RESEARCH ARTICLE

Glutathione-S-Transferase Polymorphisms (GSTM1, GSTT1 and GSTP1) and Acute Leukemia Risk in Asians: a Meta-analysis

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Abstract

The association between glutathione-S-transferase polymorphisms (GSTM1, GSTT1 and GSTP1) and risk of acute leukemia in Asians remains controversial. This study was therefore designed to evaluate the precise association in 23 studies identified by a search of PubMed and several other databases, up to December 2013. Using random or fixed effects models odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Heterogeneity across studies was assessed, and funnel plots were constructed to test for publication bias. The meta-analysis showed positive associations between GST polymorphisms (GSTM1 and GSTT1 but not GSTP1) and acute leukemia risk [OR=1.47, 95% CI 1.18-1.83]; (OR=1.32, 95% CI 1.07-1.62); (OR=1.01, 95% CI 0.84-1.23), respectively) and heterogeneity between the studies. The results suggested that the GSTM1 null genotype and GSTT1 null genotype, but not the GSTP1 polymorphism, might be a potential risk factors for acute leukemia. Further well-designed studies are needed to confirm our findings.

Keywords: Acute leukemia - glutathione-S-transferase - GST - polymorphism - meta-analysis

Introduction

Acute leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), is a malignancy which is seen in both adults and children. The risk for acute leukemia has been associated with various factors, including genetic disorders, physical and chemical exposure and chemotherapy (Bonaventure et al., 2012; Wong et al., 2010; Deschler et al., 2006). Some enzymes are predominantly involved in the metabolism of carcinogens (Arruda et al., 2001) and lead to variability among individuals in their ability to metabolize environmental carcinogens.

Research on genetic factors that affect cancer susceptibility has the potential to improve our understanding of acute leukemia etiology. Glutathione-S-Transferase (GST) is a group of polymorphic enzymes of phase II which catalyse conjugation of glutathione onto the reactive electrophilic agents on the exogenous and endogenous compounds. Thus, GST polymorphisms have been considered as possible risk factors of acute leukemia. Functional polymorphisms have been reported in at least three of the genes that code for GSTs including GSTM1, GSTT1, and GSTP1. Polymorphism in GST genes lead to either decreased activity of the enzyme or complete loss of enzyme activity. Both GSTM1 and GSTT1 genes, exhibited a greater degree of polymorphism, one of them being the complete deletion of the gene that causes the loss of enzymatic activity (Alves et al., 2002). GSTP1 (Ile105val) single nucleotide polymorphism affects substrate specific catalytic activity of the enzyme and its thermal stability (Ntais et al., 2005; Sundberg et al., 1998). Published studies have focused on GSTM1, GSTT1 and GSTP1 genetic variation with respect to various cancers, including acute leukemia. In Asians, although there are many studies assessing the association between GST polymorphisms and acute leukemia, the association between GST polymorphisms and acute leukemia is still inconclusive (Sasai et al., 1999; Balta et al., 2003; Yuan et al., 2003; Feng et al., 2004; Haranatha et al., 2006; Aydin-Sayitoglu et al., 2006; Dunna et al., 2013). In 2005, Ye et al. conducted a meta-analysis and concluded that the GSTM1 status, but not the GSTT1 status and GSTP1 Val status, was associated with acute leukemia risk in Asians (Ye et al., 2005). However, several new studies with more data have been published since 2005. What’s more, some previous meta-analysis studies about the association between GST polymorphisms and acute leukemia risk just focused on Childhood acute leukemia (Tang et al., 2013) or one of the types of acute leukemia (Das et al., 2009; Xu et al., 2013). Therefore, to derive a more precise estimation of the association in Asians, with big sample size, we performed a meta-analysis of 23 studies including 3504 cases and 4876 controls.
Materials and Methods

Identification of relevant studies

The comprehensive search strategy was used to find eligible studies for this meta-analysis. Published studies were found through PubMed, Springer Link, Google Scholar, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) Database and Wanfang (Chinese) Database, using the following keywords “GST”, “Gluthatione S-transferase” and “leukemia”, “AML”, “ALL”. What’s more, we also searched the reference list of relevant publications to identify additional studies manually. All researches were limited to English or Chinese language articles published up to December 2013 and availability of paper and limited to humans species for review.

