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

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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 RIDS5B, 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-methylenetetrahydrofolate (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 uridylic acid to thymidylic acid, 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 “([methyltetrahydrofolate 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)
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 I² statistics [41], which can be calculated from basic results obtained from a typical meta-analysis as I²=100% × (Q–df)/Q, where Q is Cochrane’s heterogeneity statistic and df is the degrees of freedom [42]. An I² 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≤0.05. 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≤0.05 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
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 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.
**Table 1.** General characteristics of eligible case-control studies.

| Studies       | Period of case diagnosis | Country       | Ethnicity | Cases/controls | Source of controls |
|---------------|--------------------------|---------------|-----------|----------------|-------------------|
| **Adult**     |                          |               |           |                |                   |
| Skibola 1999  | Apr.1991–Dec.1996        | UK            | Caucasian | 71/114         | Population        |
| Deligezer 2003| Not described            | Turkey        | Caucasian | 62/161         | Not described     |
| Gemmati 2004  | Jan.1990–Dec.2001        | Italy         | Caucasian | 114/257        | Population        |
| Timuragaoglu 2006 | Not described    | Turkey        | Caucasian | 33/82          | Population        |
| Chen 2006     | Jan.2004–Nov.2004        | China         | Asian     | 22/157         | Population        |
| Zhang 2007    | Jan.2003–Oct.2006        | China         | Asian     | 46/80          | Population        |
| Oh 2007       | May.2001–Jan.2002        | Korea         | Asian     | 118/427        | Population        |
| Kim 2009      | Jan.1997–Dec.2006        | Korea         | Asian     | 107/1700       | Population        |
| Lv 2010       | 2002–2007                | China         | Asian     | 127/182        | Hospital          |
| **Children**  |                          |               |           |                |                   |
| Franco 2001   | Jan. 1991–Jan.2000       | Brazil        | Mixed     | 71/71          | Population        |
| Balta 2003    | Feb.2000–Feb.2002        | Turkey        | Caucasian | 142/185        | Population        |
| Krajnovic 2004| Aug.1988–May.2001        | Canada        | Caucasian | 270/300        | Hospital          |
| Jiang 2004    | Oct.2001–Aug.2002        | China         | Asian     | 29/67          | Population        |
| Schnakenberg 2005 | Jul.1999–Feb.2001    | Germany       | Caucasian | 443/379        | Population        |
| Thirumaran 2005 | 1983–2003              | Germany       | Caucasian | 453/1448       | Population        |
| Oliveira 2005 | Not described            | Portugal      | Caucasian | 103/111        | Population        |
| Yu 2006       | Nov.1996–Jun.2003        | China         | Asian     | 51/53          | Not described     |
