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Cholesteryl ester transfer protein genotype modifies the effect of apolipoprotein ε4 on memory decline in older adults

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ABSTRACT

Apolipoprotein ε4 (ApoE4) is a strong genetic risk factor for sporadic Alzheimer's disease and memory decline in older adults. A single-nucleotide polymorphism in the cholesteryl ester transfer protein (*CETP*) gene (isoleucine to valine; *V405*) is associated with slower memory decline and a lower risk of Alzheimer's disease. As both genes regulate cholesterol, we hypothesized that the favorable CETPV405 allele may buffer the effect of ApoE4 on memory decline in older adults. Using linear regression, we examined the interactive effect of ApoE4 by CETPV405 on memory decline among 909 community-dwelling, nondemented, older adults (≥70 years) from the Einstein Aging Study. Episodic memory was measured using the picture version of the Free and Cued Selective Reminding Test with immediate recall (pFCSRT+IR). There was a significant *ApoE* × *CETP* interaction on decline in pFCSRT+IR scores ($p = 0.01$). ApoE4 carriers experienced faster decline than noncarriers among CETPI405I homozygotes ($p = 0.007$) and in CETPI405V heterozygotes ($p = 0.015$) but not in CETPV405V homozygotes ($p = 0.614$). Results suggest that the CETPV405 allele buffers ApoE4-associated memory decline in a gene dose-dependent manner.

1. Introduction

The apolipoprotein ε4 (ApoE4) allele is the most common genetic risk factor for sporadic Alzheimer's disease (AD; Strittmatter et al., 1993) and has also been associated with accelerated memory decline in older adults (Bretsky et al., 2003; Hall et al., 2014). ApoE4 carriers have aberrant cholesterol homeostasis and greater β-amyloid plaque deposition (Kok et al., 2009), a pathologic hallmark of AD (Puglielli et al., 2003). Many ApoE4 carriers do not develop AD, suggesting that gene–gene or gene–environment interactions may modify the risk of memory decline and dementia.

One candidate gene–gene interaction is the ApoE and the cholesteryl ester transfer protein (CETP) genes given that they are both expressed in the brain, linked to cerebral cholesterol metabolism and associated with cognitive function. There is a functional genetic variant at codon 405 of *CETP* in which the ancestral isoleucine allele is replaced by valine (NCBI dbSNP rs5882; CETPV405). Compared with *CETP* isoleucine allele homozygotes (CETPI405I), The CETPV405 allele is associated with reduced CETP-protein levels and higher high-density lipoprotein cholesterol (HDL-C) levels (Thompson et al., 2008). Whereas ApoE4 promotes the production of amyloid beta (Aβ), the higher HDL-C levels associated with the CETPV405 allele hinder the aggregation of Aβ into amyloid plaques (Olesen and Dago, 2000).

The CETPV405 variant was initially identified as a "longevity genotype" based on the observation that allele frequency increased with age (Barzilai et al., 2003). Subsequently, longitudinal studies in older adults found an association between the CETPV405 allele and lower rate of memory decline and a reduced risk of incident dementia (Chen et al., 2014; Lythgoe et al. 2015; Sanders et al., 2010; Yu et al., 2012), although not consistently (Johnson et al., 2007; Qureischie et al., 2008). Although not consistently (Jun et al., 2016), previous studies have reported evidence of the interactive effects of the *ApoE* and *CETP* genes on risk of AD (Arias-Vásquez et al., 2007; Murphy et al., 2012; Rodríguez et al., 2006). Furthermore, a structural neuroimaging study reported a CETPV405 by ApoE4 interaction on volume loss in the medial temporal lobe (MTL) over a 12-month period (Murphy et al., 2012). In a recent study of 4,486 adults aged 65 years and older, Lythgoe et al. (2015)

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found an ApoE4-moderated effect of CETPV405 on cognitive decline across 12 years of follow-up. Specifically, they found a stronger protective effect of the *CETP* Valine allele on cognitive decline as measured by a global measure of cognitive function (Modified Mini-Mental State Exam scores) among ApoE4 carriers versus non-carriers. We sought to further these findings by being the first to examine the interactive effect of CETPV405 and ApoE4 on decline in the cognitive domain that is most relevant to AD and regulated by the MTL, episodic memory, among older adults. Previous studies examined the moderating role of *ApoE* on the cognitive effects of *CETP* genetic variants; however, because the effect of ApoE4 on cognitive decline is robust and well established, unlike CETPV405, we focused on the moderating role of CETPV405 on the cognitive effects of ApoE4. We hypothesized that the effect of ApoE4 on memory decline would be greatest in *CETP* isoleucine homozygotes (CETPI405I), whereas among CETPV405 carriers, the effect of ApoE4 on memory decline would be attenuated in a dose-dependent manner.

