Oncology and Translational Medicine
DOI 10.1007/s10330-021-0527-7

October 2022, Vol. 8, No. 5, P217–P225

ORIGINAL ARTICLE

Relationship between *IKZF1* polymorphisms and the risk of acute lymphoblastic leukemia: a meta-analysis*

Sisi Wang, Chuyang Lin (Co-first author), Tingting Xi, Yu Tong, Jinlin Wu (✉)

Department of Pediatrics; Key Laboratory of Birth Defects and Related Disease of Women and Children, Ministry of Education; West China Second University Hospital, Sichuan University, Chengdu 610041, China

Abstract

Objective The aim of the study was to systematically evaluate the correlation between *IKZF1* polymorphisms and the risk of acute lymphoblastic leukemia.

Methods Computer databases including PubMed, EMBASE, and Web of Science were searched for case-control studies on the association between *IKZF1* polymorphisms and the risk of acute lymphoblastic leukemia. The retrieval period was from the establishment of the database to November 2020. Two researchers independently screened the literature, extracted the data, evaluated the risk of bias in the included studies, and used Stata 14.0 software for meta-analysis.

Results A total of 48 case-control studies were included, with 10 520 and 44 049 cases in the case and control groups, respectively. The meta-analysis results showed that rs4132061 and rs11978267 of *IKZF1* were significantly correlated with the risk of acute lymphoblastic leukemia (ALL).

Conclusion Current evidence indicates that rs4132061 and rs11978267 of *IKZF1* are significantly associated with the risk of B-cell ALL.

Received: 11 October 2021
Revised: 25 April 2022
Accepted: 6 July 2022

Key words: *IKZF1*; gene polymorphism; acute lymphoblastic leukemia (ALL); meta-analysis; systematic reviews; case-control study

Childhood leukemia is the most common malignancy in childhood, accounting for 1/4 of all childhood malignancies [1]. Acute lymphoblastic leukemia (ALL) accounts for approximately 80% of all childhood leukemia cases, with a peak prevalence at the age of 2 to 5 [1–2]. According to the immunophenotype, ALL can be divided into B-cell ALL (B-ALL) and T-cell ALL (T-ALL), accounting for 85% and 15% of the cases, respectively [3]. The pathogenesis of ALL remains inconclusive, but in recent years, great progress has been made in understanding the genetic factors related to the pathogenesis of ALL. With the development of sequencing technology and genome-wide association studies, more polymorphism sites associated with ALL have been identified [4–8], most of which encode hematopoietic transcription factors. An increasing number of studies have found that alteration of *IKZF1* (IKAROS zinc finger 1) is correlated with the occurrence of ALL. The *IKZF1* gene is located on the long arm of chromosome 7 and encodes the early lymphoid transcription factor IKAROS, a DNA-bound zinc finger transcription factor that plays an important role in hematopoiesis, particularly in the maturation and differentiation of lymphoid progenitor cells [9]. Studies have confirmed that the loss of *IKZF1* expression is an independent risk factor for ALL recurrence and poor prognosis [10]. However, the results of the association between single nucleotide polymorphisms (SNPs) in the *IKZF1* gene and ALL risk were inconsistent. There are some SNPs in the *IKZF1* gene, including rs6964823, rs4132601, rs6944602, and rs11978267. Previous studies have revealed that rs4132601 and rs11978267 polymorphic sites of *IKZF1* in different ethnic groups are associated with the occurrence of ALL; however, the conclusion remains unclear, and this contradiction may

✉ Correspondence to: Jinlin Wu. Email: wujl_2000@sina.com
* Supported by the National Key Project of Neonatal Children (No. 1311200003303), Grants from the Science and Technology Bureau of Sichuan Province (No. 2021YJ0211), and Grants from the Health Planning Committee of Sichuan Province (No. 20PJ070).

be at least partially attributed to the small sample size and ethnic differences in the whole study. Therefore, this study adopted a meta-analysis method to systematically summarize all qualified data to provide more reliable evidence and explore the relationship between *IKZF1* polymorphisms and the risk of ALL to provide a basis for clinical decision-making.

Materials and methods

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (S1 File) and Meta-Analysis on Genetic Association Studies Checklist (S2 File).

Eligibility criteria

Inclusion criteria: (1) Case-control-designed studies. (2) The association between *IKZF1* polymorphisms and ALL risk was evaluated. (3) Sufficient data on allele or genotype distribution in patients and controls. (4) Met the Hardy-Weinberg equilibrium (HWE). (5) Full-text English.

Exclusion criteria: (1) Editorials and review articles. (2) Republished papers. (3) Lack of complete data or sufficient information.