| Kim 2006      | Jul.1996–Jun.2002        | Korea         | Asian     | 66/100         | Population        |
| Reddy 2006    | Sep.2003–May.2005        | India         | Asian     | 135/142        | Population        |
| Chatzidakis 2006 | 1997–2004              | Greece        | Caucasian | 52/88          | Population        |
| Kamel 2007    | Jan.2003–Sep.2003        | Egypt         | Egyptians | 88/311         | Population        |
| Petra 2007    | Not described            | Slovenia      | Caucasian | 68/258         | Population        |
| Giovannetti 2008 | Not described        | Indonesia     | Asian     | 65/32          | Population        |
| Alcasabas 2008 | Jan.2001–Dec.2005       | Philippines   | Asian     | 189/394        | Population        |
| Yang 2009     | Jan.2008–Mar.2009        | China         | Asian     | 78/129         | Hospital          |
| de Jonge 2009 | Not described            | Netherlands   | Caucasian | 245/496        | Population        |
| Tong 2010     | Jan.2007–Jun.2009        | China         | Asian     | 361/508        | Population        |
| Yeoh 2010     | 1988–2008                | Singapore     | Asian     | 318/345        | Population        |
| Sadananda Adiga 2010 | Apr.2006–Feb.2008  | India         | Asian     | 86/99          | Population        |
| Yu 2010       | Mar.2008–Feb.2010        | China         | Asian     | 45/70          | Hospital          |
| Damnjanovic 2010 | Not described     | Serbia        | Caucasian | 78/412         | Population        |
| Sood 2010     | Not described            | India         | Asian     | 95/255         | Population        |
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 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         |
| Pietrzky 2009 [51]       | Jan.2004–Sep.2006        | Poland  | Caucasian | 403/1000       | Population         |
| Amigou 2012 [44]         | 2003–2006                | French  | Caucasian | 434/427        | Population         |
| 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         |
| Bolufier 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 (T vs. CC) | Recessive model (T vs. CC+CT) | Dominant model (T+CT vs. CC) | CT vs. CC |
|-------------------------|--------------------------|---------------------------|-------------------------------|-----------------------------|----------|
|                         | OR (95% CI)              | P<sub>h</sub> or P<sub>F</sub> | OR (95% CI)                  | P<sub>h</sub> or P<sub>F</sub> | OR (95% CI) | P<sub>h</sub> or P<sub>F</sub> |
| Total 51                | 0.92 (0.84, 1.01)        | <0.00001                   | 0.08 (0.73, 1.05)             | <0.00001                   | 0.15 (0.81, 1.10) | <0.00001 |
| Age                     | 0.94 (0.81, 1.10)        | <0.00001                   | 0.89 (0.79, 1.00)             | <0.00001                   | 0.94 (0.81, 1.10) | <0.00001 |
| Child 35                | 0.09 (0.81, 1.10)        | <0.00001                   | 0.09 (0.85, 0.97)             | <0.00001                   | 0.10 (0.73, 1.29) | <0.00001 |
| Adult 9                 | 0.47 (0.73, 1.20)        | <0.00001                   | 0.63 (0.67, 1.24)             | <0.01                   | 0.57 (0.71, 1.21) | <0.05         |
| Mixed 7                 | 0.91 (0.71, 1.21)        | <0.00001                   | 0.91 (0.71, 1.21)             | <0.00001                   | 0.93 (0.71, 1.21) | <0.00001 |

