Association of Glutathione S-Transferase M1 null genotype with inflammatory bowel diseases
A systematic review and meta-analysis
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Abstract
Background: Ulcerative colitis (UC) and Crohn disease (CD) are the 2 main types of inflammatory bowel diseases (IBDs). Several studies have been conducted to investigate the association of Glutathione S-Transferase M1 (GSTM1) null genotype with UC and CD, but the results are inconsistent. Here, we performed a meta-analysis to clarify this controversy based on relative large sample size.

Methods: A systematic article searching was conducted in the PubMed, EMBASE, SCOPUS, WOS, ProQuest, Chinese National Knowledge Infrastructure (CNKI), and Chinese Wanfang databases up to August 31, 2019. Meta-analysis results were synthesized by using crude odds ratio (OR) with its 95% confidence interval (CI). Heterogeneity, sensitivity analysis, subgroup analysis, and publication bias were assessed by using STATA 11.0 software.

Results: A total of 15 relevant studies including 4353 IBDs patients (1848 CD cases, 2505 UC cases) and 5413 controls were included in this meta-analysis. Totally, we found a significant association between GSTM1 null genotype and risk to IBDs in the overall populations (OR = 1.37, 95%CI = 1.13–1.65, P = .001). Stratified by ethnicity, we found a significant association between GSTM1 null genotype and risk to IBDs in the Asian population (OR = 2.54, 95%CI = 2.15–3.00, P = .001), but not in the Caucasian population. Stratified by disease type, we found a significant association between GSTM1 null genotype with CD in the Asian population (OR = 2.37, 95%CI = 1.11–5.06, P = .026), and with UC in the Asian (OR = 2.48, 95%CI = 1.93–3.20, P = .001) population. In addition, funnel plot and Egger linear regression test suggests no publication bias in all genetic models.

Conclusion: GSTM1 null genotype is associated with susceptibility to IBD, UC, and CD in the Asian population. Further well-designed studies are still needed to confirm these findings.

Abbreviations: CD = Crohn disease, CI = confidence interval, GSTM1 = Glutathione S-Transferase M1, IBD = inflammatory bowel disease, OR = odds ratio, ROS = reactive oxygen species, UC = ulcerative colitis.

Keywords: Crohn disease, Glutathione S-Transferase M1, meta-analysis, polymorphism, ulcerative colitis

1. Introduction
Inflammatory bowel diseases (IBDs) are a group of chronic and nonspecific inflammatory diseases that mainly comprise ulcerative colitis (UC) and Crohn disease (CD). Clinical features in both disorders include diarrhea, abdominal pain, weight loss, and increased risk of developing colorectal cancer. The precise etiology of IBDs is not yet fully understood, but evidence suggested that multiple factors, such as the heredity, environment, infection, and immunity and the interactions among each other, contribute to the development and exacerbation of the diseases. In past years, with the wide application of genome-wide association studies and candidate gene association studies, considerable susceptibility loci for the predisposition of IBDs has been identified in the populations of Northern European origin, such as NOD2, ATG16L1, and IRGM. Up to now, more than 30 single-nucleotide polymorphisms are definitively known to be associated with IBDs, although these loci account only for a minority of the genetic variance to IBDs in this population.

Glutathione S-transferases (GSTs) are a family of enzymes that have an essential role within cells, including the conjugation and detoxification of toxic or carcinogenic compounds, such as reactive oxygen species (ROS). Polymorphisms in GSTs can lead to a decreased enzymatic function, and an inadequate detoxification of ROS might modulate the susceptibility for IBD. Biopsies of colonic mucosa of IBD patients showed an increased ROS production compared with healthy controls. A reduced enzymatic function of GSTs and there with impaired scavenging of ROS can contribute to a state of oxidative stress, which can trigger the onset of IBD.

