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RESEARCH ARTICLE

P53 codon 72 Arg/Pro polymorphism and glioma risk: an updated meta-analysis

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Abstract P53 codon 72 Arg/Pro is a C/G variation upstream of the p53 gene on human chromosome 17p13. Many case–control studies have investigated the association between p53 codon 72 Arg/Pro polymorphism and glioma risk but provided inconsistent findings. To better understand the pathogenesis of glioma, we performed the current meta-analysis by pooling data from all available individual studies. According to the inclusion criteria, ten independent publications with 11 case–control studies were included into this meta-analysis. The pooled odds ratio (OR) with 95 % confidence interval (95 % CI) was calculated to estimate the effect of p53 codon 72 Arg/Pro variant on the development of glioma. Overall, no appreciable correlation was observed among the total studies in all gene models ($OR_{Pro\ allele\ vs.\ Arg\ allele}$=1.04, 95 % CI=0.90–1.20, P_{OR}=0.581; $OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.95, 95 % CI=0.80–1.14, P_{OR}=0.614; $OR_{Pro/Arg\ vs.\ Arg/Arg}$=1.01, 95 % CI=0.79–1.29, P_{OR}=0.993; $OR_{Pro/Arg\ +\ Pro/Pro\ vs.\ Arg/Arg}$=1.03, 95 % CI=0.82–1.29, P_{OR}=0.799; $OR_{Pro/Pro\ vs.\ Arg/Arg\ +\ Pro/Arg}$=1.02, 95 % CI=0.86–1.22, P_{OR}=0.785). In stratified analyses by ethnicity, source of controls, and glioma subtypes, the p53 codon 72 Arg/Pro polymorphism did not alter the risk for glioma in population-based, hospital-based, astrocytoma, and oligodendroglioma studies among Caucasian. Interestingly, the Pro/Pro genotype seemed to be negatively associated with the glioma risk among patients with glioblastoma ($OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.68, 95 % CI=0.48–0.95, P_{OR}=0.026). Our study suggests that the polymorphism of p53 codon 72 Arg/Pro may play a protective role in the development of glioblastoma. The relationship of p53 codon 72 Arg/Pro polymorphism with the susceptibility to glioma needs further estimation by more individual studies with high quality across ethnicities.

Keywords P53 · Glioma · Polymorphism · Meta-analysis

Introduction

Glioma is the most common and the worst prognosis on primary central nervous system tumors, making up approximately 30 % of all brain and central nervous system tumors and 80 % of all malignant brain tumors [1, 2]. Even with aggressive treatments such as surgery, radiation, and chemotherapy, the median survival is very low, particularly for patients with malignant glioma. The etiology and pathogenesis of glioma have remained poorly understood to date. Several occupations, environmental carcinogens, *N*-nitroso compound diet, and therapeutic X-irradiation have been established as risk factors for glioma [3, 4]. However, occupational and environmental exposures are not enough to account for the development of glioma, in that the genetic predisposition is also related to the glioma development [2]. Single nucleotide polymorphisms (SNPs) of Fc-epsilon RI-alpha, X-ray cross-complementing group 1 Arg399Gln, and epidermal growth factor gene are demonstrated to exert risk effects on glioma [5–7].

The mammalian p53 family consists of p53, p63, and p73 [8]. The human p53 is the most frequently mutant gene in human tumors and located on chromosome 17p13 with the function of tumor suppression through cell cycle arrest and apoptosis [9]. It encodes a protein, namely p53, which plays vital roles in DNA repair, cell signaling transduction, and

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the cell cycle control to maintain the genomic stability [10, 11]. The p53 can be activated and upregulated by stresses such as DNA damages, abnormal cell proliferation signals, and ultraviolet light [10]. The p53 protein, as a powerful tumor suppressor, is an attractive cancer therapeutic target, which also holds promise as a drug target for novel therapies in glioma [12]. Nevertheless, the mutated p53 may exert tumor-promoting effects in response to cellular stress. Through the use of linkage studies and genome-wide association studies, several p53 SNPs including p53 codon 72 Arg/Pro have been indicated in the development of malignant tumors [13–16]. Regarding the susceptibility to glioma, a number of case–control studies have investigated the role of p53 codon 72 Arg/Pro polymorphism in the glioma pathogenesis [17–26], while the findings were inconsistent and ambiguous across different individual studies among ethnicities. Therefore, we performed the current meta-analysis of all published case–control studies thus far and aimed to provide a better understanding on the molecular mechanism of glioma.

Materials and methods

Eligible studies

We searched the PubMed, Embase, Web of Science, and China National Knowledge Infrastructure (CNKI) databases to identify potentially relevant studies concerning the relationship of p53 codon 72 Arg/Pro polymorphism and the susceptibility to glioma. Case–control studies with sufficient available data for calculating the odds ratio (OR) and 95 % confidence interval (95 % CI) were retrieved by use of the following items: "p53," or "p53 codon 72," or "p53 codon 72 Arg/Pro," or "rs1042522"; and "glioma," or "brain tumor," or "astrocytomas," or "glioblastoma," or "oligodendroglioma," or "oligoastrocytoma," or "neuroepithelial tumor"; and "polymorphism," or "polymorphisms," or "mutation." Reviews and family-based and case-only studies were all excluded. The irrelevant studies and studies with overlapping data were also not included. The references of all eligible publications were hand-checked for additional relevant case–control studies.

