RESEARCH ARTICLE

Association Between XRCC1 Gene Polymorphisms and Risk of Glioma Development: A Meta-analysis

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Abstract

Objective: Previous studies of the association between X-ray cross-complementing group 1 (XRCC1) gene polymorphisms and the gliomas risk have yielded conflicting results, and thus a meta-analysis was performed to provide a more accurate estimation. Methods: A computerized literature search of 5 electronic databases was conducted to identify the relevant studies. Fixed or random effect models were selected based on the heterogeneity test. Publication bias was estimated using Begg's funnel plots and Egger's regression test. Results: A total of 11 studies (3,810 cases and 6,079 controls), 7 studies (2,928 cases and 5,048 controls), and 4 studies (1,461 cases and 2,593 controls) were finally included in the analyses of the association between XRCC1 Arg399Gln, Arg194Trp, and Arg280His polymorphisms and glioma risk, respectively. The pooled results showed that GlnGln carriage was associated with moderately increased risk of gliomas in Asians (GlnGln vs. ArgArg, OR=1.490, 95%CI 1.031-2.153; GlnGln/ArgGln vs. ArgArg, OR=1.321, 95%CI 1.037- 1.684), whereas a marginal association was revealed in Caucasians. For the Arg194Trp polymorphism, although a significant association was shown in the homozygous genotype comparisons (TrpTrp vs. ArgArg, OR = 2.209, 95%CI 1.398- 2.945), no significant link was found on subgroup analysis stratified by ethnicity. With regard to the Arg280His polymorphism, no significant association was found in each comparison. No particular study was found to significantly influence the pooled results, and no potential publication bias was detected. Conclusions: This meta-analysis suggested that the XRCC1 Arg399Gln polymorphism is moderately associated with increased risk of gliomas in Asians, while Arg194Trp and Arg280His polymorphisms demonstrated no significant influence. Due to the limited studies and the potential confounders, further studies are needed to confirm these results.

Keywords: XRCC1 - DNA repair gene - gliomas - gene polymorphism

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Introduction

Gliomas are tumors of glial origin of the central nervous system (CNS), exhibiting various degrees of differentiation inside the same tumor (Kyritsis et al., 2010). Gliomas account for almost 80% of primary malignant brain tumors, and result in more years of life lost than do any other tumors (Schwartzbaum et al., 2006). While the exact molecular causes of gliomas remain unclear, ionizing radiation (IR) and genetic alterations have been demonstrated to be established risk factors for gliomas (Schwartzbaum et al., 2006). It has been well recognized that DNA damage is an important mechanism in the development of various cancer including gliomas. If damaged DNA is not repaired, mutations and development of cancer occurs. In this perspective, polymorphisms of DNA repair genes are plausible candidates which can modify the risk of gliomas.

At present, increasing studies have been conducted to investigate the potential association between DNA repair genes and the risk of gliomas (Goode et al., 2002; Felini et al., 2007; Liu et al., 2008; Kyritsis et al., 2010; Zhou et al., 2011; Custodio et al., 2012). Among them, X-ray cross-complementing group 1 (XRCC1), an important gene responsible for base escision repair (BER) of single-strand breaks (SSBs), has gained increasing interest in recent years. XRCC-1 is located on chromosome 19 q13.2, encoding an 70 kD enzyme involved in the BER pathway, amending small lesions such as single-strand breaks, non-bulky adducts oxidative damage, alkylation, methylation and also acts as an alternative route of DNA double-strand break (DSB) nonhomologous end-rejoining (Taylor et al., 2002; Caldecott, 2003; Audebert et al., 2004; Brem and Hall, 2005; Wong and Wilson, 2005). Several nonsynonymous single nucleotide polymorphisms (SNPs) have been reported in XRCC1 genes, among which the Arg399Gln (rs25487), Arg194Trp (rs1799782) and Arg280His (rs25489), were the most investigated one.

Wang et al. firstly investigated the association of XRCC1 gene polymorphisms and the gliomas risk (Wang et al., 2004). Since then, a series of studies especially conducted in recent years for the associations between

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XRCC1 gene polymorphisms and the risk of gliomas have been published. Unfortunately, these epidemiological studies performed in different countries have yielded conflicting results from strong links to no association. The inconsistency of these studies may be explained by the relatively small sample size, difference in population background and study design, etc. Therefore, a timely meta-analysis summarized the results of these studies would provide more accurate estimate of the associations between XRCC1 gene polymorphisms and risk of gliomas.

