Int J Clin Exp Med 2016;9(7):13562-13572
www.ijcem.com /ISSN:1940-5901/IJCEM0024248

Original Article

The X-ray repair cross complementing group 1 Arg194Trp polymorphism is a risk factor for glioma: evidence from 15 case-control studies

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Received January 17, 2016; Accepted May 17, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Gliomas are the most common type of primary brain tumors. The X-ray repair cross complementing group 1 (XRCC1) Arg194Trp variant affects the proliferating cell nuclear antigen (PCNA) binding region, which suggests that this mutation may contribute to glioma genesis. A number of articles have examined the association between XRCC1 Arg194Trp and the susceptibility to glioma. However, the results were conflicting. Methods such as the test of heterogeneity, sensitivity analysis, meta-analysis, and assessment of publication bias were all performed in our present meta-analysis, addressing a total of 6,839 patients and 9,173 healthy people. In the overall analysis the XRCC1 Arg194Trp polymorphism indicated a significant association with glioma susceptibility in a homozygous co-dominant model (for TrpTrp vs. ArgArg: OR=1.64, 95% CI=1.26-2.14, I^2=51.3%). In addition, analysis of subgroups presented an increased hazard in Asians and populations-based on both hospitals and populations. The results suggest that the XRCC1 Arg194Trp polymorphism is a genetic risk factor for glioma, especially in Asian populations.

Keywords: XRCC1, Arg194Trp polymorphism, glioma, meta-analysis

Introduction

Gliomas are the most common type of primary brain tumors [1], with an incidence rate of roughly 6/100,000 per year worldwide. Despite the advances in neurosurgery and chemotherapy, median survival of only 12 to 15 months among patients in the United States with glioblastoma, the most common type of glioma [2]. Nowadays, the cause of glioma is still unknown and the etiology has been poorly understood, and may be multifactorial resulting from the interaction of intrinsic and environmental factors [3, 4]. The only established environmental risk factor is the common exposure to therapeutic or high-dose ionizing radiation [4-6].

X-ray repair cross complementing group 1 (XRCC1) acts as a scaffolding protein that functions in the repair of base excision and DNA single-strand breaks [7, 8], the two most common repair pathways in cellular DNA [9]. XRCC1 interacts with a number of proteins crucial to the BER/SSBR pathways, including OGG1, NEIL2, NTH1, MPG, UNG2, AP endonuclease-1 (APE-1), poly (ADP-ribose) polymerase, DNA polymerase β, and DNA ligase 3 [9-15]. Eight non-synonymous coding single nucleotide polymorphism sites were detected in XRCC1, three were related to glioma in former extensively studies. These are: Arg194Trp (R194W, rs17-99782, exon 6), Arg280His (R280H, rs25489, exon 9) and Arg399Gln (R399Q, rs25487, exon 10). Among them, the XRCC1 Arg194Trp variant located in the proliferating cell nuclear antigen (PCNA) binding region, which suggests that this mutation may result in glioma genesis. However, these studies have failed to yield a consistent conclusion [16-30].

Recently, Jiang L [31] reported that XRCC1 Arg194Trp polymorphism might take no influence on the susceptibility of glioma; however, only four literatures were included in this meta-analysis. And Li J [32] reported that XRCC1 Arg194Trp polymorphism led to susceptibility to

Table 1. Characteristics of Studies on XRCC1 Arg194Trp Polymorphism and Glioma Risk included in the meta-analysis

First author	Year	Country	Ethnicity	Cancer type	Cases	Controls	Source of controls	Genotyping method	Frequency of Trp-allele in controls	P_{HWE} in controls
Liu	2007	China	Asian	Glioma	756	736	HB	MassARRAY	0.308	Y
Kiuru	2008	Eropean	Caucasian	Glioma	700	1556	PB	PCR-RFLP	0.06	Y
Liu	2009	USA	Caucasian	Glioma	210	365	PB	MassARRAY	0.004	Y
Mckean	2009	USA	Caucasian	Glioma	962	1922	HB	TaqMan	0.07	Y
Rajaraman	2010	USA	Caucasian	Glioma	342	468	HB	TaqMan	0.08	Y
Zhou	2011	China	Asian	Glioma	271	289	HB	PCR-RFLP	0.25	Y
Hu	2011	China	Asian	Glioma	127	249	HB	PCR-CTPP	0.22	N
Custodio	2011	Brasil	Mixed	Glioma	80	100	PB	PCR-RFLP	0.31	N
Wang	2012	China	Asian	Glioma	624	580	HB	PCR-RFLP	0.21	Y
Liu	2012	China	Asian	Glioma	444	442	HB	MassARRAY	0.14	N
Luo	2013	China	Asian	Glioma	297	415	HB	PCR-RFLP	0.17	N
Pan	2013	China	Asian	Glioma	444	443	HB	MassARRAY	0.15	N
Li	2014	China	Asian	Glioma	370	346	HB	PCR-RFLP	0.278	Y
Xu	2014	China	Asian	Glioma	886	886	HB	PCR-RFLP	0.22	Y
Gao	2014	China	Asian	Glioma	326	376	HB	MassARRAY	0.146	N

