Cancer Research Journal
2023; 11(4): 142-155
http://www.sciencepublishinggroup.com/j/crj
doi: 10.11648/j.crj.20231104.14
ISSN: 2330-8192 (Print); ISSN: 2330-8214 (Online)

GATA3 rs3824662, *IKZF1* (rs4132601& rs11978267), and *ARID5B* (rs10821936 & rs10994982) Gene Polymorphisms in Egyptian Adult Patients with Acute Leukemia

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To cite this article:

Samy Mohammed Attallah, Youssef Mohammed Mosaad, Mona Mohamed. Taalab, Noha Nasser Eisa, Amal Mahmoud Hammad et al. (2023). *GATA3* rs3824662, *IKZF1* (rs4132601& rs11978267), and *ARID5B* (rs10821936 & rs10994982) Gene Polymorphisms in Egyptian Adult Patients with Acute Leukemia. *Cancer Research Journal*, *11*(4), 142-155. https://doi.org/10.11648/j.crj.20231104.14

Received: October 27, 2023; **Accepted**: November 21, 2023; **Published**: December 8, 2023

Abstract: *GATA3, IKZF1, and ARID5B* polymorphisms are validated risks of pediatric acute lymphoblastic leukemia (ALL) in numerous ethnicities, whilst, their role in adult patients with acute leukemia is less well defined. *Objective:* The study aims to investigate the association between the GATA3 rs3824662, IKZF1 (rs4132601& rs11978267), and ARID5B (rs10821936 & rs10994982) and the susceptibility to adult acute leukemia, as well as their impact on the treatment outcome. *Methods:* Real-time PCR was performed for the 5 SNPs in 91 patients (53 ALL and 38 AML) and 194 healthy controls. *Results:* IKZF1 rs4132601 G allele, G/G and G/T genotypes, as well as G/A haplotype of IKZF1 rs4132601/rs11978267 were significantly higher in ALL vs. healthy controls (p-values were <0.001, 0.001, 0.012, and 0.036, respectively) and in AML vs. healthy controls (p-values were <0.001, 0.001, 0.001, and 0.005, respectively). ARID5B rs10821936 C allele, C/C and C/T genotypes, as well as C/A haplotype of rs10821936/rs10994982 were significantly higher in ALL vs. healthy controls (p-values were <0.001, <0.001, 0.005, and 0.036, respectively), and only C allele and C/C genotype in AML vs. healthy controls (p-values were 0.002 and 0.017, respectively). Shorter Overall Survival (p = 0.003) and lack of remission (p=0.041) were significantly higher in ALL patients harboring IKZF1 rs4132601 G/G genotype. *Conclusion:* IKZF1 rs4132601 and ARID5B rs10821936 are potential risky SNPs for the development of acute leukemia in Egyptian adults. Furthermore, ALL patients with the IKZF1 rs4132601 GG genotype are probably more prone to poor outcome.

Keywords: *GATA3* rs3824662, *IKZF1* rs4132601, *IKZF1*rs11978267, *ARID5B* rs10821936, *ARID5B* rs10994982, ALL, AML

1. Introduction

Acute leukemias (AL) are a diverse group of genetic hematologic disorders. They include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and Acute leukemia of mixed or ambiguous lineage, by the revised classification of the World Health Organization (WHO) [1, 2]. This classification was based on immunophenotypic, cytogenetic, and molecular genetic findings. For proper diagnosis, prognosis, and evaluation of therapy, acute leukemia patients require pivotal clinical, morphologic, Immunophenotyping, karyotyping, fluorescence in situ hybridization, and molecular genetic testing [2, 3].

Adult ALL differs from pediatric ALL with regard to the incidence, frequency, molecular, and cytogenetic abnormalities. Adult ALL arises from multipotent stem cells and shows variation in the incidence in different populations [4, 5]. AML is characterized by impaired myeloid differentiation, diverse clinical presentations, different morphology, immunophenotypes, and genetic abnormalities [6]. Although, Genome wide association studies (GWAS) have linked between pediatric ALL and polymorphic variants in many genes such as *GATA3, IKZF1* and *ARID5B* [7], however, no genetic predisposition could be detected in most patients [8].

The pediatric ALL susceptibility risk and poor outcome in different ethnicities has been linked to Single Nucleotide Polymorphisms (SNPs) in GATA3 rs3824662 [9-12], *ARID5B (*rs7073837, rs10740055, rs7089424, rs10821936, and rs10994982 [13-18], and *IKZF1* (rs6964823, rs4132601, rs6944602, and rs11978267) [19-21]. Alongside these results, the heterogeneity of acute leukemias owing to variation in incidence, ethnicity, environmental factors, and cytogenetic derangement makes it rational to study the effects of *GATA3*, *IKZF1*, and *ARID5B* genes polymorphism in adult acute leukemia as has been extensively studied in pediatric patients [22-25].

The present retrospective study aims to investigate the association of GATA3 rs3824662, IKZF1 (rs4132601& rs11978267), and ARID5B (rs10821936 & rs10994982) SNPs in adult Egyptian patients with ALL and AML as well as their impact on treatment outcome.

2. Patients and Methods

2.1. Patients and Healthy Controls

Two groups were included in the current work: the acute leukemias group and the healthy controls. The acute leukemias group included 91 adult patients; 53 ALL (36 males & 17 females) and 38 AML (20 males & 18 females). ALL and AML adult cases were recruited from patients who attended the hematology oncology clinic in the Oncology Center, Mansoura University (OCMU) between May 2011 and June 2015. The inclusion criteria were newly diagnosed denovo acute leukemia cases. Patients with acute promyelocytic leukemia, previous exposure to chemotherapy or radiotherapy, and those with prior hematologic neoplastic disorders were excluded from the study.

Informed consent was obtained from the patients for participation in the study. The Mansoura University IRB approved the present work (R. 22.04.1698).

Diagnosis of acute leukemia is made up of morphology, cytochemistry, and Immunophenotyping (CD34, CD117, CD33, CD13, HLA-DR, CD65, cytoplasmic MPO, CD14, CD36, CD64, CD41, CD61, CD235a, CD36, TdT, CD3, CD5, CD7, CD2, CD4, CD8, CD10, CD19, CD20, CD22, and CD79a). The patients' clinical, and laboratory data were obtained from the electronic database of the Oncology Center, Mansoura University. The study included 194 healthy controls recruited from blood bank donors.

Typing of *GATA3* rs3824662, *IKZF1* (rs4132601& rs11978267), and *ARID5B* (rs10821936 & rs10994982) SNPs.