Data extraction

Two investigators extracted data independently by reading through the full texts. Disagreements were resolved by consensus. For each study, the following data were extracted: the first author's name, publication year, ethnicity, country of origin, study design, genotyping method, inclusion criteria for patients and controls, sample size, definition of glioma, glioma subtypes, source of controls, the mean age of cases and controls, the Hardy–Weinberg equilibrium (HWE) for the genotype distribution in controls, and the frequency of genotype in cases and controls (Arg/Arg, Pro/Pro, and Arg/Pro).

Statistical analysis

The pooled ORs with corresponding 95 % CIs were calculated to assess the association between p53 codon 72 Arg/Pro polymorphism and the glioma risk. Five gene contrast models were evaluated including the comparisons for Pro allele vs. Arg allele, Pro/Pro vs. Arg/Arg, Pro/Arg vs. Arg/Arg, Pro/Arg+Pro/Pro vs. Arg/Arg, and Pro/Pro vs. Arg/Arg+Pro/Arg. We conducted stratified analysis by ethnicity, source of controls, and glioma subtypes to further estimate the gene association. The HWE for genotype distribution in controls was estimated by the chi-square test, and a P value less than 0.05 was considered statistically significant. Sensitivity analysis by sequential omission of each study one at a time was carried out to investigate the impact of individual study on the pooled effect. The between-study heterogeneity was checked by use of I^2 statistic test and chi-square-based Q statistic test [27, 28]. The value of P less than 0.05 indicated significant heterogeneity among the included studies, and thus the random-effect model was applied (DerSimonian and Laird method) to calculate the pooled ORs with corresponding 95 % CIs [29]. Otherwise, the fixed-effect model (the Mantel–Haenszel method) was adopted when there was no obvious heterogeneity among individual studies [30]. Egger's linear regression test and Begg's graphical methods were both used to estimate the publication bias risk in our study [31, 32]. The meta-analysis was done by use of STATA 12.0 (StataCorp LP, College Station, Texas).

Results

The characteristics of eligible studies

There were 15 relevant publications retrieved after a comprehensive search of the PubMed, Embase, Web of Science, and CNKI databases [17–26, 33–37]. Among them, five were excluded due to overlapping data, case-only design, and not related to p53 codon 72 mutation, respectively [33–37]. According to the source of controls, the publication by Malmer et al. was regarded as two independent case–control studies. Totally, 10 individual publications with 11 case–control studies were included into this meta-analysis involving 3,281 cases and 4,626 controls [17–26]. The genotype distribution in controls of case–control studies were all in agreement with HWE. Based on ethnicity, studies were performed as follows: one with 301 cases and 302 controls were among Asians [26]; eight with 2,802 cases

and 4,112 controls were among Caucasians [17–22, 24]; and two with 178 cases and 212 controls were among the mixed population [23, 25]. Regarding the source of controls, eight including 2,124 cases and 3,256 controls were population-based case–control studies [17, 19, 20, 22–26], while two with 1,022 cases and 1,253 controls were hospital-based case–control ones [20, 21], and still one could not be characterized due to insufficient information [18]. The characteristics of all included studies were presented in Table 1 in details.

Meta-analysis results

As shown in Table 2, the overall pooled ORs indicated that the p53 codon 72 variant exerted no risk effect on the glioma development under all comparisons ($OR_{Pro\ allele\ vs.\ Arg\ allele}$=1.04, 95 % CI=0.90–1.20, P_{OR}=0.581; $OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.95, 95 % CI=0.80–1.14, P_{OR}=0.614; $OR_{Pro/Arg\ vs.\ Arg/Arg}$=1.01, 95 % CI=0.79–1.29, P_{OR}=0.993; $OR_{Pro/Arg\ +\ Pro/Pro\ vs.\ Arg/Arg}$=1.03, 95 % CI=0.82–1.29, P_{OR}=0.799; $OR_{Pro/Pro\ vs.\ Arg/Arg\ +\ Pro/Arg}$=1.02, 95 % CI=0.86–1.22, P_{OR}=0.785) (Table 2 and Fig. 1). Sensitivity analysis did not alter the pooled results among total included studies (data not shown).

