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Association of *p53* Arg72Pro and *MDM2* SNP309 polymorphisms with glioma

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ABSTRACT. Epidemiological studies of the association of variants *p53* Arg72Pro and *MDM2* single-nucleotide polymorphism 309 (SNP309) with glioma risk have produced inconsistent results. The aim of the current study was to evaluate the association of these 2 variants with glioma susceptibility using a meta-analysis approach. For *p53* Arg72Pro, 10 case-control studies including 2587 glioma patients and 4061 unrelated controls were identified. The pooled odds ratios (ORs) for Arg/Pro heterozygotes and Pro/Pro homozygotes were 1.08 [95% confidence interval (95%CI) = 0.85-1.37] and 1.08 (95%CI = 0.85-1.36), respectively, when compared to Arg/Arg carriers. Under the dominant effect model, Pro allele carriers also showed no significantly elevated glioma risk (pooled OR = 1.11, 95%CI =

0.90-1.38), and similar results were found under the recessive-effect model (pooled OR = 1.17, 95%CI = 0.85-1.61). For variant *MDM2* SNP309, 3 case-control studies including 606 cases and 309 controls were identified. A marginal association with glioma risk was found for heterozygous G/T carriers (pooled OR = 1.95, 95%CI = 1.00-3.81), whereas homozygous G/G carriers showed an increased but not significantly elevated risk of glioma (pooled OR = 2.14, 95%CI = 0.71-6.45) compared with that of T/T homozygotes. We also found no significant association between the *MDM2* SNP309 polymorphism and glioma risk (pooled OR = 1.86, 95%CI = 0.94-3.67 and pooled OR = 1.25, 95%CI = 0.62-2.56, respectively) under the dominant and recessive models. Taken together, the current data suggested that the 2 polymorphisms may not contribute to glioma susceptibility.

Key words: *p53*; *MDM2*; Glioma risk; Polymorphisms; Meta-analysis

INTRODUCTION

Glioma is the most frequent central nervous system tumor that occurs in the brain or spine. In terms of cell type, glioma can be divided into ependymoma, astrocytoma, oligodendroglioma, and mixed glioma subtypes. According the World Health Organization classification, glioma can be categorized into 4 grades, from the least advanced disease with the best prognosis (grade I) to the most advanced disease with the worst prognosis (grade IV) (Louis et al., 2007). Environmental and genetic factors involved in the progression of glioma are not completely understood. Some studies have reported that dietary, personal, and residential exposures may lead to glioma development (Wrensch et al., 2005), whereas others have suggested that genetic alterations may be involved (Gu et al., 2009). Gene mutations such as epidermal growth factor receptor amplification or nuclear factor kappa B inhibitor alpha deletion have been reported in the development of glioma (Hunter et al., 1995; Bredel et al., 2011). Recently, genome-wide association studies have reported that single nucleotide polymorphisms (SNPs) in the loci at 5p15.33 (rs2736100, *TERT*), 8q24.21 (rs4295627, *CCDC26*), 9p21.3 (rs4977756, *CDKN2A/CDKN2B*), 20q13.33 (rs6010620, *RTEL1*), and 11q23.3 (rs498872, *PHLDB1*) are associated with glioma susceptibility (Shete et al., 2009; Wrensch et al., 2009). However, additional factors that contribute to glioma susceptibility require further investigation.

The well-known tumor suppressor gene *p53* participates in many cellular functions, including cell cycle arrest, apoptosis, DNA repair, and cell migration. Approximately half of glioma patients reportedly manifest *p53* mutations that may cause glioma (Ohgaki et al., 2004). *MDM2* is a well-known protein that negatively regulates *p53* activity and whose amplification has also been found in approximately 10-15% of malignant gliomas (Biernat et al., 1997; Suzuki and Iwaki, 2000). Because *MDM2* is an E3 ligase, its overexpression enhances the degradation of *p53* through the proteasomal pathway (Haupt et al., 1997; Kubbutat et al., 1997). *MDM2* also facilitates *p53* nuclear exportation and decreases the DNA binding ability of *p53* to its target genes, which attenuates *p53* tumor suppression in cells (Oliner et al., 1993; Kussie et al., 1996). Given the importance of *p53*

