

doi:10.3969/j.issn.1673-5374.2013.26.008 [http://www.nrronline.org; http://www.sjzsyj.org] Gu XQ, Sun HY, Chang LP, Sun R, Yang HF, Zhang XW, Cong XL. Correlation between X-ray cross-complementing group 1 polymorphisms and the onset risk of glioma: a meta-analysis. Neural Regen Res. 2013;8(26):2468-2477.

Correlation between X-ray cross-complementing group 1 polymorphisms and the onset risk of glioma A meta-analysis

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Research Highlights

(1) Evidence for the role of single nucleotide polymorphisms of the X-ray cross-complementing group 1 (XRCC1) gene as genetic markers for glioma risk is conflicting. Therefore, we performed a meta-analysis to identify statistical evidence for an association between the XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and glioma risk by accumulating all published data.

(2) Experimental design was strict and reasonable, and every possible mode of inheritance was considered. Dominant and recessive genetic models were assumed and, at the same time, the relationship between homozygous mutant genotype frequencies and mutant gene frequency and glioma incidence was investigated.

(3) Meta-analysis results verified that the XRCC1 Arg399Gln polymorphism may be a biomarker of glioma susceptibility, especially in Asian populations. The Arg194Trp and Arg280His polymorphisms were found not to be associated with overall glioma risk.

Abstract

OBJECTIVE: To evaluate the association of X-ray cross-complementing group 1 (XRCC1) Arg399Gln, Arg194Trp and Arg280His polymorphisms with the risk of glioma.

DATA SOURCES: A systematic literature search of papers published from January 2000 to August 2012 in PubMed, Embase, China National Knowledge Infrastructure database, and Wanfang database was performed. The key words used were "glioma", "polymorphism", and "XRCC1 or X-ray repair cross-complementing group 1". References cited in the retrieved articles were screened manually to identify additional eligible studies.

STUDY SELECTION: Studies were identified according to the following inclusion criteria: case-control design was based on unrelated individuals; and genotype frequency was available to estimate an odds ratio (*OR*) and 95% confidence interval (*CI*). Meta-analysis was performed for the selected studies after strict screening. Dominant and recessive genetic models were used and the relationship between homozygous mutant genotype frequencies and mutant gene frequency and glioma incidence was investigated. We chose the fixed or random effect model according to the heterogeneity to calculate *OR* and 95% *CI*, and sensitivity analyses were conducted. Publication bias was examined using the inverted funnel plot and the Egger's test using Stata 12.0 software.

MAIN OUTCOME MEASURES: Association of XRCC1 Arg399Gln, Arg194Trp, and Arg280His polymorphisms with the risk of glioma, and subgroup analyses were performed according to different ethnicities of the subjects. Xinquan Gu, Ph.D., Professor.

Xinquan Gu and Hongyan Sun contributed equally to this article.

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Received: 2013-06-03 Accepted: 2013-08-25 (N20120912001)

Funding: The Fundamental Research Funds for Jilin University in China, No. 450060445246; the High-Tech Industrial Development Project of Jilin Province in China, No. 20090633; and the Scientific Research Foundation of Jilin Province in China, No. 20130206001YY, 20120713 and 200905169; the Scientific Research Foundation of Changchun in China, No. 12SF29. Author contributions: Cong XL, Gu XQ, Sun HY, Chang LP designed the study. Yang HF, Sun HY, and Sun R performed the experiments. Sun HY, Zhang XW, and Sun R performed the statistical analysis and wrote the manuscript. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Author statements: The manuscript is original, has

not been submitted to and is not under consideration by another publication, has not been published previously in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations. **RESULTS:** Twelve articles were included in the meta-analysis. Eleven of the articles were concerned with the Arg399Gln polymorphism and glioma onset risk. Significantly increased glioma risks were found only in the dominant model (Gln/Gln + Gln/Arg *versus* Arg/Arg: OR = 1.26, 95%CI = 1.03-1.54, P = 0.02). In the subgroup analysis by ethnicity, significantly increased risk was found in Asian subjects in the recessive (OR = 1.46, 95%CI = 1.04-2.45, P = 0.03) and dominant models (OR = 1.40, 95%CI = 1.10-1.78, P = 0.007), and homozygote contrast (OR = 1.69, 95%CI = 1.17-2.45, P = 0.005), but not in Caucasian subjects. For association of the Arg194Trp (eight studies) and Arg280His (four studies) polymorphisms with glioma risk, the meta-analysis did not reveal a significant effect in the allele contrast, the recessive genetic model, the dominant genetic model, or homozygote contrast.