Gene Jet DNA purification kit (Thermo Scientific, lot 00138029, Lithuania, EU) was used for DNA extraction. TaqMan® SNP Genotyping Assays (Applied Biosystem, USA) were used to genotype the samples. *GATA3* rs3824662 ID is C__27522049_10 and the VIC for A allele (AGGAAGGCGCCTTTGCATGCACTG) and Fam for C allele (AGC GTGTTTGTGTTTAATCTCAGGG) were used for typing. The *IKZF1* rs4132601 G allele (TGCAATCACAGAGAAAGATGCGCCT) and T allele (ATCCAAGTTAATATCTCTAA GGTGA). *IKZF1* rs11978267 A allele (GGGAAGGAATTATCCATGCAATCAC) and G allele (CATAAACTTCTACCTACCCTCCCCT). The *ARID5B* rs10821936 C allele (TCT GTGTGCAGTTACTATAGTTGTA), and T allele (CTAGTGTTTCAAGGCACCGGGGAA). *ARID5B* rs10994982 A allele (CTTTTAAATATCTTTTGAGAATGCA) and G allele (CACTGACTCTGTACCTCAGATGTGC). Applied Biosystems software (version 1.7, Foster, USA) was used for allele and genotype identification.

2.2. Statistical Analysis

Revision, coding, and tabulation of data were done by the Statistical Package for Social Science (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, and Version 25.0. Armonk, NY: IBM Corp.). Non-numerical data was presented as frequency and percentage. The normality of data distribution was checked using the Kolmogorov-Smirnov test. Chi-square test was used to test for Hardy–Weinberg equilibrium expectations. Prediction of risk association was done by logistic regression analysis using generalized linear models. Calculation of the Odds ratio and 95% confidence interval were done. Estimation of haplotypes was done using the HaploView program (version 4.2) [26]. Survival analysis was estimated by the Kaplan–Meier test and the Log-Rank test was used to determine the statistical significance of differences among curves. A significant P value was determined if the value was less than 0.05 at a confidence interval of 95%.

3. Results

The demographic, laboratory, and treatment characteristics of adult ALL and AML patients were shown in Table 1. In regard to AML patients, complete remission (CR) has been achieved in 26 cases (68.4%), all of them aged less than 65 years, and absence of CR was reported in 12 cases (6 cases were less than 65 years and 6 cases were older than 65 years). Concerning ALL patients, CR has been achieved in 30 cases (56.6%), all of them aged less than 65 years, and absence of CR was found in 23 cases (11 cases were less than 65 years and 12 cases were older than 65 years).

Table 1. *Patients' baseline demographic and disease characteristics.*

	Adult ALL		**Adult AML**
	(N=53)		**(N=38)**
Age at diagnosis (years); mean ± SD (min, max)	37.1±12.3(19,76)		44.5±11.5(3,76)
Male; n (%)	36 (67.9)		20 (52.6)
Female; n (%)	17 (32.1)		18 (47.4)
Laboratory data; median (range)			
Total leucocytic count ($x10^9$/L)	43 (3-319)		22.9 (1.4-213)
Hemoglobin concentration (g/dL)	8.2 (4.8-16.5)		8.2 (4.5-101)
Platelet count ($x10^9$/L)	33 (2-241)		30 (2-270)
Peripheral blasts (%)	44 (12-78)		45.5 (12-85)
Marrow blasts (%)	67 (23-95)		70 (25-0.95)
LDH (U/mL)	1032 (192-4274)		756 (192-2453)
FAB classification; n (%)			
L1	13 (24.5)	M0	2 (5.3)
L2	35 (66)	M1	5 (13.2)
L3	5 (9.4)	M2	7 (18.4)
		M4	13 (34.2)
		M5	7 (18.4)
		M6	3 (7.9)
		M7	1 (2.6)
Immunophenotype; n (%)			
B-ALL	46 (86.8)	cMPO	36 (94.7)
T-ALL	7 (13.2)	CD13	32 (84.2)
		CD33	35 (92.1)
		CD117	30 (78.9)
		HLA-DR	21 (55.3)
		CD34	19 (50)
		CD14	20 (52.6)
		CD11b	18 (47.4)
Treatment outcome; N (%)			
Complete remission (CR)	30 (56.6)		26 (68.4)
Induction death (ID)	12 (22.6)		6 (15.8)
Refractory disease (RD)	11 (20.8)		6 (15.8)
Relapse; N (%)	8 (26.7)		8 (30.8)
Survival times			
OS; cumulative survival (%)	46.6		34.4
Mean (months) (95% CI)	26.1 (20.4-31.8)		23.6 (17.7-29.5)
DFS; cumulative survival (%)	52.9		40.8
Mean (months) (95% CI)	31.4 (25.5-37.3)		25.1 (19.4-30.8)

Cumulative survival, cumulative proportion surviving at 48 months; relapse percentage is calculated out of those achieved complete remission.

The allele and genotype distribution of the five studied SNPs (*GATA3* rs3824662, *IKZF1* rs4132601, *IKZF1* rs11978267, *ARID5B* rs10821936 and *ARID5B* rs10994982) in adult Egyptian patients with AML (38 patients) and ALL (53 patients) were compared with their distribution in 194 age matched healthy controls. The frequencies of the G allele of the *IKZF1* rs4132601 were higher in patients with ALL ($p<0.001$, OR=1.67) and AML ($p<0.001$, OR=1.86). Furthermore, the *ARID5B* rs10821936 C allele was significantly presented in ALL ($p<0.001$, OR=1.61) and AML patients ($p=0.022$, OR=1.38). The allele distribution of *GATA3* rs3824662, *IKZF1* rs11978267, and *ARID5B* rs10994982 showed non-significant differences between acute leukemia patients and healthy controls as shown in Tables 2 and 3.

Table 2. *Comparison of GATA3 rs3824662, IKZF1 (rs4132601& rs11978267) and ARID5B (rs10821936 & rs10994982) alleles and genotypes in adult ALL patients versus healthy controls.*

	Healthy Controls (n=194)	**Adult ALL (n=53)**	***P value***	**OR(95% CI)**
	N (%)	**N (%)**		
GATA3 rs3824662				
CC	116 (59.8%)	29 (54.7%)		Reference
CA	64 (33%)	19 (35.8%)	0.607	1.188 (0.617-2.284)