2. Methods

2.1. Participants

Participants were recruited from the Einstein Aging Study (EAS), a prospective study that aims to identify risk factors for cognitive decline and incident dementia in a community-dwelling sample of ethnically and/or racially diverse, older adults. Systematic sampling procedures are used to recruit participants who are at least 70 years of age, ambulatory, and proficient in English. Sampling frames have been generated from Medicare enrollee lists (1993–2004) and Bronx County Voter Registration lists (since 2004). A total of 2,238 participants were enrolled in the EAS between October 1993 and November 2014. Among the 2,238 participants enrolled, 950 consented to genotyping and had valid genotyping data. Participants who were clinically diagnoses with dementia at the time of study enrollment were excluded from analyses (n = 38). Diagnosis of dementia was assigned by consensus at clinical case conferences using standardized clinical criteria provided by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association, 1994). Three participants were also excluded because they had no memory performance data (Free and Cued Selective Reminding Test [FCSRT] scores). Consequently, 909 participants were included in analyses. The use of human subjects and the study protocol were approved by the local institutional review board, and institutional review board-approved informed consent forms were obtained at clinic visits.

2.2. Procedure

2.2.1. Overall EAS protocol

EAS procedures have been previously described (Katz et al., 2012). Annual clinic visits at the EAS Clinic involve assessments of sociodemographic characteristics (age, sex, race and/or ethnicity, and so forth), medical history, and current medical status. Trained neuropsychological assistants administered a standard neuropsychological and clinical test battery at each annual clinic visit.

2.2.2. Outcome measure of memory decline

The FCSRT is an episodic memory test that controls attention and the strategy used during the encoding phase of a memory task. We used the picture version of the FCSRT with immediate recall (pFCSRT+IR), previously described in detail (Grober et al., 2000). Briefly, the test involves the learning of 16 unrelated pictures by identifying and naming each picture. After all 16 are correctly identified, the participant recalls as many of the pictures as possible in a "free recall" trial. There are 3 free recall trials, and this analysis uses the sum of correctly recalled pictures across trials (pFCSRT+IR; score range 0–48). pFCSRT+IR scores have been found to be predictive of incipient dementia (Buschke, 1984; Grober et al., 2000).

2.2.3. Independent measures

DNA was genotyped for the CETPV405 and ApoE4 single-nucleotide polymorphisms (SNPs). A phlebotomist drew 20 cc whole blood samples from participants who had provided genotyping consent at the EAS clinic. DNA was extracted from whole blood or was isolated from buffy coat that had been stored at −70°C using the Puregene DNA Purification System (Gentra System Inc, MN) at the Albert Einstein General Clinical Research Center. DNA was genotyped for the CETPV405 SNP (NCBI dbSNP rs5882) and for the 2 *ApoE* SNPs, rs429358 (position 112) and rs7412 (position 158). The primers used for amplification and sequencing were designed using the PSQ version 1.0.6 software (Biotage), and the reverse primer was biotinylated for all variants. Genotyping was performed using a Pyrosequencing PSQ HS 96A system 1.2 (http://www.pyrosequencing.com) according to manufacturer's instructions.

We examined the 3 possible CETPV405 genotypes: isoleucine homozygotes (CETPI405I), CETPV405I heterozygotes (CETPI405V), and Valine homozygotes (CETPV405V). *ApoE* genotype was categorized into ApoE4 carriers and noncarriers because of the low prevalence of ApoE4 homozygotes (1.7%) in our study. The more common genotype of ApoE4 noncarriers served as the reference group.

