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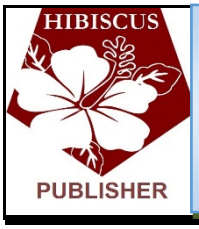

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Association between *ARID5B* Polymorphisms and the Risk for Childhood B- Acute Lymphoblastic Leukaemia

Chow Yock Ping[1], Noraidatulakma Abdullah[1] and Nor Adzimah Johdi[1]*

[1]UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia, Kuala Lumpur Campus, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur, Malaysia.

*Corresponding author:
Dr. Nor Adzimah Johdi,
KM Medical Molecular Biology Institute (UMBI),
Universiti Kebangsaan Malaysia,
Kuala Lumpur Campus,
Jalan Yaacob Latif,
56000 Cheras,
Kuala Lumpur,
Malaysia
Email: adzimah@ppukm.ukm.edu.my

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ABSTRACT

B-cell precursor acute lymphoblastic leukemia (B-ALL) is the commonest cancer in children, comprising over 80% of the entire childhood leukemia. However, the etiology of childhood B-ALL remains poorly understood and genetic susceptibility is a major risk factor for this disease. *ARID5B* appeared as one of the most promising genetic markers with nearly a 3-fold increased risk of disease. Method: In this meta-analysis, a total of six candidate *ARID5B* polymorphisms (i.e. rs10821936, rs10994982, rs7089424, rs10821938, rs10740055, and rs7073837) which have been analyzed in at least 2 studies were included for analysis of the risk association between *ARID5B* polymorphisms and childhood B-ALL. Results: Pooled analysis revealed that the dominant model of these six *ARID5B* polymorphisms was associated with an increased risk of childhood B-ALL. However, subgroup analysis based on ethnicity suggested that only four polymorphisms (i.e. rs10821936, rs10994982, rs7089424 and rs10821938) consistently conferred increased risk to childhood B-ALL across different populations, whereas the other 2 polymorphisms (rs10740055, rs7073837) were causative to Caucasians (OR=2.01, 95% CI=1.66-2.44; OR= 1.98, 95% CI=1.69-2.31) but maybe protective for Asian (OR=0.49, 95% CI=0.22-1.09; OR=0.95, 95% CI=0.43-2.09) respectively. Conclusion: Our meta-analysis demonstrated could serve as promising markers for assessing the susceptibility risk to childhood B-ALL in both the Asian and Caucasian populations. Further development of a multigene panel inclusive of *ARID5B* is desirable for screening children with a higher risk of developing B-ALL and to improve clinical management of the disease.

INTRODUCTION

B-cell precursor acute lymphoblastic leukemia (B-ALL) is the commonest cancer in children, comprising over 80% of the entire childhood leukemia [1]. The etiology of childhood B-ALL remains poorly understood. Epidemiological studies suggest that genetic susceptibility is a major risk factor, whilst the environmental risk factors, such as exposure to radiation and carcinogens, smoking, and obesity have a relatively minor contribution [2, 3]. Earlier studies have shown that the incidence of childhood B-ALL is significantly higher in Caucasians and lower in African Americans and Asians [4-7]. Moreover, it is well recognized that some markers are universal across ethnic groups while others are ethnic-specific. In recent years, molecular-based studies have led to the discovery of a long list of candidate markers associated with childhood ALL via large-scale genome-wide association studies (GWAS) [8-16]. Among those, *ARID5B* appeared as one of the most promising markers with nearly a 3-fold increased risk of disease. *ARID5B* encodes for a member of the AT-rich interaction domain (ARID) family of transcription factors and has roles in embryogenesis and growth regulation [17-19]. Loss of ARID5B impaired B-cell progenitors' development in homozygous knockout mice [19, 20]; however, its role in driving leukemogenesis is not fully understood. Until now, the association between *ARID5B* polymorphisms (i.e., rs10821936, rs10994982, rs7089424, rs10821938, rs7073837, rs10740055) and childhood B-ALL risk has been investigated in different populations, including Caucasians [8-9, 14, 21-31], African Americans [32], Asians [5,11, 33-34, 51] and mixed populations [35-36]. Meta-analyses

