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Longitudinal Modeling of Cognitive Aging and the TOMM40 Effect

Richard J. Caselli, MD[1,5], **Amylou C. Dueck, PhD**[7], **Matthew J. Huentelman, PhD**[2,5], **Michael W. Lutz, PhD**[3,6], **Ann M. Saunders, PhD**[3,6], **Eric M. Reiman, MD**[2,4,5], and **Allen D. Roses, MD**[3,6]

[1]Department of Neurology, Mayo Clinic Arizona

[2]Neurogenomics Division, Translational Genomics Research Institute

[3]Department of Medicine, Duke University

[4]Banner Alzheimer Institute

[5]Arizona Alzheimer Research Consortium

[6]Deane Drug Discovery Institute

[7]Biostatistics, Mayo Clinic Arizona

Abstract

Background—*TOMM40* (translocase of the outer mitochondrial membrane pore subunit) is in linkage disequilibrium with apolipoprotein E (APOE). APOE e4 is linked to long (L; 21–29 T residues) poly-T variants within intron 6 of TOMM40 while APOE e3 can be associated with either with a short (S; <21 T residues) or very long (VL; >29 T residues) variant. To assess the possible contribution of TOMM40 to Alzheimer's disease (AD) onset, we compared the effects of *TOMM40* and *APOE* genotype on preclinical longitudinal memory decline.

Methods—An *APOE* e4 enriched cohort of 639 cognitively normal individuals age 21–97 years of known *TOMM40* genotype underwent longitudinal neuropsychological testing every two years. We estimated the longitudinal effect of age on memory using statistical models that simultaneously modeled cross sectional and longitudinal effects of age on the auditory verbal learning test long term memory score (AVLT) by APOE, TOMM40, and the interaction between the two.

Results—There were significant effects overall for both *TOMM40* (p=0.04 linear effect, p=0.03 quadratic effect) and *APOE* (p=0.06 linear effect, p=0.008 quadratic effect) with no significant interaction (p=0.63). These differences were age-dependent: there was a significant *TOMM40* effect prior to age 60 (p=0.009) characterized by flattened test-retest improvement (VL/VL subgroup only) but no significant *APOE* effect; and a significant *APOE* effect after age 60

Corresponding Author: Richard J. Caselli, MD, Department of Neurology, Mayo Clinic Arizona, 13400 East Shea Boulevard, Scottsdale, Arizona 85259; Phone 480-301-6574; Fax 480-301-8451; Caselli.Richard@Mayo.edu.

Conflicts

Dr. Roses is president of 3 companies filed as S Corporations in North Carolina: Cabernet Pharmaceuticals, Shiraz Pharmaceuticals, and Zinfandel Pharmaceuticals. Dr. Saunders is married to Dr. Roses. Drs. Caselli, Dueck, Huentelman, Lutz, and Reiman have no relevant disclosures.

(p=0.006) characterized by accelerated memory decline (e4 carriers) but no significant *TOMM40* effect.

Conclusion—Both TOMM40 and APOE significantly influence age-related memory performance, but appear to do so independently of each other.

Keywords

TOMM40; APOE; preclinical Alzheimer's disease; cognitive aging; age-related memory loss; mitochondria; very long term memory; test-retest effects

1. Introduction

Mitochondrial alterations have long been suspected of contributing to the pathophysiology of, or even possibly causing Alzheimer's disease (AD) as well as other neurodegenerative illnesses[1]. Oxidative stress[2], vascular endothelial dysfunction[3], hypoxia[4], glucose deprivation[5], and mitochondrial dysfunction[6] all promote amyloidogenesis. The *TOMM40* gene encodes the translocase of the outer mitochondrial membrane pore subunit through which cytoplasmic proteins pass[7]. Apolipoprotein (apoe) e4 and e3 isoforms interact with the outer mitochondrial membrane leading to mitochondrial dynamic dysfunction[8]. Other aggregating proteins, including amyloid precursor protein accumulates in these pores also contributing to mitochondrial dysfunction[9].

