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The *CETP* I405V polymorphism is associated with an increased risk of Alzheimer's disease

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Summary

The cholesteryl ester transfer protein (*CETP*) gene plays an essential role in regulating cholesterol homeostasis and is a candidate susceptibility gene for late-onset Alzheimer's disease (AD). Recent finding suggests that the *CETP* I405V polymorphism (rs5882) is associated with a slower rate of memory decline and a lower risk of incident dementia. Using data from two ongoing epidemiologic clinical–pathologic cohort studies of aging and dementia in the United States, the Religious Order Study and the Memory and Aging Project, we evaluated the association of the *CETP* I405V polymorphism (rs5882) with cognitive decline and risk of incident AD in more than 1300 participants of European ancestry. Our results suggest that the *CETP* I405V polymorphism was associated with a faster rather than a slower rate of decline in cognition over time, and an increased risk of incident AD. This finding is consistent with data showing that the *CETP* I405V is associated with increased neuritic plaque density at autopsy.

Key words: association study; cognitive decline; Alzheimer's disease; cholesteryl ester transfer protein.

Introduction

Late-onset Alzheimer's disease (AD) is among the most common and disabling conditions of aging and is accompanied by severe memory loss and decline in daily living functions. Recent genome-wide association studies have identified a growing number of validated susceptibility loci for late-onset AD, including *CR1*, *CLU*, *PICALM*, and *BIN1*, in addition to the well-known apolipoprotein E (*APOE*) locus (Harold *et al.*, 2009; Lambert *et al.*, 2009; Seshadri *et al.*, 2010). Given the central role of *APOE* in lipid metabolism, other genes in this pathway have also been considered as candidate AD susceptibility genes. Production of amyloid beta, a central piece in the pathological process in AD, may be regulated in part by cholesterol (Sparks *et al.*, 1994; Michikawa, 2003). Dysregulation of cholesterol homeostasis manifests as abnormal levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and HDL/LDL ratio (Zhu *et al.*, 2005). HDL is essential in limiting the amount of cholesterol deposition and removing excess cholesterol load in the cell, and reduced levels of HDL have been associated with the risk of AD (Merched *et al.*, 2000; Brewer, 2004).

Cholesteryl ester transfer protein (*CETP*) regulates cholesterol homeostasis via the transfer of cholesteryl esters from HDL to LDL in exchange for triacylglycerols (TG) (Tall, 1993; Barter & Kastelein, 2006). Several single-nucleotide polymorphisms (SNPs) within *CETP* have been suggested to influence the enzymatic activity or gene expression level. In particular, the Taq1B polymorphism (rs708272) is reported to be associated with lower plasma *CETP* concentrations and higher HDL cholesterol levels (Fidani *et al.*, 2004); C629A (rs1800775) within the gene promoter is associated with decreased expression (Dachet *et al.*, 2000); and I405V (rs5882) is associated with reduced *CETP*, higher HDL levels, and increased lipoprotein particle sizes (Blankenberg *et al.*, 2003). Studies of the link between *CETP* polymorphisms and susceptibility for late-onset AD have been equivocal. Among these, the Taq1B polymorphism was found to have no association with clinically diagnosed AD in several studies (Fidani *et al.*, 2004; Zhu *et al.*, 2005; Chen *et al.*, 2008). Alternatively, one study in the Spanish population found a lower risk of AD in subjects homozygous for C629A, but no association with I405V (Rodriguez *et al.*, 2006). Another study in the subjects of European ancestry found that I405V homozygosity was associated with increased susceptibility for AD, but only in the absence of the *APOE* ε4 allele (Arias-Vasquez *et al.*, 2007). In other reports, neither C629A nor I405V had significant effect on the risk of AD or age-related cognitive change (Johnson *et al.*, 2007; Chen *et al.*, 2008; Qureischie *et al.*, 2008).

In many of these studies, the sample sizes were relatively small and the results relied on cross-sectional case–control analyses. Recently, it has been proposed that more power may be gained through the use of endophenotypes such as level of cognition, change in cognitive function, and markers of neuropathology (Kennedy *et al.*, 2003; McQueen *et al.*, 2007; Bennett *et al.*, 2009; Shulman *et al.*, 2010). A recent study on the relation of *CETP* I405V with longitudinal memory decline and incidence of AD dementia found that valine homozygosity was protective (Sanders *et al.*, 2010).