2.2.4. Clinical covariates

To assess functional ability, participants completed the Lawton Brody Activities of Daily Living questionnaire which includes the subscale of Instrumental Activities of Daily Living (IADL; Lawton and Brodie, 1969). Scores ranged from 0 (low function, dependent) to 8 (high function, independent). A medical comorbidity index was calculated using data from self-report questionnaires administered annually and defined as the combined presence of the following health conditions: hypertension, diabetes, angina, myocardial infarction, congestive heart failure, stroke, Parkinson's disease, rheumatoid arthritis, chronic obstructive pulmonary disease, and depression (score range: 1–10).

2.3. Statistical analysis

Demographic and baseline characteristics within each *ApoE* and *CETP* genotype group were assessed using summary statistics. Comparisons between *ApoE* and *CETP* genotype groups were performed using Kruskal–Wallis tests or analysis of variance for continuous variables and χ^2 tests for categorical variables. We used a χ^2 test to determine if *ApoE* and *CETP* genotype distributions met Hardy–Weinberg equilibrium.

Linear mixed effects models with random intercepts and random slopes were used to examine the separate and joint effects of *ApoE* and *CETP* genotypes on the rate of decline in pFCSRT+IR scores and test the hypothesis that the *CETP* Valine allele demonstrates a gene-dose effect in its buffering of ApoE4-associated memory decline. Models stratified by genotype and models including interaction terms were used for these analyses. All analyses were adjusted for age, sex, education, ethnicity and/or race (non-Hispanic white, non-Hispanic black, and Asian/other), IADL, and the medical comorbidity index. All covariates were predetermined based on biological plausibility and/or potential for confounding of the relationship between *ApoE*/*CETP* genotype and pFCSRT+IR performance. To examine a more homogeneous population, sensitivity analyses including only non-Hispanic white study participants was performed; it was not possible to repeat such

analyses in other ethnic and/or racial groups because of limited sample size. At last, because the ApoE2 allele of the *ApoE* ε polymorphism may have a protective effect on cognitive decline and AD risk that counters the deleterious ApoE4 effect (Suri et al., 2013), we also examined the interactive effect of *CETP* and ApoE2 carrier status on rate of pFCSRT+IR decline among ApoE4 noncarriers in a secondary analysis. All statistics were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA).

3. Results

Table 1 summarizes participant demographic, clinical, and cognitive characteristics at baseline based on *CETP* and *ApoE* genotype. The sample included 909 older adults (60.1% female) with an average age of 78.5 years and a mean of 13.2 years of education. The sample was predominantly white (66.9%). Subjects were followed for an average of 4.7 years with a median of 4 annual administrations of the pFCSRT+IR per person (range 1–16). Seventy-eight percent of participants had at least one follow-up pFCSRT+IR. The distribution of number of repeated pFCSRT+IR administrations did not differ by *CETP* genotype ($p = 0.36$) or *ApoE* genotype ($p = 0.55$). ApoE4 carriers were significantly younger ($p = 0.004$) and consisted of a significantly higher proportion of whites ($p < 0.0001$) compared with ApoE4 noncarriers. Among *CETP* genotype groups, there were significant differences in race ($p < 0.0001$), IADL scores ($p = 0.04$), and pFCSRT+IR scores ($p = 0.01$). The genotype distributions met Hardy–Weinberg equilibrium for both the *CETP* ($p = 0.10$) and *ApoE* ($p = 0.21$) SNPs.