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Human GSTs can be divided in 4 main classes, GST Alpha (GSTA), GST Mu (Glutathione S-Transferase M1 [GSTM1]), GST Pi (GSTP1), and GST Theta (GSTT1). For GSTM1, 3 alleles have been described of which one, GSTM1*0, is characterized by a gene deletion, leading to a nonfunctional protein. The distributions of GSTM1*0 allele in different populations were fluctuated, with African population being 33% to 48%, Asian population being 33% to 63%, European population being 39% to 62%, and American population being 23% to 62%.\textsuperscript{16} In the past decade, an increasing number of studies have been conducted to explore the association between GSTM1 null genotype and susceptibility to IBDs in different populations.\textsuperscript{16–31} However, the role of GSTM1 null genotype in the progression of UC and CD remain undetermined.

We performed a comprehensive literature search in the above databases. We only find one systematic reviews on the association between GSTM1 null genotype and IBD.\textsuperscript{16} In their meta-analysis, relevant articles for the analyses were retrieved by searching PubMed, EMBASE, and Web of Science on October 13, 2013. They did not conduct subgroup analysis according to ethnicity.

Therefore, in the present study, we conducted an overview of systematic reviews and meta-analyses in a comprehensive manner, including different ethnicities and genotype models, in order to assess the association between GSTM1 null genotype and the risk of IBD. Cumulative meta-analyses were also performed to investigate the tendency of results in genotype models with possible risk for IBD.

In form of PICOS (participants, interventions, comparisons, outcomes, and study design), the study was described as follows: P: This study focused on participants diagnosed with IBD. I: The associations between GSTM1 null genotype and IBD susceptibility. C: Unrelated healthy subjects without autoimmune diseases, tumors, and IBD family history. O: The influence of GSTM1 null genotype on IBD susceptibility will be demonstrated as the pooled effect size (odds ratio [OR] with 95% confidence interval [CI]) of multiple research articles; We will also analyze the effect of moderators and confounders: disease type, ethnicity, genotyping method, and publication year; Cumulative meta-analyses were also performed to investigate the tendency of results of genotype distributions with possible risk for IBD. S: Case–control studies which have explored the relationship of GSTM1 null genotype and IBD susceptibility. In addition, to be included, we will accept peer-reviewed papers, published in English and Chinese language, featuring patients of any ethnicity, with no date limits, including published, and unpublished data.

2. Materials and methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analysis. The role of GSTM1 null genotype in the progression of UC and CD remains undetermined. Thus, the aim of this study was to clarify the relationship between GSTM1 null genotype and IBD risk by mean of a systematic review and meta-analysis. The protocol was registered in PROSPERO.

2.1. Identification of eligible studies

A comprehensive literature search in the following databases: PubMed, EMBASE, SCOPUS, WOS, ProQuest, Chinese National Knowledge Infrastructure (CNKI), and Chinese Wanfang, with search time ranged from database inception to August 31, 2019. The search terms and keywords were as follows: “polymorphisms or variants,” “Glutathione S-Transferase M1 or GSTM1,” and “ulcerative colitis or Crohn’s disease or inflammatory bowel disease.” We limited our results to studies published in English or Chinese. The detailed search strategies were presented in supplementary Table S1, http://links.lww.com/MD/D313. References from retrieved papers were also examined for additional studies that not included in the above databases. Gray literature were searched according to CADTH Grey Matters Light.

2.2. Inclusion criteria

Studies were included in the meta-analysis if they met the following criteria: study on the genetic relationship of GSTM1 with UC or CD or IBD; case–control study design; genotype distributions were available for both cases and controls to calculate an OR and its 95%CI; diagnosis of IBD was made on clinical, radiological, endoscopic, and histopathological findings according to Lennard–Jones criteria; and controls were unrelated healthy subjects without autoimmune diseases, tumors, and IBD family history. Exclusion criteria were as follows: abstract, case report, editorial comment, and review; repeated publication; studies with insufficient genotypic data; and studies performed on animal models.