In order to follow up this finding, we used data from two ongoing cohort studies of aging and dementia, the Religious Orders Studies (ROS) and the Memory and Aging Project (MAP), to assess whether *CETP* I405V is related to change in cognition over time and risk of incident AD, as well as AD neuropathology at autopsy.

Results

Genotype data

Genotype data were available on 1709 study participants. Three hundred and twenty-five participants were excluded from the analysis owing to the following criteria: 111 had dementia at baseline, eight self-reported non-European ancestry, 133 did not have information on *APOE*, and 73 had no follow-up evaluations (34 died prior to the first follow-up, 14 were yet to have the first follow-up, and 25 had only one valid cognitive

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measure). This resulted in a sample of 1384 participants (Table 1). The rs5882 allele frequencies satisfied Hardy–Weinberg equilibrium in the cohorts, both separately and combined. These frequencies are comparable to those reported in previous studies (Rodriguez *et al.*, 2006). The genotypic frequencies of the two cohorts did not differ ($\chi^2 = 0.55$, df = 2, $P = 0.76$).

Demographic characteristic of the cohorts

Although the two cohorts differ in some demographic characteristics, the percentage of *APOE* ε4 carriers in ROS and MAP did not differ ($P = 0.48$). The desire to maximize power together with the absence of significant difference in genotypic frequencies led us to combine data from the two cohorts for analyses, similar to what was done in previous studies (Chibnik *et al.*, 2011). The mean (± SD) age at enrollment was 78.3 (± 7.3) years. The average length of follow-up was 7.5 years. The mean (± SD) level of education was 16.3 (± 3.5) years, and 971 (70.1%) of the participants were women; 329 (23.8%) of the participants had at least one ε4 allele (Table 2).

Association of *CETP* I405V with the change in global cognition

We first examined the association of the *CETP* I405V variant with the rate of cognitive decline using the global measure of cognition. Based on prior work (Sanders *et al.*, 2010), our primary analyses tested the recessive genetic model comparing homozygotes for the minor allele (V/V) to the heterozygous (I/V) and homozygous major allele (I/I) classes. By examining the coefficients of the interaction between the genotype and time since baseline, we were able to test the SNP effect on change in cognition (Table 3). Participants with V/V had a steeper decline in global cognition as compared to those with I/V or I/I ($\beta = -0.025$, SE = 0.012, $P = 0.038$). Figure 1 displays the mean trajectories of global cognition for the groups with different I405V genotype, controlling for age, gender, years of education, and *APOE*.

Association of *CETP* I405V with the change in cognitive domains

Because prior publications suggest that the I405V variant may have a selective effect on change in episodic memory, we examined its relation to domain-specific summary measures of cognition. Analyses of five separate cognitive domains indicate that whereas the polymorphism was not associated with the rate of decline in episodic memory (Table 2), it was associated with a greater rate of decline in working memory (Table 3).

Table 1 Cholesteryl ester transfer protein I450V allele and genotype frequencies, *n* (%)

	ROS and MAP (*n* = 1384)	ROS (*n* = 641)	MAP (*n* = 743)
Allele			
I (isoleucine)	2004 (72.4)	920 (71.8)	1084 (72.9)
V (valine)	764 (27.6)	362 (28.2)	402 (27.1)
Genotype			
I/I	710 (51.3)	322 (50.2)	388 (52.2)
I/V	584 (42.2)	276 (43.1)	308 (41.5)
V/V	90 (6.5)	43 (6.7)	47 (6.3)
HWE	$\chi^2 = 4.31$, $P = 0.04$	$\chi^2 = 2.50$, $P = 0.11$	$\chi^2 = 1.88$, $P = 0.17$

ROS, the Religious Order Study; MAP, the Memory and Aging Project.

