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Original Article

An assessment of *CETP* sequence variation in relation to cognitive decline and dementia risk

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Abstract: The gene encoding the cholesteryl ester transfer protein (*CETP*) plays an integral role in lipid metabolism. We evaluated common genetic variation spanning *CETP* for association with cognitive decline as well as incident and prevalent dementia and Alzheimer disease risk. Data from four population-based twin studies and a case-control sample were included, encompassing an analysis sample of 1513 dementia cases and 2137 controls with available *CETP* genotypes and covariates. Memory and perceptual speed performance was assessed over 16 years in up to 1540 participants. Only sporadic associations were observed across 26 markers and were largely consistent with statistical noise. Polymorphism in CETP is unlikely to contribute to cognitive change or dementia risk.

Keywords: Alzheimer disease, dementia, cognitive decline, CETP association, cholesteryl ester transfer protein

Introduction

Genetic association studies of dementia and Alzheimer disease risk are abundant, with four genes now identified that exhibit significant association in a genome-wide context, including *CLU*, *CR1*, *PICALM*, and the well-established genetic risk factor, *APOE* [1-3]. In contrast, studies of genetic association with cognitive decline that predate overt disease are less common and with relatively equivocal results for candidates beyond *APOE* [4, 5]. The association of *APOE* with dementia provides a strong indication that lipid metabolism is integrally involved in the disease. Variation in APOE is the strongest common genetic determinant of serum LDL, whereas variants of the gene encoding the cholesteryl ester transfer protein (*CETP*) are the strongest determinants of serum HDL [6]. As such, *CETP* has also emerged as an intriguing candidate for dementia risk and cognition [7-10] and was recently highlighted in a report of the common V405I variant in *CETP* in relation to episodic memory decline and incident dementia [11]. In the present study, we sought to further investigate *CETP* in relation to cognitive decline and dementia, by assessing a relatively large sample with longitudinal cognitive measures, and by providing coverage of the full extent of common genetic variation in the *CETP* genomic region.

Materials and methods

The present study drew participants from four related twin studies of aging stemming from the population-based Swedish Twin Registry and an independent non-twin case-control Swedish AD sample [12, 13]. Across samples, *CETP* genotypes and covariates were available for 1513 dementia cases (including 252 incident cases) and 2137 controls, with 572 men and 941 women in the dementia group and 957 men and 1180 women in the control group. There were 1233 with possible or probable AD diagnoses (122 were incident cases). Average age-at-sampling across cases and controls (N=3650) was 77.9 ± 8.5 (SD) years and available age-at-onset for dementia/AD cases (N=1424) was 75.3 ± 8.3 (SD) years. The samples were described in detail recently [13]. In brief, the twin samples are derived from the Swedish Adoption/Twin Study of Aging (SATSA) [14, 15], the Origins of Variance in the Oldest-Old (OCTO-

Twin) [16], Sex Differences in Health and Aging Study (GENDER) [17], and the Study of Dementia in Swedish Twins (HARMONY) [18]. The case-control sample was comprised of unrelated individuals recruited from three prospective studies of patients with dementia from Mölndal, Piteå, and Malmö, Sweden [13].

Memory and perceptual speed performance were assessed over 16 years in up to 1540 participants. Cognitive measures were available from the SATSA, GENDER, OCTO-Twin studies and for the present analysis included: Thurstone Picture Memory (all studies), Digit Span (SATSA and OCTO-Twin), and Symbol Digit (all studies), representing episodic memory, working memory, and speed of cognitive processing respectively [15, 16]. The median age at first testing was 74.0 years (interquartile range = 15.8, range= 50.1 to 93.3) with a median follow-up time of 7.8 years (interquartile range = 5.2, range= 0 to 17.8). Among MZ pairs, 88 twins with cognitive data but without genotyping were assigned their cotwin's *CETP* genotypes.

First available HDL lipid values from the SATSA and OCTO-Twin studies were considered for analysis with *CETP* markers. Only non-demented individuals who had at least one *CETP* marker and complete covariate data were included (N=983). The average HDL value was 1.50 mmol/L (SD=.43, range=3.50). Log-transformed values were used for analysis with a mean logged value of .37 (SD=.28).

