Research Article

Glutathione S-transferase gene polymorphisms and risk of nasal or colorectal polyposis

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We observed inconsistent conclusions regarding the genetic role of glutathione S-transferase gene polymorphisms, including glutathione S-transferase M1 (GSTM1), glutathione S-transferase T1 (GSTT1) present/null, and glutathione S-transferase pi (GSTP1) Ile105Val polymorphisms, in the susceptibility to nasal or colorectal polyposis (NP or CP). Thus, we aimed to perform a meta-analysis to comprehensively evaluate this association by applying Stata/SE software. After the heterogeneity assumption, Mantel–Haenszel statistics were used to obtain the odds ratio (OR), 95% confidence interval (95% CI) and P-value of the association test (PA). We obtained a total of 235 articles by searching online databases. After screening, ten eligible case–control studies were finally enrolled in our meta-analysis. For the meta-analysis of the GSTT1 gene under present versus null, we observed a decreased risk of NP [OR = 0.65; PA = 0.018], but not CP. In addition, we did not detect any evident association between the GSTM1 present/null polymorphism and NP or CP risk. For the meta-analysis of the GSTP1 Ile105Val polymorphism, compared with controls, an increased risk of NP cases was detected under the models of Val versus Ile (OR = 1.36; PA = 0.027), Ile/Val versus Ile/Ile (OR = 1.70; PA = 0.011) and Ile/Val+Val versus Ile/Ile (OR = 1.65; PA = 0.010). In conclusion, the null genotype of the GSTT1 polymorphism may be linked to an increased susceptibility to NP, whereas the Ile/Val genotype of the GSTP1 Ile105Val polymorphism may be associated with a decreased risk of NP.

Introduction

Polyposis refers to a chronic disorder characterized by the presence of polyps, which are neoplasms that grow on the mucosal surface of human organs or tissues, including the nasal cavity, vocal cord, stomach, or colorectal area [1–3]. The type of polyposis (e.g., nasal polyposis or colorectal polyposis [NP or CP], etc.) is named according to its location [1–3]. NP, a chronic and complicated inflammatory disorder with the formation of mostly benign polyps within bilateral nasal cavities, encompasses a series of pathological features, such as epithelial cell proliferation, eosinophil infiltration, and glandular changes [4,5]. Colorectal polyps are mostly regarded as a type of benign tumor, but some show malignant tendencies, and hence the removal of polyps is an effective approach to prevent the occurrence of cancer [6].

Although the exact etiology of polyposis remains to be elucidated, chronic stimulation and genetic factors may partly account for the presence of polyps [7,8]. Genetic variants reportedly involved in the complicated etiology or pathogenesis of NP or CP are increasingly reported [7,9,10].

The proteins glutathione S-transferase M1 (GSTM1), glutathione S-transferase T1 (GSTT1), and glutathione S-transferase pi (GSTP1), which are encoded by the GSTM1, GSTT1, and GSTP1 genes, respectively, are the three most common classes (mu, theta, and pi) of glutathione S-transferases in the human body [11,12]. The present/null polymorphism is the common variant of the GSTM1 and GSTT1 genes, while Ile105Val (rs1695) and Ala114Val (rs1138272) are the two common polymorphisms of the GSTP1 gene [11,12]. Conflicting conclusions on the associations between polymorphisms of GSTM1, GSTT1,
and GSTP1 and the risk of NP or CP have been reported [12–21]. No specific meta-analysis of this topic has been performed. Thus, we are interested in quantitatively examining such an association by pooling published related evidence together.