Search strategy

A systematic electronic search of the PubMed, EMBASE, and Web of Science databases for original articles was performed to identify potentially relevant articles and abstracts to collect case-control studies on the correlation between *IKZF1* polymorphisms and the risk of ALL. The search time limit was set from the establishment of the database to November 2020. The search terms included *IKZF1*, IKAROS zinc finger 1, acute leukemia, acute lymphoblastic leukemia, ALL, rs4132601, rs11978267, polymorphism, variant, mutation, 7p12.2, allele, genotype, case, and control. The language was restricted to English. PubMed was used as an example (Fig. 1).

Data extraction and quality assessment

Two investigators independently screened the literature, extracted the data from the selected eligible studies, and cross-checked them. Disagreements were resolved through discussion or by a third reviewer. In the literature screening, the title was first read, followed by the abstract and full text to determine whether to include the study once irrelevant literature had been excluded. If necessary, the original study author was contacted via email or telephone to obtain undetermined but important information for the study. Data extraction content included (1) basic information of the included studies: study title, first author, publication time, ethnicity, etc.; (2) baseline characteristics, allele frequency, and gene detection methods of the study subjects; (3) key elements of bias risk assessment; and (4) outcome indicators and outcome measurements of concern. The Newcastle-Ottawa Scale was used to evaluate the risk of bias in the included case-control studies, with a score ≥ 5 included in the meta-analysis[11]. The results of the quality assessments are shown in the S3 File.

Statistical analysis

All statistical tests were performed using Stata version 14.0. The HWE was calculated using the Chi-squared test for each study in the control groups ($P < 0.05$, defined as departure from HWE). The pooled odds ratios (ORs) with 95% confidence intervals (CIs) to assess the strength of the association of the *IKZF1* polymorphism with ALL risk in five genetic models were evaluated using the Z test. Heterogeneity was evaluated using the Chi-squared Q-test and I^2. If $I^2 > 50\%$ or $P < 0.05$, significant heterogeneity was indicated. A random-effects model was used to calculate the ORs and 95% CIs. Otherwise, a fixed-effects model was used. Stratified analyses were performed based on ethnicity and subtype of leukemia. The Begg's test was used to estimate potential publication bias. Statistical significance was set at $P < 0.05$. Sensitivity tests carried out by omitting each of the studies discussed the association of rs4132061 or rs11978267 with ALL susceptibility. The pooled OR and 95% CI were not significantly different, which in turn confirmed the robustness of the relationship between rs4132061 or rs11978267 and ALL predisposition.

Results

Literature screening results

The initial database search identified 79 potentially relevant studies. Based on the selection in accordance with the inclusion criteria, 27 articles were included. The genotype distributions in the controls of the 27 studies were fitted into the HWE, except for three [12–14]. After assessing the quality of the studies, three studies were excluded because they scored less than five points [15–17]. Finally, 48 studies from 21 publications were included [6–7, 12, 14, 18–34], comprising 10 520 cases and 44 049 controls.

#1 IKZF1 OR Ikaros zinc finger 1 OR rs4132601 OR rs11978267 OR 7p12.2

#2 acute lymphoblastic leukemia

#3 polymorphism OR variation OR allele OR genotype

#4 #1 AND #2 AND #3

Fig. 1 Search strategy on PubMed

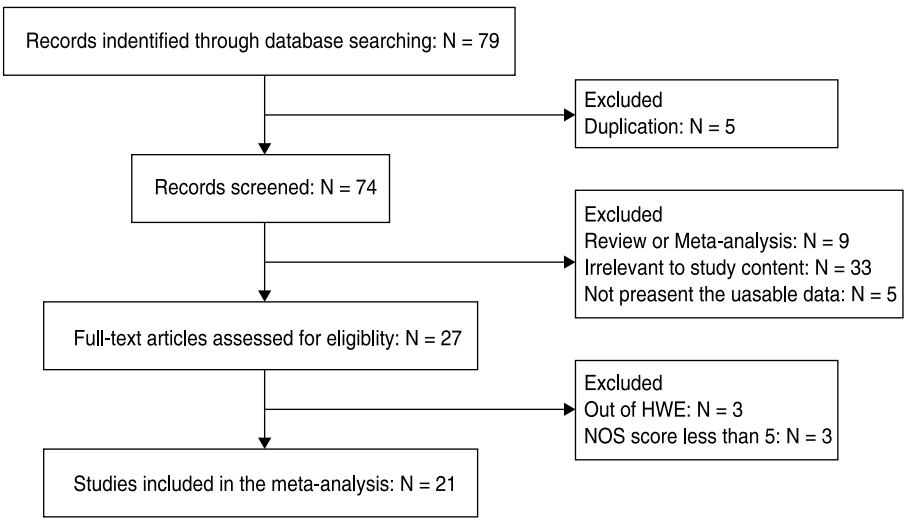

Fig. 2 Flow diagram of literature selection

There were 39 studies from Caucasians, seven studies from Asians, and two studies from Africans. The flowchart of the selection process is shown in Fig. 2. Detailed characteristics of the included studies are presented in Table 1.