2.3. Quality score assessment

The Newcastle-Ottawa scale was used to evaluate the quality of studies. The scale was constituted of 3 aspects as selection, comparability, and exposure with a maximum score of 9.\textsuperscript{31} A total score of ≤3, 4–6, ≥7 was considered to indicate low, medium, and high-quality studies, respectively. Any disagreements were adjusted by a 3rd reviewer.

2.4. Data extraction

Two investigators independently and carefully extracted available data from each eligible study. The following details were extracted from all eligible studies: the fist author’s name; year of study publication; origin of participants; race of included subjects; sample size of cases and controls; and genotype distribution of cases and controls. Discrepancies were resolved by discussion within our research team.

2.5. Statistical analysis

The effect sizes were calculated using ORs and 95%CI to evaluate the association between the GSTM1 null genotype and IBD, UC, and CD risk. Only studies with similar designs were included in the forest plot, as meta-analysis can provide misleading results if different study designs and studies variations across studies are grouped together. For this reason, in order to avoid methodological heterogeneity in meta-analysis, only case–control studies were grouped. Heterogeneity among the eligible studies was analyzed by the chi-square test based on the Q statistic, with significant heterogeneity considered to be present when the P-value < .1.\textsuperscript{122} Heterogeneity was also quantified by the I² test, the values of I² in 0% to 25%, 26% to 50%, and 50% to 100% were considered as lower, moderate, and high heterogeneity, respectively. The fixed-effects model on the Mantel–Haenszel method was used to estimate the pooled OR if I² < 50%; otherwise, the random-effects model on the DerSimonian–Laird method was used.
We evaluated the potential publication bias by using the Begg funnel plot and the Egger linear regression test,\(^\text{[33,34]}\), which measures funnel plot asymmetry on the natural logarithm scale of the effect size. One-way sensitivity analysis was used to assess which study has a significant impact on the stability of results. All statistical analyses were performed using STATA version 11.0 software (STATA Corporation, College Station, TX). The \(P\)-value of 2-sided less than .05 was considered statistically significant.

3. Results

3.1. Characteristics of eligible studies

As Figure 1 shows, the selection process of the studies involved in this meta-analysis was according to PRISMA flow diagram. Firstly, we found 220 potentially relevant papers from databases. A search of the Grey Literature Report and OpenGrey databases revealed there were no unpublished studies (gray literature). Among these, 72 duplicates were removed from retrieval, and another 102 studies were removed due to irrelevant topics, reviews, and not about IBDs or GSTM1 null genotype. The remaining 46 studies underwent full publication review carefully, 31 studies were excluded due to insufficient data for calculating OR and 95\%CI. Finally, thus, there were 15 studies included in this meta-analysis. The IBD patients in all of the included studies were random recruited in hospitals. The basic characteristics of these studies are shown in Table 1.

3.2. GSTM1 null genotype with IBDs

The detailed results of the association between GSTM1 null genotype and risk of IBDs are shown in Table 2. The heterogeneity analysis of GSTM1 null genotype showed...
significant heterogeneity in the overall population, but it was resolved by subgroup analysis based on ethnicity. Overall, significant associations between GSTM1 null genotype and risk for IBDs were found in the overall population (OR = 1.37, 95% CI = 1.13–1.65, P = .001). Stratified by ethnicity, we found a significant association between GSTM1 null genotype and risk to IBDs in the Asian population (OR = 2.54, 95% CI = 2.15–3.00, P = .001) (Fig. 2A), but not in the Caucasian population (OR = 1.01, 95% CI = 0.93–1.10, P = .837). Stratified by publication year, we found a significant association between GSTM1 null genotype and risk to IBDs in the years before (OR = 1.40, 95% CI = 1.10–1.78, P = .006) and after 2010 (OR = 1.38, 95% CI = 1.06–1.83, P = .048) (Table 2).

