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Association between MTHFR C677T Polymorphism and Risk of Acute Lymphoblastic Leukemia: A Meta-Analysis Based on 51 Case-Control Studies

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Manuscript Preparation E
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Background: Studies and systematic reviews have reached inconsistent conclusions on the role of 5, 10-methylenetetrahydrofolate reductase (MTHFR) polymorphism *C677T* in acute lymphoblastic leukemia (ALL) risk.

Material/Methods: The present meta-analysis comprising of 51 case-control studies, including 7892 cases and 14 280 controls was performed to reevaluate the association between MTHFR C677T polymorphism and ALL risk.

Results: Statistical differences were found in the dominant model (TT+CT *vs.* CC, odd ratio (OR)=0.89, 95% CI, 0.79–1.00, *P*=0.04) and the CT *vs.* CC (OR=0.89, 95% CI, 0.80–1.00, *P*=0.05), but not in the allele contrast model (T *vs.* C, OR=0.92, 95% CI, 0.84–1.01, *P*=0.08), additive model (TT *vs.* CC, OR=0.87, 95% CI, 0.73–1.05, *P*=0.15), or recessive model (TT *vs.* CT+CC, OR=0.94, 95% CI, 0.81–1.10, *P*=0.44) in overall populations. In the subgroup analyses stratified by age (children and adults) and ethnicity (Asian and Caucasian), no significant associations between MTHFR C677T polymorphism and ALL risk were observed.

Conclusions: The current study found no sufficient evidence of a protective role of MTHFR C677T polymorphism in ALL susceptibility.

MeSH Keywords: **5,10-Methylenetetrahydrofolate Reductase (FADH2) • Meta-Analysis • Precursor Cell Lymphoblastic Leukemia-Lymphoma**

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Background

Acute lymphoblastic leukemia (ALL) originates from an expansion of monoclonal malignant T or B lymphoid cells and can occur at any age, with peak incidence at 2–5 years of age [1]. The etiology of ALL is complex; it is considered to be associated with both endogenous and exogenous factors. Confirmed risk factors include congenital genetic disorders (e.g., Down syndrome, neurofibromatosis, Fanconi's anemia) and adverse environmental exposures (e.g., ionizing radiation, benzene). However, these risk factors only account for less than 10% of ALL patients [2], leaving most of the patients with still unknown causes.

With the advent of the genome-wide association study (GWAS) era, many researchers began to focus on genetic variability in drug metabolism, DNA repair, and cell-cycle checkpoints that may interact with environmental, dietary, maternal, and other external factors to affect leukemogenesis. Currently, it has been determined that variations of the genes RID5B, IKZF1, CEBPA, and CDKN2A/B are associated with increased susceptibility to ALL. However, the number of confirmed genetic risk factors is still limited, with many remaining to be identified [3–5].

Methylenetetrahydrofolate reductase (MTHFR) is the most critical enzyme in the folate metabolism [6,7], catalyzing irreversible conversion of 5,10-methylenetetrahydrofolate (5,10-MTHF) to 5-methyltetrahydrofolate (5-MTHF), which is the predominant circulating form of folate. 5,10-MTHF is the intracellular coenzyme form of folate and is required for conversion of uridylate to thymidylate, which inhibits misincorporation of uridylate into DNA. Thus, folate is an important factor in DNA synthesis. In addition, MTHFR causes methylation of homocysteine into methionine, leading to methylation of DNA. Many studies have reported that aberrant DNA methylation plays important roles in the pathogenesis of many hematological malignancies through regulation of gene transcription and imprinting [8–13].

