

RESEARCH COMMUNICATION

An Updated Pooled Analysis of Glutathione S-transferase Genotype Polymorphisms and Risk of Adult Gliomas

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Abstract

Objective: Glutathione S-transferases (GSTs) are multifunctional enzymes that play a crucial role in the detoxification of both the endogenous products of oxidative stress and exogenous carcinogens. Recent studies investigating the association between genetic polymorphisms in GSTs and the risk of adult brain tumors have reported conflicting results. The rationale of this pooled analysis was to determine whether the presence of a GST variant increases adult glioma susceptibility by combining data from multiple studies. **Methods:** In our meta-analysis, 12 studies were identified by a search of the MEDLINE, HIGHWIRE, SCIENCEDIRECT and EMBASE databases. Of those 12, 11 evaluated GSTM1, nine evaluated GSTT1 and seven evaluated GSTP1 Ile105Val. Between-study heterogeneity was assessed using χ^2 -based Q statistic and the I^2 statistic. Crude odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to estimate the association between GSTM1, GSTT1 and GSTP1 polymorphisms and the risk of adult gliomas. **Results:** The quantitative synthesis showed no significant evidence to indicate an association exists between the presence of a GSTM1, GSTT1 or GSTP1 Ile105Val haplotype polymorphism and the risk of adult gliomas (OR, 1.008, 1.246, 1.061 respectively; 95% CI, 0.901-1.129, 0.963-1.611, 0.653-1.724 respectively). **Conclusions:** Overall, this study did not suggest any strong relationship between GST variants or related enzyme polymorphisms and an increased risk of adult gliomas. Some caveats include absence of specific raw information on ethnic groups or smoking history on glioma cases in published articles; therefore, well-designed studies with a clear stratified analysis on potential confounding factors are needed to confirm these results.

Keywords: Glutathione S-transferases - GSTM1 - GSTT1 - GSTP1 - adult gliomas

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Introduction

Gliomas are the most common form of primary brain neoplasms in adults, with the major histopathological classifications being oligodendroglioma, astrocytoma and glioblastoma multiforme, among several other subtypes. Despite recent advances in diagnostic strategies, such as some specific gene and protein labeling approaches, the prognosis for patients with these brain tumors remains poor. New approaches are urgently needed to provide highly specific tumor risk and/or susceptibility assessments for these refractory and fatal tumors.

Glutathione-S-transferases (GSTs, Enzyme Commission (EC) number 2.5.1.18) are an important family of biotransformation enzymes that participate in detoxification reactions by conjugating the tripeptide glutathione (GSH). GSTs are involved in the detoxification of electrophilic compounds such as carcinogens and cytotoxic drugs and protect tissues from the entry of these compounds into the body as either food additives or drugs that undergo glutathione conjugation (Vogl

et al., 2004; Dahabreh et al., 2010). In addition, these enzymes are thought to play a role in protecting DNA from oxidative damage (Little et al., 2006). Based on their sequence homology and immunological cross-reactivity, human cytosolic GSTs have been grouped into several families; the most frequently mentioned are designated as GST-Mu (GSTM), GST-Theta (GSTT) and GST-Pi (GSTP) (Hashibe et al., 2003; Egan et al., 2004; Nebert and Vasiliou, 2004). Because GSTs are important in the cellular detoxification of carcinogens, genetic variants of GSTs have been studied extensively in relation to cancer risk. A search of the literature prior to June 2011 revealed thousands of studies regarding the relationship between GST genotypes and breast (Bailey et al., 1998), lung (Zheng et al., 2006), colon (Zhong et al., 1993), brain (Lai et al., 2005), bladder (Hung et al., 2004), prostate (Ntais et al., 2005) and other types of cancer (Gao et al., 2011). These studies have primarily focused on single nucleotide polymorphisms (SNPs) in GSTM1, GSTT1, and GSTP1.

