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Original Article

A meta-analysis study on XRCC1 Arg399Gln polymorphism and hematological malignancies

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Abstract: Background: Many previous studies have investigated the correlation between the Arg399Gln polymorphisms in X-ray repair cross-complementing group 1 (XRCC1) gene and hematological malignancies. However, their results were not incomplete agreement. Methods: 29 studies were included and dichotomous data are presented as the odds ratio (OR) with a 95% confidence interval (CI). Results: The results of our study indicate that XRCC1 399Gln allele among the pooled Asian population were more likely to show high risk of hematological malignancies development. For further analysis, the results indicated XRCC1 399Gln polymorphism could increase the susceptibility to leukemia *(allele model: pooled OR=1.174, P=0.006; Recessive model: pooled OR=1.324, P=0.002)*, especially in Acute Lymphoblastic Leukemia *(allele model: pooled OR=1.279, P=0.005; Recessive model: pooled OR=1.439, P=0.007),* but no association with lymphoma was found. Conclusion: The XRCC1 399Gln polymorphism could increase the risk of developing hematological malignancies susceptibility, especially in Asians and Leukemia.

Keywords: XRCC1 gene, hematological malignancies, polymorphism, meta-analysis, leukemia

Introduction

Hematological malignancies are tumors that affect blood, bone marrow, and lymph nodes, which may derive from either of the two major blood cell lineages: myeloid and lymphoid cell lines. The myeloid cell line normally produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells; the lymphoid cell line produces B, T, NK and plasma cells. Lymphomas, lymphocytic leukemias, and myeloma are from the lymphoid line, while acute and chronic myelogenous leukemia, myelodysplastic syndromes and myeloproliferative diseases are myeloid in origin [1]. DNA repair genes are being increasingly studied in genetic association studies because of their critical role in maintaining genome integrity. Sequence variants in DNA repair genes are thought to modulate DNA repair capacity and consequently have been associated with altered cancer risk and the response of cancer cells to anticancer drugs. Deficiencies in the DNA repair system may affect genome integrity, leading to the development of malignancies, including hematological malignancies [2]. Recently, many researches had found the polymorphisms in some DNA repair genes could affect the function of DNA repair and play an important role in tendencies to certain diseases [3, 4]. To date, numbers of studies have investigated gene XRCC1 Arg399Gln polymorphisms on susceptibility to hematological malignancies, but the single study remained incomplete agreement. We have summarized those individual studies finds in **Table 1**. Meta-analysis is a powerful method for quantitatively summarizing the results from single study, which can increase the sample size and reduce the probability of random error. Therefore, the goal of this meta-analysis was to quantitatively assess the association of XRCC1 Arg399Gln polymorphism with hematological malignancies.

Materials and methods

Literature search strategy

Relevant studies were systematically searched by using the NCBI, Medline, Web of Science and Embase databases (The last retrieval date was December, 19, 2014, the search terms was “hematological malignancies” or “cancer” or “leukemia” or “Lymphoma” or “multiple myelo-

