Association of glutathione S-transferase M1 and T1 genotypes with asthma

A meta-analysis

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Abstract

Background: We performed an updated meta-analysis to clarify the relationship between glutathione S-transferase Mu and theta (GSTM1 and GSTT1, respectively) null/positive genotypes and asthma.

Methods: We performed a literature search using PubMed and Web of Science databases in August 2019. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the role of GSTM1 and GSTT1 genotypes in the risk of asthma.

Results: Overall, we found a significant association with asthma risk in the general population for both the GSTM1 genotype (OR = 1.21; 95% CI: 1.07–1.35; P < .001; I² = 69.5%) and the GSTT1 genotype (OR = 1.61; 95% CI: 1.30–2.00; P < .001; I² = 83.6%). Moreover, significant associations between both genotypes and asthma risk were also found by age stratification. Furthermore, for GSTM1 we found significant associations in populations living in Asia, Europe, and Russia, but not in Africa. Conversely, for GSTT1, we found a significantly increased risk in populations living in Asia, Europe, Africa, and Russia. In addition, a significant association was found for both genotypes with a sample size <500, but not a sample size >2000.

Conclusion: Our meta-analysis provides evidence that GSTM1 and GSTT1 genotypes could be used as asthma-associated biomarkers.

Abbreviations: CI = confidence interval, GSTM1 = glutathione S-transferase M1, GSTS = glutathione S-transferases, GSTT1 = glutathione S-transferase T1, OR = odds ratio, ROS = reactive oxygen species.

Keywords: asthma, glutathione S-transferase M1, glutathione S-transferase T1, meta-analysis

1. Introduction

Glutathione S-transferases (GSTs) are a family of enzymes with an essential role in cells, such as the conjugation and detoxification of toxic or carcinogenic compounds like reactive oxygen species (ROS).[1] Polymorphisms in GSTs can lead to a decreased enzymatic function and inadequate detoxification of ROS might modulate the susceptibility to asthma.[2] Biopsies of the colonic mucosa of asthma patients showed an increased ROS production compared with healthy controls.[3] A reduced enzymatic function of GSTs coupled with impaired scavenging of ROS can contribute to a state of oxidative stress, which can trigger the onset of asthma.[4] Human GSTs can be divided into 4 main classes: GST Alpha (GSTA), GST Mu (GSTM1), GST Pi (GSTP1), and GST Theta (GSTT1). For GSTM1, 3 alleles have been described so far. In particular, GSTM1*0 is characterized by gene deletion, leading to a nonfunctional protein. In the past decade, an increasing number of studies have been conducted to explore the associations between GSTM1 and GSTT1 null genotypes and the susceptibility to asthma in different populations. However, the role of GSTM1 and GSTT1 null genotypes in the progression of asthma is controversial.

In this study, we performed an updated meta-analysis to clarify the relationship between GSTM1 and GSTT1 null/positive genotypes with asthma.

2. Methods

2.1. Literature search, selection, and data collection

This meta-analysis included papers investigating the association between asthma risk and GSTM1 and GSTT1 null/positive genotypes that were published on PubMed and Web of Science [Information sources] between January 2000 and August 2019 [Protocol and registration]. The following search terms were used: asthma, asthmatic, GSTM1, GSTT1, polymorphism, mutation, and variant [Search]. Studies that met the following criteria were included: should include investigation on the asthma risk with either GSTM1 or GSTT1 null/positive genotypes; is a case–control study with an appropriate control group; genotype
distributions of both cases and controls need to be available for estimating the odds ratio (OR) with a 95% confidence interval (CI) and the P-value [Eligibility criteria, Study selection]. Data abstraction and analysis were performed by 2 different researchers (XS and YR) and reported on standardized forms including the first 3 authors, year of publication, country of origin, ethnicity, age, sample size, asthma definition, genotyping method, and genotype number in cases and controls [Data collection process, Data items]. Genotype distributions for both cases and controls were assessed as outcome measures. Additional subgroup analyses were performed in an attempt to gain more insight into the parameters or conditions that might improve the outcome in future studies [Data collection process, Data items, Additional analyses].

This study was approved by the Ethic Committee of the First Affiliated Hospital of China Medical University.

2.2. Data analysis

For the meta-analysis, pooled ORs and 95% CIs were calculated using either the fixed effects model or the random-effects model. The chosen model was based on the results of a heterogeneity test, an Chi-squared-based Q test, as previously reported.[5] If the Q test reported a P value >.1, a fixed-effects model was used according to the Mantel–Haenszel method; otherwise, a random-effects model was used according to the DerSimonian and Laird method [Summary measures, Synthesis of results].

Publication bias was tested using Begg funnel plot and Egger test.[6] Publication bias was confirmed if the funnel plot was asymmetric and Egger test reported a P value <.05 [Risk of bias in individual studies, Risk of bias across studies].

