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BRAIN RESEARCH

Research Report

Cholesteryl ester transfer protein polymorphism D442G associated with a potential decreased risk for Alzheimer's disease as a modifier for APOE ε4 in Chinese

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ABSTRACT

There is compelling evidence indicating that reduction of high-density lipoprotein (HDL) level is associated with increased risk of Alzheimer's disease (AD). It is known that the levels of HDL are regulated by cholesteryl ester transfer protein (CETP) and several single nucleotide polymorphisms (SNPs) in the CETP gene have been shown to be associated with the levels of HDL. Therefore, it is assumed that the CETP gene is a reasonable candidate for modifying the susceptibility in AD. In the present study, we investigated the association of four CETP SNPs (D442G, L296Q, Taq1B and I405V) with the risk for sporadic AD in Northern Han-Chinese. One hundred and seven AD cases and 115 age and gender-matched controls were genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP), denaturing high performance liquid chromatography (DHPLC) and DNA sequencing. The frequency of DG genotype ($P=0.035$) or G allele ($P=0.038$) for the CETP (D442G) polymorphism was greater in control subjects than in AD patients. The age- and sex-adjusted odds radio for DG vs. DD genotype was 0.202 (95% CI 0.043–0.958, $P=0.044$). When the sample was stratified by APOE ε4 carrier status, the same tendency ($P=0.042$ for DG genotype, $P=0.046$ for G allele) was observed in the presence of APOE ε4, but not in the absence of APOE ε4 ($P=0.284$ for DG genotype, $P=0.298$ for G allele). However, these results became not statistically significant after correcting for multiple testing (Bonferroni) because of limited number of our sample. Our current results suggest that G allele of CETP D442G may have a potential protective effect against the development of AD, especially in APOE ε4 carriers, in Northern Han-Chinese, possibly through regulating the HDL level in the brain.

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1. Introduction

Several lines of evidence support that decreased levels of HDL are associated with increased risk for Alzheimer's disease (AD). The levels of HDL cholesterol in serum were shown to reduce in AD patients than in normal controls and the degree of the reduction was correlated with the severity of AD (Merched et al., 2000). The reduction in the levels of HDL cholesterol was also found in the cerebrospinal fluid (CSF) of AD patients (Mulder et al., 1998) and there was a strong correlation between CSF and serum HDL cholesterol levels (Fagan et al., 2000). In addition, Chong et al. (2002) showed that treatment with statin, a cholesterol-lowing drug, was followed by a decreased prevalence of AD, increased HDL cholesterol levels and the HDL/LDL and HDL/total cholesterol ratios. Furthermore, APOE ε4, a major genetic risk factor for sporadic AD (SAD), is associated with a lower HDL level (Schmidt et al., 2000). More importantly, there is only high-density lipoprotein (HDL) in the central nervous system (CNS), which is segregated from the systemic circulation by the blood–brain barrier (Michikawa, 2004).

Cholesteryl ester transfer protein (CETP), a glycoprotein that mediates the transfer of cholesteryl esters from HDL to very low-density lipoprotein (VLDL) in exchange for triacylglycerols from the latter, plays a crucial role in the regulation of serum HDL levels (Yamashita et al., 2000). Increased CETP activity results in decreased levels of HDL (Van der Steeg et al., 2004). Studies have shown that several single nucleotide polymorphisms (SNPs) in the CETP gene, such as D442G, Taq1B and I405V, strongly influence CETP activity and HDL levels (Arai et al., 2005; Boekholdt and Thompson, 2003). Therefore, there is a reason to believe that CETP gene polymorphisms may modify the susceptibility to AD.

