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ORIGINAL RESEARCH

The association between *XRCC1* Arg399Gln polymorphism and risk of leukemia in different populations: a meta-analysis of case-control studies

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Background: Associations between Arg399Gln single-nucleotide polymorphism (SNP) in the *XRCC1* gene and leukemia susceptibility have been studied extensively, however, the results are inconsistent. The aim of this study was to determine these associations using meta-analytical methods.

Methods: A meta-analysis was performed to examine the associations between *XRCC1* Arg399-Gln SNP and leukemia risk. A literature search of PubMed and Web of Science databases was conducted to identify relevant studies published up to March 10, 2015. The references of the retrieved articles were also screened. All the statistical analyses were conducted using Review Manager software.

Results: The *XRCC1* Arg399Gln SNP was found to be associated with increased childhood risk of acute lymphoblastic leukemia among Asians under the dominant (odds ratio [OR] 2.11, 95% confidence interval [CI] 1.50–2.97, $P<0.0001$), allele contrast (OR 1.72, 95% CI 1.33–2.23, $P<0.0001$), and homozygote contrast (OR 2.34, 95% CI 1.25–4.36, $P=0.008$) models. However, no association was found in Caucasians between the SNP and risk of either chronic myeloid leukemia or chronic lymphocytic leukemia under any contrast model.

Conclusion: The findings of the current meta-analysis indicate that the *XRCC1* Arg399Gln SNP is a risk factor for childhood lymphoblastic leukemia in Asians.

Keywords: Arg399Gln, AML, ALL, CML, CLL, susceptibility

Introduction

Leukemia is a malignant neoplasm of blood-forming tissues[1] that can be classified into the following four groups according to the cell type and growth rate: acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL).[2] Despite numerous studies on leukemogenesis, the mechanism underlying the development of these cancers is yet to be fully elucidated.

DNA repair pathways play a vital role in maintaining genetic integrity, and it is becoming clear that defects in repair pathways are connected to many different types of diseases, including leukemia.[3] It has been reported that impaired DNA repair may be associated with increased susceptibility to human cancers.[4] The *XRCC1* gene is one of the most important DNA repair genes, and plays a key role in the process of base excision repair.[1] *XRCC1* single-nucleotide polymorphism (SNP) Arg399Gln at codon 399 has been extensively examined and is associated with diminished capacity to remove DNA adducts, causing DNA damage due to oxidation.[5] Therefore, the Arg399Gln SNP may contribute to leukemia.

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Studies of the association between *XRCC1* SNPs and leukemia have produced conflicting findings, possible reasons for which include differences in ethnicity and sample size. The aim of the present meta-analysis was to obtain a more accurate picture with regard to the role of the *XRCC1* Arg399Gln SNP in the risk of leukemia.

Materials and methods

Search strategy

Computerized searches of the PubMed and Web of Science databases were conducted using a combination of the following keywords: "XRCC1" ("X-ray repair cross complementing 1" OR "X-ray repair cross complementing group 1" OR "X-ray cross complementing repair gene 1"), "AML" ("acute myeloid leukemia" OR "acute myeloblastic leukemia" OR "acute myelocytic leukemia"), "ALL" ("acute lymphocytic leukemia" OR "acute lymphoblastic leukemia"), "CLL" ("chronic lymphocytic leukemia" OR "chronic lymphoblastic leukemia"), "CML" ("chronic myeloid leukemia" OR "chronic myelocytic leukemia" OR "chronic myeloblastic leukemia"), "leukemia", and "hematological malignancies". All references cited in the selected studies were also reviewed to identify additional relevant work.

Inclusion criteria

Published studies were included if they satisfied the following criteria:

1. Only studies published in journals in English were included in the analysis;
2. Used a case-control design;
3. Focused on the association between the *XRCC1* Arg399Gln SNP and risk of AML, ALL, CML, or CLL;
4. Provided sufficient data on the distribution of the *XRCC1* Arg399Gln SNP in leukemia and in controls, or sufficient information for such data to be calculated.

Data extraction

The following information was extracted from each study: first author, publication year, subjects' ethnicity, disease type, number of cases and controls, Hardy–Weinberg equilibrium (HWE) for the controls' distribution of genotypes, and main results about associations between the *XRCC1* Arg399Gln SNP and risk of leukemia.

Statistical analysis

The association between the *XRCC1* Arg399Gln SNP and risk of different types of leukemia in different populations was evaluated under the allele contrast (Gln versus Arg), homozygote contrast (Gln/Gln versus Arg/Arg), dominant (Gln/Gln + Arg/Gln versus Arg/Arg), and recessive (Gln/Gln versus Arg/Gln + Arg/Arg) models. Studies wherein the distribution of the *XRCC1* Arg399Gln genotypes among the controls deviated from HWE were excluded from the meta-analysis.

Review Manager software (version 5.3) was used for the meta-analysis. Raw data of genotype distribution were used to calculate the study-specific estimates of odds ratios (ORs) and 95% confidence intervals (CIs). The heterogeneity of the studies was assessed using Cochran's Q test, and was considered statistically significant at $P<0.10$. Heterogeneity was also quantified using the heterogeneity index (I^2) statistic, with $I^2>50\%$ indicating the presence of a high degree of heterogeneity.[6]

The strength of associations between the *XRCC1* Arg399Gln SNP and different types of leukemia risk was assessed by the ORs and the corresponding 95% CIs. The significance of the pooled ORs was determined by the Z-test, and the threshold for significance was set at $P<0.05$. The fixed-effects model (Mantel–Haenszel methods) was used when there was no substantial heterogeneity. In the event of substantial heterogeneity, sensitivity analysis was performed by excluding individual studies; outlying studies were identified and excluded, and the I^2 estimates for these different sets of studies were examined. The random-effects model (DerSimonian and Laird's method)[7] was used when removal of particular studies did not render the heterogeneity insignificant (ie, $I^2<50\%$).