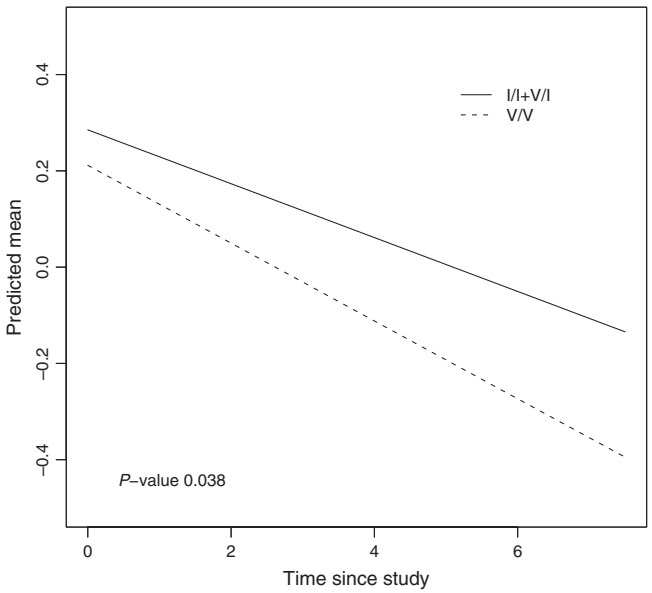

Fig. 1 Decline of global cognition for groups with different I405V genotype. Estimated mean trajectories of global cognition over time for groups with different I405V genotype, adjusted for baseline age, sex, education, and apolipoprotein E. The dotted line represents a typical subject with valine homozygote ($rs5882^{V/V}$), and the solid line refers to the one who had the other genotypes.

Subjects with V/V declined 50% faster compared with the other genotypes ($\beta = -0.024$, SE = 0.010, $P = 0.011$).

Association of *CETP* I405V with incident AD

We next examined the association between I405V and incident AD. Among the 1384 study participants nondemented at baseline and with at least one follow-up evaluation, 335 (24.2%) developed incident AD (Table 4). A chi-square test did not indicate an association between the SNP genotype (I/I, I/V, and V/V) and incident AD ($\chi^2 = 0.62$, df = 2, $P = 0.73$).

Cox proportional hazard models were used to examine the time to incident AD as the outcome of interest. Time was right censored at the last evaluation for those who did not receive the corresponding diagnoses. We again used a recessive model comparing the risk of $rs5882^{V/V}$ to that of the other genotypes, and controlling for age, sex, education, and *APOE*. The result shows that subjects with V/V genotype had higher risk of incident AD (HR = 1.63, 95% CI = 1.05–2.61, $P = 0.028$). This is illustrated in Fig. 2, which shows the cumulative hazard of AD between V/V (dotted) and the reference genotypes (solid).

Association between *CETP* I405V and AD pathology

The final set of analyses examined the relationship between *CETP* and measures of AD pathology obtained at autopsy. At the time of this analysis, we have almost 590 deceased participants with postmortem data. Depending on the distribution of the pathologic outcomes, a series of models were performed to investigate the association between pathologic outcomes and I405V genotype, controlling for age at death, sex, level of education, and *APOE*. We evaluated the association of the polymorphism with each of the following four pathologic outcomes separately, namely the global measure of AD pathology, and separate measures of neuritic and diffuse plaques and neurofibrillary tangles. As shown in Table 5, the result indicates that for subjects with neuritic

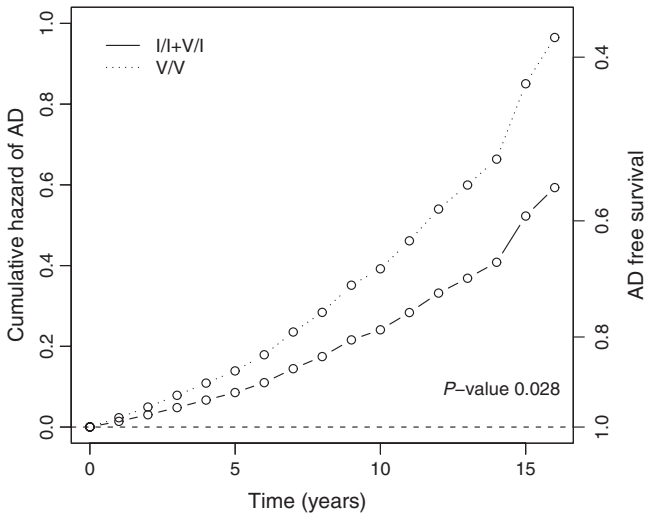

Fig. 2 Risk of incident Alzheimer's disease (AD) for groups with different I405V genotype. Estimated cumulative hazard of AD between rs5882$^{V/V}$ (dotted) and the reference genotypes (solid), adjusted for baseline age, sex, education, and apolipoprotein E. Additional scale for AD-free survival was shown on the right axis.