Inclusion and exclusion criteria

All identified studies were reviewed independently for eligibility by two authors. Studies were included in the meta-analysis if they met the following criteria: (1) Concerning the relationship between GST genetic polymorphisms (including GSTM1 or GSTT1 or GSTP1 or at least two of them) and acute leukemia; (2) A case-control study; (3) Providing complete data on genotype of the GST polymorphism (s) for calculating an odd ratio (OR) with 95% confidence interval (CI); (4) The distribution of the genotypes in control groups was in Hardy-Weinberg equilibrium; (5) studies about Asian population. The exclusion criteria include: (1) A review or case report; (2) A duplicated study. If studies contained overlapping cases and/or controls, the largest study was preferred.

Data extraction

All data were independently abstracted by two investigators (Tang ZH, Zhang C) using the standard protocol. The following variables were recorded: the first author’s name, publication year, country where the studies were performed, number of cases and controls for each genotype, source of controls, participant age.
### Statistical analysis

The strength of correlation between GST gene polymorphisms (GSTM1, GSTT1, GSTP1) and acute leukemia was assessed by ORs with 95% CIs. We focused on the null alleles of the GSTM1 and GSTT1 genes and the Val105 allele of the GSTP1 gene in this meta-analysis. A chi-square test was used to determine whether the frequencies observed in the genotype groups conformed to Hardy Weinberg-Equilibrium (HWE) expectations. Considering possible heterogeneity across the studies, I² statistics were used to assess heterogeneity. I²>50% indicated an obvious between-study heterogeneity (Higgins et al., 2003). OR (95% CI) was calculated by the random effects model (DerSimonian et al., 1986); otherwise, the fixed effects model was used (Mantel et al., 1959). If between-study heterogeneity was present, a sensitivity analysis was performed based on the magnitude of Q statistic (Lohmueller et al., 2003). OR (95% CI) was calculated by the random effects model (DerSimonian et al., 1986); otherwise, the fixed effects model was used (Mantel et al., 1959). If between-study heterogeneity was present, a sensitivity analysis was performed based on the magnitude of Q statistic (Lohmueller et al., 2003).

### Results

#### Characteristics of Eligible Studies

A total of 417 studies, based on the search criteria, were preliminarily eligible. Detailed process for selecting eligible studies was showed in Figure 1. Among these, two studies (Dunna et al., 2012; Zhou et al., 2013) were excluded for HWE deviation. Finally, 23 studies, which control individuals did not depart from HWE (P-value of HWE >0.05, respectively), were included in the meta-analysis. A total of 3504 cases and 4876 controls were included in this study, and the characteristics of eligible studies were listed in Table 1-3.

#### Meta-analysis

##### Characteristics of studies

Overall, the frequency of GSTM1 null genotype was 56.32% and 50.49% in cases and controls, respectively; the frequency of GSTT1 null genotype was 37.67% and 37.00%, respectively; while the Ile/Val GSTP1 polymorphism, the prevalence of Val in cases and controls was 21.76% and 21.56%, respectively.

##### Association of GSTM1 null genotype with acute leukemia

For the GSTM1 null genotype, the overall OR of the acute leukemia risk association with the polymorphism was 1.47 (95% CI 1.18-1.83), with a statistically significant between-study heterogeneity. However, when four outlying studies were excluded (Aydin-Sayitoglu et al., 2006; Haranatha et al., 2006; Naoe et al., 1997; Sasai et al., 1999), the OR was 1.27 (95% CI 1.01-1.60), with a statistically significant between-study heterogeneity.