Genetic markers in *CETP* (including 20kbp upstream of the transcription start site and 20kbp downstream of longest known 3'UTR) were selected with previous association study findings, functional candidature, linkage disequilibrium (LD), and Illumina SNP design score as criteria. Prioritization encompassed markers in exons, within 80bp of exon boundaries, and within 1kb upstream from the 1st exon or downstream from the last exon of any predicted gene in the UCSC genome browser, and SNPs that tag LD blocks. Genotyping was conducted using the Illumina GoldenGate assay system on Illumina BeadStation 500GX equipment. Prior to genotyping, all samples were subjected to Whole Genome Amplification (WGA) with standard kits using Phi29 DNA polymerase (Amersham). Hardy-Weinberg equilibrium (HWE) for individual loci was assessed using the Pearson χ^2 statistic. For primary analyses, we used genotypes for 26 of 32 tested CETP SNPs that had success rates of 91-98.4% across samples. For the remaining six SNPs, three assays gave no results, and three had both low call rates (<80%) and deviated significantly from HWE and were thus excluded.

Multilevel models were applied to longitudinal cognitive data using SAS PROC MIXED (SAS Institute, Inc., Raleigh, NC) with full maximum likelihood estimation [19]. The fitted quadratic growth model characterized cognitive change in terms of performance level at age 75 years (i.e., intercept, I), linear slope at age 75 years (S), and quadratic trend over age (Q). Both fixed and random effects were estimated to reflect the average trajectory and variation in trajectories, respectively. Twin pair dependencies were accounted with estimation of between- and within-pair random effects. A baseline model was fitted with covariates (number of APOE e4 alleles, sex, education level, and an illness sum score adapted from Sanders et al [11]). In subsequent models, each *CETP* SNP was entered as a predictor of the growth components (I, S, Q). No particular genetic model was assumed for any *CETP* SNP where genotype was treated as a class variable. An omnibus difference chi-square test with 6 df indicated the extent of improvement in fit by adding the *CETP* SNP as a predictor of growth processes. Probabilities associated with the chi-square difference test are reported in **Table 1.**

To account for pair dependency in tests of association with dementia outcomes, we used alternating logistic regression (ALR), including both members of the pair while accounting for MZ and DZ pair correlation structures [20, 21]. Case-control participants were treated as incomplete DZ pairs. ALR analyses were performed using SAS PROC GENMOD (SAS Institute, Inc., Raleigh, NC). The type 3 probabilities with 2 degrees of freedom are presented in **Table 2**, adjusted for sex, last age at follow-up, and *APOE* e4 alleles. Cox proportional hazard models were fitted to onset age for dementia outcomes, over pairs and stratified by twin type, using SAS PROC PHREG (SAS Institute, Inc., Raleigh, NC). Robust sandwich estimates were obtained in order to adjust for pair dependencies and probabilities associated with Wald chi-square tests of each CETP SNP are reported. Probabilities are shown in **Table 3**, adjusted for sex and number of *APOE* ε4 alleles.

Table 1. Probabilities of the association of CETP SNPs with cognitive decline and HDL levels

