TP53 codon 72 polymorphism and glioma risk: A meta-analysis

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Abstract. *TP53* codon 72 polymorphism has been reported to affect regulatory networks central to glioma development. Although a number of published studies noted the association between *TP53* codon 72 polymorphism and glioma risk, their conclusions were inconsistent. A meta-analysis was used to assess the possible association between *TP53* codon 72 polymorphism and glioma risk. The PubMed databases were searched, relevant articles were identified and data were retrieved based on the inclusion criteria. The odds ratio (OR) and 95% confidence interval (95% CI) were determined on the pooled dataset. We retrieved eight different studies including 2,260 glioma cases and 3,506 controls. However, no association was found between the *TP53* codon 72 polymorphism and glioma risk regarding the comparison between glioma cases and the controls. By further stratification based on criteria such as tumor grade, and the geographical location of the patients and the relevant controls, we found a significant association in the subgroup of patients with high-grade glioma in Europeans compared to controls in two models of *TP53* codon 72 polymorphism, which include the dominant model [C/C + G/C vs. G/G: OR=1.35, 95% CI (1.14, 1.59), P=0.0005, P_h=0.13] and the additive model [C allele vs. G allele: OR=1.16, 95% CI (1.02, 1.33), P=0.03, P_h=0.37]. Our analysis suggests that *TP53* codon 72 polymorphism is associated with an increased risk of high-grade glioma development in Europeans.

Introduction

Central nervous system tumors are the most common pediatric neoplasms, corresponding to approximately 20-23% of all cases of childhood cancer, and less than 2% of adult tumors (1). The prognosis for patients with primary central nervous system tumors, such as glioma, remains poor. The principal human tumor-suppressor gene *TP53* encodes a protein, p53, activated by stresses such as DNA damage, aberrant growth signals and ultraviolet light. p53 acts as a nuclear transcription factor, binds to particular DNA sequences and activates the expression of adjacent genes, which directly or indirectly results in cell death or inhibition of cell divisions (2). Therefore, proper function of tumor-suppressor genes including *TP53* is highly correlated with cancer risk. Approximately 25% of gliomas carry mutations in the *TP53* gene (3).

A number of polymorphisms have been identified within the *TP53* gene thus far, both in coding and non-coding regions (4). These polymorphisms include the serine 47 (5), the codon 72 (C→G, Pro→Arg) (6), intron 3 (+16 bp) and intron 6 (G→C) (7). Among these polymorphisms, the *TP53* codon 72 polymorphism, which is located in a proline-rich region in exon 4, is the most frequently studied. The codon 72 polymorphism involves a guanine to cytosine nucleotide exchange, leading to a non-conservative change from arginine to proline (8,9). In a cell-based study, an increase in apoptosis rate by up to 15-fold was found for the Arg72 variant cells as compared to that in the Pro72 variant (10). In addition, an association between the Arg72 variant and increased risk of epithelial cancer (11,12) was reported. Certain authors found alternate correlations, i.e., an association between the Pro72 *TP53* variant and increased cancer risk (13,14), whereas other authors (40,41) failed to confirm the link between *TP53* codon 72 variants and the risk of cancer.

Studies exist regarding the association of the *TP53* codon 72 polymorphism with susceptibility to the development of gliomas (15-21,42). However, the results obtained thus far were inconsistent. For example, Parhar *et al* (20) suggested a possible association between the codon 72 polymorphism and susceptibility to brain tumors, particularly high-grade astrocytomas. El Hallani *et al* (15) suggested that the codon 72 polymorphism was associated with the age-related onset of grade IV glioblastoma. Other investigators found that the codon 72 polymorphism is not correlated with susceptibility to glioma development (18,19,21,42). This discrepancy in the results may be due to different sample sizes, ethnicities or qualities including the genotyping method and study type among the various studies.

In this study, we performed a meta-analysis on the most current published reports in the region, to obtain the most

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precise estimation of the association between *TP53* codon 72 polymorphism and the risk of human glioma.