by Guo et al. [37] and Zeng et al. [38] evaluated only the association between rs10821936, rs10994982 and rs7089424 with the risk of childhood ALL (B-ALL & T-ALL). Since then, additional case-control studies have been conducted to investigate the association of rs10821936 [25, 28-29, 34, 36] and rs7089424 [16, 31, 34, 36] with childhood ALL risk. Tao et al showed that rs7089424 and rs10994982 were susceptible in B-ALL in the Chinese pediatric population via PCR and mass spectrometry [51]. We believe it is important to re-examine the effects of these *ARID5B* polymorphisms (rs10821936, rs10994982, rs7089424), as well as three others commonly studied *ARID5B* polymorphisms (rs10821938, rs7073837, rs10740055) concerning the susceptibility to childhood B-ALL. We aim to assess the association of 6 candidate *ARID5B* polymorphisms, i.e. rs10821936 (10 eligible case-control studies), rs10994982 (6 eligible case-control studies), rs7089424 (6 eligible case-control studies), rs10821938 (2 eligible case-control studies), rs10740055 (3 eligible case-control studies), rs7073837 (4 eligible case-control studies), and their susceptibility to childhood B-ALL by stratifying the populations into Caucasians, African Americans, Asians, and mixed ethnic groups

MATERIALS AND METHODS

Search Strategy

All available studies associated with *ARID5B* and childhood B-ALL risk were identified using the keywords "(leukemia or leukaemia) and (*ARID5B* or AT-rich interactive domain 5B)" by searching the following databases: PubMed, Cochrane library, Google Scholar, and Science Direct (Up to Jan 2021). In addition, other relevant publications found by manually searching references were also included. Two investigators (CYP and NA) independently reviewed the literature.

Inclusion and Exclusion Criteria

The inclusion criteria for the eligible studies were (1) studies evaluating the association between *ARID5B* polymorphisms and childhood B-ALL risk, (2) case-control studies, (3) the frequencies of the genotypes for cases and controls are available for calculating odds ratios (ORs) and 95% confidence intervals (CIs), (4) the distribution of the genotype in control groups was in Hardy-Weinberg equilibrium (HWE) and (5) articles written in English. The criteria used to exclude studies were (1) case report, letter, editorial article, review, and meta-analysis, (2) not a case-control study, (3) studies on adult leukemia, (4) the distribution of the genotypes in control groups was not in HWE, (5) the genotypes data of *ARID5B* polymorphisms for cases and controls were not available, and (6) the genotypes data for each childhood leukemia type were not available. The selection process was documented in a flow chart as recommended in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement following the PRISMA Recommendations [39].

Data extraction

All the data were carefully extracted independently by two investigators (CYP & NA) from each publication, according to the inclusion and exclusion criteria listed above. The discrepancies during data extraction were resolved by consensus. A third investigator (NAJ) was consulted to resolve any disagreement. The extracted data included author, year of publication, country of origin, the ethnicity of patients, genotyping methods, number of cases and controls, types of leukemia, and the genotypes distribution of cases and controls. The study populations were categorized as Caucasians, African Americans (Blacks), Asians, or Mixed ethnic groups.

Statistical analysis

The association between *ARID5B* polymorphisms and leukemia risk was determined by evaluating the pooled OR with 95% CI according to the dominant model. The significance of the summary OR was determined with a Z test and $p<0.05$ was considered as statistically significant. The between-study heterogeneity was assessed by χ^2 based on Cochran's Q statistic (40) and the degree of heterogeneity was assessed by I^2 statistic [41]. If the heterogeneity was significant (I^2 value >50% or $p<0.10$), the random-effects model/DerSimonian and Laird method were used to estimate the pooled OR (42). Otherwise, if the heterogeneity was insignificant (I^2 value <50% or $p>0.10$), then the fixed-effects model/Mantel-Haenszel method was used [43]. Potential publication bias was estimated by Egger's test ($p<0.05$ was considered representative of statistically significant publication bias) [44] and visualized by using Begg's funnel plot [45]. All statistical tests were performed using the STATA version13.0 (STATA Corporation, College Station, TX).