CONCLUSION: The XRCC1 Arg399Gln polymorphism may be a biomarker of glioma susceptibility, especially in Asian populations. The Arg194Trp and Arg280His polymorphisms were not associated with overall glioma risk.

Key Words

neural regeneration; meta-analysis; glioma; X-ray cross-complementing group 1; gene polymorphism; meta-analysis; susceptibility; onset risk; gene mutation; grants-supported paper; neuroregeneration

INTRODUCTION

Malignant glioma is the most common primary brain tumor in adults^[1]. Astrocytic, oligodendroglial and ependymal origins account for more than 80% of all brain tumors^[2]. Glioblastoma is the most frequent (65%) and malignant histological type^[3]. The incidence rates of brain tumors have been rather stable since the introduction of CT and MRI; what is more, there is a tendency of higher rates in more developed and industrialized countries^[4]. The etiology and pathogenesis of glioma are still unclear. In humans, the only confirmed environmental risk factor for brain tumors is ionizing radiation^[5-11]. Many kinds of DNA damage, such as oxidative damage to nucleotide bases, single or double-strand breaks in DNA chains, and DNA-protein or DNA-DNA covalent cross-links, may be induced by ionizing radiation, which, however, only accounts for a minority of brain neoplasms. Some reports^[12-14] have indicated that Caucasians have a higher incidence of brain tumors than Asian or black populations, but this finding may reflect socioeconomic differences and under-ascertainment in some regions, rather than differences in genetic susceptibility. Currently, it is believed that variability in DNA repair capacity plays an important role as a modifier of cancer risk^[15]. Single nucleotide polymorphisms within the DNA repair genes have been associated with increased risk of several cancer types^[16]. A large number of genes in different pathways are involved in DNA strand repair to maintain genomic stability^[17].

X-ray cross-complementing aroup 1 (XRCC1) is a DNA repair gene that participates in the base excision repair pathway. XRCC1 is located on human chromosome 19q13.2 and spans a genetic distance of 32 kb, including of 17 exons that encode a 70-kDa protein^[18-19], which functions in the repair of single-strand damage, the most common lesions in cellular DNA^[20]. Biological and biochemical evidence has indicated a direct role for XRCC1 in base excision repair^[21], because it interacts directly with poly (ADP-ribose) polymerase, DNA polymerase-β, and DNA ligase III. Eight nonsynonymous coding single nucleotide polymorphisms were reported in XRCC1 and three of them have been investigated widely because they lead to amino acid changes in the XRCC1 protein; namely, the single nucleotide polymorphisms in codon 194 in exon 6 (base C to T; amino acid Arg to Trp), codon 280 in exon 9 (base G to A; amino acid Arg to His), and codon 399 in exon 10 (base G to A, amino acid Arg to GIn)^[22-24].

To date, many studies have been performed to investigate the association between the XRCC1 polymorphisms and risk of cancers such as breast cancer^[25], and gastroesophageal cancer^[26], but the number of studies that focused on glioma is relatively small^[27]. Evidence regarding the role of the single nucleotide polymorphisms in XRCC1 as genetic markers for glioma risk is inconsistent^[27-32]. The relatively small sample sizes, weak effects, or low penetrances that have been used in published studies may be some of the reasons for the contradictory results. Therefore, we performed a meta-analysis to identify statistical evidence for the association between the XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and glioma risk by examining all the published data.

MATERIALS AND METHODS

Data retrieval

A systematic literature search in PubMed, Embase, the China National Knowledge Infrastructure database (www.cnki.net), and the Wanfang database (www. wanfangdata.com.cn) was performed to identify studies that evaluated XRCC1 polymorphisms and glioma risk (search was last updated on August 1, 2012 from January, 2000). The search terms were as follows: "glioma", "polymorphism or variant or variation" and "XRCC1 or X-ray repair cross-complementing group 1". The languages of the articles were limited to English and Chinese. References cited in the retrieved articles were also screened manually to identify additional eligible studies.

Inclusion and exclusion criteria

Inclusion criteria were defined as follows: (1) case-control design was based on unrelated individuals, and "glioma", or "glioblastoma", or "astrocytoma"; (2) genotype frequency was available for the cases and controls, and at least one of the three polymorphisms, Arg399Gln, Arg194Trp, or Arg280His was studied. Exclusion criteria were: (1) abstracts, reviews, and unpublished reports were not considered; (2) investigations in subjects with family history or cancer-prone disposition were excluded; (3) if more than one study by the same authors using the same case series was published, then only the most recent or complete study was included.

