Association of a Functional Polymorphism in the Cholesteryl Ester Transfer Protein (CETP) Gene With Memory Decline and Incidence of Dementia

Amy E. Sanders, MD
Cuiling Wang, PhD
Mindy Katz, MPH
Carol A. Derby, PhD
Nir Barzilai, MD
Laurie Ozelius, PhD
Richard B. Lipton, MD

S THE POPULATION AGES, THE public health and economic burdens of age-associated cognitive decline and dementia will continue to increase. Only the apolipoprotein (APOE [ε4 isoform]) has been conclusively associated with increased genetic susceptibility for the most common dementia, sporadic late-onset Alzheimer disease (AD).1 Genes identified through associations with exceptional longevity are logical targets to explore for potentially beneficial associations with cognitive decline and dementia risk.2

Some studies have suggested that the APOE ε2 allele is associated with both increased lifespan and lower dementia risk.3 Like APOE, the cholesteryl ester transfer protein gene (CETP) is involved in central nervous system cholesterol homeostasis and has been associated with exceptional longevity.4,5 At codon 405 (exon 14), a functional single-nucleotide polymorphism (SNP) substitutes valine (V) for isoleucine (I; “ancestral allele”; NCBI SNP rs5882; V405) and is associated with lower CETP protein serum concentrations and activity and correspondingly increases in high-density lipoprotein (HDL) levels and lipoprotein (HDL/LDL [low-density lipoprotein]) particle sizes.6,7 These changes may have additional protective associations with cardiovascular disease, although the precise nature and potential mediators of these relationships are debated.7,8

Context Polymorphisms in the cholesteryl ester transfer protein (CETP) gene have been associated with exceptional longevity and lower cardiovascular risk, but associations with memory decline and dementia risk are unclear.

Objective To test the hypothesis that a single-nucleotide polymorphism (SNP) at CETP codon 405 (isoleucine to valine V405; SNP rs5882) is associated with a lower rate of memory decline and lower risk of incident dementia, including Alzheimer disease (AD).

Design, Setting, and Participants Prospective cohort study comprising 608 community-dwelling adults without dementia aged 70 years or older from the Einstein Aging Study with CETP genotype available. Fifteen participants with prevalent dementia were excluded, and 70 without follow-up—63 lost to follow-up and 7 new to the study—were excluded from the Cox proportional hazards model, which included 523 participants in the analysis. Standardized neuropsychological and neurological measures were administered annually from 1994-2009. Linear mixed-effects models adjusted for sex, education, race, medical comorbidities, and apolipoprotein (APOE) ε4 examined associations of V405 genotype with longitudinal performance on cognitive tests of episodic memory (Free and Cued Selective Reminding Test [FCSRT]), possible scores of 0-48, attention (Digit Span), and psychomotor speed (Digit Symbol Substitution). The V405 genotype was the main predictor of incident dementia or AD in similarly adjusted Cox proportional hazards models with age as the time scale.

Main Outcome Measures Memory decline and incident dementia.

Results Valine allele frequency was 43.5%. A total of 40 cases of incident dementia occurred during follow-up (mean [SD], 4.3 [3.1] years). Compared with isoleucine homozygotes, valine homozygotes had significantly slower memory decline on the FCSRT (0.43 points per year of age for isoleucine; 95% confidence interval [CI], −0.58 to −0.29 vs 0.21 points per year of age for valine; 95% CI, −0.39 to −0.04; difference in linear age slope, 0.22; 95% CI, 0.02 to 0.41; P = .03) and no significant differences on the Digit Span or Digit Symbol Substitution tests. Valine homozygotes also had lower risk of dementia (hazard ratio, 0.28; 95% CI, 0.10-0.85; P = .02) and AD (hazard ratio, 0.31; 95% CI, 0.10-0.95; P = .04).

Conclusion This preliminary report suggests that CETP V405 valine homozygosity is associated with slower memory decline and lower incident dementia and AD risk.
The CETP gene was identified as a “longevity gene” in a sample of Ashkenazi Jews by Barzilai and colleagues in 2003: valine homozygosity occurred in 24.8% of centenarians compared with 8.6% among controls. In a cross-sectional follow-up study, Ashkenazi centenarians with good cognitive function had increased frequency of the V405 polymorphism; in an independent cohort valine homozygosity was approximately 5-fold higher in Ashkenazi individuals aged 75 to 85 years without dementia compared with those with dementia. Case-control studies in non-Ashkenazi populations have also reported protective associations between CETP SNPs and dementia prevalence, although replication has been inconsistent.