and *MDM2* in cells, many studies have been designed to evaluate the variants on these genes and their association with cancer susceptibility. Two variants, *p53* Arg/Pro and *MDM2* SNP309, have been widely studied in many types of cancer. The *p53* Arg/Pro variant displays an amino acid change at codon 72 in exon 4 and decreases the pro-apoptosis activity of *p53* (Dumont et al., 2003). *MDM2* SNP309 locates at the promoter of the gene and the T to G change increases the affinity of transcription factor *Sp1* and further enhances the transcription of *MDM2* (Bond et al., 2004).

Many studies have suggested a significant association between these variants and the risk of lung, colorectal, gastric, and other cancers (Dai et al., 2009; Liu et al., 2011). Other studies have evaluated the association between these 2 variants and glioma risk, although the results have been inconsistent. A study conducted by Parhar et al. (2005) has suggested a possible association between the *p53* Arg72Pro polymorphism and glioma susceptibility, particularly for high-grade astrocytomas. However, other studies have reported no association between the variant and glioma risk (Wang et al., 2004; Malmer et al., 2005). With respect to *MDM2* SNP309, 2 reports have found no correlation with glioma risk (El Hallani et al., 2007; Tsuiki et al., 2007), whereas a study conducted by Khatri et al. (2008) has found that allele G may be a low-penetrance susceptibility allele for glioblastoma multiforme.

Because the associations between these 2 polymorphisms and glioma risk remain elusive, we conducted a systematic assessment of published studies and a meta-analysis to evaluate the correlation of the 2 variants and glioma susceptibility. Our results show that neither of these variants has a statistically significant association with the glioma risk based on the current published data.

MATERIAL AND METHODS

Identification and selection of eligible studies

We searched the PubMed database for eligible studies that had been published online before December 2011. The terms glioma, glioblastoma, ependymocytoma, oligodendroglioma, or astrocytoma in combination with *p53*, *MDM2*, rs1042522, rs2279744, *p53* codon 72, or *MDM2* SNP309 were used to identify studies that evaluated *p53* Arg/Pro and *MDM2* SNP309 polymorphisms and glioma risk. References within the identified publications were also checked to find any studies missed in the database search.

Eligible studies included in the meta-analysis met the following criteria: 1) they assessed the association of *p53* Arg/Pro and *MDM2* SNP309 polymorphisms and the risk of glioma; 2) they provided sufficient data for the frequency of the genotypes, and 3) they were case-control, cohort, or cross-sectional studies reported in the English language.

Data extraction

Two of the authors individually reviewed the selected articles, and the details of the studies were extracted from the eligible publications: first author name, publication year, design of the study, country of origin, sample size, and genotype distribution data of the variants in the cases and controls (Tables 1 and 2).

Statistical methods

We used the Pearson chi-square test for goodness of fit to determine whether any study departed from Hardy-Weinberg equilibrium (HWE) for the genotype distribution in the control group. For each study, the association of the 2 variants and glioma susceptibility was presented as the crude odds ratio (OR) and its 95% confidential of intervals (95%CI) based on the genotype frequencies in the cases and controls. The standard inverse variance weighting method was used to calculate the pooled ORs and their 95%CIs under the fixed-effect model. The DerSimonian-Laird method (DerSimonian and Laird, 1986) was used to calculate the pooled estimate and its 95%CI under the random-effect model. We investigated the association between the 2 genetic variants and glioma risk under homozygote and heterozygote comparisons and dominant and recessive genetic models.

