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Association of *TRAF1* Gene Polymorphisms (rs3761847 and rs10818488) with Susceptibility to Acute Lymphoblastic Leukemia: A Case-Control Study

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Abstract
Background: The Single-nucleotide polymorphisms (SNPs) rs3761847 (G/A) and rs10818488 (A/G), located within the Tumor Necrosis Factor Receptor-Associated Factor 1 (*TRAF1*) gene, have been investigated as candidate genetic variants that may influence *TRAF1* related immune and inflammatory signaling, including NF-kB dependent pathway. The present case-control study aimed to investigated whether the genotype distribution of the *TRAF1* rs3761847 and rs10818488 polymorphisms are associated with susceptibility to acute lymphoblastic leukemia (ALL) in an Iraqi population.
Methods: This case-control study included 100 patients with confirmed ALL and 150 healthy controls. Genotyping was performed using TaqMan allelic discrimination assays, and association analyses was conducted under five genetic models.
Results: The TRAF1 rs3761847 and rs10818488 polymorphisms were associated with lower odds of ALL in the studied Iraqi population, particularly under the heterozygous, dominant, over-dominant, and allelic models. These findings suggest a potential contribution of TRAF1 genetic variations to ALL susceptibility.
Conclusion: In conclusion, theTRAF1 rs3761847 and rs10818488 polymorphisms were associated with lower odds of ALL in Iraqi population, particularly under the heterozygous, dominant, over-dominant, and allelic models.

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Keywords: Acute Lymphoblastic Leukemia, TRAF1, rs3761847, rs10818488, Iraqi population

1. Introduction

Acute lymphoblastic Leukemia (ALL) represent the most common cancer in pediatric population. It is characterized by heightened proliferation of leukemic blasts and their spread into peripheral blood and extramedullary hematopoietic and non-hematopoietic organs, such as kidneys, spleen, liver, lung, , testes, lymph nodes, and brain (Brown *et al*., 2020) [3]. ALL is a predominant contributor to mortality from disease in children and adolescent under 19 years, and an important factor of cancer-associated fatalities in adults, with over 150,000 new diagnosis worldwide in 2019 (Zhang *et al*., 2023) [21].

Numerous investigations from different countries have analyzed juvenal cohorts to identify factors linked to heightened prevalence of ALL. significantly, factor such as race, age, genetic susceptibility, ethnicity, and white blood cell (WBC) count have been shown to affect risk, with the United States reporting a pronounced peak incidence throughout childhood (Lim *et al*., 2014) [10]. The treatment modalities and clinical results in ALL are influenced by many factors, one of which is age, which is a significant prognostic factor. Treatment modalities don't explain why pediatric and adults patients have different clinical outcome (Neaga *et al*., 2021) [12].

The real patho-physiological mechanism is unclear. Nevertheless, extensive research has established a strong correlation between ALL and inherited genetic predisposition, genomic variation in oxidative stress enzymes ,specific environmental risk factors, and alterations in the immunological environment of bone marrow (Abdalhabib *et al*., 2022) [1].

Tumor necrosis factor (TNF) receptor associated factor 1 (*TRAF1)* gene transmits signal related to tumor necrosis factor (TNF) receptor associated factor 1, (*TRAF1)* which is linked to various TNF receptor family members and modulate cytokine signaling pathways, such as TNFα through interactions with divers protein kinases and adaptor proteins (Lee and Choi, 2007) [9]. In contrast to TRAF2, which is expressed continuously and has a transcript in nearly all the tissues, TRAF1 is an NF-κB inducible protein, with reduced has more limited expression in the lung, spleen, and testis under normal conditions (Rothe *et al*., 1994) [17]. There is a significant role for the TRAF family in tumors as well, with different members either driving or inhibiting malignancy in different tumor types (Wu *et al*., 2015; Wang *et al*., 2018) [18, 19]. The predominant TRAF proteins have conventional architectures, including zinc finger motifs, N-terminal RING finger domain, C-terminal TRAF domain. There analogous structural features dictate a shared role in modulating intracellular signal transduction and functioning as E3 ubiquitin ligase (Häcker *et al*., 2011; Pineda *et al*., 2007) [6, 15].