Materials and methods

Database search strategy
We retrieved articles from four electronic databases, PubMed, Web of Science (WOS), Embase, and China National Knowledge Infrastructure (CNKI), published up to January 2018. For example, the PubMed database was searched using the following medical subject heading (MeSH) terms: ((((((((((Polyps[MeSH Terms]) or Polyp) or Adenomatous Polyps) or Intestinal Polyps) or Colonic Polyps) or Nasal Polyps) or Intestinal Polyp) or Colonic Polyp) or Nasal Polyp) or Adenomatous Polyp) and (((((((((((Glutathione S-Transferase pi[MeSH Terms]) or Glutathione S Transferase pi) or GST Class-phi) or Class-phi, GST) or GST Class phi) or Glutathione Transferase P1-1) or Glutathione Transferase P1 1) or Transferase P1-1, Glutathione) or GSTP1 Glutathione D-Transferase) or D-Transferase, GSTP1 Glutathione) or GSTP1 Glutathione D Transferase) or Glutathione D-Transferase, GSTP1 (Glutathione) or GSTP1 or GSTP1)) or (((((((Glutathione S-transferase M1[MeSH Terms]) or Gstm1 protein, mouse) or glutathione S-transferase, mu 1 protein, mouse) or glutathione S-transferase, mu 1 protein, rat) or glutathione S-transferase, mu 1 protein, human) or glutathione S-transferase M1, human) or Gstm1)) or (((((((glutathione S-transferase T1[MeSH Terms]) or glutathione S-transferase theta 1) or glutathione S-transferase T1, human) or glutathione S-transferase theta 1, human) or GSTT1)) or ((((((((glutathione S transferase M1[MeSH Terms]) or Gstm1 protein, mouse) or glutathione S-transferase, mu 1 protein, mouse) or glutathione S-transferase, mu 1 protein, rat) or glutathione S-transferase, mu 1 protein, human) or glutathione S-transferase theta 1) or glutathione S-transferase GSTT1) or Gsst1 protein, mouse) or glutathione S-transferase, theta 1, protein, mouse) or Gsst1 protein, rat) or glutathione S-transferase theta 1, rat) or GSTT1 protein, human) or glutathione S-transferase theta 1 protein, human) or GSTT1)).

Study screening strategy
We designed our screening strategy according to the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)’ [22]. The main exclusion criteria were as follows: (1) review or meta-analysis; (2) meeting abstract; (3) other genes/diseases; (4) non-polymorphism data; (5) cell data; (6) data without genotype; and (7) duplicated studies. For eligible case–control studies, the complete genotype frequency data of GSTM1, GSTT1, and GSTP1 gene variants in both polyposis cases and negative controls were available.

Data extraction strategy
We thoroughly extracted the following basic information from each retrieved case–control study via a predesigned table: first author name, publication year, country, ethnicity, gene, present/null frequencies of the GSTM1 and GSTT1 genes, the Ile/IIe, Ile/Val, and Val/Val genotype frequencies of the GSTP1 Ile105Val polymorphism, disease type, genotyping method, source of control, and sample size. We also evaluated the study quality and asked for missing data by emailing the original authors.

Statistical analysis
We used Stata/SE software (StataCorp, U.S.A.) for our statistical analysis. A fixed-effect model was used for Mantel–Haenszel statistics when the P-value of heterogeneity from Cochran’s Q statistic >0.1 or I² value <50.0%. We obtained the value of the summary odds ratio (OR), 95% confidence intervals (95% CIs), and P-value of the association test (P_A). The P_A of less than 0.05 was deemed statistically significant. The present versus null genetic model was used for the GSTM1 and GSTT1 genes, and the allele (Val versus Ile), homozygote (Val/Val versus Ile/Ile), heterozygote (Ile/Val versus Ile/Ile), dominant (Ile/Val+Val/Val versus Ile/Ile), and recessive (Val/Val versus Ile/Ile+Ile/Val) models were used for the GSTP1 gene.

We performed subgroup meta-analyses according to ethnicity (Caucasian/Asian), disease type (NP/CP), source of control (population/hospital-based), and country (The Netherlands/Germany). We also performed the Begg’s/Egger’s tests to assess the publication bias among the selected studies and sensitivity analyses to measure the statistical stability of the results.

Results

Case–control study inclusion
As per the flow diagram in Figure 1, we obtained eligible case–control studies for our meta-analysis. First, we retrieved a total of 235 records (24 records from PubMed, 26 records from WOS, 64 records from Embase, and 121 records from CNKI) by searching online databases. Second, we excluded 41 records because of duplication and another 194 records from
Figure 1. Flow chart for inclusion of eligible case–control studies

due to the exclusion criteria (details shown in Figure 1). Third, after assessing the 11 remaining full-text articles for eligibility, we further ruled out one article without genotype frequency data. Ultimately, ten eligible articles [12–21] were collected. Table 1 shows the basic information of the case–control studies. The present/null polymorphisms of the GSTM1 and GSTT1 genes and the Ile105Val polymorphism of the GSTP1 gene were tested.

