Original Article

DNA repair gene *XRCC1* polymorphisms and susceptibility to childhood acute lymphoblastic leukemia: a meta-analysis

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Objective: To estimate the relationship between genetic polymorphisms of X-ray repair cross-complementing group 1 (*XRCC1*) and the susceptibility to childhood acute lymphoblastic leukemia (ALL).
Methods: Relevant case-control studies were enrolled in the meta-analysis. We applied Rev Man 4.2 software to pool raw data and test studies' heterogeneity and to calculate the incorporated odds ratio (OR) and 95% confidence interval (95% CI).
Results: Our data showed that the OR for the Gln allele of the Arg399Gln polymorphism, compared with the Arg allele, was 1.35 (95% CI, 1.16-1.57; P<0.0001) for childhood ALL patients. Similarly, the homozygous genotype Gln/Gln and heterozygous genotype Arg/Gln both significantly increased the risk of childhood ALL compared with the wild genotype Arg/Arg (OR =1.58; 95% CI, 1.13-2.21; P=0.008; OR =1.51; 95% CI, 1.21-1.87; P=0.0002). The dominant model of Arg399Gln was associated with childhood ALL risk (OR =1.54; 95% CI, 1.25-1.89; P<0.0001). The ethnic subgroup analysis demonstrated that the Gln allele in all five ethnic groups was prone to be a risk factor for childhood ALL just with different degrees of correlation while Arg194Trp SNP showed a protective or risk factor or irrelevant thing in different races.
Conclusions: *XRCC1* 399 polymorphism may increase the risk of childhood ALL. Different ethnic groups with some gene polymorphism have different disease risks.

Key Words: X-ray repair cross-complementing group 1 (*XRCC1*); gene polymorphism; childhood; acute lymphoblastic leukemia (ALL)

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant tumor in the children which comprises over 80% of all the acute leukemia. It is estimated that approximately 33.6 in every 1,000,000 children under 15 years old will develop ALL (1). The etiology and pathogenesis of ALL are unclear up to now. Previous studies make a plausible hypothesis that crucial sequential events involving specific chromosomal translocations or fusion genes as the first hits to initiate ALL and further genetic or epigenetic events such as gene deletions or mutations as the second hits to cooperate to the outbreak of ALL (2-5). One of the most important initiating events is thought to result from the misrepair of double-strand DNA breaks (DSB) during non-homologous end-joining (NHEJ) (6-8). Considering roles in repairing of DSB, X-ray repair cross-complementing group 1 (*XRCC1*) gene is one of the most important DNA repair genes (9,10). XRCC1 also participates in single-strand DNA break (SSB) repair pathway for the repair of DNA destruction which occurs very frequently in mammals and base excision repair (BER) pathway which operates on small lesions caused normally by endogenous substances or xenobiotics. Moreover, it is reported that DNA repair

function could be modified by genetic polymorphisms (11). It could cause genetic instability and even carcinogenesis if DNA repair capacity is of deficiency (12,13). Also reported by relevent studies, the disruption of *XRCC1* in mice results in early embryonic lethality in the BER pathway (14,15), and an excess of deletions found among induced mutations in EM-C11 (one cell line identified as defective in XRCC1 function) perhaps result from reduced ligation efficiency of SSB (16). Therefore, the size of DNA repair capacity modified by *XRCC1* gene polymorphisms makes different hereditary susceptibility to ALL in different population. In other words, *XRCC1* gene polymorphisms may be associated with childhood ALL. There are three common single nucleotide polymorphism (SNP) sites in *XRCC1* gene encoding region, which are codon 399 (extron 10, G→A, Arg→Gln), codon 194 (extron 6, C→T, Arg→Trp), and codon 280 (extron 9, G→A, Arg→His) respectively. Molecular epidemiological studies on the association between genetic predisposition of children ALL and *XRCC1* polymorphisms have presented some contradictory results (17-24). In this paper, we performed a quantitative synthesis by meta-analysis method to evaluate the size of the association between *XRCC1* polymorphisms and children ALL.

Materials and methods

Search strategy

All the studies were identified by a computerized literature search of the PubMed, EMBASE, Elsevier Science Direct, ProQuest and SpringerLink with the keywords of "XRCC1" or "X-ray repair cross-complementing group 1" or "DNA repair gene", "polymorphism" or "variant" or "Arg399Gln, Arg194Trp, Arg280His", "acute lympho* leukemia", "childhood" or "pediatric". We also searched the database of Chinese National Knowledge Infrastructure (CNKI), Halis, and ChinaInfo using "ALL" and "genetic polymorphism" as the keywords. All finished prior to Dec 1st, 2010 in any language. References of the retrieved publications were also screened.