A substantial candidate gene study (rs10818488) (Kurreeman *et al*., 2007) [8] and one GWAS (rs3761847) found two single-nucleotide polymorphisms (SNPs) in the TRAF1 locus that were significantly related with rheumatoid arthritis (RA) in Europeans in 2007 (Plenge *et al*., 2007) [16]. Based on its biological roles, the TRAF1 gene and the 9q33-34 region that carries it may be involved in the development of ALL.

ALL risk has been linked to variations in the TRAF1 gene in a number of populations one of which being the population of the Kingdom Saudi Arabia (Alkhulaifi *et al*., 2024) [2]. Discordant results have been reported, and allele frequencies and association patterns differ across populations, and findings have been inconsistent. To our knowledge, data on these variants in Iraqi patients with ALL are limited or lacking. Consequently, this investigation focused on the correlation between the TRAF1 rs3761847, and rs10818488 polymorphisms and predisposition to ALL in an Iraqi population.

2. Materials and Methods

2.1. Study Design and Population Study

This case-control study included a convenience sample of 250 participants divided to 150 healthy controls and 100 cases of acute Lymphoblastic Leukemia (ALL) recruited at the Middle Euphrates Cancer Center in Najaf, Iraq with a confirmed diagnosis of ALL per WHO classification criteria. Laboratory analysis was conducted at the AL-Ameen Research Center, during the period from January 2026 to July 2026. Patients with prior cancer history, other hematological disorders, or concurrent chronic illness were excluded.

2.2. Biological Samples and Genotyping

Following the instructions provided by the manufacture, genomic DNAs were isolated from whole blood using DNA extraction kit (QIAGEN, Germany) according to the manufacturer. Peripheral venous blood (5 mL) was obtained in EDTA from all participants to ascertain *TRAF1* gene polymorphisms (rs10818488 and rs3761847).

TaqMan SNP primers for allelic discrimination were synthesized. Fluorescent dyes have been employed to label the probes specific to each allele (VIC and FAM) for TaqMan allelic discrimination SNP primers. Probes are utilized in a real-time PCR assay using an apparatus (Applied Biosystems, model 7500) characterized the alleles of each DNA specimen. Fluorescein-amidite tagged SNP primers and probes that have been manufactured for application in real-time PCR. The subsequent 20 µL utilized for the reaction comprised 10.0 µL of Universal Master Mix II by TaqMan 2×, 1.0 µL of Assay Mix for Genotyping SNP (20×), 1.0 µL of template for DNA, with 8.0 µL of RNase water free. For the purpose of real-time PCR genotyping, a thermal cycler (Applied Biosystems, 7500 RT-PCR system) was utilized. After 10 min denaturation step at 95ºC, the denaturation step consisted of 40 cycles at 95ºC each, and the annealing/ extension stage lasted 1 min at 60ºC. The quality control procedure involved re-genotyping about 5% of the samples, and the result showed complete agreement.

2.3. Statistical Analysis

The data analysis was conducted using SPSS software version 26 (SPSS Inc, Chicago, USA). The mean ± SD was utilized to report all continuous variables, whereas absolute numbers and percentages were used to report categorical data. A t-test or Mann-Whitney U test was used to compare continuous variables, and the Kolmogorov-Smirnov test was used to validate their normal distribution. When comparing categorical variables, the Chi-square or Fisher exact test were utilized. Results were presented with 95% confidence intervals (95%CI) for the crude odds ratios (ORs). A significant result was defined as a P value < 0.05.

3. Results

3.1. Baseline Characteristics

The fundamental traits in the study participants are illustrated in Table 1. There were 100 cases and 150 controls. In many instances, the count of male participants was marginally greater, although the disparity lacked statistical significance (P=0.160). The ages of cases and controls were similar (P=0.270).

Table 1: Baseline characteristics of the study participants.

Characteristic	ALL Patients (n = 100)	Controls (n = 150)	P value
Males, n (%)	65 (65.0%)	110 (73.3%)	0.160
Females, n (%)	35 (35.0%)	40 (26.7%)	
Age, (years), Mean ± SD	9.4 ± 4.7	10.1 ± 5.1	0.270

SD: standard deviation; P values for age by independent t-test; sex by chi-square.

