Three Polymorphisms of XRCC1 (Arg194Trp, Arg280His, Arg399Gln) and the Risk of Gliomas: a Meta-analysis

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Gliomas are one of the most common malignant tumors in the central nervous system. At present, many publications have assessed the association between the polymorphisms of *XRCC1* and glioma susceptibility. However, the results remain inconclusive. In this study, we aimed to exhaustively assess the association between the polymorphisms of *XRCC1* (including Arg194Trp, Arg280His, Arg399Gln) and the incidence risk of gliomas. Firstly, studies which related to the genetic polymorphisms of *XRCC1* and glioma susceptibility were searched for in PubMed, Cochrane, CBM, Wanfang, and CNKI databases. Then the related data was extracted and analyzed by Revman 5.3 software. Finally, 19 case-control studies involving 7,024 glioma patients and 8,425 control subjects were included. The cumulative meta-analysis showed that there is no obvious association between *XRCC1* Arg194Trp or Arg280His polymorphisms and a high risk of gliomas, but the Arg399Gln polymorphism of *XRCC1* may be an important factor in the development of gliomas, especially in an Asian population.

Keywords: XRCC1; Polymorphisms; Glioma; Meta-analysis

Introduction

Gliomas, which originate from the brain or spinal cord, are one of the most common malignant tumors in the central nervous system (CNS) at present, as they account for more than 90% of malignant brain tumors. Although there are many advanced diagnostic tools and therapeutic methods, gliomas are still incurable and have a poor prognosis and low survival rate[1,2]. This is mainly due to a glioma's aggressive growth around brain tissue and how to determine the tumor boundary is difficult, which complicates removing it surgically. Furthermore, glioma is one of the tumors that has a large number of blood vessels in vivo and glioma cells have a strong proliferation capacity[3]. At present, due to the factors of blood-brain barrier and the irreversible toxic effects, the common anti-tumor drugs have a very poor effect in glioma treatment. The glioma pathogenesis is related to multiple processes as affected by dozens of regulatory factors[4], and exact causes are still unclear. According to the analysis of epidemiological investigations, the only certain environmental cause of gliomas is radiation exposure, especially ionizing radiation and X-ray exposure[5,6].

As it is well known, most tumors are caused by the interaction of environmental and genetic factors. However, not all those who are exposed to ionizing radiation and X-rays will suffer from gliomas. Their incidence may be related to other factors, among which genetic polymorphisms may be the important. Environmental carcinogens or metabolites can cause the damage of DNA, if the intracellular DNA repair gene is defective and the damaged gene cannot be repaired in time, this results in an increased mutation rate and gene instability, which causes cell proliferation and differentiation out of control, and increases the susceptibility of developing a tumor.

XRCC1 belongs to the family of nucleotide resection and repair (NER) genes, and is a key gene in the NER pathway. Studies have shown that the polymorphisms of *XRCC1* may lead to the damage of the NER mechanism and cause the instability of genomes, thereby increasing the likelihood of tumor occurrence[7,8]. Up to now, many scholars have researched the association between *XRCC1* polymorphisms and glioma susceptibility, but the results are inconsistent. To better understand the causes of gliomas and provide an accurate theory for the development of clinical studies, in this study, we sought to make a systematic and objective evaluation of the association between *XRCC1* polymorphisms and glioma susceptibility using the method of Evidence-Based Medicine (EBM).

Materials and Methods

Search Strategy

The PubMed, Cochrane, CBM (Chinese Biomedical Database), Wanfang and CNKI (China National Knowledge Internet) databases were comprehensively searched (the last search was updated on July 1, 2017) using the following terms: ("polymorphism" OR "mutation" OR "variant") AND ("glioma" OR "brain tumor" OR "glioblastoma" OR "glial cell tumors" OR "brain neoplasms") AND ("*XRCC1*" OR "x-ray cross complementing group 1"). During the searching process, the language restrictions were not set, and for the possible references listed in the review, we made a second search and used manual retrieval if necessary. All the studies searched were published.

Eligibility Criteria

The retrieved literature was included according to the following criteria: (1) the study must be involved with *XRCC1* polymorphisms (including the sites of Arg399Gln or Arg194Trp or Arg280His) and gliomas; (2) the design was a case-control study or a cohort study; (3) it must have detailed data from studies that included the distribution of genotypes, sample size, odds ratio (OR) and 95% CIs; (4) the patients in the case group had gliomas diagnosed microscopically; (5) the distribution of genotypes in the control group conformed to Hardy-Weinberg Law (HWE).