Inclusion criteria

The inclusion criteria comprise: (I) only the case-control studies on the association between *XRCC1* polymorphisms and the risk of children ALL were considered; (II) at least one of the *XRCC1* polymorphisms, Arg399Gln, Arg194Trp and Arg280His, was included; (III) essential information about the distribution on genotype frequency should be described in details, and the data should be extractable; (IV) there were detailed descriptions on study subject and DNA sources; and (V) the authors must offer sample size, odds ratios (OR) and 95% confidence interval (95% CI).

Exclusion criteria

The exclusion criteria comprise: (I) review or abstract; (II) only with case or non-case-control studies; (III) adult ALL or adult and childhood ALL; (IV) no relationship between studies and ALL; and (V) without essential information. Additionally, we selected the latest one when some literatures were repeated.

Data extraction

Two investigators independently extracted and checked the information, and discussed with each other to reach a consensus. The data included author, journal, the year of publication, country of origin, race, demographic characteristics, sample size of the cases and controls, genotyping information, OR, 95% CI, and matching factors.

Quality score assessment

The same two reviewers independently assessed the quality of studies by quality assessment scores which were modified from previous meta-analyses of molecular association studies (25-27) (*Table 1*). And the scores were based on both traditional epidemiologic considerations and genetic issues (28,29). Total scores ranged from 9 to 12 (*Table 2*).

Statistical analysis

A Q-statistic test was performed to analyze the heterogeneity of the included literatures. And we set the significance level at 0.1 (30). If $P \geq 0.1$, which means there was no heterogeneity between the individual studies, a fixed-effects model (Peto Mantel-Haenszel) would be used to pool the results, otherwise, a random-effects model (DerSimonian and Laird) was used (31). All of the statistical analyses were performed with Review Manager 4.2 to show the combined results by drawing forest plot.

We used the meta-analysis method to evaluate the relationship between the risk of childhood ALL and the

Table 1 Scale for quality assessment of molecular association studies of childhood ALL

Criteria	Score
Representativeness of cases	
Consecutive/randomly selected from case population with clearly defined sampling frame	2
Consecutive/randomly selected from case population without clearly defined sampling frame	1
No method of selection described	0
Representativeness of controls	
Controls were consecutive/randomly drawn from the same sampling frame(race)as cases	2
Controls were consecutive/randomly drawn from a different sampling frame as cases	1
Not described	0
Ascertainment of childhood ALL	
Clearly described objective criteria for diagnosis of child ALL	2
Diagnosis of child ALL by clinical feature or by patient history	1
Not described	0
Ascertainment of controls	
Controls were from the healthy population	2
Controls were subjects who did not report ALL or other cancer	1
Not described	0
Genotyping examination	
Genotyping done under “blinded” condition	1
Unblinded or not mentioned	0
Hardy-Weinberg equilibrium	
Hardy-Weinberg equilibrium in control group	2
Hardy-Weinberg disequilibrium in control group	1
No checking for Hardy-Weinberg equilibrium	0
Association assessment	
Assess association between genotypes and child ALL with appropriate statistics and matching for confounders	2
Assess association between genotypes and child ALL with appropriate statistics without matching for confounders	1
Inappropriate statistics used	0
Total	13

Table 2 The scores of the six studies' quality assessment

Criteria	Batar B	Tumer TB	Pakakasama S	Meza-Espinoza JP	Stanczyk M	Joseph T
Representativeness of cases	2	2	2	2	2	2
Representativeness of controls	2	2	2	2	2	2
Ascertainment of childhood ALL	2	2	2	1	2	0
Ascertainment of controls	2	2	2	2	2	1
Genotyping examination	0	0	0	0	0	0
Hardy-Weinberg equilibrium	2	0	2	2	1	2
Association assessment	2	1	1	1	2	2
Total	12	9	11	10	11	9

Arg399Gln, Arg194Trp and Arg280His polymorphisms. OR and 95% CI were chosen as the effect magnitude and significance level as α=0.05. Statistical tests were two-sided test. For Arg399Gln, we compared allele Gln with allele Arg on the risk of developing children ALL. Arg/Arg wild genotype was selected as reference to compare the risk of children ALL patients with homozygote Gln/Gln genotype and heterozygote Arg/Gln genotype. Supposing the mutated gene was the dominant gene, the OR of the dominant model (Arg/Gln+Gln/Gln *vs.* Arg/Arg) and the recessive model (Gln/Gln *vs.* Arg/Gln+Arg/Arg) was calculated. The same method was applicable to Arg194Trp and Arg280His. At the same time, we also did the subgroup analysis and the sensitivity analysis and provided publication bias estimate with funnel plot.

