

Abstract

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Association of a functional polymorphism in the cholesteryl ester transfer protein (CETP) gene with memory decline and incidence of dementia.

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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) epsilon4 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.

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