Results of allele analysis

rs4132061

A total of 29 studies in the 18 included articles analyzed the correlation between the rs4132061 polymorphism and the risk of ALL. Heterogeneity was observed in the allele model (I^2 = 55.1%, P = 0.00), and we applied a random-effects model to conduct the meta-analysis. The G allele exhibited a significant 1.46-fold increased risk of developing ALL compared with the A allele (OR = 1.46, 95% CI: 1.36–1.57, P < 0.001). Through sensitivity analysis, the meta-analysis showed that rs4132061 G *vs.* T was significantly associated with the risk of ALL (I^2 = 0.0%, OR = 1.33, 95% CI: 1.29–1.38, P < 0.001) after exclusion of references [19, 23–25]. This demonstrates that the results obtained were statistically robust. The effect of the rs4132061 polymorphism on ALL was further evaluated using a stratification analysis of ethnicity and ALL type. A higher risk was detected in Europeans (OR = 1.54; 95% CI: 1.46–1.61, P < 0.001) or B-ALL (I^2 = 5.0%, OR = 1.56; 95% CI: 1.48–1.65, P < 0.001; Fig. 3).

rs11978267

A total of 12 articles and 19 studies were included (Table 1), and a significant association with the risk of ALL was found (I^2 = 64.3%, OR = 1.33, 95% CI: 1.21–1.45). Sensitivity analysis was performed to exclude studies that had a significant impact on heterogeneity [4, 8, 18–19, 24]. Meta-analysis showed a significant correlation, as described above. In subgroup analysis, a significantly increased ALL risk was found in the B-cell ALL subgroup (I^2 = 5.0%, OR = 1.39, 95% CI: 1.27–1.51, P < 0.001; Fig. 4).

Genotype analysis

rs4132061

A total of 23 studies in 15 articles reported the genotype distribution of rs4132061. The pooled OR revealed a significant association between ALL risk and the rs4132061 polymorphism in all comparisons (GG *vs.* TT: OR = 2.41, 95% CI: 2.10–2.77, P < 0.001; GT *vs.* TT: OR = 1.52, 95% CI: 1.37–1.69, P < 0.001; GG *vs.* TT + GT: OR = 1.94, 95% CI: 1.72–2.19, P < 0.001; GG + GT *vs.* TT: OR = 1.71, 95% CI: 1.52–1.93, P < 0.001). Stratification analysis according to ethnicity showed that the rs4132601 polymorphism was associated with a high risk of ALL in all genetic models in Caucasians. The GG, TG, and TT + GG genotypes may increase the risk of ALL in Asians (Table 2). The results of subgroup analysis by ALL subtype showed that ALL gene models were significantly associated with the risk of ALL in B-ALL. In T-ALL, there is no evidence that the rs4132061 polymorphism is associated with ALL risk.

rs11978267

Six of the eligible studies reported rs11978267 genotype distribution. A significantly increased risk of ALL was observed among individuals with the homozygous GG genotype (GG *vs.* AA: OR = 1.687, 95% CI: 1.311–2.171, P < 0.001; GG *vs.* AA + GG: OR = 1.687, 95% CI: 1.311–2.171, P < 0.001; Table 2).

Publication bias

Begg's test was used to detect publication bias in the included studies, and the results showed no significant publication bias (P = 0.205; Fig. 5).