Heterogeneity between the studies was quantified using the Cochran Q test in combination with the I^2 statistic, which represents the percentage of variability across studies that is attributable to heterogeneity rather than to chance. Heterogeneity among studies was considered significant when P was less than 0.1 for the Q-test or when the I^2 value was greater than 25%. If significant heterogeneity was found among the studies, the overall pooled estimate under the random-effect model rather than the fixed-effect model was acceptable, and vice versa. The publication bias of the selected studies was examined with funnel plots and further assessed using the tests of asymmetry of Begg and Egger (Begg and Mazumdar, 1994; Egger et al., 1997). P values less than 0.05 were considered to be statistically significant in the meta-analysis. All the statistical analysis was performed with the R software and its Meta package (www.r-project.org).

RESULTS

Association between *p53* Arg72Pro and glioma susceptibility

We identified 10 reports that evaluated the association of *p53* Arg72Pro and glioma susceptibility (Wang et al., 2004; Parhar et al., 2005; Malmer et al., 2005, 2007; Rajaraman et al., 2007; Idbaih et al., 2008; Lima-Ramos et al., 2008; Pinto et al., 2008; El Hallani et al., 2009; and Jha et al., 2011; see Table 1). Included were 2587 cases and 4061 controls, and all data were used in the current meta-analysis. Two of the studies reported a statistically significant association between *p53* Arg72Pro and glioma risk; the others found no significant association of this allele and glioma risk (Parhar et al., 2005; Jha et al., 2011). The study conducted by Parhar et al. (2005) suggested a possible association between *p53* Arg72Pro polymorphisms and susceptibility to brain tumors, particularly for high-grade astrocytoma. The study reported by Jha et al. (2011) in an Indian population suggested a significantly increased risk for glioma associated with the Pro allele of *p53* codon 72. However, the study conducted by Jha et al. (2011) showed a significant departure of the *p53* Arg/Pro allele from HWE in the control groups (P = 0.005).

From the meta-analysis, we found that the pooled OR for heterozygous carriers of Arg/Pro was 1.08 with a 95%CI of 0.85-1.37 compared to Arg/Arg homozygous carriers under the random-effect model (Figure 1A). The fixed-effect model showed similar results (OR = 1.05, 95%CI = 0.94-1.17). The Q-test and I^2 statistic showed significant heterogeneity between studies [Q = 37.3, degrees of freedom (d.f.) = 9, P < 0.0001; I^2 = 75.9%; Table 3]. The Begg rank correlation test and the Egger linear regression test showed no published bias (P = 0.9287

and 0.7139, respectively). The pooled OR for homozygous Pro/Pro carriers was 1.08 with a 95%CI = 0.85-1.46 (Figure 1B). We also found significant heterogeneity among the studies (Q = 10.99, d.f. = 9, P = 0.2765; I^2 = 18.10%; see Table 3). No asymmetry of the funnel plot was found (Begg and Egger tests, P = 0.089 and 0.089, respectively), indicating the absence of publication bias. Under the dominant model, the pooled OR for Pro allele carriers was 1.11 (95%CI = 0.90-1.38). Under the random-effect model, significant heterogeneity among studies was found (Q = 32.48, d.f. = 9, P = 0.0002; I^2 = 72.3%; Figure 1C). Begg and Egger tests showed that no publication bias was present (P = 0.4208 and 0.3171, respectively).

Table 1. Main characteristics of the 10 studies included in the meta-analysis for *p53* Arg72Pro and glioma risk.

Study (first author, year)	Study type	Location	Sampe size (case/control)	Genotype distribution (case/control)		
				Arg/Arg	Arg/Pro	Pro/Pro
Wang, 2004	Case-control	USA	309/342	165/194	126/128	18/20
Malmer, 2005	Population-based case-control	Sweden	205/374	116/211	59/106	30/57
Parhar, 2005	Case-control	USA	135/117	38/72	94/42	3/3
Malmer, 2007	Population-based case-control	Nodic-UK	680/1555	361/801	241/556	34/104
Rajaraman, 2007	Hospital-based case-control	USA	388/553	213/300	146/209	27/38
Idbaih, 2007	Population-based case-control	France	275/144	149/87	108/49	18/8
Lima-Ramos, 2007	Hospital-based case-control	Portugal	171/526	101/298	56/197	14/31
Pinto, 2008	Population-based case-control	Brazil	94/100	53/48	34/42	7/10
Hallani, 2010	Population-based case-control	France	254/238	140/142	92/82	22/14
Jha, 2010	Population-based case-control	Indian	76/112	24/27	27/70	33/15