Table 1. Findings of the studies included in this meta-analysis

Study	Year	Country	Disease	Cases			Controls			*P* for HWE	Quality	Conclusion
				GG	GA	AA	GG	GA	AA			
Sorour [5]	2013	Egypt	leukemia	9	27	54	1	27	33	0.08	7	The distribution of XRCC1Arg 339Gln genotypes showed a significant difference between patients and controls (P=0.025)
Annamaneni [6]	2013	Indian	leukemia	80	191	79	54	235	61	0.01	7.5	The results seem to suggest that XRCC1 gene might have an important role in CML progression but not in its causation
Bănescu [7]	2013	Romania	leukemia	13	23	33	10	46	91	0.21	8	Our study suggests the involvement of*XRCC1* Arg194Trp and Arg399Gln polymorphisms in the genetic predisposition to AML. These two *XRCC1* polymorphisms could also be prognostic markers in AML as they were significantly associated with overall survival
Duman [8]	2012	Turkey	leukemia	16	50	7	5	26	19	0.36	7	The Arg399Gln polymorphism may be etiologically associated with CLL; however, it does not seem to increase SCE frequency
Kim [9]	2012	Korea	leukemia	26	155	234	91	693	914	0.05	6	These results indicate that*ERCC1* and*GSTT1*-null polymorphisms may have an effect on AML risk that is dependent on smoking exposure
Abramenko [10]	2012	Ukraine	leukemia	8	28	27	15	41	38	0.48	7.5	These preliminary data suggest a possible modifying role of Lys751Gln *XPD* polymorphism for the development of CLL, especially in radiation-exposed persons
Canalle [11]	2011	Brazil	leukemia	17	72	112	23	152	186	0.27	8	The results suggest that polymorphism in TYMS may play a protective role against the development of childhood ALL
Tumer [12]	2010	Turkey	leukemia	27	77	63	20	78	92	0.56	8	This is the first study showing combined associations of XRCC1 399Gln, CYP2E1*5B and *6 alleles with the risk of development of childhood ALL
Stanczyk [13]	2010	Poland	leukemia	18	45	34	24	57	50	0.28	6	We suggest that polymorphisms of BER genes may be used as an important predictive factor for acute lymphoblastic leukemia in children
Espinoza [14]	2009	Mexico	leukemia	12	51	57	8	47	65	0.90	7	Individually, the 194Trp, 280His, and 399Gln alleles were not associated with significantly increased risk for ALL in these Mexican children
Ganster [15]	2009	Austria	leukemia	64	192	173	52	193	184	0.89	7.5	These data suggest that inborn genetic polymorphisms may predict the outcome of CLL
Batar [16]	2008	Turkey	leukemia	5	13	15	8	24	20	0.86	6	These results suggest that the risk of childhood ALL may be associated with DNA repair mechanisms, and understanding these mechanisms will help identify individuals at increased risk of developing childhood ALL, and also should be lead to improved treatment of ALL

Deligezer [2]	2007	Turkey	leukemia	30	121	103	29	101	96	0.76	6	To our knowledge, this is the first study to investigate the role of any XRCC1 polymorphism in CML and our findings do not support a role of codon 399Gln polymorphism in CML
Pakakasama [17]	2007	Thailand	leukemia	9	60	39	18	124	175	0.51	6.5	The XRCC1 194Trp allele and haplotype B showed a protective effect against development of childhood ALL. In contrast, individuals with the XRCC1 399Gln allele and haplotype C were associated with increased risk for this disease
Matullo [18]	2006	Mixed	leukemia	28	74	67	128	482	484	0.63	7	XRCC1-399 Gln/Gln variant homozygotes [odds ratios (OR)=2.20, 95% confidence intervals (CI)=1.16-4.17] and XRCC3-241 Met/Met homozygotes (OR=0.51, 95% CI=0.27-0.96) and leukemia
Joseph [16]	2005	India	leukemia	16	46	55	9	33	75	0.06	6	The risk of ALL was higher in males with codons 194 and 399 polymorphisms than in females
Zhang [19]	2005	China	leukemia	12	39	48	7	37	55	0.82	7	*XRCC* 1 399 homozygotes was associated with leukemia
Zhu [19]	2005	China	leukemia	16	44	45	7	39	62	0.79	9	*XRCC* 1 399 homozygotes was associated with leukemia
Seedhouse [20]	2002	UK	leukemia	24	57	52	47	76	55	0.54	8	Our data provide evidence of a protective effect against AML in individuals with at least one copy of the variant *XRCC1* 399Gln allele compared with those homozygous for the common allele
Ozdemir [21]	2011	Turkey	leukemia and lymphoma	15	42	33	15	50	34	0.62	7	There was also statistically increased risk for severe mucositis in patients with XRCC1Arg399Gln polymorphism
Li [22]	2014	China	Lymphoma	16	101	165	12	89	130	0.51	8.5	Combined genotype analyses of *XRCC* 399-280-194 results showed that the combined genotype was not associated with risk of NHL overall
Monroy [23]	2011	USA	Lymphoma	20	106	73	10	53	37	0.15	6.5	We observed that, in combination, allelic variants in the *XPC Ala499Val*, *NBN Glu185Gln*, *XRCC3 Thr241Me*, *XRCC1 Arg194Trp* and *XRCC1 399Gln* polymorphisms modify the risk for developing HL
Kim [24]	2010	Korean	Lymphoma	26	155	234	91	693	914	0.05	9	XRCC1 showed very strong linkage disequilibrium (LD) and consisted of one haploblock. The frequency of XRCC1 haplotype A (194Arg-280Arg-399Arg) was significantly lower in DLBCL patients compared to controls (OR, 0.60-95% CI, 0.15-0.81; P=0.001)
Barıs [25]	2009	Turkey	Lymphoma	5	13	15	8	24	20	0.89	7	*XRCC1 194Trp allele may be associated with a protective effect against development of childhood B-cell lymphoma*
Liu [26]	2009	China	Lymphoma	15	88	118	11	98	145	0.26	6	When stratified by smoking status, however, the XRCC1Arg-399Gln variant genotypes (homozygotes and heterozygotes) were associated with a 3.0-fold risk of follicular lymphoma among heavy smokers