As expected, there was a significant interaction between *CETP* and *ApoE* genotypes on the rate of decline in pFCSRT+IR performance ($p = 0.01$). Table 2 displays the rates of decline in pFCSRT+IR scores by *ApoE* genotype groups in analyses adjusted for age, education, sex, race, IADL, and medical comorbidities and stratified by *CETP* genotype. Among CETPI405I homozygotes, ApoE4 carriers showed a faster decline in pFCSRT+IR scores than noncarriers by 0.70 points per year (−1.02 vs. −0.32, $p = 0.007$). The difference in the rates of decline between ApoE4 carriers and noncarriers was reduced but remained significant among CETPI405V heterozygotes (difference = −0.49 points/year, $p = 0.01$). Among CETPV405V homozygotes, there was no difference in the rates of decline between ApoE4 carriers and noncarriers (difference = 0.11 points/year, $p = 0.61$). When analyses were stratified on ApoE4 status, the rate of decline in *CETP* Valine homozygotes was significantly slower than that in CETPI405I homozygotes among ApoE4 carriers (difference = 0.72 points/year, $p = 0.02$) but not among ApoE4 noncarriers (difference = −0.09 points/year, $p = 0.768$). The expected longitudinal trajectories of pFCSRT+IR scores over time by *ApoE* and *CETP* genotype are depicted in Fig. 1; ApoE4 carriers who are CETPV405V homozygotes resemble ApoE4 noncarriers more than ApoE4 carriers who are CETPI405I homozygotes. Among ApoE4 carriers, as the number of Valine alleles increased, protection from ApoE4-associated memory decline also increased (estimate = 0.37 points/year, $p = 0.01$). Results were similar when analyses were restricted to the non-Hispanic white subgroup (Supplementary Table 1), albeit they were not significant, possibly because of reduced sample size. When examining ApoE2 carriers versus noncarriers (excluding ApoE4 carriers), the ApoE2 allele did not show a significant protective effect on decline in pFCSRT+IR performance ($p = 0.44$). In addition, there was no interactive effect of *CETP* and ApoE2 carrier status on rate of decline in pFCSRT+IR performance ($p = 0.88$) indicating that the interactive effect of *CETP* and *ApoE* genotype on pFCSRT+IR decline is contingent on ApoE4, but not ApoE2, carrier status.

Table 2
Rate of decline (points per year) in pFCSRT+IR scores stratified by *ApoE* and *CETP* genotype (adjusting for age, sex, education, race, IADL, and the medical comorbidity index)

CETP Genotype	ApoE4− B (SE)	ApoE4+ B (SE)	*p*-value[a]
CETPI405I homozygotes	−0.32 (0.08)	−1.02 (0.25)	0.007
CETPI405V heterozygotes	−0.27 (0.07)	−0.75 (0.19)	0.015
CETPV405V homozygotes	−0.41 (0.10)	−0.30 (0.20)	0.614

Key: ApoE4, apolipoprotein ε4 allele; CETPI405I, cholesterol ester transfer protein isoleucine homozygotes; CETPV405I, cholesterol ester transfer protein valine heterozygotes; CETPV405V, cholesterol ester transfer protein valine homozygotes; pFCSRT+IR, picture version of the Free and Cued Selective Reminding Test with immediate recall; SE, standard error.
[a] For test of difference in rates between ApoE4+ and ApoE4−.

4. Discussion

In support of our hypothesis, we found that the *CETP* Valine allele carriers had a lower rate of ApoE4-associated memory decline in a dose-dependent manner. The adverse effect of the ApoE4 allele on episodic memory decline is striking among persons with the ancestral CETPI405I genotype. In the CETPI405I

Table 1
Participant characteristics at baseline by *ApoE/CETP* genotype group

Characteristics	Genotype group					
	CETPI405I homozygotes (N = 312)		CETPV405I heterozygotes (N = 420)		CETPV405V homozygotes (N = 177)	
	ApoE4+	ApoE4−	ApoE4+	ApoE4−	ApoE4+	ApoE4−
N	70	242	91	329	43	134
Age at baseline, y, mean (SD)	77.0 (4.5)	78.6 (5.3)	78.0 (5.5)	78.8 (5.2)	77.3 (4.3)	78.9 (5.8)
Education, y, mean (SD)	13.5 (3.4)	13.3 (3.7)	13.9 (3.4)	13.1 (3.6)	12.1 (3.4)	12.9 (3.6)
Female (%)	62.9	58.3	59.3	57.8	60.5	67.9
Race						
White[a] (%)	68.6	83.5	54.9	69.0	37.2	48.5
Black[a] (%)	25.7	12.4	39.6	24.0	62.8	42.5
Asian/other race (%)	5.7	4.1	5.5	7.0	0.0	9.0
Follow-up time, y, mean (SD)	4.0 (3.3)	4.2 (3.7)	4.0 (4.0)	4.4 (3.9)	4.7 (4.1)	4.7 (4.1)
Medical comorbidity index, mean (SD)	1.7 (1.3)	1.7 (1.1)	1.8 (1.4)	1.8 (1.1)	1.9 (1.1)	1.9 (1.2)
IADL, mean (SD)	6.6 (1.5)	6.4 (1.6)	6.6 (1.5)	6.4 (1.7)	6.6 (1.5)	6.8 (1.6)
pFCSRT+IR score, mean (SD)	31.3 (6.6)	31.1 (5.9)	29.5 (5.8)	30.1 (5.9)	30.2 (6.6)	30.5 (5.3)