3.2. Genotype Distribution

The genotype and allele frequencies for rs3761847 and rs10818488 are displayed in Table 2. In the genotyping analysis of rs3761847, utilizing the codominant model (reference: A/A), the heterozygous G/A genotype exhibited a significant correlation with reduced ALL risk (OR = 0.51, 95% CI: 0.30–0.89; P = 0.016). The G/G genotype did not reach significance (P = 0.185). The dominant model (G/A + G/G vs. A/A) exhibited a significance (OR = 0.52, 95% CI: 0.31-0.87; P = 0.013), as did the over-dominant model (OR = 0.57; 95% CI: 0.34-0.97; P = 0.036). Examination at the allele level revealed that the G allele was markedly lower odds (OR = 0.65, 95% CI: 0.44-0.96; P = 0.029). In the genotyping assessment of rs10818488, The A/G heterozygous within the codominant mode was associated with lower odds of ALL (OR = 0.41, 95% CI: 0.23-0.71; P = 0.001), but the G/G did not reach significance (P = 0.069). The dominant and over-dominant models were both significant (OR = 0.42, 95% CI: 0.25-0.71; P = 0.001, OR = 0.48, 95% CI: 0.28–0.81; P = 0.006, respectively). The G allele was markedly lower odds at the allele level (OR = 0.55; 95% CI: 0.37-0.82; P= 0.003). Genotype distribution among controls were consistent with Hardy-Weinberg equilibrium for rs3761847 (χ^2 = 0.080, P = 0.777) and rs10818488 (χ^2 = 0.010, P = 0.922) using Pearson's chi-square test.

Table 2: Association of the polymorphisms with ALL risk.

Genetic Model / Genotype	ALL n (%)	Control n (%)	Crude OR	95% CI	P value
Codominant rs3761847 (G/A), χ^2 = 0.080, P = 0.777					
A/A (Ref.)	56 (56.0)	60 (40.0)	1.00	-	-
G/A	34 (34.0)	71 (47.3)	0.51	0.30–0.89	0.016
G/G	10 (10.0)	19 (12.7)	0.56	0.24–1.32	0.185
Dominant (G/A+G/G vs. A/A)	44 (44.0)	90 (60.0)	0.52	0.31–0.87	0.013
Recessive (G/G vs. A/A+G/A)	10 (10.0)	19 (12.7)	0.77	0.34 –1.73	0.519
Over-dominant (G/A vs. A/A+G/G)	34 (34.0)	71 (47.3)	0.57	0.34–0.97	0.036
Allele Frequencies					
A allele (Ref.)	146 (73.0)	191 (63.7)	1.00	-	-
G allele	54 (27.0)	109 (36.3)	0.65	0.44–0.96	0.029
Codominant rs10818488 (A/G), χ^2 = 0.010, P = 0.922					
A/A (Ref.)	60 (60.0)	58 (38.7)	1.00	-	-
A/G	30 (30.0)	71 (47.3)	0.41	0.23–0.71	0.001
G/G	10 (10.0)	21 (14.0)	0.46	0.24–1.10	0.069
Dominant (A/G+G/G vs. A/A)	40 (40.0)	92 (61.3)	0.42	0.25–0.71	0.001
Recessive (G/G vs. A/A+A/G)	10 (10.0)	21 (14.0)	0.68	0.36–1.35	0.350
Over-dominant (A/G vs. A/A+G/G)	30 (30.0)	71 (47.3)	0.48	0.28–0.81	0.006
Allele Frequencies					
A allele (Ref.)	150 (75.0)	187 (62.3)	1.00	-	-
G allele	50 (25.0)	113 (37.7)	0.55	0.37–0.82	0.003

OR: odds ratio; CI: confidence interval; Bold values indicate significant associations. Bold values indicate significant associations.

3.3. Allelic Discrimination Cluster Plot of *TRAF1* Gene Polymorphisms

Allelic discrimination cluster plots generated from Applied Biosystems, model 7500 analysis are presented in Figure 1. Three clearly separated clusters in each plot correspond to: homozygous Allele 1 (VIC), heterozygous, and homozygous Allele 2 (FAM). Non-template controls (NTC) cluster near the origin. Distinct cluster separation observed across all 250 samples demonstrates the reliability of genotyping for both SNPs.