Smedby [27]	2006	Denmark and Sweden	Lymphoma	56	206	166	75	269	249	0.85	8	We conclude that polymorphic variation in the XRCC3 gene, but not in ERCC2 or XRCC1, may be of importance for susceptibility to follicular lymphoma, perhaps primarily in current smokers
Matsuo [28]	2004	Japan	Lymphoma	11	94	155	30	183	287	0.91	7.5	These data suggest that *XRCC1* Gln399Arg polymorphism plays a limited role in lymphomagenesis
Cifci [29]	2011	Turkey	Multiple myeloma	11	24	25	9	24	37	0.12	7	When the genotype frequencies of XPD (Llys75 1Gln) and XRCC1 (Arg39 9Gln) genes were examined in the patient and control groups, no significant difference was detected

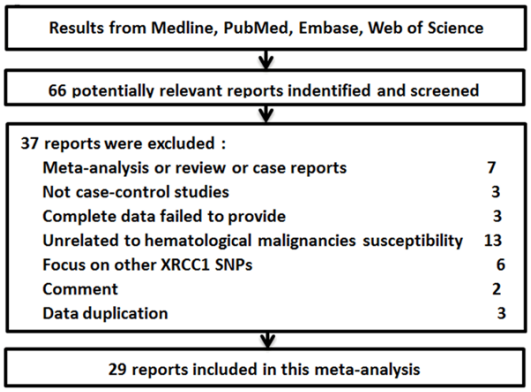

Figure 1. A flow diagram of the study selection process.

ma", "polymorphism" or "mutation", "XRCC1" or "X-ray repair cross-complementing group 1"). All searched studies were retrieved and only published studies with full-text articles were included. When 2 or more publications with duplicate samples, only the newest study was included in this research. The flow chart of the study including process was shown in **Figure 1**.

Inclusion and exclusion criteria

The inclusion criteria was as follows: (1) the study was about the XRCC1 polymorphisms and susceptibility to any type of hematological malignancies; (2) a case-control study; (3) non-cancer patients or healthy subjects as controls; (4) the data that study provided was fit to this meta-analysis; (5) the frequencies of genotype or allele in case and control groups could be collected. The exclusion criteria were: (1) animal studies; (2) the reported data did not meet this study needed; (3) the reported data was not adaptable for our pooled study; (4) the study focused on other cancers.

Data extraction

Based on the selection criteria, two reviewers, Xuewen Yang and Limin Ma, extracted and integrated the data independently (including control type, study design, first author's name, publication year, and the frequencies of genotype or allele in case and control groups). The quality scoring system was first reported by Thakkinstian: total scores ranged from 0 (lowest) to 10 (highest). Articles with scores equal to or higher than 7 were considered "high-quality" studies, whereas those with scores less than 7 were considered "low-quality" studies. The predefined criteria were shown in **Appendix 1**.

Statistical analysis

Allele frequencies at the XRCC1 Arg399Gln SNPs from the respective studies were determined by the allele counting method. Dichotomous data are presented as the odds ratio (OR) with a 95% confidence interval (CI). Statistical heterogeneity was measured using the Q-statistic ($P \leq 0.10$ was considered to be representative of statistically significant heterogeneity) by χ^2-based Q-test. We also quantified the effect of heterogeneity using the I^2-statistic, which measures the degree of inconsistency in the studies by calculating what percentage of the total variation across studies is due to heterogeneity rather than by chance. The I^2 takes values between 0% and 100%, with higher values denoting greater degree of heterogeneity (I^2 = 0% to 25%, none heterogeneity; I^2 = 25% to 50%, moderate heterogeneity; I^2 = 50% to 75%, large heterogeneity; I^2 = 75% to 100%, extreme heterogeneity). A fixed effects model was used when there was no heterogeneity of the results of the studies. Otherwise, the random effects model was used. Dependent on the results of heterogeneity test among individual studies, the fixed effect model (Mantel-Haenszel) or random effect model (DerSimonian and Laird) was selected to summarize the combined OR and their 95% CI. To establish the effect of clinical heterogeneity between studies on meta-analyses' conclusions, subgroup analysis was conducted on the basis of race. Visual inspection of asymmetry in funnel plots was conducted. Begg's rank correlation method and Egger weighted regression method were also used to statistically assess the publication bias ($P \leq 0.05$ was considered to be representative of statistically significant publication bias). All the statistical analysis was conducted by using STATA statistical package (version 10, STATA, College Station, TX, USA) and $P \leq 0.05$ was considered to be statistically significant.