The apolipoprotein E (*APOE*) e4 allele influences risk and age of onset of AD in a gene-dose dependent fashion[10], and the apoe e4 isoform itself is toxic to mitochondria[8,11]. Deep sequencing of the *APOE-TOMM40* linkage disequilibrium region recently revealed a variable–length, deoxythymidine homopolymer (poly-T) within intron 6 of the *TOMM40* gene that sorts nonrandomly with *APOE* alleles, and that Roses and colleagues have suggested may have an effect on AD risk and age of onset[12–14]. Currently, the length of the poly-T homopolymer is categorized as short (14–20 repeats), long (21–29 repeats) or very long (more than 29 repeats). Among Caucasians, *APOE* e4 is usually linked to long (L) variants while APOE e3 is primarily associated with either with a short (S) or very long (VL) poly-T variant of *TOMM40*[13]. Associations within non-Caucasian populations, as well as the *TOMM40* associations with the *APOE* e2 allele are still under study.

Correlations between age of symptomatic AD onset in a clinical series of thirty-four *APOE* e3/4 heterozygotes as well as in an autopsy series of 22 *APOE* e3/3 individuals have showed that those with a "long-long" *TOMM40* genotype (in which L and VL variants were grouped together) had a younger age of onset than those with an SL or SS genotype[14]. Using a cohort genetically enriched with *APOE* e4 carriers, we were able to show that age-related memory decline accelerates preclinically in APOE e4 carriers beginning around age 55–60 years[15]. If *TOMM40* further influences AD age of onset either in conjunction with or instead of *APOE*, then it should also alter preclinical cognitive aging patterns in a similar way. We therefore performed *TOMM40* genotyping of our *APOE* e4 enriched cohort to compare the age-related trajectories of preclinical memory change among *TOMM40* genotype subgroups.

2. Methods

2.1. Study population

From January 1, 1994 through August 6, 2007 cognitively normal residents of Maricopa County age 21 years and older were recruited through local media ads, underwent *APOE* genotyping and longitudinal neuropsychological assessment[15]. Demographic, family, and medical history data were obtained on each individual undergoing *APOE* genotyping, and

identity was coded by a study assistant. Ancestral origin was self-reported. Genetic determination of *APOE* allelic status was performed using a polymerase chain reaction (PCR) based assay.

All identified e4 homozygotes (HMZ) were matched by age, gender, and education to one e3/4 heterozygote (HTZ) and two non-carriers. We identified more HTZ and non-carriers than HMZ, (especially those persons over age 70 years reflecting the greater number of e4 HMZ developing MCI and AD by this age) who were also eligible for enrollment. Each participant had screening tests to establish their neuropsychiatrically normal state including a neurological examination, the Folstein Mini-Mental Status Exam (MMSE), the Hamilton Depression (Ham-D) Rating Scale, the Functional Activities Questionnaire (FAQ), Instrumental Activities of Daily Living (IADL), and Structured Psychiatric Interview for DSM-IIIR. We excluded anyone with potentially confounding medical, neurologic, or psychiatric problems. None met the published criteria for mild cognitive impairment (MCI)[16], AD[17], other forms of dementia or major depressive disorder[18]. Entry criteria for all participants included a score of at least 27 on the MMSE (and scoring at least 1 out of 3 on the recall subtest), a score of 10 or less on the Ham-D rating scale at the time of their first visit, and no indication of loss of function on the FAQ and IADL.

We also excluded from the analysis anyone who subsequently met published criteria for MCI, AD, or any other form of dementia during follow-up, and thus excluded 16 participants (four non-carriers, four heterozygous persons and 8 homozygous persons).

2.2. TOMM40

Genotyping of the genetic variants was performed by a sequencing vendor (Polymorphic DNA Technologies, Alameda CA, http://www.polymorphicdna.com). Four polymorphisms were analyzed for each genomic sample: rs8106922, rs429358, rs7412, and rs10524523. Polymorphisms rs429358 and rs7412 define the *APOE* genotype, and rs8106922, within *TOMM40*, is a key polymorphism identified in previous studies (phylogenetic and genome-wide association) as associated with risk of AD. The fourth polymorphism, rs10524523, is a homopolymer length polymorphism (poly-T) located in an intronic region of *TOMM40*. In the human reference sequence, the number of T residues in the homopolymer, “N”, is 35, and the specific variation described by rs10524523 is a 19 base pair deletion, making the homopolymer T16 (N=16 T residues) the variant allele. In the Duke/Polymorphic haplotyping work, other alleles of this homopolymer have been observed, with values of N ranging from 14 to 46 residues. For each genomic sample, Polymorphic simultaneously PCR amplified each polymorphism and then performed bidirectional direct Sanger sequencing of the DNA templates on an ABI 3730xl sequencing platform and sequence data analysis. The *TOMM40* poly-T lengths for each chromosome were converted to genotypes using the following standards[3]: short (S) poly-T (14–20 T residues), long (L) poly-T (21–29 T residues), and very long (>29 residues).

