Genetic Polymorphisms of Glutathione *S*-Transferases and the Risk of Adult Brain Tumors: A Meta-analysis

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Abstract

Background: **Studies investigating the association between genetic polymorphisms of glutathione *S*-transferases (*GST*) and risk of adult brain tumors have reported conflicting results. The rationale of this meta-analysis was to determine whether *GST* variants increase the susceptibility of adult brain tumors by pooling data.**

Methods: **Two investigators independently searched the HuGENet database, MEDLINE, EMBASE, conference articles, and manually reviewed bibliographies of retrieved articles. Papers were included if they were observational studies investigating the influence of *GSTM1*, *GSTT1*, *GSTP1 I105V*, or *GSTP1 A114V* on the development of adult brain cancers. Potential sources of heterogeneity between studies were explored in a meta-regression.**

Results: **We identified eight eligible studies, which included 1,630 cases of glioma, 245 cases of meningioma, and 7,151 controls. Using the random effects model, there was no association between any of the *GST* variants and the risk of glioma [overall odds ratio (OR), 1.08; 95% confidence interval (95% CI), 0.95-1.22]. Subgroup analyses also showed no relationship between *GST* variants and histopathologic groups; the overall ORs were 1.13 (95% CI, 0.88-1.43) for high-grade glioma and 1.08 (95% CI, 0.76-1.55) for low-grade glioma. A random effects meta-regression suggested that the use of in-hospital controls produced larger effect estimates in glioma than the use of population controls (overall OR, 1.30; 95% CI, 1.03-1.65). The *T1* null genotype was significantly associated with a risk of meningioma (OR, 1.95; 95% CI, 1.02-3.76), but the *M1* variant was not.**

Conclusion: **This study did not suggest any relationship between *GST* variants and risks of glioma; the *T1* null genotype may influence the susceptibility of meningioma, but larger studies are needed to substantiate this relationship.** (Cancer Epidemiol Biomarkers Prev 2005;14(7):1784–90)

Introduction

Except ionizing radiation, no environmental carcinogens have been firmly associated with the etiology of brain tumors. Studies in rats showed that brain tumors can be induced by various carcinogenic substances (1, 2), but observational studies in human showed no definitive association between occupational or environmental exposures and brain tumor incidence (3, 4). These negative findings may reflect the difficulty in characterizing exposure, particularly as a dose-response relationship. In addition, many individuals could be exposed to multiple rather than single toxic agents over time. Therefore, some investigators have turned to study genetic associations, such as genes involved in metabolizing chemicals [i.e., glutathione *S*-transferases (*GST*)], because genotype measurements are less prone to recall bias.

The GSTs are involved in phase II detoxification that protects cells from attack by reactive electrophiles (5). They catalyze the conjugation of glutathione to electrophilic species (such as chemical carcinogens and cytotoxic chemotherapeutic agents), which is the first step that leads to the elimination of toxic compounds. Although polymorphisms have been described in several of *GST* gene families, most attention has focused on allelism in *GSTμ* (*GSTM1*), *GSTθ* (*GSTT1*), and *GSTπ* (*GSTP1;* refs. 5, 6). *GSTM1* and *GSTT1* homozygotes (null genotype) have no enzymatic activities. *GSTP1* has two polymorphisms: *I105V* and *A114V*, and evidence suggests that individuals with the *I105V Val/Val* allele may have lower affinity for electrophilic substrates and heat stability compared with the wild type (7, 8).

Because genetic variants of *GSTs* may reduce the cell's ability to metabolize toxins, their associations with cancers have been investigated extensively in epidemiologic studies (9-15). Likewise, there have been a number of reports on the relationship between *GST* variants and risk of brain cancers, but the results were conflicting. Brain tumors are uncommon cancers in adults, and recruiting sufficient subjects into case-control studies takes a lengthy period of time. As a first step to resolve these inconsistent findings, we did a meta-analysis. By pooling studies together, we also hope to increase the power of observing a small to moderate association.