Main results

Characteristics of studies

There were 29 relevant studies with 4847 cases and 8485 controls were involved in the meta-analysis. Among those studies, 21 studies were about leukemia, 7 studies were about

Table 2. XRCC1 Arg399Gln polymorphisms and hematological malignancies

Comparisons	Stratification	Subgroups	n	OR (95% CI)			Homogeneity			Publication Bias	
				OR	*CI*	*P value*	*Q*	*P*	I^2 (%)	*PB*	*PE*
Allele model *(Gln vs. Arg)*	over-all	-	30	1.125	1.035-1.223	0.005	54.66	0.003	46.9	0.805	0.918
	Subtypes	leukemia	21	1.174	1.048-1.317	0.006	47.88	0.001	58.2	0.231	0.182
		lymphoma	7	1.027	0.924-1.141	0.622	2.97	0.812	0.0	0.532	0.371
	Ethnicity	Africans	2	0.927	0.607-1.416	0.725	0.73	0.394	0.0	0.343	0.433
		Americans	2	1.119	0.860-1.456	0.403	0.76	0.382	0.0	0.783	0.832
		Asians	18	1.170	1.041-1.316	0.008	37.26	0.003	54.4	1.000	0.276
		Caucasians	8	1.076	0.927-1.250	0.336	14.97	0.036	53.2	0.49	0.558
Dominant *(Gln/Gln+ Gln/Arg vs. Arg/Arg)*	over-all	-	30	1.119	0.997-1.255	0.056	57.30	0.001	49.4	0.621	0.733
	Subtypes	leukemia	21	1.175	0.997-1.384	0.054	52.28	0.001	61.7	1.000	0.829
		lymphoma	7	1.026	0.896-1.175	0.710	2.61	0.855	0.0	0.763	0.652
	Ethnicity	Africans	2	0.673	0.399-1.135	0.138	0.58	0.448	0.0	0.368	0.350
		Americans	2	1.148	0.805-1.638	0.447	0.49	0.484	0.0	0.230	0.558
		Asians	18	1.194	1.004-1.420	0.045	44.92	0.001	62.2	0.176	0.163
		Caucasians	8	1.084	0.939-1.252	0.272	7.95	0.337	11.9	0.133	0.277
Recessive *(Gln/Gln vs. Arg/Arg+ Gln/Arg)*	over-all	-	30	1.248	1.094-1.424	0.001	32.41	0.30	10.5	0.133	0.115
	Subtypes	leukemia	21	1.324	1.109-1.580	0.002	27.11	0.132	26.2	0.368	0.350
		lymphoma	7	1.063	0.833-1.356	0.624	2.87	0.824	0.0	0.230	0.558
	Ethnicity	Africans	2	2.720	0.732-10.104	0.135	1.23	0.268	18.5	0.721	0.975
		Americans	2	1.210	0.659-2.221	0.539	0.48	0.487	0.0	0.49	0.729
		Asians	18	1.310	1.110-1.545	0.001	15.24	0.578	0.0	0.297	0.269
		Caucasians	8	1.155	0.879-1.517	0.301	12.95	0.073	46.0	0.368	0.346