Meanwhile, we also made a series of exclusionary criteria as follows: (1) if the experiment designs were obviously different from other studies; (2) if the necessary data described above was not listed; (3) if the studies had repeated reports, were of poor quality, or had incomplete data or reviews.

Data Extraction

All included literature was read by two researchers with appropriate backgrounds, and the relevant data extracted included the first author's name, year of publication, ethnicity of subjects, source of control, genotyping method, sample size of cases and control group, genotype frequency, OR, and its 95% CIs. All disagreements were resolved with a third researcher's intervention and the final conclusion was decided *via* a vote.

Data Analysis

For each study, whether the distribution frequency of genotypes in control group was consistent with Hardy-Weinberg Law was tested using the Chi-square test. Revman 5.3 software was used to perform the meta-analysis. Meanwhile, we assume the mutant allele is a gene susceptible of developing gliomas. Four genetic models were used to analyze the relationship between the polymorphisms of *XRCC1* and the incidence risk glioma, including an allele contrast model (mut *vs* wild), dominant model (mut/mut+mut/wild *vs* wild/wild), recessive model (mut/mut *vs* mut/wild+wild/wild), and homozygote comparison model (mut/mut *vs* wild/wild).

Subsequently, the heterogeneity among included studies was detected using I^2 statistics, and the value of I^2 was used to assess the degree of heterogeneity[9]. If there was no obvious heterogeneity, a fixed effect model was employed; otherwise, a random effects model was used. The OR and its 95% CI were calculated to estimate the association between the polymorphisms of *XRCC1* and the incidence risk of glioma under the aforementioned four genetic models. Sensitivity analysis was applied by excluding a single study each time to explore the stability of overall results. The publication bias was calculated by a funnel plot analysis and a Egger linear regression test[10].

Results

Characteristics of Included Studies

According to the included and excluded criteria described above, 19 case-control studies involving 7,024 glioma patients and 8,425 control subjects were included in this meta analysis (**Figure.1**)[11-29]. Among the 19 included literatures, 13 studies had reported the polymorphism of Arg194Trp and the genotype distribution of control subjects in 9 studies were consistent with HWE; 8 studies had reported the polymorphism of Arg280His and the genotype distribution of control subjects in 6 studies were consistent with HWE; 17 studies had reported the polymorphism of Arg399Gln and the genotype distribution of control subjects in 14 studies were consistent with HWE. The detailed information of the SNPs studied in this meta-analysis was shown in **Table.1** and **Table.2**.

Meta-Analysis of *XRCC1* Arg194Trp Polymorphism

As shown in **Table.3**, the results of three genetic

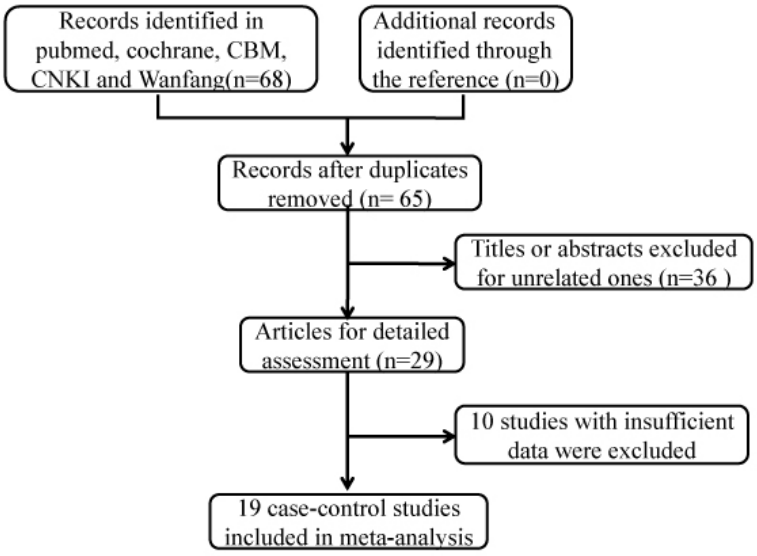

Figure.1 A flow diagram of the study selection process.