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Table 2. Characteristics of Studies on GSTT1 (Null Genotype) Status and the Risk of Acute Leukemia

| First author (year) | Country      | Cases (n) | Frequency of null genotypes (%) | Controls (n) | Frequency of null genotypes (%) | Control Sources | Leukemia types | Age |
|---------------------|--------------|-----------|---------------------------------|--------------|---------------------------------|----------------|----------------|-----|
| Sasai (1999)        | Japan        | 18        | 12                              | 43           | 13                              | PB             | t-AML          | Adults |
| Sasai (1999)        | Japan        | 22        | 7                               | 43           | 13                              | PB             | AML            | Adults |
| Naoe (2000)         | Japan        | 411       | 197                             | 150          | 81                              | PB             | t-AML          | Adults |
| Balta (2003)        | Turkey       | 139       | 29                              | 185          | 42                              | PB             | AML            | Childhood |
| Balta (2003)        | Turkey       | 31        | 2                               | 185          | 42                              | PB             | ANLL           | Childhood |
| Zhang (2003)        | China        | 32        | 19                              | 146          | 72                              | PB             | AML            | Childhood |
| Feng (2004)         | China        | 49        | 30                              | 146          | 72                              | PB             | AML            | Childhood |
| Wang (2004)         | China        | 67        | 41                              | 146          | 72                              | PB             | AML            | Childhood |
| Joseph (2004)       | India        | 118       | 17                              | 118          | 10                              | PB             | AML            | Childhood |
| Zou (2004)          | China        | 16        | 14                              | 183          | 89                              | PB             | AML            | All ages |
| Zou (2004)          | China        | 25        | 14                              | 183          | 89                              | PB             | AML            | All ages |
| Liu (2005)          | China        | 112       | 57                              | 204          | 100                             | HB             | ALL            | Childhood |
| Liu (2005)          | China        | 120       | 66                              | 204          | 100                             | HB             | ANLL           | Childhood |
| Haranatha (2006)    | India        | 135       | 48                              | 146          | 23                              | PB             | AML            | Childhood |
| Aydin-Sayitoglu (2006) | Turkey    | 119       | 29                              | 140          | 29                              | PB             | AML            | Childhood |
| Aydin-Sayitoglu (2006) | Turkey    | 119       | 2                               | 140          | 29                              | PB             | AML            | Adults    |
| Aydin-Sayitoglu (2006) | Turkey    | 44        | 6                               | 140          | 29                              | PB             | AML            | Childhood |
| Aydin-Sayitoglu (2006) | Turkey    | 50        | 15                              | 140          | 29                              | PB             | AML            | Adults    |
| Majumdar (2007)     | India        | 110       | 16                              | 144          | 11                              | PB             | AML            | All ages   |
| Jiang (2008)        | China        | 88        | 44                              | 120          | 59                              | HB             | ALL            | Childhood |
| Jiang (2010)        | China        | 89        | 54                              | 90           | 44                              | HB             | ALL            | Childhood |
| Suneetha (2011)     | India        | 92        | 11                              | 150          | 20                              | HB             | ALL            | All ages   |
| Chan (2011)         | Singapore    | 185       | 64                              | 177          | 49                              | PB             | ALL            | Childhood |
| Chauhan (2003)      | India        | 120       | 26                              | 202          | 58                              | PB             | AML            | Adults    |
| Kim (2012)          | Korea        | 415       | 214                             | 1700         | 859                             | PB             | AML            | Adults    |
| Li (2012)           | China        | 41        | 24                              | 100          | 44                              | HB             | ALL            | Childhood |
| Dunna (2013)        | India        | 142       | 57                              | 251          | 39                              | PB             | AML            | All ages   |
| Dunna (2013)        | India        | 152       | 38                              | 251          | 39                              | PB             | AML            | All ages   |