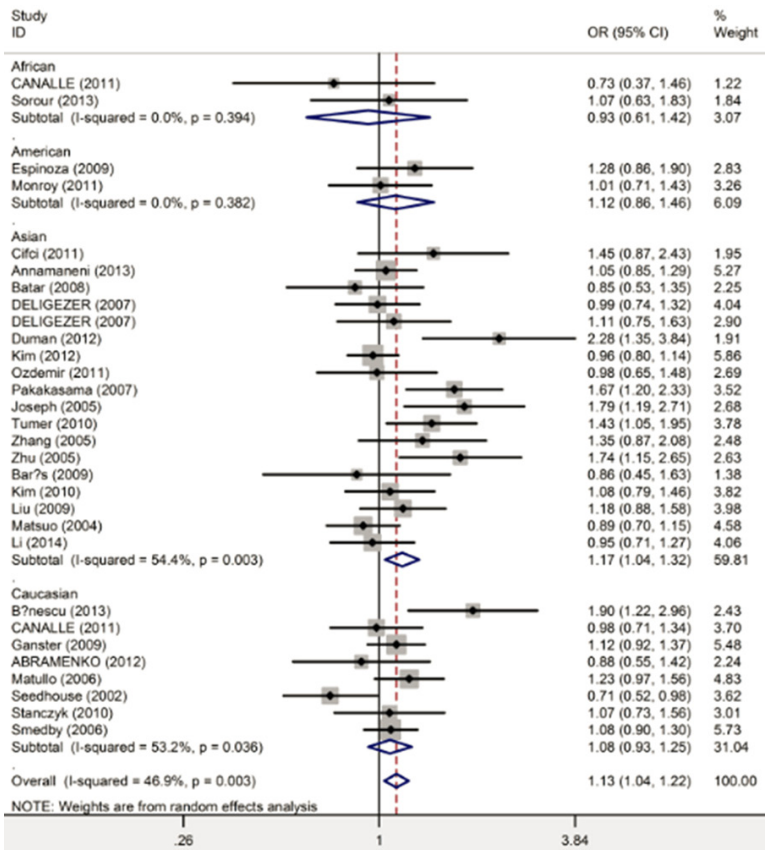

Figure 2. Forest plot of the XRCC1 Arg399Gln polymorphism and hematological malignancies by ethnicity (Gln allele vs Arg allele).

Lymphoma, 1 study was about leukemia and Lymphoma, and only 1 study was about multiple myeloma. The characteristics of each study were presented in **Table 1**.

Quantitative data synthesis

Hematological malignancies cases and controls were compared to investigate the relationship between XRCC1 Arg399Gln polymorphism and hematological malignancies. As **Table 2** and **Figure 2** shown, the carriers of the XRCC1 399Gln allele were more likely to have Hematological malignancies than 399Arg allele in the over-all group and the Asians subgroup but not in the other ethnicity people (P<0.05). Meantime, we found the similar results in Recessive model, that XRCC1 399 Gln/Gln genotype was associated with risk of Hematological malignancies in over-all group

Table 3. XRCC1 Arg399Gln polymorphisms and leukemia

Comparisons	Stratification	Subgroups	n	OR (95% CI)			Homogeneity			Publication Bias	
				OR	CI	*P* value	Q	P	I^2 (%)	PB	PE
Allele model *(Gln vs. Arg)*	Ethnicity	Asians	11	1.277	1.076-1.514	0.005	29.78	0.001	66.4	0.014	0.003
		Europeans	7	1.075	0.891-1.298	0.451	14.97	0.020	59.9	0.099	0.088
	Acute/chronic	Acute	15	1.191	1.017-1.394	0.030	38.07	0.001	63.2	0.222	0.070
		Chronic	5	1.122	0.918-1.371	0.260	9.06	0.060	55.8	0.154	0.064
	subtypes	Myeloid	7	1.029	0.869-1.218	0.742	13.03	0.042	54.0	0.225	0.216
		Lymphoblastic	13	1.269	1.087-1.480	0.002	25.44	0.013	52.8	0.143	0.161
		ALL	10	1.279	1.077-1.519	0.005	16.90	0.050	46.2	0.176	0.230
		CLL	3	1.273	0.817-1.983	0.286	7.75	0.021	74.2	0.161	0.127
		AML	5	1.055	0.801-1.391	0.702	12.83	0.012	68.8	0.072	0.081
		CML	2	1.026	0.866-1.216	0.767	0.10	0.749	0.0	0.188	0.260
Dominant model *(Gln/Gln+ Gln/Arg vs. Arg/Arg)*	Ethnicity	Asians	11	1.366	1.039-1.795	0.025	39.16	0.001	74.5	0.052	0.055
		Europeans	7	1.063	0.886-1.275	0.510	7.75	0.257	22.6	0.458	0.166
	Acute/chronic	Acute	15	1.198	0.980-1.463	0.078	35.07	0.001	60.1	0.245	0.805
		Chronic	5	1.145	0.762-1.721	0.515	16.14	0.003	75.2	0.031	0.014
	subtypes	Lymphoblastic	7	1.342	1.067-1.687	0.012	30.40	0.002	60.5	0.248	0.163
		Myeloid	13	0.934	0.764-1.142	0.507	9.53	0.146	37.1	0.929	1.000
		ALL	10	1.330	1.047-1.689	0.019	18.51	0.030	51.4	0.075	0.128
		CLL	3	1.606	0.710-3.636	0.256	11.22	0.110	82.2	0.368	0.346
		AML	5	0.984	0.743-1.303	0.910	7.55	0.004	47.0	0.188	0.131
		CML	2	0.858	0.608-1.212	0.385	1.61	0.204	38.1	0.624	0.217
Recessive model *(Gln/Gln vs. Arg/Arg+ Gln/Arg)*	Ethnicity	Asians	11	1.388	1.125-1.712	0.002	10.86	0.369	7.9	0.210	0.282
		Europeans	7	1.185	0.847-1.659	0.322	12.58	0.050	52.3	0.260	0.172
	Acute/chronic	Acute	15	1.343	1.041-1.732	0.023	21.12	0.099	33.7	1.000	1.000
		Chronic	5	1.291	0.957-1.743	0.095	5.59	0.232	28.4	0.128	0.152
	subtypes	Myeloid	7	1.243	0.831-1.859	0.289	16.58	0.011	0.0	0.805	0.543
		Lymphoblastic	13	1.374	1.115-1.694	0.003	9.54	0.656	63.8	0.788	0.249
		ALL	10	1.439	1.105-1.874	0.007	6.51	0.688	0.0	0.211	0.149
		CLL	3	1.279	0.792-2.063	0.314	2.71	0.257	26.3	0.805	0.934
		AML	5	1.304	0.710-2.395	0.393	12.90	0.012	69.0	0.340	0.249
		CML	2	1.256	0.698-2.258	0.075	2.79	0.095	64.2	0.405	0.761