Stratified analysis among Caucasians

The included studies were primarily conducted in Caucasians, Asians, and the mixed population. The stratified analysis in Caucasians showed that the p53 codon 72 polymorphism was not related to the glioma risk under all gene models ($OR_{Pro\ allele\ vs.\ Arg\ allele}$=1.09, 95 % CI=0.93–1.27, P_{OR}=0.297; $OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.94, 95 % CI=0.76–1.16, P_{OR}=0.550; $OR_{Pro/Arg\ vs.\ Arg/Arg}$=1.17, 95 % CI=0.92–1.48, P_{OR}=0.206; $OR_{Pro/Arg\ +\ Pro/Pro\ vs.\ Arg/Arg}$=1.16, 95 % CI=0.92–1.46, P_{OR}=0.207; $OR_{Pro/Pro\ vs.\ Arg/Arg\ +\ Pro/Arg}$=0.93, 95 % CI=0.76–1.14, P_{OR}=0.473) (Table 2).

Stratified analysis by source of controls

No significant association was observed either in population-based studies or hospital-based studies (Table 2). Interestingly, the pooled ORs for all gene comparisons by use of the fixed-effect model suggested that the p53 codon 72 variant was negatively associated with the glioma pathogenesis, although with a lack of evidence for statistical significance ($OR_{Pro\ allele\ vs.\ Arg\ allele}$=0.92, 95 % CI=0.80–1.05, P_{OR}=0.231; $OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.82, 95 % CI=0.58–1.17, P_{OR}=0.280; $OR_{Pro/Arg\ vs.\ Arg/Arg}$=0.93, 95 % CI=0.78–1.12, P_{OR}=0.442; $OR_{Pro/Arg\ +\ Pro/Pro\ vs.\ Arg/Arg}$=0.92, 95 % CI=0.77–1.09, P_{OR}=0.310; $OR_{Pro/Pro\ vs.\ Arg/Arg\ +\ Pro/Arg}$=0.85, 95 % CI=0.60–1.19, P_{OR}=0.344) (Table 2).

Table 1 Characteristics of all case–control studies in this meta-analysis

Study	Ethnicity	Origin	Source of controls	Matching	Genotyping methods	Cases			Controls		
						Pro/Pro	Pro/Arg	Arg/Arg	Pro/Pro	Pro/Arg	Arg/Arg
Wang et al. [17]	Caucasian	USA	Population-based	Age, sex, and ethnicity	PCR-RFLP	18	126	165	20	128	194
Parhar et al. [18]	Caucasian	USA	NR	NR	PCR-RFLP	3	94	38	3	42	72
Idbaih et al. [19]	Caucasian	France	Population-based	Age and sex	Taqman	18	108	149	11	57	107
Malmer et al. [20]	Caucasian	Nordic UK	Population-based	Age, gender, sample size and geographic region	Taqman	34	241	361	104	556	801
Malmer et al. [20]	Caucasian	Nordic UK	Hospital-based	Age, gender, sample size and geographic region	Taqman	34	241	361	34	189	251
Rajaraman et al. [21]	Caucasian	USA	Hospital-based	Age, gender, ethnicity, sample size and residential	Taqman	27	146	213	56	297	426
Lima-Ramos et al. [22]	Caucasian	Europe	Population-based	Sex	PCR-RFLP	14	56	101	31	197	298
Pinto et al. [23]	Mixed	Brazil	Population-based	Age and sex	PCR-RFLP	7	34	53	10	42	48
El Hallani et al. [24]	Caucasian	France	Population-based	Ethnicity	Taqman	22	92	140	14	82	142
Jha et al. [25]	Mixed	India	Population-based	Age and sex	Sequence analysis	24	27	33	27	70	15
Jin et al. [26]	Asian	China	Population-based	Ethnicity and residential	Sequence analysis	63	146	92	45	157	100

PCR-RFLP polymerase chain reaction–restriction fragment length polymorphisms, *NR* not reported

Stratified analysis by glioma subtypes

As presented in Table 2, we carried out stratified analysis among patients with astrocytomas, glioblastoma, and oligodendroglioma. The Pro/Pro genotype seemed to play a protective role in the development of glioblastoma ($OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.68, 95 % CI=0.48–0.95, P_{OR}= 0.026). Nevertheless, no significant association was found under other gene contrast models regarding the risk for glioblastoma (Table 2). In addition, the pooled ORs showed a negative relationship between the p53 codon 72 variant and the risk for astrocytomas and oligodendroglioma, but without statistical significance (Table 2).

Heterogeneity analysis

There was significant between-study heterogeneity among all included studies in comparisons of Pro allele vs. Arg allele, Pro/Arg vs. Arg/Arg, and Pro/Arg+Pro/Pro vs. Arg/Arg (for Pro allele vs. Arg allele: I^2=68.5 %, P_H< 0.001; for Pro/Arg vs. Arg/Arg: I^2=81.7 %, P_H<0.001; and for Pro/Arg+Pro/Pro vs. Arg/Arg: I^2=80.6 %, P_H< 0.001) (Table 2). The stratified analyses indicated that the heterogeneity was not attributed to the hospital-based studies on the susceptibility to glioma (Table 2).

Publication bias

The analyses of Egger's linear regression test and Begg's graphical methods showed that there was no publication bias risk in the current meta-analysis (Fig. 2).

