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Association between *glutathione S-transferase P1 Ile (105) Val gene* polymorphism and chronic obstructive pulmonary disease: A meta-analysis based on seventeen case–control studies

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ABSTRACT

Introduction: Previous studies have shown that *glutathione S-transferase P1* (*GSTP1*) was associated with chronic obstructive pulmonary disease (COPD). However, the association between *GSTP1 Ile (105) Val* gene polymorphism and COPD remains controversial. To drive a more precise estimation, we performed a meta-analysis based on published case–control studies.

Methods: An electronic search of PubMed, EMBASE, Cochrane library, Web of Science and China Knowledge Resource Integrated (CNKI) Database for papers on *GSTP1 Ile (105) Val* gene polymorphism and COPD risk was performed. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association in the homozygote model, heterozygote model, dominant model, recessive model and an additive mode. Statistical heterogeneity, test of publication bias and sensitivity analysis was performed. The software STATA (Version 13.0) was used data analysis.

Results: Overall, seventeen studies with 1892 cases and 2012 controls were included in this meta-analysis. The *GSTP1 Ile (105) Val* polymorphism showed pooled odds ratios for the homozygote comparison (OR = 1.501, 95%CI [0.862, 2.614]), heterozygote comparison (OR = 0.924, 95%CI [0.733, 1.165]), dominant model (OR = 1.003, 95%CI [0.756, 1.331]), recessive model (OR = 1.510, 95%CI [0.934, 2.439]), and an additive model (OR = 1.072, 95%CI [0.822, 1.398]).

Conclusions: In conclusion, the current meta-analysis, based on the most updated information, showed no significant association between *GSTP1 Ile (105) Val* gene polymorphism and COPD risk in any genetic models. The results of subgroup analysis also showed no significant association between *GSTP1 Ile (105) Val* gene polymorphism and COPD risk in Asian population and Caucasian population. Further studies involving large populations and careful control with age, sex, ethnicity, and cigarette smoking are greatly needed.

1. Introduction

Chronic obstructive pulmonary disease (COPD), as a significant major cause of chronic morbidity and mortality worldwide, is characterized by incompletely reversible airflow limitation and persistent airway inflammation (Hanania and Marciniuk, 2011). Previous studies have demonstrated that chronic inflammation and varying degrees of emphysematous alveolar destruction are the key pathological features of the disease (Stockley et al., 2009). Some studies have revealed that an imbalance of endogenous proteinases and antiproteinases, inflammatory cells, proinflammatory mediators, and oxidative stress were responsible for the pathogenesis of COPD (Vestbo et al., 2013). Genetic factors and environmental exposures like tobacco smoke are also involved in the pathogenesis of COPD (Restrepo, 2015). Tobacco smoke is regarded the most important risk factor for COPD, and smokers account for 80–90% of all COPD patients (Wang et al., 2014a).

However, only 10–15% of smokers develop clinically significant COPD (Mannino et al., 2002; Salvi, 2014). Many COPD patients have a family history and several studies have showed that the individual's risk differences to tobacco smoke injury may be related to genetic factors and the genetic factors may also play an important role in the pathogenesis of COPD (Hoidal, 2001; Molfino, 2004). Therefore, it is widely believed that COPD results from an interaction between genetic factors and environmental exposures. A lot of candidate gene studies have been carried out to identify genetic susceptibility factors for COPD over the past few years (Wang et al., 2013a, 2014b; Castellucci et al., 2015; Cheng et al., 2015; Murphy et al., 2015).