and the Asians subgroup ($P<0.05$) other non-Gln/Gln genotype. The results of subtype analysis indicated XRCC1 Arg399Gln polymorphism could increase the susceptibility to leukemia (allele model: pooled OR=1.174, 95% CI=1.048-1.317, P=0.006; Recessive model: pooled OR=1.324, 95% CI=1.109-1.580, $P=0.002$), but not lymphoma.

We performed more detailed subgroup analysis according to 2 main subtypes of Hematological malignancies, leukemia and lymphoma. As **Table 3** and **Figure 3** shown, XRCC1 399Gln was associated with risk of leukemia in Asian people but not Europeans in Allele and Recessive models (allele model: pooled OR=1.277, 95% CI=1.076-1.514, P=0.006; Recessive model: pooled OR=1.388, 95% CI=1.125-1.712, P=0.002). In the stratified analysis according to acute/chronic leukemia and Myeloid/Lymphoblastic, we found XRCC1 399Gln was only associated with acute leukemia and Lymphoblastic leukemia (acute leukemia: allele model: pooled OR=1.191, 95% CI=1.017-1.39, P=0.030; Recessive model: pooled OR=1.343, 95% CI=1.041-1.732, $P=0.023$. Lymphoblastic leukemia: allele model: pooled OR=1.269, 95% CI=1.087-1.480, $P=0.002$; Recessive model: pooled OR=1.374, 95% CI=1.115-1.694, $P=0.003$). In the subtype analysis of Acute Lymphoblastic Leukemia (ALL), Chronic Lymphoblastic Leukemia (CLL), Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML), XRCC1 Arg399Gln polymorphisms revealed statistically significant different only in Acute Lymphoblastic Leukemia (allele model: pooled OR=1.279, 95% CI=1.077-1.519, $P=0.005$; Recessive model: pooled OR=1.439, 95% CI=1.105-1.874, $P=0.007$).