2.3. Neuropsychological Testing

As previously described[15], we selected a single measure of long-term memory loss, the Long Term Memory (LTM; Trial 7) score of the Auditory Verbal Learning Test (AVLT) (score range from worst to best is 0–15)[19] as the primary endpoint. The AVLT was administered to participants as part of a standardized battery of neuropsychological tests at baseline and then at intervals of one to two years. (Duration of participation is until death, onset of MCI or dementia, or the participant’s decision to stop.)

2.4. Statistics

To isolate the effect of longitudinal cognitive change, we used a statistical method to separate baseline from change in performance over time[20]. To assess the linear and quadratic effect of TOMM40 (S carriers versus L/L, L/VL, or VL/VL variant) and APOE (e4 noncarriers versus carriers) and the linear interaction between TOMM40 and APOE on cognitive change, a previously described mixed model[21] was modified to include a term for the quadratic effect of a binary risk factor. To compare the cognitive change between TOMM40 S/S and VL/VL variants within the APOE e3/3 group and to compare cognitive change between APOE e4/4 subjects with the TOMM40 L/L variant to the TOMM40 VL/VL group, a previously described mixed model[21] was applied without modification. Finally, to assess early (before age 60) and late (after age 60) effects of TOMM40 (S carriers versus L/L, L/VL, or VL/VL variants) and APOE (e4 noncarriers versus carriers), the following piecewise linear model for Y_{ij} (the j^{th} response for the i^{th} individual) was developed:

$$E(Y_{ij}|b_{1i}) = \beta_1 + \beta_2 APOE_i + \beta_3 TOMM40_i + \beta_4 Age_{i1} + \beta_5 APOE_i \times Age_{i1} + \beta_6 TOMM40_i \times Age_{i1} + \beta_7 APOE_i \times TOMM40_i \times Age_{i1} + \beta_8 Age_{ij} + \beta_9 APOE_i \times Age_{ij} + \beta_{10} TOMM40_i \times Age_{ij} + \beta_{11} APOE_i \times TOMM40_i \times Age_{ij} + \beta_{12} Age_{ij,60} + \beta_{13} APOE_i \times Age_{ij,60} + \beta_{14} TOMM40_i \times Age_{ij,60} + \beta_{15} APOE_i \times TOMM40_i \times Age_{ij,60} + b_{1i},$$

where $APOE_i$ is the APOE status for the i^{th} individual (1=e4 carrier; 0=e4 noncarrier); $TOMM40_i$ is the TOMM40 status for the i^{th} individual (1= L/L, L/VL, or VL/VL variant; 0=S carrier); Age_{ij} is the age of the i^{th} individual at the time of the j^{th} response; $Age_{ij,60}$ is the maximum of Age_{ij} minus 60 or zero; and b_{1i} is an individual specific random effect allowing each subject to have a different intercept. This model allows for comparison of the constant annual change (i.e., slope) before age 60 and after age 60 between the TOMM40 groups and between the APOE groups. Age 60 was selected because it was approximately equal to the median entry age. Modeling was carried out using SAS PROC MIXED (SAS Version 9, SAS Institute, Cary, NC). Baseline characteristics and followup were compared among groups by using the two-sample t-test/analysis of variance (ANOVA) F-test or Pearson chi-square test.

3. Results

639 individuals between ages 21 and 97 had the following *TOMM40* genotypes: S/S (n=88), L/L (n=54), VL/VL (n=110), S/L (n=107), S/VL (n=193), and L/VL (n=87). Table 1 summarizes the demographic data. They did not differ in years of education (15.6 +/− 2.5, p=0.99), gender (69.6% women, p=0.22), racial background (99.4% Caucasian, p=0.68), proportion with more than one followup visit (81.2%, p=0.76), or duration of followup (6.1 +/−3.1 years, p=0.27), but family history of dementia in a first degree relative was highest in the L/L subgroup (81.1%; p<0.001) reflecting the known linkage disequilibrium with *APOE* e4.