*PB, Population-based; HB, Hospital-based; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia*
al., 2006; Majumdar et al., 2008; Chauhan et al., 2011; Dunna et al., 2013), the heterogeneity was no longer statistically significant, with the amended overall OR was 1.41 (95% CI 1.27-1.57). The pooled ORs were 1.58 (95% CI 1.14-2.20) and 1.39 (95% CI 1.02-1.90), respectively, in AML and ALL (Table 4). Heterogeneity between studies was shown for both ALL and AML. For AML, after three outlying studies were excluded (Majumdar et al., 2008; Chauhan et al., 2011; Dunna et al., 2013), the heterogeneity was no longer statistically significant, with the amended OR was 1.24 (95% CI 1.06-1.45). And for ALL, after one outlying study were excluded (Aydin-Sayitoglu et al., 2006), the heterogeneity was no longer statistically significant, with the amended OR was 1.56 (95% CI 1.36-1.79). By considering study control sources subgroup, the overall ORs were 1.43 (95% CI 1.36-1.51) and 1.34 (95% CI 1.15-1.56), respectively, in Population-based and Hospital-based, with evidences of heterogeneity exist in both of them.

Association of GSTT1 null genotype with acute leukemia

For the GSTT1 null genotype, the overall OR of the acute leukemia risk association with the polymorphism was 1.32 (95% CI 1.07-1.62). After tests for heterogeneity fund that the heterogeneity was significant. However, when four outlying studies were excluded (Sasai et al., 1999; Zou et al., 2004; Aydin-Sayitoglu et al., 2006; Dunna et al., 2013), the heterogeneity was no longer statistically significant, with the amended OR was 1.18 (95% CI 1.06-1.31). The pooled ORs were 1.37 (95% CI 0.98-1.91) and 1.29 (95% CI 0.98-1.69), respectively, in AML and ALL (Table 4). And there was a significant heterogeneity among studies for both AML and ALL. For AML, after two outlying studies were excluded (Sasai et al., 1999; Dunna et al., 2013), the amended OR was 1.03 (95% CI 0.89-1.20), with the heterogeneity was no longer statistically significant. For ALL, after two outlying studies were excluded (Zou et al., 2004; Aydin-Sayitoglu et al., 2006), the heterogeneity was no longer statistically significant, with the amended OR was 1.34 (95% CI 1.15-1.56). Restricting analyses to control sources subgroup, the overall ORs were 1.34 (95% CI 1.03-1.74) and 1.22 (95% CI 0.97-1.54), respectively, in Population-based and Hospital-based. The heterogeneity was significant in Hospital-based, but not in Population-based.

Association of GSTP1 Ile105val polymorphism with acute leukemia

For GSTP1 Ile105val polymorphism, the overall OR of the association between acute leukemia risk and the polymorphisms was 1.01 (95% CI 0.84-1.23). There was an evidence of heterogeneity across overall studies. However, after one outlying study was excluded (Yuan et al., 2003), the heterogeneity was no longer statistically significant.
significant, with the amended overall OR was 1.00 (95% CI 0.88-1.13). The pooled ORs in AML and ALL was 0.83 (95% CI 0.61-1.13) and 1.14 (95% CI 0.90-1.44), respectively (Table 4). Heterogeneity between studies was shown for AML. For AML, the amended OR was 0.90 (95% CI 0.75-1.06). Restricting analyses to control sources, the overall ORs were 0.91 (95% CI 0.79-1.05) and 1.13 (95% CI 0.68-1.87), respectively, in Population-based and Hospital-based, the heterogeneity was significant in Hospital-based, but not in Population-based.

Association of GSTM1 and GSTT1 null genotypes with acute leukemia and subgroup analysis

The association between acute leukemia and joint of GSTM1 and GSTT1 null genotypes was also estimated in this study. There are seven studies, and the overall OR of the acute leukemia risk association with the polymorphism was 2.02 (95% CI 1.58-2.59). Tests for heterogeneity showed no evidence across studies. The pooled ORs were 2.14 (95% CI 1.47-3.11) and 1.96 (95% CI 1.36-2.82), respectively, in AML and ALL. Considering the region, ages may be confounding factors, so the analyses were also conducted based on them. The analyses data were listed in table 4.

