GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Association between *MTHFR* 677C/T polymorphism and psoriasis risk: a meta-analysis

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Genet. Mol. Res. 14 (2): 3869-3876 (2015)
Received August 12, 2014
Accepted December 8, 2014
Published April 22, 2015
DOI http://dx.doi.org/10.4238/2015.April.22.16

ABSTRACT. Previous studies investigating the association between methylenetetrahydrofolate reductase (*MTHFR*) 677C/T polymorphisms and psoriasis risk have reported inconsistent results. The present meta-analysis aimed to comprehensively evaluate the association between *MTHFR* 677C/T polymorphism and psoriasis risk. The studies regarding the association between *MTHFR* 677C/T polymorphism and psoriasis risk were retrieved from the PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure, and Chinese Biomedical databases. Data were extracted and statistical analysis was performed with the program STATA 12.0. A total of seven studies involving 1290 psoriasis cases and 1068 healthy controls were retrieved. Combined analysis showed that there was no significant difference in *MTHFR* 677C/T genotype distribution between psoriasis and control subjects in the comparisons C *vs* T, CC *vs* CT + TT, CC + CT *vs* TT, CC *vs* TT,

and CC *vs* CT [respectively: odds ratio (OR) = 0.98, 95% confidence interval (CI) = 0.76-1.26, P = 0.882; OR = 1.11, 95%CI = 0.81-1.51, P = 0.526; OR = 0.79, 95%CI = 0.53-1.19, P = 0.261; OR = 0.88, 95%CI = 0.51-1.52, P = 0.648; OR = 1.19, 95%CI = 0.90-1.58, P = 0.217]. Subgroup analysis by ethnicity also showed no significant association between *MTHFR* 677C/T polymorphism and psoriasis risk in both Asian and Caucasian populations. In conclusion, this meta-analysis indicates that *MTHFR* 677C/T polymorphism may not be associated with psoriasis risk.

Key words: Methylenetetrahydrofolate reductase; Polymorphism; Psoriasis; Meta-analysis

INTRODUCTION

Psoriasis is a common chronic and recurrent inflammatory skin disease characterized by epidermal hyperplasia, abnormal keratinocyte differentiation, and local accumulation of acute and chronic inflammatory cells (Krueger et al., 1990; Zenz et al., 2005), which affects approximately 2% of the population worldwide (Ni and Chiu, 2014). Although the exact pathogenesis of the disease has not yet been clarified, it is widely accepted that genetic, environmental, and immunological factors act together or individually to precipitate the disease (Krueger and Bowcock, 2005).

Methylenetetrahydrofolate reductase (MTHFR), a crucial enzyme in the metabolism of folate, catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is the precursor of S-adenosylmethionine (SAM). SAM is a universal methyl donor for methylation reactions, including DNA methylation (Selhub and Miller, 1992). The *MTHFR* gene is located at chromosome 1 (1p36.3). The most studied C677T polymorphism in the *MTHFR* gene results in a thermolabile variant (T) with reduced activity of the enzyme (Friso et al., 2002).

A significant association between MTHFR 677C/T gene polymorphism and psoriasis was reported in a Chinese population (Baiqiu et al., 2000). This finding seemed to be biologically plausible, as MTHFR is associated with DNA methylation reactions (Stern et al., 2000) and DNA methylation disorders might play a role in the etiopathogenesis of psoriasis (Ruchusatsawat et al., 2006; Zhang et al., 2007). Moreover, a lower frequency of the tyrosine phosphatase (*SHP-1*) gene and *p16* gene demethylation has been observed in psoriatic skin lesions (Ruchusatsawat et al., 2006; Zhang et al., 2007). However, several case-control studies carried out subsequently have reported inconsistent results (Weger et al., 2008; Vasku et al., 2009; Liew et al., 2012; Asefi et al., 2014). Therefore, we performed the present meta-analysis to comprehensively evaluate the association between the *MTHFR* C677T polymorphism and psoriasis risk based on all eligible case-control studies.