Herein, we investigated associations between V405 genotype and longitudinal memory performance and risk for incident dementia or AD in a community-based sample of healthy older adults without dementia at baseline. We hypothesized that the valine allele would be associated with less age-associated memory decline and lower risk of incident dementia.

**METHODS**

**Participants**

The Einstein Aging Study is a prospective cohort study designed to identify factors predicting cognitive decline and incident dementia in a racially and ethnically diverse community-dwelling population of elderly individuals. Study design and methods for recruitment and annual assessments have been previously described. Briefly, potential participants were systematically recruited from population lists of Medicare recipients (1994-2004) or Bronx County registered voters (2004-2009). Eligible participants were aged 70 years or older, resided in the Bronx, and had sufficient command of English to participate in neuropsychological testing. Exclusion criteria included audiovisual impairment severe enough to interfere with cognitive testing, inability to ambulate, and institutionalization. Written informed consent was obtained from each individual at study entry according to protocols approved by the institutional review board of the Albert Einstein College of Medicine. Annual in-person evaluations occurred at the Einstein Aging Study Aging Research Center located on the Einstein campus.

Since 1994, the Einstein Aging Study has enrolled 1910 individuals; 1215 consented to have blood samples drawn and 608 had DNA extracted and genotyping performed. Availability of CETP and APOE genotypes determined preliminary eligibility for this investigation (n=608). Participants with dementia at baseline (n=15) were excluded from all analyses (n=593). Those without follow-up visits (n=70) were additionally excluded from the incident dementia analysis (n=523). Compared with 523 included individuals, the 70 excluded for lack of follow-up did not differ statistically in age (78.5 vs 78.4 years, P=.81), sex (61% vs 63% women, P=.76), race (69% vs 67% white, P=.75; 26% vs 27% African American, P=.78), educational level (13.9 vs 14.4 years, P=.64), baseline cognition (Blessed Information Memory Concentration score, 2.1 vs 1.9, P=.88), or genotype frequency for APOE ε4 (22% vs 28%, P=.34) or CETP (valine homozygotes 21% vs 14% and valine heterozygotes, 45% vs 60%, P=.06). Reasons for lack of follow-up included interval occurrence of an exclusion criterion after study entry (n=3), moved (n=4), became too ill to continue (n=6), loss of contact (n=6), less than a year as a study participant (n=7), death (n=12), and declined or unavailable to continue (n=32).

Of the 607 individuals with blood samples but no genotype performed, long-banked buffy coat did not yield high-quality DNA for 174 participants, so these individuals were excluded from the current analysis, as were 33 individuals with prevalent dementia. Two hundred twenty-seven have had only their baseline visit and consequently no follow-up data are available. Because this is an ongoing cohort study with analyses being continuously performed, a total of 173 samples remain to be genotyped. Statistical comparison between individuals with and without genotyping revealed that the 2 groups were similar in sex and racial distribution, but those who were genotyped were significantly younger with a mean (SD) age of 78.6 (5.2) vs 79.5 (5.5) years (P<.001); better educated, 14.0 (3.5) vs 12.5 (3.6) years of education (P<.001); and at baseline had better global cognitive function scores, 2.2 (2.2) vs 3.9 (3.8) measured by the Blessed Information Memory Concentration test (P<.001) and better episodic memory performance, 30.6 (6.2) vs 28.0 (8.1), on the Free and Cued Selective Reminding Test (FCSRT) (P<.001) than those who were not genotyped.

**Demographic and Clinical Information**

Trained research assistants used structured questionnaires to obtain sociodemographic information (age, sex, race, Ashkenazi heritage, and years of education) and medical history at each annual visit. We obtained information on race and ethnicity to explore possible confounding by genetic admixture. Participants self-identified their race/ethnicity and religious background to the research assistants who asked “To which race group do you belong?” and “What is your religious preference?” Because the CETP gene was associated with longevity in Ashkenazi Jews and because our current sample was not restricted to Ashkenazi Jews, we used an indicator variable to adjust for Ashkenazi heritage in both longitudinal analyses. Response options for race/ethnicity were white, black, Hispanic/white, Hispanic/black, Asian, or other. For religious background, options were Protestant, Catholic, Jewish, or other; individuals could decline to endorse a preference. Using baseline medical history, we tabulated a medical comorbidity index score (range, 0-10) from dichotomous self-report (present vs absent) of hypertension, diabetes, angina, myocardial infarction, congestive heart failure, stroke,
Parkinson disease, rheumatoid arthritis, chronic obstructive pulmonary disease, and depression." Depressive symptoms were assessed using the 15-item Geriatric Depression Scale. Functional status was assessed using the Lawton-Brody scale of instrumental activities of daily living (range, 0-8; higher scores better).  