	Healthy Controls (n=194)	Adult ALL (n=53)	*P value*	OR(95% CI)
	N (%)	N (%)		
AA	14 (7.2%)	5 (9.4%)	0.525	1.429 (0.476-4.288)
C	296 (76.3%)	77 (72.6%)		Reference
A	92 (23.7%)	29 (27.4%)	0.442	1.118 (0.842-1.485)
IKZF1 rs4132601				
TT	118 (60.8%)	19 (35.8%)		Reference
TG	66 (34%)	25 (47.2%)	0.012*	1.628 (1.114-2.38)
GG	10 (5.2%)	9 (17%)	0.001*	2.774 (1.49-5.165)
T	302 (77.8%)	63 (59.4%)		Reference
G	86 (22.2%)	43 (40.6%)	<0.001*	1.671 (1.275-2.189)
IKZF1 rs11978267				
AA	122 (62.9%)	38 (73.1%)		Reference
AG	59 (30.4%)	11 (21.2%)	0.167	0.747 (0.494-1.13)
GG	13 (6.7%)	4 (7.5%)	0.648	0.841 (0.401-1.767)
A	303 (78.1%)	87 (83.7%)		Reference
G	85 (21.9%)	17 (16.3%)	0.209	0.814 (0.591-1.122)
ARID5B rs10821936				
TT	86 (44.3%)	10 (18.9%)		Reference
TC	91 (46.9%)	31 (58.5%)	0.005*	1.816 (1.199-2.750)
CC	17 (8.8%)	12 (22.6%)	<0.001*	2.830 (1.599-5.009)
T	263 (67.8%)	51 (48.1%)		Reference
C	125 (32.2%)	55 (51.9%)	<0.001*	1.61 (1.249-2.075)
ARID5B rs10994982				
AA	53 (27.3%)	13 (24.5%)		Reference
AG	93 (47.9%)	25 (47.2%)	0.811	1.096 (0.518-2.321)
GG	48 (24.7%)	15 (28.3%)	0.572	1.274 (0.551-2.949)
A	199 (51.3%)	51 (48.1%)		Reference
G	189 (48.7%)	55 (51.9%)	0.562	1.076 (0.84-1.379)

*Significant (p <0.05).

On the other hand, significant associations were found between adult ALL and the GG and TG genotypes of *IKZF1* rs4132601 (p=0.001, OR=2.77, p=0.012, OR=1.62 respectively) and between adult ALL and the homozygous CC (p<0.001, OR=2.83) and the heterozygous TC (p=0.005, OR=1.81) of *ARID5B* rs10821936. At the same time, AML was associated with *IKZF1* rs4132601 GG genotype (p=0.001, OR=2.04), and TG genotype (p=0.001, OR=3.3). As regard, the *ARID5B* rs10821936, the association was found only with the homozygous CC genotype (p=0.017, OR=2.09). The genotype distribution of *GATA3* rs3824662, *IKZF1* rs11978267, and *ARID5B* rs10994982 showed no significant findings with either adult ALL or AML patients.

Table 3. *Comparison of genotypes and alleles of the studied SNPs in adult AML patients versus healthy controls.*

	Healthy Controls (n=194)	Adult AML (n=38)	*P* value	OR (95% CI)
	N (%)	N (%)		
GATA3 rs3824662				
CC	116 (59.8%)	21 (55.3%)		Reference
CA	64 (33%)	11 (28.9%)	0.897	0.972 (0.631-1.497)
AA	14 (7.2%)	6 (15.8%)	0.122	1.646 (0.875-3.094)
C	296 (76.3%)	53 (69.7%)		Reference
A	92 (23.7%)	23 (30.3%)	0.232	1.205 (0.887-1.638)
IKZF1 rs4132601				
TT	118 (60.8%)	10 (26.3%)		Reference
TG	66 (34%)	21 (55.3%)	0.001*	3.303 (1.673-6.521)
GG	10 (5.2%)	7 (18.4%)	0.001*	2.046 (1.332-3.144)
T	302 (77.8%)	41 (53.9%)		Reference
G	86 (22.2%)	35 (46.1%)	<0.001*	1.862 (1.390-2.495)
IKZF1 rs11978267				
AA	122 (62.9%)	23 (60.5%)		Reference
AG	59 (30.4%)	11 (28.9%)	0.978	0.994 (0.646-1.53)
GG	13 (6.7%)	4 (10.5%)	0.435	1.321 (0.656-2.661)
A	303 (78.1%)	57 (75%)		Reference
G	85 (21.9%)	19 (25%)	0.557	1.101 (0.799-1.518)
ARID5B rs10821936				
TT	86 (44.3%)	11 (28.9%)		Reference
TC	91 (46.9%)	19 (50%)	0.226	1.304 (0.849-2.002)
CC	17 (8.8%)	8 (21.1%)	0.017*	2.098 (1.143-3.852)
T	263 (67.8%)	41 (53.9%)		Reference
C	125 (32.2%)	35 (46.1%)	0.022*	1.387 (1.048-1.835)

	Healthy Controls (n=194) N (%)	Adult AML (n=38) N (%)	*P* value	OR (95% CI)
ARID5B rs10994982				
AA	53 (27.3%)	10 (26.3%)		Reference
AG	93 (47.9%)	16 (42.1%)	0.833	0.951 (0.593-1.524)
GG	48 (24.7%)	12 (31.6%)	0.551	1.171 (0.697-1.969)
A	199 (51.3%)	36 (47.4%)		Reference
G	189 (48.7%)	40 (52.6%)	0.532	1.091 (0.83-1.433)

*Significant (p <0.05).

The distribution of *IKZF1* (rs4132601& rs11978267) and *ARID5B* (rs10821936 & rs10994982) haplotypes was analyzed and presented in Table 4. The GA haplotype of *IKZF1* (rs4132601& rs11978267) showed a significant higher frequency in adult ALL (p=0.036) and AML (p=0.005). In contrast, patients with ALL showed association only with the CA haplotype of the *ARID5B* (rs10821936 & rs10994982) (p=0.036).

Table 4. *Comparison of the frequency of IKZF1 and ARID5B haplotypes in adult leukemia patients and the healthy controls.*

		Healthy Controls (n=194)	Adult ALL (n=53)			Adult AML (n=38)		
		Frequency	Frequency	*P value*	OR (95% CI)	Frequency	*P value*	OR (95% CI)
IKZF1 haplotypes								
	TA	0.606	0.521	Reference		0.420	Reference	
rs4132601-	GA	0.175	0.301	0.036*	1.497 (1.173-2.303)	0.345	0.005*	1.841 (1.197-2.833)
rs11978267	TG	0.152	0.112	0.781	0.926 (0.537-1.594)	0.124	0.667	1.138 (0.633-2.044)
	GG	0.067	0.065	0.967	0.984 (0.466-2.08)	0.111	0.208	1.578 (0.775-3.214)
ARID5B haplotypes								
	TA	0.352	0.217	Reference		0.251	Reference	
rs10821936-	TG	0.326	0.283	0.480	1.182 (0.743-1.879)	0.293	0.715	1.097 (0.667-1.805)
rs10994982	CA	0.161	0.261	0.036*	1.722 (1.035-2.866)	0.222	0.284	1.365 (0.773-2.413)
	CG	0.161	0.239	0.058	1.647 (0.984-2.756)	0.234	0.183	1.462 (0.836-2.554)

*Significant (p <0.05).

No associations were found when comparing the frequency of the studied SNPs with demographic, laboratory data, remission, and relapse (data not shown) except for the observed decreased incidence of remission in patients carrying the GG genotype (p=0.003, OR=4.77) and G allele (p=0.034, OR=1.7) of the *IKZF1* rs4132601. Tables 5 and 6.

