

Meta-analysis of Cytochrome P4501A1 MspI Gene Polymorphism and Childhood Acute Leukemia

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Abstract

Objective To investigate the relationship between cytochrome P4501A1 (CYP1A1) *Msp* I gene polymorphism and childhood acute leukemia (AL).

Methods Relevant literature was extensively searched and screened by Pubmed and Wanfang Database, Chinese Science Journal Database and Chinese Journal Net. Various data consolidation, combined OR values and their 95% CI were tested by RevMan 4.2; Funnel plots were used for the bias analysis.

Results Six related literatures were found to meet the requirements. According to heterogeneity results, there was no significant difference in homozygous types ($P > 0.05$), while there was significant difference in two others types ($P \text{ all} < 0.05$). For wild CYP1A1 *Msp*I homozygous for the reference group, Combined OR of heterozygous mutation, homozygous, heterozygous + homozygous mutation in AL and control groups were 1.18, 0.96, and 1.10 respectively. Subgroup analysis: Z values of CYP1A1 *Msp*I homozygous, heterozygous + homozygous in the acute lymphoblastic leukemia (ALL) and the control group were 0.10 and 0.76 respectively, Z values in non-acute lymphoblastic leukemia and control group were 0.74 and 0.75.

Conclusion There is no correlation between CYP1A1 *Msp*I gene polymorphism and the susceptibility of childhood AL.

Key words: Acute leukemia; Cytochrome P4501A1; Genetic polymorphism; Meta-analysis

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INTRODUCTION

Cytochrome P450 is not only a group of isoenzymes coded by the super family gene with related structures and functions, but also the most abundant, distributed and broad catalytic spectrum Phase I metabolism enzymes in nature^[1]. Among them, the cytochrome P4501A1 (CYP1A1) is a common kind of cytochrome, and CYP1A1 *Msp*I is one of the most common polymorphisms of CYP1A1, which refers to T→C

transition at 6 235 bp allele in 3' UTR of CYP1A1 forming three *Msp*I endonuclease recognizing genotypes: wild, homozygous and heterozygous types^[2]. Extensive studies have been carried out on the association between CYP1A1 *Msp*I gene polymorphism and the risk factors of acute leukemia (AL) home and abroad^[3-9]; however, these studies yielded inconsistent results. Therefore, we carried out a meta-analysis of literature on CYP1A1 *Msp*I gene polymorphism and the risk factors of AL published home and abroad in order to conduct an

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overall evaluation of the relationship between CYP1A1MspI gene polymorphism and childhood acute leukemia (AL), which provides evidence for risk factors of the childhood AL.

MATERIALS AND METHODS

Research Materials

Related literature on CYP1A1MspI gene polymorphism and AL published in journals in Chinese and other languages from January 1999 to February 2010 was collected.

Literature Resources

For English literature retrieval: the keywords of "acute leukemia, CYP1A1/ P450, gene polymorphism child" were used to retrieve related literature at Pubmed website and Wanfang Database, Chinese Science Journal Database and China Journal Net. Classification of language was not limited. Professional personnel went through the whole retrieval process independently and results were summarized in the end.

Criteria for Literature Inclusion and Exclusion

Literature inclusion criteria: Raw materials were published literature in public; the sample group had clear diagnosis according to childhood AL diagnosis criteria^[10]; the research was a case control study on the CYP1A1MspI gene polymorphism and AL; similar research methods were adopted in all literature; the AL group and the control group were tested by and in consistent with Hardy-Weinberg equilibrium.

Literature exclusion criteria: There was no control group; there was also no sample cases number in the CYP1A1MspI genotype group or the AL group; research methods differed from other literatures; the AL group and the control group failed Hardy-Weinberg equilibrium test; the study was a repeated research, of bad quality or with little information.

Statistical Analysis

RevMan 4.2 was used to perform Meta-analysis. The heterogeneity of results in all literature was assessed. α value less than 0.05 would be considered significant, which serves the test criterion. If no significant heterogeneity was found, articles would be analyzed by the fixed effects model to merge data, and OR and 95% CI

value would be calculated. If significant heterogeneity was found, the subgroup would be accessed according to distinct research characteristics to seek the sources of heterogeneity and the data-merging analysis would be assessed with the random effects model^[11]. The OR and 95% CI values were used to assess the risk relationship between CYP1A1MspI gene and AL. The wild genotype frequencies were used as control in this study to evaluate the relationship between CYP1A1MspI gene heterozygous and mutation homozygous and childhood AL in order to discover the possible effect genotype.