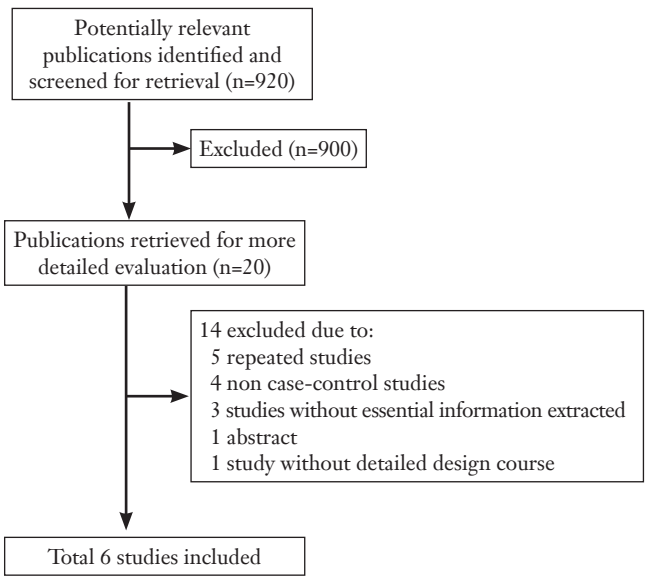

Figure 1 Flow diagram

Results

Eligible studies

According to the search criteria, there were total 6 English studies (17-24) including 679 cases and 950 controls accepted for our meta-analysis by screening among the 20 candidate literatures (*Figure 1*). Five articles were case-control studies based on healthy people, the rest one based on hospital people (23), all of whom from the six literatures came from different races, but the cases and controls in each study were from the same ethnic group. All patients of the total studies were less than sixteen years old while controls from different researches had different age ranges excepted that two studies had no description about the age of controls (19,22). The sex ratio varied in each literature. Three articles were matched by age, gender or race (17,20,23). Hardy-Weinberg equilibrium (HWE) test was made in five articles (16-18,20,21). All the studies used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method to identify *XRCC1* polymorphism genotype. Genomic DNA was extracted from the venous blood of patients, who were in remission, therapy or diagnosis. There were five researches having illustration on the diagnosis of childhood ALL (17-22), and only Tumer TB *et al.* made the risk stratification of children ALL in proportion. *Table 3* describes characteristics of included literatures. *Tables 4,5,6* describe the distribution of *XRCC1* Arg399Gln, Arg194Trp, Arg280His genotype in childhood ALL cases and controls.

Quantitative synthesis

Six studies including 679 cases and 950 controls on relationship between *XRCC1* Arg399Gln polymorphism and children ALL were accepted for our meta-analysis, five articles including 582 cases and 819 controls on the

Table 3 Characteristics of the case-control studies included in the meta-analysis

Author [year]	Country	Cases	Controls	Age (mean age/year) (case/control)	Gender (case M:F/control M:F)	Matching factor
Batar B [2009]	Turkey	70	75	1-15 (5.9±3.66)/1-14 (6.61±4.31)	44:26/36:39	age, gender
Tumer TB [2010]	Turkey	167	190	1.5-15.5 (7.2±3.8)/12-65 (30.5±11)	100:67/74:116	No
Pakakasama S [2007]	Thailand	108	317	10m*-14.9 (6.3)/__	62:46/163:154	No
Meza-Espinoza JP [2009]	Mexico	120	120	1-14 (7)/__	65:55/84:36	No
Stanczyk M [2011]	Poland	97	131	(5.4±2.5)/(6.2±2.8)	69:28/59:72	race
Joseph T [2005]	India	117	117	≤14/≤14	67.5%:32.5%/__	age, gender

*, month; M, male; F, female

Table 4 Distribution of *XRCC1* Arg399Gln genotype among childhood ALL cases and controls

	Cases			Controls			OR (95% CI)	
	Arg/Arg	Arg/Gln	Gln/Gln	Arg/Arg	Arg/Gln	Gln/Gln	Arg/Gln *vs.* Arg/Arg	Gln/Gln *vs.* Arg/Arg
Batar B	24	37	9	24	37	14	1.00 (0.45-2.21)	1.56 (0.51-4.84)
Tumer TB	63	77	27	92	78	20	1.40 (0.90-2.30)	2.00 (1.00-3.80)
Pakakasama S	39	60	9	175	124	18	2.17 (1.37-3.45)	2.24 (0.94-5.37)
Meza-Espinoza JP	57	51	12	65	47	8	1.24 (0.73-2.11)	1.71 (0.65-4.48)
Stanczyk M	34	45	18	50	57	24	1.12 (0.66-1.90)	1.02 (0.52-1.99)
Joseph T	55	46	16	75	33	9	1.90 (1.08-3.35)	2.42 (1.00-5.89)

Table 5 Distribution of *XRCC1* Arg194Trp genotype among childhood ALL cases and controls

