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Meta-analysis

MTHFR 677 T variant contributes to diabetic nephropathy risk in Caucasian individuals with type 2 diabetes: A meta-analysis

Sheng Yang[a,*,1], Jingwen Zhang[b,1], Chang Feng[a], Guoliang Huang[b,*]

[a] Department of Endocrinology, Shengjing Hospital of China Medical University, Shenyang 110004, China
[b] Department of Endocrinology, Fujian Institute of Endocrinology, Union Hospital of Fujian Medical University, Fuzhou 350001, China

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ABSTRACT

Objective. Previous studies regarding the association between 5,10-methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and diabetic nephropathy (DN) risk in Caucasian individuals with type 2 diabetes reported conflicting results. To derive a more precise estimation of this association, a meta-analysis was performed.

Materials/Methods. Odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were pooled to assess the association between MTHFR C677T polymorphism and DN risk. Finally, 10 case–control studies with a total of 1590 DN cases and 1555 type 2 diabetic controls without DN were included.

Results. Overall, there was an association between MTHFR C677T polymorphism and increased risk of DN under four comparison models ($OR_{T\ vs.\ C}$=1.50, 95% CI 1.07–2.02, P=0.02; $OR_{TT\ vs.\ CC}$=2.09, 95% CI 1.07–4.08, P=0.03; $OR_{TT\ vs.\ TC+CC}$=1.70, 95% CI 1.10–2.63, P=0.017; $OR_{TC+TT\ vs.\ CC}$=1.85, 95% CI 1.19–2.88, P=0.006). Sensitivity analysis suggested exclusion of any single study did not materially alter the overall pooled ORs above.

Conclusions. This meta-analysis supports that there is an association between MTHFR C677T polymorphism and DN risk, and MTHFR 677 T variant contributes to increased risk of DN in Caucasian individuals with type 2 diabetes.

1. Introduction

Diabetic nephropathy (DN) is one of the most serious microvascular complications of type 2 diabetes, and it is the primary cause of end-stage renal disease (ESRD) worldwide [1–3]. The etiology of DN is multi-factorial and involves both environmental and genetic factors, and it's still a major challenge for clinicians and researchers to elucidate pathogenesis and identify patients at risk [4–6]. Methylenetetrahydrofolate reductase (MTHFR) converts 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate and directs the homeostasis between DNA synthesis and methylation [7]. The MTHFR 677C>T (rs1801133) polymorphism in the gene encoding the N5, N10-MTHFR enzyme changes the amino

Abbreviations: DN, diabetic nephropathy; ESRD, end-stage renal disease; HWE, Hardy–Weinberg equilibrium; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio; 95% CI, 95% confidence interval.

* *Corresponding authors.* Yang Sheng, Department of Endocrinology, Shengjing Hospital of China Medical University, 36 of San Hao Street, Shenyang 110004, China. Tel.: +86 024 83956319. Guoliang Huang, Department of Endocrinology, Fujian Institute of Endocrinology, Union Hospital of Fujian Medical University, Fuzhou 350001, China.
E-mail addresses: yangsh19@yahoo.com.cn (S. Yang), huangguoliang17@yahoo.cn (G. Huang).

[1] These authors contributed equally to this work.

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acid 222 from Alanine to Valine and decreases the MTHFR enzyme activity, which has been studied as a candidate genetic risk factor for DN [8,9]. As T allele dose increases, this functional polymorphism causes a graded elevation in tHcy in the mild–moderate range, most pronounced in individuals with low dietary folate consumption [9]. Previous case–control studies investigating the association between MTHFR C677T polymorphism and DN risk in Caucasian population have so far provided conflicting results [10–20]. Though two meta-analyses have been published to assess the association between MTHFR C677T polymorphism and DN risk, data from those two studies had several limitations to assess the association in Caucasian individuals with type 2 diabetes [19,20]. Thus, the association between MTHFR C677T polymorphism and DN risk in Caucasian individuals with type 2 diabetes was still unclear, and we performed a meta-analysis of all available studies to comprehensively assess this association in Caucasian population.