models (allele contrast, dominant model, homozygote model) showed there was no obvious association between the *XRCC1* Arg194Trp polymorphism and a high risk of gliomas, and the total odds ratio (OR) and its 95% confidence interval (95% CI) of each genetic model are: for allele comparison model (Trp *vs* Arg), OR=0.95, 95% CI=[0.75, 1.21]; for dominant model (TrpTrp+ArgTrp *vs* ArgArg), OR=1.06, 95% CI=[0.94, 1.20]; for recessive model (TrpTrp *vs* ArgTrp+ArgArg), OR=0.64, 95% CI=[0.44, 0.92]; for homozygote comparison model, OR=1.47, 95% CI=[1.00, 2.16].

Meanwhile, we analyzed the heterogeneity of the data in each genetic model, and the results showed that the dominant model (I^2=35%, P=0.14), recessive model (I^2=55%, P=0.02), and homozygote comparison model (I^2=55%, P=0.02) had no obvious heterogeneity, but data analysis of the allele contrast comparison (I^2=88%, P<0.00001) had a high heterogeneity. Then we made a subgroup analysis and the results showed no obvious association between the *XRCC1* Arg194Trp polymorphism and a high risk of gliomas both in Asian and Caucasian subgroups.

Meta-Analysis of *XRCC1* Arg280His Polymorphism

As shown in **Table.4**, the results of allele contrast and dominant genetic comparisons model suggested there was no obvious association between the Arg280His polymorphism of *XRCC1* and high incidence of gliomas. What follows was the meta-analysis of an allele contrast model (His *vs* Arg), dominant model (HisHis+ArgHis *vs* ArgArg), recessive model (HisHis *vs* ArgArg+ArgHis) and homozygote model (HisHis vs ArgArg). For His *vs* Arg, OR=0.84, 95% CI=[0.64, 1.11]; for HisHis+ArgHis *vs* ArgArg, OR=0.82, 95% CI=[0.64, 1.04]; for HisHis *vs* ArgArg+ArgHis, OR=0.46, 95% CI=[0.23, 0.90]; for HisHis *vs* ArgArg, OR=0.4, 95% CI=[0.22, 0.90]. Moreover, the heterogeneity test showed no obvious heterogeneity was found in the recessive model (I^2=32%, P=0.19) and homozygote model (I^2=38%, P=0.15), but high heterogeneity existed in the allele contrast comparison (I^2=77%, P=0.0006) and dominant model (I^2=63%, P=0.02). Then, we further performed a subgroup analysis and the results indicated there was no obvious association between the Arg280His polymorphism of *XRCC1* and a high risk of gliomas both in Asian and Caucasian populations.

Meta-Analysis of XRCC1 Arg399Gln Polymorphism

As shown in **Figure.2**, the results of four genetic comparison models suggested that the Arg399Gln polymorphisms of *XRCC1* noticeably increased the incidence risk of gliomas. The heterogeneity analysis showed that for an allele contrast comparison (Gln *vs* Arg), OR=1.22, 95% CI=[1.11, 1.33], I^2=48% (P=0.04); for dominant model (GlnGln+ArgGln *vs* ArgArg), OR=1.26, 95% CI=[1.12, 1.41], I^2=44%, (P=0.06); for recessive model (Gl-

Table.1 Characters of included studies.