	Cases			Controls			OR (95% CI)	
	Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg	Arg/Trp	Trp/Trp	Arg/Trp *vs.* Arg/Arg	Trp/Trp *vs.* Arg/Arg
Batar B	52	16	2	64	11	0	0.56 (0.22-1.41)	–
Tumer TB	140	27	0	159	26	5	1.20 (0.70-2.10)	–
Pakakasama S	62	44	2	150	145	22	0.73 (0.47-1.15)	0.22 (0.05-0.96)
Meza-Espinoza JP	80	34	6	86	31	3	1.18 (0.66-2.09)	2.15 (0.52-8.89)
Joseph T	77	32	8	91	22	4	1.72 (0.92-3.20)	2.36 (0.69-8.15)

Table 6 Distribution of *XRCC1* Arg280His genotype among childhood ALL cases and controls

	Cases			Controls			OR (95% CI)	
	Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His	Arg/His *vs.* Arg/Arg	His/His *vs.* Arg/Arg
Pakakasama S	94	14	0	272	42	3	0.97 (0.50-1.85)	–
Meza-Espinoza JP	87	31	2	88	31	1	1.01 (0.57-1.81)	2.02 (0.18-22.72)
Joseph T	76	38	3	85	30	2	1.42 (0.80-2.50)	1.68 (0.27-10.31)

XRCC1 Arg194Trp polymorphism of the developing risk of children ALL were included, and three literatures including 345 cases and 554 controls on the *XRCC1* Arg280His polymorphism of the developing risk of children ALL were included. All the DNA samples were from peripheral venous blood. And the cases' DNA samples were extracted from different stages including primary diagnosis, treatment and complete remission. Only Stanczyk M *et al.* had DNA duplicate detection and none had blind method on *XRCC1* genotyping. Tumer TB and Stanczyk M also discussed the association of *XRCC1* Arg399Gln polymorphism and together with other genes polymorphisms with the developing risk of children ALL.

Arg399Gln

No significant between-study heterogeneities were found concerning the relationship between *XRCC1* Arg399Gln polymorphism and children ALL with P>0.1. Hence, we used a fixed-effects mode to pool data. The risk of ALL for children with Gln allele was 1.35 times to that with Arg allele, which had statistically significant difference (P<0.0001). Compared to Arg/Arg wild genotype, both of the homozygote Gln/Gln genotype and heterozygote Arg/Gln genotype could increase the risk of children ALL. (Gln/Gln *vs.* Arg/Arg: OR, 1.58; 95% CI, 1.13-2.21; P=0.008) (Arg/Gln *vs.* Arg/Arg: OR, 1.51; 95% CI, 1.21-1.87; P=0.0002). Similarly, the Arg399Gln dominant model was also associated with childhood ALL (Arg/Gln+Gln/Gln *vs.* Arg/Arg: OR, 1.54; 95% CI, 1.25-1.89; P<0.0001). However, no associations were found in the recessive model (Gln/Gln *vs.* Arg/Gln+Arg/Arg: OR, 1.32; 95% CI, 0.96-1.80; P=0.09) (*Table* 7). From the forest plot we can see that the Gln allele in all five ethnic groups was prone to be associated with childhood ALL just with different degrees of correlation, and Thai race and Indian race had

Table 7 Meta-analysis of *XRCC1* Arg399Gln polymorphisms and risk of childhood ALL

	Cases	Controls	OR (fixed) (95% CI)	P
Gln *vs.* Arg	1,358	1,900	1.35 (1.16-1.57)	<0.0001
Gln/Gln *vs.* Arg/Arg	363	574	1.58 (1.13-2.21)	0.008
Arg/Gln *vs.* Arg/Arg	588	857	1.51 (1.21-1.87)	0.0002
Arg/Gln+Gln/Gln *vs.* Arg/Arg	679	950	1.54 (1.25-1.89)	<0.0001
Gln/Gln *vs.* Arg/Gln+Arg/Arg	679	950	1.32 (0.96-1.80)	0.09