The recessive model also showed no statistically significant association between the *p53* Arg/Pro polymorphism and glioma risk (pooled OR = 1.17, 95%CI = 0.85-1.61; Figure 1D) for homozygous *p53* Arg/Arg carriers compared with *p53* Arg/Pro and *p53* Pro/Pro carriers. No significant heterogeneity among the studies was found, nor was significant publication bias present. The study conducted by Jha et al. (2011) showed significant departure from HWE in the meta-analysis. We repeated the meta-analysis after excluding this study, but no significant change in the overall results was found. These data together suggested that *p53* Arg/Pro is not associated with glioma risk.

Association between *MDM2* SNP309 and glioma risk

Three studies evaluating the association of *MDM2* SNP309 and glioma risk were identified in our literature search (El Hallani et al., 2007; Tsuiki et al., 2007; and Khatri et al., 2008; see Table 2). The 3 reports had recruited 606 cases and 390 controls. Among them, studies reported by El Hallani et al. (2007) and Tsuiki et al. (2007) found no significant association between the *MDM2* SNP309 variant and glioma risk. The study conducted by Khatri et al. (2008) with 98 glioblastoma multiforme patients and 102 cancer-free controls showed that allele G confers an increased risk of glioma; however, the study showed significant deviation from HWE for the allele distribution in the control group (P < 0.001).

Our meta-analysis showed that heterozygous G/T carriers had a marginally statistically significant increased risk of glioma, with a pooled OR = 1.95 (95%CI = 1.00-3.81; Figure 2A) under the random-effect model (Q = 5.63, d.f. = 2, P = 0.0598; I^2 = 64.50%; see Table 3). However, no significantly increased risk was found for homozygous G/G carri-