Materials and methods

Eligibility of relevant studies. We searched the National Library of Medicine (PubMed) database, using the terms '(p53 OR *TP53*) AND ((brain tumor) OR glioma) AND polymorphism' (the latest search was performed on June 3, 2011). In addition, we sent e-mails to the corresponding authors of the studies to retrieve the original data. The inclusion criteria were as follows: a) case-control studies with non-related subjects; b) sufficient data to calculate the odds ratio (OR); c) no deviation from the Hardy-Weinberg equilibrium (HWE) for the genotype distribution of the controls; and d) English articles. We excluded the following studies: a) studies that contained overlapping data; b) studies in which the number of wild-type genotypes could not be ascertained; and c) studies in which family members were studied.

Data extraction. All abstracts were read and articles were screened for suitability by two independent researchers (M.S. and R.H.). These investigators also read the full texts to extract data and reach a consensus on all of the eligible items: the first author, year of publication, country of study population, genotyping method, genotype frequency and source of the relevant control.

Meta- and statistical analysis. The meta-analysis evaluated the association between glioma risk and *TP53* codon 72 polymorphism, which included the dominant model (G/G + G/C versus C/C), the recessive model (G/G versus G/C + C/C) and the additive model (G allele versus C allele). The strength of association was assessed by the OR with a corresponding 95% confidence interval (95% CI). The heterogeneity among these studies was checked by Q statistics, and was considered statistically significant when $P_h<0.10$ (22). Study heterogeneity was quantified by the I^2 metric, which is independent of the number of studies in the meta-analysis ($I^2<25\%$ no heterogeneity; $25\leq I^2\leq 50\%$ moderate heterogeneity; $I^2>50\%$ extreme heterogeneity) (23). The combined OR of each study was estimated by the fixed-effects (FE) model (Mantel-Haenszel) at $P_h\geq 0.10$. Otherwise, the random-effects (RE) model (DerSimonian and Laird) was applied (24). The studies were further stratified by glioma grade (high-grade gliomas, WHO classification III and IV; and low grade gliomas, WHO classification I and II) and the high-grade gliomas were subgrouped by geographical locations including Europe, America and Asia.

To assess the stability of the results, sensitivity and publication bias analysis were also performed. For the sensitivity analysis, one study was omitted each time to reflect the effect of the individual data-set to the pooled OR (25). Publication bias was investigated by Begg's test ($P<0.05$ was considered to indicate statistical significance) (26) and Egger's test ($P<0.05$ was considered to be statistically significant) (27). Deviations from HWE for controls were analyzed by the Chi-square goodness of fit test. Statistical analyses were performed using the Review Manager 5.0 software (The Cochrane Collaboration, Oxford, England) and STATA version 11 (STATA Corporation, College Station, TX, USA).

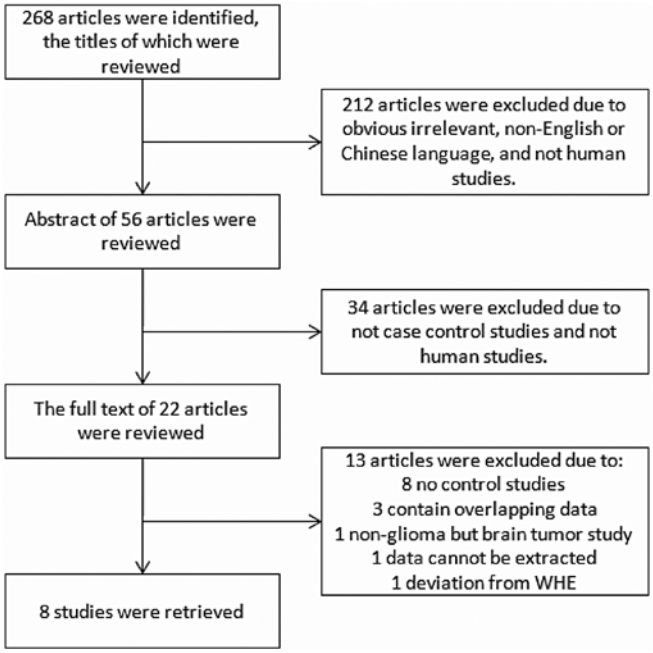

Figure 1. The flow chart of study identification, including inclusion and exclusion criteria.