Neuropsychological Assessment
At baseline and at each annual evaluation, cognitive status was assessed by a comprehensive neuropsychological battery comprising tests of global cognition and the specific cognitive domains of attention, episodic and visual memory, executive function, language, and visuospatial ability. Administration by trained neuropsychological assistants was standardized according to Einstein Aging Study protocols based on published guidelines. For this study, we report premorbid intelligence, global cognitive status, and results from representative domain-specific cognitive tests of attention, psychomotor speed, and episodic memory. The vocabulary subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) served as a “hold” test, estimating crystallized intelligence less vulnerable to the effects of aging and not expected to decline as a consequence of dementia. Global cognition was assessed via the Blessed Information Memory Concentration test, which correlates well with AD neuropathology.  

Domain-specific cognitive tests were the Digit Span and Digit Symbol Substitution WAIS-R subtests, and free recall was assessed with the FCSRT.  

We selected the FCSRT to test our prior hypothesis of a protective association between V405 genotype and episodic memory based on its demonstrated operating characteristics. Digit Span was used to assess attention, which is unlikely to decline as a result of dementia and when impaired is more commonly a consequence of cerebrovascular disease. Digit Symbol Substitution was chosen as a test of psychomotor processing speed, which may exhibit age-associated decline but is less sensitive to dementia.  

Dementia Diagnosis
The Einstein Aging Study neuropsychologist and neurologist met monthly in diagnostic consensus case conferences that included review of all available clinical and neuropsychological data. Dementia diagnoses were based on standardized clinical criteria from the Diagnostic and Statistical Manual (Fourth Edition) (DSM-IV) and required impairment in memory plus at least 1 additional cognitive domain, accompanied by evidence of functional decline. Alzheimer disease was diagnosed in participants with dementia who met clinical criteria for probable or possible disease established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.  

Genotyping
All blood samples for genotyping were obtained after participants gave written informed consent. The phlebotomist drew 20 mL of whole blood at the Aging Research Center; samples were centrifuged and stored in aliquots in a −70°C freezer. Subsequently, DNA was isolated directly from buffy coat using the Puregene DNA Purification System (Gentra System, Minneapolis, Minnesota). Amplification and sequencing primers for genotyping of the target V405 SNP (rs5882) and for the 2 APOE SNPs, rs429358 (position 112) and rs7412 (position 158), were designed using PSQ version 1.0.6 software (BioSet, Uppsala, Sweden); in each case the reverse primer was biotinylated. Genotyping was performed using a Pyrosequencing PSQ HS 96A system (http://www.pyrosequencing.com) according to manufacturer’s instructions.  

Statistical Analysis
We classified participants dichotomously based on whether incident dementia occurred during follow-up. Time of dementia diagnosis was assigned the visit date immediately preceding the consensus conference making the diagnosis. The V405 genotype was dichotomized into homozygote (V-V) and heterozygote (I-V) groups; isoleucine homozygotes served as the reference group in all longitudinal analyses. Baseline demographic and clinical characteristics were compared using either the Wilcoxon rank sum or Kruskal-Wallis tests for continuous variables; χ2 or Fisher exact tests were used as appropriate for categorical variables.  

Associations between V405 genotype and longitudinal performance in episodic memory, attention, and psychomotor speed were examined with linear mixed-effects models using age (centered at 85 years) as the time scale and adjusted for sex, educational level, race/ethnicity, and presence of an APOE ε4 allele. Indicator variables coded for African American race and Ashkenazi heritage. The V405 genotype groups were separately compared with the isoleucine reference group. The main outcome of interest was repeated measures of individual free recall scores on the FCSRT. For each V405 group the β coefficient for the difference in linear age slope estimated the change in cognitive score per additional year of age compared with the reference group. A quadratic age term tested whether an accelerated nonlinear trend was present. Performance on tests of attention and psychomotor speed were similarly modeled.  