Potential publication bias was estimated by constructing funnel plots. If most of the data appeared at the top of a funnel plot and was distributed roughly symmetrically, this would suggest the absence of obvious publication bias, and vice versa.[8] There was no need to construct funnel plots when there were too few (ie, less than five) analyzed studies.

Results

Overview of the study characteristics

A flowchart depicting the study selection process is shown in Figure 1. In total, 746 articles were selected on the basis of various combinations of the keywords listed in the "Methods and materials" section. Checking for duplicates resulted in the removal of 660 articles. Of the remaining 86 articles, 65 were excluded for the following reasons: lack of relevance, since the articles did not explore the association between *XRCC1* SNPs and leukemia risk (n=23); did not focus on susceptibility to leukemia (n=24);

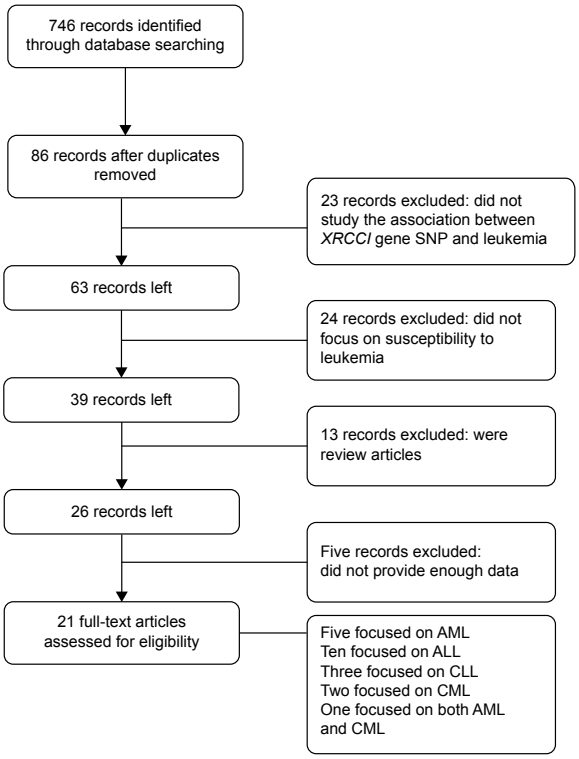


Figure 1 Flowchart of study selection.
Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; SNP, single-nucleotide polymorphism.

were review articles (*n*=13); or provided insufficient data (*n*=5). Thus, only 21 articles qualified for inclusion in this meta-analysis, among which 5, 10, 3, 2, and 1 focused on AML,[3,9–12] ALL,[13–22] CLL,[23–25] CML,[26,27] and both AML and CML,[28] respectively.

Basic data for every eligible study were extracted and are listed in Table 1. In one article,[16] in which different ethnic populations were evaluated, data for each ethnicity were collected separately and were treated in the present analysis as independent studies. Moreover, another included article[28] provided separate data for two types of leukemia; further, data for each leukemia type were analyzed as if they were from different studies. As a result, data from a final total of 23 studies were finally included in this meta-analysis. However, the genetic distributions of the control groups did not conform with HWE in three of these studies,[10,11,27] which were thus excluded from the meta-analysis. The distribution of the remaining studies regarding meta-analysis of the association between *XRCC1* Arg399Gln SNP and risk of each type of leukemia was as follows: ALL, eleven studies (1,088 cases and 1,588 controls); AML, four studies (345 cases and 651 controls); CML, two studies (338 cases and 406 controls); and CLL, three studies (712 cases and 614 controls).

Table 1 Study characteristics

Study	Year	Ethnicity	Cancer	Case/control	P_{HWE} in control	Main results
Abramenko et al[24]	2012	Caucasian	CLL	178/103	0.4845	N
Annamaneni et al[27]	2013	Asian	CML	350/350	0.0000	(+)
Banescu et al[9]	2014	Caucasian	AML	69/147	0.2195	(+)
Banescu et al[26]	2014	Caucasian	CML	156/180	0.8041	N
Batar et al[19]	2009	Caucasian	ALL	70/75	0.9687	N
Canalle et al[16]	2011	Caucasian	ALL	178/223	0.3209	N
Canalle et al[16]	2011	Mixed	ALL	28/141	0.6087	N
Celkan et al[20]	2008	Caucasian	ALL	52/60	0.8248	N
Deligezer et al[28]	2007	Caucasian	AML	72/226	0.7629	N
Deligezer et al[28]	2007	Caucasian	CML	182/226	0.7629	N
Dincer et al[14]	2015	Caucasian	ALL	30/30	0.1259	N
Duman et al[23]	2012	Caucasian	CLL	73/50	0.3636	(+)
Ganster et al[25]	2009	Caucasian	CLL	461/461	0.8988	N
Goricar et al[13]	2015	Caucasian	ALL	121/184	NA	N
Joseph et al[22]	2005	Asian	ALL	117/117	0.0619	(+)
Kim et al[11]	2012	Asian	AML	415/1,700	0.0058	N
Meza-Espinoza et al[18]	2009	Mixed	ALL	120/120	0.8992	N
Ozcan et al[12]	2011	Caucasian	AML	36/100	0.4692	(–)
Pakakasama et al[21]	2007	Asian	ALL	108/317	0.5146	(+)
Seedhouse et al[3]	2002	Caucasian	AML	168/178	0.0541	(–)
Sorour et al[10]	2013	Caucasian	AML	90/60	0.0245	(+)
Stanczyk et al[15]	2011	Caucasian	ALL	97/131	0.2815	N
Tumer et al[17]	2010	Caucasian	ALL	167/190	0.5694	(+)

Abbreviations: N, no association between SNP and leukemia susceptibility; (+), SNP associated with increased leukemia susceptibility; (–), SNP associated with decreased leukemia susceptibility; NA, not available; SNP, single-nucleotide polymorphism; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; P_{HWE} in control, probability of adherence to the Hardy–Weinberg equilibrium.

