RESEARCH ARTICLE

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Association of Two *ARID5B* Gene Variant Single Nucleotide Polymorphisms with Acute Lymphoblastic Leukemia in the Egyptian Population

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Abstract

Background: ARID5B SNPs have been linked to ALL in many research studies in which it was identified as a risk factor. From this context, we had great interest to investigate the relationship between ARID5B rs4948488 and ARID5B rs2893881 genotypes and ALL susceptibility and relapse in this study. **Materials and Methods:** Peripheral blood mononuclear cells were analyzed for ARID5B rs4948488 and rs2893881 gene polymorphisms by real-time quantitative polymerase chain reaction in 80 ALL patients and 80 controls. **Results:** Our results showed that the C/C genotype of ARID5B rs4948488 and A/G genotype and G-allele of rs2893881 were linked to higher ALL incidence. Regarding the relapse of ALL, rs4948488 C/C genotype and C-alleles were significantly associated with relapse of ALL. Meanwhile, rs4948488 C/C genotype and rs2893881 A/A genotype and A-allele are associated with T-ALL, while rs2893881 A/G genotype and G-allele are associated with B-ALL. **Conclusion:** The results of our study suggested that ARID5B rs4948488 and rs2893881 SNPs might be used risk factors for genetic susceptibility for B-ALL and T-ALL, and that ARID5B s4948488 is related to relapse in ALL patients.

Keywords: Acute lymphoblastic leukemia- SNPs- ARID5B- genotyping

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Introduction

Acute lymphoblastic leukemia (ALL) is an uncontrolled malignant proliferation of clonal lymphoid progenitors in the bone marrow, peripheral blood and other hemopoietic organs as liver and spleen. The ALL is characterized by genetic aberrations involved in differentiation and proliferation of lymphoid progenitor cells (Aref et al., 2021). In adults, 75% of ALL cases originate from B-cell precursors while 25% from T-cell precursors (Terwilliger and Abdul-Hay, 2017). The differentiation process of lymphocytes from pluripotent progenitor hematopoietic stem cells located in the bone marrow is activated by transcription factors and functional signal transduction (Aref et al., 2021). ALL is considered a group of B/T-precursor lymphoid cancer cells that block differentiation and stimulate abnormal cell proliferation and survival (Zhou et al., 2012). ALL usually appears as a de novo malignancy. Genetic alterations are highly specific in ALL but are not the only risk factor to cause leukemia, for example, t (12; 21), t (1;19) and t (9;22) [Philadelphia chromosome] (Mullighan et al., 2009). The ALL etiology is assumed to be multifactorial and is the result of interplay between environmental and genetic variables (Tao et al., 2019). Interestingly, the exact cause of the disease is still unclear.

Genome-wide association studies (GWAS) identified common single-nucleotide polymorphisms (SNPs), including ARIDB5 gene SNPs, that are specifically correlated with ALL susceptibility (Papaemmanuil et al., 2009; Treviño et al., 2009). ARID5B gene, a member of the AT-rich interaction domain (ARID) family of transcription factors, are located on chromosome 10q21.2, plays an essential role in embryonic development, cell growth, and differentiation through inhibiting the expression of specific genes through tissue specificity (Huang et al., 1996; Wilsker et al., 2002). ARID5B gene mainly acts as a transcriptional modulator affecting expression of target genes by attracting PHF2, the catalyst for histone demethylation (Wang et al., 2020). Several allele polymorphisms, localised in intron 3 of the ARIDB gene, such as rs10824936, rs10994982, rs7089424, rs7073837, and rs10740055 and rs10994982, have been found as possible risk factors for childhood ALL (Papaemmanuil et al., 2009; Treviño et al., 2009; Linabery et al., 2013; Wang et al., 2013; Lin et al., 2014). Other SNPs located in intron 2 of the ARID5B gene, including rs4948488 and rs2893881, and rs6479778) were significantly associated with pediatric ALL relapse rate (Xu et al., 2012). One metanalysis revealed that ARID5B SNPs rs10994982

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was significantly linked to the risk of B-hyperdiploid ALL development (Yang et al., 2019). Despite our inherited genetic polymorphisms remain unchanged throughout life, it is assumed that the impact of these inherited variants change as we get older, hence, leading to age-related differences in ALL development (Perez-Andreu et al., 2015).