### 3.3. GSTM1 null genotype with CD

The detailed results of the association between GSTM1 null genotype and risk of CD are shown in Table 2. Overall, no significant association was found in the overall population (OR = 1.25, 95% CI = 0.97–1.61, P = .089). However, stratification by population, significant associations were found in the Asian population (OR = 2.37, 95% CI = 1.11–5.06, P = .026), but not in the Caucasian population (OR = 1.10, 95% CI = 0.90–1.32, P = .342).

### Table 1

Characteristics of inclusive literature and distribution of GSTM1 genotypes on case and control groups.

| Author [ref.]  | Year | Country | Ethnicity | NOS scores | Disease | Sample size | Genotype in case | Genotype in control | Significance of differences |
|----------------|------|---------|-----------|------------|---------|-------------|------------------|----------------------|---------------------------|
| Broekman [18]  | 2014 | Netherlands | Caucasian | 7 | CD | 552 | 972 | 289 | 263 | 530 | 442|
| Broekman [18]  | 2014 | Netherlands | Caucasian | 7 | UC | 233 | 972 | 54 | 179 | 203 | 789|
| Buyukgoze [17] | 2013 | Turkey | Caucasian | 5 | UC | 161 | 198 | 81 | 80 | 85 | 113|
| de Jong [18]   | 2014 | Netherlands | Caucasian | 7 | CD | 151 | 149 | 82 | 69 | 74 | 75|
| Duncan [19]    | 1995 | England | Caucasian | 6 | CD | 110 | 373 | 68 | 42 | 203 | 170|
| Duncan [19]    | 1995 | England | Caucasian | 6 | UC | 230 | 373 | 112 | 118 | 203 | 170|
| Ernst [20]     | 2010 | Denmark | Caucasian | 7 | UC | 386 | 791 | 215 | 171 | 417 | 374|
| Ernst [20]     | 2010 | Denmark | Caucasian | 7 | CD | 563 | 791 | 296 | 267 | 417 | 374|
| Feng [21]      | 2016 | China | Asian | 6 | UC | 78 | 78 | 46 | 32 | 31 | 47|
| Hertervig [22] | 1994 | Sweden | Caucasian | 5 | CD | 100 | 449 | 65 | 64 | 219 | 230|
| Karban [23]    | 2011 | Israel | Caucasian | 5 | CD | 431 | 369 | 205 | 226 | 205 | 164|
| Karban [23]    | 2011 | Israel | Caucasian | 5 | UC | 131 | 369 | 65 | 66 | 205 | 164|
| Mittal [24]    | 2007 | India | Asian | 5 | CD | 20 | 164 | 9 | 11 | 49 | 115|
| Mittal [24]    | 2007 | India | Asian | 5 | UC | 85 | 164 | 52 | 33 | 49 | 115|
| Senhaji [25]   | 2014 | Morocco | African | 5 | UC | 77 | 100 | 42 | 35 | 51 | 49|
| Senhaji [25]   | 2014 | Morocco | African | 5 | UC | 33 | 100 | 20 | 13 | 51 | 49|
| Varzari [26]   | 2015 | Moldova | Caucasian | 5 | UC | 128 | 136 | 76 | 52 | 75 | 61|
| Wu [27]       | 2010 | China | Asian | 6 | UC | 252 | 628 | 175 | 77 | 318 | 310|
| Ye [28]       | 2011 | China | Asian | 5 | UC | 270 | 623 | 191 | 79 | 260 | 363|
| Momin [29]    | 2017 | Iran | Asian | 6 | CD | 12 | 243 | 9 | 3 | 115 | 128|
| Momin [29]    | 2017 | Iran | Asian | 6 | UC | 94 | 243 | 56 | 38 | 115 | 128|
| Xu [30]       | 2007 | China | Asian | 6 | UC | 68 | 140 | 43 | 25 | 63 | 77|

CD = Crohn disease, GSTM1 = Glutathione S-Transferase M1, NOS = Newcastle-Ottawa scale, UC = ulcerative colitis.