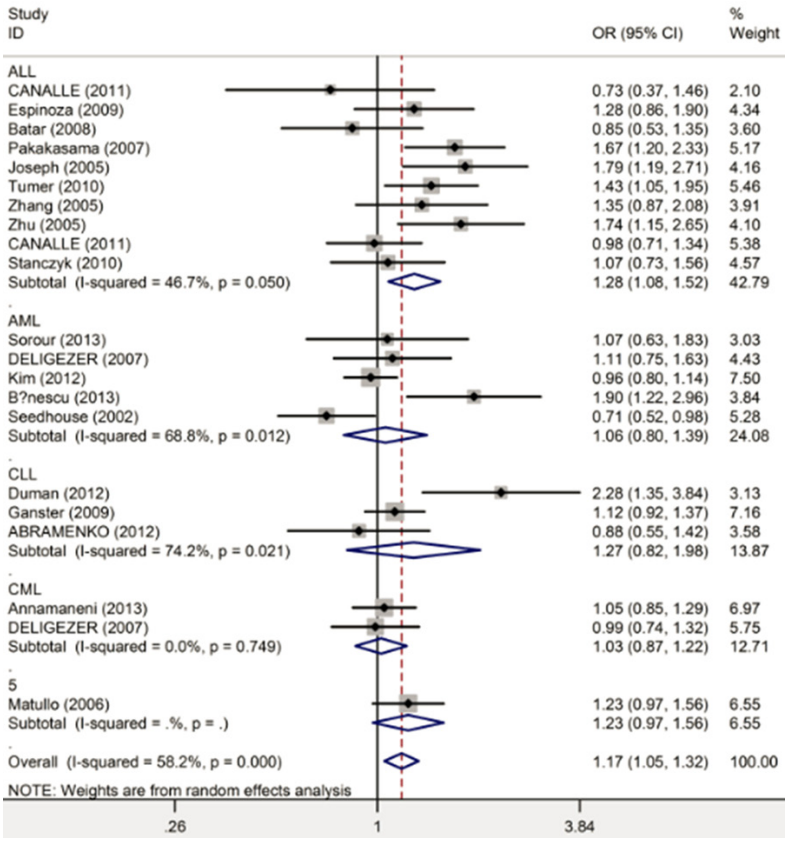

Figure 3. Forest plot of the XRCC1 Arg399Gln polymorphism and leukemia by subtypes (Gln allele vs Arg allele).

As **Table 4** and **Figure 4** shown, no association of XRCC1 Arg399Gln polymorphisms and non-Hodgkin lymphoma was found, not only in overall group, but also in diffuse large B cell lymphomas and follicular lymphomas.

Heterogeneity

The heterogeneity was reckoned between each of the studies using the Q statistic. We found heterogeneity exist in some subgroups-analysis, but was not serious. So random-model was used to pool the single result.

Sensitivity analysis

"Trim and Filled" and "Influence Meta-analysis" were conducted to reflect the influence of the individual dataset to the pooled ORs. The test results indicated that our results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures, and no publication bias was found.

Discussion

DNA repair system is a key role in protecting against carcinogenesis, which may fall in to four categories-direct repair, excision repair, mismatch repair (MMR), and DNA break repair [30]. Among them, excision repair has two pathways, base excision repair (BER) and nucleotide excision repair (NER). XRCC1 gene is an important multidomain protein which participates in removing single-strand breaks (SSBs) and the BER pathway. It participates in single-strand breaks pathway mainly by interacting with the nicked DNA with at least three different enzymes (poly-ADP-ribose polymerase (PARP), DNA ligase III, and DNA polymerase β). Recent studies have shown that the polymorphisms of XRCC1 genes is associated with development of cancer due to impairment of DNA repair capacity [31], such as lung cancer [32], gastric cancer [33], colon cancer [34] and so on. Because of the important role of maintenance of genome integrity, single-nucleotide polymorphisms (SNP) have aroused great public concern in genetic study filed [35]. In XRCC1 gene, there are common non-synonymous SNPs which could lead to amino acid substitutions at codons 194 (exon 6, C to T, Arg to Trp), 280 (exon 9, G to A, Arg to His) and 399 (exon 10, G to A, Arg to Gln) has been studied hotly. The codon 399 polymorphism is localized in the BRCT-1 domain through which it interacts with DNA ligase III (11) and poly (ADPribose) polymerase, and the mutation could to affect DNA repair capacity.

In the present study, we hypothesized that the XRCC1 Arg399Gln polymorphisms might play an important role in the hematological malignancies risk. The results of this study shown that the XRCC1 399Gln polymorphism could increase the risk of developing hematological

Table 4. XRCC1 Arg399Gln polymorphisms and non-Hodgkin lymphoma

Comparisons	Subgroups	n	OR (95% CI)			Homogeneity			Publication Bias	
			OR	*CI*	*P value*	*Q*	*P*	*I² (%)*	*PB*	*PE*
Allele model (Gln vs. Arg)	overall	5	1.029	0.921-1.148	0.616	2.96	0.706	0.0	0.510	0.333
	DLBCL	4	1.070	0.894-1.281	0.461	1.71	0.636	0.0	0.321	0.333
	FL	3	1.117	0.951-1.312	0.177	1.16	0.559	0.0	0.645	0.288
Dominant (Gln/Gln+ Gln/Arg vs. Arg/Arg)	overall	5	1.027	0.892-1.183	0.711	2.61	0.760	0.0	0.397	0.589
	DLBCL	4	1.043	0.834-1.305	0.712	1.85	0.605	0.0	0.360	0.535
	FL	3	1.113	0.952-1.301	0.130	0.77	0.681	0.0	0.480	0.324
Recessive (Gln/Gln vs. Arg/Arg+ Gln/Arg)	overall	5	1.069	0.828-1.380	0.610	2.85	0.722	0.0	0.696	0.332
	DLBCL	4	1.269	0.823-1.959	0.281	0.50	0.918	0.0	0.510	0.650
	FL	3	1.088	0.771-1.534	0.632	0.86	0.652	0.0	0.321	0.333

DLBCL, diffuse large B cell lymphomas; FL, follicular lymphomas.