Publication Bias

Plots of the ORs (95% CI) of acute leukemia associated with GST polymorphisms were showed in Figure 2. The funnel plots were symmetrical, with neither the funnel plots nor the Begg’s and Egger’s tests (data not shown) found any obvious evidence for the publication bias. Figure 3 showed Funnel plot.

Discussion

Up to now, numerous of studies have indicated that GST polymorphisms may contribute to the risk of acute leukemia, including AML and ALL. However, the results of these studies assessing the association of acute leukemia risk with GST genotypes have been contradictory. The results may be due to the small sample size and limited power of individual study. Hence, with hope, this meta-analysis was performed that increasing the sample size will reveal a stronger conclusion.

For the overall data, the results showed that the association between GST polymorphisms (GSTM1, GSTT1 and GSTP1) and acute leukemia risk were 1.47 (95% CI 1.18-1.83), 1.32 (95% CI 1.07-1.62), 1.01 (95% CI 0.84-1.23), respectively. There were some evidences of heterogeneity across studies. Seven studies were the major sources of heterogeneity (Sasai et al., 1999; Yuan et al., 2003; Zou et al., 2004; Aydin-Sayitoglu et al., 2006; Majumdar et al., 2008; Chauhan et al., 2011; Dunna et al., 2013). It might attribute to uncontrolled confounding and inherent bias of study design. For instance, three studies used samples matched age and sex (Zhang et al., 2003; Joseph et al., 2004; Haranatha et al., 2012). Numerous of studies used samples matched age and sex (Zhang et al., 2003; Joseph et al., 2004; Haranatha et al., 2006; Jiang et al., 2008; Jiang et al., 2010; Suneetha et al., 2011; Li et al., 2012). Numerious of studies used samples matched age and sex (Zhang et al., 2003; Joseph et al., 2004; Haranatha et al., 2006; Jiang et al., 2008; Jiang et al., 2010; Chauhan et al., 2011; Dunna et al., 2013), however, others had not. Some studies used samples may have heterogeneous ethnic origin. What’s more, the samples size and selection bias may produce heterogeneity. Although some evidences of heterogeneity were present across studies, yet studies that contribute to heterogeneity do not significantly influence the estimate of the overall OR.

Considering that the GST genotypes frequencies might be different between the Population-based and Hospital-based controls. The subgroup analysis base on control sources was conducted. All of the overall ORs were not changed, except GSTT1 base on control sources from Hospital-based. Since Hospital-based controls might not be always truly representative of the general population, which may show that using Population-based controls is more appropriate in the association studies.