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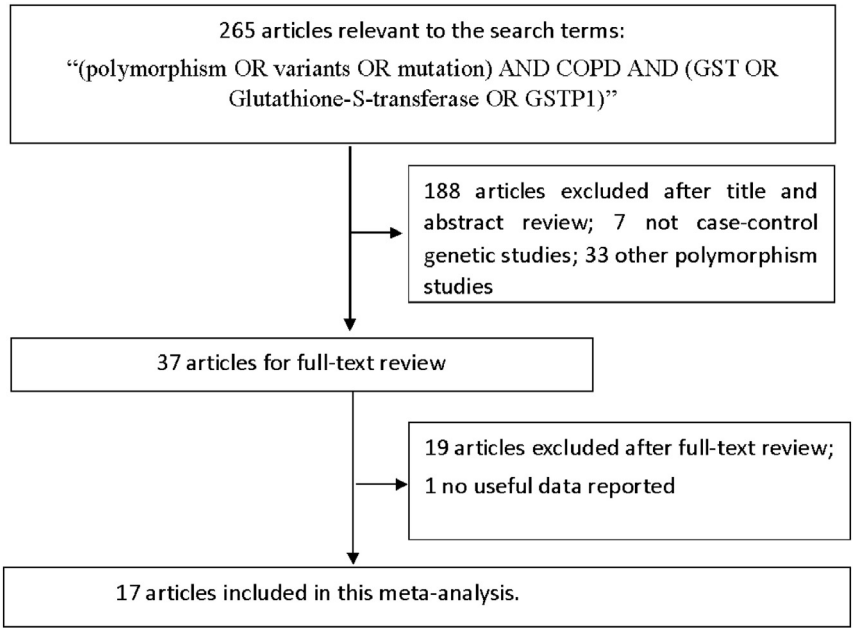

Fig. 1. Flow diagram of search strategy and study selection.

Previous studies have demonstrated that the development of COPD may be associated with the genetic variation in the enzymes that detoxify cigarette smoke products, such as *glutathione S-transferases* (*GSTs*). *GSTs*, a functionally diverse family of enzymes, were involved in the conjugation of a wide range of electrophilic substances with glutathione, facilitating detoxification, metabolism and excretion of the smoke products. Of the six classes of *GSTs*, i.e. *alpha* (*GSTA*), *mu* (*GSTM1*), *pi* (*GSTP1*), *theta* (*GSTT1*), *sigma and kappa*, *GSTP1* was expressed more abundantly in respiratory tissue (Cantlay et al., 1994). A number of studies have focused on the relationship between *GSTP1 105Val/Val* genotype and COPD risk in different ethnic populations with conflicting results, probably due to small sample sizes in those studies. Meta-analysis is a good statistical method to combine the results from multiple studies in an effort to increase power, improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree. Yan et al. performed a meta-analysis included ten studies with a total of 1140 cases and 1263 controls and suggested a significant association between *GSTP1* gene polymorphism and COPD risk (Yan et al., 2010). Based on the most updated information and the current available evidence, we performed this updated meta-analysis to drive a more precise estimation of *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk.

2. Materials and methods

2.1. Search strategy

This meta-analysis was performed according to the standard MOOSE guideline (Stroup et al., 2000).PubMed, EMBASE, Cochrane library, Web of science and China Knowledge Resource Integrated Database (until May 1, 2015) were searched using search terms as "(*polymorphism OR variants OR mutation*) *AND COPD AND* (*GST OR Glutathione-S-transferase OR GSTP1*)". Studies published in English or in Chinese language were selected. Case–control studies containing available genotype frequencies of *GSTP1 Ile* (*105*) *Val* were chosen. Related reference articles were also searched to identify other relevant publications. Unpublished data were not included.

Table 1
Characteristics of studies included in this meta-analysis.