HWE, Hardy-Weinberg equilibrium; Y, Yes; N, No; HB, Hospital based; PB, Population based; RFLP, Restriction fragment length polymorphisms polymerase chain reaction.

glioma in Asian but not Caucasian population; however, only fourteen literatures were included in this meta-analysis and some data from original research was wrong. Subsequently seven molecular epidemiologic studies on the association between this polymorphism and glioma risk also demonstrated contradictory results. Here, we update previous meta-analyses, with additional data to evaluate the effect of XRCC1 Arg194Trp polymorphism on glioma incidence. In this meta-analysis, we tried to aim at obtaining outline risk evaluates for the XRCC1 Arg194Trp associated with glioma risk.

Materials and methods

We thoroughly searched all of the available electronic databases such as Web of Science, PubMed, EMBASE, The Cochrane Library, The China National Knowledge Infrastructure (CNKI) Platforms, VIP and Wan Fang using such terms ("glioma" or "gliomas" or "glioblastoma" or "astrocytoma" or "ependymoma" or "oligodendroglioma" or "oligoastrocytoma cancer" or "brain cancer" or "brain tumor"), ("XRCC1" or "Arg194Trp" or "A194T" or "rs1799782" or "X-ray cross-complementing group 1" or "DNA repair gene" or "DNA repair genes" or "X-ray repair cross-complementation group 1" or "X-ray repair cross-complementing group 1" or "BER") and ("variant" or "variants" or "variation" or "polymorphism" or "polymorphisms" or "mutation" or "gene mutant" or "genotypes" or "SNP" or "SNPs" or "single nucleotide polymorphism") (last search was updated on May 1, 2016).

The inclusion criteria indicators of this meta-analysis were: 1) XRCC1 Arg194Trp polymorphism and glioma; 2) sufficient maternal genotype data for calculating an odds ratio (OR) with a 95% confidence interval (CI); and 3) published in English. The criteria for the exclusion of studies are as follows: 1) not relate to the XRCC1 Arg194Trp polymorphism and glioma; 2) not a primary case-control study; 3) no usable or sufficient maternal genotype data reported.

Data collection

The first author, publication year, country of origin, ethnicity, sources of controls, genotyping method, frequency of Trp-allele in controls, number of detected cases and controls were collected independently by two authors (HT.Q and YF.X) in **Table 1**.

Odds ratio (OR) plus 95% CIs was used to estimate the strength of association between glioma risk and the XRCC1 Arg194Trp polymorphism. The pooled ORs were presented for the additive model (Trp versus Arg), homozygous co-dominant model (TrpTrp versus ArgArg), heterozygote co-dominant model (ArgTrp versus ArgArg), dominant model (TrpTrp+ArgTrp versus

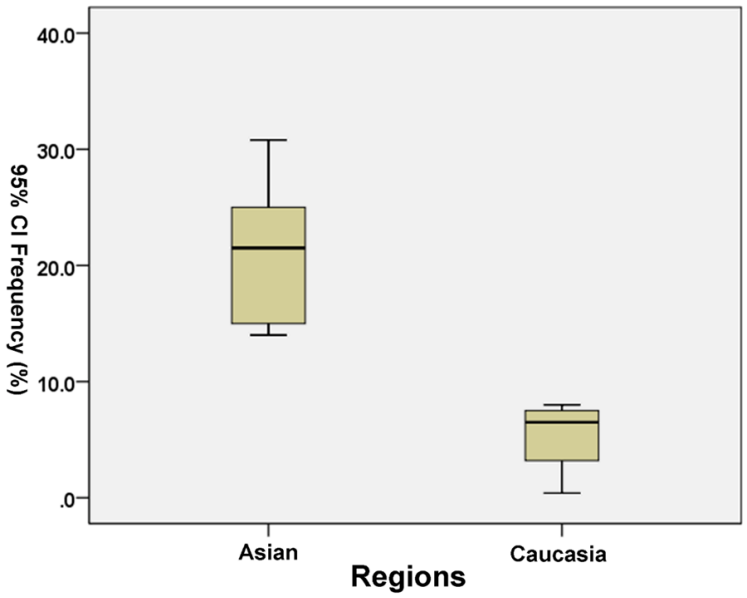

Figure 1. Allele frequencies and their 95% CIs of the XRCC1 Arg194Trp Polymorphism among control subjects by Different Regions.

ArgArg) and recessive model (TrpTrp versus TrpArg+ArgArg).

Statistical methods

First, we assessed HWE for the controls in each study. X^2 test of heterogeneity was calculated in comparison with pooled articles, when *P* value was >0.10 we applied fixed-effects model (Mantel-Haenszel); in contrast, the random-effects models (Der Simonian and Laird) was used. Subgroup analyses were also conducted by ethnicity, source of control, genotyping method, HWE and sample size. Also, the methods of sensitivity analyses and publication bias were performed. In the process of each analysis a single article was removed, and then we analyzed the rest of the articles respectively. The methods of Egger and Begg were to test the publication bias. The result consists of the Begg's funnel plot and Egger's test. All statistical analyses were performed using the STATA software version 12 (Stata Corporation, College Station, TX). Two-sided *P* values less than 0.05 were considered statistically significant.

