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Research paper

Genetic polymorphism of *MTHFR* C677T and premature coronary artery disease susceptibility: A meta-analysis

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ABSTRACT

The association between 5, 10-methylenetetrahydrofolate reductase (*MTHFR*) C677T gene polymorphism and premature coronary artery disease (PCAD) is controversial. To explore a more precise estimation of the association, a meta-analysis was conducted in the present study. The relevant studies were identified by searching PubMed, EMBASE, the Web of Science, Cochrane Collaboration Database, Chinese National Knowledge Infrastructure, Wanfang Database and China Biological Medicine up to November, 2014. The meta-analysis was performed by STATA 11. 21 studies with a total of 6912 subjects, including 2972 PCAD patients and 3940 controls. The pooled analysis showed that *MTHFR* C677T gene polymorphism was probably associated with PCAD (CT vs. CC: OR = 1.13, 95% CI = 1.01–1.27; dominant model: OR = 1.16, 95% CI = 1.04–1.29; recessive model: OR = 1.19, 95% CI = 1.00–1.40; allele analysis: OR = 1.17, 95% CI = 1.01–1.34). Subgroup analysis by plasma homocysteine concentration showed a significant association in the homocysteine >15 μmol/L subgroup (CT vs. CC: OR = 1.44, 95% CI = 1.10–1.88; TT vs. CC: OR = 2.51, 95% CI = 1.12–5.63; dominant model: OR = 1.51, 95% CI = 1.16–1.96; recessive model: OR = 2.33, 95% CI = 1.05–5.20; allele analysis: OR = 1.48, 95% CI = 1.18–1.87). Subgroup analysis by continent displayed a significant association among the Asian population (CT vs. CC: OR = 1.51, 95% CI = 1.23–1.86; TT vs. CC: OR = 2.81, 95% CI = 1.87–4.23; dominant model: OR = 1.65, 95% CI = 1.35–2.01; recessive model: OR = 2.22, 95% CI = 1.53–3.21; allele analysis: OR = 1.61, 95% CI = 1.37–1.89). The statistical stability and reliability was demonstrated by sensitivity analysis and publication bias outcomes. In conclusion, the meta-analysis suggests that *MTHFR* C677T gene polymorphism may be associated with PCAD.

1. Introduction

Coronary artery disease (CAD) is still one of the vital causes of death and disability in the world. Premature coronary artery disease (PCAD) is a special form of CAD, which occurs in men <55 years old and women <65 years old (Tonstad and Westheim, 2002). Compared with conventional CAD, PCAD may cause heavier burden on the health system of various countries (Dogra et al., 2012).

Evidence has suggested that high homocysteine (Hcy) level is a risk factor for PCAD (Sadeghian et al., 2006; Puri et al., 2003; Nikfardjam et al., 2001). The most common genetic defect resulting in high Hcy level is the 677C → T mutation in 5,10-methylenetetrahydrofolate reductase (*MTHFR*). In the past few decades, several studies about *MTHFR* C677T gene polymorphism were performed. Some studies demonstrated that *MTHFR* C677T gene polymorphism was associated with PCAD (Tomaiuolo et al., 2012; Sarecka-Hujar et al., 2012). However, others drew the opposite conclusion (Saffari et al., 2013; Eftychiou et al., 2012). To date, no meta-analysis has been conducted to obtain an accurate evaluation. Therefore, in the present study, a meta-analysis was conducted to evaluate the association between *MTHFR* C677T gene polymorphism and PCAD.

2. Methods

2.1. Search strategy

A critical review of literatures from PubMed, EMBASE, the Web of Science, Cochrane Collaboration Database, Chinese National Knowledge Infrastructure, Wanfang Database and China Biological Medicine (up to November, 2014) was performed to identify the relevant studies, using the following terms: ('*MTHFR*' OR 'methylenetetrahydrofolate reductase') AND ('genetic polymorphism' OR 'allele' OR 'genotype') AND ('young' OR 'premature') AND ('coronary artery disease' OR 'myocardial infarction' OR 'angina'). Meanwhile, the references used in the eligible articles or textbooks were also reviewed as sources to find potential

Abbreviations: CAD, coronary artery disease; PCAD, premature coronary artery disease; Hcy, homocysteine; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg Equilibrium.

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studies. The search was done with language limitation in English and Chinese. For studies with overlapping data or on the same population, only the one with the largest group of subject or the most recent one was included.

2.2. Inclusion and exclusion criteria

Studies included in our meta-analysis had to be consistent with the following criteria: (1) the association between *MTHFR* C677T gene polymorphism and PCAD was involved; (2) the study should be a case–control study; (3) all patients had been diagnosed with PCAD. In addition, PCAD was defined as CAD occurred in men <55 years old and women <65 years old (Tonstad and Westheim, 2002); (4) the study should provide the total number of cases and controls, and also the number of cases and controls for each genotype; (5) the study was of sufficiently high quality.

Studies were excluded when they were: (1) reviews, letters or case reports; (2) duplicate publications of data from the same study.

2.3. Data extraction

Information was carefully extracted independently by two authors and any disagreements were resolved by the third author. For studies with inadequate information, authors were contacted if possible. The following data were extracted: first author's name, publication year, ethnicity, study design, source of controls, mean age, age range, mean plasma Hcy concentration, number of cases and controls, genotype distribution in cases and controls and genotyping method.