Author	Year	Ethnicity	Source of controls	Adjustment for smoking	Case				Control				HWE(P)
					Total	105Ile/Ile	105Ile/Val	105Val/Val	Total	105Ile/Ile	105Ile/Val	105Val/Val	
Harries et al.	1997	Caucasian	Healthy controls	No	79	34	35	10	155	79	66	10	0.4396
Ishii et al.	1999	Asian	Healthy controls	Yes	53	42	11	0	50	26	22	2	0.3104
Lu et al.	2002	Asian	Healthy controls	Yes	97	70	22	5	67	41	24	2	0.4940
Yim et al.	2002	Asian	Checkup	No	89	63	24	2	94	57	35	2	0.1995
Zhang et al.	2003	Asian	Healthy controls	Yes	57	47	5	5	48	44	3	1	0.0110
Cheng et al.	2004	Asian	Checkup	Yes	184	97	78	9	212	99	98	15	0.1591
Gaspa et al.	2004	Caucasian	Checkup	No	75	35	35	5	90	47	36	7	0.9767
Xiao et al.	2004	Asian	Healthy controls	Yes	100	70	29	1	100	57	40	3	0.1959
Hu et al.	2005	Asian	Healthy controls	Yes	50	45	3	2	68	59	5	4	0.0000
Rodriguez et al.	2005	Caucasian	Checkup	No	98	52	36	10	198	97	88	13	0.2372
Calikoglu et al.	2006	Caucasian	Healthy controls	Yes	144	88	42	14	150	57	57	36	0.0059
Fang et al.	2006	Asian	Healthy controls	No	87	65	18	4	91	74	16	1	0.8972
Vibhuti et al.	2007	Asian	Healthy controls	Yes	202	105	75	22	136	90	42	4	0.7336
Yeung et al.	2007	Asian	Healthy controls	Yes	163	112	43	8	161	112	47	2	0.2280
Lakhdar et al.	2010	Caucasian	Healthy controls	Yes	234	81	104	49	182	84	79	19	0.9468
Wu et al.	2014	Asian	Healthy controls	Yes	150	113	18	19	150	132	11	7	0.0000
Zuntar et al.	2014	Caucasian	Healthy controls	No	30	10	16	4	60	34	25	1	0.1314

Table 2
Results of the overall meta-analysis.

Contrast	OR,95% CI	Heterogeneity	Z and P
Homozygote	1.501, [0.862, 2.614]	Chi-squared = 52.95 (d.f. = 16) p = 0.000, I-squared = 69.8%	z = 1.44, p = 0.151
Heterozygote	0.924, [0.733, 1.165]	Chi-squared = 36.65 (d.f. = 16) p = 0.002, I-squared = 56.3%	z = 0.67, p = 0.503
Dominant	1.003, [0.756, 1.331]	Chi-squared = 62.67 (d.f. = 16) p = 0.000, I-squared = 74.5%	z = 0.02, p = 0.984
Recessive	1.510, [0.934, 2.439]	Chi-squared = 41.41 (d.f. = 16) p = 0.000, I-squared = 61.4%	z = 1.68, p = 0.093
Additive	1.072, [0.822, 1.398]	Chi-squared = 85.96 (d.f. = 16) p = 0.000, I-squared = 81.4%	z = 0.51, p = 0.610

2.2. Inclusion and exclusion criteria

Eligible studies were selected following inclusion criteria: 1) *GSTP1 Ile* (*105*) *Val* polymorphism and COPD risk; 2) human case–control design; 3) application of standardized clinical or pathologic criteria for the diagnosis of COPD; 4) studies that reported the frequency of the *GSTP1 Ile* (*105*) *Val gene* polymorphism as number of cases and controls according to the three variant genotypes of either polymorphisms; and 5) published in English or Chinese. The criteria for the exclusion of studies are as follows: 1) not related to the *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk; 2) not a primary case–control study; 3) no usable or sufficient genotype data reported; 4) studies whose allele frequency in the control population deviated from the Hardy–Weinberg Equilibrium (HWE) at a p value equal or less than 0.01; 5) case reports, letter to Editor, book chapters or reviews. The study inclusion and exclusion procedures are summarized in Fig. 1.

2.3. Data extraction

The data from all qualified studies were extracted by two investigators independently according to the selection standard listed above. Discrepancies were solved through discussion until agreement was reached. The following information was extracted: the first author's name, year of publication, Ethnicity, the source of control group evidence of Hardy-Weinberg equilibrium (HWE) in controls, the sample size, number of cases and controls with the three genotypes.