4. Discussion

The TNFR superfamily member involved in signal transduction pathway, TRAF1 is an aptamer molecule that promotes survival. Refractory chronic lymphoblastic leukemia (CLL) is one of several B-cell leukemias characterized by overexpression of this gene. In the context of CD40 signal transduction in lymphoma, Edilova et al. found that PKN1, a protein kinase C-related protein kinase N1, safeguards TRAF1 from degradation induced by CIAP. In screening a collection of 700 kinase inhibitors, two PKN1 inhibitors, XL-228 and,OTSSP167 were identified that can lower TRAF1 expression in the CLL cell from patients, hence triggering cell death (Edilova *et al*., 2021) [4]. In a separate investigation on CLL, Xiao et al. revealed that human antigen R (HuR) protein holds significant promise for CLL treatment. HuR can is able to directly communicate with TRAF1, impede the reduction of TRAF1 activity, amplify the apoptosis and inflammatory responses, and elevate sensitivity of CLL cells' to pharmaceutical agents, indicating that targeting the HuR-TRAF1 interaction may offer a novel approach to address drug resistance in CLL (Xiao *et al*., 2020) [20].

There is substantial evidence indicating modified expression of TRAF1 in lymphoid neoplasms (Munzert *et al*., 2002) [11]. A variety of human B malignancies such as non-Hodgkin lymphoma (NHL), Burkitt's lymphomas, and B cell chronic CLL, exhibit persistent signaling through TRAF1 interaction with TNFRs, including CD30 and the EBV protein LMP1, which is believed to enhance TRAF1 expression via NF-κB signaling (Horie *et al*., 2002; Gricks *et al*., 2004) [5, 7]. Furthermore, B-CLL receive signals via CD40L, which can stimulate CD40-mediated TRAF1 expression (Pascutti *et al*., 2013) [14].

This research represents the inaugural examination of the Tumor necrosis factor (TNF) receptor associated factor 1 (TRAF1) rs3761847 and rs10818488 gene polymorphisms concerning acute lymphoblastic leukemia (ALL) susceptibility in the Iraqi population, employing single-nucleotide polymorphism (SNP) level analysis. The results indicate that the G/A codominant, dominant, over-dominant, G allele of rs3761847 polymorphism, G/A codominant, dominant, over-dominant, and G allele of rs10818488 genotypes are significantly linked with lower odds ratio of

ALL. These findings are align with those presented by Alkhulaifi *et al*. (2024) [2] in Saudi patients (Alkhulaifi *et al*., 2024) [2].

The rs10818488 polymorphism may play a role in the modulation of the adjacent TRAF1 gene (Kurreeman *et al*., 2007) [8]. A subsequent investigation revealed a significant difference in the expression levels of TRAF1 between carriers and non-carriers of the rs10818488 risk allele in phorbol myristate acetate-stimulated lymphoblastoid cell lines, suggesting that this polymorphism could influence the development of rheumatoid arthritis (RA) by regulating TRAF1 expression in response to particular stimulation signals (Nishimoto *et al*., 2010) [13]. Consequently, several researches were made to analyze the link between the TRaF1 rs10818488 polymorphism and RA across various ethnic communities, however the results have been contradictory. Beside the rs10818488 polymorphism, the rs3761847 polymorphism was identified as significantly linked with RA at a genome-wide level of significance from a GWAS (Plenge *et al*., 2007) [16].