Materials and Methods

Literature and search strategy

A computerized literature search was performed to identify the relevant studies from 5 electronic databases including PubMed, ISI Web of Science, China National Knowledge Infrastructure (CNKI), Database of Chinese Scientific and Technical Periodicals (VIP), and China Biology Medical literature database (CBM). The following key words were jointly used: ("X-ray cross-complementing group 1" or "XRCC1" or "DNA repair gene") and ("glioma" or "glioblastoma" or "astrocytoma") and ("polymorphism" or "gene mutant"). The reference lists of review articles and the references cited in the retrieved studies were hand-searched for the collection of omitted relevant studies. If more than one article were published using the same case series, only the study with largest sample size was selected. The literature search was updated on Jun, 2012.

Inclusion criteria

The studies included must meet the following criteria: (1) evaluating the association between XRCC1 Arg399Gln (rs25487) and/or Arg194Trp (rs1799782) and/or Arg280His (rs25489) polymorphisms and the risk of gliomas; (2) case-control or cohort design; (3) the study was published in English or Chinese; (4) providing sufficient data for calculation of odds ratio (ORs) with the corresponding 95% confidence interval (95%CI). All identified studies were reviewed independently by two investigators to determine whether an individual study was eligible for inclusion in this meta-analysis.

Data extraction

Two investigators independently extracted the data from all eligible publications according to the criteria. The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity of the study population; (5) source of control subjects; (6) numbers of cases and controls; (7) gender and age of enrolled subjects; and (8) numbers of genotypes in cases and controls.

Statistical analysis

χ^2 analysis with exact probability was used to test departure from Hardy-Weinberg equilibrium (HWE) for the genotype distribution in controls. The association between XRCC1 gene polymorphisms and risk of gliomas was estimated by calculating pooled ORs and 95%CI. We estimated the risk for mutant alleles, variant homozygous genotypes and heterogeneous genotypes compared with the wild-type homozygous genotypes, respectively, and then for the combination of homozygous and heterogeneous genotypes compared with the wild type genotypes. The significance of the pooled effect size was determined by Z test. Heterogeneity among studies was assessed using Q test as well as the I^2 statistic (Higgins and Thompson, 2002). The DerSimonian and Laird random effect model (REM) was used as the pooling method when $I^2 > 50\%$, otherwise, the Mantel-Haenszel fixed effect model (FEM) was considered to be the appropriate choice (Higgins and Thompson, 2002). Subgroup analyses were stratified by ethnicity, source of control, and the methods for genotyping. Sensitivity analysis was undertaken by removing an individual study each time to check whether any of single study could bias the overall estimate (Tobias, 1999). Begg's funnel plots and Egger's regression test were undertaken to assess the potential publication bias (Harbord et al., 2006). Probability less than 0.05 was judged significant except for the I^2 statistic. Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of studies

A total of 47 relevant studies concerning XRCC1 gene polymorphisms and the risk of gliomas were identified. 36 studies were excluded, while 11 studies mainly published in 2007-2012 were finally included in the analysis (Wang et al., 2004; Felini et al., 2007; Kiuru et al., 2008; Liu et al., 2009; McKean-Cowdin et al., 2009; Rajaraman et al., 2010; Yosunkaya et al., 2010; Custodio et al., 2011; Hu et al., 2011; Liu et al., 2011; Zhou et al., 2011). The study by Kiuru et al. enrolled subjects from four countries including Demark, Finland, Sweden, and UK, but did not provide the genotypes of cases and controls of each country, thus was still considered as one study (Kiuru et al., 2008). Among these relevant studies, 3 studies investigated 2 polymorphisms, while 4 studies investigated 3 polymorphisms, and thus a total of 11, 7, and 4 studies were finally included in the analysis of associations between XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms and the risk of gliomas, respectively. All the included studies were case-control design, and used peripheral blood samples for DNA extraction. Genotyping was performed by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), TaqMan, and etc. Most of the studies did not mention the ionizing radiation of enrolled subjects, while higher ionizing exposure rate in cases was reported in 4 studies (Liu et al., 2009; Hu et al., 2011; Liu et al., 2011; Zhou et al., 2011). The detailed characteristics of the included studies were shown in the Table 1.