RESULTS

Literature Retrieval Results

Fourteen articles were searched in total with 1 article from China Journal Net 12 from PubMed and 1 from Wanfang Database and Chinese Science Journal database. 7 articles were excluded during the first round screening; during the second round screening, 1 article was excluded as it was written by the same author with the similar methods and contents. Another article was also excluded because of the few number of collected samples. Only 6 articles^[12-17] were included in the final evaluation, which were all case control study, including 837 cases in the AL group and 1 252 cases in the control group. The accepted studies were from Canada, France, Turkey, India, Cuba, and China.

Heterogeneity of Accepted Literature

The heterogeneity test of CYP1A1MspI gene heterozygous showed $\chi^2=11.68$, $P>0.05$, which indicated that there was no significant heterogeneity among these studies; however, the heterogeneity test of CYP1A1MspI gene homozygous and (heterozygous+ homozygous) showed $\chi^2=16.38$ and, 14.77 with P all <0.05 , which indicated that significant heterogeneity existed among these studies.

Results of Meta-analysis

Evaluation of the relationship between CYP1A1MspI gene heterozygous and childhood AL: Based on the heterogeneity results, the fixed effects model was used in order to calculate the combined OR and 95% CI, which were 1.18 (0.94-1.49), $Z=1.41$, $P>0.05$, indicating that there was no significant difference between the two groups (Figure 1).

Review: Meta-analysis of cytochrome P4501A1 MspI gene polymorphism and childhood acute leukemia
 Comparison: 01 AL group and control group
 Outcome: 01 heterozygous

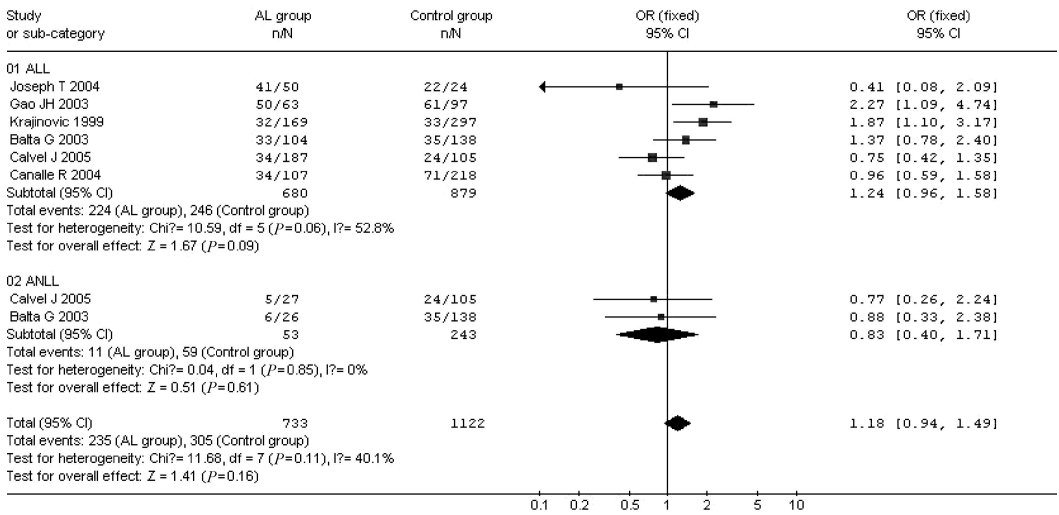


Figure 1. Combined analysis of CYP1A1 MspI gene heterozygous and childhood AL.

Evaluation of the relationship between CYP1A1 MspI gene homozygous and childhood AL: based on the heterogeneity results, the fixed effects model was used in order to calculate the

combined OR and 95% CI, which were 0.96 (0.31-3.00), Z=0.07, P>0.05, indicating that there was no significant difference between the two groups (Figure 2).