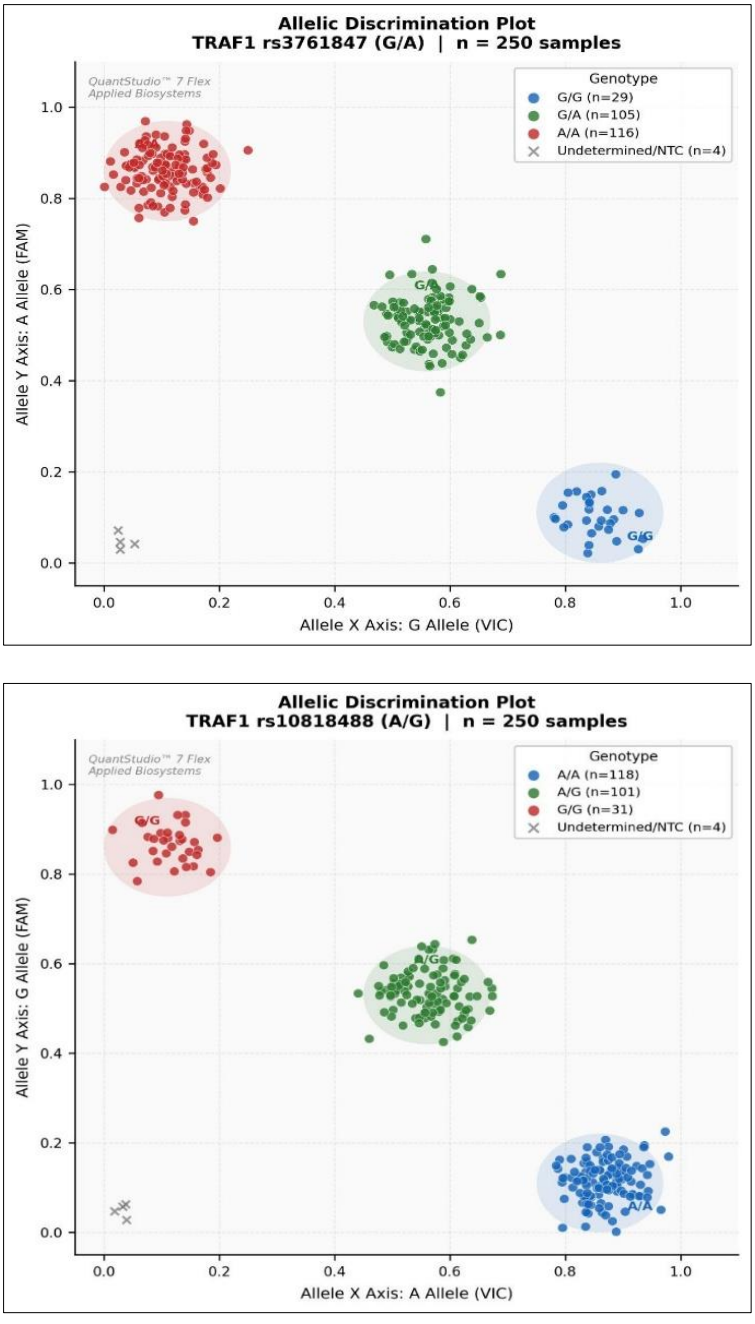


Fig 1: Cluster plot of TaqMan allelic discrimination for TRAF1 rs3761847. Blue: GG homozygous (n = 29); Green: GA heterozygous (n = 105); Red: AA homozygous (n = 116); Grey crosses: NTC. VIC detects G allele; FAM detects A allele. While, TaqMan allelic discrimination for TRAF1 rs10818488. Blue: AA homozygous (n = 118); Green: AG heterozygous (n = 101); Red: GG homozygous (n = 31); Grey crosses: NTC. VIC detects A allele; FAM detects G allele.

The current research has certain limitations that must be recognized. Firstly, the sample sizes of our case-control study is inadequate, resulting in a diminished capacity to identify relationships with a moderate effect size. Second, the majority of earlier investigations concerning the TRAF1 rs10818488 and rs3761847 polymorphisms have focused on patients with RA in RA patients, while information about these variants in ALL remain scare (Alkhulaifi *et al*., 2024) [2]; Consequently, the opportunity to compare our results with other ALL research was limited.

In conclusion, our research explored the association between TRAF1 gene polymorphisms and ALL risk among Iraqi patients, our data suggest the results indicate that the G/A codominant, over-dominant, dominant, G allele of rs3761847 polymorphism, G/A codominant, over-dominant, dominant, and G allele of rs10818488 genotypes are significantly associated with lower odds ratio of ALL.

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CRediT Authorship Statement

All authors participated in this research, including conception and design (ESA, AMO), data acquisition (ESA, SQK), data analysis and interpretation (AMO), material support (ESA, SQK), study supervision (AMO, ESA), and drafting the article or critically revising (AMO, SKQ).

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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