMM40* and FH Effects on Global Decline over 3 Years

For CDR-sob, no effects were significant when considering FH. For FHM, a *TOMM40* * FHM * Time interaction [$F=2.187$, Estimate $\pm$ SE=2.854 $\pm$ 0.961, $p=.025$] showed that global decline varied among *TOMM40* groups based on FHM status. For FHM-, a marginally lower CDR-sob at baseline was seen among VL/VL vs. S/S, where by 3 years later S/VL and VL/VL genotypes showed less decline compared to S/S [$D_{\text{Korr}}=0.286$] (Figure 4, left panel). By contrast, FHM+ VL/VL carriers did not differ at baseline from S/S, but showed more progressive decline after 3 years [$D_{\text{Korr}}=-0.337$] (Figure 4, right panel).

For MMSE, a *TOMM40* * FH * Time effect [$F=1.960$, Estimate $\pm$ SE=1.179 $\pm$ 0.662, $p=.048$] revealed a weak pattern similar to CDR-sob. For instance, FH– VL/VL vs. S/S subjects showed less progressive decline [$D_{\text{Korr}}=0.1$]. However, FH+ VL/VL did not differ from S/S at baseline or over the course of 3 years. For FHM, a similar *TOMM40* * FHM * Time interaction [$F=2.452$, Estimate $\pm$ SE=1.091 $\pm$ 0.660, $p=.012$] showed that VL/VL vs. S/S carriers had marginally higher MMSE scores at baseline, where 3 years later the S/S genotype showed greater decline compared to S/VL or VL/VL [$D_{\text{Korr}}=0.125$] (Supplemental Figure A.3, left panel). FHM+ participants did not differ at baseline or up to 3 years later (Supplemental Figure A.3, right panel).

4. Discussion

In this report, we found in middle-aged and aged cohorts that FH altered *TOMM40* ‘523 poly-T genotype associations on memory, and additionally in aged participants both global decline and cognitive impairment risk. Specifically, VL genotype was related to ameliorative (FH–) or deleterious (FH+) effects on memory factors, RAVLT immediate memory, CDR-sob, and MMSE scores. FHM had stronger effects relative to FH in the old age cohort.

4.1. FH and *TOMM40* Interact to Affect Memory Decline in Late Middle-Age

Within WRAP, Johnson et al.[6] originally found gene-dose associations (S/S, S/VL, VL/VL) with worse RAVLT total recall and retrieval from primacy, where S/S vs. VL/VL subjects showed differences of over half a standard deviation (Cohen’s $D=0.599$ to 0.718). Comparatively, by 7–10 years later, we found for the delayed memory factor that FH– S/S and VL/VL differed by a Cohen’s $D=1.126$, where for FH+ that difference was Cohen’s $D=-1.322$. These findings were stronger than for the immediate memory factor, perhaps because delayed memory is a more sensitive cognitive feature for detecting decline related to AD[36]. Caselli et al.[10] noted that non-*APOE4* S/S vs. VL/VL subjects showed less RAVLT decline in middle-age, but a flat slope after age 60, indicating that initial differences in cognitive performance abated over time. Yet, in this report, VL/VL homozygotes differed from other genotypes at baseline (mean age=54.20) and showed less (FH–) or more (FH+) decline by the last available study visit (mean age=63.21).

4.2. FH and *TOMM40* Interact to Affect Memory Decline in Old Age

FH and *TOMM40* poly-T genotype showed similar effects in ADNI. Effects were stronger in FHM than FH, which may be due to age-related mitochondrial dysfunction[37]. Unlike WRAP, *TOMM40* VL effects among FH– and FH+ groups were similar at baseline, but over time showed progressive gene-dose differences in memory and global decline. These results may explain the null ADNI findings of Jun et al.[14], and in particular Cruchaga and colleagues[13] noting later age of onset among *APOE* $\epsilon 3$ homozygotes with VL carriage. Indeed, given the opposing effects we see for FH– and FH+ in ADNI, *TOMM40* VL effects would largely cancel out when collapsed across FH status. Hayden and colleagues[9] also found a mild but significant gene-dose response (S/S, S/VL, VL/VL) for improved global function. Comparably, we found that FH– VL carriers showed less decline in CDR-sob and MMSE scores.

4.3. FH and *TOMM40* Affect Mitochondrial Function in Old Age

Importantly, among a subset of ADNI subjects, FH modified VL carriage associations of CSF AST, a biomarker of mitochondrial function[20, 21] that is higher in AD CSF[22] and cortical tissue[23]. As glucose metabolism decreases in AD, alternative sources of energy are utilized to sustain energy-intensive synaptic processes. Cytosolic AST may through the malate-aspartate cycle maximize ATP production[21], as well as maintain ATP and antioxidative capacity in neural cells[38].