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

| Ethnicity | Number of studies | C677T 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<sub>value</sub>           | P<sub>value</sub>             | P<sub>value</sub>             | P<sub>value</sub>             |
| Asian     | 26               | 0.95 (0.84, 1.07)              | 0.39 (0.72–1.18)            | 0.003                          | 0.53 (0.79, 1.06)              | 0.92 (0.75, 1.05)             |
| Caucasian | 20               | 0.92 (0.79, 1.06)              | 0.24 (0.64–1.18)            | 0.0001                         | 0.36 (0.72, 1.20)              | 0.89 (0.77, 1.08)             |
| Other     | 5                | 0.83 (0.60, 1.13)              | 0.01 (0.44–1.00)            | 0.19                            | 0.05 (0.50, 1.11)              | 0.15 (0.34, 0.97)             |

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

1. Inaba H, Greaves M, Mullighan CG: Acute lymphoblastic leukemia. Lancet, 2013; 381: 1943–55
2. Wiemels J: Perspectives on the causes of childhood leukemia. Chem Biol Interact, 2012; 196: 59–67
3. Sherborne AL, Hosking FI, Prasad RB et al: Variation in CDKN2A at 9p21.3 influences childhood acute lymphoblastic leukemia risk. Nat Genet, 2010; 42: 492–94
4. Prasad RB, Hosking FI, Vijayakrishnan J et al: Verification of the susceptibility loci in DNA methylation with DNA methylation status. Nat Genet, 2010; 42: 1001–5
5. Narayanan S, McConnell I, Little J et al: Associations between two common variants C677T and A1298C in the methylenetetrahydrofolate reductase gene and measures of folate metabolism and DNA stability. Mol Genet. Metab, 1998; 64: 169–72
6. Agirre X, Roman-Gomez J, Vazquez I et al: Abnormal methylation of the methylenetetrahydrofolate reductase gene and its relationship to methylenetetrahydrofolate reductase gene polymorphisms. J Mol Med (Berl), 2001; 79: 522–28
7. Skibola CF, Smith MT, Kane E et al: Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukemia in adults. Proc Natl Acad Sci USA, 1999; 96: 12810–15
8. Agire K, Roman-Gomez J, Vazquez I et al: Abnormal methylation of the common PARK2 and PCARG promoter is associated with downregulation of gene expression in acute lymphoblastic leukemia and chronic myeloid leukemia. Int J Cancer, 2000; 114: 1945–53
9. Claus R, Plass C, Armstrong SA, Bullinger L: DNA methylation profiling in acute myeloid leukemia: from recent technological advances to biological and clinical insights. Future Oncol, 2010; 6: 1415–31
10. McCovern AP, Powell BE, Chevassut TJ: A dynamic multi-compartmental model of DNA methylation with demonstrable predictive value in hematological malignancies. J Theor Biol, 2012; 310: 14–20
11. Rollor A, Grossmann V, Bacher U et al: Landmark analysis of DNMT3A mutations in hematological malignancies. Leukemia, 2013; 27: 1573–78
12. Solaray E, Bernard OA, Tefferi A et al: The Ten-Eleven Translocation-2 (TET2) gene in hematopoietic and hematopoietic diseases. Leukemia, 2014; 28: 485–96
13. Goyette P, Pai A, Milos R et al: Gene structure of human and mouse methylenetetrahydrofolate reductase (MTHFR). Mamm Genome, 1998; 9: 652–66
14. Fossett F, Blom HJ, Milos R et al: A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet, 1995; 10: 111–13
15. Lievers KJ, Boers GH, Verhoef P et al: A second common variant in the methylenetetrahydrofolate reductase (MTHFR) gene and its relationship to MTHFR enzyme activity, homocysteine, and cardiovascular disease risk. J Mol Med (Berl), 2001; 79: 522–28
16. Weiberg I, Tran P, Christensen B et al: A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Mol Genet Metab, 1998; 64: 169–72
17. Tong N, Fang Y, Li J et al: Methylenetetrahydrofolate reductase polymorphisms and risk of childhood acute lymphoblastic leukemia in a Chinese population. Cancer Sci, 2010; 101: 782–86
18. Damjanov T, Milicic R, Novkovic T et al: Association between the methylenetetrahydrofolate reductase polymorphisms and risk of acute lymphoblastic leukemia in Serbian children. J Pediatr Hematol Oncol, 2010; 32: e149–50
19. Chatzidakis K, Goulas A, Athanasiadou-Pipopoulos F et al: Methylenetetrahydrofolate reductase C677T polymorphism: association with risk for childhood acute lymphoblastic leukemia and response during the initial phase of chemotherapy in Greek patients. Pediatr Blood Cancer, 2006; 47: 147–51
20. Franco BF, Simeos BP, Tone LG et al: The methylenetetrahydrofolate reductase C677T gene polymorphism decreases the risk of childhood acute lymphocytic leukemia. Br J Haematol, 2001; 115: 616–18