RESULTS

Characteristics of the Eligible Studies

The flowchart summarising the selection process of the studies is shown in **Fig. 1**. The combined search yielded 328 references from PubMed, Science Direct, Google Scholar, and Cochrane Library databases (after removal of duplicates). One additional article was identified from manually searching references cited in the published articles. After reviewing the titles and abstracts, 291 non-relevant articles were removed. The full-text articles of the remaining 38 articles were reviewed in detail. Subsequently, an additional 23 studies were excluded (3 were reviews or meta-analysis [37-38, 46], 3 were just case studies [14, 20], 14 studies did not supply the genotype data for calculating OR [7, 11, 15-16, 23-24, 27, 30,31, 47], 2 were studies on adult leukemia [49-50], and 1 was a study on acute myeloid leukemia [30] giving a final total of 15 studies in our meta-analysis. Eight studies involved Caucasians, 1 study involved African Americans, 4 studies involved Asians, and 2 studies had patients from a mixed population. The characteristics of the 15 studies are summarized in Table 1. Notably, the distribution of the rs10821936, rs10994982, and rs7089424 by Kennedy et al [36], and rs7089424 by Lin et al [33] did not conform with the HWE ($p<0.01$) and were excluded from the meta-analysis.

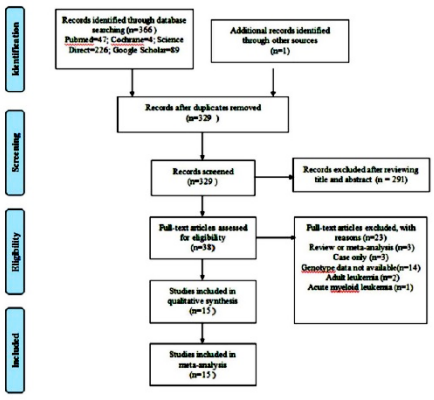

Fig. 1. Flow chart of selection of studies for inclusion in the meta-analysis.

Table 1. Characteristics of studies included in the meta-analysis.

First Author	Year	Country	Ethnicity	Genotyping Method	Genotypes frequencies Case/Control			HWE (*p*-value)
***ARID5B* (rs10821936)**					**TT**	**TC**	**CC**	
Kreile	2016	Latvia	Caucasian	PCR-RFLP	38/81	24/31	14/9	0.023
Emerenciano	2014	Brazil	Caucasian	Taqman	42/200	83/205	32/68	0.192
Ross	2013	USA	Caucasian	Taqman	39/169	42/171	18/43	0.9794
Gutierrez Camino	2013	Spain	Caucasian	Taqman	55/169	90/150	59/49	0.0922
Healy	2010	Canada	Caucasian	ASPE	76/127	129/99	67/36	0.0229
Trevino	2009	USA	Caucasian	Affymetrix array	91/7820	189/816 6	94/1957	0.0109
Yang	2010	USA	Black	Affymetrix array	31/77	32/29	5/6	0.1555
Bhandari	2016	India	Asian	Taqman	18/33	91/78	53/39	0.61
Wang	2013	China	Asian	SNaPshot	135/277	256/301	98/94	0.4008
Kennedy	2015	USA	Mixed	Taqman	39/104	72/69	44/50	0
Linabery	2013	USA	Mixed	Taqman	185/169	309/171	157/43	0.9794
***ARID5B* (rs10994982)**					**GG**	**GA**	**AA**	
Emerenciano	2014	Brazil	Caucasian	Taqman	18/96	75/214	68/163	0.0957
Gutierrez Camino	2013	Spain	Caucasian	Taqman	33/95	95/178	67/94	0.5659
Ross	2013	USA	Caucasian	Taqman	27/101	42/187	25/95	0.649
Healy	2010	Canada	Caucasian	ASPE	50/72	125/129	100/63	0.7257
Trevino et al.	2009	USA	Caucasian	Affymetrix array	60/4615	171/897 3	139/432 8	0.796
Kennedy	2015	USA	Mixed	Taqman	55/90	78/78	25/43	0.0013
Linabery	2013	USA	Mixed	Taqman	119/101	265/187	219/95	0.649
***ARID5B* (rs7089424)**					**TT**	**TG**	**GG**	
Gutierrez Camino	2013	Spain	Caucasian	Affymetrix array allele-specific	55/163	92/155	54/52	0.1272
Prasad	2010	Germany	Caucasian	PCR	392/836	694/838	288/190	0.3449
Papaemmanuil	2009	UK	Caucasian	Affymetrix array	231/105 2	409/104 8	181/290	0.2451
Bhandari	2016	India	Asian		19/29	93/83	50/38	0.1753
Lin	2014	Taiwan	Asian	HRM	20/36	17/26	8/18	0.0048
Vijayakrishnan	2010	Thailand	Asian	allele-specific PCR	44/55	91/86	37/39	0.6212
Kennedy	2015	USA	Mixed	Taqman	37/113	80/68	43/46	0
***ARID5B* (rs10821938)**					**CC**	**CA**	**AA**	
Gutierrez Camino	2013	Spain	Caucasian	Taqman allele-specific	47/127	89/170	69/72	0.2681
Vijayakrishnan	2010	Thailand	Asian	PCR	25/38	73/84	74/60	0.3936
***ARID5B* (rs10740055)**					**AA**	**AC**	**CC**	
Healy	2010	USA	Caucasian	ASPE	41/67	117/132	108/64	0.9491
Papaemmanuil	2009	UK	Caucasian	Affymetrix array	115/583	396/113 5	313/620	0.1631
Lin	2014	Taiwan	Asian	HRM	33/46	12/34	0/0	0.0158
***ARID5B* (rs7073837)**					**CC**	**CA**	**AA**	
Gutierrez Camino	2013	Spain	Caucasian	Affymetrix array	32/119	96/157	58/73	0.1149
Healy	2010	USA	Caucasian	ASPE	67/93	28/127	75/44	0.954
Papaemmanuil	2009	UK	Caucasian	Affymetrix array	186/870	427/111 9	211/391	0.33
Lin	2014	Taiwan	Asian	HRM	14/24	8/37	23/19	0.5232