Reference	Country	Research type	Genotyping method	Case (Male/Female)	Control (Male/Female)
Wang, 2016	China Han	case-control	Sequencing	368(189/179)	346(170/176)
Franceschi, 2016	Tuscan	case-control	Sequencing	85(49/36)	168(99/79)
Fan, 2016	China Han	case-control	PCR-RFLP	115(49/66)	228(104/124)
Wang, 2015	China	case-control	PCR-RFLP	387(187/200)	400(199/201)
Xu, 2014	China	case-control	PCR-RFLP	886(487/399)	886(483/403)
Li, 2014	China	case-control	Sequencing	368(189/179)	346(170/176)
Jin, 2014	China Han	case-control	PCR-RFLP	620(387/233)	630(402/228)
Hu, 2013	China Han	case-control	PCR-RFLP	366(216/150)	377(288/139)
Pan, 2013	China Han	case-control	Sequenom MassARRAY	443(257/186)	443(257/186)
Luo, 2013	China	case-control	Sequenom MassARRAY	297(170/127)	415(250/165)
Wang, 2012	China Han	case-control	PCR-RFLP	624(319/305)	580(303/277)
Liu, 2012	China	case-control	Sequenom MassARRAY	312(185/127)	312(171/141)
Zhou,2011	Southern China	case-control	PCR-RFLP	271(168/103)	289(180/109)
Hu, 2011	China	case-control	PCR-CTPP	127(87/40)	249(166/83)
Custodio, 2011	Caucasian	case-control	Sequencing	80(52/28)	100(63/37)
Yosunkaya, 2010	Turkey	case-control	PCR-RFLP	119(~)	180(~)
Rajaraman, 2010	Caucasian	case-control	TaqMan assays	489(~)	489(~)
Felini, 2007	Caucasian	case-control	PCR-RFLP	366(~)	427(~)
Kiuru, 2008	Caucasian	case-control	PCR-RFLP	699(~)	1549(~)

Notes: (1) Abbreviation, PCR-RFLP: cleaved amplification polymorphism sequence-tagged sites; PCR-CTPP: polymerase chain reaction with confronting two-pair primers. (2) "~" represents the numbers of male or female was not reported detailly.

nGln *vs* ArgGln+ArgArg), OR=1.32, 95% CI=[1.16, 1.51], I^2=4% (*P*=0.41); for homozygote model (GlnGln *vs* ArgArg), OR=1.46, 95% CI=[1.24, 1.73], I^2=29% (*P*=0.17). Meanwhile, the Arg399Gln polymorphisms of *XRCC1* was further analyzed in the subgroup. As shown in **Table.5**, the Arg399Gln polymorphisms of *XRCC1* might bring about higher risk of gliomas in Asian populations, but these results were not found in Caucasians. For *XRCC1* Arg399Gln polymorphisms in Asians, Gln *vs* Arg: OR=1.33, 95% CI=[1.23, 1.45]; GlnGln+ArgGln *vs* ArgArg: OR=1.41, 95% CI=[1.27, 1.58]; GlnGln vs ArgGln+ArgArg: OR=1.51, 95% CI=[1.27, 1.80]; GlnGln *vs* ArgArg: OR=1.76, 95% CI=[1.46, 2.11].

Sensitivity and Publication Bias Analysis

In addition, in order to evaluate the stability of the meta-analysis, we made a sensitivity analysis using a single variable sensitivity analysis to test whether the study had a significant effect on the overall outcome, and the results suggested the pooled ORs were statistically robust and reliable. Meanwhile, as shown in **Figure.3**, the results of funnel plots suggested no obvious publication bias existed, especially in the analysis of *XRCC1* Arg399Gln polymorphism, and the funnel plot of each genetic models all showed symmetry.

Discussion

For a long time, tumors have been considered a synthetic disease and caused by multiple factors, including genetic and environmental factors. Over the course of a lifetime, the body suffers damage from external environments, environments that could lead

Table.2 The genotype distribution of *XRCC1* in each study.

Reference	Arg194Trp (Case/Control)			Arg280His (Case/Control)			Arg399Gln (Case/Control)		
	Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/Gln	Gln /Gln
Wang, 2016	182/175	171/151	15/20	302/251	61/79	5/16	142/176	167/132	59/38
Franceschi, 2016		~			~		39/81	28/66	16/21
Fan, 2016	31/82	58/109	26/37		~		42/92	51/99	22/37
Wang, 2015		~			~		45/211	164/157	178/32
Xu, 2014	525/540	301/311	60/35	618/621	177/178	91/87	451/469	365/372	70/45
Li, 2014	183/175	171/151	16/20	302/251	61/79	5/16	142/176	167/132	59/38
Jin, 2014		~			~			~	
Hu, 2013		~			~		157/196	165/151	44/30
Pan, 2013	301/327	116/101	27/6		~		226/244	190/178	27/21
Luo, 2013	204/297	63/96	30/22		~		111/189	134/181	51/45
Wang, 2012	376/355	218/205	30/20	506/473	115/98	3/9	270/300	279/232	75/48
Liu, 2012	294/334	105/89	45/19		~			~	
Zhou,2011	145/159	113/117	14/13	218/240	45/44	8/5	121/147	113/118	37/24
Hu, 2011	71/163	38/64	18/22	72/153	28/58	27/38	58/145	48/75	21/29
Custodio, 2011	15/67	31/4	34/29		~		23/29	33/20	24/51
Yosunkaya, 2010		~			~		15/91	67/71	37/18
Rajaraman, 2010	304/394	38/73	0/1	312/417	28/48	0/1	142/205	164/201	44/72
Felini, 2007		~			~		158/180	155/196	53/51
Kiuru, 2008	626/1377	71/177	3/2	633/1399	67/157	1/4	284/645	324/728	91/176