		Trait (N)			
Position	RS#	Thurstone (1540)	Digit Span (1194)	Symbol Digit (1493)	HDL* (983)
55538741	rs247611	4.33E-01	5.88E-01	7.42E-01	8.70E-01
55542640	rs9989419	2.89E-01	5.36E-02	9.41E-01	1.42E-01
55549518	rs6499863	2.12E-01	1.11E-01	**3.33E-02**	5.13E-01
55550712	rs12708967	2.23E-01	**3.49E-02**	4.82E-01	7.43E-02
55550825	rs3764261	4.17E-01	**3.94E-02**	4.99E-01	**9.60E-04**
55551693	rs12447924	5.72E-01	2.18E-01	4.83E-01	6.48E-01
55552029	rs17231506	9.45E-02	**3.18E-02**	4.19E-01	**6.20E-04**
55552737	rs1800775	7.31E-01	5.06E-01	1.43E-01	**2.85E-02**
55554734	rs1864163	3.41E-01	9.44E-01	**3.60E-02**	**2.90E-04**
55556073	rs9929488	1.97E-01	6.81E-01	**2.44E-02**	**1.03E-02**
55556759	rs7203984	9.06E-01	8.19E-01	2.10E-01	**1.23E-03**
55562390	rs7205804	3.34E-01	3.40E-01	1.01E-01	**1.29E-02**
55562802	rs1532625	2.86E-01	3.28E-01	1.04E-01	**9.70E-03**
55563051	rs12708974	5.49E-01	**1.92E-02**	7.11E-01	6.87E-01
55564693	rs9930761	3.51E-01	2.29E-01	2.89E-01	5.20E-01
55564854	rs5883	4.38E-01	6.33E-01	1.78E-01	**3.79E-02**
55566889	rs289717	3.55E-01	5.58E-02	4.91E-01	9.79E-01
55568744	rs12720898	8.16E-01	**1.51E-02**	4.58E-01	2.71E-01
55572592	rs5880	9.59E-01	6.39E-01	1.20E-01	**3.60E-04**
55573046	rs1800774	7.18E-01	4.19E-01	2.28E-01	1.26E-01
55573593	rs5882	5.13E-01	1.82E-01	7.60E-02	4.66E-01
55575163	rs1801706	1.17E-01	**4.01E-03**	8.96E-01	5.17E-01
55575263	rs289742	9.47E-01	2.08E-01	3.45E-01	5.65E-02
55577033	rs289745	**9.62E-03**	5.88E-02	5.99E-01	9.53E-01
55577828	rs17369163	9.56E-01	5.02E-02	1.81E-01	3.13E-01
55578934	rs12934552	2.46E-01	9.85E-01	9.65E-02	8.25E-01

Note. The sample sizes (N) reflect those with at least one CETP marker and covariates. The probabilities shown are not corrected for multiple testing. The cognitive performance outcomes are adjusted for the number of APOE ε4 alleles, sex, education level, and an illness comobidity sum (hypertension, diabetes, angina, myocardial infarction, congestive heart failure, stroke, Parkinson disease, rheumatoid arthritis, emphysema and bronchitis).The probabilities reported for HDL levels were adjusted for sex, age at HDL sampling and the number of APOE ε4 alleles. *Non-demented individuals only.

Results and discussion

Across all cognitive outcomes there was no convincing evidence of association after correcting for the number of tests (286 tests; see **Tables 1-3**). While a strict Bonferroni correction is overly conservative given trait and marker correlation, generously assuming an average correlation of 0.5 across traits would suggest p-values below 2.96E-03 would survive testing (Note: The average absolute correlation among cognitive, HDL, and dementia status traits was 0.23. However, incident dementia/AD and total dementia/AD are overlapping traits. Thus, we assumed a higher correlation, thereby increasing the possibility for markers to survive testing and balancing the chance of being overly conservative). Only one marker achieved this threshold for incident dementia risk (rs9929488). Notably, there was no association with rs5882 (V405I) with any of the cognitive outcomes (see **Table 1**) or incident dementia risk (see **Tables 2-3**) (cf. [11]). We briefly review the results across outcomes.

For the measure of episodic memory, Thurstone Picture Memory, only one uncorrected *p*-value < 0.05 was observed for rs289745 (*p* = 9.62E-03) (see **Table 1**). The Digit Span memory task showed six uncorrected signals below p < 0.05 with no evidence for rs5882, and none below a *p* of 2.96E-03. The Symbol Digit perceptual