Results

Literatures

The characteristics of the selected studies are summarized in **Table 1**. In total 593 studies meet our search terms, and 15 eligible studies were finally included in this meta-analysis. Totally, 6,839 patients and 9,173 healthy people were used for this meta-analysis. Among our analysis nine studies of study population were Asians and four of them were Caucasians, three studies were population-based controls and twelve studies were hospital-based controls. The distributions of the genotypes in the control groups in 6 studies were not in HWE. All of included articles were able to analyze for the allele model, homozygous co-dominant model, heterozygote co-dominant model, additive model, dominant model and recessive model.

Meta analysis

Overall, the Trp194 allele was 16.47% (95% CI, 11.33-21.61) among all over the glioma, which was between Caucasian and Asian. There were significant differences in terms of the variant Trp194 allele frequency between the only two ethnicities (Caucasians, 5.35%; 95% confidence interval (95% CI), -0.06-10.76; Asian, 20.92%; 95% CI, 16.77-25.07; p=0.000, **Figure 1**).

ArgArg or Arg genotype was as reference group in our meta-analysis. All ORs and 95% CIs were in **Table 2**. In short, among pooled analysis XRCC1 Arg194Trp polymorphism indicated a significant association with glioma susceptibility (for Trp vs. Arg: OR=1.17 (**Figure 2**), 95% CI=1.02-1.33, I^2=76.2%; for TrpTrp vs. ArgArg: OR=1.64 (**Figure 3**), 95% CI=1.26-2.14, I^2= 51.3%; for ArgTrp vs. ArgArg: OR=1.07, 95% CI=0.92-1.24, I^2=69.6%; for TrpTrp vs. ArgArg +ArgTrp: OR=1.46 (**Figure 4**), 95% CI=1.25-1.72, I^2=22.1%; for ArgTrp+TrpTrp vs. ArgArg: OR=1.15, 95% CI=0.98-1.34, I^2=74.6%). The forest plot of homozygous co-dominant model, additive model and recessive model result were shown in **Figures 2**-**4**.

Subgroup analysis

The similar association between Arg194Trp polymorphism and glioma risk was discovered

Table 2. Meta-analysis of the association between XRCC1 Arg194Trp polymorphism and cancer risk

Variables	No. of studies	Homozygous co-dominant		Heterozygous co-dominant		Recessive		Dominiant		Additive	
		TrpTrp vs. ArgArg	P_{het} [b]	ArgTrp vs. ArgArg	P_{het} [b]	(TrpTrp vs. ArgTrp+ArgArg)	P_{het} [b]	(TrpTrp+ArgTrp vs. ArgArg)	P_{het} [b]	Trp vs. Arg	P_{het} [b]
All	15	**1.64 (1.26, 2.14)**	0.011	1.07 (0.92, 1.24)	0.000	**1.46 (1.25, 1.72)**	0.280	1.15 (0.98, 1.34)	0.000	**1.17 (1.02, 1.33)**	0.000
HWE[a]	9	1.20 (0.97, 1.49)	0.425	0.96 (0.88, 1.05)	0.826	1.20 (0.97, 1.48)	0.386	0.98 (0.90, 1.07)	0.713	1.01 (0.94, 1.09)	0.478
Ethnicity											
Asian	10	**1.53 (1.20, 1.95)**	0.069	1.06 (0.97, 1.16)	0.772	**1.49 (1.18, 1.88)**	0.084	**1.13 (1.03, 1.23)**	0.275	**1.18 (1.06, 1.31)**	0.020
Caucasian	4	1.13 (0.46, 2.78)	0.552	0.87 (0.74, 1.02)	0.621	1.15 (0.47, 2.82)	0.556	0.88 (0.75, 1.03)	0.580	0.89 (0.77, 1.03)	0.549
Mixed	1	**5.24 (2.48, 11.06)**	/	**34.62 (10.61, 112.91)**	/	1.81 (0.97, 3.36)	/	**8.80 (4.37, 17.70)**	/	**3.61 (2.33, 5.60)**	/
Source of controls											
Hospital	12	**1.47 (1.24, 1.75)**	0.115	1.02 (0.94, 1.11)	0.459	**1.44 (1.22, 1.70)**	0.141	1.09 (0.98, 1.21)	0.063	**1.13 (1.01, 1.26)**	0.002
Population	3	**3.90 (2.07, 7.33)**	0.186	2.58 (0.70, 9.57)	0.000	**1.77 (1.01, 3.09)**	0.490	1.88 (0.60, 5.88)	0.000	1.45 (0.63, 3.35)	0.000
Genotype method											
PCR-RFLP	7	**1.74 (1.14, 2.65)**	0.014	1.17 (0.87, 1.56)	0.000	**1.53 (1.21, 1.92)**	0.286	1.25 (0.95, 1.64)	0.000	1.22 (0.99, 1.50)	0.000
MassARRAY	5	1.59 (0.98, 2.56)	0.032	1.09 (0.95, 1.25)	0.441	1.54 (0.99, 2.40)	0.055	1.18 (0.96, 1.44)	0.069	1.21 (0.97, 1.52)	0.004
TaqMan	2	0.85 (0.24, 3.02)	0.642	0.85 (0.69, 1.05)	0.210	0.87 (0.24, 3.08)	0.658	0.85 (0.69, 1.04)	0.186	0.86 (0.71, 1.04)	0.178
PCR-CTPP	1	1.88 (0.95, 3.72)	/	1.36 (0.84, 2.22)	/	1.70 (0.88, 3.31)	/	1.49 (0.97, 2.31)	/	**1.48 (1.05, 2.10)**	/
Sample size in cases											
>800	8	**1.58 (1.15, 2.17)**	0.095	0.99 (0.91, 1.09)	0.201	**1.47 (1.20, 1.80)**	0.135	1.05 (0.91, 1.21)	0.015	1.08 (0.93, 1.26)	0.001
<-800	7	**1.68 (1.04, 2.71)**	0.014	1.34 (0.92, 1.98)	0.000	**1.45 (1.11, 1.72)**	0.331	1.39 (0.98, 1.97)	0.000	**1.31 (1.01, 1.71)**	0.000