Meta-analysis results

A total of 11 studies containing 3810 cases and 6079 controls were included for the analysis of XRCC1 Arg399Gln polymorphism and the risk of gliomas, while 7 studies containing 2928 cases and 5048 controls, and 4 studies containing 1461 cases and 2593 controls were

Table 1. Characteristics of Individual Studies for the Association Between XRCC1 Polymorphisms and Gliomas Risk

First author	Year	Country	Ethnicity	Sex[a]	Age[b]	IR exposure[c]	Source of control[d]	Genotypes distributione						Genotyping metod[f]
								Case			Control			
								11	12	22	11	12	22	
Arg399Gln (rs25487)														
Zhou	2011	China	Asian	62.0/62.3	47.8/46.9	4.4/1.0	Hospital-based	121	113	37	147	118	24	TaqMan
Liu	2011	China	Asian	58.4/58.4	>50	12.4/2.2	Hospital-based	29	37	23	27	34	28	TaqMan
Hu	2011	China	Asian	69/67	49.5/48.9	11.0/4.4	Hospital-based	58	48	21	145	75	29	PCR-CTPP
Custodio	2011	Brazil	Mixed	65/63	45/45	NA	Population-based	23	33	24	29	20	51	PCR-RFLP
Yosunkaya	2010	Turkey	Caucasian	39.5/33.9	52.4/49.7	NA	Hospital-based	15	67	37	91	71	18	PCR-RFLP
Rajaraman	2010	USA	Caucasian	54.7/46.1	51.2/49.2	NA	Hospital-based	142	164	44	205	201	72	TaqMan
Mckean-Cowdin	2009	USA	Caucasian	61.0/51.1	56.3/53.6	NA	Mixed	397	461	145	844	865	262	Several methods
Liu	2009	USA	Caucasian	56.8/43.6	NA	9.4/5.9	Population-based	149	162	62	169	145	50	MassARRAY
Kiuru	2008	Several	Caucasian	60.8/45.2	48.2/51.8	NA	Population-based	284	324	91	645	728	176	PCR-RFLP
Felini	2007	USA	Caucasian	NA	NA	NA	Population-based	158	155	53	180	196	51	PCR-RFLP
Wang	2004	USA	Caucasian	54.0/48.8	44.1/43.8	NA	Mixed	134	138	37	131	162	49	PCR-RFLP
Arg194Trp (rs1799782)														
Zhou	2011	China	Asian	62.0/62.3	47.8/46.9	4.4/1.0	Hospital-based	145	112	14	159	117	13	TaqMan
Hu	2011	China	Asian	58.4/58.4	49.5/48.9	11.0/4.4	Hospital-base	71	38	18	163	64	22	PCR-CTPP
Custodio	2011	Brazil	Mixed	65/63	45/45	NA	Population-based	15	31	34	67	4	29	PCR-RFLP
Rajaraman	2010	USA	Caucasian	54.7/46.1	51.2/49.2	NA	Hospital-based	304	38	0	394	73	1	TaqMan
Mckean-Cowdin	2009	USA	Caucasian	61.0/51.1	56.3/53.6	NA	Mixed	842	117	3	1664	252	6	Several methods
Liu	2009	USA	Caucasian	56.8/43.6	NA	9.4/5.9	Population-based	180	29	1	310	52	3	MassARRAY
Kiuru	2008	Several	Caucasian	60.8/45.2	48.2/51.8	NA	Population-based	626	71	3	1377	177	2	PCR-RFLP
Arg280His (rs25489)														
Zhou	2011	China	Asian	62.0/62.3	47.8/46.9	4.4/1.0	Hospital-based	218	45	8	240	44	5	TaqMan
Hu	2011	China	Asian	69/67	49.5/48.9	11.0/4.4	Hospital-based	72	28	27	153	58	38	PCR-CTPP
Rajaraman	2010	USA	Caucasian	54.7/46.1	51.2/49.2	NA	Hospital-based	312	28	0	417	48	1	TaqMan
Kiuru	2008	Several	Caucasian	60.8/45.2	48.2/51.8	NA	Population-based	633	67	1	1399	157	4	PCR-RFLP