Table 2. Probabilities of the association of CETP SNPs with dementia risk

Position	RS#	Incident Dementia	Incident AD*	Total Dementia	Total AD
55538741	rs247611	6.20E-01	7.05E-01	9.29E-02	1.52E-01
55542640	rs9989419	6.11E-01	3.63E-01	4.24E-01	3.10E-01
55549518	rs6499863	2.76E-01	9.60E-01	1.39E-01	1.52E-01
55550712	rs12708967	**1.53E-02**	3.35E-01	1.56E-01	1.15E-01
55550825	rs3764261	8.13E-01	7.02E-01	9.24E-01	7.14E-01
55551693	rs12447924	**4.62E-02**	1.37E-01	6.17E-01	7.36E-01
55552029	rs17231506	8.42E-01	6.16E-01	4.65E-01	3.32E-01
55552737	rs1800775	6.48E-01	6.27E-01	1.29E-01	**1.44E-02**
55554734	rs1864163	**1.17E-02**	2.73E-01	4.32E-01	4.57E-01
55556073	rs9929488	**2.50E-03**	1.16E-01	3.87E-01	7.79E-01
55556759	rs7203984	**7.50E-03**	6.39E-02	6.34E-01	5.39E-01
55562390	rs7205804	3.87E-01	4.15E-01	9.99E-01	7.41E-01
55562802	rs1532625	2.58E-01	4.82E-01	9.97E-01	7.43E-01
55563051	rs12708974	5.91E-01	6.78E-01	3.51E-01	8.34E-02
55564693	rs9930761	4.36E-01	5.32E-01	4.81E-01	3.72E-01
55564854	rs5883	2.55E-01	4.72E-01	4.31E-01	2.13E-01
55566889	rs289717	6.88E-01	8.50E-01	6.67E-01	6.18E-01
55568744	rs12720898	9.15E-01	9.08E-01	9.73E-01	9.80E-01
55572592	rs5880	6.20E-01	9.87E-01	2.78E-01	2.61E-01
55573046	rs1800774	6.12E-02	8.45E-02	3.97E-01	2.59E-01
55573593	rs5882	6.62E-01	8.75E-01	**3.47E-02**	**2.81E-02**
55575163	rs1801706	5.07E-01	8.98E-01	4.79E-01	3.17E-01
55575263	rs289742	3.95E-01	9.07E-01	1.90E-01	2.24E-01
55577033	rs289745	7.51E-01	7.68E-01	2.05E-01	1.05E-01
55577828	rs17369163	2.01E-01	6.55E-02	3.21E-01	1.62E-01
55578934	rs12934552	1.73E-01	9.35E-01	9.23E-01	9.15E-01
	APOE	**6.49E-07**	**5.00E-05**	**3.72E-57**	**2.14E-59**
	N cases	252	122	1513	1233
	N Total	2389	2259	3650	3370

Note. The sample sizes (N) reflect those with at least one CETP marker and covariates. The probabilities shown are not corrected for multiple testing. The ALR probabilities shown for dementia outcomes are adjusted for sex, last age at sampling, and the number of APOE ε4 alleles.

* For analyses of incident AD, rs12708974 and rs9930761 were recoded to combine the rare homozygote with the heterozygote for analysis.

speed task showed three uncorrected signals below $p < 0.05$, again with no evidence for rs5882, and none below a p of 2.96E-03.

Among dementia outcomes, as noted, the highest uncorrected significance was obtained for marker rs9929488 and risk of incident dementia ($\chi^2(2)=11.96$, $p = 0.0025$) and survived a threshold of $p < 2.96E-03$ (see **Table 2**). The C/C genotype showed a significantly increased risk of incident dementia relative to the G/G genotype (OR 1.87, 95% CI 1.06, 3.29). The C/G heterozygote also showed increased risk relative to G/G but was not individually significant (OR 1.19, 95% CI 0.67, 2.12). This marker also exhibited uncorrected significance for Symbol Digit ($\chi^2(6)= 14.52$, $p = 0.024$), with the C/G and to a lesser extent the C/C genotype showing faster rates of decline compared to the G/G genotype, similar to the findings of increased dementia risk. This marker was in relatively low LD with rs5882 ($r^2 = 0.0041$). The greatest density of uncorrected signals was obtained for ALR analyses of incident dementia risk (5 markers at $p < 0.05$). However, all of these markers were in relatively high LD with rs9929488. For total dementia (combining incident and prevalent dementia cases), only rs5882 showed an uncorrected $p < 0.05$ in ALR analyses ($p = 0.0347$) and for total AD it was only one of two signals below $p < 0.05$ ($p = .0281$), with none below a p of 2.96E-03.