MATERIAL AND METHODS

Literature search

The studies regarding the association between *MTHFR* gene 677C/T polymorphism and psoriasis risk published up to May 2014 without language restrictions were independently

searched by two authors in the PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical (CBM) Literature Database, using the following terms: ("MTHFR" or "methylenetetrahydrofolate reductase") and ("psoriasis" or "psoriasis" or "psoriatic") and ("polymorphism" or "SNP" or "single nucleotide polymorphism" or "variation" or "mutation"). The bibliographies of retrieved articles were manually searched to find additional relevant studies.

Study selection

Studies were included in this meta-analysis if they met the following criteria: (a) case-control studies focused on associations between *MTHFR* 677C/T polymorphism and psoriasis risk; (b) 95% confidence intervals (CIs) for odds ratios (ORs) were available or could be calculated; (c) the distribution of genotypes in the control group was consistent with the Hardy-Weinberg equilibrium (HWE). When we retrieved repetitive publications, only one publication was included. Family-based studies were excluded.

Data extraction

The following data from the included studies were extracted independently by two authors: the first author, the year of publication, the country of subject recruitment, the subjects' ethnicities, the sample size, and the genotype frequencies in psoriasis cases and controls. In cases of conflicting evaluation, disagreements were resolved through discussion between the authors.

Statistical analysis

Genotype distributions in the controls were tested for HWE using the Pearson χ^2 test (Schaid and Jacobsen, 1999). Between-study heterogeneity was checked using the Cochran Q-statistic and the I^2 test (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). When $P < 0.1$ for the Q-test or $I^2 > 50\%$ indicated the existence of heterogeneity, a random-effects model was used; otherwise, a fixed-effects model was applied. ORs with corresponding 95%CIs were calculated to assess the association between *MTHFR* gene 677C/T polymorphism and psoriasis risk in five genetic models: C *vs* T, CC *vs* CT + TT, CC + CT *vs* TT, CC *vs* TT and CC *vs* CT. The significance of the pooled ORs was determined using the Z-test. To evaluate whether the association showed any ethnicity-specific effects, we analyzed the data for separate subgroups defined by ethnicity. Sensitivity analysis was performed by sequential omission of individual studies and recalculating the results to assess the stability of the results. Begg's funnel plots and the Egger tests were used to investigate whether publication bias might affect the validity of the estimates (Peters et al., 2006). All the statistical tests were conducted using the STATA 12.0 software.

RESULTS

Characteristics of studies included

The flow chart of the selection of studies and specific reasons for exclusion from the meta-analysis are shown in Figure 1.

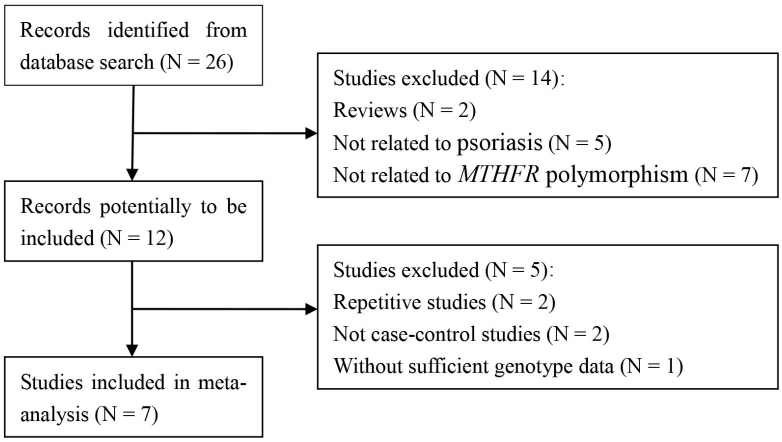

Figure 1. Flow chart of the selection of studies and specific reasons for exclusion from the meta-analysis.

The search strategy retrieved 26 potentially relevant studies. In accordance with the inclusion criteria, seven case-control studies with 1290 psoriasis cases and 1068 healthy controls were included in this meta-analysis. Of the seven eligible studies, five were conducted in Asian populations and the remaining two were conducted in Caucasian populations. The publication year of the included studies ranged from 2000 to 2014. Five articles were written in English and the remaining two were written in Chinese. The distribution of genotypes in the control group of each included study was consistent with HWE (all $P > 0.05$). The control group was chosen from healthy individuals without any systemic or dermatologic diseases. The characteristics of the studies included are summarized in Tables 1 and 2.