The exact role of these ARIDB SNPs in the etiology of ALL remains unknown, and several studies have assessed the relationships between *ARID5B* gene polymorphisms and the risk of childhood ALL. Some of these studies have shown that ARID5B SNPs such as rs10824936, rs10994982, rs7089424, rs7073837, and rs10740055 were significantly related to the risk of development of childhood ALL in Caucasian populations (Papaemmanuil et al., 2009; Treviño et al., 2009; Healy et al., 2010; Prasad et al., 2010; Pastorczak et al., 2011; Chokkalingam et al., 2013). Interestingly, differences in the frequencies of the risk alleles among Caucasian, African, Asian, and Hispanic populations have been found, with Hispanic populations showing the highest risk (Al-Absi et al., 2017; Archer et al., 2017; Kreile et al., 2018; Urayama et al., 2018).

Until now, the pathogenesis of how these ARID5B genetic variants predispose to ALL is not well understood. Therefore, extensive research is highly required to detect the underlying mechanisms and confirm the diagnostic ability and therapeutic importance of ARID5B in ALL.

As these genetic variant alleles related to ALL risk have not been comprehensively examined in the adult population and as SNPs in ARID5B were never studied for the possibility of being linked to ALL in the Egyptian populations, we decided to conduct this case–control study to validate the relationship between ARID5B SNPs rs4948488, rs2893881 and the risk of ALL in the Egyptian adult population.

Materials and Methods

Study Subjects

The study was conducted on 80 patients previously diagnosed with ALL and 80 control subjects of matched age and sex. The patients were recruited from the Hematology department of Alexandria University Hospitals from April 2019 to December 2020. The control subjects were patients suffering from hypersplenism, iron deficiency anemia and primary immune thrombocytopenia. The sample size was calculated using the G power version 3.1 statistical software program with 0.05 level of significance and 80% power of the study. All study subjects signed a written informed consent showing the nature and goal of the study in details. The study was approved by the authorization of the Medical Ethics Committee of Alexandria Faculty of Medicine.

ALL patients were diagnosed by morphology, immunophenotyping, cytogenetic analysis and molecular biology testing. The clinical risk classification was determined based on the NCCN guidelines (Alvarnas et al., 2015).

Genomic DNA extraction

Genomic DNA extraction was extracted adapting the protocol provided by the manufacturer from EDTA whole blood using QIAamp DNA Blood Mini Extraction Kit (QIAGEN, USA). The amount and purity of the extracted nucleic acids were confirmed using Nanodrop 2000 spectrophotometer (NanoDrop Techchnologies). A 260/280 ratio of 1.7 up to 2.0 indicated high quality DNA.

PCR amplification

ARID5B gene SNPs rs4948488 and rs2893881 were carried out on STRATAGENE real-time PCR system using TaqMan platform (Applied Biosystems, USA). The PCR reaction mix included 12.5 uL Taqman Universal PCR mix, 0.5 uL Taqman SNP Genotyping Assay x20, 2 uL extracted DNA and DNase free water to a final volume of 20 uL. The PCR reaction used the Taqman alleleic discrimination system (Drug metabolism Genotyping asays, Applied Biosystems, ID C_26140121_10 for rs4948488, ID C_1730543_10 for rs2893881, Foster City, CA). The thermal cycling program was carried out as follows: initial denaturation step at 94^{o}C for 15 minutes followed by 45 cycles of denaturation at 94^{o}C for 20 seconds, 56^{o}C for 30 seconds, and 72^{o}C for one minute, and a final extension step at 72^{o}C for 3 minutes.