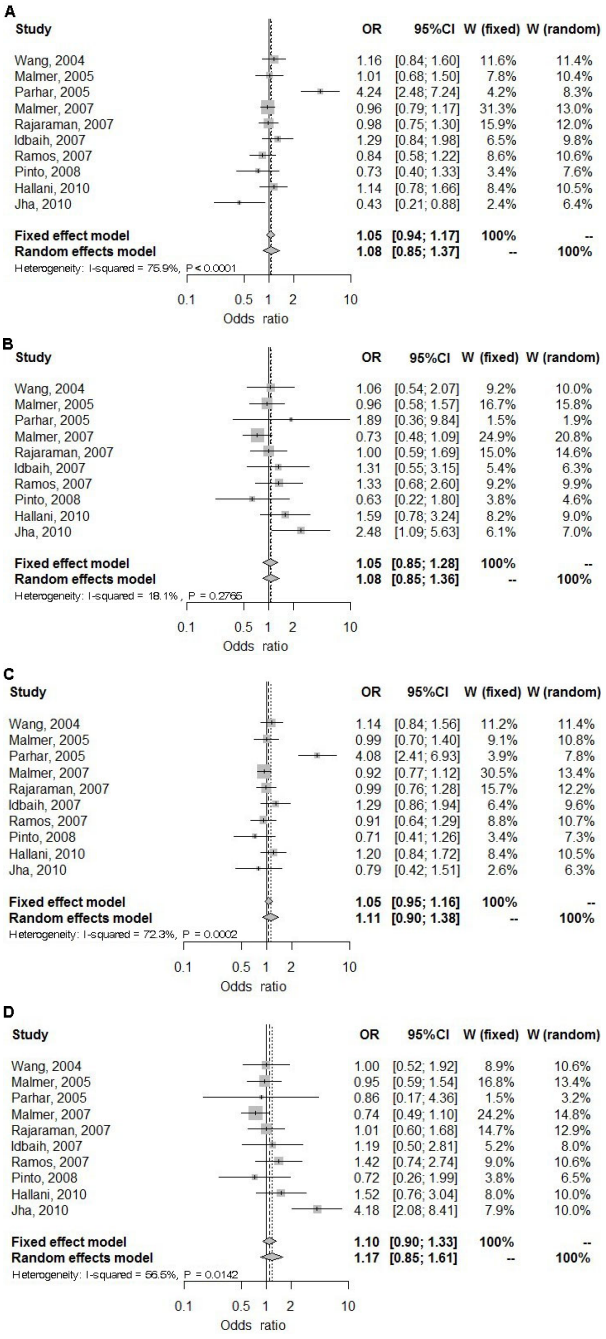

Figure 1. Forest plot of the glioma risk and the *p53* Arg72Pro for: **A.** *p53* Arg72Pro heterozygosity (Arg/Pro *vs* Arg/Arg); **B.** *p53* Arg72Pro homozygosity (Pro/Pro *vs* Arg/Arg); **C.** dominant model (Arg/Pro and Pro/Pro *vs* Arg/Arg), and **D.** recessive model (Pro/Pro *vs* Arg/Pro and Arg/Arg). The box size represents the study weight under the random-effect model. OR = odds ratio; 95%CI = 95% confidence interval.

Table 2. Main characteristics of the three studies included for *MDM2* SNP309 and glioma risk.

Study (first author, year)	Study type	Location	Sampe size (case/control)	Genotype distribution (case/control)		
				T/T	T/G	G/G
Hallani, 2007	Population-based case-control	France	254/238	98/109	114/96	42/33
Tsuiki, 2007	Hospital-based case-control	Japan	254/50	62/15	126/18	66/17
Khatri, 2008	Hospital-based case-control	USA	98/102	5/23	79/74	14/5