[a]Conforming to Hardy-Weinberg equilibrium in controls; [b]*P* value of the Q-test for heterogeneity test. The numbers in parentheses represent 95% confidence interval. The bold numbers mean that the OR values for the contrast models are significant.

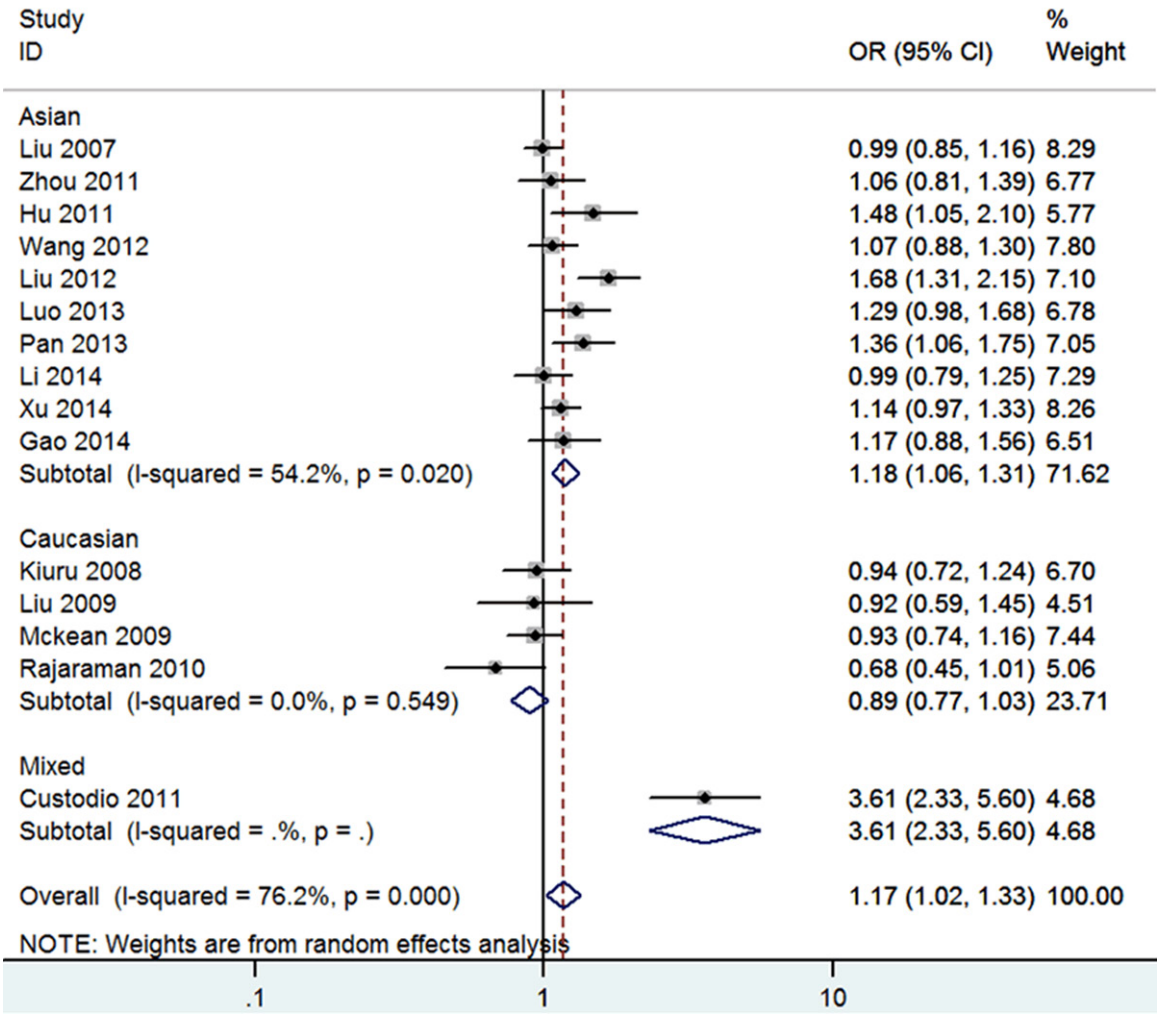

Figure 2. Forest Plot of Glioma Risk Associated with the XRCC1 Arg194Trp Polymorphism (Trp vs. Arg) in Overall and Different Ethnicity. The overall odds ratio (OR) is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a gray square. The overall OR is indicated by a blue diamond.