To estimate the risk of incident dementia and AD as a function of the V405 group, we used nested Cox proportional hazard models with delayed entry and age as the time scale. In cohort studies, age is preferred to follow-up time as the time scale because the hazard function can be directly interpreted as the age-specific incidence function for dementia; inclusion of age as a nonparametric term in this manner provides a more flexible and effective control than treating age as a covariate.  

Hazard ratios (HRs) were estimated using the V405 groups as categorical predictor variables, with isoleucine homozygotes as the reference. Time to event was the interval between age at baseline and age at dementia or AD diagnosis or last contact, as appropriate. In model 1, we adjusted for sex, race/ethnicity (coded as above), and years of education. Model 2 included the covariates in model 1 plus an additional adjustment for the medical comorbidity in-
The statistical software packages SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) and S-Plus 8.0 (Insightful Corp, Seattle, Washington) were used for all analyses. Two-sided probability values less than .05 were considered statistically significant in all tests, including the Fisher exact test.

RESULTS

Demographic Characteristics

In the study sample of 523 individuals, 40 incident cases of dementia occurred (Table 1). Frequency of the APOE ε4 allele (23%) was similar to other racially and ethnically diverse cohorts in US urban centers.33,34 At first evaluation, compared with individuals who did not develop dementia throughout follow-up, those who developed dementia were older,
less educated, and had poorer performance in global cognition, psychomotor speed, and episodic memory. The groups did not differ by sex, race, Ashkenazi heritage, CETP or APOE genotype, or medical comorbidity burden.

Allele frequency for valine was 43.5% for the study cohort: 235 of the 523 participants (45%) were heterozygotes; 110 (21%) were valine homozygotes; and 178 (34%) were isoleucine homozygotes. Genotype frequencies differed marginally from Hardy-Weinberg equilibrium ($\chi^2 = 3.86, P = .05$), possibly consistent with a longevity effect on allele distribution.$^{33,36}$ Demographic characteristics and baseline neuropsychological test results among the 3 genotype groups were similar except for premorbid intelligence and race/ethnicity (Table 2). Compared with 37% in whites, valine frequency was 60% in African Americans, similar to frequencies previously reported elsewhere.$^{37}$ African Americans were a median age of 77.2 years (interquartile range [IQR], 7.0 years) vs 78.3 years (IQR, 8.2 years) among non–African Americans, and the proportion of women was greater in the African American (79%) than non–African American (53%) group ($P < .001$). African Americans had a median of 12.5 years of education (IQR, 4.0; range, 3-20 years) vs 14.0 years (IQR, 4.0; range, 4-22 years) among non–African Americans ($P = .001$), a median baseline Blessed Information Memory Concentration score of 3.0 (IQR, 4.0; range, 0-8) vs 1.0 (IQR, 3.0; range, 1-10) among non–African Americans ($P < .001$), and a higher percentage with an APOE e4 allele (31% vs 23%, $P = .008$) than non–African Americans. The median baseline medical comorbidity index scores were similar among groups: 1 (IQR, 1; range, 0-6) for African Americans and 1 (IQR, 1; range, 0-5) for non–African Americans. Ninety-three African Americans (69%) reported hypertension vs 224 non–African Americans (58%) ($P = .02$), but only 4 (3%) African Americans reported myocardial infarction vs 39 (10%) non–African Americans ($P = .01$). Rate of self-reported stroke was similar: 13 (10%) African Americans vs 32 (9%) non–African Americans ($P = .60$). Crude dementia incidence rates among Afri-