Table 2 Demographics of participants in the ROS and MAP cohorts

	ROS/MAP *n* = 1384
Age at enrollment	78.3 ± 7.3
Female, *n* (%)	971 (70.1)
Education	16.3 ± 3.5
Years of follow-up	7.5 ± 4.0
Any apolipoprotein E ε4, *n* (%)	329 (23.8)

ROS, the Religious Order Study; MAP, the Memory and Aging Project.

Table 3 Cholesteryl ester transfer protein I405V genotype on the decline in cognition

	Effect on change of cognition	
rs5882$^{V/V}$†	Estimates (SE)	*P*
Global cognition	−0.025 (0.012)	**0.038**
Episodic memory	−0.024 (0.015)	0.099
Semantic memory	−0.020 (0.013)	0.141
Working memory	−0.024 (0.010)	**0.011**
Perceptual speed	−0.020 (0.013)	0.143
Visuospatial abilities	−0.012 (0.011)	0.268

†rs5882$^{I/I+I/V}$ were used as reference. The *P*- values in bold indicate statistical significance.

Table 4 Distribution of incident Alzheimer's disease (AD) by cholesteryl ester transfer protein I405V genotype, *n* (column %)

	Incident AD subjects	Control subjects
rs5882$^{I/I}$	175 (52.24)	535 (51.05)
rs5882$^{I/V}$	136 (40.60)	447 (42.65)
rs5882$^{V/V}$	24 (7.16)	66 (6.30)

plaques, those with V/V had a higher density ($P = 0.038$). This result provides additional support for the *CETP* associations with the rate of cognitive decline and risk of incident AD and further suggests a potential mechanism.

Discussion

The *CETP* I405V polymorphism has recently been suggested to have a protective effect on memory decline and risk of incident dementia (Sanders *et al.*, 2010), although prior studies were equivocal (Rodriguez *et al.*, 2006; Arias-Vasquez *et al.*, 2007). Using data from two ongoing epidemiologic clinical–pathologic cohort studies, we investigated the association of I405V with cognitive decline, risk of incident AD, as well as AD pathology. Contrary to Sanders *et al.*, our results suggest that I450V was associated with a steeper decline in global cognition, an association that appears to be primarily related to decline in working memory. Moreover, valine homozygotes showed a higher risk of incident AD and, among deceased subjects, a greater density of neuritic plaques. Together, these data suggest that the *CETP* I405V polymorphism is associated with an increased risk of AD.

Several plausible factors might have contributed to the lack of agreement between our findings and those of Sanders *et al.* First, the discordant direction of effect could be due to population stratification and distortions in allele frequencies associated with a mixed race/ethnicity cohort. In contrast to Sanders *et al.*, our study was restricted to analyses of a homogenous population, including only participants of European ancestry in order to minimize potential confounding because of population stratification. This could be important because, based on HapMap data, the allele frequency of the I405V polymorphism differs substantially across race and ethnicity (International HapMap Consortium, 2007). The minor allele frequency of I405V in our cohort (27.6%) was lower than that reported in the Sanders *et al.*'s study (43.5%). Notably, that study included subjects of African American ancestry, in whom the valine allele is in fact the predominant variant (66%) – i.e., the minor allele rs5882^{V} in Europeans becomes the major allele in the African American population. A second possible explanation for the difference in the direction of the allelic association is the potential presence of genetic modifiers that vary by race/ethnicity. In this model, the putative valine risk allele that we observe in European ancestry subjects might behave instead as a protective allele in a predominantly African American cohort, because of the variation at additional unknown genes. Ultimately, it will be important to evaluate *CETP* I405V in a variety of homogeneous cohorts to differentiate among these potential explanations. Finally, it remains possible that the discordant findings reflect statistical fluctuation around the null hypothesis