Statistical Analysis

SPSS software version 22 was used for statistical analysis of collected data. χ^2 test was used to determine the Hardy–Weinberg equilibrium for each SNP. Chi-square test was also used to test for allele frequencies and genotype distributions of the SNPs to compare between patients and controls. Quantitative data were presented as mean and standard deviation (SD) or median (minimum–maximum). Unpaired Student's t-test was used to compare between two groups of numerical normal distribution data. Mann-Whitney test was used to test for difference between 2 groups. In addition, the odds ratios (OR) and 95% CI were obtained by using Logistic regression analysis. P values less than 0.05 were considered statistically significant.

Results

Demographic and Clinicopathologic data of study participants

In this study, ALL patients group included 54 (67.5%) men and 26 (32.5%) women, with mean age of 51.1±19.2 years. The control group included 63 (78.8%) men and 17 (21.3%) women, with mean age of 57.6±6.9 years. There was not any statistical significance between both groups in sex (p=0.108) and age (0.072). The characteristics of the study participants are summarized in Table 1.

On the other hand, Table 1 shows that hemoglobin level, WBC count and platelets count are statistically significant between the CLL patients and the controls (p<0.001).

Table 2 presents the clinicopathologic data of CLL patients. There was not statistical significance between both groups regarding blasts in PB or BM, organomegaly,

Table 1. Comparison between the Two Studied Groups According to Demographic Data and Laboratory Investigations

	Patients (n = 80)	Control (n = 80)	p
Age (years)			
Mean ± SD.	51.1 ± 19.2	57.6 ± 6.9	0.072
Median (Min. – Max.)	56 (16 – 89)	57 (38 – 74)	
Gender			
Male	54 (67.5%)	63 (78.8%)	0.108
Female	26 (32.5%)	17 (21.3%)	
Hb (mg/dl)			
Mean ± SD.	10.2 ± 2.2	14.1 ± 1.1	<0.001*
Median (Min. – Max.)	10.8 (5 – 13.1)	14.5 (12.1 – 15.9)	
WBCs ($\times 10^3$/ul)			
Mean ± SD.	5.2 ± 2.4	6.7 ± 1.8	<0.001*
Median (Min. – Max.)	5.2 (1.5 – 15)	6.4 (4.3 – 10.2)	
PLT ($\times 10^6$/ul)			
Mean ± SD.	133.2 ± 51.1	229.2 ± 48.4	<0.001*
Median (Min. – Max.)	120 (30 – 260)	241 (126 – 368)	

SD, Standard deviation; U, Mann Whitney test; χ^2, Chi square test; p, p value for comparing between the studied groups; *, Statistically significant at $p \leq 0.05$

Table 2. Comparison between B-ALL and T-ALL According to Different Parameters in Patients Group (n = 80)

	Total (n = 80)	B-ALL (n = 50)	T-ALL (n = 30)	p
Age (years)				
Mean ± SD.	51.1 ± 19.2	51.3 ± 18.9	50.8 ± 20	0.735
Median (Min. – Max.)	56 (16 – 89)	56 (16 – 89)	52.5 (19 – 89)	
Gender (%)				
Male	54 (67.5)	33 (66)	21 (70)	0.712
Female	26 (32.5)	17 (34)	9 (30)	
Blast PB				
Mean ± SD.	5.3 ± 19.3	4.7 ± 17.5	6.2 ± 22.3	0.306
Median (Min. – Max.)	0 (0 – 88)	0 (0 – 88)	0 (0 – 88)	
Blast BM				
Mean ± SD.	13.8 ± 26.9	9.7 ± 19.6	20.6 ± 35.3	0.187
Median (Min. – Max.)	4 (1 – 93)	5 (1 – 88)	3 (1 – 93)	
Organomegaly	23 (28.8)	13 (26)	10 (33.3)	0.483
Relapse (%)				
NCR	24 (30)	14 (28)	10 (33.3)	0.614
CR	56 (70)	36 (72)	20 (66.7)	
Overall survival (%)				
Alive	52 (65)	30 (60)	22 (73.3)	0.226
Died	28 (35)	20 (40)	8 (26.7)	
Cytogenetic (%)				
Ph-	49 (61.3)	30 (60)	19 (63.3)	0.767
Ph+	31 (38.8)	20 (40)	11 (36.7)	
Flow (%)				
Negative	50 (62.5)	30 (60)	20 (66.7)	0.551
Positive	30 (37.5)	20 (40)	10 (33.3)	