**GSTM1 and GSTT1 polymorphism**

We first performed a meta-analysis to study the genetic relationships between the present/null polymorphisms of the GSTM1 and GSTT1 genes and the risk of polyposis. As shown in Table 2, there was no high degree of heterogeneity in the present versus null model of GSTM1 (I² value = 0.0%, $P$-value of Cochran’s $Q$ statistic test $[PH] = 0.686$, and GSTT1 [I² value = 31.4%, $PH = 0.157$]); consequently, a fixed-effect model was selected for the Mantel–Haenszel statistics. As shown in Table 2, 3345 cases and 3807 controls were included for the quantitative synthesis of the GSTM1 present/null polymorphism, while 2840 cases and 3086 controls were available for the GSTT1 polymorphism. In the pooled estimates of the overall meta-analysis, no difference between the case and control groups for the risk of polyposis was observed for GSTM1 [Table 2, $P_A = 0.838$] and GSTT1 ($P_A = 0.914$).
Table 1 Basic information of case–control studies

| First author, year [REF] | Country          | Ethnicity | Gene    | Case  | Control | Method |
|--------------------------|------------------|-----------|---------|-------|---------|--------|
|                          |                  |           |         | Total | Present/null | Disease | Total | Present/null | Source |
| Arbag, 2006 [18]         | Turkey           | Asian     | GSTM1   | 98    | 55/43    | NP      | 102   | 55/47        | PB     |
|                          |                  |           | GSTT1   | 98    | 65/33    | NP      | 102   | 78/24        | PB     |
| Berkhout, 2008 [19]      | The Netherlands  | Caucasian | GSTM1   | 85    | 38/47    | CP      | 215   | 100/115      | PB     |
|                          |                  |           | GSTT1   | 85    | 60/25    | CP      | 214   | 165/49       | PB     |
| Fruth, 2011 [15]         | Germany          | Caucasian | GSTM1   | 69    | 34/35    | CP      | 49    | 23/26        | HB     |
|                          |                  |           | GSTT1   | 69    | 52/17    | NP      | 49    | 36/13        | HB     |
|                          |                  |           | GSTP1   | 69    | 27/28/14 | NP      | 49    | 28/16/5      | HB     |
| Gawronska, 1999 [13]     | Poland           | Caucasian | GSTM1   | 27    | 10/17    | CP      | 145   | 73/72        | PB     |
| Hamachi, 2013 [21]       | Japan            | Asian     | GSTM1   | 455   | 200/255  | CP      | 1052  | 506/546      | HB     |
| Lamberti, 2002 [20]      | Germany          | Caucasian | GSTT1   | 455   | 258/197  | CP      | 1052  | 552/500      | HB     |
| Lin, 1998 [17]           | U.S.A.           | Mixed     | GSTM1   | 402   | 185/217  | CP      | 171   | 8/9          | HB     |
| Ozcan, 2010 [12]         | Turkey           | Asian     | GSTT1   | 406   | 336/70   | CP      | 172   | 144/28       | PB     |
| Tiemersma, 2004 [14]     | The Netherlands  | Caucasian | GSTT1   | 406   | 336/70   | CP      | 148   | 125/23       | NR     |
| Tijhuis, 2005 [16]       | The Netherlands  | Caucasian | GSTT1   | 746   | 363/383  | CP      | 698   | 320/378      | HB     |

#, genotype frequency of GSTP1 gene (Ile/Ile, Ile/Val, Val/Val); 1, chronic rhinosinusitis without nasal polyps; 2, healthy tissue controls of inferior turbinate; 3, healthy individuals; 4, hereditary non-polyposis colorectal cancer. Abbreviations: HB, hospital-based control; NR, not reported; PB, population-based control; REF, reference.

Furthermore, we performed subgroup meta-analyses by disease type (NP/CP), source of control (population/hospital-based), country (The Netherlands/Germany), and ethnicity (Caucasian/Asian) for both the GSTM1 and GSTT1 genes. As shown in Table 3, a decreased risk of NP was detected for the GSTT1 gene in the subgroups 'NP', OR = 0.65, 95% CI = 0.45–0.93, $P_A$ = 0.018 and 'population-based' (OR = 0.70, 95% CI = 0.53–0.93, $P_A$ = 0.014) under the present versus null model. No differences between the cases and controls were observed for the other subgroups (all $P_A > 0.05$). We also constructed forest plots of the subgroup analysis by disease type for the GSTM1 (Figure 2) and GSTT1 (Figure 3) genes. These plots indicated that the GSTT1 null genotype may be associated with susceptibility toward NP.