All the statistical analyses were performed using Stata, version 12.0 (Stata Corporation, College Station, TX) and Comprehensive Meta-Analysis, version 2.0 (Englewood, NJ).

3. Results

3.1. Characteristics of the studies included in the meta-analysis

We performed a final search on August 31, 2019, which resulted in 292 articles. The majority of the articles were excluded for the following reasons: wrong type of study, animal studies, article duplication, review, or commentary articles. Of the remaining 45 articles, a total of 41 case–control studies[7–37] met the inclusion criteria and were included in the meta-analysis (Fig. 1).
| First author | Year | Country | Ethnicity | Case age, yrs | Asthma definition | Genotyping method | GSTM1 (null/present) | GSTT1 (null/present) |
|--------------|------|---------|-----------|--------------|------------------|------------------|-------------------|-------------------|
| [1] Arbag H | 2006 | Turkey  | Asia      | Adults (36.37 ± 14.17) | Diagnosed by a physician | PCR              | 12 19             | 47 55             |
| [2] Bibuselkova E | 2009 | Slovakia | Europe   | Children (12 ± 0.3) | GINA criteria | PCR              | NA NA             | NA NA             |
| [3] Beiran N | 2012 | India   | Asia      | Adults (38.11 ± 16.20) | Diagnosed by a physician | PCR              | 191 219           | 163 253           |
| [4] Castro-Giner F | 2009 | Sweden, UK, Spain, Germany, France and Belgium | Europe | Adults (20–44) | Based on a questionnaire | PCR              | 152 175           | 506 1254          |
| [5] Chung HW | 2002 | Korea   | Asia      | Not available | According to symptom | PCR              | 16 17             | 31 35             |
| [6] Ebrahimi M | 2004 | Ukraine | Europe    | Adults (44.68 ± 1.22) | Diagnosed by a physician. Multiplex PCR | PCR              | 39 56             | 128 125           |
| [7] El-Aal AAA | 2012 | Egypt   | Africa    | Children (5–14) | GINA criteria | Multiplex PCR    | NA NA             | NA NA             |
| [8] Fedorova I | 2009 | Russia  | Asia      | Children (1–18) | Based on clinical and laboratory data | PCR              | 35 47             | 53 49             |
| [9] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [10] Fedorova I | 2009 | Russia  | Asia      | Children (1–18) | Based on clinical and laboratory data | PCR              | 35 47             | 53 49             |
| [11] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [12] Fedorova I | 2009 | Russia  | Asia      | Children (1–18) | Based on clinical and laboratory data | PCR              | 35 47             | 53 49             |
| [13] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [14] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [15] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [16] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [17] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [18] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [19] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [20] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [21] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [22] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [23] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [24] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [25] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [26] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [27] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [28] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [29] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [30] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [31] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [32] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [33] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [34] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [35] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [36] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [37] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [38] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [39] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [40] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [41] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [42] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |
| [43] Ercan H | 2006 | Turkey  | Asia      | Children (8.1 ± 13.2) | Diagnosed by a physician | PCR              | 124 179           | 100 151           |

GINA = Global Initiative on Asthma, ISAAC = International Study of Asthma and Allergies in Childhood, NA = not available, ND = no data, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism.
Characteristics and genotype distribution of each included study are shown in Table 1.

3.2. Meta-analysis results
The meta-analysis of the association between GSTM1 and GSTT1 null/positive genotypes with asthma risk is summarized in Figures 2–4. When we pooled all groups, we chose the random effects model since we found statistically significant heterogeneity.

3.3. Analysis of the overall population
For the GSTM1 null/positive genotypes, 40 studies with a total of 7733 cases and 18,986 controls were included in the meta-analysis. For the GSTT1 null/positive genotype, 34 studies with a total of 6185 cases and 15,166 controls were included. The pooled results showed a significant association for both the GSTM1 genotypes (OR = 1.21; 95% CI: 1.07–1.35; P < .001; I^2 = 69.5%) and GSTT1 genotypes (OR = 1.61; 95% CI: 1.30–2.00; P < .001; I^2 = 83.6%) and asthma risk in the overall population.

3.4. Subgroup analysis by age
In the subgroup analysis by age, we found a significantly increased risk of asthma for GSTM1 in children (OR = 1.18; 95% CI: 1.02–1.37; P = .000; I^2 = 59.6%), adults (OR = 1.22; 95% CI: 0.99–1.49; P = .000; I^2 = 76.3%), and in the studies with both types of patients (OR = 1.46; 95% CI: 0.86–2.50; P = .000; I^2 = 85.3%), but not in the studies with nonavailable related information (OR = 1.08; 95% CI: 0.60–1.93; P = .963; I^2 = 0.0%) (Fig. 2A). Regarding GSTT1, we found a significant association in children (OR = 1.19; 95% CI: 0.95–1.48; P = .008; I^2 = 54.3%), adults (OR = 1.79; 95% CI: 1.27–2.51; P < .001; I^2 = 86.8%), and in the studies with both types of patients (OR = 2.85; 95% CI: 0.71–11.42; P < .001; I^2 = 94.8%) (Fig. 2B).