Data extraction

Two investigators independently extracted the following terms from all the eligible publications: first author, year of publication, country of origin and ethnicity of the subjects, characteristics of the cancer cases and controls (population-based, hospital-based, or mixed controls), and genotyping information. For studies that included subjects from different ethnic groups, the data were extracted separately and categorized as Caucasian, Asian, or mixed. Mixed was used when ethnicity information was insufficient and the ethnic groups could not be determined based on the data presented in the article. The two investigators examined the terms and, where necessary, reached a consensus after discussion.

Main outcome measures

Association of the XRCC1 Arg399GIn, Arg194Trp, and Arg280His polymorphisms with the risk of glioma. Subgroup analyses were performed according to different ethnicities of the subjects.

Statistical analysis

For the Arg399Gln and Arg194Trp polymorphisms, we evaluated risk based on an additive model (399Gln allele *versus* 399Arg allele, and 194Trp allele *versus* 194Gln), a dominant model (Gln/Gln + Gln/Arg *versus* Arg/Arg, and Trp/Trp + Trp/Arg *versus* Arg/Arg), a recessive model (Gln/Gln *versus* Arg/Gln + Arg/Arg, and Trp/Trp *versus* Arg/Trp + Arg/Arg), and homozygote contrast (Gln/Gln *versus* Arg/Arg, and Trp/Trp *versus* Arg/Arg). For Arg280His, because of rare variant frequency in the data, we evaluated only the risk of the 280His allele *versus* the 280Arg allele, and a dominant model (His/His + Arg/His *versus* Arg/Arg).

The association between the XRCC1 polymorphisms and the risk of glioma was, measured by odds ratio (OR) and 95% confidence interval (CI) using the RevMan (Review Manager) 5.0 software (http://ims.cochrane.org/ revman). The significance of OR was evaluated using a Z-test and considered statistically significant when P was < 0.05. Subgroup analyses were performed according to the different ethnicities. Heterogeneity among studies was evaluated using a Q-test^[33], and P < 0.10was considered significant. Heterogeneity was calculated using the l^2 metric^[34], which is independent of the number of studies used in a meta-analysis^[35]. When P > 0.10, the pooled OR was calculated by the fixed-effects model; otherwise, the random-effects model was adopted. Hardy-Weinberg equilibrium among the controls for each study was examined using Pearson's chi-square test (P < 0.05 was taken to indicate deviation from Hardy-Weinberg equilibrium). Sensitivity analysis was carried out by including and excluding studies that were not in Hardy-Weinberg equilibrium^[36]. Publication bias was assessed using Egger's test and an inverted funnel plot^[37]. All statistical analyses were performed using RevMan 5.0 and the Stata 12.0. software (Stata-Corp LP, College Station, Texas, USA).

RESULTS

Retrieval results

After an initial search, 45 results were identified and 17 case-control studies were selected for further evaluation. After reading the full texts of the articles, five studies were excluded. One study was excluded because the subjects had a family history or cancer-prone disposition^[38], three were excluded because they reported non-applicable data^[39-41], and one control study was excluded because of overlapping or duplicated data^[42]. Thus, 12 studies remained for data extraction (Figure 1). Seven case-control studies were performed using Caucasian subjects^[27-32, 43], four used Asian subjects^[44-47], and one study used mixed subjects^[48].



Figure 1 Flow diagram showing the selection process for the articles used in this study.

General characteristics of included studies

The 12 included studies were all case-control studies. The characteristics of each case-control study are listed in Table 1.

Meta-synthesis results XRCC1 Arg399GIn and glioma

Among the selected articles, there were 3 786 glioma cases and 6 038 controls for Arg399Gln from 11