Table 1 Characteristics of the included articles

(A) rs4132601

First author	Year	Country	Ethnicity	Disease	Case					Control					Case/Control	HWE *P* for controls
					TT	TG	GG	T	G	TT	TG	GG	T	G		
Mosaad. a	2020	Egyptian	Caucasian	B-ALL	55	72	15	182	102	249	162	25	660	212	142/436	0.841036
Mosaad. b	2020	Egyptian	Caucasian	T-ALL	15	12	4	42	20	249	162	25	660	212	31/436	0.841036
Urayama	2018	Japan	Asian	B-ALL	–	–	–	958	96	–	–	–	7050	714	527/3882	–
Lopes	2017	Brazilian	Caucasian	B-ALL	120	98	28	338	154	246	192	29	684	250	276/467	0.292591
Bhandari	2016	Indian	Asian	B-ALL	69	67	26	205	119	78	61	11	217	83	162/150	0.844204
Kreile	2014	Latvian	Caucasian	B-ALL	35	32	8	102	48	63	44	7	170	58	76/121	0.852246
Burmeister. a	2014	German	Caucasian	B-ALL	86	111	30	283	171	811	574	116	2196	806	227/1501	0.305358
Burmeister. b	2014	German	Caucasian	T-ALL	51	40	4	142	48	811	574	116	2196	806	95/1501	0.305358
Orsi. a	2012	France	Caucasian	B-ALL	148	166	47	462	260	817	632	93	2266	818	361/1542	0.043056
Orsi. b	2012	France	Caucasian	T-ALL	15	23	3	53	29	817	632	93	2266	818	41/1542	0.043056
Peyrouze. a	2012	France	Caucasian	B-ALL	–	–	–	97	55	–	–	–	252	108	76/180	–
Peyrouze. b	2012	France	Caucasian	T-ALL	–	–	–	108	40	–	–	–	252	108	74/180	–
Ellinghaus. a	2012	Germany	Caucasian	B-ALL				553	285				683	265	419/474	–
Ellinghaus. b	2012	Germany	Caucasian	B-ALL	–	–	–	528	284	–	–	–	2456	908	406/1682	–
Ellinghaus. c	2012	Italy	Caucasian	B-ALL	–	–	–	362	212	–	–	–	857	301	287/579	–
Vijayakrishnan. a	2010	Thailand	Asian	B-ALL	122	49	1	293	51	145	36	1	326	38	172/182	0.435546
Vijayakrishnan. b	2010	Thai	Asian	T-ALL	13	3	2	29	7	145	36	1	326	38	18/182	0.435546
Prasad. a	2010	German	Caucasian	B-ALL	471	552	166	1494	884	811	574	116	2196	806	1193/1516	0.305358
Prasad. b	2010	UK	Caucasian	B-ALL	60	96	32	216	160	206	133	21	545	175	191/361	0.938949
Papaemmanuil. a	2009	UK	Caucasian	B-ALL	172	205	82	549	369	751	564	123	2066	810	459/1438	0.244163
Papaemmanuil. b	2009	UK	Caucasian	T-ALL	19	16	9	54	34	751	564	123	2066	810	44/1438	0.244163
Papaemmanuil. c	2009	UK	Caucasian	B-ALL	129	191	45	449	281	533	358	69	1451	523	365/960	0.963117
Papaemmanuil. d	2009	UK	Caucasian	T-ALL	19	17	3	55	23	533	358	69	1451	523	39/960	0.963117
Mahjoub	2019	Tunisian	African	ALL	73	73	24	219	121	76	68	6	220	80	170/150	0.051360
Bahari	2016	Iranian	Asian	ALL	23	59	28	105	115	52	45	23	149	91	110/120	0.025812
Rudant	2015	France	Caucasian	ALL	175	202	57	552	316	211	167	37	589	241	434/415	0.631803
Wang	2013	China	Asian	ALL	415	141	12	971	165	504	159	9	1167	177	568/672	0.370420
Lautner-Csorba	2012	Hungary	Caucasian	ALL	246	229	68	721	365	307	181	41	795	263	543/529	0.053063
Pastorczak	2011	Poland	Caucasian	ALL	178	165	46	521	257	389	270	56	1048	382	389/715	0.341676

(B) rs11978267

First author	Year	Country	Ethnicity	Disease	Case					Control					Case/Control	HWE *P* for controls
					TT	TG	GG	T	G	TT	TG	GG	T	G		
Mosaad. a	2020	Egyptian	Caucasian	B-ALL	82	47	13	211	73	239	165	32	643	229	142/436	0.841036
Mosaad. b	2020	Egyptian	Caucasian	T-ALL	19	10	2	48	14	239	165	32	643	229	31/436	0.841036
Urayama	2018	Japanese	Asian	B-ALL	–	–	–	957	97	–	–	–	7010	753	527/3882	–
Lopes	2017	Brazilian	Caucasian	B-ALL	133	87	26	353	139	258	175	34	691	243	276/467	0.292591
Orsi. a	2012	France	Caucasian	B-ALL	–	–	–	462	260	–	–	–	2266	818	361/1542	0.043056
Orsi. b	2012	France	Caucasian	T-ALL	–	–	–	53	29	–	–	–	2266	818	41/1542	0.043056
Peyrouze. a	2012	France	Caucasian	B-ALL	–	–	–	99	53	–	–	–	252	108	76/180	–
Peyrouze. b	2012	France	Caucasian	T-ALL	–	–	–	108	40	–	–	–	252	108	74/180	–
Ellinghaus. a	2012	Germany	Caucasian	B-ALL	–	–	–	545	293	–	–	–	673	275	419/474	–
Ellinghaus. b	2012	Germany/ Australian	Caucasian	B-ALL	–	–	–	536	276	–	–	–	2456	908	406/1682	–
Ellinghaus. c	2012	Italy	Caucasian	B-ALL	–	–	–	189	385	–	–	–	868	290	287/579	–
Mariana	2014	brazilian	Caucasian	ALL	80	62	12	222	86	271	182	37	724	256	154/490	0.404219
Linabery	2013	U.S	Caucasian	ALL	321	299	110	941	519	204	152	28	560	208	574/384	0.965647
Heng Xu. a	2013	USA	Caucasian	ALL	–	–	–	1186	758	–	–	–	1996	776	574/2601	–
Heng Xu. b	2013	USA	African	ALL	–	–	–	130	48	–	–	–	2208	518	128/1075	–
Heng Xu. c	2013	USA	Caucasian	ALL	–	–	–	421	189	–	–	–	1492	524	143/640	–
Ross	2013	USA	Caucasian	ALL	53	31	12	137	55	204	152	28	560	208	96/384	0.965647
Lautner-Csorba	2012	Hungary	Caucasian	ALL	248	230	65	726	360	308	181	40	797	261	543/529	0.067779
Treviño	2009	USA	Caucasian	ALL	–	–	–	387	247	–	–	–	26219	9697	317/17958	–

