RESEARCH ARTICLE

The MTHFR C677T Polymorphism and Risk of Acute Lymphoblastic Leukemia: an Updated Meta-analysis Based on 37 Case-control Studies

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Abstract

Background: The C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) has been associated with acute lymphoblastic leukemia (ALL). However, results were conflicting. The aim of this study was to quantitatively summarize the evidence for the MTHFR C677T polymorphism and ALL risk. Methods: Electronic searches of PubMed and the Chinese Biomedicine database were conducted to select case-control studies containing available genotype frequencies of C677T and the odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of any association. Results: Case-control studies including 6,371 cases and 10,850 controls were identified. The meta-analysis stratified by ethnicity showed that individuals with the homozygous TT genotype had decreased risk of ALL (OR= 0.776, 95% CI: 0.687-0.877, p< 0.001) in Caucasians (OR= 0.715, 95% CI: 0.655-0.781, p= 0.000). However, results among Asians (OR=0.711, 95% CI: 0.591-1.005, p= 0.055) and others (OR=0.913, 95% CI: 0.656-1.271, p= 0.590) did not suggest an association. A symmetric funnel plot, the Egger’s test (P=0.093), and the Begg’s test (P=0.072) were all suggestive of the lack of publication bias. Conclusion: This meta-analysis supports the idea that the MTHFR C677T genotype is associated with risk of ALL in Caucasians. To draw comprehensive and true conclusions, further prospective studies with larger numbers of participants worldwide are needed to examine associations between the MTHFR C677T polymorphism and ALL.

Keywords: MTHFR C677T - meta-analysis - acute lymphoblastic leukemia - risk factor

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Introduction

Acute lymphoblastic leukaemia (ALL) is the maximum common pediatric leukemia accounting for 25-30% of all cases of childhood malignancies (Krajinovic et al., 1999). The disease-free survival of childhood ALL has surpassed 80% in the developed countries over the last years. Nevertheless, almost 20% of the children with ALL either revert or do not respond to treatment (Karathanasis et al., 2011). Even though the scientific, pathological and immunophenotypic types of the disease are well acknowledged, about leukemogenesis is little known (Krajinovic et al., 1999). A range of factors might be related to the biologic mechanisms and etiology of ALL. It is generally considered that the development of ALL is a comprehensive result of environment, genetic risk factors, and gene-environment interactions (Robien et al., 2003; Scelo et al., 2009). Folate deficiency and aberrant metabolism have been reported to be associated with ALL (Yang et al., 2011). Polymorphisms in genes involved in folate transport, metabolism, and distribution in vivo drew widespread attention in the last decade (McNeer 2011). The polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene C677T, has been associated with acute lymphoblastic leukemia. because they reduced MTHFR enzyme activity, leading to enhanced availability of 5,10-methylenetetrahydrofolate in the DNA synthesis pathway and reduced uracil misincorporation into DNA (Skibola et al., 1999).

The human MTHFR gene contains 11 exons, located on chromosome 1p36.3, and encodes methylenetetrahydrofolate reductase (MTHFR) a key enzyme in folate and homocysteine metabolism. MTHFR catalyzes the biologically irreversible reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which provides the methyl group for the remethylation of homocysteine to methionine (Bailey et al., 1999). In the MTHFR enzyme, several
single nucleotide polymorphisms including the two most important, C677T and A1298C, can affect folate and total homocysteine (tHcy) status. The MTHFR C677T, which involves a cytosine (C) to a thymine (T) substitution at position 677, changes an alanine to a valine in the enzyme. The C677T increases thermolability of MTHFR and causes impaired folate binding and reduced activity of the MTHFR enzyme (Frosst et al., 1995). MTHFR C677T is associated with decreased concentrations of folate in serum, plasma, and red blood cells, and mildly increased plasma total homocysteine (tHcy) concentration (Frosst et al., 1995). Base on its biological functions, MTHFR C677T can be seen as a candidate gene for Acute lymphoblastic leukaemia. Accumulating studies have investigated the association between this polymorphism and Acute lymphoblastic leukaemia. However, the results were inconsistent. Therefore, we conducted a meta-analysis to quantitatively assess the effect of the MTHFRC677T polymorphism on the risk of Acute lymphoblastic leukaemia.