in the subgroup analyses. In the subgroup analyses were based on Ethnicity, sources of control, genotype method and sample size in included cases. The results of subgroup analysis were robust, which did not vary materially after we excluded the study not fit in with HWE. The following is significant results to describe.

Among subgroup of ethnicity, only in Asian existed significant results were in following genetic models: additive model (for Trp vs. Arg: OR=1.18, 95% CI=1.06-1.31, I^2=54.2%), homozygous co-dominant model (for TrpTrp vs. ArgArg: OR=1.53, 95% CI=1.20-1.95, I^2=43.4%) and recessive model (for TrpTrp vs. ArgArg+ArgTrp: OR=1.49, 95% CI=1.18-1.88, I^2=41.0%) dominant model (for ArgTrp+TrpTrp vs. ArgArg: OR=1.13, 95% CI=1.03-1.23, I^2=18.3%), respectively (**Table 2**). While in Caucasian subgroup it suggested that XRCC1 Arg194Trp polymorphism was no association with glioma. As well in population-based subgroups, similar significant results were found in subgroup of hospital. The detailed information was in **Table 2**. Additionally, most models presented significantly increased risks when the Genotype method was PCR-RFLP.

Test for heterogeneity, sensitivity analyses and publication bias

Pooled comparisons and subgroup analyses were examined the heterogeneity. In additive and homozygous co-dominant models, among