studies^[27-32, 43-45, 47-48]. The genotype and allele distributions for each case-control study are shown in Table 2. GIn399 allele frequencies among the Caucasian and Asian controls were 35.00% and 30.86%, respectively. Significant heterogeneity existed between the 11 comparisons ($l^2 = 85\%$, P < 0.001) when considering Arg399GIn. There was no evidence that the GIn allele was associated with glioma cancer risk among the studied populations. The pooled OR was 1.17, 95%CI = 0.98–1.40, by the random-effects model (Z = 1.73, P =0.08). No significant difference in glioma risk was found in the recessive model (OR = 1.16, 95%Cl = 0.89-1.51, P = 0.28). In the dominant model, however, significant differences in glioma risk were found (Gln/Gln + Gln/Arg versus Arg/Arg: OR = 1.26, 95%Cl = 1.03–1.54, P = 0.02; Figure 2). Individuals carrying the XRCC1 Gln/Gln genotype did not show elevated cancer risk compared with individuals with the Arg/Arg genotype (OR = 1.39, 95%Cl = 1.00-1.93, P = 0.05). To study ethnic effects, a subgroup meta-analysis was performed for the Caucasian and Asian populations. No effect of Gln on susceptibility was observed in the Caucasian subgroups (OR = 1.19, 95% CI =0.95–1.50, P = 0.13), but Gln increased glioma risk in the Asian subgroups (OR = 1.34, 95%Cl = 1.12-1.60, P = 0.002). Significantly increased risk was also found for Asian subjects using the recessive (OR = 1.46, 95% CI =1.04-2.05, P = 0.03) and dominant models (OR = 1.40,95%Cl = 1.10-1.78, P = 0.007), and homozygote contrast (OR = 1.69, 95% CI = 1.17 - 2.45, P = 0.005).

XRCC1 Arg194Trp and glioma

Eight of the studies included 3 448 glioma cases and 5 683 controls for Arg194Trp^[32-38,40]. The genotype and allele distributions for each study are listed in Table 3. We analyzed the data using the allele contrast (Gln *versus* Arg), recessive and dominant models (Figure 3), and homozygote contrast (Gln/Gln *versus* Arg/Arg). The Trp194 allele frequency of 27.6% in the Asian controls was significantly higher than the frequency of 6.6% found in the Caucasian controls. Overall, no significant differences were found in the glioma patients and controls in the four comparisons and no significant associations were found in populations with different ethnicity.

XRCC1 Arg280His and glioma

Four studies^[27, 32, 44-45] that reported 1 439 glioma cases and 2 564 controls were included. The genotype and allele distributions for each study are shown in Table 4. To date, only four studies investigated the Arg280His polymorphism and cancer risk; therefore, we did not perform stratification analysis because each subgroup included only two studies.

First author	Year	Ethnicity	Country	SNP studied	Case/control	Design of experiment
Luqiu Zhou ^[44]	2011	Asian	China	Arg399Gln, Arg194Trp, Arg280His	271/289, 271/289, 271/289	Hospital-based case-control study
Xuebin Hu ^[45]	2011	Asian	China	Arg399Gln, Arg194Trp, Arg280His	127/249, 127/247, 127/249	Hospital-based case-control study
Li-E Wang ^[28]	2004	Caucasian	USA	Arg399Gln	309/342	Hospital-based case-control study
Martha J. Felini ^[29]	2007	Caucasian	USA	Arg399Gln	366/427	Population-based case-control study
Elif Yosunkaya ^[30]	2010	Caucasian	Turkey	Arg399Gln	119/180	Hospital-based case-control study
Yanhong Liu ^[31]	2009	Caucasian	USA	Arg399GIn, Arg194Trp	373/364, 210/365	Population-based case-control study
Preetha Rajaraman ^[32]	2010	Caucasian	USA	Arg399Gln, Arg194Trp, Arg280His	350/478, 342/468, 340/466	Hospital-based case-control study
Anne Kiuru ^[27]	2008	Caucasian	Denmark Finland Sweden UK	Arg399Gln, Arg194Trp, Arg280His	699/1 549, 700/ 1 556, 701/1 560	Population-based case-control study
Roberta McKean-Cowdin ^[43]	2009	Caucasian	USA	Arg399Gln, Arg194Trp	1 003/1 971, 962/1 922	2 Hospital-based case-control study
Yanhong Liu ^[46]	2007	Asian	China	Arg194Trp	756/736	Hospital-based case-control study
Jianming Liu ^[47]	2011	Asian	China	Arg399GIn	89/89	Hospital-based case-control study
A.C. Custódio ^[48]	2011	Mixed	Brazil	Arg399Gln, Arg194Trp	80/100, 80/100	Hospital-based case-control study

SNP: Single nucleotide polymorphism.