Table 1. The Distribution of the MTHFR C677T Variant for Cases and Controls

| Author, year | Case | Control | Ethnicity | Country | P* |
|--------------|------|---------|-----------|---------|----|
| Azhar et al., 2012 | 35 | 31 | 6 | 65 | 34 | 10 | Other | Iran | 0.089 |
| Chan et al., 2011 | 140 | 43 | 2 | 122 | 51 | 4 | Asian | Indonesia | 0.620 |
| Yang et al., 2011 | 96 | 180 | 96 | 84 | 168 | 115 | Asian | China | 0.136 |
| Sood et al., 2010 | 54 | 38 | 3 | 173 | 71 | 11 | other | India | 0.290 |
| Yeo et al., 2010 | 184 | 111 | 23 | 163 | 150 | 32 | Asian | Singapore | 0.765 |
| Lightfoot et al., 2010 | 374 | 341 | 90 | 359 | 314 | 84 | Caucasian | UK | 0.223 |
| Damjanovic et al., 2010 | 45 | 28 | 5 | 163 | 190 | 59 | Caucasian | Serbia | 0.762 |
| Tong et al., 2010 | 135 | 192 | 34 | 173 | 257 | 73 | Asian | China | 0.152 |
| Lv et al., 2010 | 38 | 65 | 24 | 72 | 83 | 27 | Asian | China | 0.700 |
| Jonge et al., 2009 | 130 | 93 | 22 | 219 | 223 | 54 | Caucasian | New Zealand | 0.805 |
| Kim et al., 2009 | 29 | 51 | 27 | 540 | 863 | 297 | Asian | Korea | 0.133 |
| Kantar et al., 2009 | 8 | 9 | 3 | 11 | 5 | 1 | other | Turkey | 0.679 |
| Alcasabas et al., 2008 | 145 | 41 | 32 | 66 | 6 | 6 | Asian | Philippines | 0.227 |
| Liu et al., 2008 | 34 | 23 | 26 | 38 | 36 | 9 | Asian | China | 0.914 |
| Giovannetti et al., 2008 | 51 | 11 | 3 | 26 | 6 | 0 | Asian | Indonesia | 0.558 |
| Giovannetti et al., 2008 | 26 | 6 | 0 | 51 | 11 | 3 | Asian | Indonesia | 0.039 |
| Giovannetti et al., 2008 | 224 | 234 | 45 | 47 | 31 | 8 | Caucasian | Surabaya | 0.391 |
| Kamel et al., 2007 | 39 | 42 | 7 | 156 | 135 | 20 | other | Egypt | 0.195 |
| Petra et al., 2007 | 30 | 33 | 5 | 112 | 110 | 36 | Caucasian | Slovenia | 0.287 |
| Oh et al., 2007 | 49 | 55 | 14 | 138 | 229 | 60 | Asian | Korea | 0.023 |
| Kim et al., 2006 | 17 | 38 | 11 | 24 | 55 | 21 | Asian | Korea | 0.313 |
| Reddy et al., 2006 | 51 | 77 | 7 | 79 | 58 | 5 | other | India | 0.148 |
| Yu, 2006 | 30 | 14 | 7 | 20 | 23 | 10 | Asian | China | 0.466 |
| Zanrosso et al., 2006 | 43 | 35 | 8 | 59 | 50 | 10 | mixed | Brazil | 0.987 |
| Zanrosso et al., 2006 | 53 | 21 | 5 | 37 | 32 | 10 | mixed | Brazil | 0.462 |
| Chatzidakis et al., 2006 | 31 | 18 | 3 | 32 | 47 | 9 | Caucasian | Greece | 0.169 |
| Oliveira et al., 2005) | 48 | 50 | 5 | 45 | 57 | 9 | Caucasian | Portugal | 0.120 |
| Schnakenberg et al., 2005 | 195 | 201 | 47 | 184 | 152 | 43 | Caucasian | Germany | 0.179 |
| Thirumaran et al., 2005 | 199 | 195 | 59 | 600 | 681 | 167 | Caucasian | Germany | 0.210 |
| Gemmati et al., 2004 | 52 | 53 | 9 | 78 | 128 | 51 | Caucasian | Italy | 0.908 |
| Balta et al., 2003 | 71 | 60 | 11 | 90 | 87 | 8 | other | Turkey | 0.020 |
| Krajnovic et al., 2004 | 112 | 127 | 31 | 126 | 128 | 46 | Caucasian | Canada | 0.159 |
| Aung et al., 2004 | 15 | 14 | 0 | 18 | 41 | 8 | Asian | China | 0.029 |
| Deligezer et al., 2003 | 27 | 31 | 4 | 74 | 73 | 14 | other | Turkey | 0.501 |
| Franco et al., 2001 | 36 | 28 | 6 | 22 | 36 | 13 | mixed | Brazil | 0.796 |
| Wiemels et al., 2001 | 98 | 91 | 27 | 89 | 79 | 32 | Caucasian | UK | 0.047 |
| Skibola et al., 1999 | 35 | 29 | 5 | 61 | 39 | 14 | Caucasian | England | 0.061 |