Combined TOMM40 and APOE genotype subgroups

To first gain an overall perspective of *TOMM40* and *APOE* effects, we condensed the large number of potential genotype combinations into four subgroups. We grouped S carriers together (n=388) and L and VL variants (L/L, L/VL, VL/VL genotypes) together (n=251) to generate two *TOMM40* groups: S carriers and L*L* (where L* can be L or VL). We also grouped *APOE* subgroups into e4 carriers and noncarriers, and thus created four subgroups: S/e4+, S/e4−, L*L*/e4+, L*L* e4−. Their cognitive aging trajectories are shown in figure 1. There were significant effects for both *TOMM40* (p=0.04 linear effect, p=0.03 quadratic

effect) and *APOE* (p=0.06 linear effect, p=0.008 quadratic effect) with no significant interaction (p=0.63).

Separate *TOMM40* and *APOE* genotype subgroups

To better understand specific *TOMM40* and *APOE* genotype effects, we next looked at specific genotype combinations that contained adequate numbers of individuals. Table 2 shows the distribution of *APOE* genotypes with *TOMM40* genotypes and demonstrates the association of the S and VL *TOMM40* variants with the e3 allele, and the L *TOMM40* variant with the *APOE* e4 allele. When only individuals with the *APOE* e3/3 genotype are considered, there is a significant difference in longitudinal memory trajectories between *TOMM40* S/S and VL/VL variants (p=0.04, linear effect, figure 2). The VL/VL group fails to show a normal test-retest effect from the earliest ages that is preserved in the S/S group. When VL/VL, S/VL, and SS groups were compared there was no evident VL gene dose effect of the test-retest flattening (linear trend, p=0.33). To compare the effect of L/L with VL/VL, we compared *APOE* e4/4 HMZ with the TOMM40 L/L genotype (the only group with a sufficient number of L/L) with the entire sample of VL/VL (none were also HMZ) (supplementary figure 1) and found that the L/L group, like the S/S group retained a normal test-retest pattern, but unlike the e3/3 subgroup, showed a striking accelerated decline in memory performance (p=0.009, quadratic effect). Because of tight linkage between e4 and L we cannot disentangle their respective effects on this decline, but more pertinently, unlike the VL/VL group, there is no loss of the normal test-retest effect.

These results suggested that there was an early effect (before age 60) attributable to *TOMM40* VL characterized by a flattened test-retest effect that may persist lifelong, and a late (after age 60) effect attributable to *APOE* e4 characterized by accelerated memory decline. To test this early *TOMM40* vs late *APOE* hypothesis, we compared *TOMM40* and *APOE* effects before and after age 60 years (the center point of our age distribution). This was formally tested by creating linear models before and after age 60 again using the following 4 subgroups: S/e4+, S/e4−, L*L*/e4+, L*L* e4− (supplementary figure 2). As suspected there was a significant *TOMM40* effect prior to age 60 (p=0.009) but no significant *APOE* effect; and a significant *APOE* effect after age 60 (p=0.006) but no significant *TOMM40* effect.

4. Discussion

APOE e4 carriers and e4 HMZ in particular are at greater risk for AD and have an earlier age of onset than e4 noncarriers. This association has been replicated many times since the original reports in the early 1990's[10]. Yet, the strong linkage disequilibrium patterns between specific alleles of *APOE* and *TOMM40* have led Roses himself and others to question whether *TOMM40* underlies or contributes to the apparent *APOE* effect, a suspicion that has received preliminary support from several small clinical series.

Although we found that the e4-L combination was associated with accelerated memory decline after age 60, the roles of *APOE* e4 and *TOMM40* L could not be separated due to strong linkage disequilibrium (table 2). Among those with the *APOE* e3/3 genotype, the *TOMM40* S/S subgroup showed a normal test-retest effect (illustrated by the positive slope of the 5 year interval changes in test performance at the younger age intervals), as did the *TOMM40L/L* subgroup (all of who also carried the APOE e4/4 genotype). The VL/VL subgroup, however, was associated with significant reduction of this test-retest effect. This "non-effect" of the VL allele on accelerated memory decline accords well with the recent clinical series by Cruchaga et al who found an association between age of AD onset and the S but not the VL TOMM40 allele, though we were unable to identify accelerated memory decline in association with the S allele as their study suggested[22].