Table 5. *Comparison of the frequency of IKZF1 genotypes in relation to remission status in acute leukemia patients.*

Adult ALL		Complete Remission(CR) (N=30) N (%)	Non remission (N=23) N (%)	*P value*	OR (95% CI)
	TT	13 (43.3%)	6 (26.1%)		Reference
	TG	15 (50%)	10 (43.5%)	0.441	1.391 (0.6-3.226)
rs4132601	GG	2 (6.7%)	7 (30.4%)	0.003*	4.774 (1.161-19.624)
	T	41 (68.3%)	22 (47.8%)		Reference
	G	19 (31.7%)	24 (52.2%)	0.034*	1.705 (1.042-2.791)
	AA	23 (76.7%)	15 (65.2%)		Reference
	AG	5 (16.7%)	6 (26.1%)	0.209	1.784 (0.723-4.405)
rs11978267	GG	2 (6.7%)	2 (8.7%)	0.198	2.745 (0.59-12.78)
	A	51 (85%)	36 (78.3%)		Reference
	G	9 (15%)	10 (21.7%)	0.372	1.328 (0.712-2.477)
Adult AML		Complete Remission (CR) (N=26)	Non remission (N=12)	*P value*	OR (95% CI)
	TT	6 (23.1%)	4 (26.7%)		Reference
	TG	15 (57.7%)	6 (40%)	0.230	0.538 (0.196-1.479)
rs4132601	GG	5 (19.2%)	5 (33.3%)	0.666	1.338 (0.356-5.025)
	T	27 (51.9%)	14 (46.7%)		Reference
	G	25 (48.1%)	16 (53.3%)	0.647	1.139 (0.654-1.983)
	AA	16 (61.5%)	7 (58.3%)		Reference
	AG	7 (26.9%)	4 (33.3%)	0.163	1.982 (0.757-5.186)
rs11978267	GG	3 (11.5%)	1 (8.3%)	0.282	2.367 (0.493-11.357)
	A	39 (75%)	18 (75%)		Reference
	G	13 (25%)	6 (25%)	1	1 (0.507-1.971)

*Significant (p <0.05).

Although the distribution of genotypes of the studied SNPs revealed no relation or impact on overall survival (OS) and disease-free survival (DFS) of ALL and AML patients (data not shown), however, adult patients with ALL who carried the GG genotype of *IKZF1* rs4132601 were more liable for shorter overall survival (p=0.041). ALL studied cases were stratified

according to Philadelphia chromosome, and OS was assessed. It was noticed that *BCR-ABL* affect the results of *GATA3* rs3824662, as those with negative *BCR-ABL* showed no significant differences among rs3824662 genotypes, while those with positive *BCR-ABL* showed significant association of lower OS probability with CA and AA respectively (Table 7).

Association of *KZF1, ARID5B* genotypes was not affected by stratifying cases according to *BCR-ABL* results. DFS was not affected by *BCR-ABL* stratification as most of positive *BCR-ABL* had no complete remission, Figures 1, 2 & 3.

Table 6. *Comparison of the frequency of GATA3 rs3824662, IKZF1 (rs4132601& rs11978267) and ARID5B (rs10821936 & rs10994982) alleles and genotypes in relation to ALL subtypes.*

	B –ALL (N=42)	**T- ALL (N=11)**	***P value***	**OR(95% CI)**
	N (%)	**N (%)**		
GATA3 rs3824662				
CC	23 (54.8%)	6 (54.5%)		Reference
CA	16 (38.1%)	3 (27.3%)	0.669	0.83 (0.354-1.949)
AA	3 (7.1%)	2 (18.2%)	0.367	1.757 (0.516-5.985)
C	62 (73.8%)	15 (68.2%)		Reference
A	22 (26.2%)	7 (31.8%)	0.601	1.172 (0.647-2.122)
IKZF1 rs4132601				
TT	14 (33.3%)	5 (45.5%)		Reference
TG	23 (54.8%)	2 (18.2%)	0.107	0.462 (0.181-1.181)
GG	5 (11.9%)	4 (36.4%)	0.343	1.639 (0.59-4.551)
T	28 (66.7%)	6 (54.5%)		Reference
G	51 (60.7%)	12 (54.5%)	0.865	1.054 (0.573-1.94)
IKZF1 rs11978267				
AA	31 (73.8%)	7 (63.6%)		Reference
AG	9 (21.4%)	2 (18.2%)	0.986	0.991 (0.372-2.639)
GG	2 (4.8%)	2 (18.2%)	0.179	2.458 (0.662-9.134)
A	71 (84.5%)	16 (72.7%)		Reference
G	13 (15.5%)	6 (27.3%)	0.213	1.524 (0.785-2.956)
ARID5B rs10821936				
TT	8 (19%)	2 (18.2%)		Reference
TC	24 (57.1%)	7 (63.6%)	0.863	1.093 (0.397-3.007)
CC	10 (23.8%)	2 (18.2%)	0.84	0.882 (0.259-2.997)
T	40 (47.6%)	11 (50%)		Reference
C	44 (52.4%)	11 (50%)	0.842	0.947 (0.552-1.624)
ARID5B rs10994982				
AA	12 (28.6%)	1 (9.1%)		Reference
AG	18 (42.9%)	7 (63.6%)	0.144	2.324 (0.749-7.207)
GG	12 (28.6%)	3 (27.3%)	0.354	1.794 (0.521-6.181)
A	42 (50%)	9 (40.9%)		Reference
G	42 (50%)	13 (59.1%)	0.447	1.235 (0.717-2.127)

Table 7. *Overall Survival (OS) of the studied patients according to Philadelphia chromosome in relation to the studied SNPs.*

		Philadelphia negative ALL N (%) 41(77.4%).		**Philadelphia positive ALL N (%) 12(22.6%).**	
		OS	**p**	**OS**	**p**
GATA3 rs3824662	CC	44.2		85.7	
	CA	66.7	0.688	50	0.026*
	AA	50		0	
IKZF1 rs4132601	TT	48.9		75	
	TG	58.4	0.780	64.3	0.114
	GG	50		0	
IKZF1 rs11978267	AA	56.8		87.5	
	AG	44.4	0.321	50	0.145
	GG	50		0	
ARID5B rs10821936	TT	28.6		33.3	
	TC	57.3	0.479	83.3	0.140
	CC	66.7		50	
ARID5B rs10994982	AA	54.5		100	
	AG	46.9	0.869	50	0.498
	GG	66.7		66.7	

*Significant ($p < 0.05$).