 Table 2
 Distribution of the XRCC1 Arg399GIn genotype and allele among patients and controls included in the meta-analysis

					Ger	otype				Allele					
First author	Year	r Ethnicity		Case (n)	Co	ontrol (<i>r</i>	1)	Case [n	%)]	Control	HWE (<i>P</i>)			
			Arg/ Arg	Arg/ Gln	Gln/ Gln	Arg/ Arg	Arg/ Gln	Gln/ Gln	Arg	Gln	Arg	Gln			
Li-E Wang ^[28]	2004	Caucasian	134	138	37	131	162	49	406(65.7)	212(34.3)	424(62.0)	260(38.0)	0.924		
Martha J. Felini ^[29]	2007	Caucasian	158	155	53	180	196	51	471(64.3)	261(35.7)	556(65.1)	298(34.9)	0.832		
Elif Yosunkaya ^[30]	2010	Caucasian	15	67	37	91	71	18	97(40.8)	141(59.2)	253(70.3)	107(29.7)	0.454		
Yanhong Liu ^[31]	2009	Caucasian	149	224		169	195								
Preetha Rajaraman ^[32]	2010	Caucasian	142	164	44	205	201	72	448(64.0)	252(36.0)	611(63.9)	345(36.1)	0.053		
Anne Kiuru ^[27]	2008	Caucasian	284	324	91	645	728	176	892(63.8)	506(36.2)	2 036(65.3)	1 080(34.7)	0.212		
Roberta	2009	Caucasian	397	461	145	844	865	262	1 255(62.6)	751(37.4)	2 553(64.8)	1 389(35.2)	0.088		
McKean-Cowdin ^[43]															
Luqiu Zhou ^[44]	2011	Asian	121	113	37	147	118	24	355(65.5)	87(34.5)	412(71.3)	166(28.7)	0.963		
Xuebin Hu ^[45]	2011	Asian	58	48	21	145	75	29	164(64.6)	90(35.4)	365(73.3)	133(26.7)	0.000		
Jianming Liu ^[47]	2011	Asian	23	37	29	28	34	27	83(46.6)	95(53.4)	90(50.6)	88(49.4)	0.026		
A.C. Custódio ^[48]	2011	mixed	23	33	24	29	20	51	79(49.4)	81(50.6)	78(39.0)	122(61.0)	0.000		

HWE: Hardy-Weinberg equilibrium.

					Geno	otype				Al	lele		
First author	Year	Ethnicity	Case (n)			Control (n)			Case [n(%)]	Control [<i>n</i> (%)]		_HWE (<i>P</i>)
		,	Arg/ Arg	Arg/ Trp	Trp/ Trp	Arg/ Arg	Arg/ Trp	Trp/ Trp	Trp	Gln	Arg	Trp	(.)
Yanhong Liu ^[31]	2009	Caucasian	209		1	362		3					
Preetha Rajaraman ^[32]	2010	Caucasian	304	38	0	394	73	1	646(94.4)	38(5.6)	861(92.0)	75(8.0)	0.209
Anne Kiuru ^[27]	2008	Caucasian	626	71	3	1 377	177	2	1 323(94.5)	77(5.5)	2 931(94.2)	181(5.8)	0.131
Roberta	2009	Caucasian	842	117	3	1 664	252	6	1 801(93.6)	123(6.4)	3 580(93.1)	264(6.9)	0.274
McKean-Cowdin ^[4]	3]												
Luqiu zhou ^[44]	2011	Asian	145	112	14	159	117	13	402(74.2)	140(25.8)	435(75.3)	143(24.7)	0.138
Xuebin Hu ^[45]	2011	Asian	71	38	18	163	62	22	180(70.9)	74(29.1)	388(78.5)	106(21.5)	0.000
Yanhong Liu ^[46]	2007	Asian	371	308	77	357	305	74	1 050(69.4)	462(30.6)	1 019(69.2)	453(30.8)	0.457
A.C. Custódio ^[48]	2011	mixed	15	31	34	67	4	29	61(38.1)	99(61.9)	138(69.0)	62(31.0)	0.000

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We used allele contrast (Gln *versus* Arg) and the dominant model (His/His + Arg/His *versus* Arg/Arg) for the analysis because His frequency was low (7.9% in the controls).

Neither the 280His allele (OR = 1.05, 95%CI = 0.88-1.25, P = 0.6) nor His/His + Arg/His (OR = 1.00, 95%CI = 0.82-1.22, P = 0.99) showed evidence of association with glioma risk (Figure 4).