Notes: "~" represents the corespondenting polymorphism was not reported.

Table.3 Summary about the meta-analysis on the association between *XRCC1* Arg194Trp polymorphism and risk of gliomas.

	Allele Contrast			Dominant Model			Recessive Model			Homozygote Model		
	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2
Overall	0.95 [0.75, 1.21]	0.69	88%	1.06 [0.94,1.20]	0.33	35%	0.64 [0.44, 0.92]	0.02	55%	1.47 [1.00, 2.16]	0.05	55%
Ethnicity												
Asian	0.99 [0.75, 1.32]	0.96	91%	1.12 [1.01, 1.24]	0.04	0%	0.62 [0.42, 0.92]	0.02	63%	1.45 [0.96, 2.18]	0.07	63%
Caucasian	0.83 [0.60, 1.14]	0.24	44%	0.81 [0.60, 1.09]	0.16	31%	0.97 [0.17,5.54]	0.98	12%	1.8 6 [0.31,11.32]	0.50	16%

Table.4 Summary about the meta-analysis on the association between *XRCC1* Arg280His polymorphism and risk of gliomas.

	Allele Contrast			**Dominant Model**			**Recessive Model**			**Homozygote Model**		
	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2
Overall	0.84 [0.64, 1.11]	0.22	77%	0.82 [0.64,1.04]	0.10	63%	0.46 [0.23, 0.90]	0.02	32%	0.44 [0.22, 0.90]	0.03	38%
Ethnicity												
Asian	0.74 [0.53, 1.04]	0.08	77%	0.80 [0.55, 1.15]	0.22	76%	0.45 [0.19, 1.08]	0.07	59%	0.43 [0.17, 1.08]	0.07	63%
Caucasian	1.08 [0.76, 1.54]	0.67	52%	0.88 [0.69, 1.14]	0.34	0%	0.52 [0.09,3.19]	0.48	0%	0.52 [0.08, 3.15]	0.47	0%

to the occurrence of a tumor *via* affect the stability of genome DNA. At present, the studies of a tumor's genetic sensitivity mainly focus on chromosome stability, DNA repair, structural changes of oncogene/tumor suppressor gene, genetic polymorphisms, *etc*.[30]. The risk of gene mutation would increase if the ability of DNA to repair was reduced or damaged. The ability of DNA to repair is the body's most important defensive barrier and a critical function, as it can repair damage caused by internal and external environments. Studies suggested that the polymorphisms of the DNA repair gene may be associated with the sensitivity of tumorigenesis and development[31]. Gliomas, which belong to a high degree of malignant tumors and are characterized by rapid growth, strong infiltration, short disease course, and high mortality, are considered a multifactorial disease. Nowadays, the causes of gliomas are still not fully understood, but one of the generally accepted causes is exposure to ionizing radiation. Hence, it is essential to understand the pathogenesis and make a risk evaluation on a genetic basis.

XRCC1 (X-ray repair cross complementing group 1) was first cloned from the gene library of a Chinese hamster ovary EM9 cell line, and was the main participant in repairing the damage induced by ionizing radiation and chemical mutagen through base-excision repair (BER) and single-stranded break repair. Single nucleotide polymorphisms (SNP), where the distribution of different genotypes in a population are caused by the insertion, deletion, or substitution of a nucleotide, were usually used to compare the nucleotide differences between patients and health populations, so as to find the corresponding genetic site and provide the preliminary research basis for gene targeted therapy[32,33]. At present, the genetic polymorphisms of *XRCC1*, which would reduce the repairing ability of the *XRCC1* gene, mainly contains Arg194Trp polymorphisms, Arg280His polymorphisms, and Arg399Gln polymorphisms. The association between genetic polymorphisms and tumors has been studied for several decades, and most results showed that the nucleotide polymorphisms were closely associated with cancer sensitivity, such as lung cancer, esophageal cancer, colon cancer, and colorectal cancer[34]. There are also numerous studies from all over the world that have reported the relationship between *XRCC1* polymorphisms and glioma risk[11-29]. For the relationship between *XRCC1* genetic polymorphisms and glioma risk, many researchers had analyzed via evidenced-medical analysis. For example, in Lu's study[35], their meta-analysis results showed that the Arg194Trp polymorphisms of XRCC1 could noticeably increase glioma risk in Asians.