Discussion

Dysregulation in cell cycle and apoptosis control is a crucial cause for malignant tumors. The p53 is a well-established tumor suppressor through cell cycle arrest and apoptosis, which has been considered as one of the most attractive targets for molecular cancer therapy [9, 38]. Mutation in p53 gene can damage the biological activity of its encoding protein and thus may contribute to various carcinogenesis. P53 codon 72 Arg/Pro polymorphism is the most extensively studied locus of p53 gene. The polymorphism at codon 72 of the p53 gene results in either a proline or an arginine. They play diverse roles in the development of cancer, suggesting different functional activities of proline and arginine [39, 40]. The mutant p53 codon 72 Arg/Pro was not associated with the risk of breast cancer among Turkish women, while the homozygote and heterozygote Pro genotypes were significantly related to the tumor stages of this cancer [41]. Conversely, Buyru et al. demonstrated that the Arg/Arg homozygote carriers in a Turkish population were more susceptible to breast cancer [40]. The varying geographical distribution, environmental exposures, study designs, and source of controls may account for the discrepancy.

The effect of p53 codon 72 Arg/Pro polymorphism on the glioma susceptibility remains rather obscure owing to the contradictory findings among different ethnicities. Parhar et al. firstly reported a positive association between the p53 codon 72 Arg/Pro polymorphism and the susceptibility to glioma, particularly the high-grade astrocytomas [18]. Besides, a previous meta-analysis by Shi et al. demonstrated that the p53 codon 72 polymorphism was associated with an elevated risk of high-grade glioma development in Europeans [42]. However, the sample size in overall cases was too limited (<1,000) to precisely estimate the relationship of p53 codon 72 variant with glioma risk due to insufficient statistical power. Our updated meta-analysis of 7,907 subjects suggested that the p53 codon 72 Arg/Pro variant may exert no effect on the glioma development among all studies ($OR_{Pro\ allele\ vs.\ Arg\ allele}$=1.04, 95 % CI=0.90–1.20; $OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.95, 95 % CI=0.80–1.14; $OR_{Pro/Arg\ vs.\ Arg/Arg}$=1.01, 95 % CI=0.79–1.29; $OR_{Pro/Arg\ +\ Pro/Pro\ vs.\ Arg/Arg}$=1.03, 95 % CI=0.82–1.29; $OR_{Pro/Pro\ vs.\ Arg/Arg\ +\ Pro/Arg}$=1.02, 95 % CI=0.86–1.22). Interestingly, the Pro/Pro genotype seemed to play a protective role in the development of glioblastoma ($OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.68, 95%CI=0.48–0.95). However, we failed to identify significant association of the p53 codon 72 Arg/Pro polymorphism with glioma risk in stratified meta-analyses of population-based, hospital-based, astrocytoma, and oligodendroglioma studies among Caucasian. Sensitivity analysis confirmed the stability and credibility of all findings. Besides, stratified analyses among Asians and the mixed population were not carried out due to limited sample size. Moreover, we did not conduct the stratified analysis by glioma grade due to insufficient available data of individual publications. More case–control studies are recommended to further elucidate the impact of mutant p53 codon 72 Arg/Pro on the susceptibility to different grades of glioma.

The p53 codon 72 Arg/Pro polymorphism exerted diverse effects on the glioma onset across ethnicities. The p53 codon 72 polymorphism was identified as a risk factor for the development of glioma in Indian population [25]. Jin and the colleagues demonstrated a 34 % increased risk of glioma among the Chinese Han carriers of Pro/Pro haplotype [26]. The study by El Hallani et al. supported a critical role of p53 codon 72 functional variation in the oncogenesis of glioblastoma in younger patients, but not the elder patients, among Caucasians [24]. Nevertheless, no statistically significant correlation was observed between the p53 codon 72 variant and the glioma risk among Caucasians [17]. In our stratified meta-analysis by ethnicity, the p53 codon 72 polymorphism did not modify the risk for glioma under all

Table 2 Summary meta-analysis results for the association of the of p53 codon 72 Arg/Pro polymorphism and glioma risk