2.4. Statistical analysis

STATA software (Version 13.0) was used for all statistical analyses. Two-sided *P* values less than 0.05 were considered statistically significant. The strength of the association between the *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk was assessed by the odds ratios (ORs) with 95% CIs. The pooled ORs were calculated for the homozygote model (*105Val/Val* vs.*105Ile/Ile*), heterozygote model (*105Ile/Val* vs.*105Ile/Ile*), dominant model (*105Val/Val* + *105Ile/Val* vs. *105Ile/Ile*), recessive model (*105Val/Val* vs. *105Ile/Val* + *105Ile/Ile*), and an additive model (*Val* vs. *Ile*) (Yang et al., 2015; Yang and Liu, 2015). For the control groups for each study, the observed genotype frequencies of the *GSTP1 Ile* (*105*) *Val* polymorphism were evaluated for Hardy–Weinberg equilibrium (Wang et al., 2013b; Ma et al., 2014; Tian et al., 2015). Cochran's Q-statistic and the I^2 metric were conducted to assess heterogeneity between studies, $P < 0.10$ and $I^2 > 50\%$ were considered to indicate the existence of significant heterogeneity (Higgins and Thompson, 2002; Jackson et al., 2012). If the heterogeneity test result returned $P > 0.1$, the pooled ORs were analyzed using the random-effects model (DerSimonian and Laird, 1986), or else, the fixed effects model was used (Mantel and Haenszel, 1959). Sensitivity analyses were also performed after sequential removal of each study (Fang et al., 2014). We

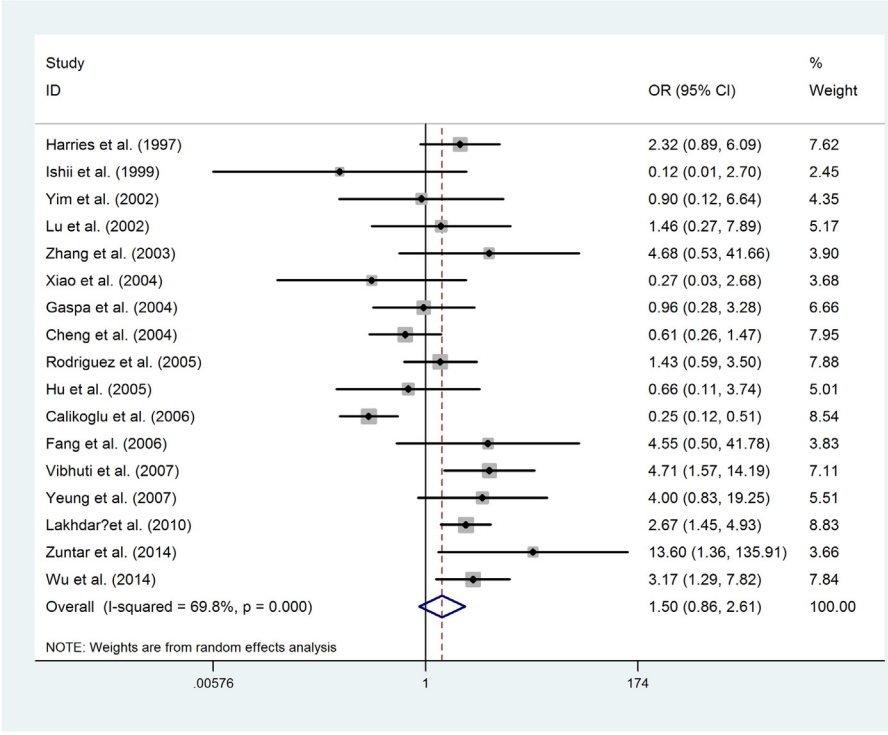

Fig. 2. Random effect forest plot of homozygote model of GSTP1 gene polymorphism.