Results

Characteristics of the retrieved studies. The search terms used for the *TP53* codon 72 polymorphism resulted in 268 articles, 22 of which were relevant upon further review. Three articles contained overlapping data (28-30), eight were no-control studies (31-37), and one was a non-glioma brain tumor study (38). In addition, deviation from HWE was found in one publication (39) and the glioma data could not be extracted from another (Fig. 1) (40). Therefore, eight studies published from 2004 to 2010, including 2,260 glioma cases and 3,506 controls, were eligible for the inclusion criteria in the meta-analysis. Table I shows the main characteristics of these studies, including the Jha study (39). The sample size in each study varies from 84 to 636. In addition, the original data of two studies were retrieved from the corresponding authors (18,41).

Gliomas from the eight eligible studies were classified according to the WHO classification criteria. Among them, six studies provided data on high-grade glioma genotype distribution, while the other two studies provided data on low-grade glioma genotype distribution (Table II). Therefore, these studies were treated as a mixed study at first, and then analyzed for high-grade and low-grade gliomas. The eight studies were conducted in different populations of various geographical locations: four were European populations (15,16,17,21), four were American (18,19,20,42) and only one was Asian (39). A stratified analysis for different geographical locations in high-grade gliomas was also conducted. However, such an analysis for geographical locations other than Europe was not performed due to insufficient data.

Meta-analysis results. Primary meta-analysis results are shown in Table III. We adopted the random-effects model to test the association between *TP53* codon 72 C allele and glioma

Table I. Characteristics of studies included in the meta-analysis.

References	Geographical location	Genotyping method	Number of cases (Age range, mean)	Number of controls (Age range, mean)	Source of controls	Matching
El Hallani *et al* (2009)	France	TaqMan	254 (19.2-83.6, 56.5)	238 (16-75, NA)	NA	Not matched
Idbaih *et al* (2007)	France	TaqMan	293 (16-84, 43)	175 (NA, NA)	NA	NA
Lima-Ramos *et al* (2008)	Europe	PCR-RFLP	171 (NA, 49.5)	526 (NA, 38.1)	Hospital-based	Gender
Malmer *et al* (2007)	Nordic-UK	TaqMan	636 (18-69, 45)	1461 (19-70, 50)	Population-based	Age, gender, geographical location
Parhar *et al* (2005)	USA	PCR-RFLP	135 (0-79, NA)	117 (NA, NA)	NA	Not matched
Pinto *et al* (2008)	Southeast Brazil	PCR-RFLP	94 (1-75, 45)	100 (18-72 45)	NA	Age, gender
Rajaraman *et al* (2007)	USA	TaqMan	386 (>18, NA)	547 (>18, NA)	Hospital-based	Age, gender, ethnicity, residential proximity to the hospital
Wang *et al* (2004)	USA	PCR-RFLP	309 (20-60, NA)	342 (20-60, NA)	Hospital-based	Age, gender, ethnicity
Jha *et al* (2010)	North India	Sequence analysis	84 (NA, NA)	112 (NA, NA)	NA	NA

NA, data not available.

Table II. Distribution of *TP53* codon 72 genotype and allele frequencies.