MTHFR gene is localized on chromosome 1p36.3 [14] and is highly polymorphic. The variant genotypes result in decreased MTHFR enzyme activity. Decreased MTHFR activity may result in mistakes during DNA replication, leading to disturbance in 5,10-MTHF metabolism, which is essential for DNA methylation, repair, and synthesis. *MTHFR C677T* and *A1298C*, the 2 most important polymorphisms in the *MTHFR* gene, contribute to the reduction of enzyme activity [15]. The *MTHFR C677T,* which has been studied extensively, involves a cytosine-to-thymine substitution at position 677, a consequence of transformation from an alanine to a valine in the enzyme. This change leads to reduced enzyme activity, and individuals heterozygous (677CT) or homozygous (677TT) for this variant had enzyme activity reduced to approximately 60% and 30%, respectively, of that of the wild type (677CC). A1298C, causing conformational changes within the MTHFR enzyme, alters enzymatic activity to a lesser extent than the C677T polymorphism does [16,17].

Previous studies investigated the association between MTHFR C677T polymorphism and ALL risk. However, findings from these studies were conflicting. Some studies [7,18–21] concluded that MTHFR C677T polymorphism was associated with a reduced ALL risk, some [22–26] indicated insignificant associations between the gene and ALL risk, and others [27] reported an increased ALL risk with MTHFR C677T. Likewise, many meta-analyses [28–36] addressing this association also arrived at inconsistent conclusions.

For independent case-control studies, this inconsistency may be attributed partly to a limited sample size in some, with insufficient statistical power to demonstrate a significant association; they also involved different populations [29] and adopted different sampling strategies. For meta-analyses, different searching strategies and inclusion criteria might have resulted in different studies included, leading to different conclusions.

There have been many recent case-control studies [22,23,27,37–39] since the previously published meta-analyses [28–33]. This new evidence necessitates reassessment of the association between MTHFR C677T polymorphism and ALL risk, as performed in this updated meta-analysis. We hope that this meta-analysis of the most comprehensive literature addressing the association will yield more convincing evidence to determine the role of MTHFR C677T polymorphism in ALL risk.

Material and Methods

Literature search

A systematic search was conducted by 2 independent authors to identify studies on the association between MTHFR C677T polymorphism and ALL risk. Search term "((methylenetetrahydrofolate reductase) OR (MTHFR gene)) AND (polymorphism OR genetics) AND (acute lymphoblastic leukemia)" was used in 3 electronic databases (PubMed, Cochrane Library, and Wanfang Data) from inception to 31st Dec, 2013. The references of recently published meta-analyses [28–33] were also checked. There was no restriction of publication language.

Inclusion and exclusion criteria

The studies included for the present meta-analysis fulfilled the following criteria: (a) case-control design, (b) investigating the association between MTHFR C677T polymorphism and ALL risk, either in adult or in childhood, and (c) published reports providing sufficient data to calculate the odds ratio (OR) and its 95% confidence interval (CI). The exclusion criteria were: (a)

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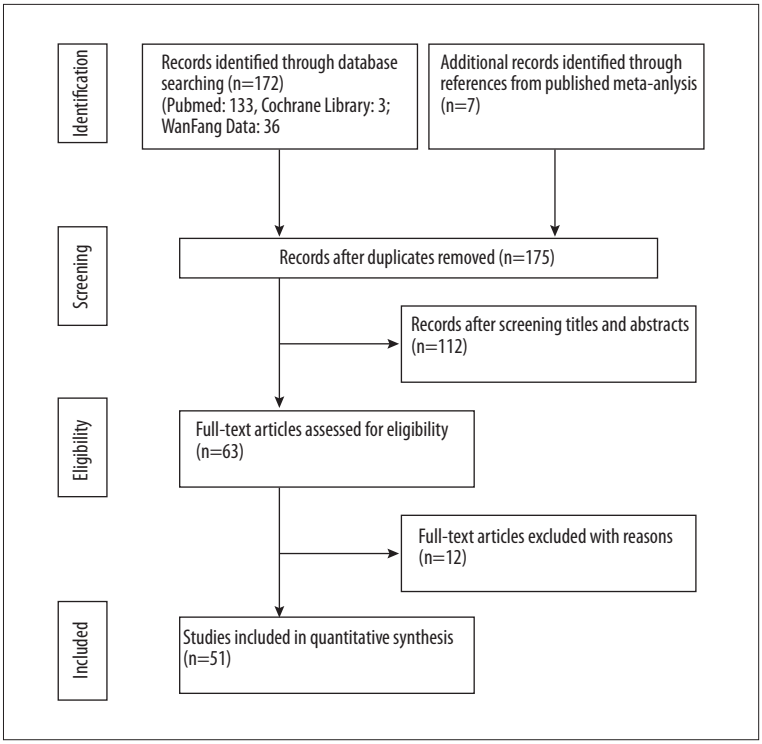