Table 5 Cholesteryl ester transfer protein I405V genotype on brain pathology

Pathologic outcomes	Model	Difference by genotype (SE)		*P*-value
Global pathology	ANCOVA	0.094 (0.062)		0.129
Neuritic plaque	Zero-inflated regression	Absolute	0.124 (0.102)	0.224
		Conditional	0.156 (0.075)	**0.038**
Diffuse plaque	Zero-inflated regression	Absolute	0.055 (0.091)	0.546
		Conditional	0.065 (0.079)	0.413
Neurofibrillary tangles	ANCOVA	0.082 (0.64)		0.203

ANCOVA, analysis of covariance.
Conditional refers to mean estimates conditional on response $Y > 0$.
Absolute is the product of conditional estimates and estimated P ($Y > 0$).
The *P* -value in bold indicate statistical significance.

and that *CETP* I405V is in fact not a true AD risk allele. While an intriguing candidate gene the *CETP* locus has not been found in the top results of recently reported AD genome-wide scans (Hollingworth *et al.*, 2011; Naj *et al.*, 2011), future analysis of *CETP* in these studies and in larger ongoing genetic meta-analyses of AD will be important to understand the full impact of this locus on cognition and AD.

One strength of our analyses is that both study cohorts have relatively long follow-up. The average follow-up times are 6 years for MAP and 10 years for the ROS. More than 300 participants have been diagnosed with incident AD, and more than 500 brains have been autopsied. This allows us to investigate the full spectrum of disease progression, ranging from trajectory of cognitive decline over time, risk of disease onset, to the neuropathology after death. The full mechanism for the association of *CETP* I405V with AD susceptibility remains to be determined. The *CETP* I405V polymorphism has previously been shown to cause decreased *CETP* protein levels and increased HDL levels (Arias-Vasquez *et al.* 2007); however, as for *APOE*, the relationship between these genes role in lipid homeostasis and promotion of AD pathology and associated cognitive impairment remains to be elaborated. Our data suggest that the polymorphism may lead to clinical AD in part through an association with neuritic plaques. This is similar to what we have reported for the *APOE* and *CR1* susceptibility loci and is consistent with the central role of amyloid pathology in the clinical manifestation of AD (Bennett *et al.*, 2003; Chibnik *et al.* 2011). Importantly, recent evidence supports a role of *APOE* in regulating the clearance of amyloid beta peptide from the brain (Castellano *et al.*, 2011), and it is possible that *CETP* also participates in this process.

Experimental procedures

Study participants

Subjects are participants enrolled in two ongoing longitudinal clinical–pathologic cohort studies, the ROS and the MAP.

Participants from ROS are older Catholic nuns, priests, and brothers who agreed to annual clinical evaluations including a medical history, cognitive function testing, neurological examination, blood specimen collection, and brain donation at the time of death. They come from about 40 groups across the United States. Since January 1994, over 1100 persons completed the baseline clinical evaluation and the follow-up rate of survivors exceeds 95%. Detailed information on the ROS study has been published elsewhere (Wilson *et al.*, 2004; Bennett *et al.*, 2006a).

Participants from MAP are residents of approximately 40 senior housing facilities in the Chicago metropolitan area, including subsidized housing facilities, retirement communities, and retirement homes. Similar to ROS, participants from MAP have consented to undergo annual uniform, structured, clinical evaluations, including a medical history, cognitive function testing, neurological examination, and blood specimen collection, and brain donation at the time of death. Since October 1997, MAP study has enrolled over 1400 participants with follow-up rate of 90% among the survivors. Further information on the MAP study has been previously published (Bennett *et al.*, 2005a, 2006a).

Both studies were approved by the Institutional Review Board of Rush University Medical Center. Informed consent and an anatomical gift act were obtained from each participant following a detailed presentation of the risks and benefits associated with studies participation.