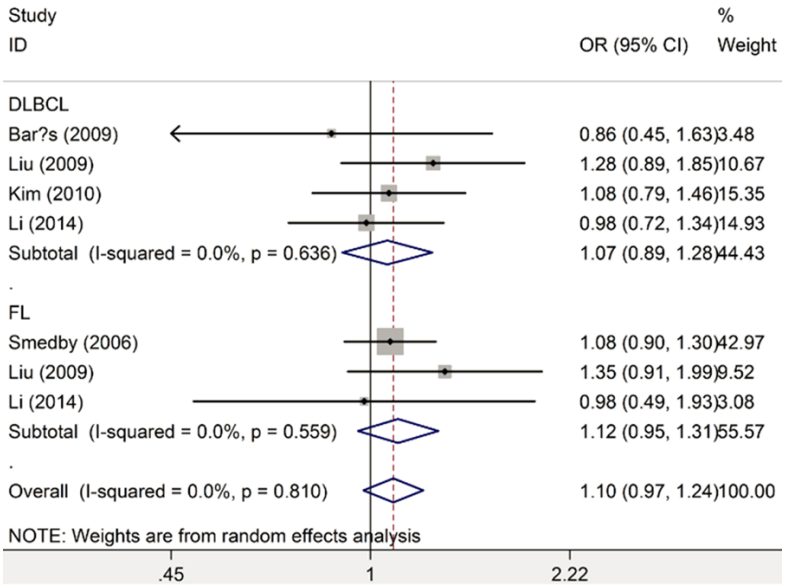

Figure 4. Forest plot of the XRCC1 Arg399Gln polymorphism and lymphoma by subtypes (Gln allele vs Arg allele).

malignancies susceptibility, especially in Asians. Previous study had found that the frequency of the 399Gln allele was different in different races, approximately 35% among people from Europe, 26% from Asia and 13% among Africans [36]. More detailed investigation found XRCC1 399Gln polymorphism was associated with Acute Lymphoblastic Leukemia but not in Chronic Lymphoblastic Leukemia, Acute Myeloid Leukemia, Chronic Myeloid Leukemia or non-Hodgkin lymphoma. While more research or large sample size study is needed to verify this results, because only 2 and 3 papers were on Chronic Lymphoblastic Leukemia and Chronic Myeloid Leukemia respectively.

It should be noted that there were some limitations in this study. Firstly, because of the language barrier in our research group, only those publications in English and Chinese were searched and reviewed, so publication bias may exist. Secondly, some subgroup analysis only involved little literatures, the results calculated by this paper were not precise. Finally, because of methodological limitation existed, many confounding factors (such as smoking, age, gender and so on) could not been matched or adjusted by statistical method, so those factors might lead to confound bias.

In conclusion, the XRCC1 399Gln polymorphism could increase the risk of developing hematological malignancies susceptibility, especially in Asians and Leukemia.

Disclosure of conflict of interest

None.

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Appendix 1. Scale for quality assessment

Criteria	Score
Representativeness of cases	
Selected from nephropathy registry or multiple nephropathy center sites	2
Selected from nephropathy department or nephropathy institute	1
Selected without clearly defined sampling frame or with extensive inclusion/exclusion criteria	0
Source of controls	
Population or community based	2
Both population-based and hospital-based/healthy volunteers blood donors	1.5
Hospital-based controls without *DN*	1
DN-free controls without total description	0.5
Not described	0
Ascertainment of DN	
Histologically or pathologically confirmed	2
Diagnosis of *DN* by patient medical record	1
Not described	0
Sample size	
>1000	2
200-1000	1
<200	0
Quality control of genotyping methods	
Clearly described a different genotyping assay to confirm the data	1
Not described	0
Hardy-Weinberg equilibrium	
Hardy-Weinberg equilibrium in controls	1
Hardy-Weinberg disequilibrium in controls	0.5
No checking for Hardy-Weinberg disequilibrium	0