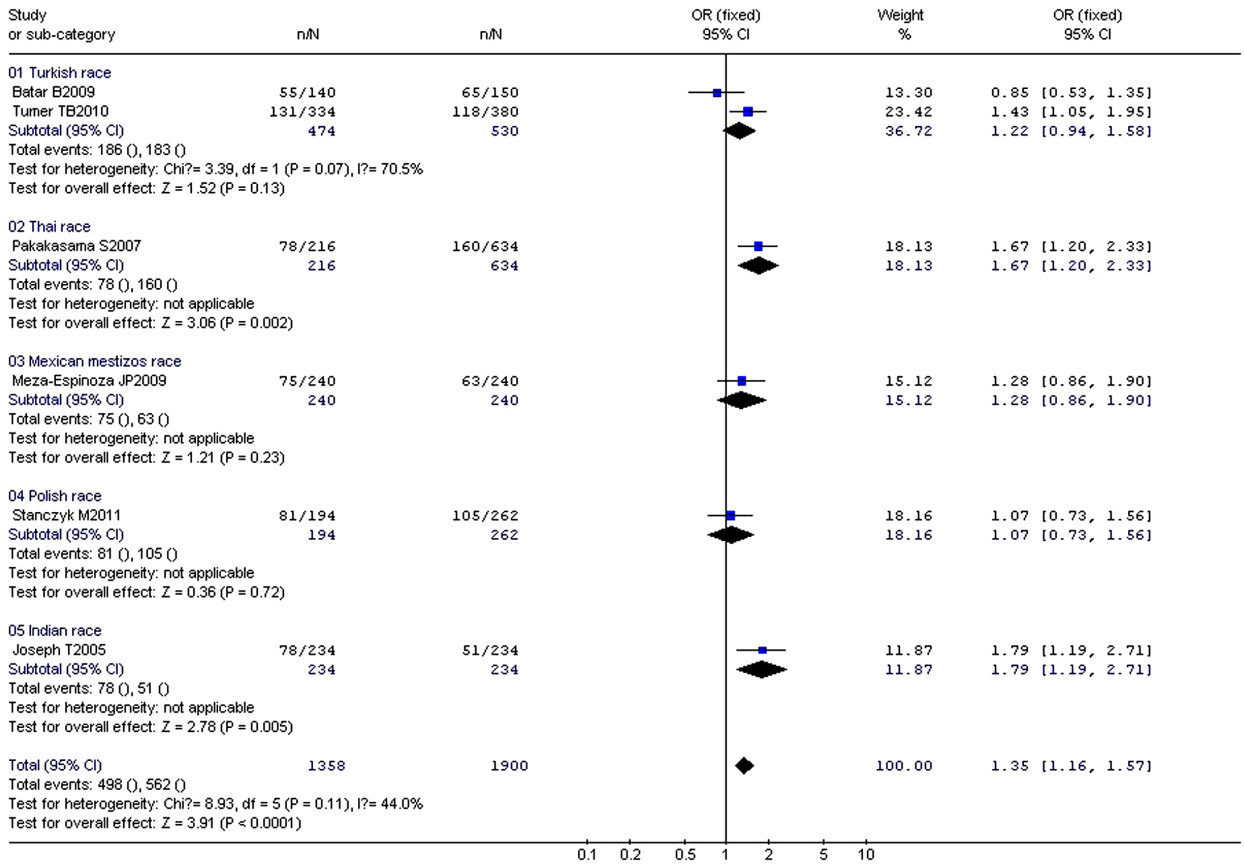

Figure 2 Forest plots of meta-analysis for *XRCC1* codon 399 Gln *vs.* Arg among 5 ethnic groups in childhood ALL. Confidence interval (CI) for each study is represented by a horizontal line (—) and the point estimate is represented by a square (■). The size of the square corresponds to the weight of the study in the meta-analysis. The CI for totals are represented by a diamond shape (♦)

statistically significant differences (OR =1.67, 95% CI, 1.20-2.33, P=0.002 in Thai race; OR =1.79, 95% CI, 1.19-2.71, P=0.005 in Indian race). The overall result (OR =1.35, 95% CI, 1.16-1.57, P<0.0001) suggested a relationship between Gln allele and childhood ALL in all different ethnic groups described above (*Figure 2*).

Arg194Trp

The studies about the relationship between *XRCC1* Arg194Trp and childhood ALL were heterogeneous (except the comparison between Arg/Trp and Arg/Arg using the fixed-effects model, P=0.17). Therefore, we used the

Table 8 Meta-analysis of *XRCC1* Arg194Trp polymorphisms and risk of childhood ALL

	Cases	Controls	OR (random) (95% CI)	P
Trp *vs.* Arg	1,164	1,641	1.15 (0.74-1.77)	0.54
Trp/Trp *vs.* Arg/Arg	429	584	0.98 (0.26-3.73)	0.97
Arg/Trp *vs.* Arg/Arg	564	785	1.12 (0.86-1.44)	0.40
Arg/Trp+Trp/Trp *vs.* Arg/Arg	582	819	1.18 (0.78-1.78)	0.42
Trp/Trp *vs.* Arg/Trp+Arg/Arg	582	819	0.96 (0.28-3.32)	0.94
Drop the Batar B'article with small sample size				
Trp/Trp *vs.* Arg/Arg	375	520	0.75 (0.17-3.24)	0.70
Arg/Trp+Trp/Trp *vs.* Arg/Arg	512	744	1.08 (0.70-1.67)	0.72
Drop the Joseph T'article with hospital-based controls				
Trp/Trp *vs.* Arg/Arg	344	489	0.71 (0.13-3.97)	0.70
Arg/Trp+Trp/Trp *vs.* Arg/Arg	465	702	1.05 (0.69-1.61)	0.82
Drop the Tumer TB'article without HWE test				
Trp/Trp *vs.* Arg/Arg	289	420	1.35 (0.35-5.19)	0.66
Arg/Trp+Trp/Trp *vs.* Arg/Arg	415	629	1.26 (0.74-2.14)	0.40