Table 1. Characteristics of the seven studies included in this meta-analysis.

First Author (year)	Country	Ethnicity	Source of controls	Sample	Cases	Controls
Baiqiu et al. (2000)	China	Asian	Population-based	Blood	39	79
Jie et al. (2007)	China	Asian	Population-based	Blood	123	129
Weger et al. (2008)	Austria	Caucasian	Population-based	Blood	310	247
Vasku et al. (2009)	Czech	Caucasian	Population-based	Blood	410	244
Dehui et al. (2012)	China	Asian	Population-based	Blood	108	102
Liew et al. (2012)	Malaysia	Asian	Population-based	Blood	200	167
Asefi et al. (2014)	Iran	Asian	Population-based	Blood	100	100

Table 2. Distribution of *MTHFR* 677C/T polymorphism in psoriasis patients and control subjects.

Study	Allele				Genotype						HWE test
	Case		Control		Case			Control			
	C	T	C	T	CC	CT	TT	CC	CT	TT	
Baiqiu et al. (2000)	35	43	95	63	8	19	12	26	43	10	Y
Jie et al. (2007)	111	135	115	143	26	59	38	21	73	35	Y
Weger et al. (2008)	396	224	328	166	133	130	47	110	108	29	Y
Vasku et al. (2009)	565	255	305	183	195	175	40	90	125	29	Y
Dehui et al. (2012)	154	62	131	73	60	34	14	42	47	13	Y
Liew et al. (2012)	359	41	290	44	159	41	0	125	40	2	Y
Asefi et al. (2014)	143	57	163	37	50	43	7	64	35	1	Y

Y = consistent with Hardy-Weinberg equilibrium (HWE).

Meta-analysis results

Significant heterogeneity between studies was observed in the comparisons of C *vs* T, CC *vs* CT + TT, CC *vs* TT, and CC *vs* CT with the Q-test and the I^2 test ($P < 0.1$ or $I^2 > 50\%$). Therefore, the random effects model was used to pool the results. Meta-analysis results identified that there was no significant difference in *MTHFR* C677T genotype distribution between psoriasis and control in the comparisons of C *vs* T, CC *vs* CT + TT, CC + CT *vs* TT, CC *vs* TT, and CC *vs* CT (respectively: OR = 0.98, 95%CI = 0.76-1.26, P = 0.882; OR = 1.11, 95%CI = 0.81-1.51, P = 0.526; OR = 0.79, 95%CI = 0.53-1.19, P = 0.261; OR = 0.88, 95%CI = 0.51-1.52, P = 0.648; OR = 1.19, 95%CI = 0.90-1.58, P = 0.217) (Table 3).

Table 3. Meta-analysis of the association between *MTHFR* 677C/T polymorphism and psoriasis risk.

Comparison	OR	95%CI	P value	Heterogeneity		Effects model
				I^2	P value	
C *vs* T	0.98	0.76-1.26	0.882	70.5%	0.002	Random
Asian	0.92	0.63-1.33	0.644	71.7%	0.007	Random
Caucasian	1.09	0.74-1.61	0.654	80.6%	0.023	Random
CC *vs* CT + TT	1.11	0.81-1.51	0.526	64.1%	0.010	Random
Asian	1.04	1.65-1.66	0.881	66.3%	0.018	Random
Caucasian	1.21	0.74-1.98	0.455	77.7%	0.034	Random
CC + CT *vs* TT	0.79	0.53-1.19	0.261	45.7%	0.087	Random
Asian	0.65	0.33-1.27	0.211	48.8%	0.099	Random
Caucasian	0.95	0.67-1.36	0.794	50.9%	0.154	Random
CC *vs* TT	0.88	0.51-1.52	0.648	60.8%	0.018	Random
Asian	0.72	0.28-1.81	0.480	63.7%	0.026	Random
Caucasian	1.08	0.52-2.24	0.836	73.3%	0.053	Random
CC *vs* CT	1.19	0.90-1.58	0.217	50.7%	0.058	Random
Asian	1.15	0.75-1.75	0.532	55.8%	0.060	Random
Caucasian	1.25	0.82-1.91	0.298	66.0%	0.086	Random

OR = odds ratio; CI = confidence interval.