References	Genotype						Allele				HWE (P)
	Cases (n) gliomas (high/low)			Controls (n)			Cases (n) gliomas (high/low)		Controls (n)		
	GG	GC	CC	GG	GC	CC	G	C	G	C	
El Hallani *et al* (2009)	140 (140/NA)	92 (92/NA)	22 (22/NA)	142	82	14	372 (372/NA)	136 (136/NA)	366	110	0.637956
Idbaih *et al* (2007)	149 (61/88)	108 (45/63)	18 (10/8)	107	57	11	431 (178/253)	155 (72/83)	271	79	0.367309
Lima-Ramos *et al* (2008)	101 (47/NA)	56 (24/NA)	14 (4/NA)	298	197	31	258 (118/NA)	84 (32/NA)	793	259	0.835726
Malmer *et al* (2007)	361 (159/NA)	241 (194/NA)	34 (10/NA)	801	556	104	309 (214/NA)	963 (512/NA)	764	2158	0.576667
Parhar *et al* (2005)	38 (8/NA)	94 (55/NA)	3 (1/NA)	72	42	3	170 (71/NA)	100 (57/NA)	186	48	0.275542
Pinto *et al* (2008)	53 (33/20)	34 (14/20)	7 (5/2)	48	42	10	140 (80/60)	48 (24/24)	138	62	0.855325
Rajaraman *et al* (2007)	213 (NA/NA)	146 (NA/NA)	27 (NA/NA)	300	209	38	572 (NA/NA)	200 (NA/NA)	809	285	0.84566
Wang *et al* (2004)	165 (NA/NA)	126 (NA/NA)	18 (NA/NA)	194	128	20	456 (NA/NA)	162 (NA/NA)	516	168	0.853764
Jha *et al* (2010)	33 (13/NA)	27 (17/NA)	24 (13/NA)	15	70	27	93 (43/NA)	75 (43/NA)	100	124	0.00512

Gliomas, all gliomas; high, high-grade gliomas; low, low-grade gliomas; NA, data not available. HWE, Hardy-Weinberg equilibrium.

Table III. The odds ratios (ORs) of *TP53* codon 72 polymorphism, glioma subtype and geographical location status with glioma.

Allele and genotype	Outcome or subgroup	Studies	Cases/controls	Statistical method	Effect estimate	P	P (Heterogeneity)	I^2 (%)
C/C + G/C vs. G/G (dominant model)								
	Gliomas	8	2260/3506	Odds ratio (M-H, Random, 95% CI)	1.17 [0.91, 1.50]	0.23	<0.0001	78
	High-grade gliomas	6	924/2617	Odds ratio (M-H, Random, 95% CI)	1.45 [0.88, 2.39]	0.15	<0.00001	87
	Low-grade gliomas	2	201/275	Odds ratio (M-H, Fixed, 95% CI)	1.20 [0.82, 1.74]	0.35	0.60	0
	High-grade gliomas in Europeans	4	808/2400	Odds ratio (M-H, Fixed, 95% CI)	1.35 [1.14, 1.59]	0.0005	0.13	47
C/C vs. G/C+ G/G (recessive model)								
	Gliomas	8	2260/3506	Odds ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.21]	0.77	0.64	0
	High-grade gliomas	6	924/2617	Odds ratio (M-H, Random, 95% CI)	0.88 [0.50, 1.56]	0.67	0.07	52
	Low-grade gliomas	2	201/275	Odds ratio (M-H, Fixed, 95% CI)	0.67 [0.30, 1.47]	0.32	0.54	0
	High-grade gliomas in Europeans	4	808/2400	Odds ratio (M-H, Random, 95% CI)	0.90 [0.43, 1.90]	0.78	0.02	71
C allele vs. G allele (an additive model)								
	Gliomas	8	2260/3506	Odds ratio (M-H, Random, 95% CI)	1.10 [0.93, 1.30]	0.27	0.002	68
	High-grade gliomas	6	924/2617	Odds ratio (M-H, Random, 95% CI)	1.23 [0.90, 1.66]	0.19	0.0003	79
	Low-grade gliomas	2	201/275	Odds ratio (M-H, Fixed, 95% CI)	1.00 [0.74, 1.35]	0.98	0.62	0
	High-grade gliomas in Europeans	4	808/2400	Odds ratio (M-H, Fixed, 95% CI)	1.16 [1.02, 1.33]	0.03	0.37	5