Association of *ARID5B* Polymorphisms and Risk of Childhood B-ALL

The association between rs10821936 (TC+CC vs. TT) and susceptibility to childhood B-ALL was analyzed in 10 studies involving 2,552 cases and 20,867 healthy controls. As depicted in the Forest plot [**Fig 2(A)**], the combined analyses suggested that the dominant model of rs10821936 significantly increased the risk of childhood B-ALL across all four ethnic groups (OR, 2.08; 95% CI, 1.86-2.32). Similarly, the subgroup analysis suggested that this marker was significantly associated with increased B-ALL risk in both Caucasians (OR=2.16; 95% CI=1.87-2.50) and Asians (OR=1.89; 95% CI=1.50-2.39) children. As there was only one study each on Blacks and Mixed population, additional replication studies are required to validate the risk effects of rs10821936 in these 2 ethnic groups.

A total of 6 studies were included to assess the risk association between rs10994982 (GA+AA vs. GG) and childhood B-ALL and comprises 1,698 cases and 19,786 controls. As shown in **Fig. 2(B)**, the combined analysis showed that the dominant model of rs10994982 was significantly associated with increased risk of childhood B-ALL among Caucasians (OR=1.65, 95% CI=1.38-1.97). Even though the rs10994982 dominant model also showed an increased risk in the Mixed population (OR=1.46, 95% CI, 1.08-1.97), additional replication studies are required to confirm the findings.

For rs7089424, 6 studies were included in the meta-analysis, in which four involved Caucasian patients and 2 involved Asian patients. As depicted in **Fig 2(C)**, the combined results demonstrated that the dominant model of rs7089424 (GT+GG vs. TT) conferred increased risk to childhood B-ALL (OR=2.02; 95% CI=1.83-2.23). Similar findings were evident in ethnicity-based subgroup analysis for both Caucasians (OR=2.07, 95% CI=1.87-2.30), and Asians (OR=1.45, 95% CI=1.00-2.10), hence suggesting the robustness of this marker in predicting susceptibility to childhood B-ALL.

There were only 2 eligible studies reported on rs10821938, involving Caucasian and Asian patients. As shown in **Fig 2(D)**, the between-study heterogeneity indicated that both studies were homogenous (I=squared=0.0%, p=0.711), and the fixed-effect model was used to calculate the combined OR. The results demonstrated that the dominant model of rs10821938 (AA +AC s CC) was significantly associated with childhood B-ALL risk (OR=1.69, 95% CI=1.23-2.33).