The exact relationship of *TOMM40* to AD pathogenesis is not yet clear, but the greatest differences between *TOMM40* variants were found prior to age 60 with attenuated decline after age 60 among the S/S and VL/VL genotypes. Notably, this effect, as well as the previously demonstrated onset of preclinical memory decline in APOE e4 carriers[15] is occurring at a younger age than the Alzheimer's Disease Neuroimaging Initiative cohort on which a current popular model of AD pathogenesis is based[23]. The posterior cingulate is a brain region that is consistently observed to be hypometabolic with FDG-PET in patients with AD and in asymptomatic *APOE* e4 carriers, including young adults[24]. In expired young *APOE* e4 carriers Valla et al have shown that posterior cingulate cortex neurons have lower mitochondrial cytochrome oxidase activity than noncarriers despite the absence of soluble or fibrillar abeta amyloid or tau pathology suggesting this may be a very early change that precedes and promotes BACE1 activity and amyloidogenesis[25]. Whether *TOMM40* variants might help to account for the observed metabolic differences in young adults warrants further study since it is a mitochondria-based alteration with functional correlations in this age range.

Some might question whether a potential limitation of our study is that it was not population based, but instead genetically enriched for *APOE* e4. Because our intent was to study the behavior of genetic subgroups rather than determine incidence or prevalence rates of symptomatic disease, and because of the pattern of linkage disequilibrium between *APOE* and *TOMM40* alleles, our genetic enrichment strategy proved to be a strength that afforded us sufficient power to assess, to the extent possible, the major *APOE-TOMM40* combinations. In the absence of random community based sampling we could risk recruiting individuals concerned about their own cognitive health perhaps due to early stage AD in some. To address this we eliminated anyone who developed clinically symptomatic MCI or dementia at any point. Further, 80% had at least two epochs of testing with mean followup duration of 6 years that further reduced the likelihood that individuals with incipient symptoms were enrolled.

Another potential limitation of our study was that we did not reproduce an extensive analysis of the haplotype structure of this region. Roses et al. presented an extensive analysis of the haplotype structure of the *TOMM40-APOE* region based on molecular or phased-separated haplotypes[13]. This analysis defined the relationship between *APOE* alleles and rs10524523 lengths. An analysis of 300 phase-separated haplotypes showed that the *APOE* e3 allele is linked to either an S or VL allele of 523 98% of the time and that the *APOE* e4 allele is linked to the L allele of 523 87% of the time. It is possible to infer the haplotype structure of *APOE* and 523 with an accuracy of between 97% and 99%. Since these results were obtained in Caucasians and the present study is nearly 100% comprised of Caucasian subjects, the same haplotypic relationship is likely to exist between the *APOE* alleles and 523 alleles in our study.