Contrast models	Studies (cases/controls)	Odds ratio		Model[a]	Heterogeneity	
		OR (95 % CI)	P_{OR}		I^2 (%)	P_H[b]
Total studies	11 (3,281/4,626)					
Pro allele vs. Arg allele		1.04 [0.90–1.20]	0.581	Random	68.5	<0.001
Pro/Pro vs. Arg/Arg		0.95 [0.80–1.14]	0.614	Fixed	36.5	0.107
Pro/Arg vs. Arg/Arg		1.01 [0.79–1.29]	0.933	Random	81.7	<0.001
Pro/Arg+Pro/Pro vs. Arg/Arg		1.03 [0.82–1.29]	0.799	Random	80.6	<0.001
Pro/Pro vs. Arg/Arg+Pro/Arg		1.02 [0.86–1.22]	0.785	Fixed	7.9	0.368
Caucasians	8 (2,802/4,112)					
Pro allele vs. Arg allele		1.09 [0.93–1.27]	0.297	Random	70.4	0.001
Pro/Pro vs. Arg/Arg		0.94 [0.76–1.16]	0.550	Fixed	3.4	0.403
Pro/Arg vs. Arg/Arg		1.17 [0.92–1.48]	0.206	Random	78.4	<0.001
Pro/Arg+Pro/Pro vs. Arg/Arg		1.16 [0.92–1.46]	0.207	Random	78.9	<0.001
Pro/Pro vs. Arg/Arg+Pro/Arg		0.93 [0.76–1.14]	0.473	Fixed	0.0	0.548
Source of controls						
Population-based studies	8 (2,124/3,256)					
Pro allele vs. Arg allele		1.01 [0.92–1.10]	0.896	Fixed	47.7	0.064
Pro/Pro vs. Arg/Arg		1.00 [0.80–1.24]	0.979	Fixed	47.6	0.064
Pro/Arg vs. Arg/Arg		0.90 [0.70–1.16]	0.428	Random	72.8	0.001
Pro/Arg+Pro/Pro vs. Arg/Arg		0.94 [0.75–1.18]	0.608	Random	69.2	0.002
Pro/Pro vs. Arg/Arg+Pro/Arg		1.10 [0.90–1.34]	0.364	Fixed	16.8	0.297
Hospital-based studies	2 (1,022/1,253)					
Pro allele vs. Arg allele		0.92 [0.80–1.05]	0.231	Fixed	0.0	0.355
Pro/Pro vs. Arg/Arg		0.82 [0.58–1.17]	0.280	Fixed	0.0	0.360
Pro/Arg vs. Arg/Arg		0.93 [0.78–1.12]	0.442	Fixed	0.0	0.572
Pro/Arg+Pro/Pro vs. Arg/Arg		0.92 [0.77–1.09]	0.310	Fixed	0.0	0.444
Pro/Pro vs. Arg/Arg+Pro/Arg		0.85 [0.60–1.19]	0.344	Fixed	0.0	0.416
Astrocytoma	3 (318/702)					
Pro allele vs. Arg allele		0.81 [0.64–1.01]	0.061	Fixed	0.0	0.595
Pro/Pro vs. Arg/Arg		0.72 [0.40–1.29]	0.268	Fixed	0.1	0.368
Pro/Arg vs. Arg/Arg		0.38 [0.14–1.00]	0.051	Random	83.7	0.002
Pro/Arg+Pro/Pro vs. Arg/Arg		0.45 [0.20–1.00]	0.051	Random	78.7	0.009
Pro/Pro vs. Arg/Arg+Pro/Arg		1.37 [0.84–2.26]	0.210	Fixed	0.0	0.909
Glioblastoma	5 (1,098/2,811)					
Pro allele vs. Arg allele		1.11 [0.99–1.25]	0.070	Fixed	7.1	0.366
Pro/Pro vs. Arg/Arg		0.68 [0.48–0.95]	0.026	Fixed	48.9	0.098
Pro/Arg vs. Arg/Arg		1.09 [0.72–1.64]	0.680	Random	82.3	<0.001
Pro/Arg+Pro/Pro vs. Arg/Arg		1.10 [0.79–1.54]	0.573	Random	75.1	0.003
Pro/Pro vs. Arg/Arg+Pro/Arg		0.75 [0.39–1.44]	0.382	Random	72.7	0.005
Oligodendroglioma	3 (251/813)					
Pro allele vs. Arg allele		0.97 [0.75–1.26]	0.843	Fixed	60.9	0.078
Pro/Pro vs. Arg/Arg		0.83 [0.45–1.54]	0.548	Fixed	61.6	0.074
Pro/Arg vs. Arg/Arg		0.74 [0.35–1.59]	0.440	Random	73.3	0.024
Pro/Arg+Pro/Pro vs. Arg/Arg		0.73 [0.34–1.57]	0.424	Random	76.5	0.014
Pro/Pro vs. Arg/Arg+Pro/Arg		0.94 [0.51–1.72]	0.841	Fixed	4.4	0.351