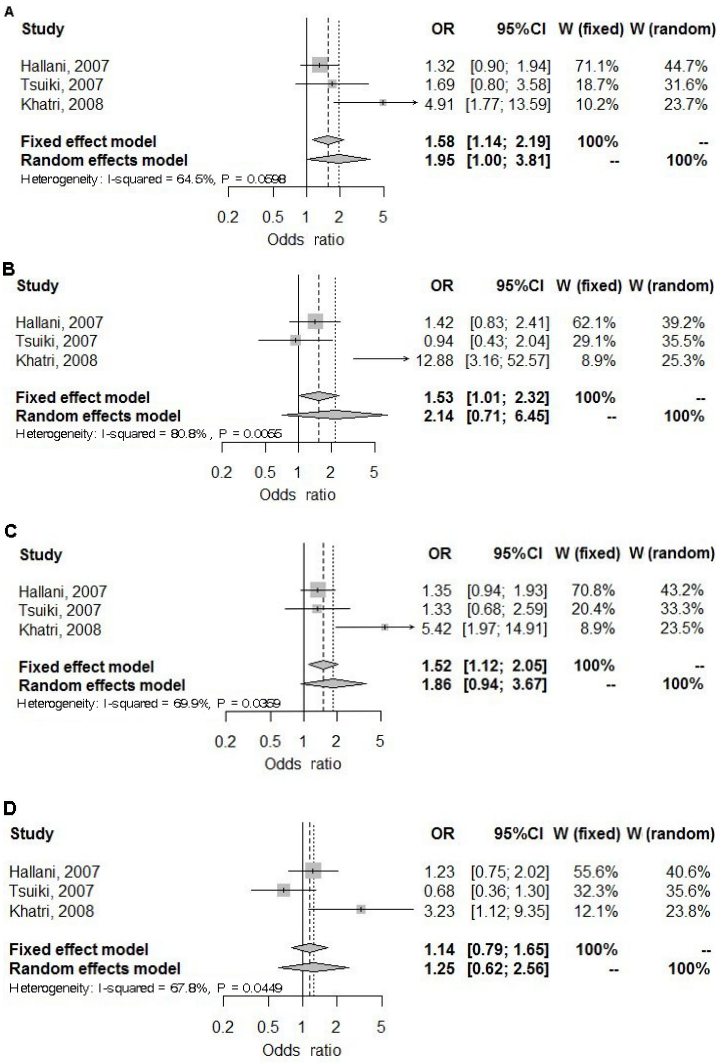

Figure 2. Forest plot of the colorectal cancer associated with: **A.** *MDM2* SNP309 heterozygosity (G/T *vs* T/T); **B.** *MDM2* SNP309 homozygosity (G/G *vs* T/T); **C.** dominant model (G/T and G/G *vs* T/T), and **D.** recessive model (G/G *vs* G/T and T/T). Box size represents the study weight under the random-effect model. OR = odds ratio; 95%CI = 95% confidence interval.

ers compared with that of homozygous T/T carriers, in which the pooled OR = 2.14 with a 95%CI = 0.71-6.45 (Figure 2B). Significant heterogeneity among the studies was found (Q = 10.42, d.f. = 2, P = 0.0055; I^2 = 80.8%; see Table 3). Under the dominant model, allele G carriers showed an 86% increased risk of glioma; however, the association was not statistically significant (Figure 2C). The recessive model showed that the pooled OR for homozygous GG carriers compared to G/T and T/T carriers was 1.25 with a 95%CI = 0.62-2.56 (Figure 2D). Significant heterogeneity among the studies was found under both the dominant and the recessive models (see Table 3). No significant publication bias was found in the meta-analysis. The study conducted by Khatri et al. (2008) showed a departure from HWE, and we excluded this study from further analysis. However, no significant change in the results was found after the exclusion. The results indicated that *MDM2* SNP309 may not be associated with glioma risk.

Table 3. Summary of the meta-analysis results for *p53* Arg72Pro and *MDM2* SNP309 and glioma risk.

Variant	Genetic model	OR-fixed-effect model	OR-random-effect model	Q	d.f.	P	I^2	Begg test	Egger test
p53 Arg72Pro	Arg/Arg	1	1						
	Arg/Pro	1.05 (0.94-1.17)	1.08 (0.85-1.37)	37.3	9	<0.0001	75.90%	0.9287	0.7139
	Pro/Pro	1.05 (0.85-1.28)	1.08 (0.85-1.36)	10.99	9	0.2756	18.10%	0.089	0.089
	Dominant	1.04 (0.95-1.16)	1.11 (0.90-1.38)	32.48	9	0.0002	72.30%	0.4208	0.3171
	Recessive	1.10 (0.90-1.33)	1.17 (0.85-1.61)	20.68	9	0.0142	56.50%	0.1797	0.3886
MDM2 SNP309	T/T	1	1						
	G/T	1.58 (1.14-2.19)	1.95 (1.00-3.81)	5.63	2	0.0598	64.50%	0.1172	0.2862
	G/G	1.53 (1.01-2.32)	2.14 (0.71-6.45)	10.42	2	0.0055	80.80%	0.6015	0.4560
	Dominant	1.52 (1.12-2.05)	1.86 (0.94-3.67)	6.65	2	0.0359	69.90%	0.1172	0.4148
	Recessive	1.14 (0.79-1.65)	1.25 (0.62-2.56)	6.21	2	0.0449	67.80%	0.6015	0.6386

OR = odds ratio; d.f. = degrees of freedom.

DISCUSSION

The *p53* Arg72Pro and *MDM2* SNP309 variants have been found to be significantly associated with susceptibility of various types of cancer, including lung (Dai et al., 2009), colorectal (Fang et al., 2011; Liu et al., 2011), and gastric (Zhou et al., 2007), among others. However, the association of these 2 variants with glioma is not fully understood. Our meta-analysis found no association of these 2 variants with glioma risk. For *p53*, the common polymorphism rs1042522, located at codon 72 of exon 4, leads to an amino acid change (Arg to Pro). *In vitro* study has demonstrated that the minor allele Pro has a decreased ability to trigger apoptosis compared to that of the Arg allele (Dumont et al., 2003). The Arg allele on *p53* showed stronger transcription activity compared with that of the Pro allele for *p53*-regulated genes such as death receptor 4, *NOXA*, *p53* upregulated modulator of apoptosis, and *p53*-induced gene 3, which are involved in the apoptosis pathways of cell models (Jeong et al., 2010). The genes induced by *p53* at the highest levels compared with baseline levels also tend to be synthesized better by the Arg allele than by the Pro allele (Jeong et al., 2010). The *p53* Arg72Pro polymorphism may influence the capability of certain conformational *p53* mutants to form stable complexes with p73, correlating with a loss of p73 DNA-binding capability and consequently affecting the capability to serve as a sequence-specific transcriptional activator