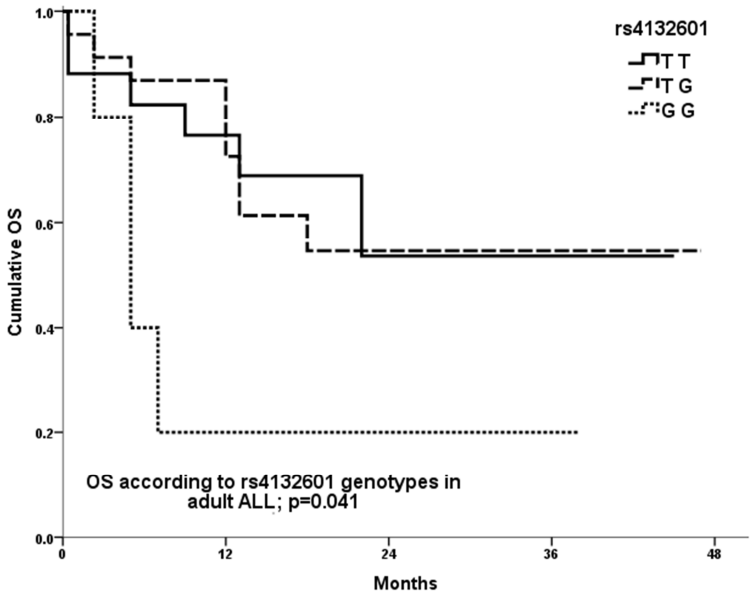


Figure 1. *OS according to IKZF1 rs4132601 genotype in adult ALL patients.*

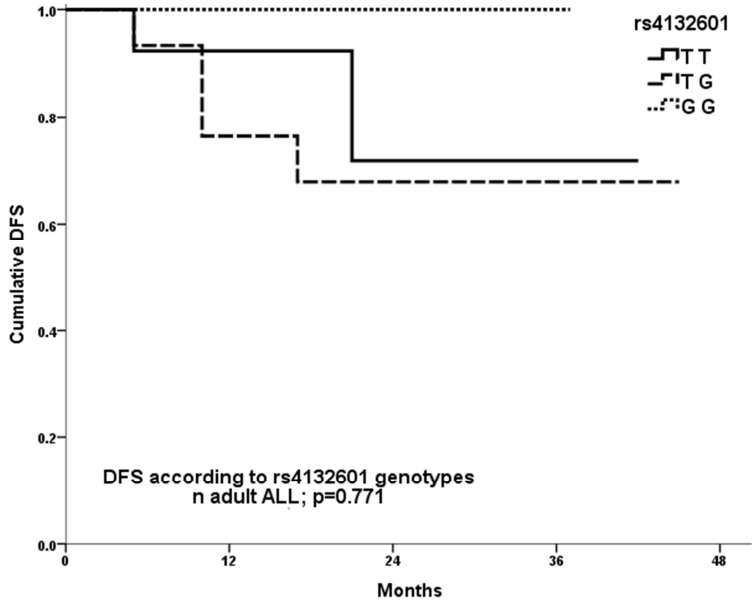
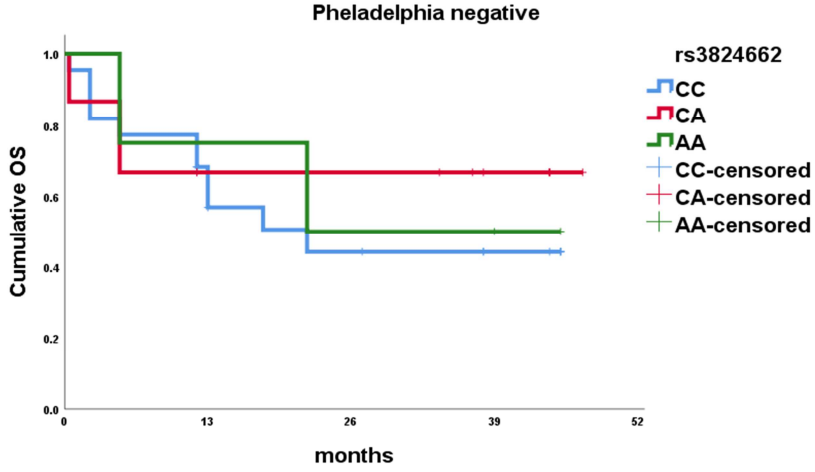
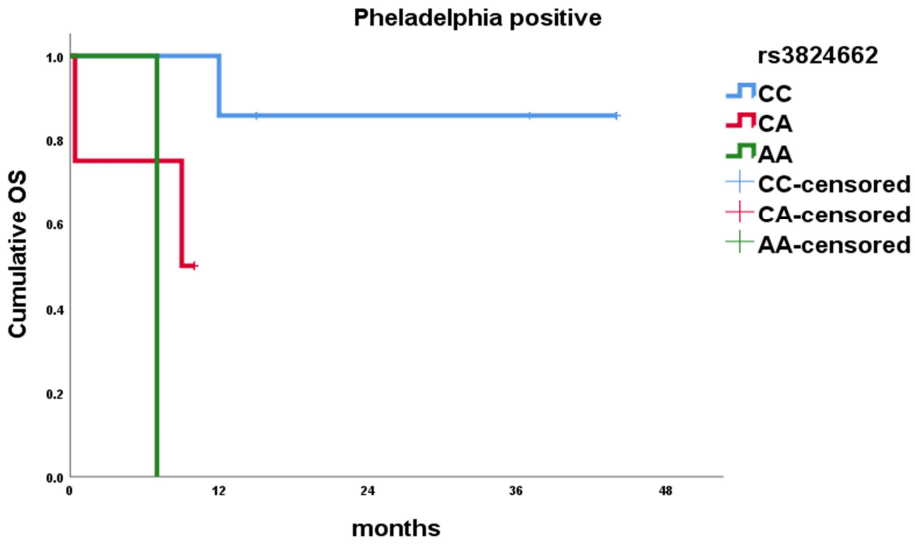


Figure 2. *DFS according to IKZF1 rs4132601 genotype in adult ALL patients.*



A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Cumulative OS
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
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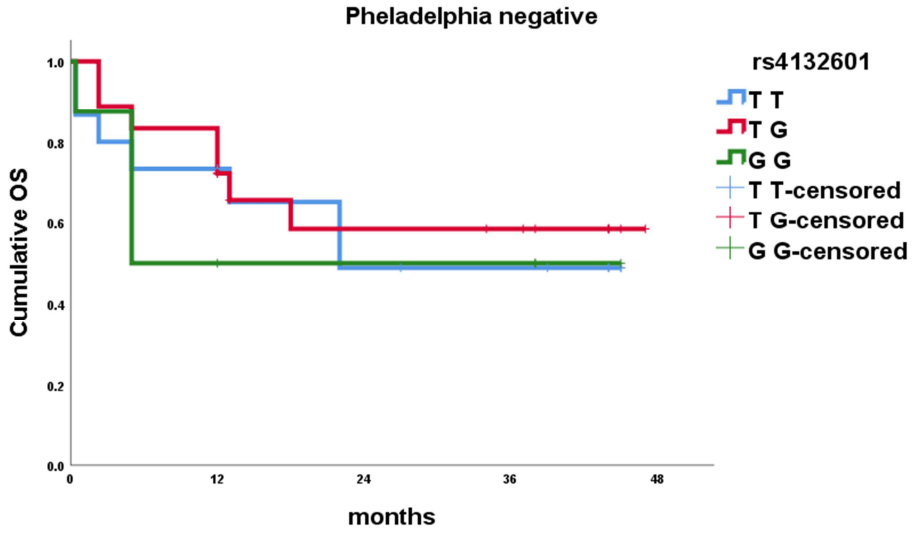
months
rs3824662
CC
CA
AA
CC-censored
CA-censored
AA-censored