### Table 2

Summary of meta-analysis on GSTM1 null genotype and IBDs susceptibility.

| Diseases | Subgroups | No. of studies | OR | 95% CI | P-value | Model | Test of association | Test of heterogeneity |
|----------|-----------|----------------|----|--------|---------|-------|---------------------|----------------------|
| IBD      | All       | 23             | 1.37 | 1.13–1.65 | .001 | R | .001 | 81.7 | .062 |
|          | Asian     | 9              | 2.54 | 2.15–3.00 | .001 | F | .183 | 30.7 | .662 |
|          | Caucasian | 13             | 1.01 | 0.93–1.10 | .837 | F | .102 | 35.1 | .185 |
|          | Before 2010 (<2010) | 11          | 1.40 | 1.10–1.78 | .006 | R | .001 | 77.8 | .106 |
|          | After 2010 (>2010) | 12           | 1.38 | 1.06–1.83 | .048 | R | .001 | 85.3 | .294 |
| CD       | All       | 9              | 1.25 | 0.97–1.61 | .089 | R | .001 | 74.3 | .093 |
|          | Asian     | 2              | 2.37 | 1.11–5.06 | .026 | F | .504 | 0.0 | .265 |
|          | Caucasian | 6              | 0.98 | 0.87–1.11 | .787 | F | .101 | 45.8 | .325 |
|          | Before 2010 (<2010) | 5          | 1.18 | 0.99–1.40 | .058 | F | .770 | 0.0 | .109 |
|          | After 2010 (>2010) | 4            | 0.93 | 0.69–1.26 | .636 | R | .085 | 54.7 | .269 |
| UC       | All       | 14             | 1.53 | 1.16–2.01 | .002 | R | .001 | 85.0 | .339 |
|          | Asian     | 6              | 2.48 | 1.93–3.20 | .001 | R | .087 | 47.9 | .595 |
|          | Caucasian | 7              | 1.02 | 0.89–1.17 | .743 | F | .129 | 41.5 | .649 |
|          | Before 2010 (<2010) | 6          | 1.57 | 1.03–2.38 | .035 | R | .001 | 88.2 | .169 |
|          | After 2010 (>2010) | 8            | 1.50 | 1.02–2.20 | .039 | R | .001 | 83.2 | .602 |

CD = Crohn disease, CI = confidence interval, F = fixed effects model, GSTM1 = Glutathione S-Transferase M1, IBD = inflammatory bowel disease, OR = odds ratio, R = random-effects model, UC = ulcerative colitis.
in the Caucasian population (OR = 0.98, 95% CI = 0.87–1.11, P = .787) (Table 2). Stratified by publication year, we found no significant association between GSTM1 null genotype and risk to CD in the years before (OR = 1.18, 95% CI = 0.99–1.40, P = .058) and after 2010 (OR = 0.93, 95% CI = 0.69–1.26, P = .636) (Table 2).

3.4. GSTM1 null genotype with UC

The detailed results of the association between GSTM1 null genotype and risk of UC are shown in Table 2. A significant association between GSTM1 null genotype and risk of UC was found in the overall population (OR = 1.53, 95% CI = 1.16–2.01, P = .002). Subgroup analysis showed that GSTM1 null genotype was associated with UC risk in the Asian population (OR = 2.48, 95% CI = 1.93–3.20, P = .001) (Fig. 2B), but not in the Caucasian population (OR = 1.02, 95% CI = 0.89–1.17, P = .743) (Table 2). Stratified by publication year, we found a significant association between GSTM1 null genotype and risk to UC in the years before (OR = 1.57, 95% CI = 1.03–2.38, P = .035) and after 2010 (OR = 1.50, 95% CI = 1.02–2.20, P = .039) (Table 2).