**GSTP1 polymorphism**

Next, we performed the overall analysis involving 298 cases and 477 controls for the association between the GSTP1 Ile105Val polymorphism and polyposis susceptibility (Table 2). Mantel–Haenszel statistics with a fixed model was
Figure 2. Subgroup analysis by disease type for the GSTM1 polymorphism

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| N         |             |   |        |
| Arbag (2006) | 1.09 (0.63, 1.91) | 2.91 |
| Fruth (2011)  | 1.10 (0.53, 2.29)  | 1.68 |
| Fruth (2011)  | 1.22 (0.59, 2.52)  | 1.63 |
| Ozcan (2010)  | 1.22 (0.70, 2.13)  | 2.80 |
| Subtotal  (I-squared = 0.0%, p = 0.989) | 1.16 (0.85, 1.58) | 9.62 |
| C         |             |   |        |
| Berkhout (2008) | 0.93 (0.56, 1.54) | 3.85 |
| Gawronska (1999) | 0.58 (0.25, 1.35) | 1.77 |
| Gawronska (1999) | 0.66 (0.19, 2.27) | 0.76 |
| Hamachi (2013) | 0.85 (0.68, 1.06) | 21.04 |
| Lamberti (2002) | 1.04 (0.73, 1.49) | 7.17 |
| Lamberti (2002) | 0.87 (0.62, 1.22) | 8.77 |
| Lin (1998)      | 1.21 (0.94, 1.55) | 13.39 |
| Tiemersma (2004) | 0.98 (0.75, 1.28) | 13.37 |
| Tijhuis (2005)  | 1.12 (0.91, 1.38) | 20.86 |
| Subtotal  (I-squared = 3.1%, p = 0.408) | 1.00 (0.90, 1.10) | 90.98 |
| Overall  (I-squared = 0.0%, p = 0.686) | 1.01 (0.92, 1.11) | 100.00 |

Figure 3. Subgroup analysis by disease type for the GSTT1 polymorphism

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| N         |             |   |        |
| Arbag (2006) | 0.61 (0.33, 1.13) | 5.50 |
| Fruth (2011)  | 1.10 (0.48, 2.55)  | 2.22 |
| Fruth (2011)  | 0.73 (0.30, 1.76)  | 2.52 |
| Ozcan (2010)  | 0.45 (0.23, 0.88)  | 5.36 |
| Subtotal  (I-squared = 6.0%, p = 0.423) | 0.85 (0.45, 0.93) | 15.50 |
| C         |             |   |        |
| Berkhout (2008) | 0.71 (0.41, 1.25) | 5.19 |
| Hamachi (2013) | 1.19 (0.95, 1.48) | 30.82 |
| Lamberti (2002) | 0.93 (0.58, 1.51) | 7.45 |
| Lamberti (2002) | 0.88 (0.53, 1.48) | 6.75 |
| Tiemersma (2004) | 1.15 (0.79, 1.66) | 10.96 |
| Tijhuis (2005)  | 1.02 (0.78, 1.33)  | 22.63 |
| Subtotal  (I-squared = 6.0%, p = 0.556) | 1.06 (0.92, 1.21) | 84.50 |
| Overall  (I-squared = 31.4%, p = 0.187) | 0.99 (0.87, 1.13) | 100.00 |
Table 2 Overall meta-analysis of the GSTP1, GSTM1, GSTT1 polymorphism and the risk of polyposis

| Gene   | Genetic models       | I²   | PH  | Fixed/random | OR   | 95% CI        | PA  | PB | PE  | Case/control |
|--------|----------------------|------|-----|--------------|------|---------------|-----|----|-----|--------------|
| GSTM1  | Present vs null      | 0.0% | 0.686 | Fixed       | 1.01 | 0.92–1.11     | 0.838 | 0.583 | 0.612 | 3345/3807     |
| GSTT1  | Present vs null      | 31.4% | 0.157 | Fixed       | 0.99 | 0.87–1.13     | 0.914 | 0.032 | 0.016 | 2840/3086     |
| GSTP1  | Val vs Ile           | 3.9% | 0.373 | Fixed       | 1.30 | 1.04–1.62     | **0.019** | 0.306 | 0.094 | 298/477       |
|        | Val/Val vs Ile/ile   | 4.9% | 0.368 | Fixed       | 1.44 | 0.93–2.24     | 0.161 | 0.306 | 0.217 | 298/477       |
|        | Ile/Val+Val vs Ile/ile| 0.0% | 0.897 | Fixed       | 1.55 | 1.12–2.16     | **0.009** | 0.734 | 0.444 | 298/477       |
|        | Ile/Val vs Ile/Val   | 0.0% | 0.784 | Fixed       | 1.52 | 1.12–2.07     | **0.007** | 0.089 | 0.060 | 298/477       |
|        | Val/Val vs Ile/Ile+Val/Val vs Ile/ile| 0.0% | 0.775 | Fixed       | 1.22 | 0.95–1.58     | 0.123 | 0.308 | 0.069 | 298/477       |