The subgroup of region (China-Japan, Others) was also

### Table 4. Main Meta-analysis of GST Polymorphisms and the Risk of Acute Leukemia

|          | GSTM1 |          | GSTT1 |          | GSTP1 |          |
|----------|-------|----------|-------|----------|-------|----------|
|          | Number of studies | Pooled odds risk (95% CI) | Heterogeneity | Number of studies | Pooled odds risk (95% CI) | Heterogeneity | Number of studies | Pooled odds risk (95% CI) | Heterogeneity |
| Region   |       |           |       |           |       |           |       |           |           |       |
| All studies | 20 | 1.47 (1.18-1.83) | 78.4 | 0 | 20 | 1.32 (1.07-1.62) | 40.6 | 0.06 | 7 | 1.01 (0.84-1.23) | 52.7 | 0.03 |
| China-Japan | 10 | 1.57 (1.25-1.96) | 33.6 | 0.11 | 10 | 1.36 (1.08-1.72) | 40.6 | 0.06 | 1 | 1.00 (0.23-4.35) | 91.5 | 0 |
| Others | 10 | 1.37 (0.98-1.92) | 86.7 | 0 | 10 | 1.19 (0.86-1.66) | 78.9 | 0 | 6 | 0.95 (0.84-1.06) | 0 | 0.65 |
| Types |       |           |       |           |       |           |       |           |           |       |
| AML | 15 | 1.58 (1.14-2.20) | 76.8 | 0 | 10 | 1.37 (0.98-1.91) | 73.9 | 0 | 3 | 0.83 (0.61-1.13) | 53.9 | 0.11 |
| ALL | 13 | 1.39 (1.02-1.90) | 80.6 | 0 | 13 | 1.29 (0.98-1.69) | 65.2 | 0 | 5 | 1.14 (0.90-1.44) | 39.8 | 0.14 |
| Age |       |           |       |           |       |           |       |           |           |       |
| Childhood | 12 | 1.54 (1.29-1.84) | 30.2 | 0.13 | 12 | 1.33 (1.09-1.62) | 31.9 | 0.12 | 4 | 1.02 (0.74-1.40) | 62.7 | 0.02 |
| Adults | 5 | 0.81 (0.48-1.37) | 86.9 | 0 | 5 | 0.93 (0.59-1.47) | 78.6 | 0 | 2 | 0.90 (0.75-1.07) | 0 | 0.32 |
| All ages | 4 | 2.49 (1.99-3.11) | 0 | 0.5 | 4 | 2.04 (1.25-3.35) | 63.8 | 0.02 | 1 | 1.24 (0.83-1.86) | 0 | 0.65 |
| Control sources | | | | | | | | | |
| PB | 15 | 1.43 (1.09-1.87) | 81.9 | 0 | 15 | 1.34 (1.03-1.74) | 74.7 | 0 | 4 | 0.91 (0.79-1.05) | 0 | 0.84 |
| HB | 5 | 1.55 (1.15-2.09) | 40.8 | 0.13 | 5 | 1.22 (0.97-1.54) | 0 | 0.67 | 3 | 1.13 (0.68-1.87) | 74.5 | 0.01 |

* Region of China and Japan; \*PB, Population-based; HB, Hospital-based; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia

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GST Polymorphisms (GSTM1, GSTT1 and GSTP1) and Acute Leukemia Risk in Asians: a Meta-analysis

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conducted. The results showed that the OR of the acute leukemia risks association with GSTM1 null genotype and GSTT1 null genotype were statistically significant in subgroup of China-Japan, with the heterogeneity was not significant across studies. While, there was a reverse results in the group of Others. Since the association between cancer and a particular polymorphic site in one population might be of limited value as a biomarker for cancer in another population (Ye et al., 2005), the reason of above-mentioned phenomenon might be due to that population were different.

The results illustrated that the OR of the acute leukemia risks association with GSTs polymorphisms were significant in group of Childhood, however, not in group of Adults. It might be due to that the genetic susceptibility of different age categories may be different, when people exposure to chemicals such as benzene and chemotherapeutic agents. Therefore, more well-designed studies, with a larger sample size, are needed to further confirm our assumption.

Deserve to be mentioned, some limitations of the current meta-analysis should be acknowledged. Firstly, the studies on the subtype of acute leukemia were not included. The more original studies based on the subtype of acute leukemia are needed to ascertain the relationship between the GST polymorphisms and risk of acute leukemia. Secondly, attributing to the unavailable original data of these eligible articles, the effects of environment exposure or lifestyle about association between GST polymorphisms and acute leukemia could not be determined by this meta-analysis. Despite these limitations, our results were also robust. Firstly, the quality of studies included in this study was met our inclusion criteria and satisfactory. Secondly, no publication bias was detected, which indicated that the pooled results should be unbiased.

In conclusion, the results of the present meta-analysis suggest that GSTM1 null genotype and GSTT1 null genotype, but not GSTP1 polymorphism, might have an association with acute leukemia risk in Asians. Thus GSTM1 null genotype and GSTT1 null genotype may play a part in leukemogenesis. More well-designed studies, with a larger sample size, are needed to further confirm our findings.

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