As demonstrated in **Fig 3(A)** and **3(B)**, rs10740055 (AC+CC vs. AA) and rs7073837 (AC+AA vs. CC) conferred an increased risk to childhood B-ALL under the dominant model with OR=2.01 (95% CI=1.66-2.44) and OR=1.98 (95% CI=1.69-.2.31) respectively in Caucasians. As there was only one study reported on Asians for rs10740055 (OR=0.49, 95% CI=0.22-1.09) and rs7073837 (OR=0.95, 95% CI=0.43-2.09) respectively, further validation is required to confirm their possible protective effects on childhood B-ALL. All the 6 SNPs were intronic variants that clustered together closely (**Fig. 4**).

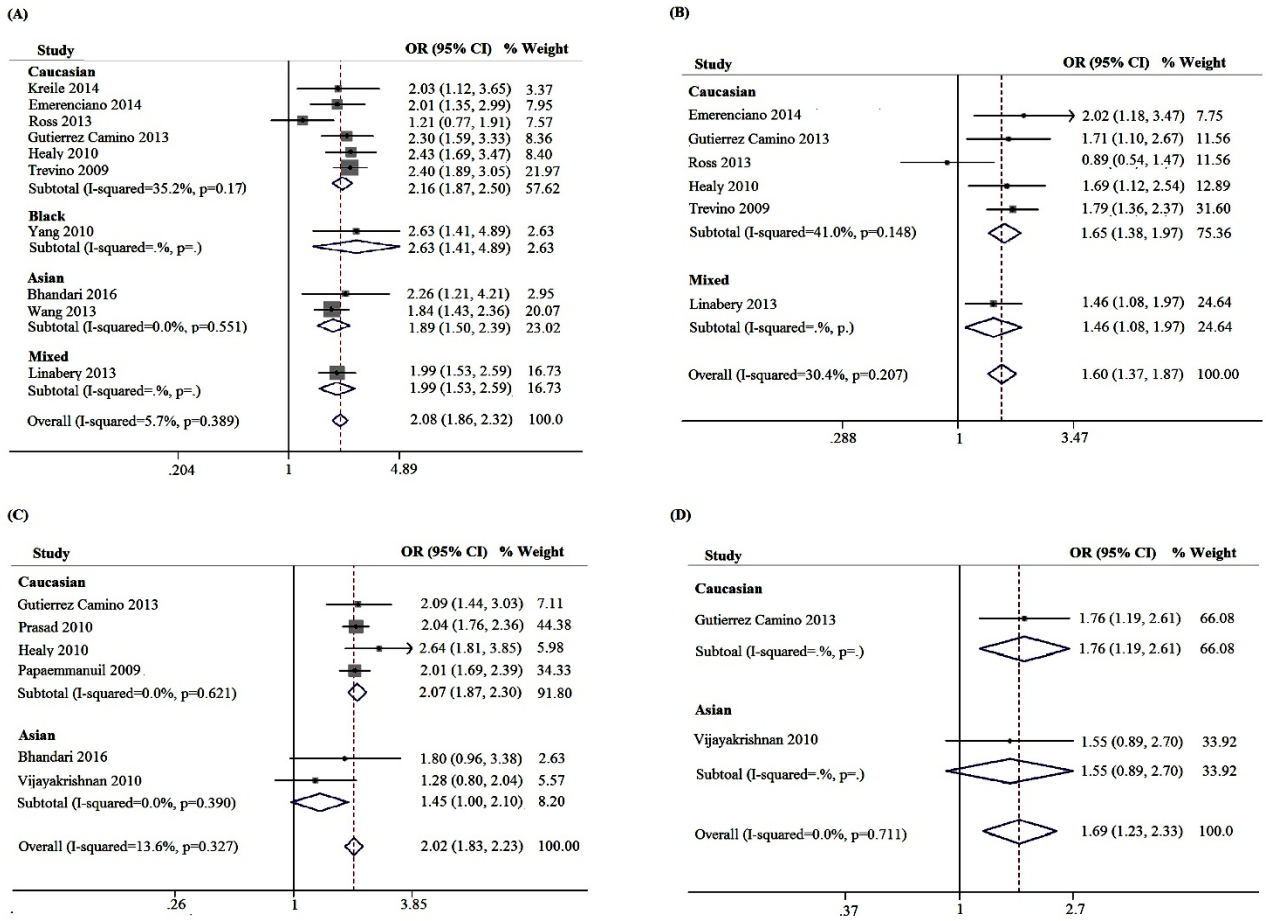