The GSTM subfamily, encoded by a 100-kb gene cluster at 1p13.3, is arranged as 5'-GSTM4-GSTM2-

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GSTM1-GSTM5-GSTM3-3'. Flanked by two almost identical 4.2-kb regions, the GSTM1 gene, composing of eight exons, is embedded in a region with extensive homologies. With the homologous recombination of the left and right 4.2-kb repeats, the GSTM1 null allele (homozygous deletion of the gene) changes into a 16-kb deletion containing the entire GSTM1 gene (Pearson et al., 1993; Roodi N et al., 2004; Parl, 2005).

GSTT1 and GSTT2 are component parts of the GSTT subfamily. The two genes, separated by approximately 50 kb, are located at 22q11.2. The GSTT1 gene consists of five exons, is embedded in a region with extensive homologies and is flanked by two 18 kb regions, HA3 and HA5, which are more than 90% homologous. The central portions of HA3 and HA5 share a 403-bp sequence with 100% identity. The GSTT1 null allele (homozygous deletion of the gene) arises from homologous recombination of the left and right 403-bp repeats, which results in a 54-kb deletion containing the entire GSTT1 gene (Parl, 2005). The single GSTP1 gene is located at 11q13, is 2.8 kb long and contains seven exons. The open reading frame starts at the 3' end of the first exon and is 630 bp long, encoding a protein of 209 amino acids. The arrows indicate polymorphic sites. Two of the polymorphisms result in amino acid substitutions at codons 105 (Ile->Val) and 114 (Ala->Val) in exons fifth and sixth, respectively (Zimniak et al., 1994; Parl, 2005; Sørensen et al., 2004).

Recently, many studies of adult brain tumors have reported that an association exists between susceptibility to brain tumors and the presence of GST variants in patients (Elxpuru et al., 1995; Hand et al., 1996; Wiencke et al., 1997; Trizna et al., 1998; Kondratieva et al., 2000; Ezer et al., 2002; De Roos et al., 2003; Wrensch et al., 2004; Pinarbasi et al., 2005; Schwartzbaum et al., 2007; Coutinho et al., 2010; Custódio et al., 2010). In contrast, Lai et al. (2005) conducted a meta-analysis of the association between genetic polymorphisms of GSTs and the risk of adult brain tumors (Lai et al., 2005), and their results did not suggest any relationship between those two. Additionally, several large-sample, case-control studies that have been conducted by various authors around the world have reported conflicting results after previous meta-analysis. To resolve these discrepancies, we carried out an updated, pooled analysis of all eligible case-control studies, including 2,325 cases of patients with gliomas and 3,551 controls, to assess the risk of developing a glioma in adults with polymorphisms in GSTM1, GSTT1, and GSTP1.

Materials and Methods

Literature search and data extraction

In order to identify the relevant papers regarding polymorphisms in GSTM1, GSTT1, and GSTP1 and associated glioma risk, we performed a systematic search of the online electronic databases MEDLINE, HIGHWIRE, SCIEDIRECT and EMBASE that were updated prior to June 20th, 2011. The search was limited to English language papers, using the terms glutathione S-transferase OR GST AND polymorphism. Additional studies were identified by a manual search

of the references of the original studies. For studies published by the same investigators that utilized the same or overlapping data, we selected those that were the most recent and included the largest number of subjects. Studies included in our meta-analysis needed to meet the following criteria: (i) included adult gliomas as the primary study objects, (ii) used a case-control design and (iii) contained available genotype frequency. Major reasons for exclusion of studies were that they (i) did not involve gliomas or brain tumors, (ii) were only relevant to predict survival in an already existing brain tumor or as markers for response to therapy and (iii) were not relevant to adults (Lai et al., 2005).

Two investigators independently extracted the data and reached a consensus on all items. For each study, the following characteristics were collected: the first author's last name, year of publication, country of origin, ethnicity, number of genotyped cases and controls, source of control groups (population- or hospital-based controls), genotyping methods and matching variables (Zhang et al., 2009; Chu et al., 2011). The data for this analysis were available from 12 case-control studies, which included 2,325 cases of patients with gliomas and 3,551 controls.