B


Pheladelphia negative
Cumulative OS
1.0
0.8
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T T
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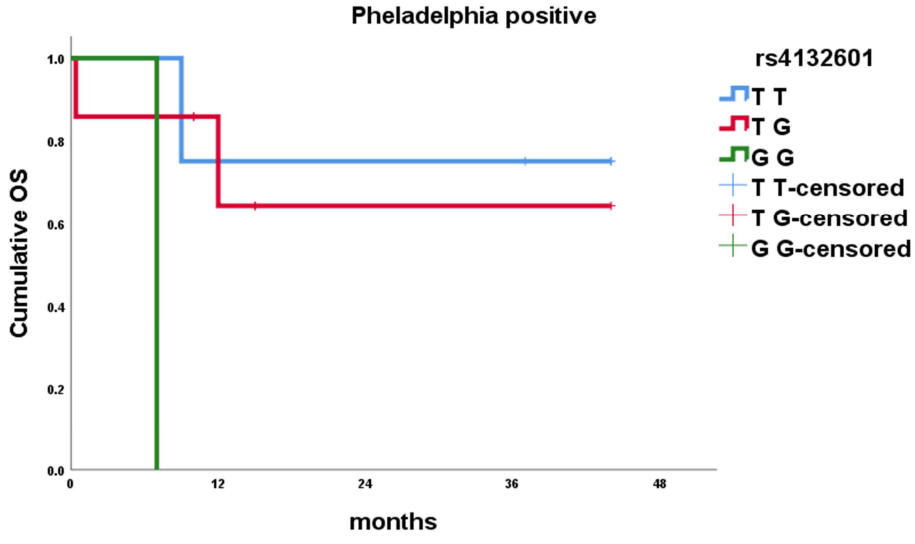
G G
T T-censored
T G-censored
G G-censored

C


Pheladelphia positive
Cumulative OS
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T T
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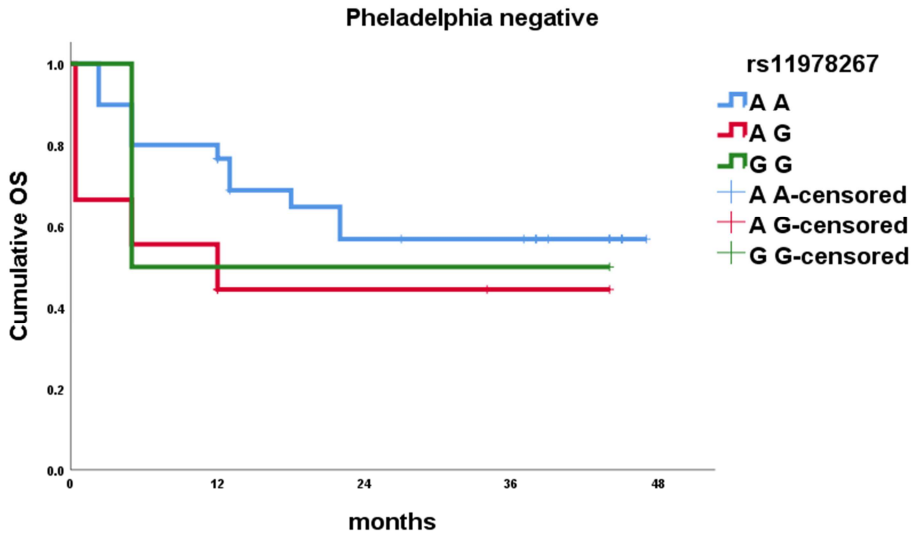
T T-censored
T G-censored
G G-censored

D


Pheladelphia negative
Cumulative OS
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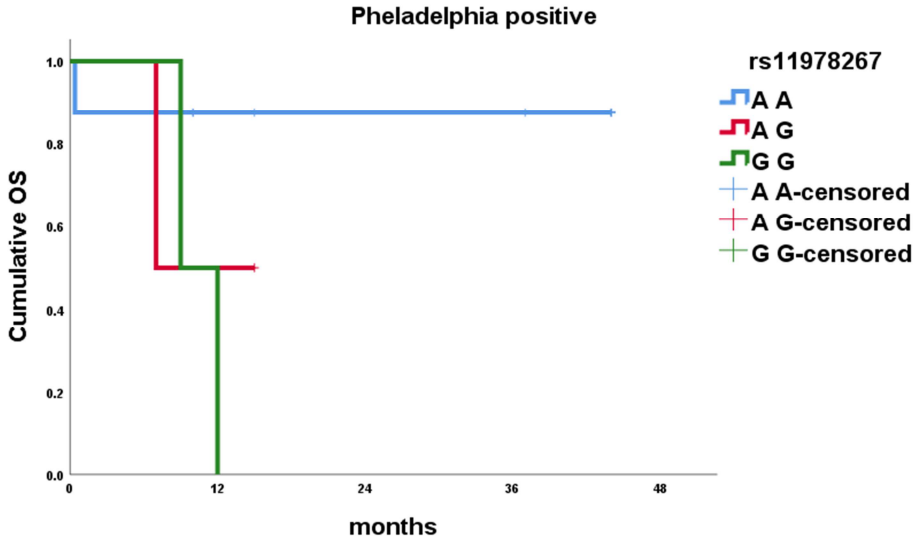
A A-censored
A G-censored
G G-censored