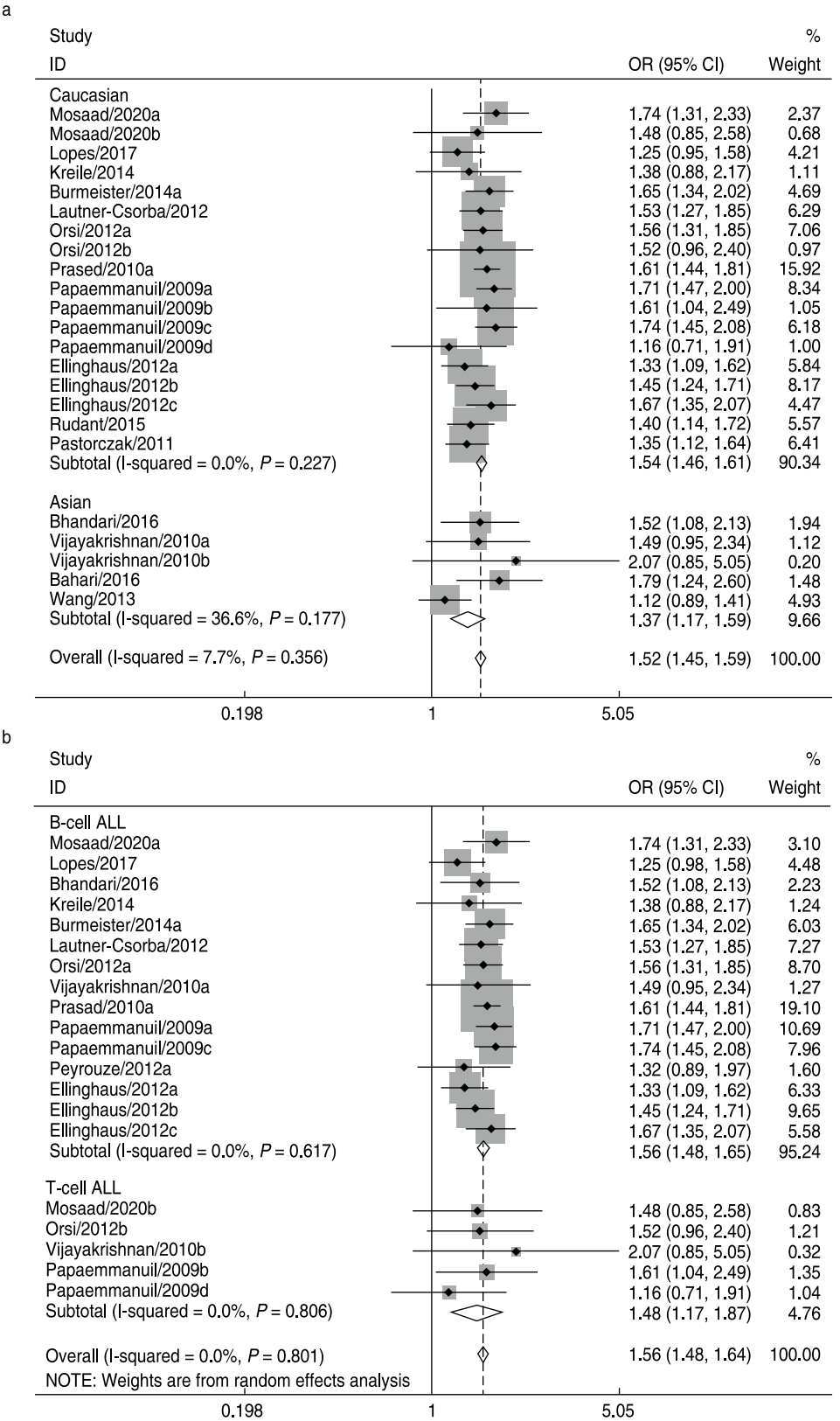

Fig. 3 Forest plots of ALL predisposition associated with rs4132061 polymorphism under genetic models. (a) Allelic model analysis (G vs. A) of rs4132061 and ALL risk among ethnicity. (b) Allelic model analysis (G vs. A) of rs4132061 and ALL risk among disease type

Table 2 Pooled ORs and 95% CIs for associations between *IKZF1* rs4132601 and rs11978267 polymorphisms and ALL risk

Genetic mode	Test of association			Test of heterogeneity		Genetic mode	Test of association			Test of heterogeneity	
	OR (95%)	*Z*	*P*	I^2	*P*		OR (95%)	*Z*	*P*	I^2	*P*
		rs4132061						rs11978267			