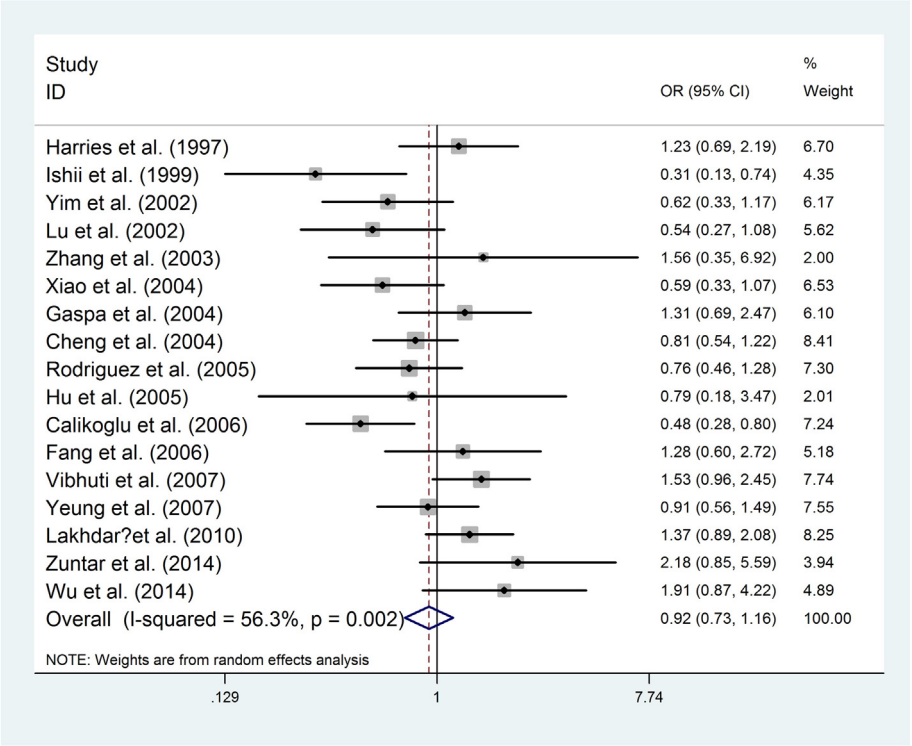

Fig. 3. Random effect forest plot of heterozygote model of GSTP1 gene polymorphism.

also tried to assess the source of heterogeneity by region, publication year, control source, and sample size (He et al., 2014; Xue et al., 2014). Lastly, Begg's funnel plot and Egger's test were used to examine statistically any publication bias (Peters et al., 2006).

3. Results

3.1. Characteristics of the included studies

In accordance with the inclusion criteria, seventeen case–control studies with 1892 cases and 2012 controls were included based on the search criteria for risk of COPD related to the *GSTP1* polymorphism (Harries et al., 1997; Yim et al., 2002; Lu and He, 2002; Ishii et al., 2003; Xiao et al., 2003; Zhang et al., 2003; Cheng et al., 2004; Gaspar et al., 2004; Rodriguez et al., 2005; Hu et al., 2005; Calikoglu et al., 2006; Fang et al., 2006; Chan-Yeung et al., 2007; Vibhuti et al., 2007; Lakhdar et al., 2010; Zuntar et al., 2014; Wu et al., 2014). All of the 17 studies were published between 1997 and 2014. No overlap occurred between the studies based on case or control participation. The characteristics of all included studies are summarized in Table 1.

3.2. Results of the overall meta-analysis

The main results of meta-analysis on the association between the *GSTP1 Ile (105) Val* polymorphism and COPD risk are listed in Table 2. The *GSTP1 Ile (105) Val* polymorphism showed pooled odds ratios for the homozygote comparison (Fig. 2, OR = 1.501, 95%CI [0.862, 2.614]), heterozygote comparison (Fig. 3, OR = 0.924, 95%CI [0.733, 1.165]), dominant model (OR = 1.003, 95%CI [0.756, 1.331]), recessive model (OR = 1.510, 95%CI [0.934, 2.439]), and an additive model (OR = 1.072, 95%CI [0.822, 1.398]).

3.3. Sub-group analysis

We performed a sub-group analysis stratified by ethnicity. There were 11 studies based on Asian population and 6 studies based on Caucasian population. The pooled OR was 1.586, 95%CI [0.814, 3.088] for Asian population, 1.476, 95%CI [0.558, 3.906] for Caucasian population in homozygote comparison. The subgroup analysis results for the all genetic models are listed in detail in Table 3.