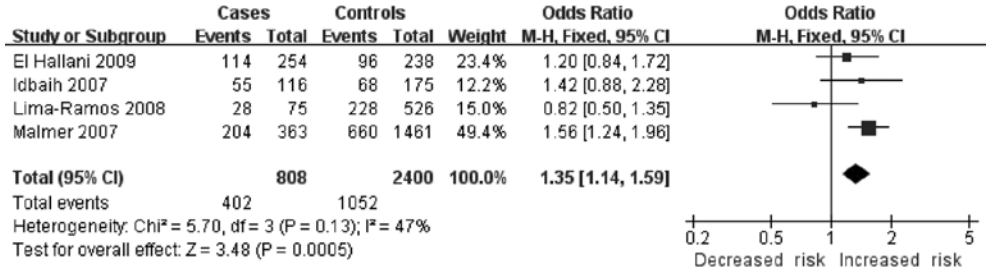

Figure 2. Overall meta-analysis for the *TP53* codon 72 polymorphism and glioma risk in the dominant model in high-grade gliomas in Europeans.

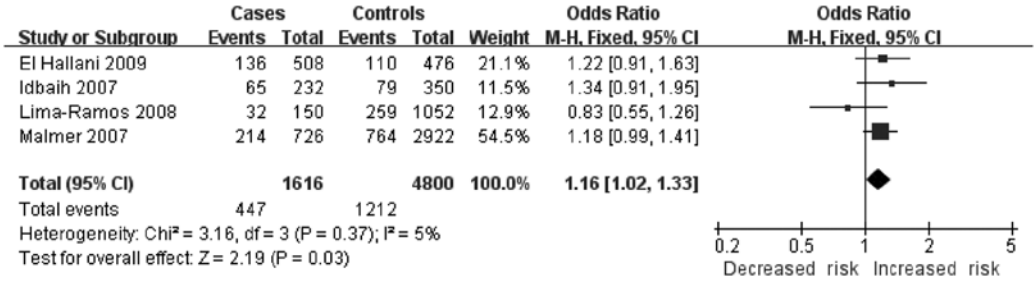

Figure 3. Overall meta-analysis for the *TP53* codon 72 polymorphism and glioma risk in the additive model in high-grade gliomas in Europeans.

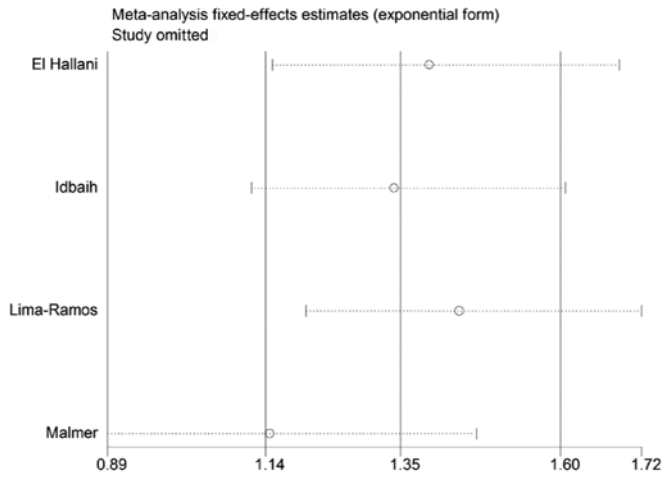

Figure 4. Sensitivity analysis for the *TP53* codon 72 polymorphism in the dominant model in high-grade gliomas in Europeans.