Materials and Methods

Study Selection and Quality Assessment. We searched the HuGENet database (last search January 2005), MEDLINE, and EMBASE (January 1980 to January 2005) using these terms: glutathione *S*-transferase, glioma, brain tumors, gene, and allele. We also did manual searches of bibliographies of retrieved articles and conference abstracts in the past 3 years (American Association of Cancer Research and Society of Neuro-oncology). Two investigators (R.L. and L.C.) independently searched and reviewed abstracts in duplicate to determine if they met inclusion and exclusion criteria; any discrepancies were resolved through discussion. We considered all languages. When there were several publications for the same population, we used the most updated article. Articles were included if they fulfilled the following inclusion criteria: (a) observational studies that investigated the associations of GST variants and risk of adult brain tumors, focusing on polymorphisms in *GSTM1*, *GSTT1*, and *GSTP1*; (b) presentation of data necessary for the calculation of odds ratios (OR). The exclusion criteria were (a) studies that used

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Table 1. Characteristics of studies on GST and risk of brain tumors

Study (first author)	Year of publication	Country	Types of brain tumor	Cases (*n*)*	Controls (*n*)*	Matching	Matching variables
Pinarbasi	2005	Turkey	Glioma and meningioma	Glioma, 31; meningioma, 23	153	Frequency	Age, gender
Wrensch	2004	U.S.A.	Glioma	458	428	Frequency	Age, race, gender
Butler	2003	U.S.A.	Glioma	325	579	Frequency	Age, gender
De Roos	2003	U.S.A.	Glioma, meningioma, and acoustic neuroma	Glioma, 422; meningioma, 172; acoustic neuroma, 79	604	Frequency	Hospital, age, gender, race, distance from home to hospital
Ezer	2002	U.S.A.	Glioma and neuroepithelial tumors	Glioma, 141; neuroepithelial tumors, 76	653-1,709§	None	None
Kondrateva	1999	Russia	Glioma	54	103	None	None
Trizna	1998	U.S.A.	Glioma	90	90	Frequency	Age, race, gender
Elexpuru-Camiruaga	1995	Great Britain	Glioma and meningioma	Glioma, 109; meningioma, 50	577	None	None

Abbreviations: GBM, glioblastoma mutiforme; A, astrocytoma; AA, anaplastic astrocytoma; ODG, oligodendroglioma; OA, oligoastrocytoma.
*The number of subjects with genotypes.
†Significant interaction of *GSTT1* and *P53* in patients with glioblastoma multiforme.
‡Significant interactions between *GSTP1 I105V* and *A114V* in glioma, *I105V* and *CYP2E12* in glioma and acoustic neuroma.
§The authors used healthy controls published in the literature; *GSTM1*: 1473, *GSTT1*: 782, *GSTP1 I105V*: 1709, *A114V*:653.
‖Significant interaction.

GST polymorphisms to predict survival in brain tumors and (b) investigations of *GST* variants as markers for response to therapy.

Two investigators (R.L. and L.C.) independently assessed methodologic quality by using a set of published criteria for observational studies and abstracted data into standardized data collection forms (4). Any disagreements were resolved by consensus and reference to the articles. Papers were rated according to four areas: (a) quality of reporting, (b) confounding, (c) bias, and (d) external validity. We did not apply weights in the analysis based on rating scores but excluded studies in the sensitivity analysis based on methodologic weakness identified during the assessment.

For each included study, the following information was recorded: the year of publication, the country of origin, types of brain tumor, the number of cases and controls for each tumor type, matching variables, sources of the control population, the number of cases and controls with the variant allele and the wild type, histopathologic subgroups, techniques of genotyping, and the testing of gene-gene and gene-environment interactions.

Meta-analysis. We calculated the pooled ORs and the 95% confidence intervals (95% CI) separately for *GSTM1*, *GSTT1*, *GSTP I105V*, and *GSTP A114V*. We did not pool the adjusted ORs because studies either did not adjust for confounders, or the adjustments were not comparable among them. We did a test of homogeneity for each *GST* variant and set the critical value of *P* at 0.2 to avoid underestimating the presence of heterogeneity. Because there are greater potentials for bias and confounding in case control studies, we chose the random effects model (DerSimonian and Laird) to pool data (16).