Review: Meta-analysis of cytochrome P4501A1 MspI gene polymorphism and childhood acute leukemia
 Comparison: 01 AL group and control group
 Outcome: 02 homozygous

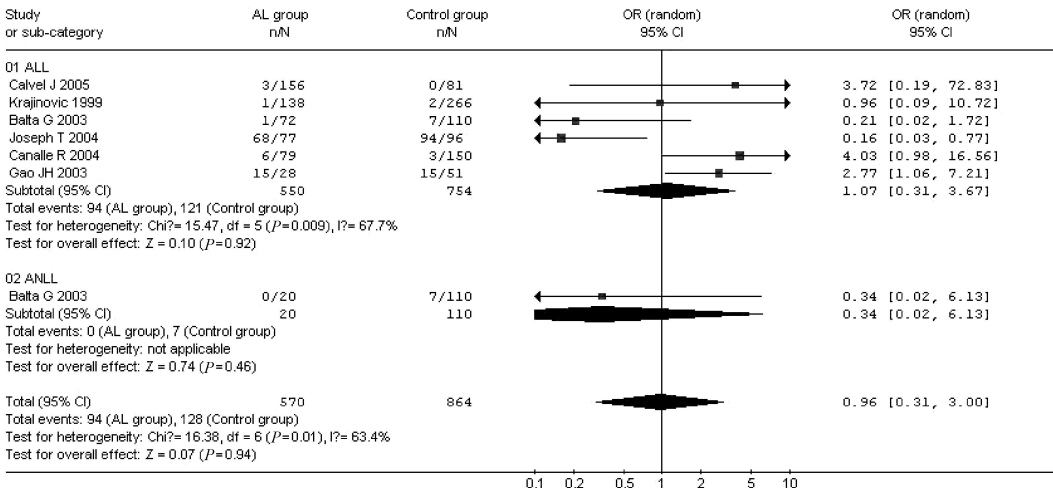


Figure 2. Combined analysis of CYP1A1 MspI gene homozygous and the risk of childhood AL.

Evaluation of the relationship between CYP1A1 MspI gene (homozygous+heterozygous) and childhood AL: there were 329 cases in the AL group and 433 cases in the control group among 6 accepted articles. Based on to the heterogeneity results, the fixed effects model was used in order to calculate the combined OR and 95% CI, which were 1.10 (0.77-1.57) respectively with Z=0.52 and P>0.05, indicating that there was no

significant difference between the two groups (Figure 3).

Subgroup Analysis

If significant heterogeneity was found in CYP1A1 MspI gene homozygous and (homozygous + heterozygous), a subgroup analysis would be performed in this study in order to seek the sources of heterogeneity by the acute leukemia type.

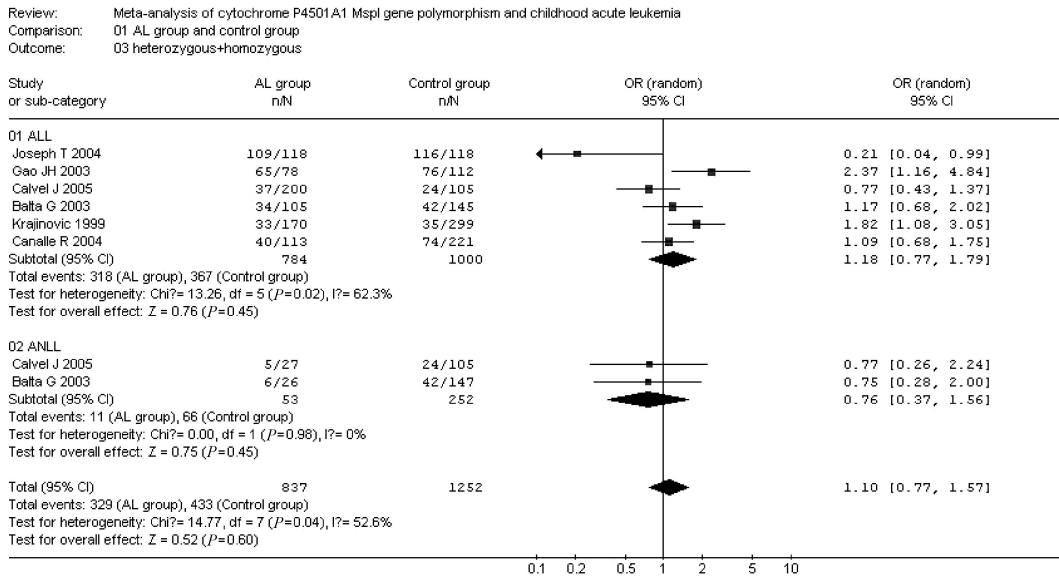


Figure 3. Combined analysis of CYP1A1 *MspI* gene (homozygous + heterozygous) and the risk of childhood AL.