3.4. Heterogeneity test

There was a significant heterogeneity, in homozygote comparison: chi-squared = 52.95 (d.f. = 16) p = 0.000, I-squared = 69.8%, and in Heterozygote comparison: chi-squared = 36.65 (d.f. = 16) p = 0.002, I-squared = 56.3%. We assessed the source of heterogeneity by region, publication year, control source, and sample size. However, we did not observe any sources that contributed to the substantial heterogeneity. The meta-regression analysis did not yield any significant difference between subgroup analysis.

3.5. Sensitivity analysis

We conducted sensitivity analyses to ascertain the primary origin of the heterogeneity. Through sensitivity analysis, the current meta-

Table 3
Results of sub-group analysis.

Ethnicity	Comparisons	Homozygote	Heterozygote	Dominant	Recessive	Additive
Caucasian	6	1.476, [0.558, 3.906]	1.040, [0.697, 1.552]	1.110, [0.664, 1.854]	1.393, [0.622, 3.118]	1.131, [0.708, 1.806]
Asian	11	1.586, [0.814, 3.088]	0.858, [0.638, 1.154]	0.948, [0.664, 1.353]	1.663, [0.914, 3.025]	1.038, [0.738, 1.460]
Overall	17	1.501, [0.862,2.614]	0.924, [0.733, 1.165]	1.003, [0.756, 1.331]	1.510, [0.934, 2.439]	1.072, [0.822, 1.398]

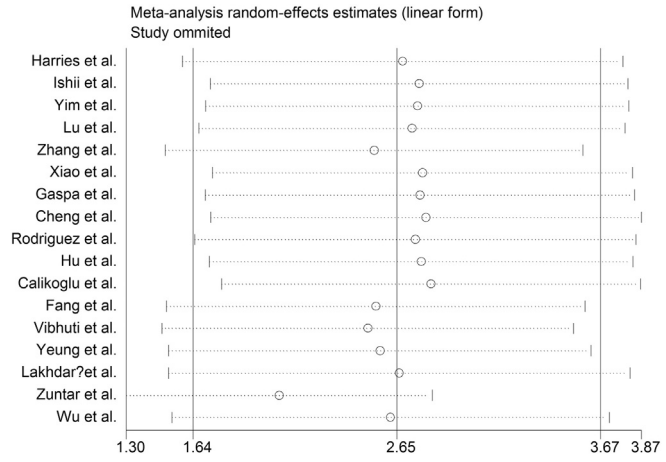

Fig. 4. Sensitivity analysis.

analysis showed that no individual study had marked effect on the pooled ORs (Fig. 4).

3.6. Publication bias

Funnel plot was generated to assess publication bias. Begg's test and Egger's test were performed to evaluate funnel plot symmetry statistically. The results showed no publication bias: Begg's test $Pr > |z| = 0.343$ and Egger's test $P > |t| = 0.263$ (Fig. 5).

4. Discussion

COPD, one of the major health challenges, is the fourth leading cause of death globally presently, and it is predicted to become the third leading cause by 2030 (Hu et al., 2015). It is likely to be a complex interplay between genetic and environmental factors. A series of different genes were considered to play important roles in the metabolism of toxic substances in cigarette smoke, airway hyperresponsiveness, and the inflammatory response to cigarette smoke (Sandford et al., 2002).GSTs are derived from a superfamily of genes; they catalyze the conjugation of reactive chemical intermediates to soluble glutathione and may play a role in cellular defense by detoxifying various toxic substrates in cigarette smoke (Ketterer, 1988).Many previous studies have explored the association between *GSTP1 105Val/Val* genotype and COPD risk in different ethnic populations with conflicting results. As so far, only one meta-analyses, which was nested in case–control studies,