E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Cumulative OS
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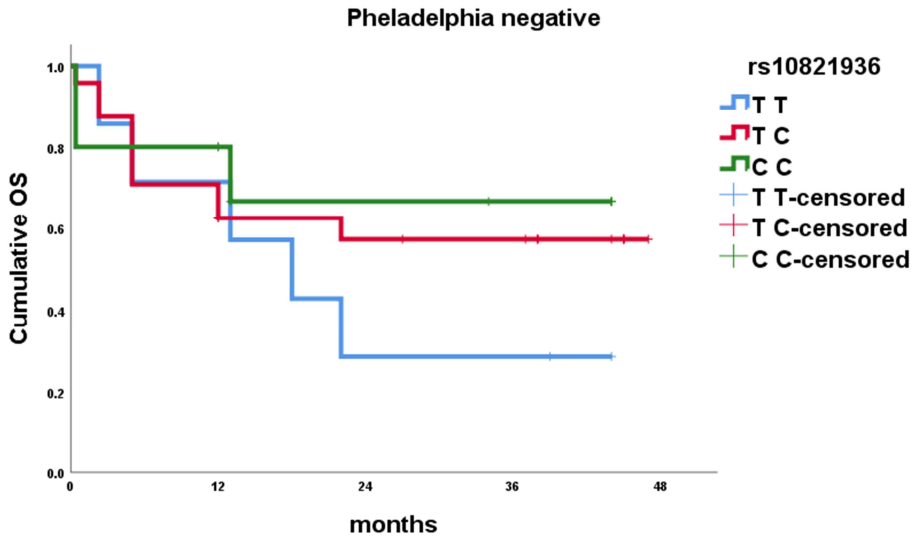
A A-censored
A G-censored
G G-censored

F


Pheladelphia negative
Cumulative OS
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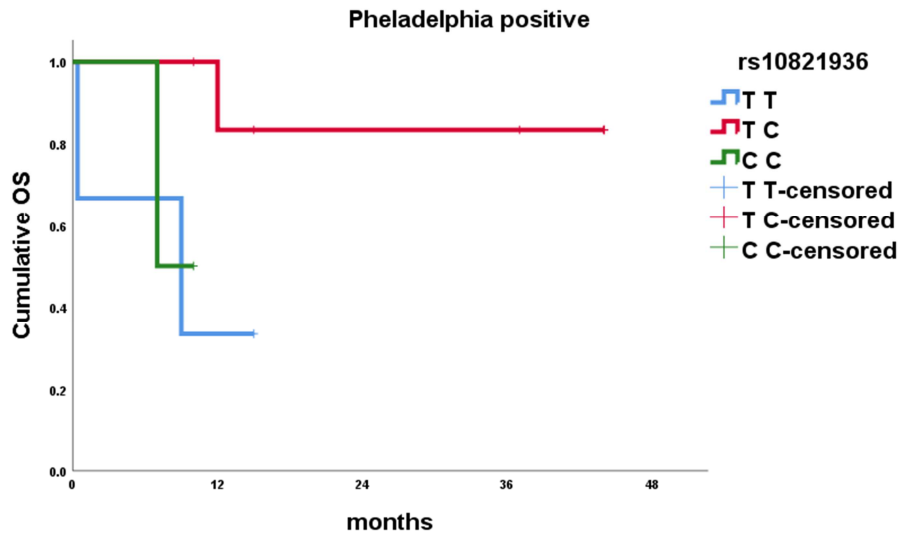
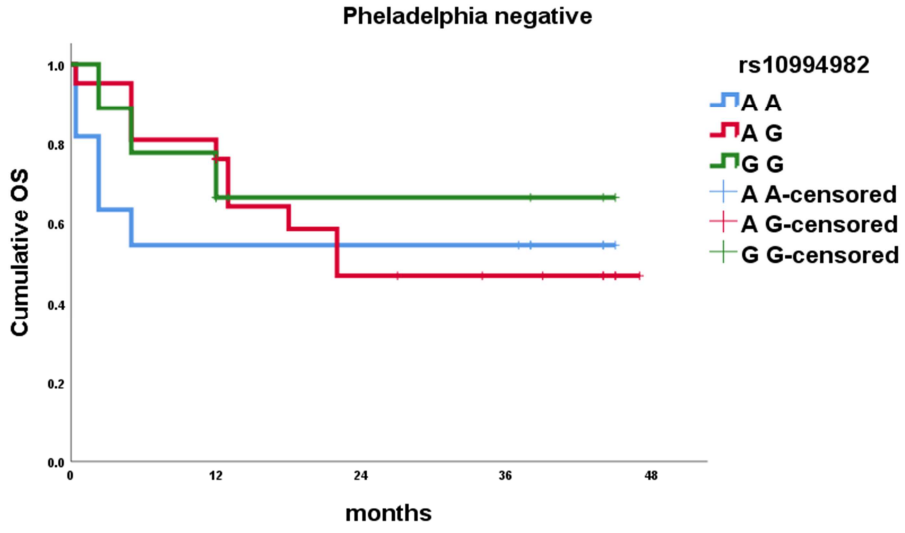
C C-censored

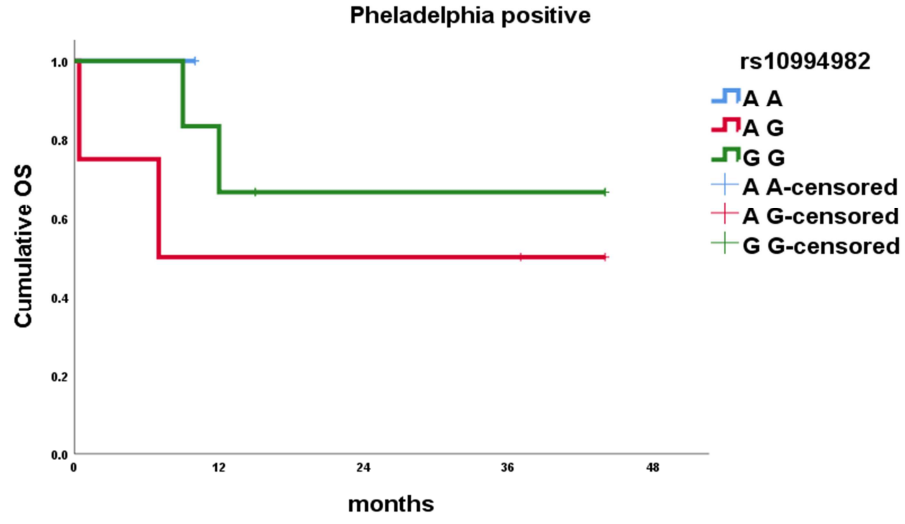
G



H



I



J

Figure 3. *OS of (A) rs3824662, BCR-ABL negative (B) rs3824662, BCR-ABL positive (C) rs4132601, BCR-ABL negative (D) rs4132601, BCR-ABL positive (E) rs11978267, BCR-ABL negative (F) rs11978267, BCR-ABL positive (G) rs10821936, BCR-ABL negative (H) rs10821936, BCR-ABL positive (I) rs10994982, BCR-ABL negative (J) rs10994982, BCR-ABL positive.*

4. Discussion

Leukemias are heterogeneous malignant disorders of the hematopoietic stem cells [8]. The prevalence of ALL shows variation in different populations [5] and several genetic SNPs in many genes (such as *ARID5B, CEBPE, GATA3* and *IKZF1)* have been linked to the susceptibility and poor outcome in pediatric ALL [7, 18, 20, 21, 27-29]. AML is the most common form of acute leukemia in adults and is characterized by clonal expansion of myeloblasts with heterogeneous genetic and epigenetic alterations [8, 30, 31].