In this meta-analysis, in order to make a fairer, more comprehensive and accurate evaluation of the association between *XRCC1* polymorphisms and glioma sensitivity, we made a meta-analysis that included three polymorphism sites (Arg194Trp polymorphism, Arg280His polymorphism and Arg399Gln polymorphism). The cumulative meta-analysis showed there was no obvious association between *XRCC1* Arg194Trp polymorphism or *XRCC1* Arg280His polymorphism and a high risk of gliomas (**Table.3** and **Table.4**), but the *XRCC1* Arg399Gln polymorphism could noticeably increase the risk of gliomas (**Table.5** and **Figure.2**). Moreover, epidemiological studies have shown that the incidence rates of gliomas are different among different races. Pinarbasi, *et al*[36] reported that the incidence rate of brain tumors in Caucasians was obviously high-

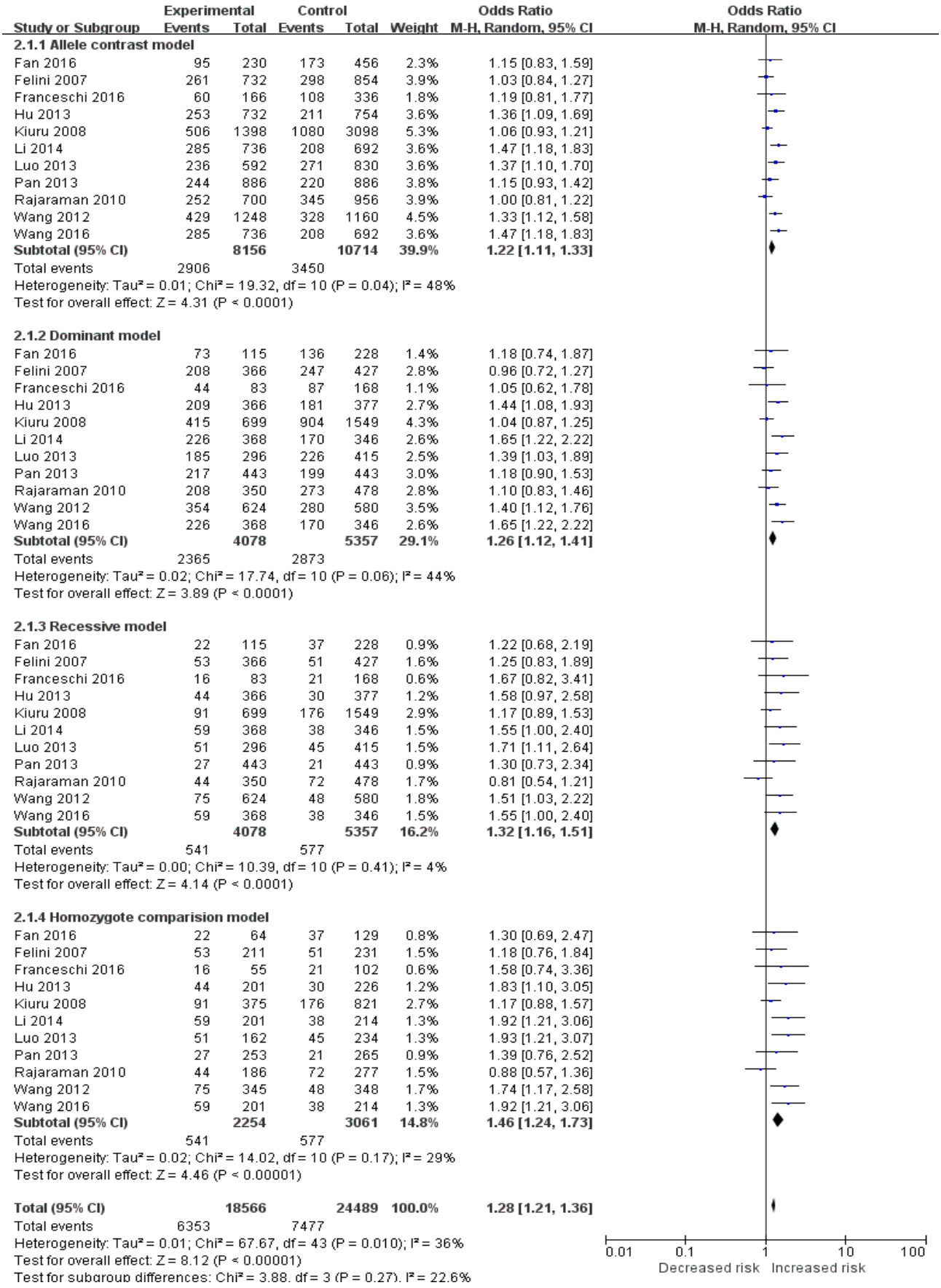

Figure.2 Forest plot of Arg399Gln polymorphism in *XRCC1* and risk of gliomas in four genetic comparison models.

Table.5 Summary about the meta-analysis on the association between *XRCC1* Arg399Gln polymorphism and risk of gliomas.

	Allele Contrast			Dominant Model			Recessive Model			Homozygote Model		
	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2	OR (95% CI)	*P* for OR	I^2
Overall	1.22 [1.11, 1.33]	0.0001	48%	1.26 [1.12,1.41]	0.0001	44%	1.32 [1.16, 1.51]	0.0001	4%	1.46 [1.24, 1.73]	0.00001	29%
Ethnicity												
Asian	1.33 [1.23, 1.45]	0.00001	0%	1.41 [1.27, 1.58]	0.00001	0%	1.51 [1.27, 1.80]	0.0001	0%	1.76 [1.46, 2.11]	0.00001	0%
Caucasian	1.06 [0.96, 1.16]	0.24	0%	1.04 [0.91, 1.18]	0.59	0%	1.12 [0.89, 1.42]	0.33	26%	1.13 [0.92, 1.38]	0.24	0%