Statistical analysis

To compare cases with controls, an analysis of GSTM1 and GSTT1 polymorphisms that contrasted the null (homozygous deletion of the gene) versus the wild type (non-deleted, heterozygous or homozygous presence of the gene) genotype was originally proposed. The analysis of GSTP1 polymorphisms was also based on the contrast of alleles. The odds ratio (OR) was used as the metric of choice. For each genetic comparison, the χ^2 -based Q statistic and I2 statistic were adopted to estimate the between-study heterogeneity for all suitable comparisons (Lau et al., 1997; Gu et al., 2009). We combined data using both fixed- (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models. A random-effects model incorporates an estimate of the between-study variance and provides wider 95% confidence intervals (95% CI) when the results of the constituent studies differ among themselves. All significance tests were two-sided at the 0.05 level (Mantel and Haenszel, 1959; Der Simonian et al., 1986; Zhang et al., 2008).

Publication bias was assessed by a funnel plot and Begg's and Egger's tests (Egger et al., 1997; Zhang et al., 2009). Finally, genotypes were selected to determine any potential significance of polymorphisms of different GST classes by sensitivity analysis. ORs were computed for the effect of each possible combination of wild type and null among GSTM1, GSTT1, and GSTP1 Ile105Val genotypes on the risk of developing a glioma in adults. Analyses were carried out using Stata statistical software (Stata 11.0, StataCorp LE).

Results

Characteristics of studies

Twelve papers met our eligibility criteria and were retrieved by our bibliographic search (Figure 1), including 2,325 cases and 3,551 controls. The characteristics of the studies included in this meta-analysis are listed in Table

Table 1. Characteristics of Literatures Included in the Meta-analysis

Study (first author)	Year of publication	Country	Ethnicity	Sample size ^c (case/control)	Source of control	Genotyping methods	Matching variable
Custódio et al.	2010	Brazil	Caucasian	80/100	PB	PCR-RFLP	Gender, Age
Coutinho et al.	2010	Brazil	Caucasian	78/347	HB	PCR-RFLP	Brazilian
Schwartzbaum et al.	2007	UK	Caucasian	230/430	PB	PCR, PCR-RFLP	Gender, Age
Pinarbasi et al.	2005	Turkey	Caucasian	31/153	HB	PCR, PCR-RFLP	Gender, Age, Smoking history
Wrensch et al. ^a	2004	USA	Mixed	184/166	PB	PCR	Gender, Age
Wrensch et al. ^b	2004	USA	Mixed	264/337	PB	PCR-RFLP	Gender, Age
De Roos et al.	2003	USA	Mixed	403/575	HB	PCR	Gender, Age, Educational level
Ezer et al.	2002	USA	Mixed	221/100	PB	PCR	Gender, Age
Kondratieva et al.	2000	Russia	Caucasian	54/103	HB	PCR	None
Trizna et al.	1998	USA	Mixed	90/90	HB	PCR	Gender, Age
Hand et al.	1996	UK	Caucasian	89/211	HB	PCR	Northern European Caucasian
Wiencke et al.	1997	USA	Caucasian	492/462	PB	PCR	Gender, Age
Camiruaga et al.	1995	UK	Caucasian	109/477	HB	PCR	Gender, Age

^aseries 1, samples in this series were collected between 1991-1994 by Wrensch et al. in the San Francisco Bay Area; ^bseries 2, samples in this series were collected between 1997-2000 by Wrensch et al. in the San Francisco Bay Area; ^csample size was exemplified with the number of cases and controls on GSTM1; PCR, Polymerase Chain Reaction-restriction; RFLP, Restriction Fragment Length Polymorphism; USA, United States of America; UK, the United Kingdom of Great Britain and Northern Ireland; PB, Population Based; HB, Hospital Based