Data in bold are PA < 0.05. Abbreviation: PE, P-value of Egger’s test.

Table 3 Subgroup meta-analysis of the GSTM1, GSTT1 polymorphism and the risk of polyposis

| Gene   | Genetic models       | Subgroup | OR   | 95% CI        | PA  | Case/control |
|--------|----------------------|----------|------|---------------|-----|--------------|
| GSTM1  | Present vs null      | NP       | 1.16 | 0.85–1.58     | 0.356 | 311/370      |
|        |                      | CP       | 1.00 | 0.90–1.10     | 0.931 | 3034/3437    |
|        |                      | PB       | 1.00 | 0.81–1.26     | 0.906 | 687/800      |
|        |                      | HB       | 1.03 | 0.92–1.15     | 0.640 | 2256/2807    |
|        |                      | The Netherlands | 1.05 | 0.90–1.23     | 0.537 | 1262/1345    |
|        |                      | Germany  | 0.98 | 0.79–1.23     | 0.883 | 942/472      |
|        |                      | Asian    | 0.91 | 0.75–1.11     | 0.351 | 628/1321     |
|        |                      | Caucasian| 0.98 | 1.01–1.14     | 0.877 | 2258/1979    |
| GSTT1  | Present vs null      | NP       | 0.65 | 0.45–0.93     | **0.018** | 311/370      |
|        |                      | CP       | 1.06 | 0.92–1.21     | 0.431 | 3034/3437    |
|        |                      | PB       | 0.70 | 0.53–0.93     | **0.014** | 687/800      |
|        |                      | HB       | 1.11 | 0.95–1.29     | 0.189 | 2256/2807    |
|        |                      | The Netherlands | 1.01 | 0.82–1.24     | 0.934 | 1262/1345    |
|        |                      | Germany  | 0.91 | 0.67–1.23     | 0.534 | 942/472      |
|        |                      | Asian    | 1.02 | 0.83–1.214    | 0.870 | 628/1321     |
|        |                      | Caucasian| 0.95 | 0.82–1.16     | 0.779 | 2258/1979    |

Data in bold are PA < 0.05. Abbreviations: PB, population-based control; HB, hospital-based control.

used (Table 2, all I² < 50.0%, PH > 0.1). We observed an increased polyposis risk in the models of Val versus Ile (OR = 1.30; 95% CI = 1.04–1.62; PA = 0.019), Ile/Val versus Ile/Ile (OR = 1.55, 95% CI = 1.12–2.16, PA = 0.009) and Ile/Val+Val/Val versus Ile/Ile (OR = 1.52, 95% CI = 1.12–2.07, PA = 0.007) but not in the other genetic models (all PA > 0.05). We obtained a similar conclusion for the subgroup ‘NP’ under the allele (Table 4, OR = 1.36, PA = 0.027), heterozygote (OR = 1.70, PA = 0.011) and dominant (OR = 1.65, PA = 0.010) models. Moreover, we detected increased risk in the subgroups ‘P-value of Hardy–Weinberg Equilibrium test (PHW) > 0.05’ and ‘Caucasian’ only in the allele and homozygote models (Table 4, OR > 1, PA < 0.05). Consequently, the Ile/Val genotype of GSTP1 Ile105Val polymorphism is more likely to be associated with an increased risk of NP.