Key: ApoE4, apolipoprotein ε4 allele; *CETP*, cholesterol ester transfer protein; CETPI405I, cholesterol ester transfer protein isoleucine homozygotes; CETPV405I, cholesterol ester transfer protein valine heterozygotes; CETPV405V, cholesterol ester transfer protein valine homozygotes; IADL, instrumental activities of daily living; pFCSRT+IR, picture version of the Free and Cued Selective Reminding Test with immediate recall; SD, standard deviation.
[a] Non-Hispanic.

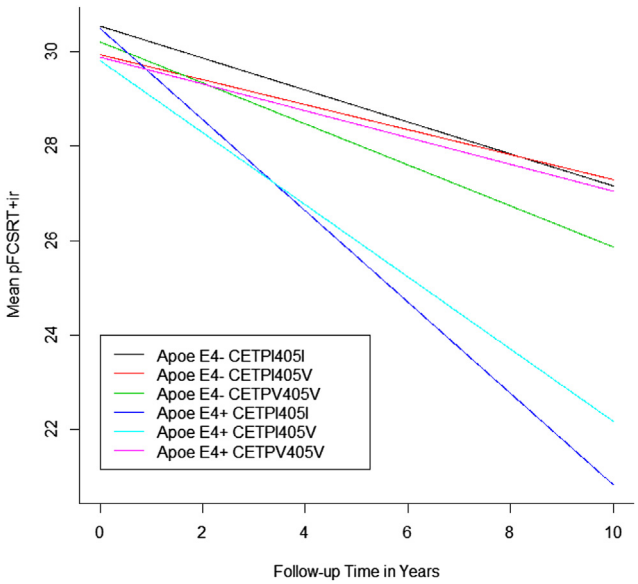

Fig. 1. Rate of decline in pFCSRT+IR performance across a 10-year, follow-up period for all ApoE/CETP genotype groups. Abbreviations: ApoE, apolipoprotein ε4 gene; CETP, cholesteryl ester transfer protein; pFCSRT+IR, picture version of the Free and Cued Selective Reminding Test with immediate recall.

group, ApoE4 participants demonstrated a decline in pFCSRT+IR scores that was greater than noncarriers by 0.62 points per year. Among CETPI405V heterozygotes, the adverse effect of the ApoE4 allele on memory decline remained significant but was ameliorated such that decline in pFCSRT+IR scores was greater in carriers versus noncarriers by 0.50 points per year. In contrast, among CETPV405V homozygotes, the adverse effect of the ApoE4 allele was eliminated as there was no significant effect of ApoE4 on rate of memory decline.

Although not consistently (Jun et al., 2016), previous studies have reported interactive effects of *CETP* genetic variants and *ApoE* genotype on risk of AD (Arias-Vásquez et al., 2007; Murphy et al., 2012; Rodríguez et al., 2006) and on global cognitive decline (Lythgoe et al., 2015). Analogous to the present findings, others have reported advantageous effects of the *CETP* Valine allele among ApoE4 carriers; including greater baseline cortical thickness, less 12-month MTL atrophy (Murphy et al., 2012) and preserved cognition over time (Lythgoe et al., 2015) among ApoE4 carriers. Conversely, findings are inconsistent when examining the effect of the *CETP* Valine allele among ApoE4 noncarriers. Whereas we did not detect an effect of the Valine allele on memory decline among noncarriers, others have reported the reverse association of the Valine allele with disadvantageous outcomes among noncarriers. Specifically, among ApoE4 noncarriers, the Valine allele was associated with greater MTL atrophy (Murphy et al., 2012) and a higher risk of dementia (Arias-Vásquez et al., 2007). Multiple factors could contribute to the discrepancies in the current and past findings including differences in study design (case control vs. cohort), cognitive outcome (cognitive decline vs. AD incidence), sample size, and sample characteristics (age, sex, and race). Similar to the present study, the only other study to examine the interactive effects of *ApoE* and *CETP* on rates of cognitive decline did not show a reversal of the Valine effect in carriers and noncarriers. Rather, they showed that a CETPV405 by ApoE4 interaction was because of a stronger protective effect of the Valine allele on cognitive decline among ApoE4 carriers versus noncarriers (Lythgoe et al., 2015). Thus, the finding of a protective effect of the *CETP* Valine allele on brain-related outcomes among ApoE4 carriers seems to be consistent across studies; however, the effect of the Valine allele among noncarriers remains to be clarified.