[a]Sex were shown as the percentage of male in cases and controls; [b]Age were shown as the mean age of case and controls; [c]the IR (ionizing radiation) were shown as the percentage of the subjects with IR exposure history in cases and controls; [d]Mixed means that population and hospital based controls were used; [e]11,12,22 represent the homozygous wild genotypes, heterozygous genotypes, and the homozygous mutant genotypes for the three SNPs, respectively; [f]genotyping methods: MassARRAY, genotyping was performed using the Sequenom MassARRAY iPLEXTM platform2; PCR-CTPP, polymerase-chain-reaction with the confronting-two-pair primer; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; NA, means not available

Table 2. Summary of ORs and 95%CI for the Association Between XRCC1 Arg399Gln (rs25487, G/A) Polymorphism and Risk of Gliomas

Variables	N[a]	Gln vs.Arg			GlnGln vs. ArgArg			ArgGln vs. ArgArg			GlnGln/ArgGln vs. ArgArg		
		OR (95% CI)	M[b]	I^2 (%)	OR (95% CI)	M[b]	I^2 (%)	OR (95% CI)	M[b]	I^2 (%)	OR (95% CI)	M[b]	I^2 (%)
Total	11	1.150 (0.975-1.356)	R	83.9	1.304(0.958-1.776)	R	79.7	1.234(1.018-1.497)*	R	72.7	1.231(1.008-1.504)*	R	78.2
Ethnicities													
Asian	3	1.226(0.923-1.630)	R	56.5	1.490(1.031-2.153)*	F	49.1	1.257(0.967-1.634)	F	0.0	1.321(1.037-1.684)*	F	20.2
Caucasian	7	1.191(0.975-1.454)	R	87.9	1.384(0.939-2.039)	R	85.2	1.199(0.943-1.525)	R	81.1	1.245(0.962-1.611)	R	85.6
Mixed	1	0.656(0.431-0.998)	—	—	0.593(0.286-1.233)	—	—	2.080(0.954-4.537)	—	—	1.012(0.529-1.937)	—	—
Source of Control													
Hospital-based	5	1.417(0.927-2.166)	R	90.5	1.191(0.823-4.433)	R	89.4	1.608(0.999-2.590)	R	81.9	1.669(0.978-2.850)	R	87.7
Population-based	4	1.035(0.880-1.218)	R	56.3	1.161(0.948-1.421)	F	25.1	1.057(0.918-1.216)	F	45.2	1.070(0.938-1.222)	F	0.0
Others c	2	0.987(0.771-1.265)	R	74.6	0.981(0.629-1.532)	R	64.6	1.006(0.750-1.349)	R	62.5	0.990(0.710-1.380)	R	73.1
Genotyping methods													
PCR-RFLP	5	1.150(0.975-1.356)	R	92.5	1.439(0.706-2.930)	R	90.4	1.407(0.882-2.245)	R	87.9	1.338(0.829-2.159)	R	90.0
others d	6	1.129(1.043-1.223)*	F	39.6	1.214(1.029-1.433) *	F	35.7	1.182(1.051-1.329)*	F	0.0	1.192(1.068-1.330)*	F	0.0

[a]N, number of comparions; [b]M, model for meta-analysis; F, fixed effect model; R, random effect model; [c]Controls of the study by Mckean-Cowdin et al., 2009 and Wang et al., 2004 were from hospital- and population-based; [d]other genotyping methods include TaqMan, MassARRAY assays, etc; " *", represents $p<0.05$; "—", means not available

included in the analysis of associations between XRCC1 Arg194Trp and Arg280His polymorphisms and the risk of gliomas, respectively. We found that the mutant allele frequency for Arg399Gln polymorphism in controls of Asians was similar to that of Caucasians (35.3% vs. 34.6%). In contrast, the mutant allele frequencies of Arg194Trp and Arg280His polymorphisms in control subjects of Asians were obviously larger than those in Caucasians (allele frequency, 25.8% vs. 7.2%, and 18.1% vs. 5.3%, respectively).