21. Nikbakht M, MalekZadeh K, Kumar Jha A et al: Polymorphisms of MTHFR and MTR genes are not related to susceptibility to childhood ALL in North India. Exp Oncol, 2012; 34: 43–48
22. Azhar MR, Rahimi Z, Vaisi-Raygani A et al: Lack of association between MTHFR C677T and A1298C polymorphisms and risk of childhood acute lymphoblastic leukemia in the Kurdish population from Western Iran. Genet Test Mol Biomarkers, 2012; 16: 198–202
23. Karathanasis NV, Stiakaki E, Goulisemos GN, Kalantzis M: The role of the methylenetetrahydrofolate reductase 677T and 1298H polymorphisms in Cretan children with acute lymphoblastic leukemia. Genet Test Mol Biomarkers, 2011; 15: 5–10
24. Sadananda Adiga MN, Chandy S, Ramachandra N et al: Methylenetetrahydrofolate reductase gene polymorphisms and risk of acute lymphoblastic leukemia in children. Indian J Cancer, 2010; 47: 40–45
25. Lightfoot TJ, Johnston WT, Painter D et al: Genetic variation in the folate metabolic pathway and risk of childhood leukemia. Blood, 2010; 115: 3923–29
26. Silva RM, Fontes AC, Silva KA et al: Polymorphisms involved in folate metabolism pathways and the risk of the development of childhood acute leukemia. Genet Test Mol Biomarkers, 2013; 17: 147–52
27. Zintzaras E, Doxani C, Rodopoulou P et al: Variants of the MTHFR gene and susceptibility to acute lymphoblastic leukemia in children: a synthesis of genetic association studies. Cancer Epidemiol, 2012; 36: 169–76
28. Yan J, Yim Y, Dreyer ZE et al: A meta-analysis of MTHFR C677T and A1298C polymorphisms and risk of acute lymphoblastic leukemia in children. Pediatr Blood Cancer, 2012; 58: S13–18
29. Wang H, Wang J, Zhao L et al: Methylenetetrahydrofolate reductase polymorphisms and risk of acute lymphoblastic leukemia evidence from an updated meta-analysis including 35 studies. BMC Med Genet, 2012; 13: 77
30. Wang H, Meng L, Zhao L et al: Methylenetetrahydrofolate reductase polymorphism C677T is a protective factor for pediatric acute lymphoblastic leukemia in the Chinese population: a meta-analysis. Genet Test Mol Biomarkers, 2012; 16: 1401–7
31. Tong N, Sheng X, Wang M et al: Methylenetetrahydrofolate reductase gene polymorphisms and acute lymphoblastic leukemia risk: a meta-analysis based on 28 case-control studies. Leuk Lymphoma, 2011; 52: 1949–60
32. Wang J, Zhan P, Chen B et al: MTHFR C677T polymorphisms and childhood acute lymphoblastic leukemia: a meta-analysis. Leuk Res, 2010; 34: 1596–600
33. Koppen II, Hermans FJ, Kaspers GJ: Folate related gene polymorphisms and susceptibility to develop childhood acute lymphoblastic leukemia. Br J Haematol, 2010; 15: 3–14
34. Zintzaras E, Koufakis T, Ziakas PD et al: A meta-analysis of genotypes and haplotypes of methylenetetrahydrofolate reductase gene polymorphisms in acute lymphoblastic leukemia. Eur J Epidemiol, 2006; 21: 501–10
35. Pereira TV, Rudnicki M, Pereira AC et al: 5-Methyltetrahydrofolate reductase polymorphisms and acute lymphoblastic leukemia risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev, 2006; 15: 1956–63
36. Zheng MM, Yue LI, Zhang HH et al: Association of single nucleotide polymorphism of methylenetetrahydrofolate reductase gene with susceptibility to acute leukemia. Zhonghua Yi Xue Yi Chuan Xue Za Zhi, 2013; 30: 451–55
37. Hussain SR, Naqvi H, Raza ST et al: Methylenetetrahydrofolate reductase C677T genetic polymorphisms and risk of leukemia among the North Indian population. Cancer Epidemiol, 2012; 36: 6227–31
38. Feng YC, Wu JR: Relationship between genetic polymorphism of methylenetetrahydrofolate reductase and the risk of childhood acute lymphocytic leukemia. Journal of Leukemia & Lymphoma, 2012; 21: 736–38
39. Zintzaras E, Lau J: Synthesis of genetic association studies for pertinent gene-disease associations requires appropriate methodological and statistical approaches. J Clin Epidemiol, 2008; 61: 634–45
40. Liberati A, Altman DG, Tetzlaff J et al: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol, 2009; 62: e1–34
41. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ, 2003; 327: 557–60
42. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997; 315: 629–34
43. Amigou A, Rudant J, Orsi L et al: Folic acid supplementation, MTHFR and MTR polymorphisms, and the risk of childhood leukemia: the ESCAPE study (SFCE). Cancer Causes Control, 2012; 23: 1265–77
45. Yang L, Liu L, Wang J et al: Polymorphisms in folate-related genes: impact on risk of acute adult lymphoblastic leukemia rather than pediatric in Han Chinese. Leuk Lymphoma, 2011; 52: 1770–76