Figure 1. Flow chart of the eligibility selection process.

not a case-control design, (b) not providing effective data, or (c) duplicated reports from the same group of patients.

Study identification

Two authors independently screened titles of all studies retrieved. The abstract of any study that was potentially relevant to the topic was reviewed. The full text was obtained if inadequate information was acquired from the abstract. The corresponding author was consulted for the final decision if any disagreement on eligibility existed between the first 2 reviewers.

Data extraction

Two authors participated in data extraction independently. Disagreement was resolved by discussion and the corresponding author's opinion was asked for when necessary. Data were collected from all studies available for meta-analysis and information on general characteristics of the eligible studies and patients.

Outcomes for meta-analysis

The association between MTHFR C677T polymorphism and ALL risk was evaluated using the following 5 models: allele contrast (T *vs.* C), additive model (TT *vs.* CC), recessive model (TT *vs.* CC+CT), dominant model (TT+CT *vs.* CC), and heterozygote *vs.* wild-type homozygous (CT *vs.* CC) [32,40].

The outcomes included results of the above 5 models for overall populations and those for subgroup analyses stratified by age (children and adults, the age cut-off values for children and adult complied with the studies included) and ethnicity (Asian and Caucasian).

Statistical analysis

Statistical heterogeneity was evaluated using I^2 statistics [41], which can be calculated from basic results obtained from a typical meta-analysis as $I^2=100\% \times (Q–df)/Q$, where Q is Cochrane's heterogeneity statistic and df is the degrees of freedom [42]. An I^2 value of 0% represents no heterogeneity, with values of 25%, 50%, 75%, or more represent low, moderate, high, and extreme heterogeneity, respectively. For outcomes of heterogeneity, when $P>0.05$, a fixed-effects model was used for analyses. Otherwise, a random-effects model was adopted for $P\leq0.05$. In this study, pooled odd ratios (OR) and their 95% confidence intervals (CI) from all eligible studies were used to assess the strength for the association between MTHFR C677T polymorphism and ALL risk according to the 5 models. The potential for publication bias was estimated by Begg's test (funnel plot method) and Egger's linear regression test ($P\leq0.05$ indicated a statistically significant publication bias) [43].

The meta-analysis was performed using Review Manager 5.2 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) for outcome measures. A *P* value of ≤0.05 was considered statistically significant. The publication

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bias analysis was performed using Stata software version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study selection and characteristics

The search process and search outcomes are listed in Figure 1. A total of 179 potentially relevant studies were identified. After the titles, abstracts, and full texts were screened and reviewed, 51 published studies [7,18–27,37–39,44–80] with a total of 7892 cases and 14 280 controls met all the inclusion criteria. Of all the eligible studies, 41 were published in English and 10 were in Chinese. Information about general characteristics of the eligible studies and patients are listed in Table 1.

Meta-analysis outcomes

Outcomes for overall populations

As shown in Table 2, no significant associations were identified in the allele contrast model [OR 0.92, 95% CI (0.84, 1.01), *P*=0.08], additive model [OR 0.87, 95% CI (0.73, 1.05), *P*=0.15], or recessive model [OR 0.87, 95% CI (0.73, 1.05), *P*=0.15]. However, statistically significant associations were found in the dominant model [OR 0.89, 95% CI (0.79, 1.00), *P*=0.04] (Table 2) and the CT *vs.* CC model [OR 0.89, 95% CI (0.80, 1.00), *P*=0.05] (Table 2).