Heterogeneity and sensitivity analysis

Significant heterogeneity between studies was observed in some comparisons, and the detailed data are shown in Table 5.

Random-effects models were used when necessary to evaluate the combined ORs. Sensitivity analysis was carried out by the sequential omission of studies that did not comply with Hardy-Weinberg equilibrium under various comparisons in all populations and in the different ethnicity subgroups. For Arg399Gln, and Gln/Gln + Gln/Arg versus Arg/Arg, the exclusion of three studies in which the genotype distributions among the controls deviated from Hardy-Weinberg equilibrium significantly influenced the result of the meta-analysis; that is, Gln/Gln + Gln/Arg versus Arg/Arg with OR = 1.26, 95% CI =1.03–1.54, P = 0.02 changed to OR = 1.25, 95% C/: 0.99–1.57, P = 0.06 after the exclusion. In the other comparisons, the significance of pooled ORs was not influenced by any single study on the population as a whole or on subgroups.

We investigated the XRCC1 Arg194Trp and Arg280His polymorphisms using the same method, and found that none of the pooled results was significantly affected by addition or removal of any individual study that deviated from Hardy-Weinberg equilibrium.

Publication bias

We performed a Begg's funnel plot and Egger's test to assess publication bias of all included studies. Publication bias for Arg399GIn was detected under the dominant model; however, the shape of the funnel plot seemed symmetrical, indicating that there was no obvious publication bias (Figure 5).

					Gen	otype								
First author	Year	Ethnicity	Case (n))	Control (n)			Case [<i>n</i> (%)]		Control [n(%)]		.HWE (<i>P</i>)	
		Tour Etrinoity	Arg/ Arg	Arg/ His	His/ His	Arg/ Arg	Arg/ His	His/ His	Arg	His	Arg	His	(/)	
Preetha Rajaraman ^[32]	2010	Caucasian	312	28	0	417	48	1	652(95.9)	28(4.1)	882(94.6)	50(5.4)	0.756	
Anne Kiuru ^[27]	2008	Caucasian	633	67	1	1 399	157	4	1333(95.1)	69(4.9)	2 955(94.7)	165(5.3)	0.854	
Lu-qiu zhou ^[44]	2011	Asian	218	45	8	240	44	5	481(88.7)	61(11.3)	524(90.7)	54(9.3)	0.085	
Xuebin Hu ^[45]	2011	Asian	72	28	27	153	58	38	172(67.7)	82(32.3)	364(73.1)	134(26.9)	0.000	

HWE: Hardy-Weinberg equilibrium.

	Case		Contr			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%CI	Year	M-H, Fixed, 95%CI
2.1.1 Caucasian								
Kiuru 2008 [27]	68	701		1560	44.4%	0.93 [0.69, 1.26]		-
Rajaraman 2010 ^[32]	28	340	49	466	18.7%	0.76 [0.47, 1.24]	2010	
Subtotal (95%CI)		1041		2026	63.1%	0.88 [0.68, 1.14]		T
Total events	96		210	0.01				
Heterogeneity: Chi ² = Test for overall effect:				= 0%				
rest for overall effect:	2 = 0.96	(P = 0	(4)					
2.1.2 Asian								
Zhou 2011 [H4]	53	271	49	289	18.8%	1.19 (0.77, 1.83)	2011	
Hu 2011 [45]	55	127	96	249	18.1%	1.22 [0.79, 1.88]		-+
Subtotal (95%CI)		398		538	36.9%	1.20 [0.89, 1.63]		*
Total events	108		145					
Heterogeneity: Chi ² =	0.01, df =	1 (P =	0.94); l ² :	= 0%				
Test for overall effect:	Z=1.19	(P = 0.1	(3)					
Total (95%CI)		1439		2564	100.0%	1.00 [0.82, 1.22]		
Total events	204	1435	355	2004	100.0%	1.00 [0.02, 1.22]		Ť
Heterogeneity: Chi#=		3 (P =		= 0%			H	
Test for overall effect:							0	.10.2 0.5 1 2 5 10
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Egger's test provided further statistical evidence that there was no significant publication bias in the metaanalysis (Egger's test: Gln/Gln + Gln/Arg *versus* Arg/Arg: t = 1.50, P = 0.167; Gln *versus* Arg: t = 0.75, P = 0.474; Trp *versus* Arg: t = 1.17, P = 0.295; and His *versus* Arg: t = -0.33, P = 0.776).