46. te Winkel ML, de Munick Keizer-Schrama SM, de Jonge R et al: Germline variation in the MTHFR and MTRR genes determines the nadir of bone density in pediatric acute lymphoblastic leukemia: a prospective study. Bone, 2011; 48: 571–77

47. Chan JY, Ugrasena DG, Lum DW et al: Xenobiotic and folate pathway gene polymorphisms and risk of childhood acute lymphoblastic leukaemia in Javanese children. Hematol Oncol, 2011; 29: 116–23

48. Yeoh AE, Lu Y, Chan JY et al: Genetic susceptibility to childhood acute lymphoblastic leukaemia shows protection in Malay boys: results from the Malaysia-Singapore ALL Study Group. Leuk Res, 2010; 34: 276–83

49. Sood S, Das R, Trehan A et al: Methyleneetetrahydrofolate reductase gene polymorphisms: association with risk for pediatric acute lymphoblastic leukaemia in north Indians. Leuk Lymphoma, 2010; 51: 928–32

50. Lv L, Wu C, Sun H et al: Combined 677CC/1298AC genotypes of methylenetetrahydrofolate reductase (MTHFR) risk susceptibility to precursor B lymphoblastic leukaemia in a Chinese population. Eur J Haematol, 2010; 84: 506–12

51. Pietrzyk JJ, Madetko-Talowska A, Bisk-Multanowski M, Oltarzewski M: Additional risk factor for the development of ALL. Pediatr Blood Cancer, 2009; 53: S15

52. Kim HN, Kim YK, Lee IK et al: Association between polymorphisms of folate-metabolizing enzymes and hematological malignancies. Leuk Res, 2009; 33: 82–97

53. de Jonge R, Tissing WJ, Hooijberg JH et al: Polymorphisms in folate-related genes and risk of pediatric acute lymphoblastic leukemia. Blood, 2009; 113: 2284–89

54. Giovannetti E, Ugrasena DG, Supriyadi E et al: Methyleneetetrahydrofolate reductase (MTHFR) C677T and thymidylate synthase promoter (TS) polymorphisms in Indonesian children with and without leukemia. Leuk Res, 2008; 32: 19–24

55. Alcasabas P, Ravindranath Y, Goyette G et al: Methylenetetrahydrofolate reductase polymorphism in Korean patients with childhood acute lymphocytic leukemia. Anticancer Res, 2008; 28: 3419–24

56. Petra BG, Janez I, Vida D: Gene-gene interactions in the folate metabolic pathway influence the risk for acute lymphoblastic leukaemia in children. Leuk Lymphoma, 2007; 48: 786–92

57. Oh D, Kim NK, Jang MJ et al: Association of the 5,10-methylenetetrahydrofolate dehydrogenase A1298C polymorphism with the risk for acute lymphoblastic leukemia in adults. Leuk Res, 2007; 31: 176–82

58. Zhang J: A study on the serum folate level and methylenetetrahydrofolate reductase genetic polymorphisms in Chinese population. J Exp Hematol, 2003; 14: 1069–73

59. Liu JX, Chen JP, Lin DX: Relationship between genetic polymorphism of methylenetetrahydrofolate reductase and the risk of childhood acute lymphoblastic leukemia. Med J Chin PLA, 2008; 33: 1291–93

60. Bolufer P, Collado M, Barragan E et al: The relationship between MTR A2756G polymorphism and acute lymphoblastic leukemia risk. © Med Sci Monit, 2015; 21: 740-478

61. Timuragalu A, Dizek S, Uysalgil N et al: Methylenetetrahydrofolate reductase C677T polymorphism and acute lymphoblastic leukemia in an Indian population. Leuk Lymphoma, 2006; 47: 1333–39

62. Reddy H, Jamil K: Polymorphisms in the MTHFR gene and their possible association with susceptibility to childhood acute lymphocytic leukemia in an Indian population. Leuk Lymphoma, 2006; 47: 1333–39

63. Kim NK, Chong SY, Jang MJ et al: Association of the methylenetetrahydrofolate reductase polymorphism in Korean patients with childhood acute lymphoblastic leukemia. Anticancer Res, 2006; 26: 2879–81

64. Hur M, Park JY, Cho HC et al: Methylenetetrahydrofolate reductase A1298C genotypes are associated with the risks of acute lymphoblastic leukaemia and chronic myelogenous leukaemia in the Korean population. Clin Lab Haematol, 2006; 28: 154–59