G *vs.* T	1.46 (1.36, 1.56)	10.44	0.000	55.1%	0.000	G *vs.* A	1.33 (1.21, 1.45)	6.19	0.000	64.3%	0.000
GT *vs.* TT	1.52 (1.37, 1.69)	7.71	0.000	48.6%	0.005	GA *vs.* AA	1.09 (0.88, 1.34)	0.77	0.441	54.2%	0.041
GG *vs.*TT	2.41 (2.10, 2.77)	12.43	0.000	19.0%	0.194	GG *vs.* AA	1.69 (1.31, 2.171)	4.07	0.000	16.8%	0.302
GG *vs.* TT + GT	1.94 (1.72, 2.19)	10.70	0.000	10.9%	0.312	GG *vs.* AA + AG	1.63 (1.31, 2.02)	4.41	0.000	0.0%	0.509
GG + GT *vs.* TT	1.71 (1.52, 1.93)	8.78	0.000	45.0%	0.023	GG + AG *vs.* AA	1.16 (0.95, 1.43)	1.45	0.147	58.7%	0.024

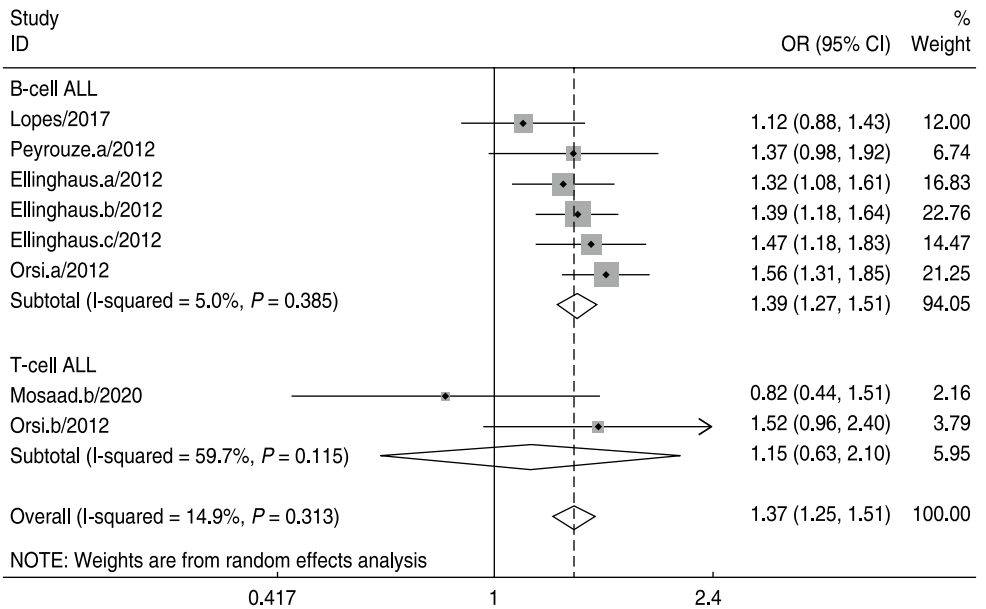

Fig. 4 Forest plots of ALL predisposition associated with rs11978267 polymorphism under genetic models