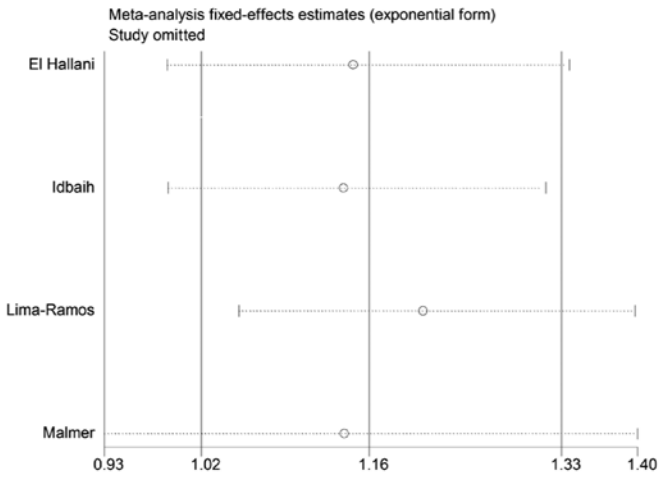

Figure 5. Sensitivity analysis for the *TP53* codon 72 polymorphism in the additive model in high-grade gliomas in Europeans.

risk. The overall OR for the C-allele was 1.10, its 95% CI was 0.93-1.30. Therefore, C allele was considered as a high-risk allele in this literature review of the data. The pooled estimates across all eight studies showed no association between *TP53* codon 72 polymorphism and glioma risk within the three genotype models: [C/C + G/C vs. G/G: OR=1.17, 95% CI (0.91, 1.50), P=0.23, P_h<0.0001], [C/C vs. G/C+ G/G: OR=0.97, 95% CI (0.77, 1.21), P=0.77, P_h=0.64], [C allele vs. G allele: OR=1.10, 95% CI (0.93, 1.30), P=0.27, P_h=0.002].

In the stratified analysis for glioma grade, no association was found between high-grade and low-grade gliomas. However, heterogeneity was detected in high-grade gliomas [C/C + G/C vs. G/G: OR=1.45, 95% CI (0.88, 2.39), P=0.15, P_h<0.00001], [C allele vs. G allele: OR=1.23, 95% CI (0.90, 1.66), P=0.19, P_h=0.0003]. Therefore, we further sub-grouped the high-grade glioma group by geographical locations. Homogeneity and significant associations were found in two models: the dominant model [C/C + G/C vs. G/G: OR=1.35, 95% CI (1.14, 1.59), P=0.0005, P_h=0.13] (Fig. 2) and the additive model [C allele vs. G allele: OR=1.16, 95% CI (1.02, 1.33), P=0.03, P_h=0.37] (Fig. 3). No other significant association was found.

Sensitivity analysis. A single study in the meta-analysis was deleted to test for the effect of that individual data set on the pooled ORs. The corresponding pooled ORs were not significantly altered in the sensitivity analysis (Figs. 4 and 5).

Publication bias. Both Begg's and Egger's test were performed to assess the publication bias. The results suggested no evidence

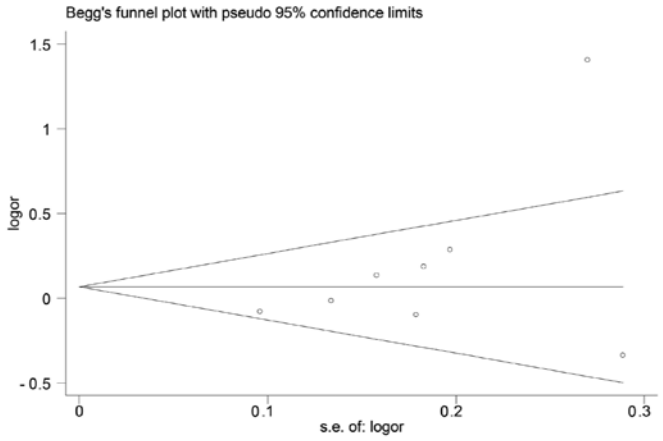

Figure 6. Begg's funnel plot of the *TP53* codon 72 polymorphism and glioma risk.