Outcomes for subgroup analyses stratified by age

A total of 35 studies investigated the association in children. Results revealed insignificant associations between MTHFR C677T polymorphism and ALL risk in all 5 models [Allele contrast model (*P*=0.09), additive model (*P*=0.13), recessive model (*P*=0.34), dominant model (*P*=0.07), CT *vs.* CC model (*P*=0.11)] (Table 2).

Nine studies reported the association in adults. Similarly, none of the 5 models revealed significant associations between MTHFR C677T polymorphism and ALL risk [Allele contrast model (*P*=0.57), additive model (*P*=0.47), recessive model (*P*=0.63), dominant model (*P*=0.57), CT *vs.* CC model (*P*=0.40)] (Table 2).

Outcomes for subgroup analyses stratified by ethnicity

Results of 26 studies showed no significant associations between MTHFR C677T polymorphism and ALL risk in Asian populations [Allele contrast model (*P*=0.39), additive model (*P*=0.53), recessive model (*P*=0.93), dominant model (*P*=0.22), and CT *vs.* CC model (*P*=0.15)] (Table 3). Likewise, no significant associations were identified between MTHFR C677T polymorphism and ALL risk in Caucasian populations [Allele contrast model (*P*=0.24), additive model (*P*=0.36), recessive model (*P*=0.56), dominant model (*P*=0.22), CT *vs.* CC model (*P*=0.29)] (Table 3).

Publication bias

Begg's test and Egger's linear regression test were performed to evaluate the publication bias of all eligible studies. Evaluation of publication bias for *MTHFR C677T* allele contrast model showed that the Egger test result was not significant (*P*=0.070) and the additive model also found no publication bias (*P*=0.163).

Discussion

Although numerous case-control studies and meta-analyses have investigated the association between MTHFR C677T polymorphism and risk for developing ALL, no definite conclusions have been reached on the role of *MTHFR* gene in ALL. Therefore, we performed a comprehensive meta-analysis of 51 independent reports, involving a total of 7892 cases and 14 280 controls, to evaluate the association. Since the power of the present analysis was based on the aggregation of published case-control studies, the findings concerning the effect of the gene under investigation can be more powerful than those by the relative individual studies. Comparisons of the C677T allele in the global populations indicate that the T allele of the C677T polymorphism is probably not be a protective factor in the susceptibility to ALL. The subgroup analyses also showed no significant effect of age or ethnicity on the role of the T allele of the C677T polymorphism in ALL.

Although many previous meta-analyses (28–36) focused on the association between MTHFR C677T polymorphism and ALL risk, conflicting conclusions derived from these studies made the role of the gene unclear. Many factors might have accounted for the disagreements. One possible reason was related to the different search strategies and databases used for the search. A reliable and convincing meta-analysis must be based on a comprehensive search of all eligible studies. To minimize selection bias, 2 measures were taken in the present study. First, we searched the Wanfang database to include all eligible studies in Chinese patients. Second, we reviewed the references in previously published meta-analyses. Consequently, the current study was based on the largest possible amount of published data, providing the most comprehensive information on the association under investigation.

In overall population analysis based on varied populations from 22 countries, insignificant differences were identified in the allele contrast model (*P*=0.08), additive model (*P*=0.15), and recessive model (*P*=0.15), but significant differences were identified in the dominant model (*P*=0.04) and CT *vs.* CC model

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Table 1. General characteristics of eligible case-control studies.