and an inducer of apoptosis (Marin et al., 2000). The Arg allele on *p53* also shows greater localization to the mitochondria, which leads to the release of cytochrome *c* into the cytosol and further enhances apoptosis activity compared to that with the Pro allele (Dumont et al., 2003).

These data indicate that the *p53* variant may have a distinct function and that the differences that occur may confer cancer risk. The polymorphism was first reported to be significantly associated with an increased risk of glioma in a study conducted by Parhar et al. (2005). The study included 92 adult and 43 pediatric cases consisting of 64 high-grade astrocytomas and 71 non-astrocytomas. However, the small sample size and the multiethnic population of the study made the results controversial. A study conducted in the Indian population also indicated that the Pro allele may increase glioma risk; however, the allele distribution in the control group showed significant derivation from HWE (P = 0.005) and may have biased the results (Jha et al., 2011). In the present meta-analysis of 2587 cases and 4061 controls, we found no statistical association for the *p53* Arg/Pro variant and glioma risk under any genetic model. The results indicated that *p53* Arg/Pro may not affect glioma risk.

An SNP in the promoter region of *MDM2* (rs2279744, T > G) that may lead to different transcription levels by *Sp1* was first reported by Bond et al. (2004). At this locus, the T to G change extends the length of a putative *Sp1* binding site and increases the affinity of this region for *Sp1* (Bond et al., 2004). It may also lead to an elevated level of *MDM2* and the subsequent attenuation of *p53* in the cell. The variant is associated with accelerated tumor formation in both hereditary and sporadic cancers. Many types of cancer have been reported to be significantly associated with the *MDM2* SNP309 variant, including non-small-cell lung cancer (Bai et al., 2009), colorectal cancer (Fang et al., 2011), and gastric carcinoma (Yang et al., 2007). The SNP309 G allele has been significantly associated with an increased risk of glioma in a study conducted by Khatri et al. (2008). However, the allele distribution in the control group showed significant departure from HWE. The other selected studies reported no significant association between SNP309 and glioma risk (El Hallani et al., 2007; Tsuiki et al., 2007). As suggested by Minelli et al. (2008), studies that deviate from HWE in a meta-analysis should be investigated further for weaknesses in their design. However, these studies should not be excluded unless other grounds for doubting the quality of the study are also present. From the pooled results of the 3 studies of *MDM2* SNP309, we found no overall significant association between the variant and glioma risk except for a marginally statistically significant increased risk of glioma in comparisons of heterozygous G/T carriers and homozygous T/T carriers in which the pooled OR was 1.95 (95%CI = 1.00-3.81) under the random-effect model. Due to the small size of the current meta-analysis - with only 606 cases and 390 controls - additional studies are needed to evaluate the association of the variant and glioma risk more fully.

Our current study had several weaknesses. First, the sample size was relatively small, and all the data were from case-control studies. Second, the type of glioma was not specified (e.g.; astrocytomas or oligodendrogliomas). Third, the ethnicity of the participants was not specified, and the majority of studies were conducted in European populations or in the Americas, so evidence is lacking from other populations. Thus, more studies that evaluate the associations of the 2 polymorphisms and glioma are needed.

In summary, the overall results from the present data suggested that the *p53* Arg72Pro and *MDM2* SNP309 polymorphisms have no statistically significant association with glioma risk, although the *MDM2-p53* pathway may be involved in glioma tumorigenesis. Additional studies are necessary to address this association.

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