Results of pooled analysis on the associations between XRCC1 Arg399Gln polymorphism and the risk of gliomas were shown in Table 2. As significant between study heterogeneity was detected (I^2>70%), thus REM was used for the analysis. The pooled results showed that 399Gln allele was not significantly associated with the gliomas risk compared with the Arg allele (OR = 1.150, 95%CI 0.975-1.356). However, significant association was found between the genotypes comparisons (ArgGln vs. ArgArg, OR = 1.234, 95%CI 1.018-1.497; GlnGln/ArgGln vs. ArgArg, OR = 1.231, 95%CI 1.008-1.504). The subgroup analysis stratified by ethnicity showed that significant associations also existed in Asians (GlnGln vs. ArgArg, OR = 1.490, 95%CI 1.031-2.153; GlnGln/ArgGln vs. ArgArg, OR = 1.321, 95%CI 1.037-1.684), whereas no significant association was found in Caucasians. The between study heterogeneity in Asians was moderately decreased. In the subgroup analysis stratified by the source of control, no significant association was found in allele comparisons as well as in the genotype comparisons. In regard to the subgroup analysis stratified by genotyping methods, significant association was found in the subgroup of other genotyping methods (Glu vs. Arg, OR=1.129, 95%CI 1.043-1.223; GlnGln/ArgGln vs. ArgArg, OR=1.192, 95%CI 1.068-1.330) (Table 2 and Figure 1).

Results of pooled analysis on the associations between

Table 3. Summary of ORs and 95%CI for the Association Between XRCC1 Arg194Trp (rs1799782, C/T) and Arg280His (rs25489, G/A) Polymorphisms and Risks of Gliomas

Contrasts Comparisons		No. of studies	Test of association			Test of heterogeneity	
			OR	95%CI	M[a]	I^2 (%)	p value[b]
Arg194Trp (rs1799782)							
Trp vs. Arg	All	7	1.159	(0.843-1.387)	R	85.4	0.000
	Asians	2	1.232	(0.887-1.712)	R	56.3	0.131
	Caucasians	4	0.890	(0.766-1.034)	F	0.0	0.549
	Mixed	1	3.612	(2.332-5.596)*	F	—	—
TrpTrp vs. ArgArg	All	7	2.029	(1.398-2.945)*	F	47.6	0.076
	Asians	2	1.530	(0.912-2.565)	F	0.0	0.383
	Caucasians	4	1.131	(0.460-2.784)	F	0.0	0.552
	Mixed	1	5.237	(2.480-11.060)*	F	—	—
ArgTrp vs. ArgArg	All	7	1.011	(0.884-1.156)	F	85.3	0.000
	Asians	2	1.143	(0.863-1.514)	F	0.0	0.391
	Caucasians	4	0.871	(0.744-1.021)	F	0.0	0.621
	Mixed	1	34.617	(10.613-112.909)*	F	—	—
TrpTrp+ArgTrp vs. ArgArg	All	7	1.232	(0.840-1.809)	R	86.7	0.000
	Asians	2	1.203	(0.924-1.568)	F	32.5	0.223
	Caucasians	4	0.877	(0.750-1.026)	F	0.0	0.580
	Mixed	1	8.798	(4.372-17.704)*	F	—	—
Arg280His (rs25489)							
His vs. Arg	All	4	1.048	(0.881-1.248)	F	36.8	0.191
	Asians	2	1.267	(0.986-1.628)	F	0.0	0.844
	Caucasians	2	0.877	(0.686-1.123)	F	0.0	0.475
HisHis vs. ArgArg	All	4	1.415	(0.875-2.299)	F	0.0	0.705
	Asians	2	1.559	(0.940-2.588)	F	0.0	0.811
	Caucasians	2	0.516	(0.084-3.160)	F	0.0	0.913
HisArg vs. ArgArg	All	4	0.957	(0.779-1.175)	F	0.0	0.743
	Asians	2	1.083	(0.767-1.528)	F	0.0	0.794
	Caucasians	2	0.895	(0.692-1.156)	F	0.0	0.516
HisHis+HisArg vs. ArgArg	All	4	1.002	(0.825-1.217)	F	0.0	0.423
	Asians	2	1.204	(0.887-1.634)	F	0.0	0.943
	Caucasians	2	0.883	(0.685-1.139)	F	0.0	0.491