Studies	Period of case diagnosis	Country	Ethnicity	Cases/controls	Source of controls
		Adult			
Skibola 1999 [7]	Apr.1991–Dec.1996	UK	Caucasian	71/114	Population
Deligezer 2003 [71]	Not described	Turkey	Caucasian	62/161	Not described
Gemmati 2004 [69]	Jan.1990–Dec.2001 Dec.1992–Dec.2001	Italy	Caucasian	114/257	Population
Timuragaoglu 2006 [61]	Not described	Turkey	Caucasian	33/82	Population
Chen 2006 [74]	Jan.2004–Nov.2004	China	Asian	22/157	Population
Zhang 2007 [77]	Jan.2003–Oct.2006	China	Asian	46/80	Population
Oh 2007 [57]	May.2001–Jan.2002	Korea	Asian	118/427	Population
Kim 2009 [52]	Jan.1997–Dec.2006 Jul.2004–Jan.2006	Korea	Asian	107/1700	Population
Lv 2010 [50]	2002–2007	China	Asian	127/182	Hospital
		Children			
Franco 2001 [21]	Jan. 1991–Jan.2000	Brazil	Mixed	71/71	Population
Balta 2003 [72]	Feb.2000–Feb.2002	Turkey	Caucasian	142/185	Population
Krajinovic 2004 [68]	Aug.1988–May.2001	Canada	Caucasian	270/300	Hospital
Jiang 2004 [75]	Oct.2001–Aug.2002	China	Asian	29/67	Population
Schnakenberg 2005 [66]	Jul.1999–Feb.2001	Germany	Caucasian	443/379	Population
Thirumaran 2005 [65]	1983–2003	Germany	Caucasian	453/1448	Population
Oliveira 2005 [67]	Not described	Portugal	Caucasian	103/111	Population
Yu 2006 [80]	Nov.1996–Jun.2003	China	Asian	51/53	Not described
Kim 2006 [63]	Jul.1996–Jun.2002	Korea	Asian	66/100	Population
Reddy 2006 [62]	Sep.2003–May.2005	India	Asian	135/142	Population
Chatzidakis 2006 [20]	1997–2004	Greece	Caucasian	52/88	Population
Kamel 2007 [58]	Jan.2003–Sep.2003	Egypt	Egyptians	88/311	Population
Petra 2007 [56]	Not described	Slovenia	Caucasian	68/258	Population
Giovannetti 2008 [54]	Not described	Indonesia	Asian	65/32	Population
Alcasabas 2008 [55]	Jan.2001–Dec.2005	Philippines	Asian	189/394	Population
Yang 2009 [76]	Jan.2008–Mar.2009	China	Asian	78/129	Hospital
de Jonge 2009 [53]	Not described	Netherlands	Caucasian	245/496	Population
Tong 2010 [18]	Jan.2007–Jun.2009	China	Asian	361/508	Population
Yeoh 2010 [48]	1988–2008	Singapore	Asian	318/345	Population
Sadananda Adiga 2010 [25]	Apr.2006–Feb.2008	India	Asian	86/99	Population
Yu 2010 [73]	Mar.2008–Feb.2010	China	Asian	45/70	Hospital
Damnjanovic 2010 [19]	Not described	Serbia	Caucasian	78/412	Population
Sood 2010 [49]	Not described	India	Asian	95/255	Population

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Table 1 continued. General characteristics of eligible case-control studies.