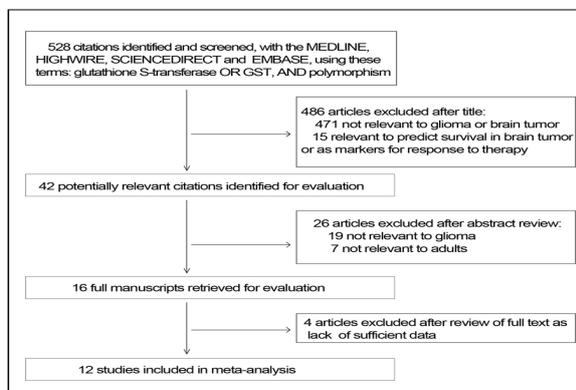


Figure 1. Selection of Studies Identified with Criteria and Exclusion in the Systematic Review on the Glutathione S-transferase Genotype Polymorphisms and Risk of Adult Gliomas. A total of 12 reports were included in the final pooled analysis

1. In 11 of these papers, GSTT1 status was determined by analyzing the gene via polymerase chain reaction (PCR) or a similar method. Furthermore, nine out of the 12 studies collected data on the association between GSTT1 status and glioma risk. Because the classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) approach has been widely used in recent years to detect genotype polymorphisms, there were seven case-control reports concerning the association between a GSTP1 Ile105Val polymorphism and the development of gliomas in adults. The corresponding point of deletion in GSTM1 and GSTT1 cannot be precisely localized because of the high sequence identity between the repeats. As a result, only the GSTP1 Ile105Val distribution among included controls was consistent with a Hardy-Weinberg equilibrium in our updated pooled analysis.

Quantitative synthesis

We observed a wide variation in the frequency of GST polymorphisms across the different studies. The analysis of the individual patient data from 11 case-control studies yielded no evidence for an increased risk of adult

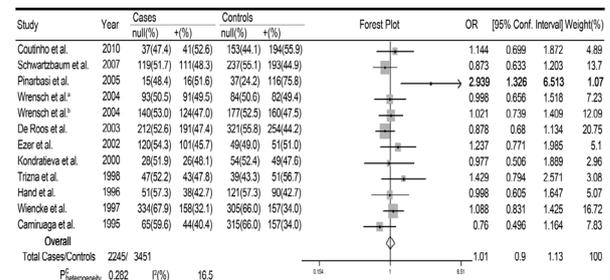


Figure 2. Forest Plot of Adult Gliomas Risk Associated with GSTM1 Polymorphism (Wild type allele vs Null allele). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI. (^aseries 1: samples in this series were collected between 1991-1994 by Wrensch et al. in the San Francisco Bay Area. ^bseries 2: samples in this series were collected between 1997-2000 by Wrensch et al. in the San Francisco Bay Area. ^cP value of Q-test for heterogeneity test. Random-effects model was used when P value for heterogeneity test <0.10; otherwise, fix-effects model was used)

gliomas associated with the null genotype at the GSTM1 locus (OR, 1.008; 95% CI, 0.901-1.129; P heterogeneity, 0.282; I square, 16.5%). None of the single-study ORs was significant, except one small study conducted by Pinarbasi et al. (2005) (Figure 2). Overall, no strong association was found between the GSTT1 null genotype and the development of an adult glioma in nine suitable candidate studies (OR, 1.246; 95% CI, 0.963-1.611; P heterogeneity, 0.008; I square, 59.9%). Based on our forest plot analysis, there were three single studies in which the total proportion weights were all over 10%, reaching 12.07% (OR, 1.74; 95% CI, 1.15-2.64, from Wrensch et al. (2004) series 2 in which samples were collected between 1997-2000), 10.12% (OR, 2.07; 95% CI, 1.22-3.51, from Hand et al. (1996)), and 11.24% (OR, 2.09; 95% CI, 1.32-3.32, from Camiruaga et al. (1995)) (Figure 3). We also found no apparent evidence of an association of the GSTP1 Ile105Val polymorphism with an increased risk of glioma in the subjects of seven studies (OR, 1.061; 95% CI, 0.653-1.724; P heterogeneity,