In the subgroup analysis based on ethnicity, the studies included were divided into Caucasian and Asian populations, and the results also showed no significant association between *MTHFR* 677C/T polymorphism and psoriasis risk in both Caucasian and Asian populations. A forest plot of psoriasis risk associated with *MTHFR* 677C/T polymorphism (CC *vs* CT + TT) is shown in Figure 2. The results for this and other genetic models are summarized in Table 3.

Sensitivity analysis and publication bias

Sensitivity analysis was performed by sequential omission of individual studies for all subjects and subgroups. The pooled ORs were not significantly altered in all subjects and subgroups by omitting any single study (data not shown). The results of sensitivity analysis indicated the stability of our results. Begg's funnel plots and the Egger tests were used to assess publication bias. The shape of the funnel plots in the recessive model seemed to be symmetrical (Figure 3), as with the other models (data not shown). The Egger tests also showed that there was no statistically significant publication bias in any genetic model (all $P > 0.05$) (data not shown).

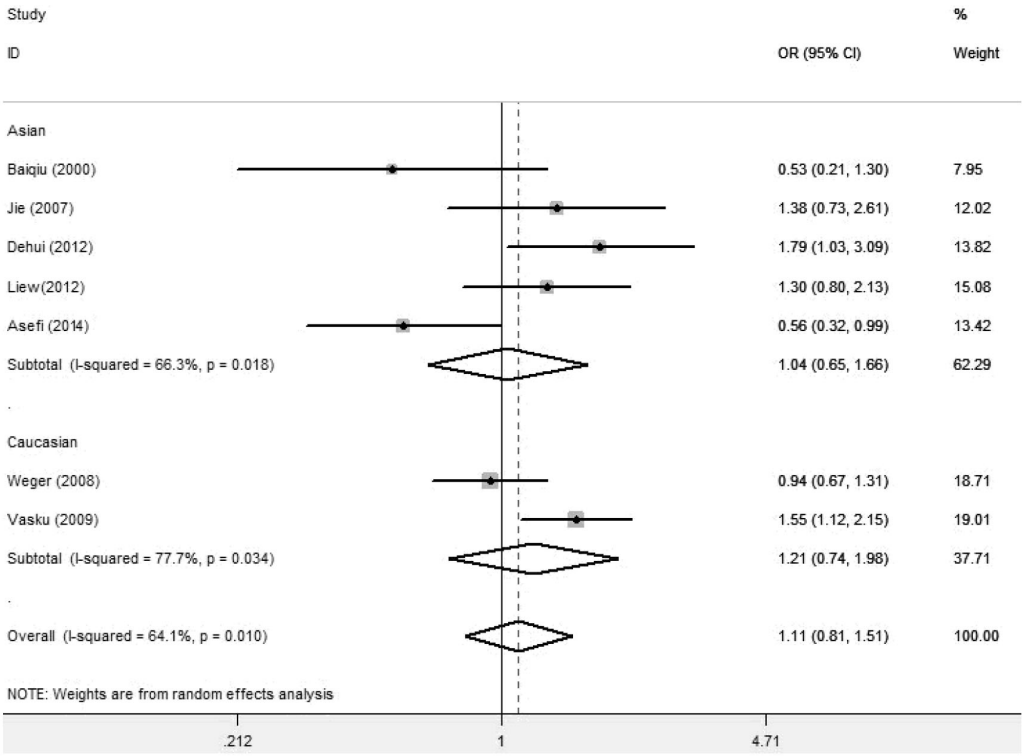

Figure 2. Forest plot of psoriasis risk associated with MTHFR 677C/T polymorphism (CC *vs* CT + TT). OR = odds ratio; CI = confidence interval.