[a]M, model for meta-analysis; F, fixed effect model; R, random effect model; [b]p value for heterogeneity based on Q test; " *", represents p<0.05; "—", means not available

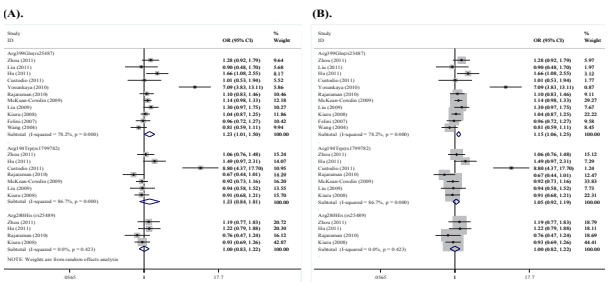

Figure 1. Meta-analysis for XRCC1 Polymorphisms and the Gliomas Risks. (A) Random effect model. Top: GlnGln/ArgGln vs. ArgArg; Middle: TrpTrp/ArgTrp vs. ArgArg; Bottom: HisHis/ArgHis vs. ArgArg. (B) Fixed effect model. Top: GlnGln/ArgGln vs. ArgArg; Middle: TrpTrp/ArgTrp vs. ArgArg; Bottom: HisHis/ArgHis vs. ArgArg. Each study was shown by a point estimate of the effect size (OR) (size inversely proportional to its variance) and its 95% confidence interval (95%CI) (horizontal lines). The white diamond denotes the pooled OR

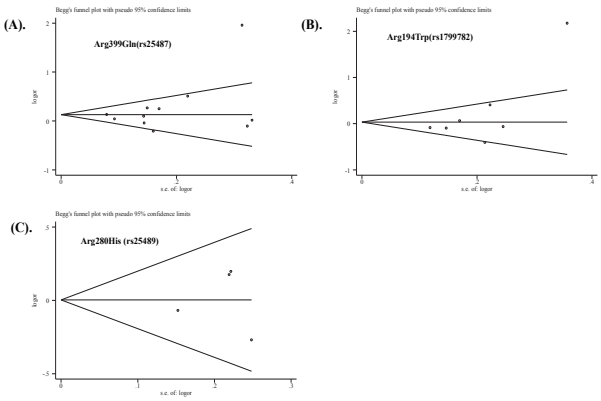

Figure 2. Begg's Funnel Plot with the Egger's Test for Publication Bias of XRCC1 Polymorphisms and the Risk of gGliomas. (A) GlnGln/ArgGln vs. ArgArg; (B) TrpTrp/ArgTrp vs. ArgArg; (C) HisHis/ArgHis vs. ArgArg. The horizontal line in the funnel plot indicates the fixed-effects summary estimate, whereas the diagonal lines pseudo-95% CI limits about the effect estimate. In the absence of publication bias, studies will be distributed symmetrically above and below the horizontal line

XRCC1 Arg194Trp and Arg280His polymorphisms and glioma risk were shown in Table 3. For the Arg194Trp polymorphism, no significant association was revealed in each genetic contrasts in the worldwide population, except for the homozygous genotype comparisons (TrpTrp vs. ArgArg, OR = 2.0209, 95%CI 1.398-2.945). As apparent difference in allele distribution between Asians and Caucasians, we only performed subgroup analysis based on ethnicity. No significant association was found in Asians as well as in Caucasians. Extreme between study heterogeneity existed for the analysis of the worldwide population, which was markedly decreased in the subgroup analysis of Asians and Caucasians. For the Arg280His polymorphism, no significant association was found in each contrast (Table 3 and Figure 1).

Sensitivity analysis and publication bias

Sensitivity analysis was undertaken by removing one individual study each time to check whether any of single

study could bias the overall estimate. No study was found to significantly influence the pooled ORs in each genetic model (data was not shown). Funnel plots were generated to assess publication bias. The Egger's test was performed to statistically evaluate funnel plot symmetry. The results suggested no publication bias for the association of the XRCC1 polymorphisms and the risk of gliomas (PEgger test = 0.251, 0.119, and 0.867 for GlnGln/ArgGln vs. ArgArg, TrpTrp/ArgTrp vs. ArgArg, HisHis/ArgHis vs. ArgArg, respectively) (Figure 2).