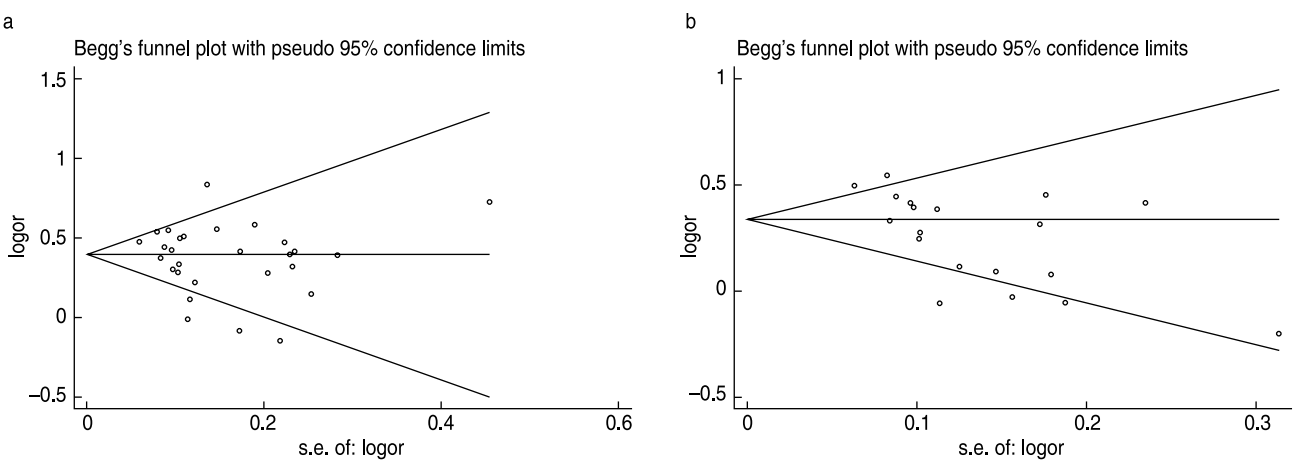

Fig. 5 Publication bias in studies of the association between *IKZF1* polymorphism and ALL risk assessed by Begg's Funnel plot (a, rs4132061; b, rs11978267)

Discussion

Regulation of oncogene expression through transcription factors that act as tumor suppressors is one of the main mechanisms regulating leukemia. Understanding this complex process is crucial for understanding the pathogenesis of leukemia and developing targeted therapies. IKAROS, encoded by *IKZF1*, is a DNA-binding