### Table 2. Characteristics of All Individuals at First Evaluation, Stratified by Cholesteryl Ester Transfer Protein V405 Genotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>Isoleucine Homozygotes (n = 178)</th>
<th>Heterozygotes (n = 235)</th>
<th>Valine Homozygotes (n = 110)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude incidence of dementia, per 100 person-years (95% CI)</td>
<td>2.48 (1.6-4.0)</td>
<td>1.56 (0.8-2.2)</td>
<td>1.05 (0.3-2.5)</td>
<td>.12</td>
</tr>
<tr>
<td>≥1 APOE e4 allele, No. (%)</td>
<td>43 (23)</td>
<td>47 (20)</td>
<td>27 (25)</td>
<td>.49</td>
</tr>
<tr>
<td>Age, median (IQR) [range], y</td>
<td>78.3 (8.1) [70.4-96.2]</td>
<td>77.7 (8.2) [66.2-91.7]</td>
<td>77.7 (9.0) [69.7-94.5]</td>
<td>.81</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>106 (59.6)</td>
<td>141 (60.0)</td>
<td>72 (65.5)</td>
<td>.56</td>
</tr>
<tr>
<td>Race/ethnicity/religious background, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>151 (84.8)</td>
<td>158 (67.2)</td>
<td>52 (47.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>African American</td>
<td>21 (11.8)</td>
<td>64 (27.2)</td>
<td>49 (44.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>6 (3.4)</td>
<td>13 (5.5)</td>
<td>9 (8.2)</td>
<td>.21</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>53 (29.8)</td>
<td>77 (32.8)</td>
<td>27 (24.6)</td>
<td>.30</td>
</tr>
<tr>
<td>Educational achievement, median (IQR) [range], y</td>
<td>14 (4) [4-20]</td>
<td>13 (4) [3-22]</td>
<td>14 (4) [5-21]</td>
<td>.14</td>
</tr>
<tr>
<td>≥Skilled or professional prior occupational attainment, No. (%)c</td>
<td>161 (90)</td>
<td>205 (87)</td>
<td>93 (83)</td>
<td>.50</td>
</tr>
<tr>
<td>Follow-up time, median (IQR) [range], y</td>
<td>3.1 (4.1) [0.9-15.5]</td>
<td>3.2 (5.0) [0.9-12.7]</td>
<td>3.1 (6.1) [0.9-14.6]</td>
<td>.63</td>
</tr>
<tr>
<td>Evaluation scores, median (IQR) [range]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical comorbidity index, self-report</td>
<td>1 (2) [2-5]</td>
<td>1 (1) [0-6]</td>
<td>1 (1) [0-5]</td>
<td>.89</td>
</tr>
<tr>
<td>Instrumental activities of daily living, self-reportd</td>
<td>7 (2) [0-8]</td>
<td>7 (3) [1-8]</td>
<td>8 (3) [1-8]</td>
<td>.43</td>
</tr>
<tr>
<td>Geriatric Depression Scalee</td>
<td>2 (2) [0-10]</td>
<td>2 (2) [0-10]</td>
<td>2 (2) [0-10]</td>
<td>.80</td>
</tr>
<tr>
<td>Blessed IMC testf</td>
<td>1 (2) [0-10]</td>
<td>1 (2) [0-10]</td>
<td>2 (3) [0-8]</td>
<td>.39</td>
</tr>
<tr>
<td>Digit span raw scoreh</td>
<td>40 (13) [6-27]</td>
<td>40 (14) [4-27]</td>
<td>13 (4) [7-25]</td>
<td>.46</td>
</tr>
<tr>
<td>Digit Symbol Substitution raw scorei</td>
<td>42 (16) [1-84]</td>
<td>41 (17) [10-81]</td>
<td>43 (20) [5-85]</td>
<td>.57</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E e4 isoform; Blessed IMC, Blessed Information-Memory Concentration test; IQR, interquartile range.

bP values are from comparison of medians among the 3 genotype groups for continuous variables; $\chi^2$ or Fisher exact test were used as appropriate for categorical variables.

cStandard Occupational Classification Manual scale from the US Department of Commerce has a range of 0 to 9. Higher scores indicate higher occupational attainment. The proportion of the sample in highest 2 tertiles of occupational attainment scores are shown.

dThe Lawton-Brody scale has a range of 0 to 48 with higher scores indicating better memory performance. Scores of 24 or less indicate impaired memory.

©2010 American Medical Association. All rights reserved.
can Americans (2.04 per 100 person-years) were higher than in non–African Americans (1.69 per 100 person-years), but the difference was not statistically significant (P = .18).