3.5. Subgroup analysis by ethnicity
Since Russia stretches across Europe and Asia, it was considered an independent ethnic group for the present meta-analysis. Based on the subgroup analysis by ethnicity, we found a significant association between GSTM1 and asthma risk in populations living in Asia (OR = 1.17; 95% CI: 0.95–1.43; P < .001; I^2 = 76.1%), Europe (OR = 1.09; 95% CI: 0.94–1.27; P = .045; I^2 = 45.0%), and Russia (OR = 1.40; 95% CI: 0.92–2.13; P = .007; I^2 = 68.9%). We found no significant association in Africa (OR = 1.50; 95% CI: 0.88–2.53; P = .05; I^2 = 61.6%) and North America (OR = 1.08; 95% CI: 0.95–1.24; P = .995; I^2 = 0.0%) (Fig. 3A). Regarding GSTT1, we found a significantly increased risk of asthma in Asia (OR = 2.19; 95% CI: 1.20–4.02; P < .001; I^2 = 90.9%), Europe (OR = 1.21; 95% CI: 0.98–1.48; P = .007; I^2 = 55.9%), Africa (OR = 1.77; 95% CI: 0.91–3.46; P = .019; I^2 = 70.0%), and Russia (OR = 2.22; 95% CI: 0.95–5.22; P < .001; I^2 = 88.1%), but not North America (OR = 1.21; 95% CI: 0.63–2.32; P = .062; I^2 = 71.3%) (Fig. 3B).

3.6. Subgroup analysis by sample size
Based on the subgroup analysis by sample size, we found a significant association between GSTM1 and asthma risk for a study sample size < 500 (OR = 1.42; 95% CI: 1.16–1.75; P < .001; I^2 = 70.2%), while we found no significant association for a sample size between 500 and 2000 (OR = 0.99; 95% CI: 0.89–1.11; P = .153; I^2 = 22.0%) and >2000 (OR = 1.03; 95% CI: 0.93–1.14; P = .381; I^2 = 2.3%) (Fig. 4A). Regarding GSTT1, we found a significantly increased risk of asthma for a sample size < 500 (OR = 1.93; 95% CI: 1.46–2.55; P < .001; I^2 = 75.4%) and a sample size between 500 and 2000 (OR = 1.24; 95% CI: 0.64–2.41; P < .001; I^2 = 94.0%), but not a sample size > 2000 (OR = 1.02; 95% CI: 0.85–1.21; P = .181; I^2 = 38.5%) (Fig. 4B).

3.7. Publication bias
Publication bias was assessed using Begg funnel plot and Egger test. We detected a significant publication bias for the GSTM1

Figure 2. Meta-analysis of glutathione S-transferase M1 null/positive (A) and glutathione S-transferase T1 null/positive (B) genotypes correlation with asthma after stratified analysis by age. CI = confidence interval, OR = odds ratio.
null/positive genotypes ($t=2.32, P=.03$, Fig. 5A) and GSTT1 null/positive genotypes ($t=3.16, P=.003$, Fig. 5B).