How *TOMM40* will ultimately fit into the pathophysiologic mechanism of AD is not yet clear, and important basic insights still await evaluation in further sufficiently large clinical cohorts. Our results show that differences in a mitochondrial protein can correlate with differences in cognition and cognitive aging that are distinct from those of apoe, and that such effects may be most evident in cohorts younger than those on which current disease models are based.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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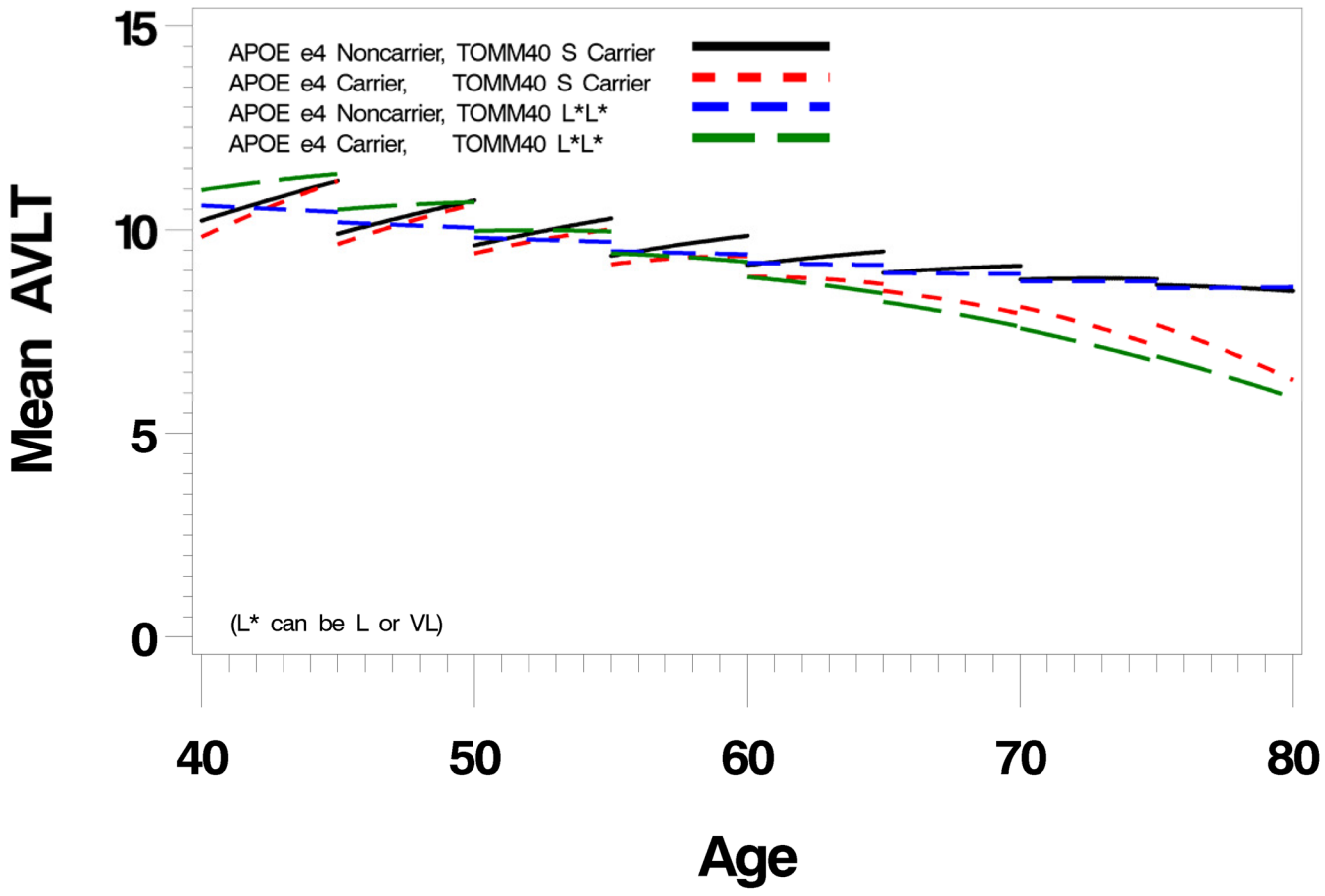

Figure 1.
Longitudinal trajectories (divided into five year intervals) of Auditory Verbal Learning Test Long Term Memory scores in four *TOMM40-APOE* defined subgroups (see text) including L*/L*/e4+, L*/L*/e4−, S/e4+, and S/e4−. There are noninteracting significant *TOMM40* and *APOE* effects with a flattening of the normal test-retest effect in the L*/L* subgroups prior to age 60, and accelerated decline in the e4+ subgroups after age 60. (L* is either the L or VL *TOMM40* allele)