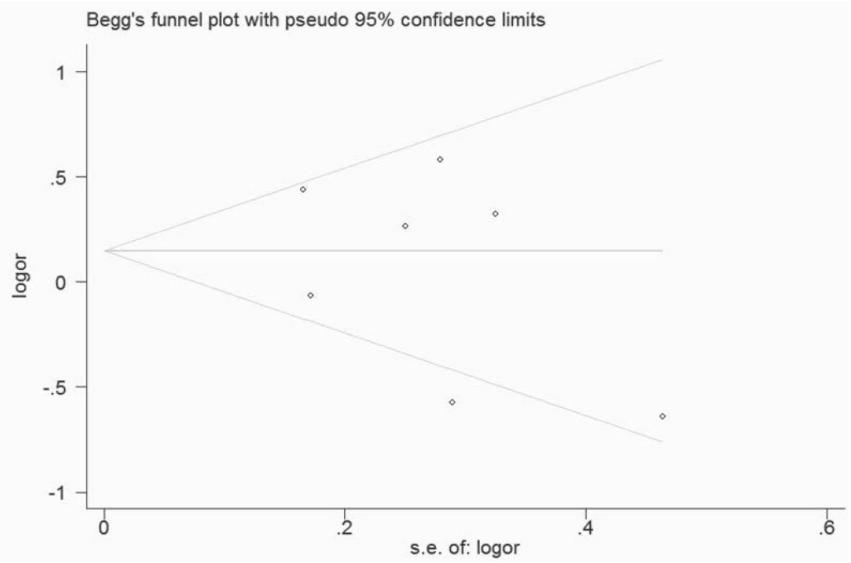

Figure 3. Evaluation of publication bias (CC *vs* CT + TT).

DISCUSSION

In the last two decades, the association between *MTHFR* gene polymorphism and psoriasis has attracted great interest amongst researchers worldwide. To date, a number of case-control studies have been performed to investigate the association between *MTHFR* 677C/T polymorphism and psoriasis risk (Baiqiu et al., 2000; Jie et al., 2007; Weger et al., 2008; Vasku et al., 2009; Dehui et al., 2012; Liew et al., 2012; Asefi et al., 2014). However, the conclusion was controversial, which may have been partly due to a small sample size in individual studies or differences in various ethnic groups. Meta-analysis has been recognized as a useful statistical method that combines findings from independent studies to precisely evaluate the effect of selected genetic polymorphism on the risk of disease (Attia et al., 2003). To the best of our knowledge, no meta-analysis has been conducted to evaluate the association between *MTHFR* C677T polymorphism and psoriasis risk. Therefore, there is a need to perform a meta-analysis using published data to clarify inconsistent findings.

Based on seven case-control studies involving 1290 psoriasis cases and 1068 healthy controls, this meta-analysis revealed that there was no significant difference in *MTHFR* C677T genotype distribution between psoriasis and control subjects in the comparisons of C *vs* T, CC *vs* CT + TT, CC + CT *vs* TT, CC *vs* TT, and CC *vs* CT, which indicated that there may be no association between *MTHFR* 677C/T polymorphism and psoriasis risk. Similarly, in the subgroup analysis by ethnicity, no significant association was found between *MTHFR* C677T polymorphism and psoriasis risk in all comparisons. Results showed obvious heterogeneity between studies, suggesting a possible role of ethnic difference in genetic backgrounds and the environment in which the subjects lived. As the eligible study number was small in this meta-analysis of *MTHFR* 677C/T polymorphism, these results still need further investigation.

Some limitations of our meta-analysis should be acknowledged. First, because of incomplete raw data on publication, some relevant studies could not be included in our analysis. Second, the number of included studies was not sufficiently large and the sample sizes of some of the included studies were relatively small, which may not provide enough statistical power to explore the real association between *MTHFR* 677C/T polymorphism and psoriasis risk. Third, the included publications were limited to Asian and Caucasian populations, so future work should examine other populations. Fourth, although no obvious publication bias was identified, potential bias cannot be completely ruled out. Finally, our results were based on unadjusted data and lacked the information for the data analysis, which may have caused serious confounding bias.

In summary, our meta-analysis of seven case-control studies suggested that *MTHFR* 677C/T polymorphism may not be associated with psoriasis risk. As few studies are available in this field and current evidence remains limited, further studies are still needed to warrant and validate our results.

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