Important sources of heterogeneity were further investigated in subgroups defined a priori. Some studies suggested that *GST* variants may preferentially influence the development of malignant glioma (17); therefore, we evaluated subgroups based on histopathology. We used three classifications: glioblastoma multiforme versus other histologies, high-grade glioma (WHO grade 3 and 4) versus low-grade glioma (WHO grade 1 and 2), and astrocytic (anaplastic astrocytoma or low-grade astrocytoma) versus oligodendroglial tumors (anaplastic oligodendroglioma, low-grade oligodendroglioma or mixed oligoastrocytoma). Other sources of heterogeneity were the type of control population and the study size. Hospital controls, in contrast to population controls, may give different estimates of the genotype-disease association, because the prevalence of their alleles may differ from that of the general

Table 2. Distribution of *GSTM1*, *GSTT1 GSTP1 I105V*, *and A114V genotypes* among brain tumors cases and controls

First author	Brain tumor type	% *GSTM1* null		% *GSTT1* null		% *I105V Val/Val*		% *114 Ala/Val or Val/Val*	
		Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Pinarbasi	Glioma	48.4	24.2	32.3	20.3	3.2	13.7	—	—
Wrensch	Glioma	52.0	51.9	20.1	21.6	10.9	12.7	15.7	14.5
Butler	Glioma	50.6	50.7	17.2	14.6	11.5	12.9	—	—
De Roos	Glioma	52.6	55.8	19.9	18.4	16.9	10.4	14.6	13.5
Ezer	Glioma	51.8	49.0	14.9	18.1	4.3	10.1	9.9	14.0
Kondrateva	Glioma	52.0	52.0	—	—	—	—	—	—
Trizna	Glioma	52.2	43.3	27.8	30.0	—	—	—	—
Elexpuru- Camiruaga	Glioma	59.6	54.6	32.1	18.4	—	—	—	—
Pinarbasi	Meningioma	47.8	24.2	26.1	20.3	8.7	13.7	—	—
De Roos	Meningioma	49.7	55.8	23.9	18.4	7.1	10.4	12.4	13.5
Elexpuru-Camiruaga	Meningioma	55.1	54.6	44.7	18.4	—	—	—	—
De Roos	Acoustic neuroma	53.4	55.8	15.7	18.4	12.5	10.4	13.7	13.5
Ezer	Neuroepithelial tumor	57.9	49.0	10.7	18.1	5.3	10.1	19.7	14.0

Table 1. Characteristics of studies on GST and risk of brain tumors (Cont'd)

Source of control	*GST M1*	*GST T1*	*GSTP I105V*	*GSTP A104V*	Glioma histopathologic subgroups studied	Gene- gene interaction	Gene- environment interaction
Hospital	X	X	X		None	None	*M1, T1* and *P1 I105V* with smoking
Population	X	X	X	X	(a) GBM versus others; (b) GBM, A and AA, ODG and OA, others	*P53 + M1, T1, P1*[†]	None
Population	X	X	X		GBM, A, ODG	None	*GST* variants with living on farm status, smoking and pesticides used
Hospital	X	X	X	X	GBM, AA Other A, ODG, Mixed OA	*I105V + A114V; I105 V + CYP2E1; I105V + T1; T1 + CYP2E1*[‡]	None
Population	X	X	X	X	AA, ODG, OA	None	None
Hospital-healthy	X				High versus low grade glioma	*M1 + L-MYC*	None
Hospital-healthy	X	X			None	*T1 + NAT2*[‖]	None
Hospital	X	X			High versus low grade glioma	*T1 + CYP2D6*	None

population (18). In addition, smaller case-control studies tend to produce larger effect size (19). Therefore, we did a random effect, multivariable meta-regression using the control source and the study size as predictors of heterogeneity. In this analysis, hospital controls were either patients or healthy blood donors/visitors recruited within a hospital setting, whereas population controls were selected through population-based sampling methods (0 = population, 1 = hospital). We coded studies with fewer than 100 cases as small and >100 as large (0 = small, 1 = large).

Publication bias was evaluated by the Egger's and Begg's funnel plot asymmetry tests (20, 21). All statistical analyses were done using Stata statistical software, version 8.2.

Results

Study Characteristics. A total of 95 abstracts were retrieved through MEDLINE, EMBASE, the HuGENet database, conference abstracts, and bibliographies of retrieved articles. Eighty-four of them were excluded based on inclusion and exclusion criteria. The articles of 11 of them were further reviewed (22-32). Three of the 11 were based on the same patient population (25, 29, 30), and the most updated series was used. We further excluded one article because it was a duplicate of another (26, 27). The final number of included publications was eight, with 1,630 cases of glioma, 245 cases of meningioma, and 7,151 controls. One of the eight was an abstract judged to have sufficient details for data pooling (32). Study characteristics were summarized in Table 1. All studies were published after 1990. Five were conducted in the United States; seven were published in English and one in Russian (translated into English for assessment). All articles investigated the association between *GST* polymorphisms and the risk of glioma; three studied this relationship in meningioma. It was not possible to do meta-analyses for acoustic neuroma and neuroepithelial tumors because there was only one study for each of them. Five studies used frequency matching, whereas the other three did not match their cases and controls. Age and sex were the common matching factors. Five studies recruited hospital controls, with three of the five from in-hospital patients. All eight studies genotyped the variant allele *GSTM1*; seven examined *GSTT1* and the five most recent series also investigated *GSTP1*. All studies used PCR-based method for genotyping. Five of the eight tested for gene-gene interactions, whereas only two examined gene-environment interactions.