3.5. Sensitive analysis and publication bias

Sensitive analysis was conducted to estimate if our results were substantially affected by the presence of any individual. Our results suggested that the pooled effects were not significantly influenced by the omission of any individual study (Fig. 3A and B). Moreover, the 2 studies were published at 1994 and 1995, which may employ the different examination method different from current clinical practice. We did subgroup analysis by the year of publication. There was a significant association between GSTM1 null genotype and risk for IBDs in the year after 1995 (OR = 1.441, 95% CI = 1.150–1.805, P = .002). The year of publication had no significant influence on the results of meta-analysis. Begg funnel plots were performed in all comparisons showed the shape was symmetrical, and Egger linear regression
analysis further indicating that no publication bias existed in this meta-analysis (Table 2 and Fig. 4A and B).

3.6. Cumulative analysis

After cumulative analysis by year sequence, OR and its CI tend to be stable and have a good change trend. The relationship has been stable since 2007 on a given set of threshold (Fig. 5).

4. Discussion

Although unknown etiology and pathology of IBDs, previous study has shown that multiple gene polymorphisms may link to the development of diseases.\cite{35} An increasing number of studies in recent years have studied the association between GSTM1 null genotype and the risk of inflammatory diseases.\cite{36,37} Nevertheless, whether it is associated specifically with the risk of IBDs remains controversial.

**Figure 4.** Begg funnel plots for association between GSTM1 null genotype and IBDs (A) and UC (B) risk in the Asian population. GSTM1 = Glutathione S-Transferase M1, IBD = inflammatory bowel disease, UC = ulcerative colitis.

**Figure 5.** Cumulative analysis of forest plots for pooled ORs for the associations between GSTM1 null genotype and IBDs risk. GSTM1 = Glutathione S-Transferase M1, IBD = inflammatory bowel disease, OR = odds ratio.
The inconsistency among different studies seems to be mainly owing to the relatively small sample size of most studies and the different populations of researches, there is little statistical power to detect a slight association between GSTM1 null genotype and susceptibility to IBDs. Another explanation is that diverse study designs and methods, differences in race and geography, and publication bias. Meta-analysis is an effective statistical method that could pool the results of several independent studies together to get comprehensive results.[38] It has been widely utilized in evaluating the relationship between candidate genes and complex diseases with genetic predisposition.[39]

This systematic review and meta-analysis was performed to determine the association between GSTM1 null genotype and susceptibility to IBDs. The results demonstrated GSTM1 null genotype was associated with IBDs in the Asian population, but not in the Caucasian population. After stratified by disease type, similar results were also presented in UC and CD. The different results presented in different populations illustrated that GSTM1 null genotype with IBDs susceptibility might be determined by ethnicity.

Glutathione is a protective compound in the body capable of removing potential toxins, GST catalyzed glutathione binding to various ROS and biotransformation to maintain the balance of oxidation-antioxidant system.[40] The mechanism that absence of GSTT1 enzyme activity in GSTT1 null individuals contributes to the risk for UC might be explained by the important role of this enzyme in the detoxification of ROS, which may provide a trigger in the etiology of IBD.[40] Also, in other inflammatory-driven diseases, such as asthma or type 2 diabetes mellitus, an increased susceptibility was found with the GSTT1 null genotype.[31,42]

Although advantage of this meta-analysis is that pooling good quality of individual study together with relative large sample size for a comprehensive result, several limitations should be addressed when interpreting our results. Firstly, we included relevant articles published only in English and Chinese so that potential language bias may exist in this study. Secondly, most of the studies are conducted in Chinese population, the number of studies was small in Caucasians subgroup analyses, which could have led to insufficient statistic power to detect slight relationships. Thirdly, several risk factors such as age, gender, genetic variants, and exposure opportunity to environmental factors and their interaction each other have impacts on onset of IBD. However, only gene polymorphisms were considered in this study. The effects of gene–gene and gene–environment interactions on the initiation and development of the disease need to be further studied in the future.

Current meta-analysis provided statistical evidence that the GSTM1 null genotype is associated with IBD, UC, and CD, especially in the Asian population and these results might not be generalized to other ethnic populations. Further studies with more sample size and including other confounding factors are still needed in the future for a definitive conclusion.

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