Fig. 2. The forest plot describing the meta-analysis for the dominant model of (A) rs10821936 (TC+CC vs. TT); (B) rs10994982 (GA+AA vs. GG); (C) rs7089424 (GT+GG vs. TT), and (D) rs10821938 (AC +AA vs. CC). The squares represent the study-specific OR and 95% CI whereas the diamond represents the pooled OR and 95% CI calculated using fixed or random effect method.

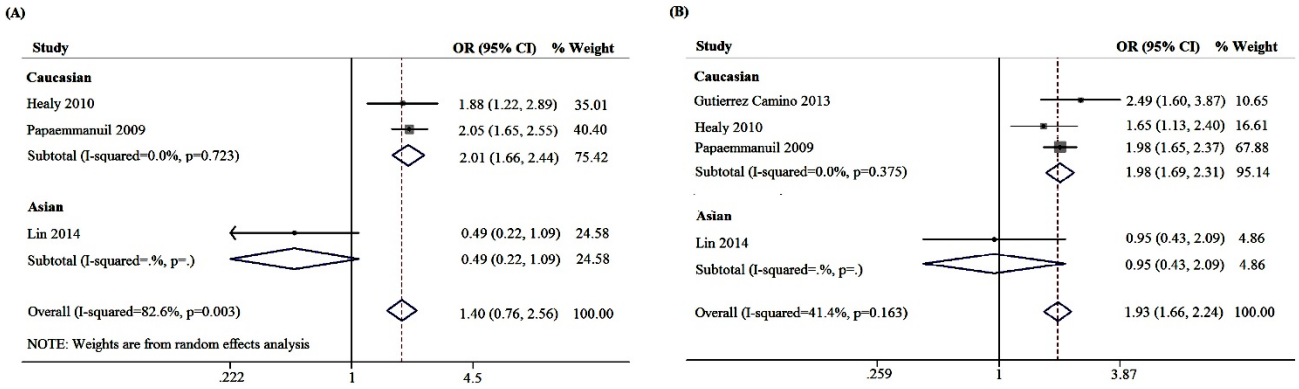

Fig. 3. The forest plot describing the meta-analysis for the dominant model of (A) rs10740055 AC+CC vs. AA) and (B) rs7073837 (AC+AA vs. CC). The squares represent the study-specific OR and 95% CI whereas the diamond represents the pooled OR and 95% CI calculated using fixed or random effect method.