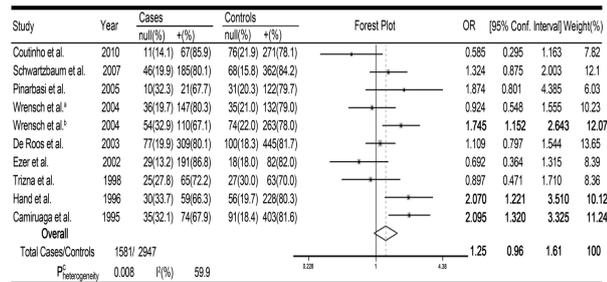


Figure 3. Forest Plot of Adult Gliomas Risk Associated with GSTT1 Polymorphism (Wild type allele vs Null allele). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI. (^aseries 1: samples in this series were collected between 1991–1994 by Wrensch et al. in the San Francisco Bay Area. ^bseries 2: samples in this series were collected between 1997–2000 by Wrensch et al. in the San Francisco Bay Area. ^cP value of Q-test for heterogeneity test. Random-effects model was used when P value for heterogeneity test <0.10; otherwise, fix-effects model was used)

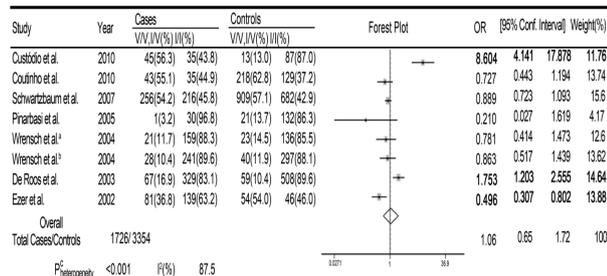


Figure 4. Forest Plot of Adult Gliomas Risk Associated with GSTP1 Ile105Val (V/V, I/V vs I/I). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI. (^aseries 1: samples in this series were collected between 1991–1994 by Wrensch et al. in the San Francisco Bay Area. ^bseries 2: samples in this series were collected between 1997–2000 by Wrensch et al. in the San Francisco Bay Area. ^cP value of Q-test for heterogeneity test. Random-effects model was used when P value for heterogeneity test <0.10; otherwise, fix-effects model was used)

<0.001; I square, 87.5%). Similarly, single papers (from Custodio et al. (2010), De Roos et al. (2003) and Ezer et al. (2002)) contained significant data, and their weight contributions for overall analysis were 11.76% (OR, 8.60; 95% CI, 4.14–17.88), 14.64% (OR, 1.75; 95% CI, 1.20–2.55), and 13.88% (OR, 0.50; 95% CI, 0.31–0.80) respectively (Figure 4).

Publication bias

As shown in Figure 5, Begg’s funnel plot and Egger’s test were both performed to assess any potential publication bias of the included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models; therefore, an Egger’s test was used to provide statistical evidence of the funnel plot symmetry. As expected, the results still did not show any evidence of publication bias (t, 2.25; P, 0.048; 95%CI, 0.019-3.811 for GSTM1; t, -0.690; P, 0.509; 95%CI, -5.915-3.186 for GSTT1; t, 0.260; P, 0.803; 95%CI, -4.813-5.960 for GSTP1).