*p value for Hardy–Weinberg equilibrium in control group

Materials and Methods

Publication Search

We searched the PubMed and Chinese biomedicine databases for all articles on the association between MTHFR C677T and acute lymphoblastic leukemia risk (last search update, march 1, 2013). The following key words were used: “MTHFR”, “polymorphism” and “Acute lymphoblastic leukaemia” or “leuki”. Case-control studies containing available genotype frequencies of C677T were chosen. Of the studies with overlapping data published by the same author, only the most recent or complete study was included in this meta-analysis.

Statistical analysis

For control group of each study, the observed genotype frequencies of the MTHFR C677T polymorphism were evaluated for Hardy Weinberg-Equilibrium (HWE) using the \( \chi^2 \) test. The strength of association between MTHFR C677T gene and Acute lymphoblastic leukaemia was evaluated using the \( \chi^2 \) test.
Table 2. ORs and 95% CI for ALL and the MTHFR C677T Polymorphism under Different Genetic Models

| Genetice model | (population) | p | p-value | Begg | Egger |
|----------------|--------------|---|---------|------|-------|
| p-value        | p-value      |    |         |      |       |
| Additive (T vs. C) | | | | | |
| Caucasian      | 0.715[0.655–0.781] | 0.000 | 0.260 | 0.493 | 0.218 |
| Asian          | 0.711[0.591–1.005] | 0.055 | 0.000 | 0.392 | 0.580 |
| Others         | 0.913[0.656–1.271] | 0.590 | 0.000 | 0.061 | 0.275 |
| overall        | 0.776[0.687–0.877] | 0.000 | 0.000 | 0.072 | 0.093 |
| Dominant (T-carriers vs. C-carriers) | | | | | |
| Caucasian      | 0.863[0.718–1.036] | 0.114 | 0.000 | 0.273 | 0.197 |
| Asian          | 0.939[0.769–1.148] | 0.025 | 0.025 | 0.815 | 0.584 |
| Others         | 1.122[0.776–1.622] | 0.001 | 0.001 | 0.297 | 0.574 |
| overall        | 0.944[0.828–1.076] | 0.000 | 0.000 | 0.289 | 0.447 |
| Recessive (TT vs. CT-carriers) | | | | | |
| Caucasian      | 0.794[0.644–0.980] | 0.143 | 0.131 | 0.002 |
| Asian          | 1.009[0.723–1.409] | 0.005 | 0.005 | 0.392 | 0.464 |
| Others         | 0.861[0.593–1.251] | 0.433 | 0.433 | 0.532 | 0.564 |