Meta-analysis results

Table 2 lists the main results of the meta-analysis. The findings are discussed for each leukemia type separately in the following section.

AML

A meta-analysis of the four studies that focused on AML was performed on data from 345 cases and 651 controls. The subjects in all four studies were Caucasians. A high degree of heterogeneity was observed under the recessive (I^2=79%, P=0.003), dominant (I^2=70%, P=0.02), allele contrast (I^2=84%, P=0.0003), and homozygote contrast (I^2=82%, P=0.0007) models. Therefore, random-effects modeling was performed for the four contrast models. The meta-analysis for these studies revealed no association between the *XRCC1* Arg399Gln SNP and the risk of AML under the recessive model (OR 0.89, 95% CI 0.33–2.44, P=0.83), dominant (OR 0.97, 95% CI 0.58–1.63, P=0.91), allele contrast (OR 0.94, 95% CI 0.55–1.59, P=0.81), or homozygote contrast models (OR 0.86, 95% CI 0.27–2.78, P=0.81).

In view of the high degree of heterogeneity, a sensitivity analysis was conducted, and the study by Banescu et al[9] was found to be an outlier. Removal of their data from the analysis reduced the degree of heterogeneity under the recessive and dominant models, but not sufficiently so under the allele contrast (I^2=65%, P=0.06; Figure 2A) and homozygote contrast models (I^2=59%, P=0.09; Figure 2B). Fixed-effects modeling was thus performed for the recessive and dominant models, and finally, the SNP was associated with AML risk under the recessive model (OR 0.58, 95% CI 0.38–0.89, P=0.01; Figure 2C) but not under the dominant model (OR 0.79, 95% CI 0.58–1.07, P=0.13; Figure 2D). Therefore, the result for AML under the recessive model is sensitive to the study by Banescu et al.[9]

ALL

Eleven of the 23 included studies investigated the distribution of *XRCC1* SNP in childhood ALL cases and controls and provided sufficient data for analysis. A meta-analysis of these eleven studies was performed, and included data from 1,088 cases and 1,588 controls.

The forest plot revealed no heterogeneity under the recessive (P=0.65, I^2=0%) and homozygote contrast (P=0.50, I^2=0%) models, and I^2<50% under the allele contrast (P=0.05, I^2=46%) model. The fixed-effects model was therefore used for these three contrast models. The degree

Table 2 Odds ratios (ORs) and heterogeneity results for *XRCC1* Arg399Gln meta-analysis

Type of cancer	Studies (n)	Ethnicity	Contrast models	ORs (95% CIs)		I^2	*P*-value
				Fixed-effects model	Random-effects model		
ALL	7	Caucasian	Recessive model	1.10 (0.79, 1.53)		0%	0.57
			Dominant model	1.00 (0.82, 1.22)		34%	0.99
			Allele contrast	1.07 (0.91, 1.26)		8%	0.39
			Homozygote contrast	1.18 (0.82, 1.69)		0%	0.37
	2	Asian	Recessive model	1.70 (0.94, 3.08)		0%	0.08
			Dominant model	2.11 (1.50, 2.97)		0%	<0.0001
			Allele contrast	1.72 (1.33, 2.23)		0%	<0.0001
			Homozygote contrast	2.34 (1.25, 4.36)		0%	0.008
	2	Mixed	Recessive model	1.60 (0.74, 3.48)		0%	0.23
			Dominant model		0.88 (0.36, 2.16)	70%	0.78
			Allele contrast	1.11 (0.79, 1.55)		47%	0.56
			Homozygote contrast	1.56 (0.71, 3.42)		0%	0.27
AML	4	Caucasian	Recessive model	0.58 (0.38, 0.89)		44%	0.01
			Dominant model	0.79 (0.58, 1.07)		49%	0.13
			Allele contrast		0.75 (0.50, 1.13)	65%	0.17
			Homozygote contrast		0.56 (0.22, 1.43)	59%	0.22
CLL	3	Caucasian	Recessive model	1.11 (0.79, 1.57)		49%	0.54
			Dominant model	1.09 (0.86, 1.39)		0%	0.46
			Allele contrast	1.08 (0.91, 1.28)		0%	0.40
			Homozygote contrast	1.16 (0.80, 1.68)		32%	0.44
CML	2	Caucasian	Recessive model	0.99 (0.62, 1.57)		0%	0.97
			Dominant model	1.11 (0.83, 1.49)		0%	0.46
			Allele contrast	1.06 (0.85, 1.32)		0%	0.60
			Homozygote contrast	1.05 (0.65, 1.71)		0%	0.84

Abbreviations: CIs, confidence intervals; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia.