In a case-control study of 286 AD patients and 315 healthy controls (mean age = 75.4), Rodríguez et al. (2006) examined the interactive effects of *ApoE* and 2 *CETP* polymorphisms (V405 and TaqI B) on AD risk. They found that the TaqI B, but not the V405, polymorphism moderated the effect of *ApoE* on AD risk. Although the Rodríguez et al. (2006) findings were with the *CETP* TaqI B and not V405 SNP, we believe these results lend credence to the hypothesis that the *ApoE* and *CETP* genes interact to impact cognitive function likely through effects on cholesterol metabolism. Given that the V405 and TaqI B polymorphisms are in strong linkage disequilibrium and other studies have reported similar effects of the 2 polymorphisms on HDL levels (Thompson et al., 2008), it is likely that the V405 or TaqIB SNPs are linked mechanistically or one SNP is a marker for the other. Our study supports the *ApoE* by *CETP* interaction and further suggests that the interactive effects may not be specific to AD risk but also pertain to age-related memory decline.

There was a significant difference in the race distribution among *ApoE* and *CETP* genotype groups. Similar to previous reports, the proportion of CETPV405V homozygotes was higher among African Americans compared with Caucasians. This race difference may reflect a differential survival advantage in carriers of the beneficial *CETP* Valine allele that are African American, a group at higher risk for death from stroke (National Center for Health Statistics, 1997) and indicators of cardiovascular disease (Rooks et al., 2002). In addition, race differences may be due, in part, to isolation by distance over evolutionary time scales. We attempted to account for the potential effects of race by including it as a confounder in our overall group analysis and by repeating analyses in a non-Hispanic, white-only subsample. Race was not a significant factor in the overall group analysis and similar results were found in the white-only subsample suggesting that results were not an artifact of a population stratification bias in an ethically and/or racially diverse population.

Previous research suggests that the effect of ApoE4 on risk of dementia tends to diminish with advanced age (Sulkava et al., 1996). It was speculated that the weakened effect of ApoE4 in the oldest old is because of survivor bias in that individuals who carry ApoE4 are likely to develop dementia in their 70s and 80s. Incident dementia cases in individuals 90 or older are less likely to be ApoE4 associated (Sulkava et al., 1996). ApoE4 is also associated with negative cardiac outcomes including atherosclerosis which adversely impact longevity and likely contribute to the increased risk of dementia (Sulkava et al., 1996). The frequency of CETPV405 alleles increases with age likely due to the survival advantage it confers (Barzilai et al., 2003). We suggest that reduced influence of ApoE4 on the genetic risk of AD may be due, at least in part, to the increased frequency of the advantageous CETPV405 allele with age.

Despite a need for caution, the relationship between cerebral cholesterol metabolism and AD risk provides a plausible biological basis for the interactive effect of *CETP* and *ApoE* on memory. ApoE and CETP are expressed in the brain (Bu, 2009; Yamada et al., 1995) and impact cholesterol and lipid homeostasis. ApoE4 is associated with hyperlipidemia and hypercholesterolemia (Mahley and Rall, 2000) and promotes the production of Aβ, a protein which in excessive amounts, may lead to amyloid plaques (Olesen and Dago, 2000). Evidence suggests that the CETPV405 allele leads to reduced local synthesis of CETP in the brain, with the associated increased level of brain HDL-C levels (Thompson et al., 2008). HDL-C reduces excess cellular cholesterol, and HDL particles interact with Aβ to hinder its aggregation into amyloid plaques