OR odds ratio, *95 % CI* 95 % confidence interval

[a] Random, random-effects model; fixed, fixed-effects model

[b] P_H, *P* values for heterogeneity analyses

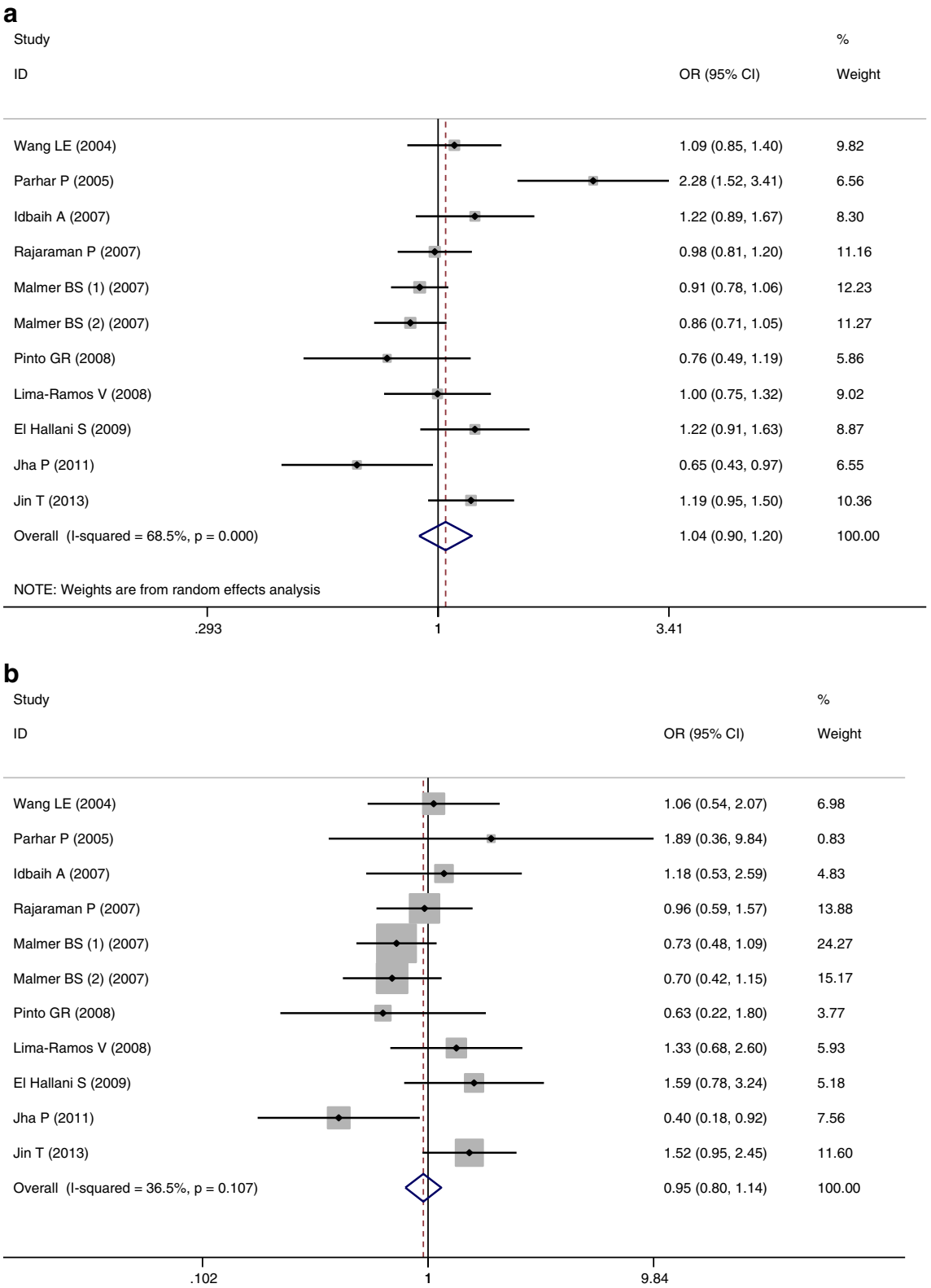

Fig. 1 Forest plots for the association between the P53 codon 72 Arg/Pro polymorphism and glioma risk. **a** Pro allele vs. Arg allele. **b** Pro/Pro vs. Arg/Arg. **c** Pro/Arg vs. Arg/Arg. **d** Pro/Arg+Pro/Pro vs. Arg/Arg. **e** Pro/Pro vs. Arg/Arg+Pro/Arg