Applying Cox proportional hazards models to dementia onset outcomes, similar to a prior study of CETP rs5882 [11], revealed only four uncorrected signals at p < 0.05 across all SNPs and dementia onset variables (see **Table 3**):

Table 3. Probabilities of the association of CETP SNPs with dementia age of onset

Position	RS#	Incident Dementia	Incident AD*	Total Dementia	Total AD
55538741	rs247611	7.65E-01	5.91E-01	8.21E-02	1.27E-01
55542640	rs9989419	3.65E-01	2.92E-01	5.95E-01	7.47E-01
55549518	rs6499863	1.65E-01	9.63E-01	3.09E-01	2.98E-01
55550712	rs12708967	5.66E-02	3.81E-01	8.03E-02	6.96E-02
55550825	rs3764261	5.91E-01	6.24E-01	3.62E-01	2.31E-01
55551693	rs12447924	**2.28E-02**	1.35E-01	6.39E-01	6.69E-01
55552029	rs17231506	7.92E-01	7.16E-01	3.92E-01	2.35E-01
55552737	rs1800775	6.91E-01	8.93E-01	1.54E-01	6.69E-02
55554734	rs1864163	6.84E-02	4.85E-01	9.98E-01	9.36E-01
55556073	rs9929488	**9.70E-03**	1.93E-01	3.42E-01	4.74E-01
55556759	rs7203984	1.09E-01	3.02E-01	9.71E-01	8.76E-01
55562390	rs7205804	1.12E-01	7.40E-01	9.81E-01	9.90E-01
55562802	rs1532625	6.73E-02	7.87E-01	9.66E-01	9.66E-01
55563051	rs12708974	6.56E-01	5.49E-01	7.75E-01	5.39E-01
55564693	rs9930761	7.08E-01	7.55E-01	7.42E-01	6.27E-01
55564854	rs5883	1.29E-01	1.23E-01	8.22E-01	6.15E-01
55566889	rs289717	9.97E-01	8.60E-01	7.49E-01	7.72E-01
55568744	rs12720898	7.76E-01	8.55E-01	6.57E-02	5.33E-02
55572592	rs5880	2.92E-01	8.63E-01	5.15E-01	5.35E-01
55573046	rs1800774	6.76E-02	7.63E-02	1.04E-01	1.39E-01
55573593	rs5882	9.28E-01	9.27E-01	**4.02E-02**	5.30E-02
55575163	rs1801706	7.43E-01	9.42E-01	4.83E-01	4.25E-01
55575263	rs289742	5.33E-01	9.57E-01	5.32E-02	6.12E-02
55577033	rs289745	4.67E-01	6.24E-01	7.93E-02	8.44E-02
55577828	rs17369163	2.78E-01	5.97E-02	3.57E-01	2.20E-01
55578934	rs12934552	4.26E-01	9.29E-01	9.82E-01	8.59E-01
	APOE	**2.48E-08**	**1.07E-05**	**1.47E-93**	**9.13E-97**
	N cases	252	122	1424	1144
	N Total	2389	2259	3561	3281

Note. The sample sizes (N) reflect those with at least one CETP marker and covariates. The Cox model probabilities for dementia onset outcomes are adjusted for sex and the number of APOE e4 alleles.

* For analyses of incident AD, rs12708974 and rs9930761 were recoded to combine the rare homozygote with the heterozygote for analysis.

three for incident dementia (rs12447924, rs9929488, rs1532625) and one for total dementia (rs5882). None of the signals were below 2.96E-03.

In contrast to the cognitive and dementia outcomes, 10 out of 26 markers were associated with HDL values at $p < .05$ (see **Table 1**). Notably, rs5882 was not associated with HDL values (see **Table 1**). Thus, while we find association of multiple *CETP* markers with HDL levels, altogether there was little compelling evidence of association of *CETP* with cognitive or dementia outcomes across the set of 26 *CETP* markers, including rs5882.

