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

Lingjing Yang a, Xixia Li a, Xiang Tong b, Hong Fan b,*

a Department of Respiration, East Branch, Sichuan Provincial People's Hospital, Sichuan Academy of Medical Science, Chengdu, China
b Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China

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).

Conclusion: 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.

© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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)”.

### Table 1

Characteristics of studies included in this meta-analysis.

| Author         | Year | Ethnicity | Source of controls | Adjustment for smoking | Total 105Ile/Ile | 105Ile/Val | 105Val/Val | Total 105Ile/Ile | 105Ile/Val | 105Val/Val | HWE(P)  |
|----------------|------|-----------|--------------------|------------------------|-----------------|-----------|------------|-----------------|-----------|------------|--------|
| 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  |
| Yin 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  |
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 I² metric were conducted to assess heterogeneity between studies, P > 0.10 and I² > 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).

![Random effect forest plot of homozygote model of GSTP1 gene polymorphism.](image-url)
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; Cheng et al., 2004; Gaspar et al., 2004; Rodriguez et al., 2005; Hu et al., 2005; Calikoglu et al., 2006; Fang et al., 2006; Vibhuti et al., 2007; Yeung 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, 1.311] | 1.510, [0.934, 2.439] | 1.072, [0.822, 1.398] |

Fig. 3. Random effect forest plot of heterozygote model of GSTP1 gene polymorphism.
Cigarette smoke contains toxic substances that can cause inflammation and airway hyperresponsiveness, which are considered important in the metabolism of toxic substances. A series of different genes 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 (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 Ile105Val genotype and COPD risk in different ethnic populations with conflicting results. As so far, only one meta-analysis, which was nested in case-control studies, have investigated the association of GSTP1 Ile (105) Val polymorphism and COPD susceptibility. Yan et al., performed a meta-analysis that 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.