Discussion

Glioma is the most common type of primary brain malignancy in adults. Despite recent advances in cancer diagnosis and therapy, the prognosis of patients with gliomas remains dismal (Sathornsumetee et al., 2007). DNA repair genes play important roles in maintaining the genome integrity, and thus polymorphisms of DNA repair genes are plausible candidates which can modify the risk of gliomas. XRRC1 is one of the most important DNA repair genes responsible for BER pathway and fixes base damage and DBS caused by IR (Tudek, 2007). Up to now, a series of studies have been performed to address the association between XRCC1 gene polymorphisms and the risk of gliomas, but yielded conflicting results. Because of the above- mentioned conflicting results from relatively small studies underpowered to detect the effects, a meta-analysis should be an appropriate approach to obtain a more definitive conclusion.

To our knowledge, this was the first meta-analysis addressing the association between XRCC1 gene polymorphisms and the gliomas risk. In this study, a total of 11 studies (3810 cases and 6079 controls), 7 studies (2928 cases and 5048 controls), and 4 studies (1461 cases and 2593 controls) were included in the analyses of the associations between XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and gliomas risks, respectively. The pooled results showed that GlnGln carrier was associated with moderately increased risk of gliomas in Asians (GlnGln vs. ArgArg, OR = 1.490, 95%CI 1.031-2.153; GlnGln/ArgGln vs. ArgArg, OR = 1.321, 95%CI 1.037-1.684), whereas only marginal association was revealed in Caucasians. However, it should be noticed that all the three studies in Asians enrolled Chinese subjects, thus the effects on people of other Asian countries such as Japan, Korea, etc were still unclear. For the Arg194Trp polymorphism, no significant association was revealed in each genetic contrasts in the worldwide population, except for the homozygous genotype comparisons (TrpTrp vs. ArgArg, OR = 2.209, 95%CI 1.398- 2.945), which might be due to the inclusion of the study by Custodio et al. (2011). In the subgroup analysis, no significant association was found in Asians as well as in Caucasians. In regard to the Arg280His polymorphism, no significant association was found in each contrast.

The XRCC1 gene encodes the XRCC1 protein, which serves as a scaffold for two other proteins, DNA ligase III and polymerase β, and also serves as a single-strand break sensor by its interaction with poly (ADP-ribose) polymerase (PARP) (Caldecott et al., 1994; Caldecott et al., 1996; Masson et al., 1998). The observed association between XRCC1 Arg399Gln gene polymorphism and the gliomas risk is biologically plausible. The Arg399Gln is located at the carboxylic acid terminal side of the polyadenosine diphosphate-ribose polymerase interacting domain, and the variant Gln allele has been shown to reduce DNA repair capacity, and thereby, increase the risk of developing glioma (Duell et al., 2000). However, the XRCC1 codon 194 and codon 280 polymorphisms located in the linker region were not found to be significantly associated with risk of gliomas, which was consistent with almost all the individual studies.

Similar to other systematic reviews and meta-analyses, our study also has some limitations. First, the present meta-analysis was based primarily on unadjusted effect estimates and CIs, thus the effect estimates were relatively imprecise. Second, relatively small sample size existed for some subgroup analyses especially for Arg194Trp and Arg280His polymorphisms, as limited studies were included. Third, cancer is known as a multifactor disease, however, the gene-gene and gene-environment interactions were not addressed in this meta-analysis, and thus the potential roles of the above gene polymorphism may be masked or magnified by other gene-gene/gene-environment interactions. Lastly, although we did not detect publication bias, selection bias may exist because only studies published in English or Chinese were retrieved.

In summary, this meta-analysis systematically analyzed the association between XRCC1 polymorphisms and the gliomas risks. The pooled results showed that the XRCC1 Arg399Gln polymorphism was moderately associated with increased risk of gliomas in Asians. In contrast, XRCC1 Arg194Trp and Arg280His polymorphisms were not significantly associated with gliomas risks. Due to the limited studies and the potential confounders, further studies are needed to confirm these results.

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