In summary, using a large informative sample with longitudinal cognitive performance data over more than 16 years, we have been unable to find convincing evidence that genetic sequence variation in *CETP* contributes to variance in cognitive decline or dementia risk. We are thus unable to replicate any of the previous five studies that have reported positive association of *CETP* with dementia risk [7-11]. Among those studies, the latter also included a detailed analysis of cognitive decline, but we were also unable to validate those results. In contrasting our results to the Sanders et al [11] study specifically, our study of cognitive performance had more than two-fold the number of participants and median follow-up time (7.8 vs 3.2 years), and with extensive overlap of ages between the studies (50.1 to 93.3 vs 65.3 to 96.2; median

age=74.0 vs 78.2 years). Moreover, our Digit Span and Symbol Digit tasks are essentially equivalent in terms of construct to the WAIS Digit Span and Digit Symbol tasks [15]. The episodic memory task in the current study, Thurstone Picture Memory, presents visual stimuli in the form of line drawings [15] similar to the Free and Cued Selective Reminding Test [11], although with a forced-choice recognition format. Nonetheless, our episodic memory task showed only one uncorrected significance below $p = 0.05$. The Sanders et al [11] study did not find association with the Digit Span and Digit Symbol tasks with their single marker, while the bulk of uncorrected associations observed in the current study were found with these tests. The Sanders et al [11] study also reported on association with incident dementia with a relatively limited sample (N=40) whereas we were able to include several-fold more individuals (N=252). The overall lack of evident association with dementia and AD in our current study is consistent with genome-wide association studies, where neither of the two largest studies performed to date implicate the CETP region [1, 2]. We specifically scrutinized the markers in our study that showed marginal evidence of association with dementia or AD (rs5882 and rs1800775) against the results of a genome-wide study [2] to which we had access. Neither of these markers were associated with AD in that study ($p = 0.085$, and $p = 0.98$, respectively. We noted from the study of Lambert et al., 2009 that the best evidence of association in the region was near marker rs8043560 ($p = 0.0022$) located in an LD block distinct from *CETP*. Moreover, given that APOE contributes to variation in both incident and prevalent dementia in the present and other samples [22] we think it is reasonable to conclude that prevalent and incident dementia should reflect similar biological mechanisms vis-à-vis *CETP*. Studies of AD risk, in particular from genome-wide association, are revealing a genetic landscape with only a handful of significant genes. The successful identification of genetic variants that contribute to variability in cognitive performance is likely to require a similar appreciation of sample size and genomic coverage.

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Ethics Approvals: The study was done in accord with the ethical standards of the Swedish Ethical Review Board and the Karolinska Institute, with approvals by the relevant local Institutional Review Boards of the investigators' institutions.
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Supplementary Table: Marker information

Marker	Position (b36)	strand	poly	call_rate%	Duplicate errors	HWE
rs247611	55538741	BOT	[T/C]	98.21	0	0.04
rs9989419	55542640	BOT	[T/C]	96.28	0	0.96
rs6499863	55549518	BOT	[T/C]	98.13	0	0.34
rs12708967	55550712	BOT	[T/C]	95.99	0	0.49
rs3764261	55550825	BOT	[T/G]	98.18	0	0.51
rs12447924	55551693	BOT	[T/C]	97.84	0	0.48
rs17231506	55552029	TOP	[A/G]	91.14	0	0.48
rs1800775	55552737	TOP	[A/C]	96.55	0	0.00
rs1864163	55554734	TOP	[A/G]	97.92	0	0.44
rs9929488	55556073	BOT	[G/C]	98.21	0	0.83
rs7203984	55556759	BOT	[T/G]	91.85	3	0.68
rs7205804	55562390	BOT	[T/C]	97.68	0	0.77
rs1532625	55562802	TOP	[A/G]	96.94	0	0.96
rs12708974	55563051	BOT	[T/C]	98.15	0	0.76
rs9930761	55564693	TOP	[A/G]	95.39	0	0.57
rs5883	55564854	TOP	[A/G]	98.42	0	0.91
rs289717	55566889	BOT	[T/C]	93.70	0	0.30
rs12720898	55568744	TOP	[A/G]	98.15	0	0.61
rs5880	55572592	BOT	[G/C]	97.60	0	0.20
rs1800774	55573046	BOT	[T/C]	97.57	0	0.80
rs5882	55573593	TOP	[A/G]	98.00	0	0.44
rs1801706	55575163	TOP	[A/G]	98.21	0	0.15
rs289742	55575263	BOT	[G/C]	97.81	0	0.73
rs289745	55577033	BOT	[T/G]	97.44	0	0.55
rs17369163	55577828	BOT	[G/C]	98.29	0	0.85
rs12934552	55578934	TOP	[A/G]	96.99	0	0.97