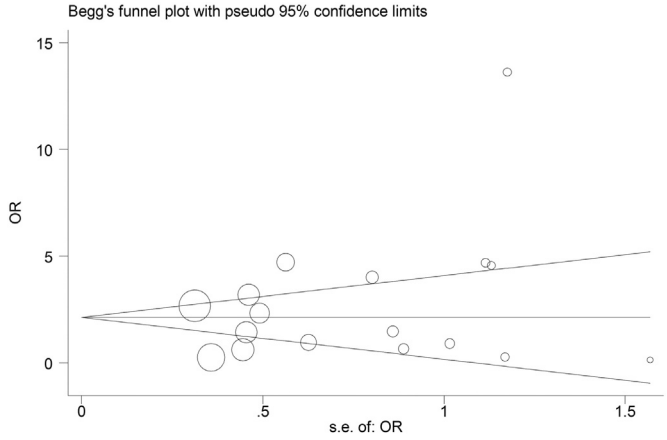

Fig. 5. Test for publication bias.

have investigated the association of *GSTP1 Ile* (*105*) *Val* polymorphism and COPD susceptibility. Yan et al. performed a meta-analysis included ten studies with a total of 1140 cases and 1263 controls and suggested a significant association between *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk (Yan et al., 2010).Considering a series of new articles have been published we performed this updated meta-analysis to drive a more precise estimation of *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk.

According to the inclusion criteria 17 studies with 1892 cases and 2012 controls were included the current meta-analysis. To the best of our knowledge, the current meta-analysis is the largest one to investigate the association between *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk. The results showed no significant association between *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk in any genetic models. The results of subgroup analysis also showed no significant association between *GSTP1 Ile* (*105*) *Val gene* polymorphism and COPD risk in Asian population and Caucasian population. There was a significant heterogeneity, and we conducted sensitivity analyses to ascertain the primary origin of the heterogeneity. Through sensitivity analysis, the current meta-analysis showed that no individual study had significant effect on the pooled ORs. Funnel plot was generated to assess publication bias. Begg's test and Egger's test were performed to evaluate funnel plot symmetry statistically. No publication bias was detected in our meta-analysis.

Of course, we should be aware of that the hypothesis considering no association between *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk merely on the basis of the negative results in this study. If a putative genetic association is of small magnitude with point estimates less than 1.5, the small and underpowered studies may be unable to identify true genetic associations (Ioannidis, 2003; Ioannidis et al., 2006; Hindorff et al., 2009). Thus, more evidence is needed to support or deny such an association. By means of meta-analysis, a statistical technique for combining the results from independent studies, we drew a more reliable conclusion on the influence of *GSTP1 Ile* (*105*) *Val* gene polymorphism on COPD risk. However, COPD might be a result of multi-factors, future research should investigate not only individual genes, but also gene–gene interactions, other SNPs such as *GSTM1*, *GSTT1*.

Several potential limitations of this meta-analysis should be discussed: 1) although the funnel plot and Begg's Test showed no publication bias, selection bias may have occurred because only studies in English or Chinese were selected; 2) there was a significant heterogeneity. We assessed the source of heterogeneity by region, publication year, control source, and sample size. However, we did not observe any sources that contributed to the substantial heterogeneity. The meta-regression analysis did not yield any significant difference between subgroup analysis. Through sensitivity analysis, the current meta-analysis showed that no individual study had marked effect on the pooled ORs. However, this study also has some clear advantages: 1) this is the meta-analysis on the most updated information; 2) we performed a sub-group analysis stratified by ethnicity; 3) sensitivity analysis showed no individual study had marked effect on the overall results; 4) the scientific search and selection method significantly increased the reality of this meta-analysis; 5) no publication bias was detected.

In conclusion, the current meta-analysis, based on the most updated information, showed no significant association between *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk in any genetic models. The results of subgroup analysis also showed no significant association between *GSTP1 Ile* (*105*) *Val* gene polymorphism and COPD risk in Asian population and Caucasian population. Further studies involving large populations and careful control with age, sex, ethnicity, and cigarette smoking are greatly needed.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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