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Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      12
         Std. Dev. of Score =    8.08
         Number of Studies =       8
                         z =    1.48
                   Pr > |z| =   0.138
                         z =    1.36 (continuity corrected)
                   Pr > |z| =   0.174 (continuity corrected)

Egger's test
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Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.3957009	.3353724	-1.18	0.283	-1.216328	.4249257
bias	3.091105	2.114638	1.46	0.194	-2.083227	8.265438

Figure 7. Begg's test (P=0.174) and Egger's test (P=0.194) of the *TP53* codon 72 polymorphism and glioma risk.

of publication bias (C/C + G/C vs. G/G: Begg's test P=0.174, Egger's test P=0.194) (Figs. 6 and 7).

Discussion

The *TP53* codon 72 polymorphism was intensively studied and reported to affect the functions of the *TP53* network, which is central to the development of gliomas, particularly high-grade gliomas. The previously published studies presented conflicting results over the association between *TP53* codon 72 polymorphism and the risk of glioma. Therefore, we conducted this meta-analysis on data collected from the most up-to-date publications to evaluate this putative association.

The tumor suppressor gene *TP53* is a core gene in the *TP53* signaling pathway and is significant in tumor suppression. The mutation of the *TP53* gene was recently defined as one of the most crucial factors in the development of malignant gliomas (43). Parhar *et al* (20) found a significant association between the G/C genotype and an increased risk for high-grade astrocytomas. However, the present results did not show any association between the type of single-nucleotide polymorphism (SNP) and the risk of high-grade gliomas. This inconsistency may be due to a number of reasons. First, our analysis stratified the data into high-grade and low-grade gliomas, whereas Parhar *et al* stratified the data into high-grade astrocytomas and non-astrocytomas. Since astrocytoma is a subtype of glioma, non-astrocytomas include other types of high-grade gliomas. Therefore, the tumor classification is different between the two studies. Second, the sample sizes were different. Parhar *et al* only included 252 subjects, whereas we included 2,145 subjects. The relatively small sample size in the study by Parhar *et al* may contribute to their conclusion. Our analysis, which combines data from all eight studies that included 2,145 subjects, should minimize the random error.

The genesis of glioma is closely associated with the interaction between environmental factors and genetic background. It was reported that the allele distribution at codon 72 of *TP53* varies depending on geographical locations (44,45). Therefore, to clarify the association between codon 72 polymorphism and the glioma risk in different genetic backgrounds and remove heterogeneity, we analyzed the collected data by subgrouping the high-grade glioma group according to the geographical locations. The results have shown that the respective SNPs at codon 72 of *TP53* are associated with an increased risk of high-grade gliomas in Europeans.

Based on the literature review of the available data, our results suggest that *TP53* codon 72 C carriers (Pro) are associated with an increased risk of high-grade glioma in Europeans. Thomas *et al* (46) indicated that the Pro72 variant induced slower kinetics of apoptosis and suppressed transformation less efficiently than the Arg72 variant. In their study, Dumont *et al* (10) reported that the Pro72 variant bears only 1/15 apoptosis-inducing ability compared to the Arg72 variant in cells with endogenous p53, as well as in cell lines containing inducible alleles encoding the Pro72 or Arg72. Thus, our results are consistent with the data describing the biological functions of p53.

However, there are a number of limitations in our analysis. Although we carefully selected studies by performing a careful search, using strict study inclusion criteria, precise data extraction and statistical analysis, significant heterogeneity between studies still exists. E-mails were forwarded to the corresponding authors of each publication. However, only two of the original sets of data were retrieved; thus, we failed to adjust our meta-analysis by age and gender. Future studies should include other co-variants, such as age, gender, ethnicity, environmental factors and lifestyle for a more comprehensive understanding of the association between the *TP53* codon 72 polymorphism and glioma risk.

In conclusion, our results confirm that *TP53* codon 72 polymorphism may be associated with an increased risk of high-grade glioma development in Europeans.

Acknowledgements

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