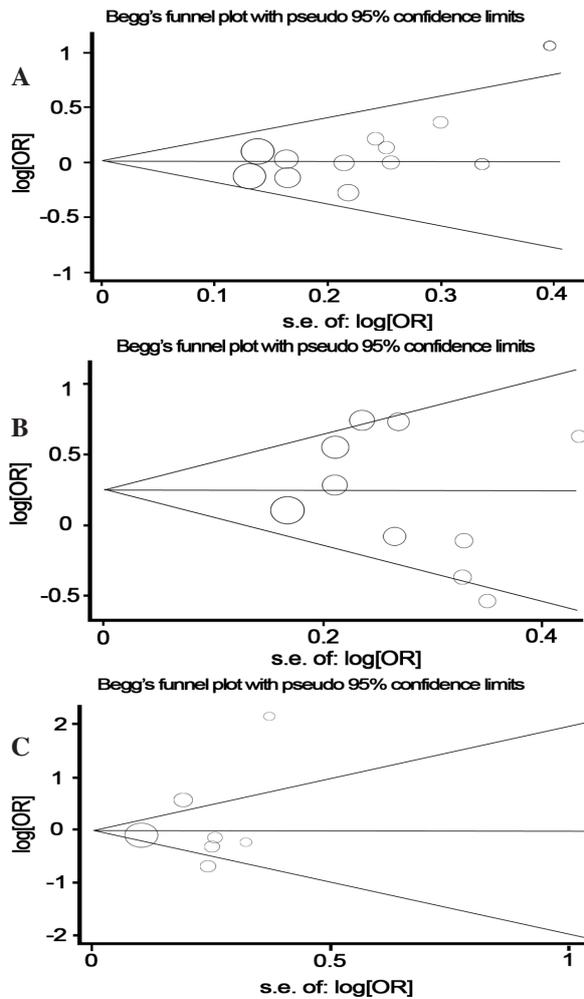


Figure 5. Begg’s Funnel Plot for Publication Bias Test of GSTM1, GSTT1, GSTP1 Ile105Val. Each point represents a separate study for the indicated association. log(OR), natural logarithm of odds ratio. Horizontal line, mean effect size. (a: Begg’s funnel plot for publication bias test of GSTM1; b: Begg’s funnel plot for publication bias test of GSTT1; c: Begg’s funnel plot for publication bias test of GSTP1 Ile105Val)

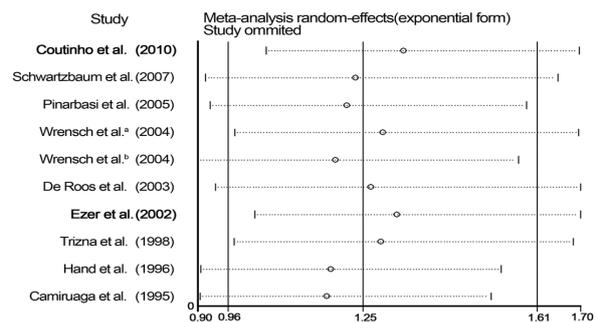


Figure 6. The Sensitivity Analysis in the Studies of association Between GSTT1 Polymorphism and Risk of Adult Gliomas (^aseries 1: samples in this series were collected between 1991–1994 by Wrensch et al. in the San Francisco Bay Area; ^bseries 2: samples in this series were collected between 1997–2000 by Wrensch et al. in the San Francisco Bay Area)

Sensitivity analysis

As shown in Figure 6, sensitivity analyses of GST polymorphisms indicated that two independent studies by Coutinho et al. (2010) and Ezer et al. (2002), with weight contributions of 7.82% and 8.39%, respectively,

were the main origin of the lack of significance in the analysis of association between a GSTT1-null genotype and adult gliomas. If these two studies were excluded, an association between a GSTT1-null genotype and glioma risk would be observed (pooled OR, 1.415; 95% CI, 1.121–1.786; P heterogeneity, 0.076; I square, 45.4%). However, there was no single study that influenced the pooled OR qualitatively, as indicated by sensitivity analyses in the analysis regarding the association between GSTM1 or GSTP1 and the development of adult gliomas, suggesting that the results of these two meta-analyses are reproducible.

Discussion

Although gliomas are one of the most common malignancies in the CNS worldwide, their pathogenesis and the molecular genetic events that contribute to their development are both poorly understood. While a trend for GST-related genetic contributions to glioma development was suggested in some of the data for a subset of the three polymorphisms, this trend has not been validated by subsequent research on much larger samples from different locations. Previous meta-analyses of these GST polymorphisms were extensively studied in terms of susceptibility for other malignancies. Some studies have found negative results for association with breast and colon cancer (Cotton et al., 2000; da Fonte et al., 2002), whereas other studies have suggested the possibility of a modest association with head and neck, lung, and bladder cancer (Cabelguenne et al., 2001; Geisler and Olshan, 2001; Engel et al., 2002; Alexandrie et al., 2004). Nevertheless, even in the latter cases, the summary ORs have been small (in the range of 1.17-1.44).