**Publication bias and sensitivity analysis**

We performed the Begg’s/Egger’s tests to evaluate publication bias. As shown in Table 2, we did not find evidence of a high degree of publication bias under all genetic models (P-value of Begg’s test [PB] > 0.05; P-value of Egger’s test [PE] > 0.05), with the exception of the present versus null model of the GSTT1 gene (PB = 0.032, PE = 0.016). We also constructed funnel plots of Begg’s test under the present versus null model of the GSTM1 (Figure 4A) and GSTT1 (Figure 4A) genes.
Table 4 Subgroup meta-analysis of the GSTP1 Ile105Val polymorphism and the risk of polyposis

| Genetic models | Subgroup | OR  | 95% CI                 | PA   | Case/control |
|----------------|----------|-----|------------------------|------|--------------|
|                | Val vs Ile |     | 1.36                  | 0.027| 213/268      |
|                | P_HWE>0.05 |     | 1.41                  | 0.011| 223/310      |
|                | Caucasian  |     | 1.41                  | 0.011| 223/310      |
|                | Val/Val vs Ile/Ile |     | 1.52                  | 0.136| 213/268      |
|                | P_HWE>0.05 |     | 1.76                  | 0.034| 223/310      |
|                | Caucasian  |     | 1.76                  | 0.034| 223/310      |
|                | Ile/Val vs Ile/Ile |     | 1.70                  | 0.011| 213/268      |
|                | P_HWE>0.05 |     | 1.48                  | 0.052| 223/310      |
|                | Caucasian  |     | 1.48                  | 0.052| 223/310      |
|                | Ile/Val+Val/Val vs Ile/Ile |     | 1.65                  | 0.010| 213/268      |
|                | P_HWE>0.05 |     | 1.13                  | 0.191| 223/310      |
|                | Caucasian  |     | 1.13                  | 0.191| 223/310      |
|                | Val/Val vs Ile/Ile+Ile/Val |     | 1.27                  | 0.141| 213/268      |
|                | P_HWE>0.05 |     | 1.29                  | 0.109| 223/310      |
|                | Caucasian  |     | 1.29                  | 0.109| 223/310      |

Data in bold are P_A<0.05. Abbreviation: P_HWE, P-value of Hardy–Weinberg Equilibrium test.

Figure 4. Begg’s test and sensitivity analysis for the GSTM1 and GSTT1 polymorphisms

(A and B) Funnel plot of Begg’s test. (C and D) Sensitivity analysis.

Furthermore, we performed a sensitivity analysis to observe the statistical stability of the above conclusions (Figure 4C for GSTM1, Figure 4D for GSTT1, others not shown).

Discussion

NP is thought to be closely associated with a group of clinical disorders characterized by chronic rhinosinusitis and shows differences in complexity and etiology [1,23,24]. A family-based genome-wide association study reported that the holocarboxylase synthetase (HLCS), major histocompatibility complex, class II, DR α (HLA-DRA), BICD cargo adaptor 2 (BICD2), V-set immunoregulatory receptor (VSIR), and solute carrier family 5 member 1 (SLC5A1) genes may be linked to the pathogenesis of chronic rhinosinusitis with nasal polyps [9]. Another study reported that NP risk is significantly associated with the present/null polymorphism of the GSTT1 gene but not the present/null polymorphism of the GSTM1 gene and the Ile105Val polymorphism of the GSTP1 gene in the Mersin region of Turkey.
Conversely, in the Konya region of Turkey, a lack of genetic impact of the GSTM1 and GSTT1 polymorphisms on the predisposition for NP was reported [18]. There is statistical correlation between the polymorphisms of the GSTT1, GSTM1, and GSTP1 genes and the genetic tendency of chronic rhinosinusitis with or without nasal polyps in Germany [15]. Accordingly, it would be of interest to evaluate the overall effect of the underlying roles of the GSTM1 present/null, GSTT1 present/null, and GSTP1 Ile105Val polymorphisms in the susceptibility towards NP or CP. Our findings suggest that the null genotype of the GSTT1 polymorphism and the GSTP1 Ile105Val polymorphism are more likely to be associated with the risk of NP. However, no association between the GSTM1 present/null polymorphism and the risk of NP or CP was observed.