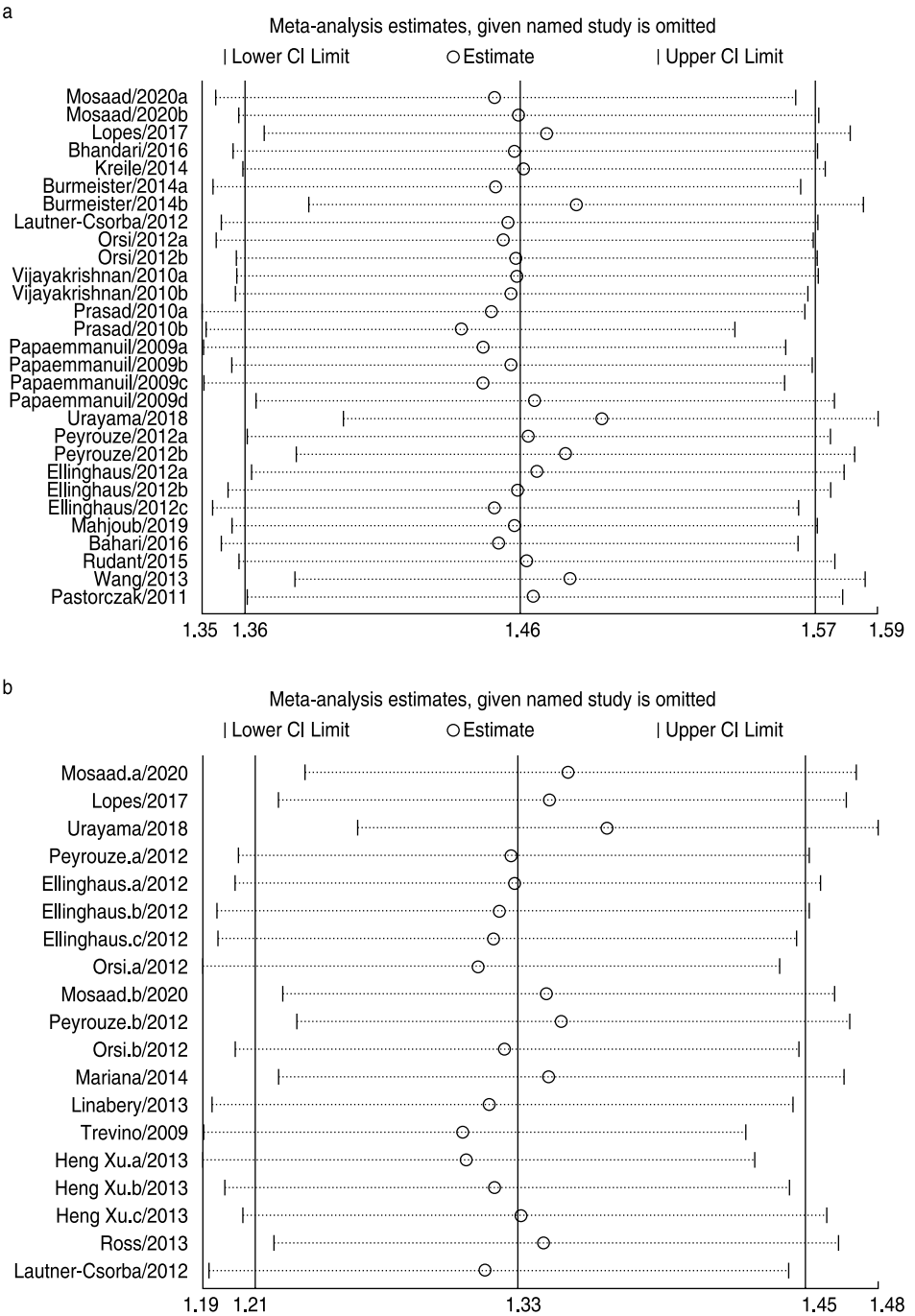

Fig. 6 Sensitivity analyses for studies on rs4132061 and rs11978267 polymorphism and ALL risk. (a) rs4132061 (G *vs.* T); (b) rs11978267 (G *vs.* A)

protein. IKAROS binds specific common binding motifs on the upstream regulatory elements of its target genes to recruit chromatin remodeling complexes to activate or inhibit transcription and plays a role in regulating lymphocyte differentiation and development [35].

In this study, a meta-analysis was performed to determine the correlation between the rs4132061 and rs11978267 loci of *IKZF1* and ALL. We observed that rs4132061 was associated with the risk of ALL in all genetic models, especially B-ALL. However, there is insufficient evidence to prove that rs4132061 is associated with the risk of T-ALL. The rs11978267 locus was associated with the risk of ALL in the GG *vs.* AA + AG and GG *vs.* AA models. Subgroup analysis showed that rs4132061 and rs11978267 were associated with the risk of ALL in the European population. In Asian populations,

rs4132061 has been associated with an increased risk of ALL. A combined analysis of 48 further studies grouped by two loci showed heterogeneity (rs4132061: I^2 = 55.1%, P = 0.00; rs11978267: I^2 = 64.3%, P = 0.00). Subgroup analysis showed that the heterogeneity of the rs4132061 locus was mainly concentrated in B-ALL (I^2 = 58.4%, P = 0.002) and Asian populations (I^2 = 57.4%, P = 0.038), and the heterogeneity of the rs11978267 locus was mainly concentrated in T-ALL (I^2 = 59.7%, P = 0.0115). In addition, sensitivity analysis (Fig. 6) was conducted, and seven documents that had a significant impact on the results were excluded [4, 8, 18–19, 23–25]. After the analysis, the results did not change, indicating that the findings are reliable.

This study had some limitations: (1) Most of the samples included in this study were from Caucasians, and the relationship between *IKZF1* polymorphisms and ALL in different ethnic groups still needs to be verified by further large-scale studies; (2) only published English literature was included in this study, which may have led to publication bias; (3) some studies have shown that the incidence of ALL is related to many environmental factors, but this study only considered genetic factors.

In conclusion, current evidence indicates that *IKZF1* polymorphisms are significantly associated with the risk of ALL, and their polymorphic loci may be effective and economical biomarkers for the diagnosis and treatment of ALL. Due to the limited quality of the included studies, the above conclusions need to be verified by further high-quality studies.

Acknowledgments

Not applicable.

Funding

This work was supported by the National Key Project of Neonatal Children (No. 1311200003303), Grants from the Science and Technology Bureau of Sichuan Province (No. 2021YJ0211 to Jinlin Wu), and Grants from the Health Planning Committee of Sichuan Province (No. 20PJ070 to Jinlin Wu).

Conflicts of interest

The authors declared no conflict of interest.

Author contributions

Sisi Wang and Chuyang Lin contributed equally to this work.

Data availability statement

Not applicable.

Ethical approval

Not applicable.

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DOI 10.1007/s10330-021-0527-7
Cite this article as: Wang SS, Lin CY, Xi TT, et al. Relationship between *IKZF1* polymorphisms and the risk of acute lymphoblastic leukemia: a meta-analysis. Oncol Transl Med. 2022;8(5):217–225.