In our study, focusing on risks of adult gliomas, superior to the previous meta-analysis, the current evidence compiled from 2,245 glioma cases and 3,451 controls; 1,581 glioma cases and 2,947 controls; and 1,726 glioma cases and 3,354 controls, is much more powerful to reveal that there is no significant increased risk for developing an adult glioma conferred by the common GST polymorphisms GSTM1, GSTT1, and GSTP1 respectively, although some statistics in latest published papers showed certain GST genotype polymorphism associated with risks of adult gliomas. It is plausible to hypothesize that the GST polymorphisms as one of low-penetrance susceptibility genes are unlikely direct prognostic candidates for susceptibility genes since they are common whereas most susceptibility genes identified thus far are rare and highly penetrant. However, while individuals with alterations of these rare genes (e.g., tumor suppressor genes) have a dramatically higher risk of cancer, more common differences in low-penetrance susceptibility genes (e.g., xenobiotic metabolism genes) could be responsible for a relatively small but presumed increase in the risk of developing adult gliomas in combination with GST genotype polymorphisms (Taningher et al., 1999; Boccia et al., 2006). Therefore, based on the latest statistics from GST-related studies after 2005, we expect further studies can involve more samples detected by different GST genotypes simultaneously

in order to find out whether there were synergy effect among them. A third potentially important finding was that, in our assessment of the association between a GSTT1-null genotype and adults with gliomas, two independent studies by Coutinho et al. (2010) and Ezer et al. (2002) with weight contributions of 7.82% and 8.39% respectively, were statistically analyzed to determine that patients who carried the GSTT1 null genotype had no increased risk of developing gliomas (Figure 6). In addition, a similar phenomenon was not observed in the GSTM1 and GSTP1 polymorphism analysis. It may suggested well-designed studies of combination with GST genotype polymorphisms analysis are needed to confirm these results. These findings and hypothesis deduced from the objective phenomenon above in our pooled analysis, distinguishable from previous meta-analysis, are suppose to give some new directions or introductions not only for clinical specialists but for next researchers with details, for example, collecting patients well-rounded information or target genotypes selection, in the realm of GST genotypes and glioma risks.

Some analytic issues should also be considered. Unfortunately, the main limitations of the study that have to be considered in interpreting the results were that there were no stratified analysis with ethnic groups or with regard to smoking history because of the lack of detailed numbers in eligible studies (even if the original reports have the relevant statistical analysis and stratified results). The lack of information regarding race and tobacco use might have affected our pooled meta-analysis results on the association between glioma susceptibility and GSTM1, GSTT1, and GSTP1 variants. Moreover, we could not address gene-gene and gene-environmental interactions. The latter may be important for genes that code for proteins with detoxifying functions, but this analysis would require detailed information on exposure to various potential carcinogens and individual-level data that are strong risk factors for the disease (Ioannidis et al., 2002; Ntais et al., 2005). In addition, due to lack of detailed specific glioma classification information from most of the published articles, our pooled analysis failed to reveal the associations of GST genotypes with different histopathological classes in adult gliomas. Further studies are necessary to better clarify the role of GSTM1, GSTT1, and GSTP1 polymorphisms in adults glioma susceptibility by ethnic groups, smoking history, and histopathological classes. Finally, only studies published in English were included and selection bias could have occurred as a result. The design of prospective cohort study in the further studies may compensate the selection bias in retrospective case-control studies.

In conclusion, this pooled analysis provides strong evidence that GSTs do not play a major role in the susceptibility to gliomas in adults. Furthermore, future studies should include a combination with GST genotype polymorphisms and clear ethnic classifications to validate these results, which also need to be replicated in different histopathological classes of gliomas. Finally, large-sample studies using standardized unbiased methods, enrolling precisely defined cancer patients and well-matched controls, and containing more detailed individual data are

needed to confirm these results.

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