random-effects model to pool data showing no association between Arg194Trp polymorphism and childhood ALL (*Table 8*). The ethnic subgroup analysis demonstrated that the relationship between Trp allele and childhood ALL in the four ethnic groups was variant. As for Thai race, it represented a protected role for Trp allele in the childhood ALL development (OR =0.67, 95% CI, 0.47-0.97, P=0.03). While as for Indian race, it may increase the risk of childhood ALL with Trp allele (OR =1.75, 95% CI, 1.07-2.89, P=0.03). The rest two ethnic groups with Trp allele provided no relationship with childhood ALL. The synthesized result revealed no relationship between Trp allele and childhood ALL in the four ethnic groups (OR = 1.15, 95% CI, 0.74-1.77, P=0.54) (*Figure 3*).

Arg280His

According to the meta-analysis, there was no relationship between *XRCC1* Arg280His and childhood ALL with no significant between-study heterogeneities using the fixed-effects model to pool data (*Table 9*). Ethnic group analysis showed no relationship between His allele and childhood ALL within each race (*Figure 4*).

Sensitivity analysis and publication bias evaluation

There were no significant changes in conclusions about the association between Arg194Trp polymorphism and childhood ALL before and after excluding some articles (*Table 8*), which might be the sources of heterogeneity. Additionally, we analyzed the publication bias by drawing funnel plot, from which we can see that six points were approximately symmetrical in the inverted funnel plot (*Figure 5*).

Discussion

Human genome DNA is composed of approximately 3 billion base pairs, which are frequently influenced by endogenous metabolite, medical medicine and massive environment mutagen resulting in the damage of DNA integrity in the physiological activity. If this damage can not be recognized and repaired in time, the error replication, gene mutation and even tumor may occur. *XRCC1* gene product is one of the important proteins participated in BER, SSB and DSB repair pathways and the gene is located at 19q13.2-13.3. It is reported that *XRCC1* gene knockout mice may die in the early embryogenesis (14) and the cells with this *XRCC1* gene defection are very sensitive to ionizing radiation and alkylating agent (9), which illustrated that *XRCC1* gene plays an important role in the DNA integrity maintaining and individual development. *XRCC1* gene has three common SNPs, codon 399, 194 and 280, which maybe change the repair ability of DNA. These genetic susceptibility genes are considered as potential hazard factors for childhood ALL (32).

Meta-analysis is a method through collecting comparable literatures published or unpublished, and applying certain