SD, Standard deviation; U, Mann Whitney test; χ^2, Chi square test; MC, Monte Carlo; p, p value for comparing between B-ALL and T-ALL

Table 3. Comparison between the Two Studied Groups According to rs4948488 and rs2893881

SNP ID		Patients (n = 80)	Control (n = 80)	p	OR (LL – UL 95%C.I)
rs4948488	Genotype				
	T/T®	32 (40)	36 (45)		1
	T/C	31 (38.8)	37 (46.3)	0.863	0.943 (0.480 – 1.850)
	C/C	17 (21.3)	7 (8.8)	0.049*	2.732 (1.004 – 7.432)
	$^{HW}\chi^2$ (p)	3.097 (0.078)	0.337 (0.561)		
	T/C + C/C	48 (60)	44 (55)	0.523	1.227 (0.655 – 2.299)
	Allele frequency				
	T®	95 (59.4)	109 (68.1)		1
	C	65 (40.6)	51 (31.9)	0.104	1.462 (0.925 – 2.313)
rs2893881	Genotype				
	A/A®	43 (53.8)	77 (96.3)		1
	A/G	35 (43.8)	3 (3.8)	<0.001*	20.891 (6.066 – 71.956)
	G/G	2 (2.5)	0 (0)	0.999	–
	$^{HW}\chi^2$ (p)	2.788 (0.095)	0.029 (0.864)		
	A/G + G/G	37 (46.3)	3 (3.8)	<0.001*	22.085 (6.428 – 75.886)
	Allele frequency				
	A®	121 (75.6)	157 (98.1)		1
	G	39 (24.4)	3 (1.9)	<0.001*	16.868 (5.091 – 55.891)

OR, Odds ratio; ®, reference group; CI, Confidence interval, LL, Lower limit; UL, Upper Limit; p, p value for Univariate regression analysis; *, Statistically significant at $p \leq 0.05$; $^{HW}\chi^2$, Chi square for goodness of fit for Hardy-Weinberg equilibrium (If $P < 0.05$ - not consistent with HWE.)

Table 4. Relation between Relapse with SNPs in Patients Group (n = 80)

		NCR (n = 24) (%)	CR (n = 56) (%)	p
rs4948488	Genotype			
	TT	1 (4.2)	31 (55.4)	<0.001*
	TC	11 (45.8)	20 (35.7)	0.395
	CC	12 (50)	5 (8.9)	<0.001*
	T/C + C/C	23 (95.8)	25 (44.6)	<0.001*
	Allele frequency			
	T	13 (27.1)	82 (73.2)	<0.001*
	C	35 (72.9)	30 (26.8)	
rs2893881	Genotype			
	A/A	13 (54.2)	30 (53.6)	0.961
	A/G	11 (45.8)	24 (42.9)	0.806
	G/G	0 (0)	2 (3.6)	FEp=1.000
	A/G + G/G	11 (45.8)	26 (46.4)	0.961
	Allele frequency			
	A	37 (77.1)	84 (75)	0.779
	G	11 (22.9)	28 (25)	

χ^2, Chi square test; p, p value for comparing between NCR and CR; *, Statistically significant at $p \leq 0.05$

cytogenetic abnormalities or flow cytometry analysis.

ARID5B rs4948488 SNPs Genotyping and ALL

A total number of 80 adult patients with ALL and 80 normal controls were analysed for the presence of ARID5B rs4948488 SNPs polymorphisms. The genotype and allele frequencies for both patients and controls are listed in Table 3. Among the patients group, 40% showed T/T genotype, 38.8% showed T/C genotype and 21.3% showed C/C genotype. Whereas among controls, 45% showed T/T genotype, 46.3% showed T/C genotype and 8.8% showed C/C genotype.

