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Association between the *CETP* polymorphisms and the risk of Alzheimer's disease, carotid atherosclerosis, longevity, and the efficacy of statin therapy

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ABSTRACT

The purpose of this meta-analysis was to detect the association between the cholesteryl ester transfer protein gene polymorphisms and the risk of Alzheimer's disease (AD), carotid atherosclerosis, longevity, and the efficacy of statin therapy. Databases of MEDLINE, EMBASE, BIOSIS, the Cochrane Library, and the Chinese National Knowledge Infrastructure were systematically searched. Thirty-two studies were included in this meta-analysis. There was no difference in the I405V, C629A, and Taq1B polymorphisms between AD and control groups. However, stratified analysis showed that AD group had higher B2B2 genotype frequency than control group in Asian populations with *APOE4*+ in Taq1B. I405V and Taq1B polymorphisms were not associated with the risk of carotid atherosclerosis and longevity. The efficacy of statin therapy was not associated with Taq1B polymorphism. In conclusion, there was no association between cholesteryl ester transfer protein gene polymorphisms and the risk of AD, carotid atherosclerosis, longevity, and the efficacy of statin therapy in the pooled effects of overall population. However, the B2B2 genotype of Taq1B was associated with increased risk of AD in the Asian populations with *APOE4*+.

1. Introduction

Alzheimer's disease (AD), carotid atherosclerosis, and dyslipidemia result in diminished quality of life, life-years lost, and enormous medical costs. Therefore, it is necessary to detect the association of genetic variants and these diseases.

Recently, the association of cholesteryl ester transfer protein (CETP) gene and dyslipidemia, the risk of AD, carotid atherosclerosis, longevity, or the efficacy of statin therapy has been widely reported (Agerholm-Larsen et al., 2000; Al-Daghri et al., 2003; Bauerfeind et al., 2002; Bercovich et al., 2006; Fiegenbaum et al., 2005; Murphy et al., 2012; Parra et al., 2012; Qureischie et al., 2009; Soyal et al., 2011; Winkelmann et al., 2003; Yu et al., 2012). Plasma CETP is an extremely hydrophobic glycoprotein with a relative molecular mass of 74,000, and consists of 476 amino acids with 4 N-linked glycosylation sites. The human *CETP* spans approximately 25 kb, encompasses 16 exons, and is found on chromosome 16q13. Several polymorphisms have been identified in the human *CETP* (Corbex et al., 2000). *CETP* regulates cholesterol homeostasis via the transfer of cholesteryl esters from high-density lipoprotein cholesterol (HDL-C) to low-density lipoprotein cholesterol (LDL-C) in exchange for triacylglycerol (TG) (Barter and Kastelein, 2006). Several single-nucleotide polymorphisms within *CETP* have been suggested to influence enzymatic activity or gene expression level. In particular, Taq1B (rs708272) is characterized by a silent base change affecting the 277th nucleotide in intron 1 of the gene and possesses a restriction site for the endonuclease Taq1. Mutant alleles of the polymorphism in the Taq1B intron 1 in the *CETP* have been associated with increased HDL-C concentrations (Fidani et al., 2004). The I405V (rs5882) located in exon 14 of the *CETP* is characterized by alteration in the primary structure of the protein. This polymorphism has been related to plasma CETP concentration and HDL-C concentrations and to the degree of carotid atherosclerosis (Kakko et al., 2000). C629A (rs1800775) within the gene promoter is associated with decreased expression (Dachet et al., 2000).

Many studies have proved that dyslipidemia is correlated to the risk of AD, carotid atherosclerosis, and longevity, such as a low concentration of HDL-C have been associated with the risk of AD (Brewer, 2004), carotid atherosclerosis (Soyal et al., 2011), and longevity (Kolovou et al., 2010).

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It is well established that the risk of AD is dependent on *APOE* genotype and the ε4 allele of *APOE* (*APOE4*+) may be related to AD (Bertram et al., 2007). However, there probably are several other genes that increase the susceptibility for AD. Recent studies of the link between *CETP* polymorphisms and the susceptibility of AD, carotid atherosclerosis, longevity, or the efficacy of statin therapy have been published, respectively, but the results are equivocal (Arai et al., 2003; Arias-Vasquez et al., 2007; Cellini et al., 2005; Chen et al., 2008; Fidani et al., 2004; Kakko et al., 2000; Kuivenhoven et al., 1998; Rodriguez et al., 2006; Soyal et al., 2011; Winkelmann et al., 2003; Zhu et al., 2005). In many of these studies, the sample sizes were relatively small. Therefore, we performed a meta-analysis of the published studies to derive a more precise estimation of the association.

