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Population-based analysis of CETP identifies association between I405V and cognitive decline: The Cache County Study

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Abstract

Cholesterol has been implicated in the pathogenesis of Late-onset Alzheimer's disease (LOAD) and the Cholesteryl Ester Transfer Protein (*CETP*) is critical to cholesterol regulation within the cell, making *CETP* an Alzheimer's disease candidate gene. Several studies have suggested that *CETP* I405V (rs5882) is associated with cognitive function and LOAD risk, but findings vary and most studies have been conducted using relatively small numbers of samples. To test whether this variant is involved in cognitive function and LOAD progression, we genotyped 4486 subjects with up to twelve years of longitudinal cognitive assessment. Analyses revealed an average 0.6-point decrease per year in the rate of cognitive decline for each additional valine ($p < 0.011$). We failed to detect association between *CETP* I405V and LOAD status ($p < 0.28$). We conclude that *CETP* I405V is associated with preserved cognition over time but is not associated with LOAD status.

Keywords

CETP; Alzheimer's; Alzheimer's disease; I405V; Cognitive Decline; Cache County

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1 Introduction

Late-onset Alzheimer's disease (LOAD) is a fatal neurodegenerative disease and is the sixth leading cause of death in the US. There are currently no successful therapies to prevent or treat LOAD, and predicting disease status remains a challenge (Ebbert et al., 2013). Apolipoprotein E (*APOE*)—a gene involved in cholesterol regulation—is the strongest predictor of genetic risk for LOAD in the general population. Cholesterol levels have since been shown to modulate LOAD risk (Hartmann, 2001). Similar to *APOE*, the Cholesteryl Ester Transfer Protein (*CETP)* gene facilitates cholesteryl ester and triglyceride exchange between lipoproteins (Plump & Breslow, 1995) and is found in the same pathway as *APOE*, making *CETP* a gene of interest in LOAD etiology.

Several studies have investigated associations between *CETP* and LOAD as well as cognitive function, but there is no clear consensus from the work to date. Barzilai et al. 2006 (Barzilai, Atzmon, Derby, Bauman, & Lipton, 2006) found an association between *CETP I405V* (rs5882) and preserved cognitive function in Ashkenazi Jews, but did not assess association with LOAD. Johnson et al. also investigated I405V and cognitive function in a Scottish cohort but found no significant association (Johnson et al., 2006). More recently, a study by Sanders et al. suggests *CETP I405V* is associated with preserved cognitive function as well as decreased LOAD and dementia risk in European Americans (Sanders et al., 2010). In the largest study to date, using nearly 6000 samples, Izaks et al. found that I405V is associated with increased cognitive function after age 65 in a Netherlands cohort, but did not investigate LOAD risk (Izaks et al., 2012). Reynolds et al. used Swedish cohorts to suggest CETP polymorphisms are unlikely to contribute to cognitive change or dementia (Reynolds, Gatz, Pedersen, & Prince, 2011). Conversely, Yu et al. suggest that CETP I405V is associated with an increased rate of cognitive decline and risk of LOAD in two European American cohorts (Yu et al., 2012). Here we further investigate the association between *CETP I405V* and LOAD and cognitive function and possible interaction with the *APOE* ε4 in the Cache County Study—a population-based sample of nearly 5000 individuals of European descent.

2 Methods

2.1 Study Population

Cache County Study on Memory Health and Aging was initiated in 1994 to investigate the association between *APOE* and environmental exposures on cognitive function and dementia (Breitner et al., 1999). A cohort comprising 5,092 Cache County, Utah residents constituting 90% of individuals aged 65+ was followed continually for over fifteen years, completing four triennial waves of data collection with additional clinical assessments for those at high risk for dementia as indicated by positive cognitive screening score and/or evidence of cognitive impairment from informant interviews. A "designated control panel" was created by age/gender/genotype-stratified random sampling from among all subjects completing initial screening (but blinded to screening result), matched to # of suspected cases of AD at 2:1 ratio, expected in youngest two age strata 65–69 and 70–74 years. The samples in the designated control panel received full clinical assessment in all waves. Collected data includes measures of cognitive performance and dementia as determined by

the Modified Mini-Mental State Examination (3MS) (Tschanz et al., 2002) as well as demographic variables, medical conditions, medication and supplement use, and environmental exposures. DNA samples were obtained from 97.6% of participants.

2.2 Genotyping

For this study, DNA samples were available for 4486 subjects. Genotyping was performed at Brigham Young University using the c_790057_10 TaqMan Assay according to the manufacturer's recommendation on the ViiA 7 apparatus using the ViiA 7 software (Applied Biosystems). Alleles were determined using the default calling criteria.

2.3 Analysis

Linear mixed effects models were used to determine the association between cognitive decline over time while controlling for the presence/absence of the *APOE* ε4 allele, age, education, and gender. Interaction terms were added to these regression models to assess the differential rate of cognitive decline by CETP genotype, as well as the modifying effects of *APOE* genotype on the association between *CETP* and 3MS. Cox Proportional Hazard models were also used to test association between genotype and LOAD-free survival. All analyses were performed using SAS version 9.3.