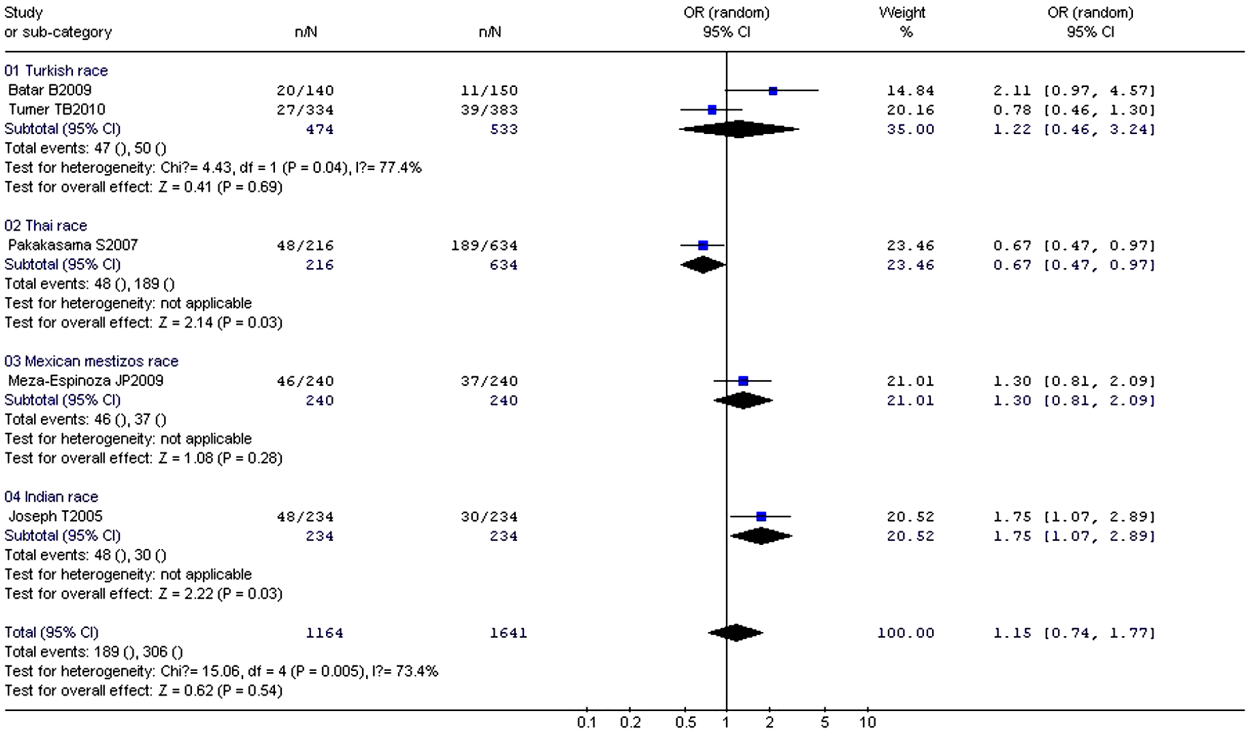

Figure 3 Forest plots of meta-analysis for *XRCC1* codon 194 Trp *vs.* Arg among 4 ethnic groups in childhood ALL. Confidence interval (CI) for each study is represented by a horizontal line (—) and the point estimate is represented by a square (■). The size of the square corresponds to the weight of the study in the meta-analysis. The CI for totals are represented by a diamond shape (♦)

Table 9 Meta-analysis of *XRCC1* Arg280His polymorphisms and risk of childhood ALL

	Cases	Controls	OR (fixed) (95% CI)	P
His *vs.* Arg	690	1,108	1.11 (0.82-1.50)	0.51
His/His *vs.* Arg/Arg	262	451	1.26 (0.37-4.24)	0.71
Arg/His *vs.* Arg/Arg	340	548	1.13 (0.80-1.59)	0.49
Arg/His+His/His *vs.* Arg/Arg	345	554	1.13 (0.80-1.57)	0.49
His/His *vs.* Arg/His+Arg/Arg	345	554	1.20 (0.36-4.05)	0.77

statistical method to synthesize the independent results of studies with the same research target to obtain a combined quantitative conclusion, or a reason why similar studies will have different results, which will be strongly scientific, repeatable and objective.

Based on our meta-analysis about the association between *XRCC1* SNPs, Arg399Gln, Arg194Trp and Arg280His, and childhood ALL, we found that the Arg399Gln SNP possibly increased the children ALL risk with no between-study heterogeneity. On the contrary, both of *XRCC1* Arg194Trp and Arg280His polymorphisms did not contribute to childhood ALL. But the Arg399Gln SNP might have small absolute risk effect for the occurrence of childhood ALL on the basis of low OR ranging from 1.32 to 1.58, which was consistent with previous genetic susceptibility researches (33-35). Additionally, some literatures reported that folate deficiency can contribute to an elevation in DNA breaks (36) and the successful repair of DNA breaks during fetal hematopoiesis can be modified by genetic and dietary factors in the folate pathway (37). Therefore, it is necessary to research the interaction between *XRCC1* repair ability and folate metabolism for the contribution to fetal ALL.

Epidemiologic data show that ethnic and racial groups differ significantly in terms of cancer incidence and