Studies	Period of case diagnosis	Country	Ethnicity	Cases/controls	Source of controls
Lightfoot 2010 [26]	1991–1996	UK	Caucasian	805/760	Population
Karathanasis 2011 [24]	1996–2002	Greece	Caucasian	35/48	Population
te winkel 2011 [46]	Not described	Netherlands	Caucasian	83/147	Population
Chan 2011 [47]	Jan.2005–Dec.2008	Singapore	Asian	185/177	Population
Lv 2011 [78]	May.2006–Nov.2009	China	Asian	176/170	Hospital
Nikbakht 2012 [22]	2007–2009	India	Asian	125/100	Population
Feng 2012 [39]	Mar.2010–Dec.2011	China	Asian	45/45	Hospital
Azhar 2012 [23]	Jun.2002–Sep.2009	Iran	Kurdish	72/109	Population
Zheng 2013 [37]	Jan.2003–Dec.2011	China	Asian	87/120	Hospital
Silva 2013 [27]	Jan.2003–Dec.2009	Brazil	Mixed	144/224	Population
Pietrzyk 2009 [51]	Jan.2004–Sep.2006	Poland	Caucasian	403/1000	Population
Amigou 2012 [44]	2003–2004	French	Caucasian	434/427	Population
		Mixed			
Chiusolo 2004 [70]	Not described	Italy	Caucasian	174/110	Population
Hur 2006 [64]	Jan.1995–Oct.2004	Korea	Asian	89/200	Population
Zanrosso 2006 [60]	Not described	Brazil	Mixed	165/198	Population
Bolufer 2007 [59]	1992–2005	Spain	Caucasian	117/331	Population
Liu 2008 [79]	Sep.2006–Oct.2007	China	Asian	83/83	Population
Yang 2011 [45]	Not described	China	Asian	361/367	Population
Hussain 2012 [38]	Mar.2006–Dec.2010	India	Asian	81/251	Not described

Table 2. Stratification analyses of MTHFR C677T polymorphism on ALL by age.

C677T	Number of studies	Allele contrast (T *vs.* C)			Additive model (TT *vs.* CC)			Recessive model (TT *vs.* CC+CT)			Dominant model (TT+CT *vs.* CC)			CT *vs.* CC		
		OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}
Total	51	0.92 (0.84, 1.01)	<0.00001	**0.08**	0.87 (0.73, 1.05)	<0.00001	**0.15**	0.94 (0.81, 1.10)	<0.00001	**0.44**	0.89 (0.79, 1.00)	<0.00001	**0.04**	0.89 (0.80, 1.00)	<0.00001	**0.05**
Age																
Child	35	0.91 (0.81, 1.01)	<0.00001	**0.09**	0.84 (0.67,1.05)	<0.00001	**0.13**	0.91 (0.76, 1.10)	0.0005	**0.34**	0.87 (0.76, 1.01)	<0.00001	**0.07**	0.84 (0.67, 1.04)	<0.00001	**0.11**
Adult	9	0.93 (0.72, 1.20)	0.0005	**0.57**	0.82 (0.47, 1.42)	0.0010	**0.47**	0.94 (0.73, 1.20)	0.007	**0.63**	0.91 (0.67, 1.24)	0.008	**0.57**	0.93 (0.71, 1.21)	0.08	**0.40**
Mixed	7	0.96 (0.79, 1.17)	0.03	**0.71**	0.95 (0.74, 1.20)	0.008	**0.65**	1.13 (0.73, 1.76)	0.002	**0.58**	0.88 (0.74, 1.04)	0.31	**0.13**	0.84 (0.70, 1.02)	0.25	**0.08**

MTHFR – methylenetetrahydrofolate reductase; ALL – acute lymphoblastic leukemia; OR – odds ratio; CI – confidence interval.

(*P*=0.05). However, the heterogeneity among the studies included regarding the 5 models was high, mostly due to the disparity in the age and ethnicity distributions between the eligible studies. Therefore, stratified analyses were further performed on age and ethnicity to reduce the heterogeneity. In subgroup analysis stratified by age, none of the 5 models for

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Table 3. Stratification analyses of MTHFR C677T polymorphism on ALL by ethnicity.

C677T	Number of studies	Allele contrast (T *vs.* C)			Additive model (TT *vs.* CC)			Recessive model (TT *vs.* CC+CT)			Dominant model (TT+CT *vs.* CC)			CT *vs.* CC		
		OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}	OR (95% CI)	P_h	P_{value}
Ethnicity																
Asian	26	0.95 (0.84, 1.07)	<0.0001	**0.39**	0.92 (0.72–1.18)	0.003	**0.53**	0.99 (0.79, 1.24)	0.005	**0.93**	0.91 (0.77, 1.06)	0.0003	**0.22**	0.89 (0.75, 1.05)	0.0006	**0.15**
Caucasian	20	0.92 (0.79, 1.06)	<0.00001	**0.24**	0.87 (0.64–1.18)	<0.00001	**0.36**	0.93 (0.72, 1.20)	<0.00001	**0.56**	0.89 (0.74, 1.07)	<0.00001	**0.22**	0.91 (0.77, 1.08)	<0.00001	**0.29**
Other	5	0.83 (0.60, 1.13)	0.01	**0.24**	0.67 (0.44–1.00)	0.19	**0.05**	0.75 (0.50, 1.11)	0.60	**0.15**	0.78 (0.63, 0.97)	0.005	**0.03**	0.83 (0.54, 1.27)	0.01	**0.39**