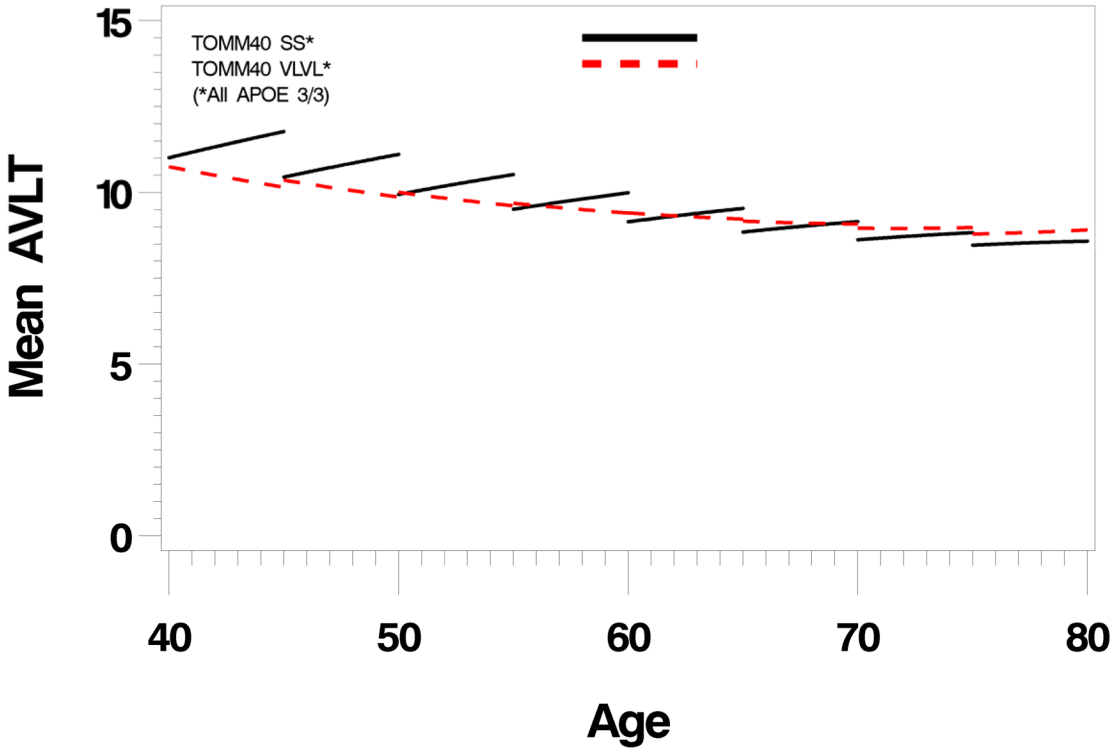

Figure 2.
Longitudinal trajectories (divided into five year intervals) of Auditory Verbal Learning Test Long Term Memory scores in people with the *APOE* e3/3 genotype subdivided into *TOMM40* S/S and VL/VL subgroups. There is a significant difference in the velocity of decline (p=0.04) between the *TOMM40* subgroups, that appears to reflect falttening of the test-retest effect in the VL/VL subgroup compared to the S/S subgroup.

Table 1

	TOMM40S/S	TOMM40 S/L	TOMM40 S/VL	TOMM40 L/L	TOMM40 L/VL	TOMM40 VL/VL	p
N	88	107	193	54	87	110	
Mean Entry Age (standard deviation)	57.8 (13.6)	57.3 (12.9)	59.3 (12.9)	56.1 (9.9)	55.3 (12.1)	60.9 (11.2)	0.02
Mean Years Education (standard deviation)	15.6 (2.3)	15.7 (2.5)	15.6 (2.5)	15.8 (2.3)	15.5 (2.6)	15.6 (2.7)	0.99
#Female (%)	67 (76.1)	72 (67.3)	127 (65.8)	42 (77.8)	65 (74.7)	72 (65.5)	0.22*
% FDR	52.9	69.8	47.6	81.1	79.1	57.3	<0.001*
%Caucasian	100	100	98.1	100	100	100	0.68*
% >1 epoch	81.8	84.1	78.8	85.2	78.2	82.7	0.76*

FDR=first degree relative with dementia. Unpaired t-tests except (*) chi square.

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Table 2

Crosstabulation of TOMM40 and APOE Genotypes

	TOMM40-S/S	TOMM40-S/L	TOMM40-S/VL	TOMM40-L/L	TOMM40-L/VL	TOMM40-VL/VL	Total
APOE-2/3	13	1	15	1	0	12	42
APOE-3/3	69	10	159	2	4	92	336
APOE-3/4	5	88	19	5	75	6	198
APOE-4/4	1	8	0	46	8	0	63
Total	88	107	193	54	87	110	639