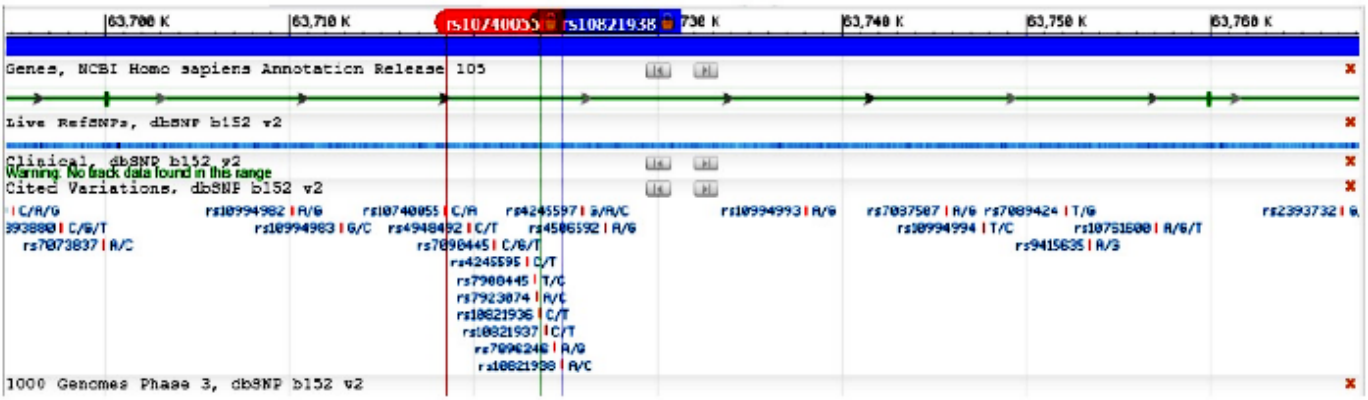

Fig. 4. The 6 SNPs were intronic variants which clustered together closely.

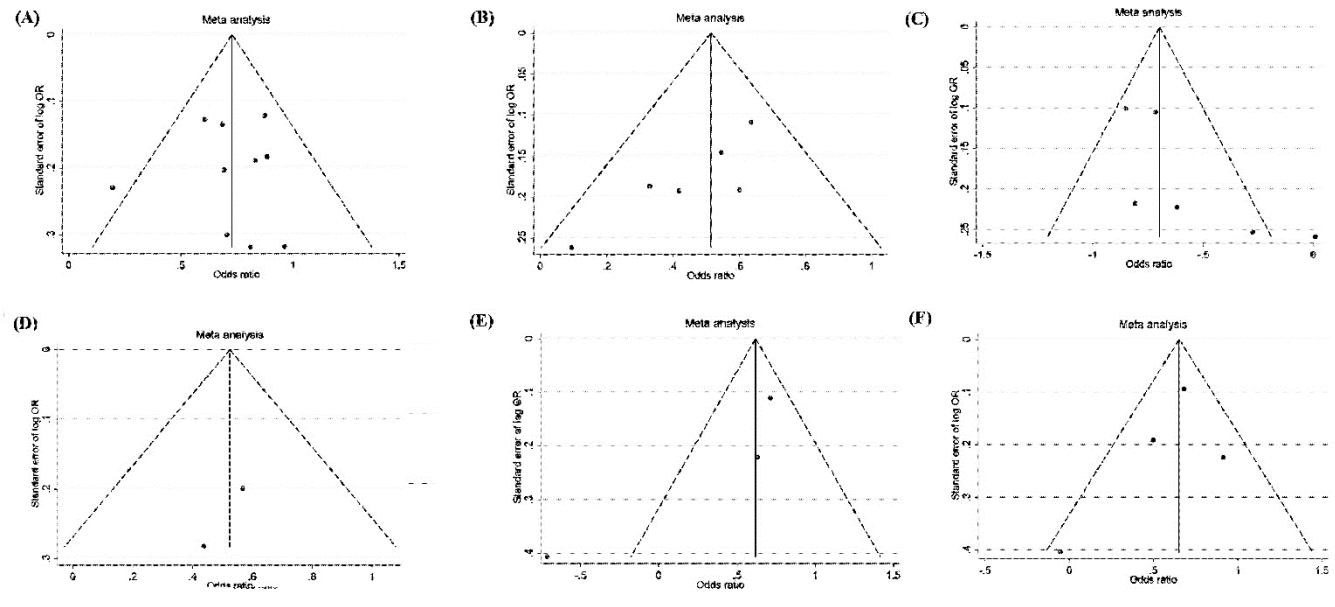

Fig. 5 Begg's funnel plots on publication bias for studies investigating association between *ARID5B* polymorphisms and childhood B-ALL risk under dominant model. (A) rs10821936 (TC+CC vs. TT); (B) rs10994982 (GA+AA vs. GG); (C) rs7089424 (GT+GG vs. TT); (D) rs10821938 (AC+AA vs. CC); (E) rs10740055 (AC+CC vs. AA); (D); (F) rs7073837 (AC+AA vs. CC). Each point represents an independent study.

Publication bias

The publication bias was assessed by both Begg's funnel plot and Egger's test. As depicted in **Fig. 5**, Begg's funnel plot did not show significant asymmetry. Similarly, Egger's test demonstrated that there was no publication bias for the five *ARID5B* polymorphisms (**Table 2**, $p > 0.01$). For the rs10821938, the *p*-value was not able to be determined (only 2 studies were involved). Taken together, the results indicated the absence of publication bias for studies included in this meta-analysis.