(Olesen and Dago, 2000). The dose-dependent nature of the interactive effect of *CETP* and *ApoE* on memory decline further supports biological plausibility for a causal relationship. Therefore, it is plausible that the dose-dependent increase in HDL-C levels associated with the addition of a CETPV405 allele reflects an increasing buffering of the effect of ApoE4 allele on amyloid plaque formation, thereby decreasing AD-associated neuropathology. As an alternative, CETPV405 is associated with a reduced risk of vascular disease including stroke (Dullaart and Sluiter, 2008; Thompson et al., 2008). Therefore, the influence on cognitive decline could be mediated through reduced vascular disease as well.

A major strength of our study is the longitudinal design. In case-control studies of older adults, carriers of longevity genes such as CETPV405 may be over represented by virtue of their longevity and perhaps extended disease duration. Therefore, in case-control studies of longevity genes in older adults, associations between longevity genes and prevalent dementia may be attenuated. However, similar to other longitudinal studies, we may have experienced selective attrition although the duration of follow-up minimizes this risk. Other study limitations include our specific assessment of episodic memory using the pFCSRT+IR, a list-learning task, which limits us in generalizing results to other types of memory including semantic, working, or other episodic memory tasks such as paragraph recall. Second, the *ApoE* gene has 3 different allelic forms (ε2, ε3, and ε4) and, thus, 6 possible genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4). Although, it would be informative to examine the interactive effects of *CETP* with the 6 possible *ApoE* genotypes, we lacked the statistical power to do so because of the small size of certain genotype groups after further stratification by *CETP* genotype. Third, there were too few African-American CETPI405I homozygotes (N = 48) to conduct analyses in an African-American-only subsample. Therefore, we are able to generalize our results to white but not older African-American adults or other ethnicity and/or race groups. There is a need for further research to replicate our findings and investigate how ethnicity and/or race impacts the interactive effects of *CETP* and *ApoE* in larger samples.

In conclusion, the present report extends previous studies by suggesting that the interactive effects of CETPV405 and ApoE4 function in a dose-dependent manner in older adults and apply to the cognitive domain most closely associated with incipient dementia, episodic memory. We found that the CETPV405 variant allele buffers the negative effects of ApoE4 on memory decline in older adults in a dose-dependent manner. Our results highlight the importance of considering the *CETP* genotype in conjunction with *ApoE* when assessing risk of memory decline. Besides the functional difficulties and compromised quality of life that accompany cognitive decline, rapid decline in episodic memory can serve as a signal for incipient dementia, particularly AD (Salmon and Bondi, 2009). The protective interaction of the CETPV405 and ApoE4 alleles has implications for the discovery of genes linked to cognitive decline and incident AD. Identifying genetic variants associated with cognitive decline can inform intervention strategies that aim to diminish risk and help to direct intervention to individuals at high risk of dementia. These findings require replication in other samples and extension to other clinical end points including incidence of mild cognitive impairment, the transitional stage between healthy cognition and dementia.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neurobiolaging.2016.02.006.

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Web Table A. Whites only - Rate of decline (points per year) in pFCSRT+ir scores within each *ApoE* and *CETP* genotype group (adjusting for age, sex, education, IADL and the medical comorbidity index)

	ApoE4 non-carriers		ApoE4 carriers		p-value*
	N	B (SE)	N	B (SE)	
CETPI405I homozygotes	202	-0.35 (0.09)	48	-0.87 (0.17)	0.008
CETPI405V heterozygotes	227	-0.25 (0.08)	50	-0.84 (0.15)	0.0007
CETPV405V homozygotes	65	-0.45 (0.12)	16	-0.28 (0.19)	0.45

*For test of difference in rates between ApoE4 carriers and ApoE4 non-carriers. ApoE4 = apolipoprotein ε4 allele. CETPI405I = cholesterol ester transfer protein isoleucine homozygotes. CETPV405I = cholesterol ester transfer protein valine heterozygotes. CETPV405V = cholesterol ester transfer protein valine homozygotes. pFCSRT+ir = picture version of the Free and Cued Selective Reminding Test with Immediate Recall pFCSRT+IR.