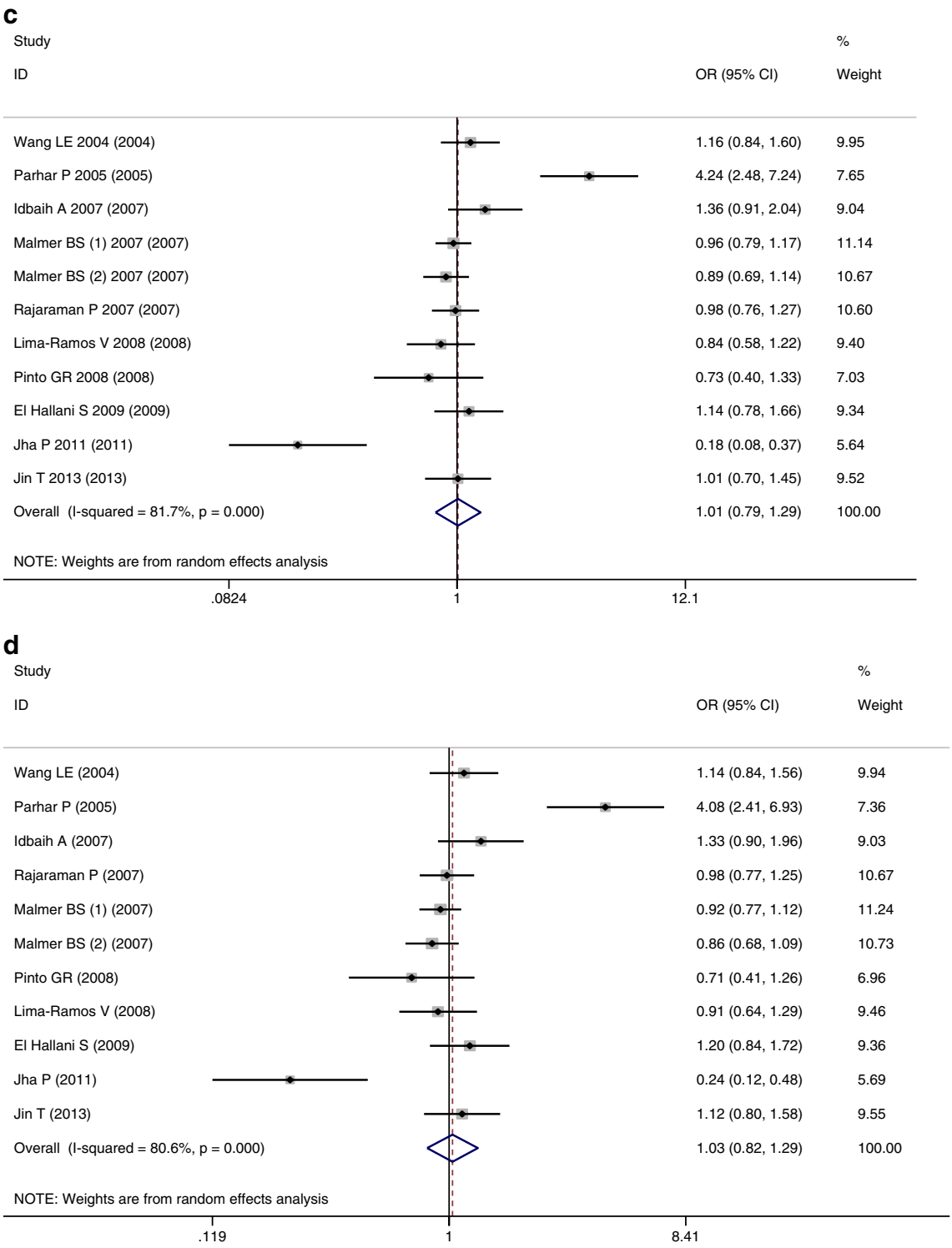

Fig. 1 (continued)

gene models in Caucasians. We failed to perform stratified analyses among Asians and the mixed population due to insufficient available case–control publications.

The association of p53 codon 72 variant with the glioma risk varies among different subtypes of this disease. Lima-Ramos et al. found no statistically significant differences of the p53 codon 72 genotype distributions in patients with distinct histological subtypes of glioma including astrocytoma, glioblastoma, as well as oligodendroglioma [22]. On the contrary, the p53 codon 72 Arg/Pro variant was elucidated

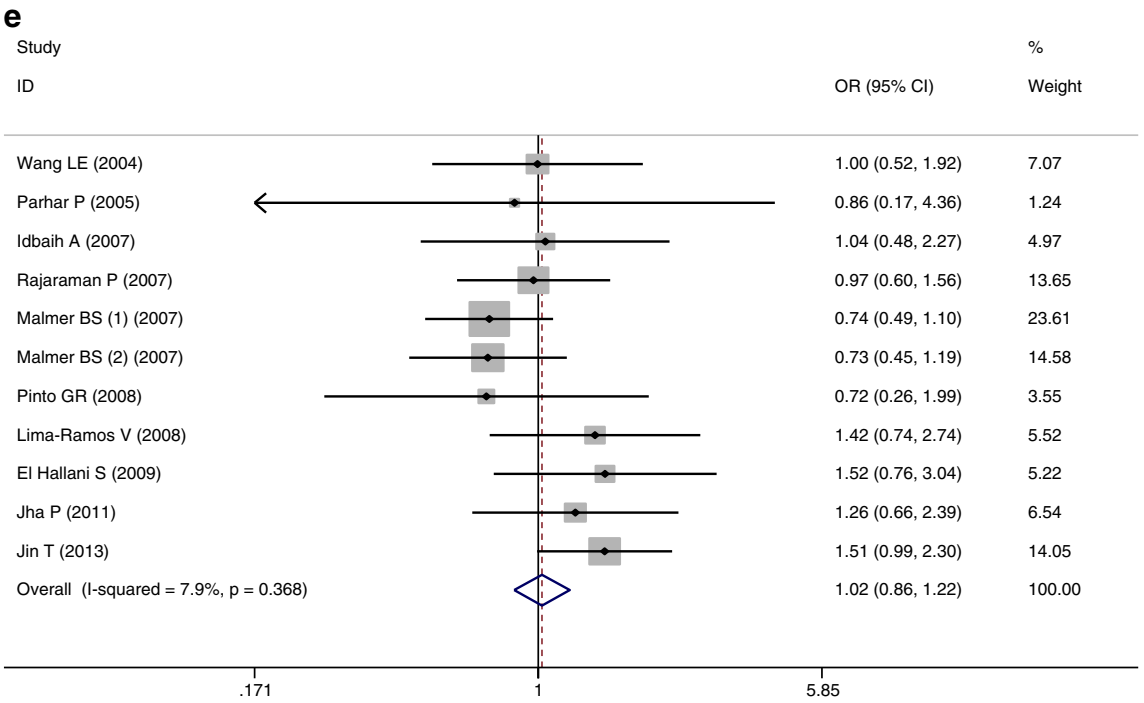

Fig. 1 (continued)