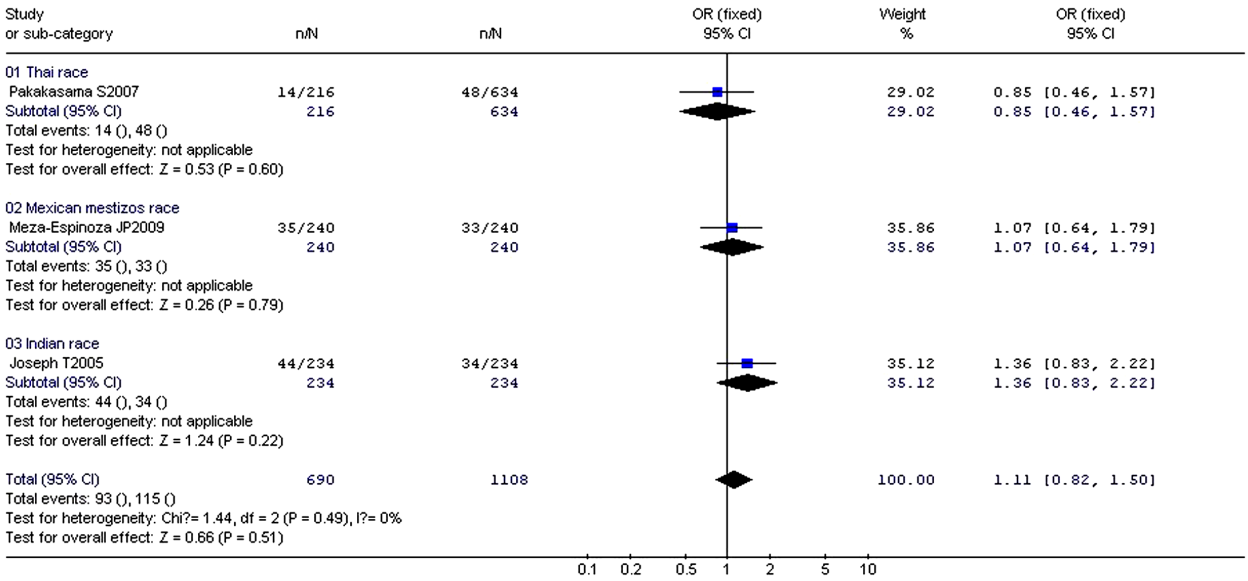

Figure 4 Forest plots of meta-analysis for *XRCC1* codon 280 His *vs.* Arg among 3 ethnic groups in childhood ALL. Confidence interval (CI) for each study is represented by a horizontal line (—) and the point estimate is represented by a square (■). The size of the square corresponds to the weight of the study in the meta-analysis. The CI for totals are represented by a diamond shape (♦)

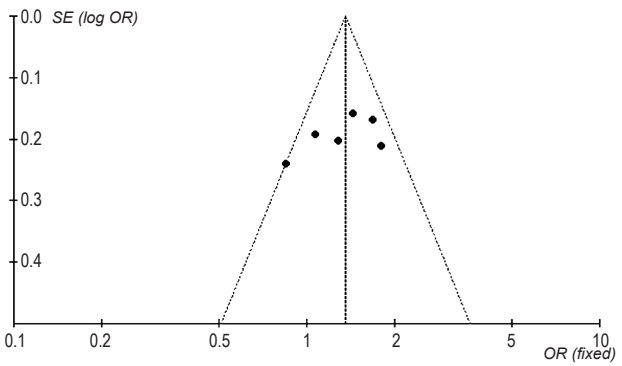

Figure 5 Funnel plot to explore publication bias

mortality rates (38). On this point, we also achieve some discoveries in this study. Our ethnic subgroup analysis manifested that *XRCC1* Arg399Gln SNP did some contributions to children with ALL in different ethnics. It seems to be a dangerous factor for childhood ALL in each race as all the ORs were above 1.0. Especially in Asia countries, such as Thailand and India, the statistical data of which had significant difference. However, the correlation between childhood ALL and Arg194Trp SNP was not the same in each ethnic. In Thai race, Arg194Trp SNP was a protective factor while in India it is a risk factor and no relationship was found in the rest ethnic groups. For Arg280His SNP, ethnic group analysis showed no association between His allele and childhood ALL within each race. The racial or ethnic variation in cancer risk may reflect differences in environmental exposures or socio-economic and demographic factors as well as inherent biological susceptibility (39). Consequently, careful attention must be paid to racial stratification when we research the relationship between gene polymorphisms and disease.

Studies about the association between *XRCC1* Arg194Trp polymorphism and childhood ALL were heterogeneous. Sensitivity analysis was conducted by excluding the relatively poor quality of literatures, but results hardly changed. It demonstrated good stability of the results, but no heterogeneous sources were found. However, perhaps racial differences are sources of heterogeneity which we have had a very detailed discussion. Additionally, publication bias assessment analysis displayed that six points in the funnel plot are basically symmetrical, indicating less impact on the results. But the conclusion should be considered preliminary because of the small number of studies included.

In our article, there are still some limitations. First, there was one study based on hospital population, which was difficult to determine whether genetic polymorphism was related to ALL or not. Perhaps this polymorphism was

associated with other disease rather than ALL. Second, only three articles matched confounding factors such as gender, age and race in the case and control group. Thus results of the rest researches might be disturbed by the unmatched confounding factors. Third, only one article did not abide by HWE among the six included studies except an article without HWE inspection, which suggested that it was wrong in genotyping or inappropriate in choosing control group (40). Forth, the overall sample sizes of included literatures are quite small. Fifth, some valuable studies are probably omitted by the impact of publication bias, because articles with positive results or in English are easier to be published. So we should have larger sample size, rigorous design approach, perfect retrieval strategy and reasonable inclusion and exclusion criteria in the future studies.

Although there were some deficiencies in this article, the comprehensive research results showed that *XRCC1* Arg399Gln polymorphism could increase the risk of childhood ALL, which was to be significant to some extent. Because this not only can deeply enhance our knowledge of the childhood ALL pathogenesis, which will offer potential targets for therapeutic intervention, but also assess the risk of childhood ALL in order to take effective measures to protect vulnerable populations. Meanwhile, it is essential to study the correlation between ALL and gene polymorphism in Chinese children. More researches are needed to investigate the relationship between DNA repair genes polymorphisms and childhood ALL.

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