Table 2 summarized the genotype frequencies of brain tumor cases and controls. The distribution of *GST* variants in the Turkish study was different from the others (31); this is most noted for the frequency of *GSTM1* null genotype in the

Table 3. Sensitivity analyses of glioma and *GST* variants

GST genotype variants	Exclusion of one study that did not recruit its own control group			Exclusion of one study with results that were outliers		
	No. studies	*n* (Ca/Co)	Pooled OR (95% CI)	No. studies	*n* (Ca/Co)	Pooled OR (95% CI)
GSTM1	7*	1,479/2,609	1.08 (0.90-1.31)	7*	1,589/3,929	0.98 (0.87-1.11)
GSTT1	6[†]	1,424/2,424	1.22 (0.94-1.58)	6[†]	1,534/3,053	0.90 (0.70-1.15)
GSTP1 I105V	4[‡]	1,227/1,832	1.00 (0.60-1.65)	4[‡]	1,337/3,388	1.10 (0.66-1.82)
GSTP1 A114V	2[§]	874/1,095	1.10 (0.85-1.42)	3[‖]	1,015/1,748	1.02 (0.80-1.30)

Abbreviations: Ca/Co, cases/controls; *n*, number of subjects with particular genotypes.
*Included (22, 23, 26, 28, 30-32).
†Included (22, 23, 28, 30-32).
‡Included (22, 30-32).
§Included (22, 30).
‖Included (22, 24, 30).

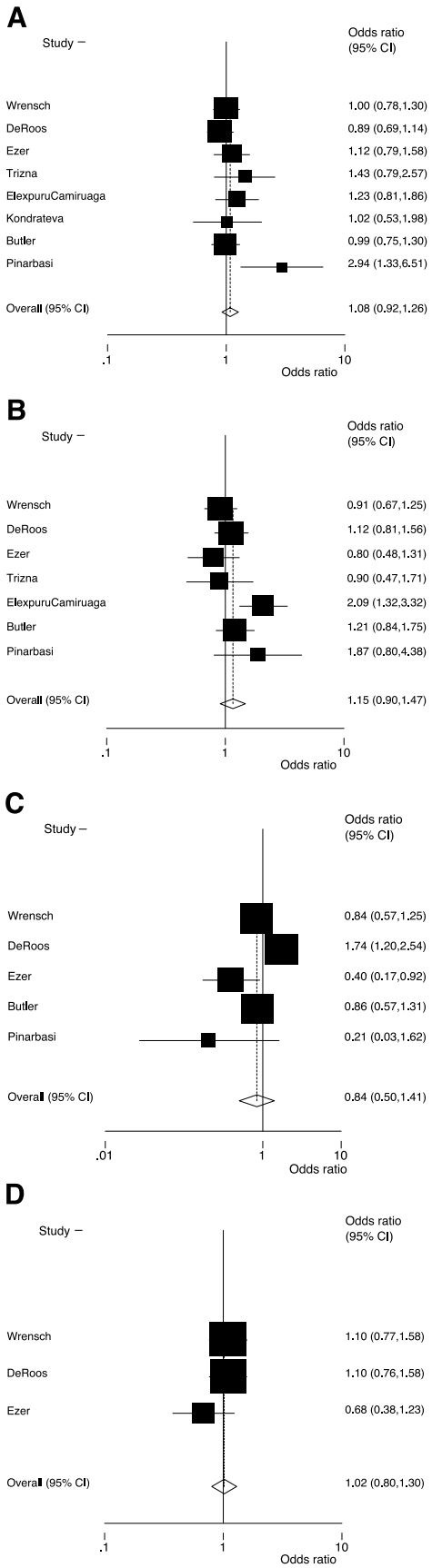

Figure 1. A. Meta-analysis of *GSTM1* and risk of glioma. **B.** Meta-analysis of *GSTT1* and risk of glioma. **C.** Meta-analysis of *GSTP1 I105V* and risk of glioma. **D.** Meta-analysis of *GSTP1 A114V* and risk of glioma.

control group, which differed significantly from that of the healthy Turkish population (33). Because their results represented outliers, we excluded this article in a sensitivity analysis (Table 3). The conclusion, nevertheless, is robust for glioma even when this article was not included.