Overall, comparative analysis revealed that rs4948488 (C/C) genotype was significantly higher among ALL

Table 5. Comparison between the Different Studied Groups According SNPs

		B-ALL (n = 50) (%)	T-ALL (n = 30) (%)	Control (n = 80) (%)	p_1	p_2
rs4948488	Genotype					
	TT	18 (36)	14 (46.7)	36 (45)	0.311	0.876
	TC	23 (46)	8 (26.7)	37 (46.3)	0.978	0.063
	CC	9 (18)	8 (26.7)	7 (8.8)	0.118	^{FE}p=0.026*
	T/C + C/C	32 (64.0)	16 (53.3)	44 (55)	0.311	0.876
	Allele frequency					
	T	59 (59)	36 (60)	109 (68.1)	0.134	0.258
	C	41 (41)	24 (40)	51 (31.9)		
rs2893881	Genotype					
	A/A	24 (48)	19 (63.3)	77 (96.3)	<0.001*	^{FE}p<0.001*
	A/G	24 (48)	11 (36.7)	3 (3.8)	<0.001*	^{FE}p<0.001*
	G/G	2 (4)	0 (0)	0 (0)	^{FE}p=0.146	–
	A/G + G/G	26 (52)	11 (36.7)	3 (3.8)	<0.001*	^{FE}p<0.001*
	Allele frequency					
	A	72 (72)	49 (81.7)	157 (98.1)	<0.001*	^{FE}p
	G	28 (28)	11 (18.3)	3 (1.9)		<0.001*

FE, Fisher Exact; p_1, p value for Chi square test for comparing between B-ALL and Control; p_2, p value for Chi square test for comparing between T-ALL and Control; *, Statistically significant at $p \leq 0.05$

cases compared with controls (p=0.049). On the other hand, ARID5B rs4948488 (T/T) and (T/C) genotypes and rs4948488 T and C alleles prevalence were statistically insignificant between both groups (Table 3). Therefore, analysing the data using Odd's ratio revealed that the risk of developing ALL was significantly associated with rs4948488 (C/C) genotype (OR=2.732, 95% CI: 1.004-7.432, p=0.049), but was not proved to be associated with rs4948488 (T/T) and (T/C) genotypes and rs4948488 T and C alleles.

Meanwhile, Table 4 shows that rs4948488 (C/C) genotypes and rs4948488 C-allelle were statistically significant with relapse frequency in ALL. Table 5 shows that rs4948488 (C/C) genotype has statistical significance between patients with T-ALL and controls.

ARID5B rs2893881 SNPs Genotyping and ALL

A total number of 80 adult patients with ALL and 80 normal controls were analysed for the presence of ARID5B rs2893881 SNP polymorphisms. The genotype and allele frequencies for both patients and controls are listed in Table 3.

Among the patients group, 53.8% showed A/A genotype, 43.8% showed A/G genotype and 2.5% showed G/G genotype. Whereas among controls, 96.3% showed A/A genotype, 3.8% showed A/G genotype and 0% showed G/G genotype.

Overall, comparative analysis revealed that rs2893881 (A/G) genotype and rs2893881 G allele were significantly higher among ALL cases compared with controls (p<0.001). On the other hand, ARID5B rs2893881 (A/A) and (G/G) genotypes and rs2893881 A allele prevalence were statistically insignificant between both groups (Table 3).

Therefore, analyzing the data using Odd's ratio revealed that the risk of developing ALL was significantly associated with rs2893881 (A/G) genotype and rs2893881 G allele (OR=20.891, 95% CI: 6.066-71.956, p<0.001 for A/G and OR=16.868, 95% CI: 5.091-55.891, p<0.001 for G allele), but was not proved to be associated with rs2893881 (A/A) and (G/G) genotypes and rs2893881 A allele. Meanwhile, table 4 shows that rs2893881 genotypes and alleles were statistically insignificant with relapse frequency in ALL.

Table 5 shows that rs2893881 (A/A) and the A allele have statistical significance with T-ALL, while rs2893881 G/G genotype and G-allele are statistically associated with B-ALL (p<0.001).