DISCUSSION

DNA damage repair plays a major role in protecting genomes from assaults of various oncogenic mutations as the result of premutational DNA damage^[49]. Base excision repair is an important pathway of damage repair. DNA damage generated by different carcinogenic agents can be repaired primarily through the base excision repair pathway, which is composed of many DNA repair genes. Human XRCC1 is an important component of the base excision repair pathway that fixes base damage and DNA single-strand breaks caused by ionizing radiation exposure^[24]. XRCC1 constitutes one of the components in the base excision repair pathway^[50]. XRCC1 was found to have no catalytic activity; rather, it acts as a physical scaffold by associating with DNA ligase III, DNA polymerase B, human apurinic/apyrimidinic endonuclease, polynucleotide kinase, and poly adenosine diphosphate ribose polymerase^[51-52].

Polymorphisms in the XRCC1 gene have been reported to be associated with altered risk of several types of cancer.

Table 5 XRCC1 polymorphisms and associated risk of glioma with the main ORs in meta-analysis

Contrast	Ethnicity	OR (95%Cl)	P for heterogeneity	ľ(%) ľ	Analysis model	P for Z-test
Arg399Gln						
Gln versus Arg	All	1.17(0.98,1.40)	0.000	85	Random	0.08
	Caucasian	1.19(0.95,1.50)	0.000	90	Random	0.13
	Asian	1.34(1.12,1.60)	0.63	0	Fixed	0.002
Gln/Gln versus Arg/Gln + Arg/Arg	All	1.16(0.89,1.51)	0.000	74	Random	0.28
	Caucasian	1.20(0.89,1.63)	0.0008	76	Random	0.23
	Asian	1.46(1.04,2.05)	0.56	0	Fixed	0.03
Gln/Gln + Gln/Arg versus Arg/Arg	All	1.26(1.03,1.54)	0.000	78	Random	0.02
	Caucasian	1.25(0.96,1.61)	0	86	Random	0.09
	Asian	1.40(1.10,1.79)	0.64	0	Fixed	0.007
Gln/Gln versus Arg/Arg	All	1.39(1.00,1.93)	0.000	80	Random	0.05
	Caucasian	1.45(0.93,2.26)	0.000	87	Random	0.10
	Asian	1.69(1.17,2.45)	0.75	0	Fixed	0.005
Arg194Trp						
Trp versus Arg	All	1.16(0.88,1.52)	0.000	86	Random	0.29
	Caucasian	0.89(0.76,1.04)	0.35	4	Fixed	0.13
	Asian	1.12(0.90,1.39)	0.1	57	Random	0.32
Trp/Trp versus Arg/Arg + Arg/Trp	All	1.22(0.95,1.55)	0.57	0	Fixed	0.12
	Caucasian	1.15(0.47,283)	0.55	0	Fixed	0.76
	Asian	1.13(0.85,1.49)	0.41	0	Fixed	0.4
	Mixed					
Trp/Trp + Trp/Arg versus Arg/Arg	All	1.21(0.87,1.70)	0.000	87	Random	0.26
	Caucasian	0.87(0.74,1.03)	0.39	0	Fixed	0.10
	Asian	1.06(0.90,1.24)	0.19	40	Fixed	0.49
Trp/Trp versus Arg/Arg	All	1.68(0.94,3.00)	0.006	67	Random	0.08
	Caucasian	1.32(0.49,355)	0.44	0	Fixed	0.59
	Asian	1.14(0.86,1.53)	0.27	23	Fixed	0.36
Arg280His						
His versus Arg	All	1.05(0.88,1.25)	0.19	37	Fixed	0.6
His/His + Arg/His versus Arg/Arg	All	1.00(0.82,1.22)	0.42	0	Fixed	0.99

Random: Random-effect model; Fixed: fixed-effect model; OR: odd ratio; Cl: confidence interval.



While the XRCC1 399Gln (G) allele was found to be a risk factor for breast^[53] and rectal cancers^[54], the Arg/Gln (AG) genotype was found to be protective against leukemia, multiple myeloma, head and neck carcinoma^[55], and the Gln/Gln (GG) genotype was protective against sporadic breast cancer^[56].