**Associations Between CETP Genotype and Longitudinal Cognitive Performance**

Baseline performance on the domain-specific cognitive tests of FCSRT, Digit Span, and Digit Symbol Substitution was similar among the 3 genotype groups (Table 2). In the linear mixed-effects model (TABLE 3), after adjustments for sex, race/ethnicity, education, medical comorbidities, and APOE status, valine homozygosity was independently associated with slower decline on the FCSRT. A quadratic trend for age was found for cognitive decline for both homozygotes and heterozygotes. Compared with an absolute linear age slope of 0.43 points per year of age (95% confidence interval [CI], −0.58 to −0.29) decline in FCSRT score in the reference group, the linear age slope in valine homozygotes was 0.22 points per year of age (95% CI, −0.39 to 0.04). Based on the difference in linear age slopes, valine homozygosity was independently associated with 0.22 points per year of age less decline on FCSRT, slower by a relative 51%. Memory decline in valine heterozygotes was similar to that of the reference group. The V405 genotype was not associated with cognitive performance on domain-specific tests of Digit Span or Digit Symbol Substitution.

**Associations Between CETP Genotype and Incidence of Dementia and Alzheimer Disease**

Of the 40 individuals with incident dementia, 35 met criteria for probable or possible Alzheimer disease. In the fully adjusted models (TABLE 4 and FIGURE 1), valine homozygosity was associated with lower risk of developing both dementia and AD. The HRs for heterozygotes were also less than 1 for both dementia and AD but were not statistically significant. Substituting combined history of hypertension, myocardial infarction, and stroke for the comorbidity index in models for dementia slightly reduced the HRs further by a small margin (HR, 0.26; 95% CI, 0.09–0.78; P = .02 for valine homozygotes; HR, 0.54; 95% CI, 0.27–1.1; P = .09 for heterozygotes).

To address the possibility that racial admixture was confounding our observations, we reran the linear mixed-effects and the final Cox proportional hazards models (minus the indicator variable for African American race) in a white-only subgroup (361 individuals, 24 incident dementia cases). Among whites, valine homozygotes declined more slowly than the reference group on the FCSRT, with a difference of 0.14

---

**Table 3.** Estimated Mean Change in Free and Cued Selective Reminding Score With Increasing Age, According to CETP V405 Genotype Group**

<table>
<thead>
<tr>
<th>CETP V405 Genotype Group</th>
<th>Free and Cued Selective Reminding Test</th>
<th>Digit Span</th>
<th>Digit Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>P Value</td>
<td>β (95% CI)</td>
</tr>
<tr>
<td>Quadratic age trend</td>
<td>−0.02 (−0.03 to 0.01)</td>
<td>.&lt;.001</td>
<td>−0.006 (−0.006 to 0.002)</td>
</tr>
<tr>
<td>Linear age slope per year in reference group</td>
<td>−0.43 (−0.58 to −0.29)</td>
<td>.&lt;.001</td>
<td>0.05 (−0.01 to 0.11)</td>
</tr>
<tr>
<td>Difference in linear age slope between valine heterozygotes and reference group</td>
<td>0.07 (−0.09 to 0.23)</td>
<td>.39</td>
<td>0.01 (−0.05 to 0.08)</td>
</tr>
<tr>
<td>Difference in linear age slope between valine homozygotes and reference group</td>
<td>0.22 (0.02 to 0.41)</td>
<td>.03</td>
<td>−0.03 (−0.10 to 0.06)</td>
</tr>
</tbody>
</table>

*Abbreviation: CI, confidence interval.
*See “Methods” section for scale ranges. Linear mixed-effect model: isoleucine homozygotes (I-I) were used as the reference group for each cognitive test. The model was centered at 85 years. and heterozygotes. Compared with an absolute linear age slope of 0.43 points per year of age (95% confidence interval [CI], −0.58 to −0.29) decline in FCSRT score in the reference group, the linear age slope in valine homozygotes was 0.22 points per year of age (95% CI, −0.39 to 0.04). Based on the difference in linear age slopes, valine homozygosity was independently associated with 0.22 points per year of age less decline on FCSRT, slower by a relative 51%. Memory decline in valine heterozygotes was similar to that of the reference group. The V405 genotype was not associated with cognitive performance on domain-specific tests of Digit Span or Digit Symbol Substitution.