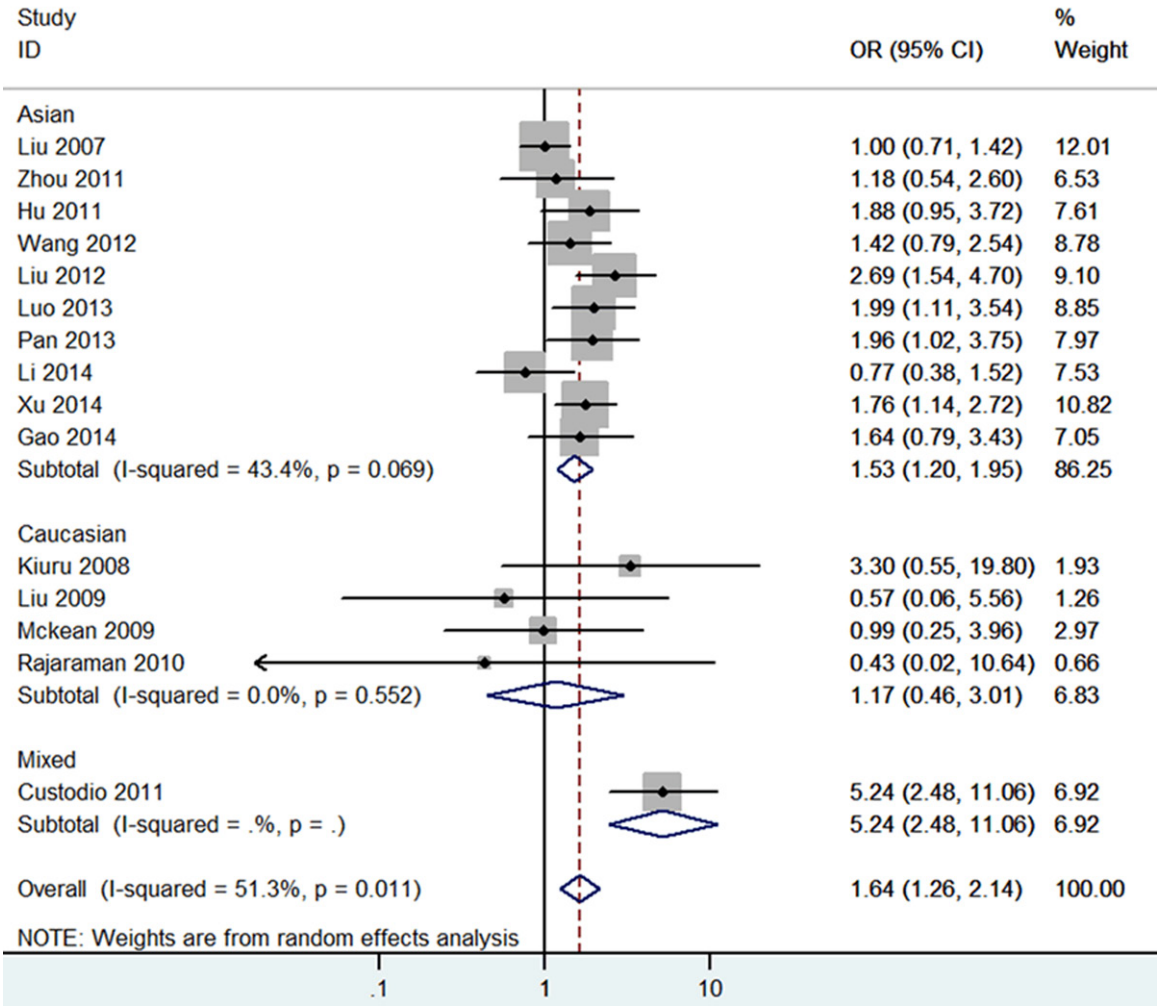

Figure 3. Forest Plot of Glioma Risk Associated with the XRCC1 Arg194Trp Polymorphism (TrpTrp vs. ArgArg) in Overall and Different Ethnicity. The overall odds ratio (OR) is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a gray square. The overall OR is indicated by a blue diamond.

pooled analysis the heterogeneity of *P* values were all <0.1, the results were shown in **Table 2**. Therefore, we performed the source of heterogeneity among Ethnicity, sources of control, genotype method, sample size of case and HWE. Sensitivity analysis was conducted by removing the single studies, one at a time and recalculating the summary ORs to identify the stability of the models. When we performed the sensitivity analyses, no matter overall analyses or subgroup analyses ORs were not altered, suggesting that our results were stability and liability statistically. Also the sensitivity result was in **Figure 5**. We conducted the Begg's funnel plot and Egger's test to test the publication bias of the eligible studies. The result showed no significant evidence of publication bias (for additive model t=1.11, P=0.287; for recessive model t=0.02, P=0.982). The Egger's funnel plot Figure was in **Figure 6**.

Discussion

Glioma is generally considered to be a gene-environment interaction disease, and a better understanding of the mechanism of glioma will help us find better ways to prevent, diagnose, or treat glioma. At present, notwithstanding some risk factors have been found, the etiology of glioma is still poorly understood [33, 34]. However, it is universally acknowledged that the genetic factors play crucial roles in the occurrence of glioma [35, 36]. Confirmed of biomarkers of genetic factors could expect to do early diagnosis, predict patient's outcome, or carry out individualized or personalized therapy. Unfortunately, up to now few genetic bio-