MTHFR – methylenetetrahydrofolate reductase; ALL – acute lymphoblastic leukemia; OR – odds ratio; CI – confidence interval.

children or for adults showed significant differences between MTHFR C677T polymorphism and ALL risk, showing the genetic variant may not be a protective factor for ALL susceptibility in childhood or in adults. However, the accurate cut-off value for children and adults was not given due to the varied definitions of the value in the studies included, which might be a source of bias and thus of high heterogeneity. In contrast, Pereira et al. [36], based on 12 studies with 2191 cases and 3437 controls, concluded that MTHFR C677T polymorphism was associated with a reduced risk of ALL for adults but not for children. Most of the subsequent meta-analyses [29–31,34,35] supported the viewpoint that MTHFR C677T polymorphism is associated with a reduced childhood ALL risk. In agreement with our findings, Wang et al. [33] found no evidence for a protective effect of MTHFR C677T polymorphism in childhood ALL. Likewise, Zintzaras et al. [28] stated that the evidence was insufficient for a definite conclusion on the association between MTHFR C677T polymorphism and ALL risk.

Similarly, subgroup analyses on ethnicity revealed insignificant associations between MTHFR C677T polymorphism and ALL risk in Asians and Caucasians. Consistent and inconsistent findings were identified regarding the ethnic difference between the present study and previously published meta-analyses. With regard to the investigations in Asian populations, Tong et al. [32] indicated that MTHFR C677T polymorphism was not associated with ALL susceptibility, which was supported by reports by Zintzaras et al. [28] and Jiang et al. [81]. However, Yan et al. [29] and Wang et al. [31] concluded that MTHFR C677T polymorphism was a protective factor in Asians. Quite different from most of the previous meta-analyses of reduced risk with MTHFR C677T polymorphism in Caucasians, we found no protective role of this gene polymorphism in Caucasians. Therefore, due to continuing controversies, more surveys are needed to reach a precise conclusion, both in Asians and Caucasians. Although the present study found no evidence for a protective effect of MTHFR C677T polymorphism in Asians or Caucasians, differences did exist among different ethnicities as Yan et al. [29] stated, like varied allele frequencies, possible gene-gene interactions from different genetic backgrounds and possible gene-environment interactions from different lifestyles.

The larger number of eligible studies in the present study may lend it sufficient power to provide convincing evidence on the association between MTHFR C677T polymorphism and ALL risk. However, the larger sample size does not mean the study is without limitations. One limitation of the present meta-analysis is the still high heterogeneity among the studies included, which was probably due to various biases during the processes of patient selection, sample testing, and outcome reporting. Another limitation was lack of evaluation of gene-gene interactions. It has been indicated that the etiology of ALL is complex [1], involving gene-gene interactions as well as gene-environment interactions. Apart from the influence of the *MTHFR* gene on ALL susceptibility, many other genes may also play a role in the development of ALL, such as *XRCC3 Thr241Met* [82], *and MTR A2756G* [83], which might have been another reason for the high heterogeneity. Therefore, future studies should focus on the effects of gene-gene interactions.

Conclusions

The present study found no evidence that MTHFR C677T polymorphism plays a protective role in the development of ALL in children, adults, Asians, or Caucasians.

Conflict of interest

We declare that all authors have no financial relationships relevant to this article.

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