Population-based analysis of cholesteryl ester transfer protein 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 12 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 < 0.01). We failed to detect the 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.

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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 United States. 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 modulated to LOAD risk (Hartmann, 2001). Similar to APOE, the cholesteryl ester transfer protein (CETP) gene facilitates cholesteryl ester and triglyceride exchange between lipoproteins (Plump and 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) found an association between CETP I405V (rs5882) and preserved cognitive function in Ashkenazi Jews but did not assess association with LOAD. Johnson et al. (2007) also investigated I405V and cognitive function in a Scottish cohort but found no significant association. More recently, a study by Sanders et al. (2010) suggests CETP I405V is associated with preserved cognitive function as well as decreased LOAD and dementia risk in European Americans. In the largest study to date, using nearly 6000 samples, Izaks et al. (2012) found that I405V is associated with increased cognitive function after age 65 years in a Netherlands cohort but did not investigate LOAD risk. Reynolds et al. (2011) used Swedish cohorts to suggest CETP polymorphisms are unlikely to contribute to cognitive change or...
dementia. Conversely, Yu et al. (2012) suggest that CETP I405V is associated with an increased rate of cognitive decline and risk of LOAD in 2 European American cohorts. Here, we further investigate the association of CETP I405V with LOAD and cognitive function as well as the possible interaction with the APOE ε4 allele 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 5092 Cache County, Utah residents constituting 90% of individuals aged 65 years and older was followed continually for over 15 years, completing 4 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 and/or 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 the subjects completing initial screening (but blinded to screening result), matched to # of suspected cases of AD at 2:1 ratio, expected in the projects completing initial screening (but blinded to screening result), matched to # of suspected cases of AD at 2:1 ratio, expected in the years. The samples in the designated control panel received full clinical assessment in all waves. Collected data include measures of cognitive performance and dementia as determined by the Modified Mini-Mental State Examination (3MS) (Tschonz 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 or the 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 and/or noncarrier strata. There was a trend toward a protective effect in ε4 noncarriers (odds ratio = 0.87, confidence interval = 0.69–1.08; p = 0.21).

A total of 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 Mini-Mental State Examination 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, we have reported the effects of CETP I405V on cognitive decline in a large, population-based sample. Our findings demonstrate a decline in the rate of cognitive decline, as measured by Mini-Mental State Examination, 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 Izsaks et al. (2012) in the largest study of the effects of CETP I405V on cognitive function to date.

We also evaluated the possibility of an APOE ε4-mediated effect of CETP on cognitive decline. Although 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; Gedraitis et al., 2009; Quereschie et al., 2008; Reynolds et al., 2011; Rodriguez 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 ε4 interact to affect LOAD risk.

Arias-Vásquez et al. (2007) found an increase in AD risk for CETP individuals homozygous for the valine allele without APOE ε4 but with no association with the risk of AD in carriers of the ε4 allele. Murphy et al. (2012) 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. Noncarriers of APOE ε4 have more atrophy and a higher risk of AD with the V allele. We failed to detect association in with AD risk in both the APOE ε4 carrier and noncarrier 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 the 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.

Disclosure statement

The authors have no conflicts to disclose.

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References