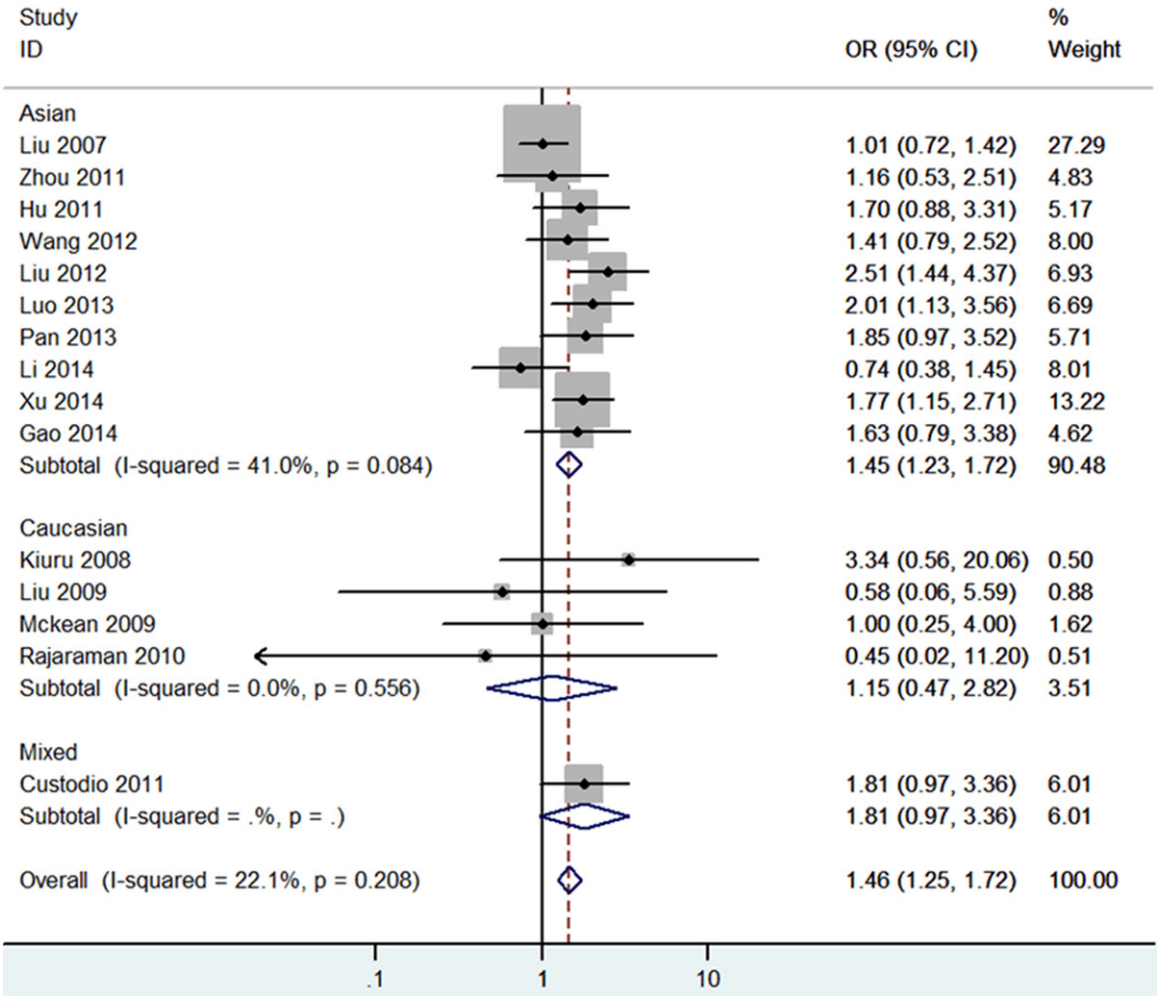

Figure 4. Forest Plot of Glioma Risk Associated with the XRCC1 Arg194Trp Polymorphism (TrpTrp vs. ArgArg+ArgTrp) in Overall and Different Ethnicity. The overall odds ratio (OR) is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a gray square. The overall OR is indicated by a blue diamond.

markers has been identified as good biomarkers for glioma patients. To find some glioma relevant genetic biomarkers is of the most importance to improve the prognosis.

It is universally acknowledged that DNA repair genes could maintain the genome integrity, and thus DNA repair genes polymorphisms are potential candidates which can modify the development of gliomas. XRCC1 is one of the most important DNA repair genes responsible for BER pathway and DBS caused by IR. The XRCC1 Arg194Trp polymorphism is located in an evolutionary conserved linker region, makes the chances of occurrence of chromosomal breaks highly increased [37]. Up to now, a number of articles have been performed to address the association between XRCC1 Arg194Trp polymorphism and the risk of gliomas, but yielded conflicting results. Contradictory results from relatively small articles and previous meta-analysis indicated that XRCC1 Arg194Trp polymorphism was no association with the development of glioma, so an updated meta-analysis should be a proper way to obtain a more definitive conclusion.

Although previous meta-analysis studies have confirmed that the results did not show any association between XRCC1 Arg194Trp polymorphism and glioma risk for all genetic models [31], even in subgroup analyses based on the source of controls, ethnicity and histological subtype. After that, published data regarding the association between Arg194Trp polymorphism and glioma risk were inconsistent.

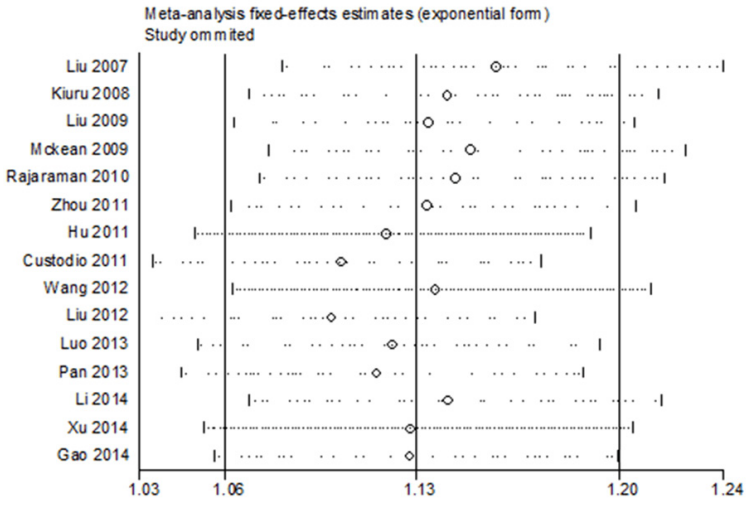

Figure 5. Outlier analysis for the XRCC1 Arg194Trp polymorphism illustrating the influence of each study on pooled OR.

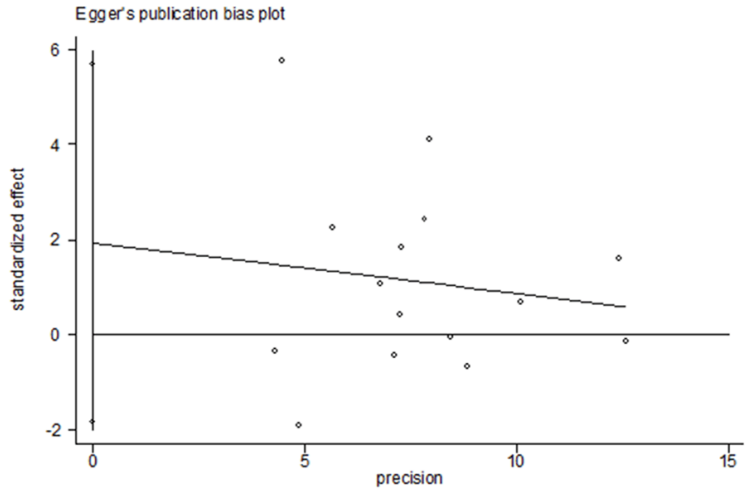

Figure 6. Egger's funnel plot of glioma risk associated with the XRCC1 Arg-194Trp polymorphism (Trp vs. Arg) in overall populations. Each point represents a separate study for the indicated association.