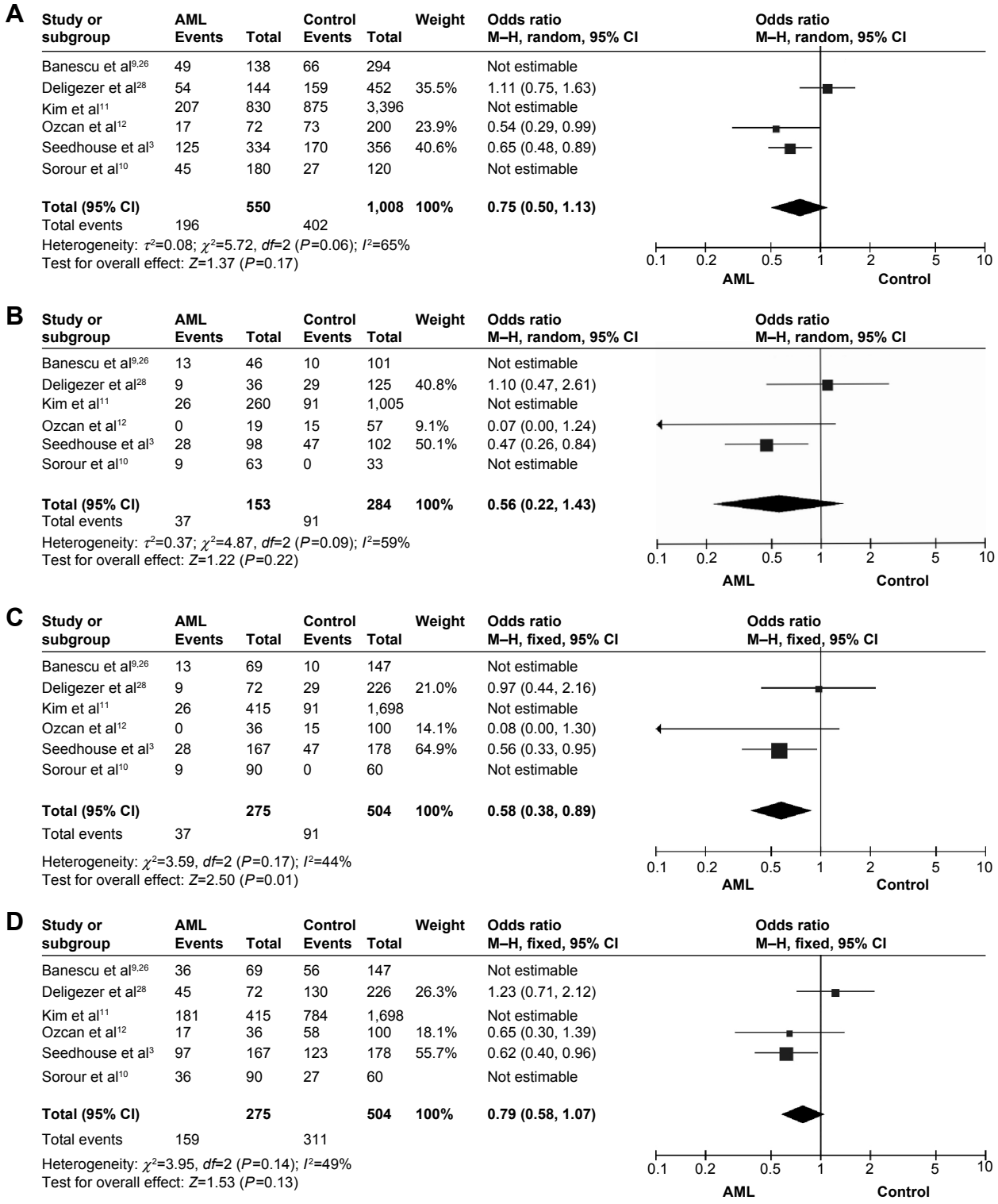


Figure 2 Meta-analysis of the association between *XRCC1* Arg399Gln SNP and AML risk under the allele contrast model (**A**), the homozygote contrast model (**B**), the recessive model (**C**), and the dominant model (**D**).
Abbreviations: SNP, single-nucleotide polymorphism; AML, acute myeloid leukemia; CI, confidence interval; M–H, Mantel–Haenszel.

of heterogeneity was high (I^2=62%, P=0.003) under the dominant model; therefore, a random-effects model was employed under that model. Finally, an association was found between the SNP and increased childhood ALL risk under the allele contrast (OR 1.21, 95% CI 1.06–1.37, P=0.003) and homozygote contrast (OR 1.41, 95% CI 1.06–1.88, P=0.02) models. The funnel plot did not reveal any obvious publication bias (Figure 3).