**Table 4.** CETP V405 Genotype and Risk for Dementia and Alzheimer Disease**

<table>
<thead>
<tr>
<th>Category</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Risk for dementia vs isoleucine homozygotes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valine heterozygotes (n = 16)</td>
<td>0.52 (0.26–1.06)</td>
<td>.07</td>
<td>0.53 (0.26–1.09)</td>
</tr>
<tr>
<td>Valine homozygotes (n = 5)</td>
<td>0.29 (0.10–0.85)</td>
<td>.02</td>
<td>0.28 (0.09–0.84)</td>
</tr>
<tr>
<td>Risk for Alzheimer disease vs isoleucine homozygotes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valine heterozygotes (n = 14)</td>
<td>0.52 (0.24–1.13)</td>
<td>.10</td>
<td>0.53 (0.25–1.2)</td>
</tr>
<tr>
<td>Valine homozygotes (n = 5)</td>
<td>0.31 (0.10–0.96)</td>
<td>.04</td>
<td>0.30 (0.10–0.94)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; HR, hazard ratio.
*P values from Cox proportional hazard models with delayed entry and age as the time scale. There were 40 incident cases of dementia (19 in the reference group) and 35 incident cases of Alzheimer disease (16 in the reference group).
*Adjusted for sex, years of education, non–Ashkenazi white race, and black race.
*Adjusted for the covariates in model 1 plus an additional adjustment for medical comorbidities as measured by the Medical Comorbidity Index.
*Adjusted for the covariates in model 2 plus an additional adjustment for presence of an apolipoprotein E ε4 allele.

©2010 American Medical Association. All rights reserved.
points per year of age in the linear age slopes, although the difference was not statistically significant ($P=.29; 95\% \text{ CI}, -0.12$ to $0.40$). In the Cox model of dementia incidence, the magnitude of the association lessened slightly compared with main results and the model was not statistically significant (HR, $0.45; 95\% \text{ CI}, 0.10$-$2.03; P $= .30$ for homozygotes; HR, $0.56; 95\% \text{ CI}, 0.23$-$1.38; P $= .21$ for heterozygotes), possibly related to lower power.

Because genotype results were not available for all individuals with blood samples, we compared dementia-free survival in those with and without genotype information. Adjusted for sex, education, race, and baseline Blessed Information Memory Concentration score, the genotyped individuals survived longer without dementia than those without genotype information (HR, $0.45; P < .001$), suggesting that genotype was not missing at random. In the multiple imputation analysis performed to allay the resulting concerns about the representativeness of our sample and the generalizability of our results, the HR for valine homozygotes was $0.44$ ($95\% \text{ CI}, 0.20$-$0.96; P $= .04$), similar to results observed in the primary analysis.

**COMMENT**

Compared with a reference group homozygous for the ancestral allele in the full sample, valine homozygosity was independently associated with slower age-associated memory decline and lower risk of incident dementia and Alzheimer disease. Main findings were statistically significant in adjusted models that included APOE status. As assessed by FCSRT, memory declined in valine homozygotes by $0.22$ points per year more slowly (relative $51\%$) than in the reference group; homozygosity was associated with lower risk of both dementia and AD. The HR for dementia and AD was lower in valine heterozygotes than individuals homozygous for isoleucine, but the difference was not statistically significant.

In the analysis of cognitive decline, our primary hypothesis was that the valine allele would be associated with slower episodic memory decline. To our knowledge, only 1 study has evaluated the CETP V405 polymorphism in the context of cognitive change. Johnson et al\textsuperscript{8} examined V405 associations with childhood IQ and life-long change in global cognition in a group of Scottish older adults. Specific cognitive domains, including memory, were examined cross-sectionally at age 79 years. They reported that CETP was associated with cardiovascular disease rate but detected no significant global longitudinal or domain-specific cross-sectional cognitive associations. In the present report, valine homozygosity was not associated with cross-sectional cognitive function, but it was associated with slightly slower memory decline. Thus, the longitudinal design of our study may account for the different results we found. Population differences may also contribute because valine was at higher frequency ($69\%$) than in our sample ($43.5\%$).

To our knowledge, this is the first study to examine associations between a CETP genotype and dementia risk in an incidence study. Of 10 case-control studies published since 2004, 3 investigated the V405 polymorphism. The single population-based case-control study reported that the V405 polymorphism was associated with an elevated odds ratio (OR) of $1.67$ for AD in non-APOE $\varepsilon 4$ carriers.\textsuperscript{9} A 2005 Spanish study reported that $\varepsilon 4$ carriers homozygous for the minor allele of the C-629 A CETP polymorphism had a lower OR ($2.33$) for AD than $\varepsilon 4$ noncarriers (OR, $7.12$) but found no association between V405 and AD.\textsuperscript{10} In 2009, Qureschie and colleagues\textsuperscript{11} reported lack of association between V405 and AD, although a CETP haplotype including valine was associated with cholesterol profiles in plasma and cerebrospinal fluid. Studies investigating other CETP polymorphisms reveal similar heterogeneous results.