3 Results

Analyses of cognitive decline and dementia-free survival included a total of 4962 subjects. Basic characteristics of these samples are provided in table 1. Analyses revealed an association between CETP I405V and slower 3MS decline. This decline occurred at a rate of 0.6 points less per year than average for each additional valine ($p < 0.011$). We detected a trend toward a mitigating effect of *APOE* genotype on the association between *CETP* and progression ($p = 0.097$ for an interaction between *APOE, CETP*, and time). Specifically, individuals with additional *APOE* ε4 alleles experienced less rapid cognitive decline relative to each additional *CETP* I405V valine replacement. For example, among those with no *APOE* ε4 alleles, each additional *CETP* valine slowed 3MS decline by 0.4 points per year, on average. However, among those with a single *APOE* ε4, each additional valine slowed the annual average decline by 1.1 points.

We failed to detect association between *CETP* I405V and LOAD status in the total sample and in the APOE ε4 carrier/non-carrier strata. There was a trend toward a protective effect in ε4 non-carriers (OR = 0.87, CI = 0.69 – 1.08; p=0.21).

931 subjects with diagnosis of AD were further analyzed for dementia progression (for sample characteristics see table 1). Our analysis of these demented subjects indicates that each additional CETP valine is associated with an average MMSE that is 0.5 points higher at dementia onset ($p = 0.03$). However, there is no evidence that the rate of subsequent progression is associated with CETP ($p = 0.28$ for CETP, time interaction).

4 Discussion

Here were have reported the effects of CETP I405V on cognitive decline in a large, population-based sample. Our findings demonstrate a decrease in the rate of cognitive decline as measured by MMSE of 0.6 points fewer per year for each additional valine. These findings reaffirm the role of *CETP* I405V in cognitive decline as previously reported by Izaks et al. in the largest study of the effects of *CETP* I405V on cognitive function to date (Izaks et al., 2012).

We also evaluated the possibility of an *APOE* ε4-moderated effect of *CETP* on cognitive decline. While our results were not significant, they show an intriguing trend, suggesting that the CETP I405V variant has a stronger protective effect on cognition in the presence of the *APOE* ε4 allele. Further analysis in independent cohorts is needed to determine the precise nature of the *APOE*-mediated effects of *CETP* I405V on cognitive decline.

We failed to detect association between CETP I405V and either risk for LOAD or rate of progression of LOAD. These findings are consistent with work by other groups, which has failed to detect association between this variants and risk for LOAD (see Alzgene.org; Arias-Vásquez et al., 2007; Chen et al., 2008; Giedraitis et al., 2009; Qureischie et al., 2008; Reynolds et al., 2011; Rodríguez et al., 2006). Our results combined with these previous reports suggest that *CETP* I405V is not a LOAD risk factor. It has been suggested that CETP I405V and APOE e4 interact to affect LOAD risk

Arias-Vásquez et al. found an increase in AD risk for *CETP* individuals homozygous for the valine allele without *APOE* ε4 but no association with risk of AD in carriers of the ε4 allele (Arias-Vásquez et al., 2007). Murphy et al. reported that carriers of the APOE ε4 with the V allele had less atrophy in the entorhinal and hippocampal cortices (early predictive places for memory problems and AD development) but no apparent effect on the risk of AD. Non-carriers of *APOE* ε4 have more atrophy and a higher risk of AD with the V allele (Murphy et al., 2012). We failed to detect association in with AD risk in both the APOE e4 carrier and non-carrier strata.

4.1 Conclusion

Our findings provide further support for decreased rate of cognitive decline in carriers of the CETP I405V variant. We failed to detect association with risk for AD and with rate of decline of AD. These results suggest that the CETP I405V variant influence general cognitive function in a manner that is not directly related to AD pathogenesis. A better understanding of the connection between *CETP* I405V and cognitive decline but not LOAD could illuminate differences between cognitive decline in the general population and cognitive decline associated with dementia.

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Highlights

- Genetic analysis of *CETP* I405V and cognitive decline in nearly 5000 samples from a population-based, 15-year longitudinal study
- Significantly lower rate of cognitive decline in carriers of *CETP* I405V variant
- Trend for an APOE ε4-moderated effect of *CETP* on cognitive decline
- No evidence of association with risk for AD or with rate of decline of AD

Table 1

Demographics.

	Total Sample	AD only
N	4962	931
Age	76/7.3	82/7.1
Percent Female	43%	39%
Follow-up Time	5.1/4.4	4.8/3.2
APOE e4	32%	48%
I405V	47/10/43	48/11/41

Age (mean/SD; age at onset is presented for AD group), Percent female, Follow-up time (mean/SD), Percent of APOE e4 carriers genotypes (APOE e4), and genotype frequencies of I405V (AA/AG/GG) are shown for the total sample and the subset with AD diagnosis.