Discussion

ARID5B has been linked to ALL in many research studies in which it was identified as a risk factor (Papaemmanuil et al., 2009; Treviño et al., 2009). In spite of this, the exact role of ARID5B genetic polymorphisms on haemopoiesis is still unknown.

In our current case-control study, we examined the relationship between ARID5B rs4948488 and ARID5B rs2893881 genotypes and ALL susceptibility and relapse. We found out that the C/C genotype of ARID5B rs4948488 were linked to higher ALL incidence. Similarly, rs2893881 A/G genotype and G- allele were associated with higher susceptibility to ALL. Regarding the relapse of ALL, rs4948488 C/C genotype and C-alleles were significantly associated with relapse of ALL. Meanwhile, rs4948488 C/C genotype and rs2893881 A/A genotype and A-allele are associated with T-ALL, while rs2893881 A/G genotype and G-allele are associated with B-ALL.

In a previous study, they reported the association between rs2393782 and rs4948488 with the risk to

childhood B-ALL (Reyes-León et al., 2019). Previous research studies showed that ARID5B rs7089424 and rs10994982 were associated with the risk of B-ALL development (Zeng et al., 2014). This might be explained by the role of recombination activation gene (RAG1) in early B-cell differentiation (Tao et al., 2019). Moreover, it was reported that ARID5B expression was linked to RAG1 expression in bone marrow explaining how it might be associated with B-ALL pathogenesis (Jensen et al., 2010).

The association of ARID5B rs4948488 and rs2893881 with B-ALL were not conclusive in previous research. For example, the study carried out on children showed that rs10994982 and rs10740055 and rs7073837 were considered as ALL risk factors (Al-Absi et al., 2017). Another study on Korean people showed that ARID5B rs7089426 was associated with pediatric ALL risk (Han et al., 2010). On the other hand, a study conducted in Thailand showed no significant relationship between ARID5B rs7089424 and B-ALL (Vijayakrishnan et al., 2010). Similarly, ARID5B rs7089424 was reported as having no statistical association with ALL in China (Lin et al., 2014).

There is no solid evidence of the pathogenesis behind these SNPs and development of ALL. Recently, rs7090445 was said to be a risk factor for ALL through lowering ARID5B expression (Lee et al., 2015; Studd et al., 2017; Ge et al., 2018). But, in order to apply this mechanism on others allele SNPs, we do recommend an expression analysis PCR tests on our patients.

Our study showed that rs4948488 C/C genotype had statistical significance with T-ALL, while rs2893881 A/A, A/G and A and G alleles showed statistical significance with both B- and T-ALL. However, the number of T-ALL patients was small. On the contrary, a previous study did not find any association between SNPs of ARID5B and T-ALL susceptibility (Papaemmanuil et al., 2009; Treviño et al., 2009; Linabery et al., 2013; Wang et al., 2013).

The main causes behind these results discrepancy are probably due to inaccurate size of the subjects sample, the selection characteristics of the research subjects, the techniques used to diagnose polymorphisms and the statistical methods used.

In conclusion, the results of our study suggested that ARID5B rs4948488 and rs2893881 SNPs might be used risk factors for genetic susceptibility for B-ALL and T-ALL, and that ARID5B s4948488 is related to relapse in ALL patients.

Several limitations of our study should be mentioned. The relatively small sample size and the detection of genotypes by allelic discrimination PCR only at the baseline level without follow up after treatment are the main limitations. Therefore, we do recommend further studies to be carried out on larger sample size and with following up the patients for a specific time period to detect any changes over time to confirm and validate our results. We do also recommend to use gene sequencing methodologies and include other immunologic genes to clarify the genetic risk factors for ALL more precisely.

Author Contribution Statement

MG and SI contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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Availability of data

Availability of data and material The data that support the findings of this study are available from the corresponding author upon request.

Ethics approval

The study was conducted after approval of the Medical Ethics Committee of Alexandria Faculty of Medicine.

Consent to participate

All study participants gave written informed consents after explaining the nature, steps and aim of the study.

Consent for publication

The Authors grant the Publisher permission to publish this work.

Conflicts of interest

Authors declare no conflict of interest.

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