2. Methods

2.1. Database search

We searched PubMed, Medline and Embase databases for studies published from January 1980 to June 2012. The following search terms were used: 1) methylenetetrahydrofolate reductase, MTHFR, and C677T; 2) diabetic nephropathy, and diabetes nephropathy; and 3) polymorphism, mutation, and genotype. No restrictions were imposed. In addition, we reviewed the reference lists of retrieved papers and recent reviews.

2.2. Study selection and data extraction

We first performed an initial screening of titles or abstracts. A second screening was based on full-text review. The inclusion criteria were: (1) case–control studies which evaluated the association between MTHFR C677T polymorphism and DN risk in type 2 diabetic patients; (2) both cases and controls were from Caucasians; (3) the controls were diabetic individuals without DN; (3) used an unrelated case–control design and had available genotype frequency for estimating an OR with its 95% CI. For studies with more than one publication describing results among the same or overlapping groups of patients or controls, the one with the largest available data was included. From each study the following information was extracted: first author, publication year, population demographics, clinical characteristics, diagnostic criteria and stage of DN, genotyping methods, and the number of cases and controls for MTHFR C667T genotype. To test the population stratification in the controls, a chi-square test was applied to determine if MTHFR C677T genotype distribution in the controls conformed to HWE (Hardy–Weinberg equilibrium).

2.3. Statistical analysis

The strength of the association between MTHFR C677T polymorphism and DN risk was measured by the pooled OR with its corresponding 95% CI. We assessed the association under four genetic models: allele genetic comparison model (T vs. C), the homozygote comparison model (TT vs. CC), the recessive genetic comparison model (TT vs. TC+CC) and the dominant genetic comparison model (TC+TT vs. CC). To assess the between-study heterogeneity more precisely, both the chi-square based Q statistic test (Cochran's Q statistic) to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated [21,22]. Heterogeneity was considered significant for $P_{\text{Cochran's Q statistic}} < 0.10$, and the random-effects model was used to pool the results [23]; on the contrary, the fixed-effects model was used to pool the results when P value of Cochran's Q statistic was more than 0.10 [24]. For obvious between-study heterogeneity, meta-regression was performed to assess the possible source of heterogeneity, such as the diabetes duration, basic clinical characteristics or genotyping method [25]. We further conducted a sensitivity analysis to examine the influence of a single study on the overall risk estimate by omitting one study in each turn [26]. Potential publication bias was assessed by visual inspection of the funnel plots in which the log ORs were plotted against their SEs [27]. We also performed Egger linear regression test at the $P<0.05$ level of significance [28]. All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas). A P value <0.05 was considered statistically significant, except where otherwise specified.

3. Results

3.1. Characteristics of included studies

A flow diagram illustrating the study selection process was shown in Fig. 1. With our search strategy 63 individual

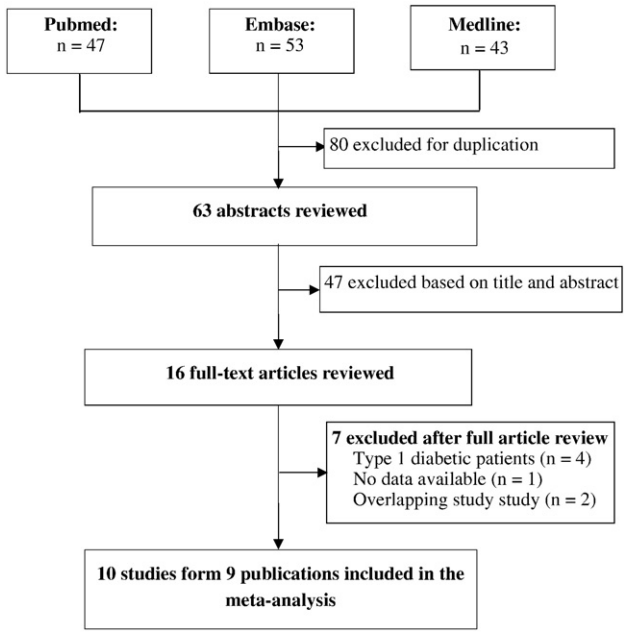

Fig. 1 – Search flow diagram for studies included in the meta-analysis.