Genotyping

DNA was extracted from whole blood, lymphocytes, or frozen postmortem brain tissue. Genotype data for the *CETP* I405V polymorphism (rs5882) were extracted from an imputed genome-wide data set generated on the Affymetrix Genechip 6.0 platform at the Broad Institute's Center for Genotyping (n = 1204) or the Translational Genomics Research Institute (n = 674). These two data sets underwent the same quality control (QC) analysis in parallel. At the conclusion of the QC pipeline, 1709 individuals were available for analysis. The imputation was performed using MACH (version 1.0.16a) and HapMap release 22 CEU (build 36). Further details on genotyping have been previously published (Chibnik *et al.* 2011). The imputed I405V polymorphism (rs5882) has an O/E ratio of 0.61 (INFO score), indicating satisfactory imputation quality.

Cognitive decline, clinical AD, and neuropathologic outcomes

Annual cognitive function data have been collected from the participants of the two cohorts. Briefly, cognitive function was assessed via a battery of 21 tests in each study, of which 19 were in common, including the Mini-Mental State Examination which was only used to describe the cohort, and complex ideational material that was only used for diagnostic classification. The remaining 17 tests were combined into a composite measure of cognition, and also separate summary measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability as previously described (Wilson *et al.*, 2007).

To compute the composite measure of global cognitive function, raw scores on each of the individual tests were converted to z-scores using the baseline mean and standard deviation of the entire cohort, and the z-scores of all 17 tests were averaged. Higher scores indicate better performance in cognitive functions. Summary scores for the five cognitive domains were derived similarly. Psychometric information on these summary scores, including factor analytic support for the five domains, is contained in previous publications (Wilson *et al.*, 2002, 2005).

The follow-up clinical evaluations on ROS and MAP participants provided data on incident dementia/AD. Clinicians review all clinical data, blinded to data from previous years, and conduct an in-person examination of each subject when feasible. The clinical diagnosis of dementia/AD follows the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria as previously described (Bennett *et al.*, 2006a). Dementia criteria require evidence of loss of cognition from a previous level of performance with impairment in multiple areas of cognition. The NINCDS/ADRDA criteria for 'probable' AD require a loss of memory and other cognitive abilities, with impairment in two or more cognitive domains, one of which must be memory, as documented by neuropsychological performance testing.

Brain autopsies were performed for nearly all cases at 12 predetermined sites across the United States including the Rush AD Center. Autopsy procedures have been described in detail (Schneider *et al.*, 2004; Bennett *et al.*, 2005b, 2006b). A composite AD pathology score was used in the analyses. It was based on the counts of neuritic and diffuse plaques and neurofibrillary tangles as previously described (Bennett *et al.*, 2003, 2006c). Separate summary measures of neurofibrillary tangles and neuritic and diffuse plaques were created in a similar fashion.

Statistical analysis

To examine the association between genotype and change in cognition, random coefficient models were used to characterize individual trajectories of change in cognition and to test the relation of the SNP with annual rate of change in cognition (Wilson *et al.*, 2002), adjusting for age, sex,

level of education, and *APOE*. In these models, our outcome of interest is decline over time, and the interaction between time and valine homozygote is used to test the hypothesis that those with $rs5882^{V/V}$ decline at a different rate than those with $rs5882^{I/V+I/I}$.

To examine the association between the polymorphism and time to incident AD, we used discrete-time proportional hazards models as our primary analyses. Only those without AD diagnosis at baseline were included. The models included a term for SNP's genotype, as well as terms to adjust for age, sex, education level, and *APOE*. These models make the assumption that the hazards conferred by the risk factor are proportional over time. The strength is that they allow for any shape of the underlying hazard function.

For the pathologic outcomes, because the data were positively skewed, square root transformation was applied. Analysis of covariance was performed to check for the association between I405V genotype and a global measure of pathology and neurofibrillary tangles. Further examination of the data showed that for the outcomes of neuritic and diffuse plaques, there were huge spikes in the distribution at zero, even after the transformation. Therefore, zero-inflated regression models were applied in order to account for these excessive zeros, where we simultaneously modeled zeros vs. nonzeros with a logistic regression and all nonzero values with a linear regression.

Finally considering this is a replication study to confirm previous findings, we imposed a nominal threshold of $P < 0.05$ for significance in our analyses. All the analyses were implemented using SAS software, version 9.2 (SAS Institute Inc, 2008).

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