Methodological differences among studies may contribute to the disparate results presented herein. We suggest that selection bias in case-control studies may be particularly problematic for polymorphisms associated with longevity. Case-control studies may be biased by factors associated with duration of disease in prevalent cases with longevity-favoring genotypes because they preferentially include dementia cases with longer survival. Based on enhanced survival, such individuals might be overrepresented among cases, spuriously attenuating any protective as-
spite higher population frequencies of creases dementia susceptibility decreases may possess a third factor that indetect. Alternatively, African Americans without lower incidence, possibly indicating a genotype-race interaction that this study was not powered to detect. Additionally, African Americans may possess a third factor that increases dementia susceptibility despite higher population frequencies of the putatively protective allele. We attempted to account for the potential effects of race by including it as a confounder in our models. After excluding African Americans in the Cox models for dementia, the magnitude of the resulting association changed only slightly but lost statistical significance. The low number of incident dementia cases prevented exploration of interactions in race-stratified analyses. These observations merit further investigation.

Our study cannot directly address the nature of causal relationships underlying the associations reported herein, limiting us to informed speculation. Although it remains unknown whether CETP polymorphisms cause specific differential rates of memory decline or dementia incidence, the basic temporal sequence of the genetic factor preceding downstream effects is indisputable. The fact that the HR for valine heterozygotes was between the HR for homozygotes and that of isoleucine homozygotes suggests a possible gene-dose relationship favoring a possible causal relationship. The CETP protein is synthesized and expressed in brain, but sparse knowledge limits speculation about CETP’s role in neurodegenerative pathophysiological mechanisms that might influence dementia risk. Growing evidence posits a mechanistic pathway linking cerebral cholesterol metabolism and AD pathology; hypothetical descriptions include genetic susceptibility conferred by cholesterol-metabolism genes such as CETP and APOE.5,60 Future studies investigating intermediate steps in the putative causal pathway—mediation by endophenotypic biomarkers, such as CETP plasma levels and protein activity, for example—might provide useful first steps toward eventual resolution of the causality question.

There are several caveats to our results. Although APOE frequency in our sample was comparable with other aging cohorts, our participants were nevertheless community-residing relatively healthy older adults living in the Bronx and we acknowledge the need to evaluate the CETP gene in other longitudinal studies with greater numbers of incident dementia cases. We used well-established procedures and standardized criteria to diagnose dementia and AD, but some misclassification may have occurred. Like any longitudinal study, ours may have had selective attrition, although the duration of follow-up helps allay this concern. At 40, the number of incident dementia cases was small. The amount of reduction in memory decline associated with a valine homozygous state was small—0.22 points per year on a scale ranging from 0 to 48.

Despite the small number of incident dementia cases and small decline in memory, this preliminary report suggests that CETP valine homozygosity is associated with slower memory decline and lower risk for incident dementia or AD. This potentially protective association is supported by several observations. First, some (but not all) prior work has shown that at cross-section valine homozygosity was associated with better mental status. Second, valine homozygosity is associated with a slower rate of memory decline in our entire sample, not just those who developed dementia. Third, the HRs in this analysis suggested a possible gene-dose relationship for the CETP gene. Finally, an association between CETP status and cognition and dementia is biologically plausible because other genes involved in lipid metabolism, including APOE, are associated with dementia risk. Future studies should further evaluate the potential protective association of the CETP gene with dementia risk.

Author Contributions: Dr Lipton had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lipton, Sanders, Barzilai, Katz, Derby. Acquisition of data: Lipton, Ozelius, Derby, Katz. Analysis and interpretation of data: Lipton, Sanders, Wang, Derby, Katz. Drafting of the manuscript: Sanders, Lipton. Critical revision of the manuscript for important intellectual content: Lipton, Sanders, Ozelius, Wang, Derby, Katz, Barzilai. Statistical analysis: Wang, Lipton, Sanders, Katz. Obtained funding: Lipton. Administrative, technical, or material support: Lipton, Katz, Sanders, Ozelius. Study supervision: Lipton.
CETP GENE, MEMORY DECLINE, AND INCIDENCE OF DEMENTIA

References