The association between the CETP SNPs and the susceptibility to AD has been investigated in European population by three research groups (Fidani et al., 2004; Rodriguez et al., 2006; Zhu et al., 2005). Among the SNPs investigated, which included Taq1B, I405V, promoter G-2708A, G-971A and C-629A, only C-629A polymorphism was found to significantly change the risk of AD with APOE ε4 in Spanish population (Rodriguez et al., 2006). So far, there is no report on the association of CETP polymorphisms with susceptibility to AD in Chinese population. In the present study, we investigated the association of CETP polymorphisms with susceptibility to AD in Northern-Han Chinese population. Four gene polymorphisms were selected for the present study. These included D442G polymorphism, which occurs more common in Asian population and has a demonstrable impact on CETP activity (Boekholdt and Thompson, 2003), a novel missense variant of L296Q (T+8A/Ex10) in exon 10 of the CETP, which is reported in Western Chinese (Zhang et al., 2004), and two functional variants (Taq1B and I405V), which are common in all populations (Boekholdt and Thompson, 2003). Our preliminary data suggest that CETP D442G polymorphism will deserve further investigation that people with G allele may have a decreased risk for AD, particularly in the APOE ε4 carriers, in Northern Han-Chinese.

2. Results

There were no significant differences in sex ($P=0.14$) and age ($P>0.05$) between AD and controls investigated for the present study. Three Taq1B genotypes (B1/B1, B1/B2, B2/B2), three I405V genotypes (I/I, I/V, V/V) and two D442G genotypes (D/D, D/G) were detected and their observed genotype and allele distributions were consistent with Hardy–Weinberg equilibrium (Taq1B, $P=0.94$; I405V, $P=0.22$; D442G, $P=0.39$). The DHPLC histogram and the sequencing picture showed that only LL genotype of L296Q was detected (Figs. 1 and 2).

As shown in Table 1, there was no significant difference in the distribution of genotype ($P=0.146$) and allele ($P=0.631$) of CETP Taq1B polymorphism between AD and control groups. When the Taq1B genotype data were stratified by APOE ε4 carrier status, no significant difference in genotype or allele frequency was observed between AD and control groups in the presence and absence of APOE ε4 (Table 2). Significant difference was neither found in the distribution of genotype ($P=0.563$) and allele ($P=0.566$) for CETP I405V polymorphism between AD and control groups, nor when the I405V genotype data were stratified by APOE ε4 carrier status (Tables 1 and 2). The frequency of DG genotype ($P=0.035$) or G allele ($P=0.038$) of CETP D442G polymorphism was significantly ($P<0.05$) larger in controls than in AD patients prior to correction for multiple testing (Table 1), and the age- and sex-adjusted odds radio (OR) for DG vs. DD genotype was 0.202(95% CI 0.043–0.958, $P=0.044$). When the sample was stratified by APOE ε4 carrier status (Table 2), the same trend was also observed in APOE ε4 carriers ($P=0.042$), but not in APOE ε4 non-carriers ($P=0.284$). However, after correcting for multiple testing (Bonferroni correction with 3 comparisons), these results became not statistically significant ($P>0.5/3$).

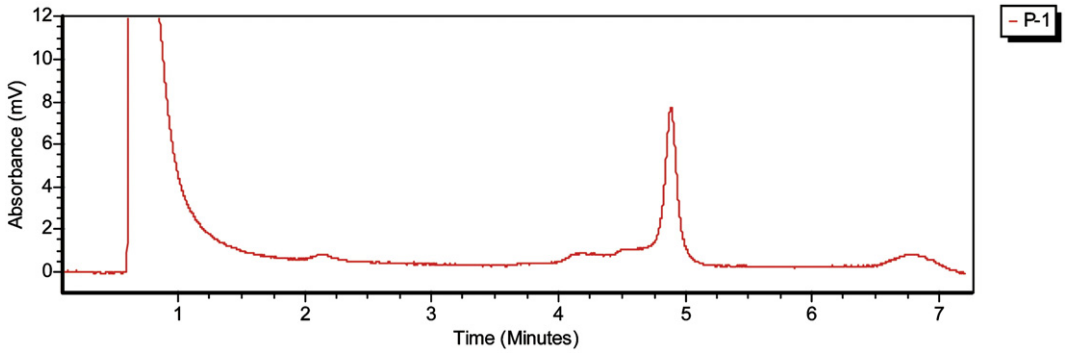

Fig. 1 – DHPLC histogram of CETP L296Q: a DNA pooling shows only a peak.