Human glutathione S-transferases are a family of multifunctional enzymes with antioxidant activity that are involved in oxidative stress, cell differentiation, inflammatory responses, drug detoxification, and chemotherapy resistance [25]. Some meta-analyses have reported different conclusions regarding the association between these variants and clinical disease risk. For instance, the GSTP1 Ile105Val polymorphism and GSTM1 null genotype but not the GSTT1 null genotype seem to increase the risk of Alzheimer’s disease [11]. Similarly, the GSTM1 null genotype but not the GSTT1 null genotype may be linked to the risk of juvenile open-angle glaucoma (JOAG) [26]. However, the null genotypes of the GSTM1 and GSTT1 genes and the combined GSTM1/GSTT1 gene may be risk factors for endometriosis [27]. Our meta-analysis data supports a genetic role of the GSTT1 null genotype and the Ile/Val genotype of the GSTP1 Ile105Val polymorphism in the risk of NP. Individuals with the GSTT1 null genotype may show partial gene deletion, followed by enzymatic activity deficiency and decreased detoxification capacity. The Ile105Val polymorphism of the GSTP1 gene leads to an amino acid change from Ile to Val at residue 105 of the GSTP1 protein, which also may decrease the catalytic activity of the enzyme. Such a change may reduce the efficient detoxification of stress-induced intermediates, which has been implicated in the presence of an inflammatory response and nasal polyps in response to increased levels of electrophilic compounds or reactive oxygen species.

There are some limitations of the present study that should be fully discussed. We endeavoured to search relevant publications by using search terms for different polyps, such as adenomatous polyps, intestinal polyps, colonic polyps, nasal polyps, and intestinal polyps, without language or region restrictions. However, only the data on nasal and colorectal polyps permitted synthesis of the data. Detailed data on genotype frequencies in both cases and controls are required to perform the overall meta-analysis and subsequent subgroup analyses. Due to restrictions of data availability, only the Ile105Val polymorphism was analyzed in our meta-analysis of the GSTP1 gene, and we were unable to explore the roles of other variants within the GSTP1 gene, such as the Ala114Val polymorphism. The possible distinct effects of different haplotypes merits further evidence. In addition, the joint effects of GSTM1, GSTT1, GSTP1, and other genes, such as cytochrome P450 family 1 subfamily A member 1 (CYP1A1), is worthy of analysis upon publication of sufficient data.

No high degree of heterogeneity in the comparisons of the GSTM1, GSTT1, and GSTP1 polymorphisms was detected in our study. For the meta-analysis of the GSTP1 Ile105Val polymorphism, we included five case–control studies from four articles [12,15,16,19]. However, we observed obvious alteration of the pooled OR and 95% CI values when one study [16] was excluded during our sensitivity analysis. Therefore, we removed the present study and performed the meta-analysis again. We recognize that the data included in our meta-analysis were very limited.

Although we obtained a positive result for the role of the GSTT1 present/null polymorphism in the risk of NP, the limitation of small sample size weakened the statistical power of our analysis to some extent. In addition, hospital-based controls were included in some studies. The genotype distribution of the GSTP1 Ile105Val polymorphism in the control group of one article [12] did not agree with Hardy–Weinberg equilibrium. It would be of great value to thoroughly evaluate the influences of additional variables, such as clinical type, gender, age, environmental exposure or lifestyle, on the roles of the above variants in the risk of developing polyposis.

In summary, we pooled published relevant data and concluded that the GSTT1 null genotype may serve as a protective factor against NP, whereas the Ile/Val genotype of the GSTP1 Ile105Val polymorphism is more likely to be associated with an increased risk of NP. More genomic tests in the future are warranted to further determine the roles of glutathione S-transferase gene polymorphisms in the genetic susceptibility to different types of polyposis.

**Author contribution**

Y.Z. and G.Z. conceived and designed the meta-analysis. Y.Z., H.Z., and G.Z. performed the literature search. Y.Z., H.Z., P.L., and G.Z. analyzed the data. Y.Z. and G.Z. wrote the paper.

**Competing interests**

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Abbreviations
BICD2, BICD cargo adaptor 2; CI, confidence interval; CNKI, China National Knowledge Infrastructure; CP, colorectal polyposis; CYP1A1, cytochrome P450 family 1 subfamily A member 1; GSTM1, glutathione S-transferase M1; GSTP1, glutathione S-transferase pi; GSTT1, glutathione S-transferase T1; HLA-DRA, major histocompatibility complex, class II, DR α; HLCS, holocarboxylase synthetase; HWE, Hardy–Weinberg Equilibrium; JOAG, juvenile open-angle glaucoma; MeSH, medical subject heading; NP, nasal polyposis; OR, odds ratio; PA, P-value of the association test; PB, P-value of Begg’s test; PC, P-value of Egger’s test; PST, P-value of Cochran’s Q statistic test; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLC5A1, solute carrier family 5 member 1; VSIR, V-set immunoregulatory receptor; WOS, Web of Science.

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