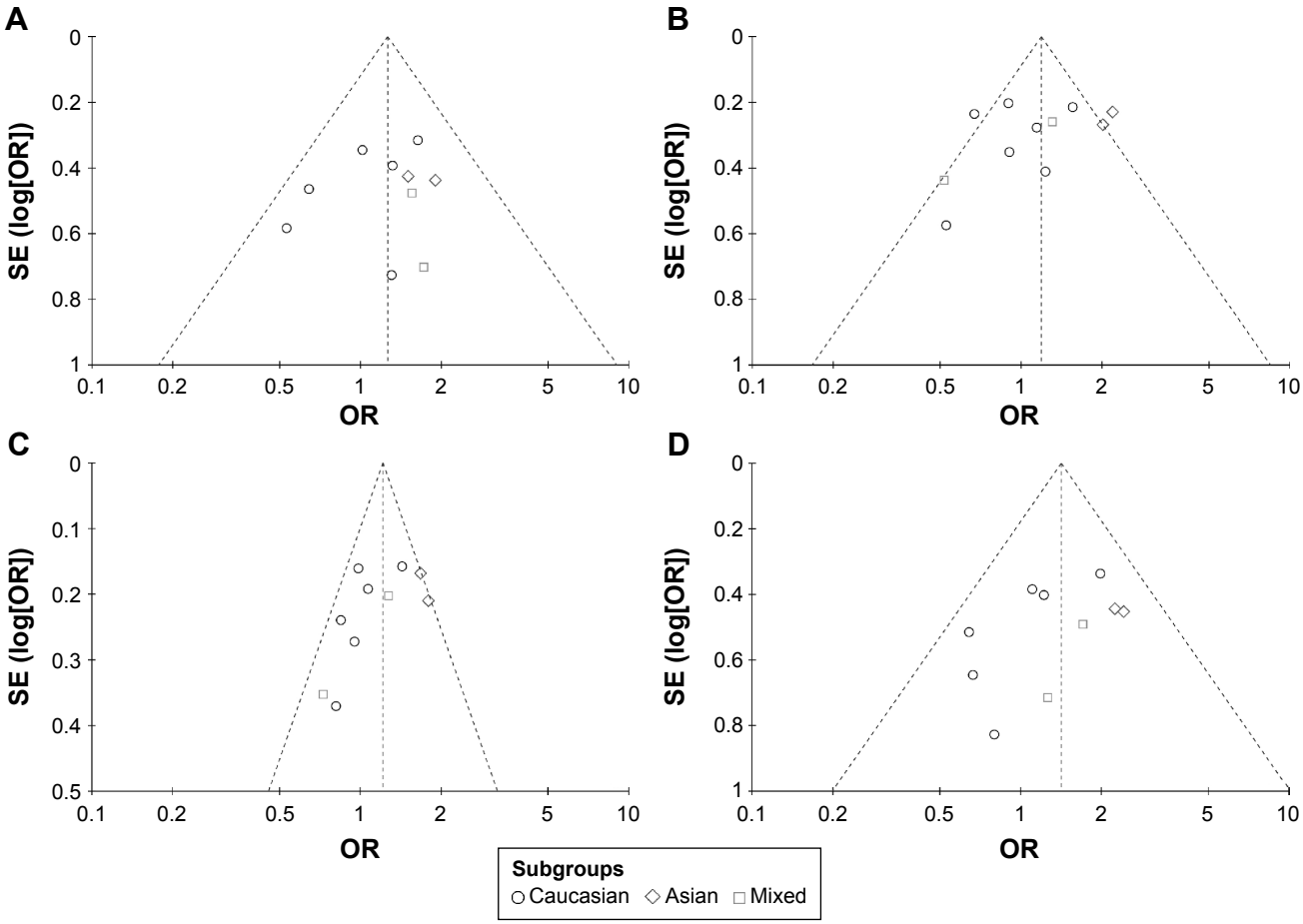


Figure 3 The funnel plots of meta-analysis for the association between *XRCC1* Arg399Gln SNP and ALL risk under the recessive model (**A**), the dominant model (**B**), the allele contrast model (**C**), and the homozygote contrast model (**D**).
Abbreviations: SNP, single-nucleotide polymorphism; ALL, acute lymphocytic leukemia; SE, standard error of the mean; OR, odds ratio.

As the different results obtained among the included studies could be attributable to population differences in Arg399Gln mutation frequency or linkage disequilibrium block, subgroup analysis according to race was conducted. In the Caucasian and Asian subgroups, heterogeneity was not found to be large (I^2<50%) under any contrast model. Therefore, the fixed-effects model was used in Caucasian and Asian subgroups under any contrast model. The Arg399Gln SNP was then found to significantly increase the risk of childhood ALL only among Asians, under the dominant (OR 2.11, 95% CI 1.50–2.97, P<0.0001; Figure 4B), allele contrast (OR 1.72, 95% CI 1.33–2.23, P<0.0001; Figure 4C), and homozygote contrast (OR 2.34, 95% CI 1.25–4.36, P=0.008; Figure 4D) models. No association was observed under the recessive model (OR 1.70, 95% CI 0.94–3.08, P=0.08; Figure 4A). Furthermore, no association between the *XRCC1* Arg399Gln SNP and risk of childhood ALL was found under any contrast model among Caucasian or mixed-race populations (Figure 4).

CML

CML was surveyed in two studies, involving data from 338 cases and 406 controls, all of whom were Caucasian. No heterogeneity was found between the two included studies under any contrast model, and so the fixed-effects model was used. Overall, the meta-analysis for those studies revealed no association between the *XRCC1* Arg399Gln SNP and risk of CML under any contrast model (Table 2).

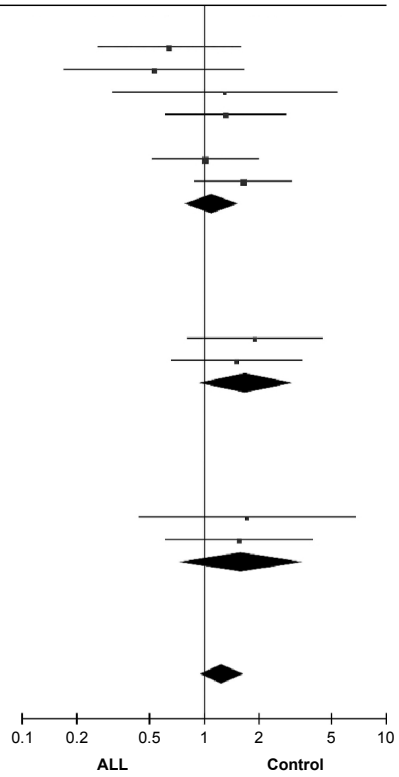
CLL

The association between the *XRCC1* Arg399Gln SNP and risk of CLL was researched in three studies with 712 cases and 614 controls, all of whom were Caucasian. The forest plot revealed a high degree of heterogeneity. Random-effects modeling was thus performed for the four contrast models. The meta-analysis for these studies revealed no association between the SNP and risk of CLL under any contrast model.

In view of such a high degree of heterogeneity, a sensitivity analysis was conducted, revealing the study of Duman et al[23]