accessed by calculating crude odds ratios (ORs) and 95% confidence intervals (CIs). The pooled ORs were performed for additive genetic model (T vs. C), dominant model (TT+CT vs. CC), and recessive model (TT vs. CT+ CC) respectively. Heterogeneity assumption was evaluated by a chi-square based Q-test. A P-value of <0.05 for the Q-test indicated heterogeneity among the studies, the summary OR estimate of each study was calculated by the random effects model (DerSimonian et al., 1986; Mantel, 1959). The potential for publication bias was examined by a Begg’s test (funnel plot method) and Egger’s linear regression test (P<0.05 considered representative of statistical significance) (Egger et al., 1997). All analyses were performed using Stata software (version 8.2; Stata Corporation, College Station, TX).

Results

Eligible studies

We identified a total of 37 relevant publications that association between MTHFR C677T and Acute lymphoblastic leukaemia, including 6371 Acute lymphoblastic leukaemia cases and 10850 controls in our meta-analysis (Table 1). Since C677T genotypes in the control group by Giovannetti (Giovannetti et al., 2008), Oh (Oh et al., 2007), Balta (Balta et al., 2003), Jiang (Jiang et al., 2004), Wiemels (Wiemels et al., 2001), were not in HWE, these data (537 cases and 944 controls) were excluded from our meta-analysis. Therefore, our final data pooling consisted of 32 publications, including 5834 cases and 9906 controls.

Meta-analysis

Differences in allelic distribution by ethnicity could be partially responsible for the observed differences in the association between MTHFR C677T and acute lymphoblastic leukaemia. The results of the association between the MTHFR C677T polymorphism and Acute lymphoblastic leukaemia and the heterogeneity test are shown in Table 2. The association was most pronounced for carriers of the T allelic gene (additive model: R=

Figure 1. Forest Plot of ORs of Recurrent Pregnancy Loss for T Allele When Compared to the C Allele. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI accessed by calculating crude odds ratios (ORs) and 95% confidence intervals (CIs). The pooled ORs were performed for additive genetic model (T vs. C), dominant model (TT+CT vs. CC), and recessive model (TT vs. CT+ CC) respectively. Heterogeneity assumption was evaluated by a chi-square based Q-test. A P-value of <0.05 for the Q-test indicated heterogeneity among the studies, the summary OR estimate of each study was calculated by the random effects model (DerSimonian et al., 1986; Mantel et al., 1959). The potential for publication bias was examined by a Begg’s test (funnel plot method) and Egger’s linear regression test (P<0.05 considered representative of statistical significance) (Egger et al., 1997). All analyses were performed using Stata software (version 8.2; Stata Corporation, College Station, TX).

Publication bias

Funnel plot and Egger’s test were performed to quantitatively evaluate the publication bias of literatures on Acute lymphoblastic leukaemia. The results of Egger’s test provided statistical evidence for funnel plot symmetry (P=0.285) in overall results, suggesting the absence of publication bias.

Discussion

Acute lymphoblastic leukaemia, an important clinical problem, has been well-studied but the mechanism of ALL is still relatively unclear. Single nucleotide polymorphisms (SNPs) can be used as a implement in investigating genetic variations and disease susceptibility. ALL is speculated to be associated with inherited thrombophilias that encompass diverse conditions including the thermolabile variant of the MTHFR (Jilma et al., 2003). Methylene tetrahydrofolate reductase is an enzyme in homocysteine metabolism. The MTHFR C677T, which is found within the enzyme catalytic domain, result in both a thermolabile protein and increased tHcy. Through its effect
risk of Acute lymphoblastic leukaemia on Caucasians, whereas did not appear to have an effect in both Asians and Others. Future well designed large studies might be necessary to validate this association in different populations incorporated with environmental factors in the susceptibility of Acute lymphoblastic leukaemia.

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