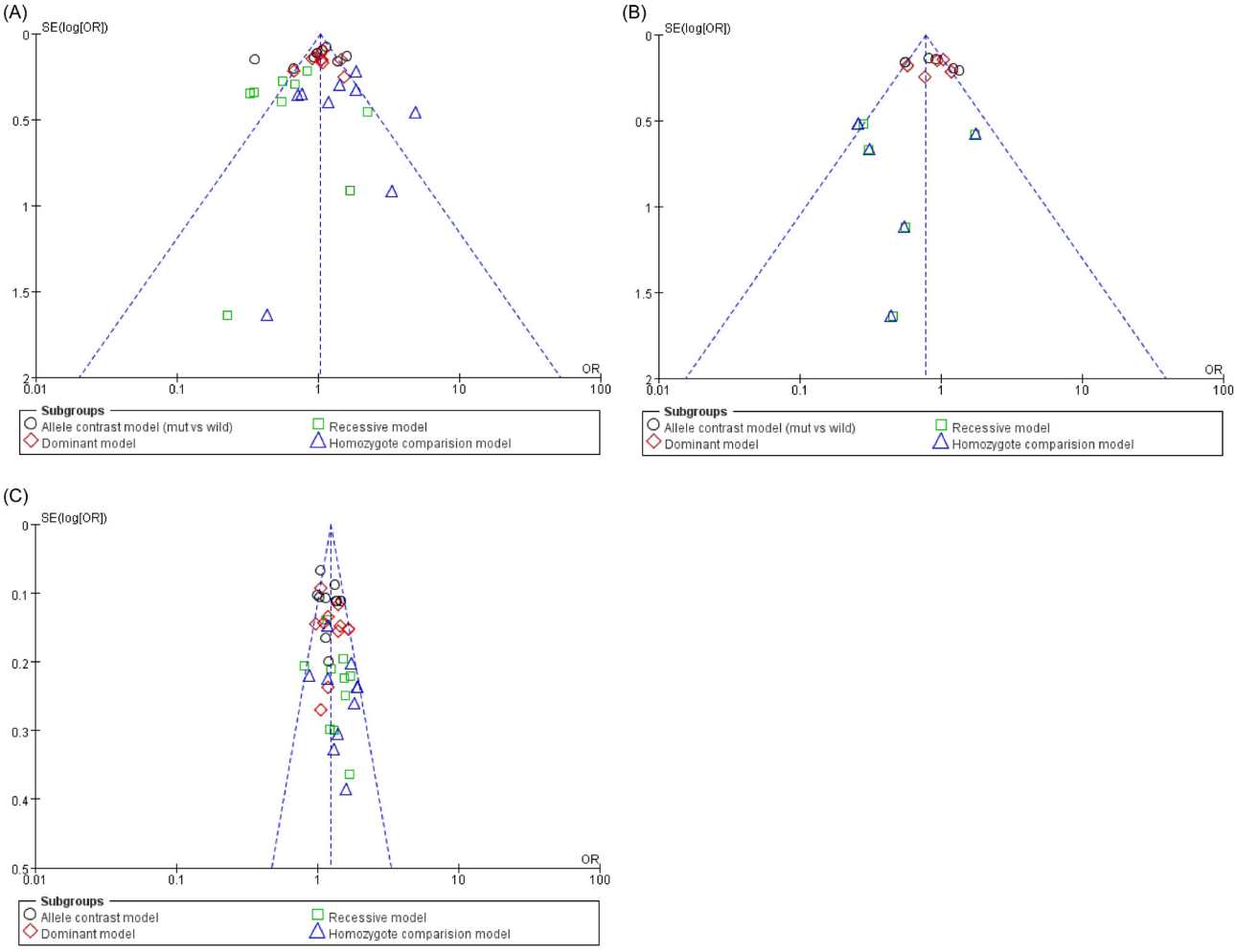

Figure.3 Funnel plot for the assessment of publication bias. (A) *XRCC1* Arg194Trp polymorphism; (B) *XRCC1* Arg280His polymorphism; (C) *XRCC1* Arg399Gln polymorphism.

er than that in Asians and Africans; among those, the glioma incidence rate in Caucasians increased twofold compared with Africans, while no difference existed in the incidence rate of a meningioma, pituitary tumors, lymphomas and other brain tumors between white and black people[37]. A Japanese study indicated that the incidence rate in Japanese populations is 50% less than that of the incidence rate in American populations[38]. According to the investigation on the epidemiology of immigrants, the

incidence rate of white people settled in Africa was also higher than that of African black people[39]. An incomplete set of statistical results taken in Shanghai from 1980 to 2006 showed the incidence rate of malignant tumors, most notably how the occurrence of gliomas increased year by year[40]. Hence, we further made a subgroup analysis according the ethnic differences, and the results showed that, in Asians and Caucasians, there was no association between the *XRCC1* Arg194Trp polymorphism, *XRCC1* Arg280His polymorphism, and the incidence risk of gliomas, but the subgroup analysis of the *XRCC1* Arg399Gln polymorphism showed this polymorphism could noticeably increase the incidence risk of gliomas in Asians, but not necessarily in Caucasians. In this study, the result of the *XRCC1* Arg194Trp polymorphism was not consistent with the results in Lu's study, in which the author suggested that the Arg194Trp polymorphism of *XRCC1* was associated with increased risk for gliomas, especially in Asians. Finally, to ensure the robustness of this meta-analysis, we further performed a sensitivity analysis, and the results indicated that the outcome of this meta-analysis was stable and reliable.

Overall, the results of this accumulated meta-analysis suggested that there is no association between the *XRCC1* Arg194Trp or Arg280His polymorphisms and the high risk of gliomas, but the *XRCC1* Arg399Gln polymorphisms may be an important factor in the development of gliomas, especially in Asians. However, an evidence-based medical analysis needs continuous development. In this study, we made a systematic assessment based on existing data resources. In the future, along with the progress of medical research and a gradual increase of studies related to *XRCC1* polymorphisms and gliomas, this meta-analysis will be further refined.

Conclusion

There is no association between the *XRCC1* Arg194Trp or Arg280His polymorphisms and the high risk of gliomas, but the *XRCC1* Arg399Gln polymorphisms may be an important factor in the development of gliomas, especially in Asians.

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