A

Study or subgroup	ALL Events	Total	Control Events	Total	Weight	Odds ratio M–H, fixed, 95% CI
Caucasian						
Batar et al[19]	9	70	14	75	12.6%	0.64 (0.26, 1.60)
Celkan et al[20]	5	52	10	60	9.0%	0.53 (0.17, 1.67)
Dincer et al[14]	5	30	4	30	3.6%	1.30 (0.31, 5.40)
Canalle et al[16]	14	173	14	223	12.1%	1.31 (0.61, 2.84)
Goricar et al[13]	0	0	0	0		Not estimable
Stanczyk et al[15]	18	97	24	131	17.9%	1.02 (0.52, 2.00)
Tumer et al[17]	27	167	20	190	16.8%	1.64 (0.88, 3.05)
Subtotal (95% CI)		**589**		**709**	**72.0%**	**1.10 (0.79, 1.53)**
Total events	78		86			
Heterogeneity: χ^2=4.79, *df*=5 (*P*=0.44); I^2=0%						
Test for overall effect: *Z*=0.56 (*P*=0.57)						
Asian						
Joseph et al[22]	16	117	9	117	8.3%	1.90 (0.80, 4.49)
Pakakasama et al[21]	9	108	18	317	9.0%	1.51 (0.66, 3.47)
Subtotal (95% CI)		**225**		**434**	**17.3%**	**1.70 (0.94, 3.08)**
Total events	25		27			
Heterogeneity: χ^2=0.14, *df*=1 (*P*=0.71); I^2=0%						
Test for overall effect: *Z*=1.75 (*P*=0.08)						
Mixed						
Canalle et al[16]	3	28	9	138	2.9%	1.72 (0.43, 6.80)
Meza-Espinoza et al[18]	12	120	8	120	7.7%	1.56 (0.61, 3.95)
Subtotal (95% CI)		**148**		**258**	**10.6%**	**1.60 (0.74, 3.48)**
Total events	15		17			
Heterogeneity: χ^2=0.01, *df*=1 (*P*=0.91); I^2=0%						
Test for overall effect: *Z*=1.19 (*P*=0.23)						
Total (95% CI)		**962**		**1,401**	**100%**	**1.26 (0.96, 1.65)**
Total events	118		130			
Heterogeneity: χ^2=6.83, *df*=9 (*P*=0.65); I^2=0%						
Test for overall effect: *Z*=1.66 (*P*=0.10)						
Test for subgroup differences: χ^2=1.99, *df*=2 (*P*=0.37); I^2=0%						



B

Study or subgroup	ALL Events	Total	Control Events	Total	Weight	Odds ratio M–H, fixed, 95% CI
Caucasian						
Batar et al[19]	46	70	51	75	6.1%	0.90 (0.45, 1.80)
Celkan et al[20]	37	52	40	60	3.9%	1.23 (0.55, 2.76)
Dincer et al[14]	19	30	23	30	3.0%	0.53 (0.17, 1.62)
Canalle et al[16]	80	173	109	223	18.5%	0.90 (0.60, 1.34)
Goricar et al[13]	57	121	105	184	15.9%	0.67 (0.42, 1.06)
Stanczyk et al[15]	63	97	81	131	8.7%	1.14 (0.66, 1.97)
Tumer et al[17]	104	167	98	190	12.5%	1.55 (1.02, 2.37)
Subtotal (95% CI)		**710**		**893**	**68.6%**	**1.00 (0.82, 1.22)**
Total events	406		507			
Heterogeneity: χ^2=9.12, *df*=6 (*P*=0.17); I^2=34%						
Test for overall effect: *Z*=0.02 (*P*=0.99)						
Asian						
Joseph et al[22]	62	117	42	117	7.1%	2.01 (1.19, 3.40)
Pakakasama et al[21]	69	108	142	317	9.4%	2.18 (1.39, 3.42)
Subtotal (95% CI)		**225**		**434**	**16.5%**	**2.11 (1.50, 2.97)**
Total events	131		184			
Heterogeneity: χ^2=0.05, *df*=1 (*P*=0.82); I^2=0%						
Test for overall effect: *Z*=4.28 (*P*<0.0001)						
Mixed						
Canalle et al[16]	9	28	66	138	5.5%	0.52 (0.22, 1.22)
Meza-Espinoza et al[18]	63	120	55	120	9.4%	1.31 (0.79, 2.17)
Subtotal (95% CI)		**148**		**258**	**14.9%**	**1.02 (0.66, 1.56)**
Total events	72		121			
Heterogeneity: χ^2=3.31, *df*=1 (*P*=0.07); I^2=70%						
Test for overall effect: *Z*=0.08 (*P*=0.94)						
Total (95% CI)		**1,083**		**1,585**	**100%**	**1.18 (1.01, 1.39)**
Total events	609		812			
Heterogeneity: χ^2=26.56, *df*=10 (*P*=0.003); I^2=62%						
Test for overall effect: *Z*=2.08 (*P*=0.04)						
Test for subgroup differences: χ^2=14.20, *df*=2 (*P*=0.0008); I^2=85.9%						

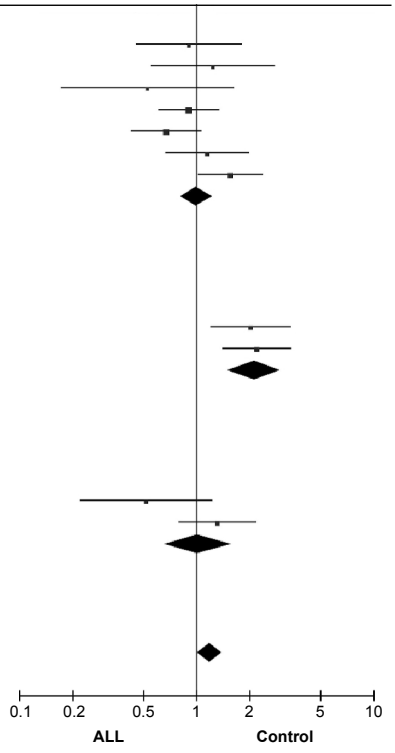
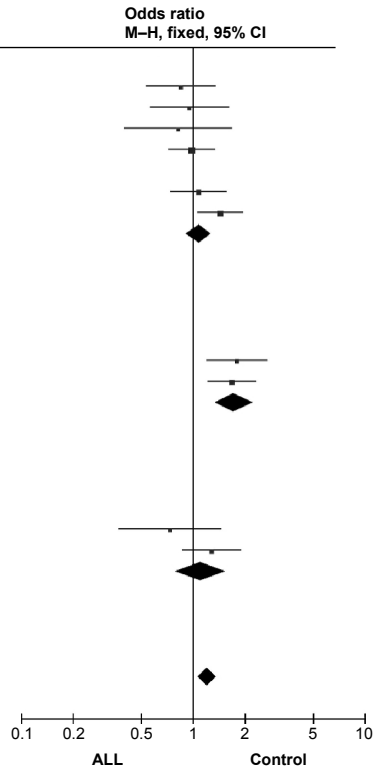