Quality Assessment of Studies. The inter-rater agreement for quality assessment was very good (Cohen's $\kappa = 0.76$). We identified several methodologic weaknesses during the assessment. In four of the eight studies, there was no demographic comparison to ascertain whether cases and controls were comparable (23, 24, 26, 28); in those that presented these data (22, 30–32), there were baseline differences between cases and controls. For example, genotyped cases were on average 5 to 6 years younger than genotyped controls in two studies (30, 31), and cases had 20% fewer men but 20% more women in another study (31).

One group of investigators did not recruit their own controls but used healthy population published in the literature as the control group (24); moreover, there was no information on their comparability. Consequently, their risk estimates might have been biased, because it is likely that these cases and borrowed ''controls'' came from different study base, geographically or temporally. After we excluded this article in the sensitivity analysis, however, the results were unchanged (Table 3).

Three of the eight studies did not adjust for potential confounders (24, 26, 31); three adjusted for all genotypes simultaneously (22, 23, 30), but there was little confounding between them. Three studies reported quality control measures for genotyping with replicates (22, 28, 30), but only one stated the reliability of their assays (22). No study mentioned blinding of the genotyping personnel. Only one investigation assessed the prevalence of *GSTP1* genotypes for departure from the Hardy-Weinberg equilibrium and showed no deviation (22). Similar calculation was impossible for *GSTM1* and *T1* genotypes because they were coded as wild type or null. No study stated whether subgroup analyses were planned a priori or on a post hoc exploratory basis. On the positive side, all had histologic confirmation of their cases.

Meta-analysis of *GST* Variants and Glioma. The results of this meta-analysis in glioma were presented in Fig. 1A-D. We found significant tests of homogeneity for *GSTM1* ($\chi^2 = 10.16$, $P = 0.18$), *GSTT1* ($\chi^2 = 12.53$, $P = 0.05$), and *GSTP1 I105V* ($\chi^2 = 16.69$, $P = 0.002$). Using the random effects model, none of the four *GST* variants showed a significant association with glioma. For histopathologic subgroup evaluations, none of the variant alleles was associated with glioblastoma multiforme versus other histologies, high-grade glioma versus low-grade glioma, and astrocytic versus oligodendroglial tumors. The results were shown in Table 4A and B.

In the random effects meta-regression, the use of hospital controls produced a significantly stronger association than the use of population controls in the *P1 I105V* variant (Table 5). For the *M1* variant, smaller studies found significantly larger effect estimates; in contrast, larger studies seemed to detect a bigger effect in the *P1 I105V* variant, but the CI was wide because there were few data points in that category. Overall, the control source but not the study size was a predictor of the between study heterogeneity when all genotypes were combined. The between study variance τ^2 was reduced from 0.039 to 0.020 after accounting for both predictors. Two of the five studies' hospital controls were healthy subjects (26, 28). When we compared only diseased hospital controls with population controls in our regression model, the control source was still a significant predictor (overall OR, 1.30; 95% CI, 1.03-1.64) but study size was not (overall OR, 0.63; 95% CI, 0.34-1.17). Likewise, we reached the same conclusion when the two studies with healthy hospital controls were analyzed as population controls (data not shown).

Table 4.