for the first time by Parhar and the colleagues [18] to exert increased risk effects on the high-grade astrocytomas. Diverse occupations, environmental factors, and genetic backgrounds may be responsible for the conflicting findings of independent studies mentioned above. In the present meta-analysis, the Pro/Pro genotype seemed to negatively correlate with the risk of glioblastoma, suggesting a protective role of p53 codon 72 Arg/Pro polymorphism in glioblastoma development. However, the significant correlation was not observed under other gene models except for the comparison of Pro/Pro vs. Arg/Arg. Furthermore, the p53 codon 72 variant was found to be negatively associated with the risk for astrocytomas and oligodendroglioma, although without statistical significance. In relation to the astrocytomas and oligodendroglioma risk, the findings may be due to chance since the overall sample sizes for studies on astrocytomas and oligodendroglioma were insufficient to make precise estimates for the gene association.

According to the source of controls, we stratified the included publications into population-based or hospital-based case–control studies. Interestingly, the pooled ORs for hospital-based studies suggested a negative association of the p53 codon 72 variant with the glioma risk, although without statistical significance ($OR_{\text{Pro allele vs. Arg allele}}=0.92$,

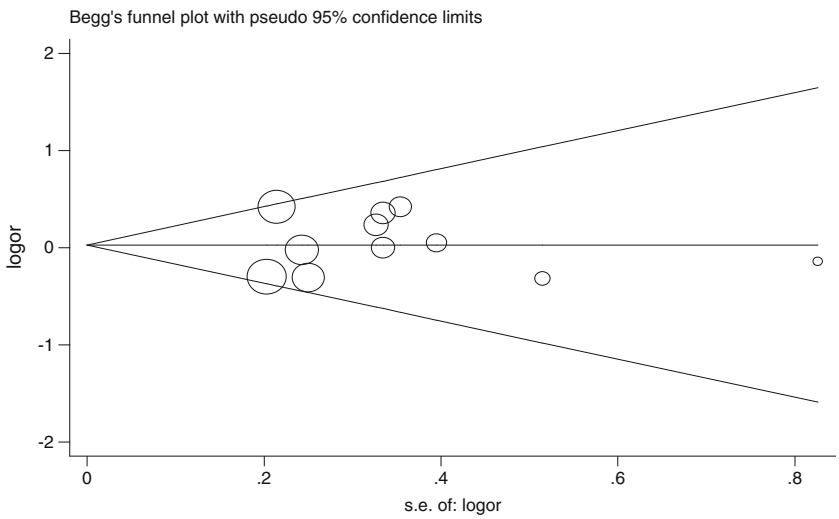

Fig. 2 Begg's funnel plot for the publication bias estimate (Pro/Pro vs. Arg/Arg+Pro/Arg, $P_{\text{Egger}}=0.806$)

95 % CI=0.80–1.05; $OR_{Pro/Pro\ vs.\ Arg/Arg}$=0.82, 95 % CI=0.58–1.17; $OR_{Pro/Arg\ vs.\ Arg/Arg}$ =0.93, 95 % CI=0.78–1.12; $OR_{Pro/Arg\ +\ Pro/Pro\ vs.\ Arg/Arg}$=0.92, 95 % CI=0.77–1.09; $OR_{Pro/Pro\ vs.\ Arg/Arg\ +\ Pro/Arg}$=0.85, 95 % CI=0.60–1.19). Nevertheless, the hospital-based subjects could not be representative of the whole population, which may lead to bias. Thus, this finding must be interpreted with caution and needs further elucidation. El Hallani et al. reported that the p53 codon 72 polymorphism alters the risk for glioblastoma among the younger patients (<45 years), but not the elder patients (>45 years), in Caucasians [24]. We did not make stratified analysis based on the mean age of cases due to limited available data. The role of p53 codon 72 variant in the glioma development across different age stages can be determined by more high-quality, independent studies in the future.

In conclusion, the present meta-analysis by pooling all available published data shows that the polymorphism of p53 codon 72 Arg/Pro may play a protective role in the development of glioblastoma. However, the precise association of p53 codon 72 mutation with the risk for glioma needs to be determined in more case–control studies across diverse ethnicities. In addition, the role of p53 codon 72 Arg/Pro polymorphism in glioma patients of various ages can be further elucidated in future studies.

Conflicts of interest None

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