Figure 4 (*Continued*)

C

Study or subgroup	ALL Events	Total	Control Events	Total	Weight	Odds ratio M–H, fixed, 95% CI
Caucasian						
Batar et al[19]	55	140	65	150	8.9%	0.85 (0.53, 1.35)
Celkan et al[20]	42	104	50	120	6.5%	0.95 (0.56, 1.62)
Dincer et al[14]	24	60	27	60	3.8%	0.81 (0.39, 1.68)
Canalle et al[16]	94	346	123	446	18.3%	0.98 (0.71, 1.34)
Goricar et al[13]	0	0	0	0		Not estimable
Stanczyk et al[15]	81	194	105	262	12.1%	1.07 (0.73, 1.56)
Tumer et al[17]	131	334	118	380	15.7%	1.43 (1.05, 1.95)
Subtotal (95% CI)		**1,178**		**1,418**	**65.2%**	**1.07 (0.91, 1.26)**
Total events	427		488			
Heterogeneity: χ^2=5.43, *df*=5 (*P*=0.37); I^2=8%						
Test for overall effect: *Z*=0.87 (*P*=0.39)						
Asian						
Joseph et al[22]	78	234	51	234	7.9%	1.79 (1.19, 2.71)
Pakakasama et al[21]	78	216	160	634	12.1%	1.67 (1.20, 2.33)
Subtotal (95% CI)		**450**		**868**	**20.1%**	**1.72 (1.33, 2.23)**
Total events	156		211			
Heterogeneity: χ^2=0.07, *df*=1 (*P*=0.80); I^2=0%						
Test for overall effect: *Z*=4.13 (*P*<0.0001)						
Mixed						
Canalle et al[16]	12	56	75	276	4.6%	0.73 (0.37, 1.46)
Meza-Espinoza et al[18]	75	240	63	240	10.1%	1.28 (0.86, 1.90)
Subtotal (95% CI)		**296**		**516**	**14.7%**	**1.11 (0.79, 1.55)**
Total events	87		138			
Heterogeneity: χ^2=1.89, *df*=1 (*P*=0.17); I^2=47%						
Test for overall effect: *Z*=0.58 (*P*=0.56)						
Total (95% CI)		**1,924**		**2,802**	**100%**	**1.21 (1.06, 1.37)**
Total events	670		837			
Heterogeneity: χ^2=16.79, *df*=9 (*P*=0.05); I^2=46%						
Test for overall effect: *Z*=2.92 (*P*=0.003)						
Test for subgroup differences: χ^2=9.50, *df*=2 (*P*=0.009); I^2=79.0%						



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Study or subgroup	ALL Events	Total	Control Events	Total	Weight	Odds ratio M–H, fixed, 95% CI
Caucasian						
Batar et al[19]	9	33	14	38	12.3%	0.64 (0.23, 1.77)
Celkan et al[20]	5	20	10	30	7.8%	0.67 (0.19, 2.36)
Dincer et al[14]	5	16	4	11	4.2%	0.80 (0.16, 4.02)
Canalle et al[16]	14	107	14	128	14.4%	1.23 (0.56, 2.70)
Goricar et al[13]	0	0	0	0		Not estimable
Stanczyk et al[15]	18	52	24	74	16.8%	1.10 (0.52, 2.34)
Tumer et al[17]	27	90	20	112	16.2%	1.97 (1.02, 3.82)
Subtotal (95% CI)		**318**		**393**	**71.6%**	**1.18 (0.82, 1.69)**
Total events	78		86			
Heterogeneity: χ^2=4.75, *df*=5 (*P*=0.45); I^2=0%						
Test for overall effect: *Z*=0.90 (*P*=0.37)						
Asian						
Joseph et al[22]	16	71	9	84	8.3%	2.42 (1.00, 5.89)
Pakakasama et al[21]	9	48	18	193	7.5%	2.24 (0.94, 5.37)
Subtotal (95% CI)		**119**		**277**	**15.8%**	**2.34 (1.25, 4.36)**
Total events	25		27			
Heterogeneity: χ^2=0.01, *df*=1 (*P*=0.90); I^2=0%						
Test for overall effect: *Z*=2.67 (*P*=0.008)						
Mixed						
Canalle et al[16]	3	22	9	81	4.3%	1.26 (0.31, 5.13)
Meza-Espinoza et al[18]	12	69	8	73	8.3%	1.71 (0.65, 4.48)
Subtotal (95% CI)		**91**		**154**	**12.6%**	**1.56 (0.71, 3.42)**
Total events	15		17			
Heterogeneity: χ^2=0.12, *df*=1 (*P*=0.73); I^2=0%						
Test for overall effect: *Z*=1.10 (*P*=0.27)						
Total (95% CI)		**528**		**824**	**100%**	**1.41 (1.06, 1.88)**
Total events	118		130			
Heterogeneity: χ^2=8.36, *df*=9 (*P*=0.50); I^2=0%						
Test for overall effect: *Z*=2.34 (*P*=0.02)						
Test for subgroup differences: χ^2=3.55, *df*=2 (*P*=0.17); I^2=43.7%						

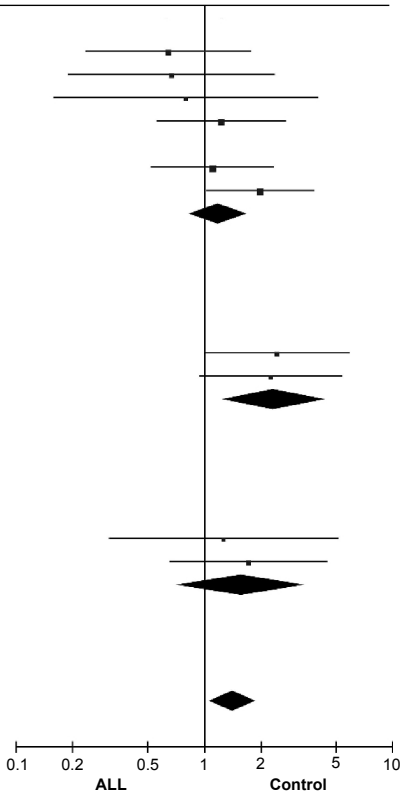

Figure 4 Meta-analysis of the association between *XRCC1* Arg399Gln SNP and ALL risk under the recessive model (**A**), the dominant model (**B**), the allele contrast model (**C**), and the homozygote contrast model (**D**).