2.4. Quality assessment of included studies

Based on Newcastle–Ottawa quality assessment scale (Stang, 2010), all included studies were assessed independently by two authors. Disagreement was resolved by consulting the third author. The quality indicators are represented by stars (*). The study with best quality can be awarded ten stars. A study is considered high quality if graded ≥six stars.

2.5. Statistical analysis

The strength of the association between *MTHFR* C677T gene polymorphism and PCAD was estimated by odds ratio (OR) and 95% confidence interval (CI). The OR and 95% CI were calculated according to co-dominant inheritance model (CT vs. CC; TT vs. CC), dominant inheritance model ((CT + TT) vs. CC), recessive inheritance model (TT vs. (CC + CT)) and allele analysis (T vs. C), respectively. The fixed and random effects models were used for non-heterogeneity and heterogeneity data respectively. Heterogeneity between the results of different studies was examined by a chi-square test (P < 0.01 was considered statistically significant) and I^2 tests (I^2 > 50%, significant heterogeneity; I^2 < 25%, insignificant heterogeneity) (Higgins et al., 2003). To explore the sources of heterogeneity, subgroup analyses were conducted by plasma Hcy concentration (>15 or ≤15 μmol/L), continent (Asia, Europe, North America or Africa) and source of controls (hospital- or population-based controls). Whether genotype frequencies meet Hardy–Weinberg Equilibrium (HWE) was tested by the χ^2 test. The sensitivity analysis was performed by omitting every study to assess the consistency of the results. To assess the potential publication bias, Begg's correlation and Egger's regression for publication bias were used (Begg and Mazumdar, 1994; Egger et al., 1997). A value of P < 0.05 indicated that there was significant publication bias. All analyses were calculated by the STATA 11 for windows (Stata, College Station, TX, USA).

3. Result

3.1. Study and data included in the meta-analysis

A flow diagram summarizing the process of study selection was shown in Fig. 1. Of the 192 potential relevant studies identified, only 21 case–control studies met all inclusion criteria. The characteristics of all included studies were listed in Table 1. The dataset represented 2972 PCAD patients and 3940 controls. No study was excluded in the meta-analysis on grounds of quality.

3.2. Pooled analysis

There were 21 studies concerning *MTHFR* C677T gene polymorphism in the present meta-analysis. Based on the values of heterogeneity (CT vs. CC: P = 0.351, I^2 = 8.3%; TT vs. CC: P = 0.001, I^2 = 55.3%; dominant model: P = 0.014, I^2 = 44.8%; recessive model: P = 0.012, I^2 = 45.6%; allele analysis: P < 0.001, I^2 = 63.1%), fixed effects models were used under the CT vs. CC, dominant and recessive genetic inheritance models, and a random effects model was used under the TT vs. CC genetic inheritance model and allele analysis. Overall, a significant association between *MTHFR* C677T gene polymorphism and PCAD was found under the CT vs. CC (OR = 1.13, 95% CI = 1.01–1.27), dominant (OR = 1.16, 95% CI = 1.04–1.29) and recessive (OR = 1.19, 95% CI = 1.00–1.40) genetic inheritance models, and allele analysis (OR = 1.17, 95% CI = 1.01–1.34). In addition, borderline significant association was also shown in the TT vs. CC genetic inheritance model (OR = 1.34, 95% CI = 0.99–1.82) (Figs. 2–5).

3.3. Subgroup analysis

In the subgroup analysis, studies were categorized by plasma Hcy concentration, continent, and source of controls. The results of the

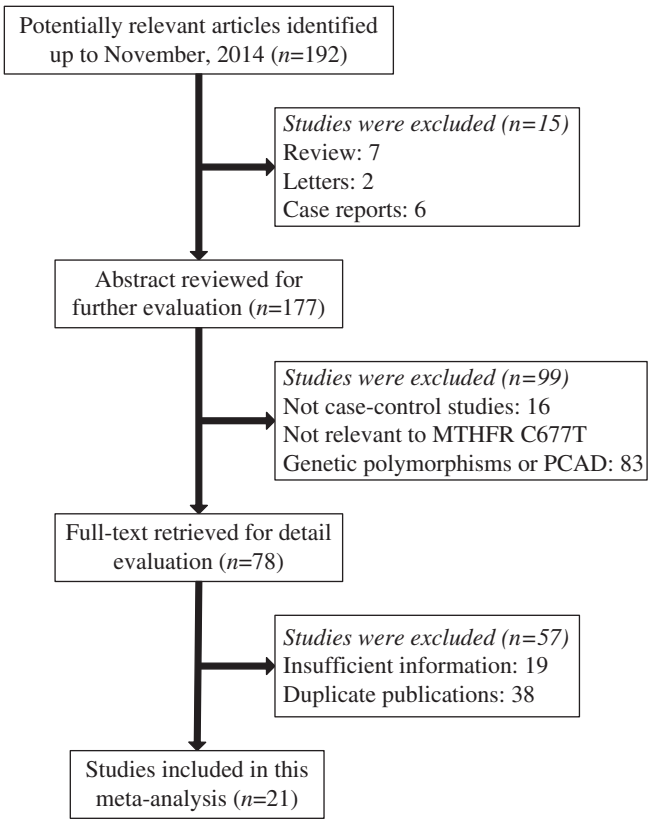

Fig. 1. Flow diagram of study selection.