65. Thirumaran RK, Gast A, Floth T et al: MTHFR genetic polymorphisms and susceptibility to childhood acute lymphoblastic leukemia. Blood, 2005; 106: 3590–91; author reply 3591–92

66. Schnakenberg E, Mehlus A, Cario G et al: Polymorphisms of methylenetetrahydrofolate reductase (MTHFR) and susceptibility to pediatric acute lymphoblastic leukemia in a German study population. BMC Med Genet, 2005; 6: 23

67. Oliveira E, Alves S, Quental S et al: The MTHFR C677T and A1298C polymorphisms and susceptibility to childhood acute lymphoblastic leukemia in Portugal. J Pediatr Hematol Oncol, 2005; 27: 425–29

68. Krajnovic M, Lamotte S, Labuda D et al: Role of MTHFR genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. Blood, 2004; 103: 252–57

69. Gemmati D, Onesto A, Scapoli CL et al: Common gene polymorphisms in the metabolic folate and methylation pathway and the risk of acute lymphoblastic leukaemia and non-Hodgkin’s lymphoma in adults. Cancer Epidemiol Biomarkers Prev, 2004; 13: 787–94

70. Chiusolo P, Reddiconuto G, Cimino G et al: Methylenetetrahydrofolate reductase genotypes do not play a role in acute lymphoblastic leukemia pathogenesis in the Italian population. Haematologica, 2004; 89: 139–44

71. Deligeler U, Akisik E, Dalay N: Genotyping of the MTHFR gene polymorphism, C677T in patients with leukemia by melting curve analysis. Mol Diagn, 2003; 7: 181–85

72. Balta G, Yuksek N, Ozurek E et al: Characterization of MTHFR, GSTM1, GSTT1, GSTPI, and CYPIA1 genotypes in childhood acute leukemia. Am J Hematol, 2003; 73: 154–60

73. Yu J: Association of drug metabolizing enzymes genetic polymorphisms with the susceptibility and methotrexate induced toxicities in childhood acute leukemia. Guangzhou: Southern Medical University, 2010

74. Chen BA, Jiang N, Li MJ et al: A new method for 5,10-methylenetetrahydrofolate reductase single nucleotide polymorphisms genotyping used to study susceptibility of hematological malignancy. J Exp Hematol, 2006; 14: 1069–73

75. Jiang H, Gu L, Xue HL et al: Methyleneetetrahydrofolate reductase gene polymorphism in childhood acute lymphocytic leukaemia. Chinese Journal of Hematology, 2004; 25: 439–40

76. Yang Z, He ZK: The association between MTHFR and RFC1 genetic polymorphisms and the risk of acute lymphoblastic leukemia in children. Human Provincial Committee of the Pharmaceutical Professional Conference, 2009; 80–83

77. Zhang J: A study on the serum folate level and methylenetetrahydrofolate reductase genetic polymorphisms in adult acute lymphocytic leukemia. Shijiazhuang: Hebei Medical University, 2007

78. Lv H, Wang W, Du ZZ et al: Relationship between genetic polymorphism of methylenetetrahydrofolate reductase and the risk of childhood acute lymphocytic leukaemia. J Clin Pediatr, 2011; 29: 414–17

79. Liu JX, Chen JP, Lin DX: Relationship between genetic polymorphism of methylenetetrahydrofolate reductase and the risk of acute lymphocytic leukemia. Med J Chin PLA, 2008; 33: 1291–93

80. Yu H, Jin RM, Bai Y et al: The relationship between the methylenetetrahydrofolate reductase C677T gene polymorphism and acute lymphocytic leukemia in children. Journal of Clinical Hematology, 2006; 19: 205–6

81. Jiang Y, Hou I, Zhang Q et al: The MTHFR C677T polymorphism and risk of acute lymphoblastic leukaemia. Med J Chin PLA, 2008; 33: 1291–93

82. Bolofer P, Barragan E, Collado M et al: Influence of genetic polymorphisms on the risk of developing leukemia and on disease progression. Leuk Res, 2006; 30: 1471–91

83. Xia J, Wang Y, Zhang H, Hu Y: Association between MTR A2756G polymorphism and childhood acute lymphoblastic leukemia: a meta-analysis. Leuk Lymphoma, 2013; 55: 1388–93