Abbreviations: SNP, single-nucleotide polymorphism; ALL, acute lymphocytic leukemia; CI, confidence interval; M–H, Mantel–Haenszel.

as an outlier. Removal of that data from the analysis reduced the heterogeneity under all of the four contrast models.

Meta-analysis using fixed-effects model for the remaining two studies revealed no association between the SNP and risk of CLL under any contrast model (Table 2). Therefore, it indicates that the result about CLL is insensitive to the study of Duman et al.[23]

Discussion

A stratified analysis by leukemia type and ethnic group was conducted in this study in order to clarify the role of the *XRCC1* Arg399Gln SNP in the development of four types of leukemia in different ethnic groups. Twenty-three studies were identified wherein research into the association between *XRCC1* Arg399Gln SNP and different types of leukemia risk was conducted. Conclusions among these studies were not consistent, indicating an urgent need for the development of a systematic method for drawing more precise conclusions. Therefore, a common method of systematic review, a meta-analysis, was conducted in the present study to integrate these apparently contradictory findings with a view to yielding more accurate results. All of the included articles were of high quality and presented a rigorous scientific design, accurate data reporting, and clear results. The main conclusion was that the presence of the *XRCC1* Arg399Gln SNP increased the risk of childhood ALL among Asians. No association was found between this SNP and either CML or CLL risk in Caucasians.

These conclusions suggest the existence of ethnic differences in childhood ALL, such that gene polymorphisms could result in ethnic-specific susceptibilities to leukemia.[29] In addition, environmental factors such as birthplace and socioeconomic status may play critical roles in the genesis of leukemia.[30] These factors might help to explain the reasons for the observed racial disparities.

The present findings suggest that the risk of childhood ALL is associated with DNA repair mechanisms. The *XRCC1* Arg399Gln SNP may be useful as an important predictive factor, and ethnic background may have an impact on the role of this polymorphism on childhood ALL. This SNP may help to identify individuals at risk of developing ALL and represents an essential source of information for improvements in the treatment of ALL treatment.

The presence of heterogeneity between studies must be borne in mind when interpreting the results of a meta-analysis.[31,32] Significant heterogeneity existed in the ALL group under the dominant model. After subgroup analyses by ethnicity, the heterogeneity decreased for Asian and Caucasian populations, but persisted in the mixed-race analysis, suggesting that ethnicity can account for the heterogeneity.

The meta-analysis for AML revealed no association between the SNP and risk of AML when random-effects modeling was performed. After excluding the study of Banescu et al,[9] an outlier that caused high heterogeneity for the analysis of AML, the fixed-effects modeling, was used for the recessive model, and we found a changed result that the SNP was associated with AML risk in this genetic model, suggesting that the association between the SNP and risk of AML was sensitive to the data from the study of Banescu et al.[9] In addition, the sample size for AML was small. Therefore, large-scale studies should be conducted in the future for more explicit and convincing results.

No association was found between the SNP and risk of either CML or CLL in Caucasians. It can be speculated that the development of chronic disease is greatly influenced by environmental factors, and that the influence of SNP might be weak. Accumulation of disadvantageous environmental factors might be required to develop chronic disease. Therefore, a study of environment–genetic interactions would be meaningful for this kind of chronic disease. Smoking and alcohol consumption are also important risk factors for leukemia.[33] Although in the present study we endeavored to extract relevant information regarding smoking and drinking from the primary literature, insufficient data were obtained. Further investigations concerning the interactions between smoking, drinking, and gene variations with CLL and CML are required.

Only Caucasian subjects were included in the meta-analyses with respect to AML, CML, and CLL; therefore, the association between the SNP and risks of AML, CML, and CLL among other races needs to be determined in the future.

A meta-analysis similar to that presented herein was performed by Huang et al in 2014,[1] who investigated the associations between *XRCC1* Arg399Gln variations and leukemia susceptibility. However, one problem with the meta-analysis was that it was compromised by the inclusion of the study of Ozdemir et al,[34] whose cohort comprised both ALL and Burkitt lymphoma patients who were not analyzed separately. Huang et al[1] included the combined ALL and Burkitt lymphoma data of Ozdemir et al[34] in their pooled ALL data, thus potentially yielding biased results. The study of Ozdemir et al[34] was excluded from the present meta-analysis, which also included a greater number of studies than did the meta-analysis performed by Huang et al.[1] In particular, the present meta-analysis of ALL included eleven articles, whereas Huang et al[1] included only eight.

The present statistically significant findings might, therefore, be more accurate than those of Huang et al.[1]

Two limitations of this meta-analysis should be considered when interpreting its findings. First, the number of eligible studies for the meta-analysis was small, and the results should thus be treated with caution. Further, this restricted the performance of the subgroup analyses. Second, only published studies were included in this meta-analysis. There is always a certain degree of publication bias, and nonsignificant or negative findings may be unpublished and thus underrepresented in the literature.

Conclusion

The findings of this meta-analysis indicate that the *XRCC1* Arg399Gln SNP is associated with increased risk of childhood ALL in Asians. Large-scale studies should be conducted in the future to verify these results.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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