4. Discussion

In a previous meta-analysis about the association between GSTM1, GSTT1, and asthma, Liang et al\[39\] included a total of 26 case-control studies. They found a significant association in the overall population, both for the GSTM1 (OR $=1.452; 95\% CI: 1.192$–$1.770$) and GSTT1 polymorphism (OR $=1.792; 95\% CI: 1.293$–$2.483$). In the subgroup analysis by age, they found that GSTM1 significantly increased the risk of asthma in both children (OR $=1.368; 95\% CI: 1.051$–$1.781$) and adults (OR $=1.859; 95\% CI: 1.183$–$2.921$). Regarding GSTT1, they found a significant association only in the adult population (OR $=2.312; 95\% CI: 1.204$–$4.439$). When they performed the analysis by ethnicity, they found a significant association between GSTM1 genotypes and asthma risk in Europe (OR $=1.303; 95\% CI: 1.018$–$1.667$), Africa (OR $=2.175; 95\% CI: 1.560$–$3.031$), and Latin America (OR $=2.265; 95\% CI: 1.375$–$3.729$). Regarding GSTT1, they found a significantly increased risk of asthma only in Asia (OR $=2.105; 95\% CI: 1.101$–$4.025$) and Russia (OR $=2.747; 95\% CI: 1.071$–$7.046$). Based on these results, they concluded that GSTM1 and GSTT1 polymorphisms could be risk
factors for asthma. Furthermore, Piacentini et al\[38\] performed a meta-analysis that included independent genetic association studies on GSTM1 and GSTT1, and they also evaluated the effects of potential confounding variables (i.e., ethnicity, population age, and urbanization) using a fixed-effects or, where appropriate, a random-effects model. In this meta-analysis, the authors found no significant association between GSTM1 gene polymorphisms and asthma susceptibility, whereas a significant association was detected for the GSTT1 genotypes (pooled OR = 1.33; 95% CI: 1.10–1.60). However, they also observed high
inter-study heterogeneity in all their general analyses (P value of the heterogeneity test <.05). However, their subsequent stratification analysis could only explain the heterogeneity in few cases. Therefore, they concluded that the interaction between genetics and the environment characterizes the disease pathogenesis. For this reason, further studies on the interactions between GST genes and potential oxidative stress sources and other antioxidant genes are needed. Recently, Turner et al. [30] investigated the frequency of GSTM1 and GSTT1 null genotypes in 3 cohorts (2362 children). They found that GSTT1 null alleles (but not other genotypes) were associated with minor increased risk for an asthma attack. However, they found no significant association between GST genotypes and asthma severity. In the same study, the interactions between GST genotypes and second-hand smoking exposure or asthma severity were nonsignificant. They concluded that there is no convincing evidence correlating GST genotypes to asthma outcomes. In contrast, Zhao et al. [41] showed that there is a significant association between GSTT1 null genotype and the increased risk of asthma in children (OR = 1.25; 95% CI: 1.02–1.54; P = .032). In the same study, population analyses showed that the GSTT1 null genotype is associated with an increased risk of asthma in Caucasians children (OR = 1.46; 95% CI: 1.04–2.03; P = .027), but not in Asians (OR = 1.03; 95% CI: 0.55–1.94; P = .928) and Africans (OR = 1.33; 95% CI: 0.92–1.91; P = .127). Moreover, Zhao et al found no evidence of publication bias in the Caucasians’ analysis. They concluded that there is a significant association between the GSTT1 null genotype and the risk of asthma in Caucasian children, but more well-designed epidemiological studies are needed to further assess this association in Asian and African children.

In the present study, we found in the overall population a significant association for both the GSTM1 null-positive genotypes (OR = 1.21; 95% CI: 1.07–1.35; P < .001; F² = 69.5%) and GSTT1 null/positive genotypes (OR = 1.61; 95% CI: 1.30–2.00; P < .001; F² = 83.6%) with asthma risk. Moreover, we found a significant association between GSTM1 and asthma risk in children (OR = 1.18; 95% CI: 1.02–1.37; P = .000; F² = 59.6%), adults (OR = 1.22; 95% CI: 0.99–1.49; P = .000; F² = 76.5%), and in studies enrolling both types of patients (OR = 1.46; 95% CI: 0.86–2.50; P = .000; F² = 85.3%), but not in studies with not available related information (OR = 1.08; 95% CI: 0.60–1.93; P = .963; F² = 0.0%). Regarding GSTT1 genotypes, a significant association was found in children (OR = 1.19; 95% CI: 0.95–1.48; P = .008; F² = 54.3%), adults (OR = 1.79; 95% CI: 1.27–2.51; P < .001; F² = 86.8%) and in studies enrolling both types of patients (OR =2.83; 95% CI: 0.71–11.42; P < .001; F² = 94.8%). Furthermore, we found a significant association between GSTM1 and asthma risk in populations living in Asia, Europe, and Russia, but not in Africa, while for GSTT1, we found a significantly increased risk of asthma in populations living in Asia, Europe, Africa, and Russia. In addition, we found a significant association between GSTM1 and GSTT1 genotypes and asthma risk when the sample size was <500, but not when it was >2000.

Our study has some limitations. The first is the insufficient sample size in some of our subgroup meta-analysis, especially when the number of studies was <3. Second, considering the publication bias, quality control of the included studies should be performed a priori to distinguish high- and low-quality studies, to perform subgroup analysis according to the studies’ quality. Third, a more accurate subgroup classification should be performed according to the patient number. Therefore, further subgroup analyses are required to achieve more robust conclusions.

In conclusion, as supported by our meta-analysis of 41 studies (40 studies with a total of 7733 cases and 18,986 controls investigating GSTM1 null/positive genotypes, whereas 34 studies with a total of 6185 cases and 15,166 control investigating GSTT1 null/positive genotypes), our study suggests that GSTM1 and GSTT1 null/positive genotypes are correlated with increased asthma risk. Although there are some limitations, our meta-analysis provides valuable information on the use of GSTM1 and GSTT1 genotypes as asthma-associated biomarkers.

Author contributions
XS and JK conceived the study and its design; XS, YR, ML, LK and JK collected the data; XS, YR, ML, LK and JK managed, analyzed, and interpreted the data. All authors have read and approved the final manuscript.

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