4.4. Limitations and Future Work

There are serious limitations that should be addressed. First, the sample size for some subgroups in ADNI was small, particularly for FH+ and FHM+ subjects, which may explain non-significant trends related to decline. We intend to re-examine these effects in additional AD cohorts. Nonetheless, we consistently found that for FH–, VL carriage was associated with lower AD risk, less mitochondrial dysfunction via the CSF biomarker AST, and less memory and global decline over time, while the opposite pattern was seen for FH+. While FH and *TOMM40* may affect mitochondrial function, it is not clear if FH is modulating *TOMM40* function by epigenetic, environmental, or other factors. It is clear that FHM affects cytochrome oxidase[17] production that impacts AD progression, and that SNPs for several mitochondrial genes contribute to a higher odds ratio for AD[39] in ADNI. While FH in WRAP and ADNI both modified *TOMM40* poly-T effects, FHM exerted modest effects in middle age but more potent associations in the aged cohort. Mitochondrial dysfunction is thought to increase with age[37], where the influence of FHM on and other components of mitochondrial bioenergetics may only be present in older subjects evincing damage due to reactive oxygen species. Despite these limitations, this report may clarify why the *TOMM40* ‘523 literature has shown beneficial, null, and/or detrimental effects. We propose that the proportion of participants with FH+ may influence *TOMM40* ‘523 effects on memory, age of onset, and other outcomes. Future work will investigate additional mitochondrial biomarkers and examine impact on neural, CSF biomarker, and metabolic outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- AD family history modifies the effect of TOMM40 '523 genotype on cognition.
- Negative family history is related to less memory decline in “very long” carriers.
- Positive family history is related to more memory decline in “very long” carriers.
- Similar interactions noted for global decline and a mitochondria biomarker.

Research in Context

Systematic Review

We searched for articles in PubMed using the keywords: Translocase of Outer Mitochondrial Membrane 40; Alzheimer's disease; mitochondrial function, aspartate aminotransferase; memory; preclinical AD; poly-T; rs10524523. We focused on human work to examine TOMM40 '523 genotype and effects on memory decline and AD risk.

Interpretation

This is the first human study to demonstrate that AD family history modifies the effect of TOMM40 '523 genotype on memory, global cognition, and a biomarker of mitochondrial function. Findings were similar across two separate cohorts of cognitively normal middle-aged and aged subjects across the AD spectrum. Varying proportions of AD family history in subjects may explain mixed findings in the TOMM40 '523 literature.

Future Directions

Data from other observational AD cohorts will be collected to confirm results. Higher sample size will allow AD age of onset and MCI conversion risk analyses. Effects on neural, metabolic, and biomarker outcomes will be assessed.

Figure 1. FH and TOMM40 ‘523 effects on delayed memory decline in late middle-age In the middle-aged
 WRAP cohort, family history (FH) modulates Translocase of Outer Mitochondrial Membrane – kD40 (TOMM40) ‘523 Short (S) vs. Very Long (VL) carriage effects on delayed memory performance. Differences are shown at baseline and the last visit 7–10 years later. *** = $p < .001$ comparing VL/VL to other genotypes at a given timepoint. Data are mean $\pm$ SD.

Figure 2. FH and TOMM40 '523 effects on mitochondrial function in old age

For the aged ADNI cohort, the effect of family history (FH) status and Translocase of Outer Mitochondrial Membrane – kD40 (TOMM40) '523 genotype on CSF aspartate aminotransferase (AST), a putative biomarker of mitochondrial function. Very Long/Very Long (VL/VL) subjects were formally excluded from FH negative (n=20) and FH positive (n=15) groups due to low sample size. Exploratory analysis showed that FH negative and FH positive VL/VL subjects had significantly higher AST levels than Short/Short (S/S) subjects. *** = $p < .001$ comparing S/VL to S/S. Data are mean $\pm$ SD.

Figure 3. FH and TOMM40 ‘523 effects on memory decline in old age

For the aged ADNI cohort, maternal family history (FHM) status modulates the effect of Translocase of Outer Mitochondrial Membrane – kD40 (TOMM40) ‘523 Very Long (VL) carriage on general memory performance. TOMM40 ‘523 genotypes showed relative changes in memory decline for FHM negative participants over time, whereas FHM positive participants showed gene-dose differences that remained constant from baseline to month 36. *** = $p < .001$ for genotype differences relative to other genotypes at a given timepoint. Data are mean $\pm$ SD.

Figure 4. FH and TOMM40 '523 effects on CDR-sob in old age

For the aged ADNI cohort, maternal family history (FHM) status modulates the effect of TOMM40 VL carriage on global function using Clinical Dementia Rating-sum of boxes (CDR-sob). #, *, ***=p < .076, .05, or .001 when comparing CDR-sob scores between genotypes at a given timepoint. Data are mean $\pm$ SD.

Table 1

Demographics and Neuropsychological Characteristics (N or mean $\pm$ SD)

	WRAP		ADNI				AD	
	CN		FH-	FH+	MCI		FH-	FH+
Sample Size	912		88	58	52		39	17
APOE2%	14.14%		18.18%	20.69%	9.01%		7.69%	5.88%
Age	54.20 $\pm$ 6.61		75.86 $\pm$ 5.04	75.79 $\pm$ 4.88	75.36 $\pm$ 8.28		77.34 $\pm$ 7.36	76.82 $\pm$ 9.41
Gender	645F, 285M		40F, 48M	29F, 29M	38F, 73M		21F, 18M	9F, 8M
Years of Education	16.08 $\pm$ 3.12		15.89 $\pm$ 2.97	16.55 $\pm$ 2.62	15.45 $\pm$ 3.17		14.23 $\pm$ 3.48	16.35 $\pm$ 2.40
MMSE	29.29 $\pm$ 0.941		29.05 $\pm$ 1.00	29.05 $\pm$ 1.03	27.04 $\pm$ 1.75		23.26 $\pm$ 2.29	23.94 $\pm$ 1.82
CDR-sob	0 $\pm$ 0		0.04 $\pm$ 0.14	0.03 $\pm$ 0.13	1.53 $\pm$ 0.77		4.22 $\pm$ 1.84	4.21 $\pm$ 1.50

AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE2*, Apolipoprotein ϵ 2; CDR-sob, Clinical Dementia Rating-sum of boxes; CN, Cognitively normal; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; WRAP, Wisconsin Registry for Alzheimer's Prevention.