However, the association between the XRCC1 polymorphisms and glioma risk has been investigated only in the past five years and the number of studies is relatively rare, and the results have been inconsistent. Five different studies concluded that XRCC1 polymorphisms lack any association with glioma risk^[27-30, 32], while a study in 2009 found the opposite result^[31]. Thus, we performed a metaanalysis to comprehensively analyze the associations. We evaluated the association between the XRCC1 polymorphisms Arg399Gln, Arg194Trp and Arg280His and risk of glioma based on 12 case-control studies. For the Arg399Gln polymorphism, an overall effect was found in the dominant model (Gln/Gln + Gln/Arg *versus* Arg/Arg), which is inconsistent with the findings of Wang *et al* ^[28], Felini *et al* ^[29], and Kiuru *et al* ^[27].

For the association of the Arg194Trp and Arg280His polymorphisms and glioma risk, the meta-analysis did not reveal a significant effect in allele contrast, the recessive genetic model, the dominant genetic model, or homozygote contrast. These findings suggest that the XRCC1 Arg194Trp polymorphism, rather than the Arg280His and Arg399Gln polymorphisms, may play a role in susceptibility to cancers^[57]. Although the association of the XRCC1 Arg194Trp and Arg280His polymorphisms with the incidence of glioma has not yet been clearly defined, these polymorphisms may have an effect on drug sensitivity and radiosensitivity. GIn399 allele frequency rates in the Caucasian and Asian controls were 35% and 30.86%, respectively. The Trp194 allele frequency was 27.6% in Asian controls, which was significantly higher than the 6.6% frequency in the Caucasian controls. These frequency rates were similar to the rates reported in a previous meta-analysis^[57]. For Gln399, in European and Asian controls, the frequency rates were 34.7% (95%Cl = 33.8-35.6) and 26.5% (95% CI = 25.6-27.4), respectively. For Trp194, the frequency rates in Caucasian and Asian controls were 6.6% (95%CI = 5.9-7.4) and 31.2% (95% CI = 29.6-32.8), respectively. This result showed that the distribution of these alleles varied among the different ethnic subgroups, and indicated that a subgroup analysis based on ethnicity should be performed. We found that GIn399 increased glioma risk in Asian populations, OR = 1.34, 95%Cl = 1.12-1.60, P = 0.002. Significantly increased risk was also found in the Asian subjects in the recessive model (OR = 1.46, 95% CI =1.04-2.45), the dominant model (OR = 1.40, 95%CI =1.10–1.79), and homozygote contrast (OR = 1.69, 95%CI = 1.17–2.45). However, the genotype distributions among the controls in the studies by Hu et al [45] and Liu et al ^[31] were not in Hardy-Weinberg equilibrium, probably because of the small sample size that was used. Because only a few studies examined the association between polymorphisms and glioma risk in Asian subjects, and the OR was not altered substantially when the subgroup in Hardy-Weinberg equilibrium was pooled, we included these two studies^[31, 45] in our analysis.

Nevertheless, final conclusions cannot be drawn by studying only the genotype distribution in the healthy controls. Other factors, such as ionizing radiation and genetic background, should be considered, and further studies in Asian populations with larger sample sizes are still needed.

There were some limitations in this meta-analysis. First, significant heterogeneity between studies was observed in some of the comparisons, mainly because of the limited sample size, variability among populations, and variations in the genotyping methods and experimental designs. Second, nine of the 12 selected studies were hospit-al-based and only three were population-based. Although the subjects were collected randomly from the general population, there is still some risk of selection bias. The genotype distributions of the controls in three of the studies deviated from Hardy-Weinberg equilibrium^[45, 47-48]. Third, only data published in the selected databases were included. It is possible that some relevant unpublished or published studies that reported invalid results

were missed, causing our results to contain some inaccuracies. Fourth, the ethnicity data were not stratified by other factors such as pathological grade and ionizing radiation exposure, because sufficient information could not be extracted from the limited number of original studies. Despite these limitations, we chose the fixed or random effect model according to the heterogeneity, and performed subgroup analysis to reduce the heterogeneity. At the same time, sensitivity and publication bias were investigated.

In conclusion, our results suggest that the XRCC1 Arg399Gln polymorphism is associated with increased risk of glioma, especially in Asian populations. The Arg194Trp and Arg280His polymorphisms lack association with glioma risk in the common population. More well-designed studies with larger sample sizes are needed to fully analyze the associations of XRCC1 polymorphisms with glioma risk, which may reveal the combined effects of related DNA repair gene polymorphisms.

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(Reviewed by Biswas M, Wysong S, Lu ZM, Liu YL) (Edited by Wang LM, Qiu Y, Li CH, Song LP, Liu WJ, Zhao M)