2. Methods

2.1. Search strategy

We sought studies published between January 1970 and July 2013 on *CETP* I405V, C629A, and Taq1B polymorphisms associated with the risk of AD, carotid atherosclerosis, longevity, and the efficacy of statin therapy. Electronic searches, limited to the English language and the Chinese language, were performed by using MEDLINE via PubMed, EMBASE, BIOSIS, Science Citation Index, the Cochrane Library database, and the Chinese National Knowledge Infrastructure database, and supplemented by scanning reference lists of articles identified for all relevant studies and review articles.

The computer-based searches combined search terms related to "cholesteryl ester transfer protein," "*CETP*", "I405V (rs5882)", "C629A (rs1800775)" or "Taq1B (rs708272)", "polymorphism", "Alzheimer's disease", "longevity", "carotid atherosclerosis", and "efficacy of statin therapy". The previously mentioned search strategy described was used to obtain titles and abstracts of studies that may have been relevant to this review. The titles and abstracts were screened by 2 authors (Qing Li and Ping Huang), who discarded studies that were not applicable. When multiple reports from the same patients were found, only the study with the most complete data set was included in the meta-analysis. But duplicate patients of different articles that have different types of data of outcomes were included. Any disagreements were arbitrated by discussion with the other reviewer (Rui-Xing Yin).

2.2. Included and excluded studies

The selection criteria for studies to be considered for this meta-analysis were as follows: (1) the studies published in peer-reviewed journals with full available text in English or in Chinese; (2) the *CETP* gene I405V, C629A, and Taq1B polymorphisms and the risk of AD, carotid atherosclerosis, longevity, or the efficacy of statin therapy; and (3) reporting at least 1 relevant outcome of association between genotype and the risk of AD, carotid atherosclerosis, longevity, or the efficacy of statin therapy. Excluded studies: studies in which it was not possible to extract data from the published results or from the authors as well as those studies that did not report appropriate outcomes were also excluded.

2.3. Types of outcome measures

The types of outcome measures were as follows: (1) relationship between the risk of AD and genotypes; (2) relationship between longevity and genotypes; (3) relationship between carotid atherosclerosis and genotypes; and (4) relationship between efficacy of statin therapy on serum lipid levels (TC (cholesterol), TG, HDL-C, and LDL-C) and genotypes. The diagnosis of AD was made in accordance with accepted criteria for dementia (DSM-III-R) (Association, 1987) and Alzheimer's disease (NINDS-ADRDA) (McKhann et al., 1984). Longevity included nonagenarian and

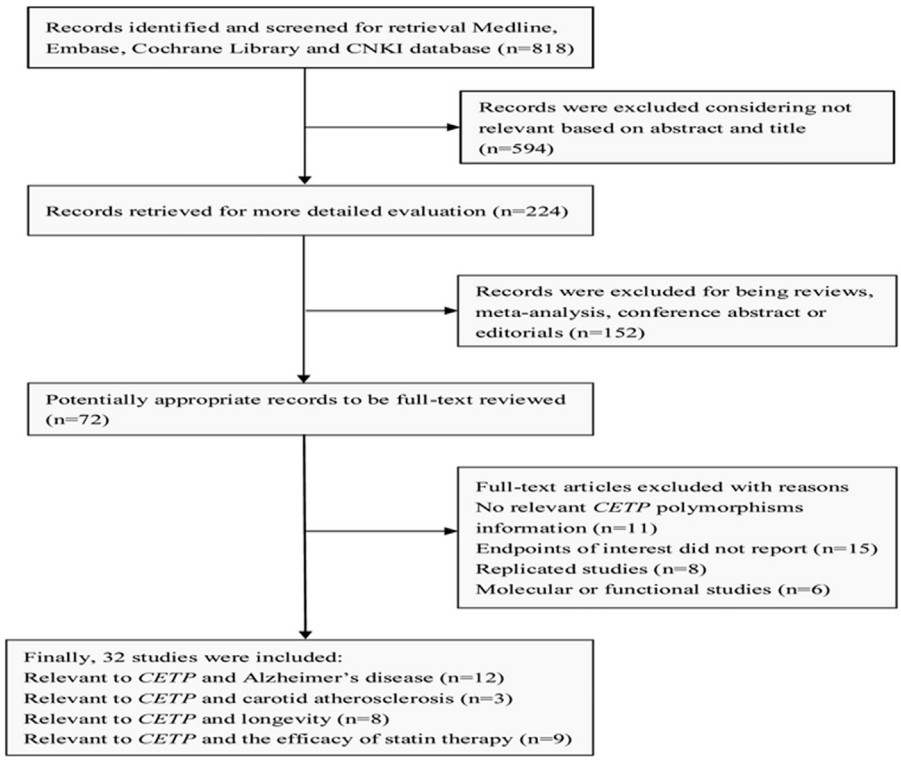

Fig. 1. Flow chart showing study selection process.