A: Subgroup analyses: GBM versus other histologies and oligodendroglial versus astrocytic tumors

Genotype variants	n* (cases/controls)	Pooled OR (95% CI)	n † (cases/controls)	Pooled OR (95% CI)
GSTM1	GBM, 410/1,107; others, 460/1,107	GBM, 1.05 (0.83-1.32); others, 0.86 (0.58-1.28)	Astro, 237/2,580; Oligo, 209/2,580	Astro, 0.98 (0.75-1.28); Oligo, 0.93 (0.52-1.68)
GSTT1	GBM, 404/1,108; others, 465/1,108	GBM, 0.96 (0.71-1.29); others, 1.05 (0.80-1.38)	Astro, 231/1,890; Oligo, 206/1,890	Astro, 0.84 (0.51-1.40); Oligo, 1.02 (0.63-1.65)
GSTP1 I105V	GBM, 445/1,100; others, 426/1,100	GBM, 1.15 (0.57-2.34); others, 1.28 (0.62-2.68)	Astro, 236/2,809; Oligo, 208/2,809	Astro, 0.86 (0.34-2.20); Oligo, 0.89 (0.49-1.63)
GSTP1 A114V	GBM, 415/1,095; others, 459/1,095	GBM, 1.10 (0.80-1.52); others, 1.10 (0.80-1.50)	Astro, 237/1,993; Oligo, 184/1,993	Astro, 1.08 (0.64-1.82); Oligo, 1.29 (0.70-2.39)

B: Subgroup analyses: high-grade versus low-grade glioma

Genotype variants	No. studies	n (cases/controls)	Pooled OR (95% CI)
GSTM1	4 ‡	HGG, 470/2,757; LGG, 176/2,757	HGG, 1.07 (0.87-1.31); LGG, 1.17 (0.58-2.39)
GSTT1	3 §	HGG, 429/1,880; LGG, 149/1,880	HGG, 1.34 (0.78-2.33); LGG, 1.07 (0.61-1.87)
GSTP1 I105V	2 ‖	HGG, 343/2,313; LGG, 136/2,313	HGG, 1.07 (0.25-4.67); LGG, 0.60 (0.14-2.61)
GSTP1 A114V	2 ¶	HGG, 346/1,257; LGG, 112/1,257	HGG, 0.91 (0.51-1.62); LGG, 1.39 (0.57-3.39)

Abbreviations: n, number of subjects with the particular genotype; GBM, glioblastoma multiforme; Astro, astrocytic tumors; Oligo, oligodendroglial tumors; HGG, high-grade gliomas; LGG, low-grade glioma.
*The number of cases and controls was based on two studies (22, 30).
†The number of cases and controls was based on three studies (22, 24, 30).
‡Included (22-24, 26).
§Included (22-24).
‖Included (22, 24).
¶Included (22, 24).

Use of either the Begg's (rank correlation test) or Egger's funnel plot asymmetry test (regression method) did not reveal any significant publication bias. Begg's test score = −1 (SD = 5.32, P = 0.85); the Egger's test β coefficient = 0.28 (95% CI, −0.23 to 0.80; P = 0.20).

Meta-analysis of *GST* Variants and Meningioma. Three studies investigated the association among *GSTM1*, *GSTT1*, and the risk of meningioma (Table 6). The test of homogeneity was significant for both the *M1* and *T1* variants (χ^2 = 6.31, P = 0.043 and χ^2 = 6.15, P = 0.046, respectively). Using the random effects model, the result for *GSTM1* was not significant, but there was a significant increase in risk associated with *GSTT1*. When we excluded the Turkish study with outlier data in a sensitivity analysis, there was only a trend of association between *GSTT1* and meningioma (OR, 2.20; 95% CI, 0.89-5.39; P = 0.08). In the meta-regression analyses, study size was not associated with estimates of effect in either variant allele. We were unable to investigate the control source as a predictor because all three studies used hospital controls.

Discussion

This meta-analysis did not find any association among *GSTM1*, *T1*, *P1* (*I105V* and *A114V*), and a risk of glioma; subgroup analyses also did not reveal any influence of *GST* polymorphisms on histopathologic subtypes of glioma. Perhaps these negative results support recent evidence that *GST* genotypes may not be accurate predictors of tissue-specific *GST* expression (34). Although *GSTM1*, *T1*, and *P1* are all expressed in the brain, P1 is the most predominant enzyme and was hypothesized to play a critical role in protecting the brain from toxic compounds (35, 36). But if the *P1* genotype obtained from the peripheral blood does not correspond to *P1* expression in the brain, we may observe no consistent relationship between this variant and brain tumors.

Although this is the first full-length meta-analysis of *GST* variants and brain tumors, there has been an abstract presented recently on the same topic (37). In that meta-analysis, the authors suggested that *GSTT1* null and *GSTP1* ^{105}*Val/Val* were risk factors for glioblastoma multiforme (OR, 1.41; 95% CI, 1.06-1.87 and OR, 1.77; 95% CI, 1.21-2.59, respectively), and *GSTT1* null was a risk factor for meningioma (OR, 1.98; 95% CI, 1.35-2.90). There was not enough detail in their presentation to ascertain why some of their results were different from ours. However, the authors included two earlier series along with the updated study (25, 29, 30). Because the participants were overlapping, inclusion of all three articles might have resulted in overrepresentation of the same data.