Table 2. Summary of the Egger's test for ARID5B polymorphism.

ARID5B Polymorphism	Egger's test (*p*-value)
rs10821936	0.88
rs10994982	0.031
rs7089424	0.091
rs10740055	0.314
rs7073837	0.497

DISCUSSION

In the past decades, many moderate-penetrance genes which conferred increased risk to childhood ALL have been identified [46]. Among these genes, *ARID5B* appeared as one of the most promising candidate's susceptibility markers, and the risk effects of numerous *ARID5B* polymorphisms in childhood ALL have been investigated across different populations [46]. Globally, B-ALL accounts for nearly 80% of childhood leukemia [1], and screening of children with a higher risk of developing B-ALL is therefore important to improve the clinical management of the disease. In this meta-analysis, our primary aim was to evaluate the association of six reported *ARID5B* polymorphisms and their susceptibility to childhood B-ALL across different ethnicities.

To date, more than 15 *ARID5B* polymorphisms have been reported to be associated with childhood ALL risk. Based on the 15 eligible case-control studies, a total of 6 *ARID5B* polymorphisms (i.e. rs10821936, rs10994982, rs7089424, rs10821938, rs10740055, rs7073837) which have been reported in at least 2/15 eligible studies were included in this meta-analysis. Our meta-analysis suggested that four *ARID5B* polymorphisms, i.e. rs10821936, rs10994982, rs7089424 and rs10821938 could serve as promising genetic susceptibility markers for screening childhood B-ALL across different ethnicities, including Caucasians (rs10821936, rs10994982, rs7089424, rs10821938), Asians (rs10821936, rs7089424, rs10821938), Blacks (rs10821936), and Mixed population (rs10821936, rs10994982). However, the usefulness of these four markers in other ethnic groups requires further investigation. Ethnicity-based subgroup analysis found that the racial disparity was evident for the dominant model of rs10740055 and rs7073837, in which Caucasians were shown to have a higher risk to childhood B-ALL whereas the Asians were shown to be protected. Considering that studies on non-Caucasians were few and the number of cases and controls was relatively small, additional replication studies are required to confirm their risk effects.

The study by Studd et al. (2016) [47] reported that ALL patients who harbored the *ARID5B* risk allele in rs7090445 (C is the risk allele) and rs7896246 (A is the risk allele) showed reduced ARID5B expression as compared to those harboring the wildtype allele, and this may have contributed to the leukemogenesis. Moreover, other than childhood leukemia, the loss of *ARID5B* function has been documented in endometrial cancer and the truncated ARID5B protein inhibited the normal function of wildtype ARID5B in the cancer cells [48]. Hence, it is of great interest to investigate the correlation of *ARID5B* risk alleles and their expression values in childhood B-ALL and to further dissect the roles of ARID5B in driving leukemogenesis.

CONCLUSION

In summary, this meta-analysis has re-evaluated the association of six *ARID5B* polymorphisms (rs10821936, rs10994982, rs7089424, rs10821938, rs10740055, rs7073837) and childhood B-ALL risk. Our meta-analysis demonstrated that rs10821936, rs10994982, rs7089424, and rs10821938 could serve as promising markers for assessing the susceptibility risk to childhood B-ALL in both the Asian and Caucasian populations. The usefulness of these four markers in screening other ethnic groups warrants further investigation. As genetic testing is increasingly being used for guiding clinical decisions, the development of a multigene panel inclusive of *ARID5B* is desirable for screening children with a higher risk of developing B-ALL and to improve clinical management of the disease.

ACKNOWLEDGEMENT

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ABBREVIATIONS

B-ALL, Acute B-lymphoblastic leukemia; Genome-wide association studies, GWAS; *ARID5B*, AT-rich interactive domain 5B; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; CI, confidence interval

CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

AUTHOR CONTRIBUTIONS

CYP and NA performed the literature search, data extraction, and statistical analysis. CYP, NA, and NAJ wrote the manuscript; CYP and NAJ critically reviewed the manuscript. NAJ did the final editing, formatting, and submission.

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