While studying the Egyptian pediatric ALL, the AA genotype of GATA3 rs3824662 was associated with ALL risk (p=0.016, OR=2.74), particularly with B-ALL (p=0.01, OR=3.01), shorter DFS (p=0.017) in univariate and (p=0.028) in multivariate cox regression analysis), an increased incidence of relapse (p=0.008), and poor prognosis (p=0.028) [12]. Contradictory to the previously reported data on Egyptian ALL children, the current study observed that the GATA3 rs3824662 has no association with the ALL susceptibility and prognosis in Egyptian adults and this could be justified by not just the difference in sample size in both groups (116 pediatric ALL versus 53 adults ALL in the current study), yet the difference in disease biology, cytogenetics, and drug resistance in both groups.

Simultaneously, the significant associations reported in the present study for the *ARID5B* rs10821936 SNP were similar to what has been reported in Egyptian pediatric ALL (p<0.001 for C allele, CC genotype, and CA haplotype, respectively) [18]. In agreement with current study, the *IKZF1* rs4132601G previously showed statistically significant associations with the risk of pediatric ALL (p=0.003), for the G allele, (p=0.009) for the GG+GT genotype, and (p=0.044) for the GG haplotype) [21].

Jain et al [32] investigated the frequency of *GATA3* rs3824662 and clinical correlation with Ph-like ALL in adult Hispanic patients. They reported an association between such SNP and susceptibility to Ph-like ALL and they observed an overrepresentation of the A allele (up to 80%) with other genetic variants such as *CRLF2*, *JAK2*, or *IKZF1*. They hypothesized that *GATA3* regulates *CRFL2* transcription, which in turn may result in overexpression of *CRLF2*. The *GATA3* rs3824662 AA genotype was associated with poor 5-year event-free-survival (EFS) in adult Hispanic patients with B-ALL [33].

IKZF1 gene encodes for transcription factor which regulates the differentiation of lymphoid linage. Point mutation or deletion in *IKZF1* gene will dysregulate the activity of IKZF1 factor and will block lymphocyte differentiation. Thus, *IKZF1* gene is involved in the pathogenesis and progression of ALL [25]. It has been reported that about 30-50 % of adult B-ALL and about 70 – 80 % of ALL with positive BCR-ABL will have *IKZF1* gene mutations or deletions. The IKZF*1* gene deletions were associated with a poor prognosis in adult patient with ALL [27, 34, 35]. Although the position of the *IKZF1* rs4132601 genetic variant is not related to the gene promoter or enhancer, however, it may affect the expression of *IKZF1* indirectly through its linkage with other SNPs (e.g., rs11978267 and rs1110701). The *IKZF1* rs4132601-rs11978267 haplotype may be responsible for the different expression patterns of *IKZF1* which may be responsible for or help in the transformation of cells into leukemic cells in a way that *IKZF1* deletions do [36].

Zhang et al [25] meta-analysis on 1008 adult ALL patients reported worse overall survival (OS) and disease-free survival (DFS) with *IKZF1* deletions. They concluded that *IKZF1* deletion is a poor prognostic factor for adults with B-ALL which necessitates justifying the therapy based on the diagnostic status of *IKZF1* in those patients. *Giebel et al* [37] conducted a multicenter study to evaluate the relationship between *IKZF1* alterations in adults with B-ALL and the outcome of allogenic hematopoietic stem cell transplant (allo-HSCT). They concluded that patients with *IKZF1* variations, it is better to carry allo-HCT during the first remission. Therefore, *IKZF1* gene status would contribute to risk stratification and treatment decisions for ALL adult patients. However, large-scale multicenter studies are needed to validate the prognostic significance of *IKZF1* genetic variations in adults with ALL.

Ikaros promotes and directs the differentiation of hematopoietic stem cells (HSCs) into the lymphocyte lineage. In the absence of Ikaros due to deletion, HSCs will be directed to the myeloid pathway. At the same time, cell growth is regulated by the *ARID5B* gene, and its expression is upregulated in patients with acute promyelocytic leukemia (APL) [20, 38]. Because the SNPs in *ARID5B* and *IKZF1* genes may affect gene expression and function, it is reasonable that these SNPs may have an impact on the risk of AL. *Cao et al* [20] case-control study on Chinese population (660 AML patients and 1,034 healthy controls) investigated the association with 6 *ARID5B* and *IKZF1* genetic variants. They found an association between the variant allele of *ARID5B* rs4509706 and *IKZF1* rs11761922 and an increased risk of AML and a significant increase in the luciferase levels was found with the combined genotype rs11761922-G and rs4509706-C.

Zhou et al. [39] investigated 569 AML patients and 410 healthy controls from West China for the association between the *ARID5B* SNPs and AML incidence, clinical presentation, and prognosis. They found an association between the rs6415872, rs2393726, rs7073837, rs10821936, and rs7089424 mutant alleles and an increased risk of Acute Promyelocytic Leukemia (APL) in males, and this effect is increased with the combined genotype of rs6415872, rs10821936, and rs7089424 and the haplotype AACCG.

As stated in the study, the small sample size of both patients and healthy controls is a limitation. It is worth noting that the samples were collected from individuals in the East Delta region, which is just one of Egypt's 29 governorates. As a result, it is recommended that a multi-center study be

conducted, including a larger number of participants from all 29 governorates.

5. Conclusion

The *IKZF1* rs4132601 and *ARID5B* rs10821936 SNPs may pose a potential risk factors for adult acute leukemia among the Egyptian population, and adult ALL patients carrying the *IKZF1* rs4132601 GG genotype may be at higher risk for poor response to therapy and short survival rates.

List of Abbreviations

ALL: Acute lymphoblastic Leukemia.
AML: Acute Myeloid Leukemia.
APL: Acute Promyelocytic Leukemia.
ARID5B: AT-Rich Interactive Domain-Containing Protein 5B.
BCR-ABL: Breakpoint Cluster Region- Abelson murine leukemia.
CD: Cluster of Differentiation.
CI: Confidence Interval.
CR: Complete Remission.
DFS: Disease Free Survival.
FAB: French-American-British.
GATA3: GATA Binding Protein 3.
GWAS: Genome Wide Association Studies.
HSCT: Hematopoietic Stem Cell Transplantation.
HLA-DR: Human Leucocyte Antigen-DR.
ID: Induction Death.
IKZF1: IKAROS family zinc finger 1.
IRB: Institutional Research Board.
LDH: lactate dehydrogenase.
MPO: Myeloperoxidase.
OR: Odds Ratio.
OS: Overall Survival.
PCR: Polymerase Chain Reaction.
RD: Refractory Disease.
SD: Standard Deviation.
SNPs: Single Nucleotide Polymorphism.
WHO: World Health Organizations.

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Conflicts of Interest

The authors declare no conflict of interest.

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