Similar to that abstract, we found a significant relationship between *GSTT1* null genotype and a risk of meningioma. The pooled estimate, however, was based on only three hospital-based studies, and the association was no longer significant after a sensitivity analysis. Therefore, we still need further investigations, especially larger population-based studies, to substantiate our findings.

Our results showed that there were some demographic differences between cases and controls. Genotyped cases (ascertained by a cancer registry) were on average 5 to 6 years younger than genotyped controls in one study due to delay in

Table 5. Results of the meta-regression

Predictors	Types of brain tumors	*GSTM1*, OR (95% CI)	*GSTT1*, OR (95% CI)	*GSTP1 I105V*, OR (95% CI)	*GSTP1 A114V*, OR (95% CI)	All genotypes combined, OR (95% CI)
Control source	Glioma	0.95 (0.72-1.24)	1.51 (0.58-2.63)	2.22 (1.40-3.53)	1.18 (0.61-2.26)	1.30 (1.03-1.65)
Study size	Glioma	0.64 (0.41-0.99)	1.22 (0.58-2.58)	8.32 (1.04-16.52)	—*	0.93 (0.64-1.36)
	Meningioma	0.52 (0.23-1.35)	0.57 (0.17-1.97)	—	—	0.56 (0.23-1.35)

*All studies have >100 cases.

Table 6. Meta-analysis of *GST* variants and meningioma

GST genotype variants	No. studies	*n* (cases/controls)	Pooled OR (95% CI)	*P*
GSTM1	3*	244/1,334	1.20 (0.66-2.16)	0.56
GSTT1	3 †	242/1,251	1.95 (1.02-3.76)	0.046

*Included (22, 23, 31).
†Included (22, 23, 31).

blood sample collection, sometimes up to 6 months after diagnosis, and specimens could not be obtained from cases with the poorest survival (30). This problem raises the possibility of case selection bias, as there is evidence to suggest that *GSTM1* null genotype is associated with time to specimen collection (from diagnosis) and longer case survival (30, 38). Another group used hospital cases shortly after diagnoses were made, thus minimizing the problem of selection bias from case survival (22). However, brain tumor patients were still on average older and more highly educated than controls. Studies that did not attempt matching may suffer potential biases induced by population stratification (24, 26, 28), as cases and controls could have different allele frequencies attributable to diversity in ethnic background but unrelated to disease status (39).

Our study has limitations. Meta-analysis of case-control studies is vulnerable to biases and confounding issues inherent in the original articles; therefore, study quality assessment and evaluation of heterogeneity are crucial. Results of the meta-regression suggested that the use of hospital controls produced stronger genotype-disease associations than the use of population controls. Perhaps, variant alleles were represented less frequently, or the wild-type alleles were found more often among in-hospital patients, and consequently, the estimates were biased away from the null. For example, *GSTT1* wild types were often found in smokers with coronary artery disease and in patients with acute pancreatitis; the *I105V Val/Val* allele is uncommon in asthmatics (40-42).

There are other potential sources of heterogeneity, but because some factors were evaluated in only one study, we were unable to explore them further in subgroup analyses or meta-regression. For example, age is a modifying factor of genotype expression (43), but only one study reported genotype-brain tumor associations stratified by age groups (22). Furthermore, *GST* variants show substantial variations in prevalence based on ethnic groups (44), but there were so few non-Caucasian patients in brain tumor cases that no study explored ethnicity as subgroups or did stratified analyses.

A meta-analysis of gene-gene interactions was not possible here, because no study reported the same interaction pairs, although five of the eight tested them. Some interactions were statistically significant (Table 2 footnote), but these results could be due to chance because the comparison groups involved very few subjects.

Only two epidemiologic studies in brain tumors investigated gene and environment interactions and found nonsignificant results (31, 32). Another study is under way in the United States (45). Given the results of this meta-analysis, *GST* variants by themselves are unlikely to be strong determinants of the susceptibility of glioma; however, whether they may act in synergy with other genes or environmental factors is the question for future studies.

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