Combined analysis of CYP1A1/*MspI* gene homozygous, (homozygous + heterozygous) and childhood acute lymphoblastic leukemia (ALL): the results showed that $Z=0.10$, 0.76 , $P>0.05$ (Figure 2, 3), indicating that there were no significant differences between cytochrome CYP1A1/*MspI* gene polymorphism and the occurrence of ALL.

Combined analysis of CYP1A1/*MspI* gene homozygous, (homozygous + heterozygous) and childhood acute non-lymphoblastic leukemia (ANLL): the results showed that $Z=0.74$ and 0.75 with $P>0.05$ (Figure 1-3), indicating that there were no significant differences between cytochrome CYP1A1/*MspI* gene polymorphism and the occurrence of ANLL.

Bias Analysis of Research Literature

Funnel plots were applied to assess the publication bias with RevMan 4.2 software. Results showed that all points in the Funnel plot were symmetrically distributed, suggesting that there was no significant bias in each CYP1A1/*MspI* genotype group.

DISCUSSION

Leukemia is one of the most common childhood malignancies, which makes up approximately more than 30% of total malignant tumor cases. In recent years, the incidences of leukemia have the tendency to rise, but its pathological mechanism still remains unclear. It is thought to result from an interaction

between genetic background and environmental factors^[18]. Environmental susceptibility is mainly relating to external chemical metabolizing enzyme gene, poison receptor gene, DNA repair enzyme and etc^[19]. Gene CYP1A1 located in the 15th chromosome with coding product enzyme, which participates in activation of polynuclear aromatic hydrocarbons carcinogens. CYP1A1 gene has genepolymorphism in human^[21]. The most common gene polymorphism is CYP1A1/*MspI* and Ile-Val. A recent study showed that the CYP1A1/*MspI* gene polymorphism was not only relating with various tumors such as lung cancer, but also with childhoods AL. Sinnett^[21] and his colleagues found that CYP1A1 gene polymorphism and genotype increased the risk of AL. Joseph etc.^[12] reported that there were significant differences in CYP1A1/*MspI* gene polymorphism between the childhood ALL group and the control group. Gao etc.^[13] found that the distribution frequencies of CYP1A1/*MspI* m1m2, m2m2 genotype and m2 alleles were significantly elevated than the control group, indicating the relation of CYP1A1/*MspI* gene polymorphism with childhood ALL. There were quite number of studies on the relationship between CYP1A1/*MspI* gene polymorphism and childhood ALL and the results from these studies were not completely unanimous. In order to obtain credible and comprehensive information on this, we performed a meta-analysis of the accepted literature on CYP1A1/*MspI* gene polymorphism and childhood ALL, which provided more comprehensive and

reliable evidence for childhood AL occurrence.

A meta-analysis is a tool to merge multiple data of the same kind to increase the sample cases in order to get more reliable results. In this study, we strictly followed the meta-analysis requirements and extensively searched and screened the literature on CYP1A1*MspI* gene polymorphism and childhood AL. The results we acquired were that the OR value and 95% CI of CYP1A1*MspI* gene homozygous, heterozygous and (homozygous + heterozygous) were 1.18 (0.94-1.49), 0.96 (0.31-3.00), and 1.10 (0.77-1.5) respectively with $Z=1.41$, 0.07, 0.52, $P>0.05$, indicating that there were no significant differences between cytochrome P450A1*MspI* gene polymorphism and the occurrence of childhood AL.

For those groups with heterogeneity, we performed the subgroup analysis by the AL immunophenotype. Firstly, the results of the combined analysis of CYP1A1*MspI* gene homozygous, (homozygous + heterozygous) and childhood ALL were $Z=0.10$, 0.76, $P>0.05$, indicating that there were no significant differences between cytochrome CYP1A1*MspI* gene polymorphism and the occurrence of ALL; secondly, the results of the combined analysis of CYP1A1*MspI* gene homozygous, (homozygous + heterozygous) and childhood ANLL showed that $Z=0.74$, 0.75, $P>0.05$, indicating that there were also no significant differences between cytochrome CYP1A1 *MspI* gene polymorphism and the occurrence of ANLL.

In conclusion, cytochrome CYP1A1*MspI* gene polymorphism may not be correlated with the occurrence of AL. However, since limited sample cases were included in this study, multicenter, large sample and case-control clinical studies should be carried out in future to verify these risk factors in order to study AL occurrence in genetic and environmental terms and make it possible for childhood AL prevention at the gene level.

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