To derive a more accurate estimation of the association between XRCC1 Arg194Trp polymorphism and glioma risk, we performed a meta-analysis. This meta-analysis, including a total of 6,839 glioma cases and 9,173 controls from 15 case-control studies, examined the potential association of the polymorphisms of the DNA repair gene XRCC1 Arg194Trp with glioma risk. We observed a random overall 17% increased risk of glioma for the Trp allele of the Arg194Trp polymorphism, compared with the wild allele (OR, 1.17; 95% CI, 1.02-1.33). We also observed a fixed overall 46% increased risk of glioma for the recessive model (for TrpTrp vs. ArgArg+ ArgTrp) (OR, 1.46; 95% CI, 1.25-1.72). Similarly, for the Arg 194Trp, the variant genotypes (TrpTrp), compared with the wild-type homozygote (Arg/Arg), were associated with a significantly increased glioma risk (OR, 1.64; 95% CI, 1.26-2.14) for ethnicity types without between-study heterogeneity. However, due to the presence of marginal statistical evidence and small sample size for Arg-194Trp, our result as regards this polymorphism should always be regarded as preliminary. However, our analysis shows that even if a general variant in the functional region of a conclusive meaningful gene had an effect on human disease, such as glioma, it may play only a tiny role in the development of glioma, which is conformed to the characteristics of low-penetrance genes [38].

Furthermore, eight recent meta-analyses by Zhang L [39], Sun JY [40], Gu X [41], Adel FM [42], He LW [43], Feng YZ [44], Xu G [45] and Li J [32] were evaluated the association between Arg194Trp polymorphism and glioma risk, which was not completely in consist with our meta-analysis results that Arg194Trp polymorphism may contribute to the susceptibility of glioma, particularly in Asian, but not in Caucasian. It is notable that given the specific multiplicity of possible comparisons and the inescapable adaptation of choosing, associations may have been detected by chance alone. Some articles have been proposed for evaluating correlations between genetic polymorphisms and disease [46]. The claim was that studies "ideally should have the large sample sizes, small *P* values, report associations that make biological sense and alleles that affect the gene product in a physiologically meaningful way" [47]. The scientific hypotheses and

sample size of the study are crucial to know the ratio of false-positive findings of meta-analysis that are attributable to constituent studies with selection bias from publication, poor study design, and non-differential misclassification errors [48].

One study conducted in region of Europe with 700 glioma patients and 1556 controls reported that no association between the Arg194Trp polymorphism and glioma cancer risk [17]. The other studies in USA consisted of a total sample size (1514 cases and 2755 controls) showed that Arg194Trp did not confer an effect on glioma [18-20]. Two of articles did not contain sex, age and other match statistic parameters, whereas since 2012, published articles included detailed statistic parameters such as smoking, drinking, cancer history of first relatives and IR exposure, which suggested that support the current meta-analysis that XRCC1 Arg194Trp may play a role in individual susceptibility to glioma.

In addition, between-study heterogeneity is a potential problem which was not avoidable. Despite several differences in the studies about ethnicity, sample sizes, source of controls, genotype method and HWE, we didn't observe significant heterogeneity between studies for the Arg194Trp polymorphism. Importantly, sensitivity analysis was preformed repeatedly after removal of each particular study. The overall statistical significance of the results in all models was not changed after each removal, suggesting that our results were stability and liability statistically. The sensitivity analysis results were showed in **Figure 5**. In view of this, the results of our meta-analysis, substantially, are sound and reliable.

Similar to other meta-analyses, our study also has a few potential limitations. First, owing to lack of adjusted variables the present meta-analysis was based primarily on unadjusted effect estimates and CIs, thus the effect estimates were relatively imprecise, a more accurate analysis could be conducted if adjusted variables were available in all articles. Second, quite small sample size existed for several subgroup analyses, such as source of controls from population. Third, glioma is known as a multifactor disease, due to lack of detailed data, such as environmental factors, physical inactivity and dietary state factors, thus the gene-gene and gene-environment interactions were not addressed in this meta-analysis. Fourth, several articles indicated that demographic parameters are not well adjusted statistically [17, 19]. Fifth, misclassifications of genotypes may also impact the results because cases were not verification by other gold standard methods in several studies, and the quality control of genotype method was also not well-verificated in some articles. Lastly, although we did not find publication bias, selection bias may exist because only literatures published in English were included.

In conclusion, our current study indicates that XRCC1 Arg194Trp polymorphism may contribute to individual susceptibility of glioma. To further evaluate gene-gene and gene-environment interactions on XRCC1 polymorphisms and glioma risk, thousands of subjects and tissue-specific biochemical characterizations are required.

Disclosure of conflict of interest

None.

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