TRAF1 Gene Polymorphisms and Their Role in Susceptibility to Acute Lymphoblastic Leukemia in Saudi Patients

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The Role of TRAF1Gene Polymorphisms in the Development and Progression of Acute Lymphoblastic Leukemia in Saudi Patients

Abstract:

Acute Lymphoblastic Leukemia (ALL) is a genetic malignancy characterized by the uncontrolled proliferation of hematopoietic precursor cells and evasion of immune surveillance. This study investigates the association between TRAF1 gene polymorphisms and the risk of developing ALL. Understanding the role of single nucleotide polymorphisms (SNPs) in the TRAF1 gene, which has been previously implicated in various immune-related disorders, may provide valuable insights into the molecular mechanisms of ALL and help identify potential therapeutic targets.

A total of 265 subjects were recruited for this study, comprising 150 ALL patients and 115 healthy controls. Genotyping was performed using TaqMan PCR, focusing on four TRAF1 SNPs: rs2239657G/A, rs2416804G/C, rs7021049G/T, and rs3761847G/A. The minor allele frequencies and genotype distributions were compared between groups, with relative risks and statistical differences evaluated. Additionally, TRAF1 mRNA expression levels were assessed in both ALL patients and healthy individuals using qRT-PCR.

The results demonstrated a significant association between the TRAF1 rs2239657G/A polymorphism and an increased risk of ALL, while the rs2416804G/C polymorphism was associated with a significantly reduced risk. Notably, TRAF1 was overexpressed in ALL patients, indicating its potential role in the pathogenesis of ALL. This overexpression suggests that TRAF1 may contribute to the interaction between inflammation and oncogenesis, providing new insights into the disease's progression and highlighting TRAF1 as a possible biomarker for therapeutic intervention.

1. *Introduction*

Leukemia, a form of blood cancer arising from hematopoietic cells, is identified as a multifaceted disease caused by diverse genetic mutations and hematologic abnormalities. Acute Lymphoblastic Leukemia (ALL), in particular, is marked by the clonal expansion of leukemic cells in the bone marrow, frequently resulting in an increased number of affected lineage cells in the peripheral blood (Tebbi, 2021). This aggressive malignancy primarily affects children and significantly impacts morbidity and mortality rates.

Leukemia ranks among the most common cancers in Saudi Arabia (Jastaniah et al., 2020). The Saudi Cancer Registry's 2013 report indicated that childhood cancers represented 6% of all cancer cases, with ALL accounting for 31%—the highest incidence among all cancer types (Ahmed et al., 2019). Over the past 15 years, leukemia incidence has risen, particularly among males, with the central region of the country reporting the highest rates. Furthermore, the 2015 report from the Saudi National Cancer Registry revealed that leukemia made up 4.5% of all female cancers and 7.5% of male cancers in the Kingdom of Saudi Arabia (Bawazir et al., 2019).

The tumor necrosis factor receptor (TNF-R)-associated factor (TRAF) family comprises intracellular proteins that serve as cytoplasmic signaling adaptor molecules. The TNF-R family includes 25 receptors that regulate various functions, including innate and adaptive immunity, tissue homeostasis, embryonic development, stress response, and apoptosis (Gissler et al., 2022). Most TNF-Rs require specific adaptor proteins such as Tumor Necrosis Factor Receptor Type 1-associated Death Domain (TRADD), Receptor-Interacting Protein (RIP), Fas-Associated Death Domain (FADD), and TRAFs to facilitate these processes.

The TRAF (TNF Receptor Associated Factor) protein family, comprising six members (TRAF1 to TRAF6), plays a crucial role in signal transduction from a variety of receptors (Xie, 2013). These proteins function as regulatory scaffolds, interacting with the cytoplasmic domains of different TNF-R (Tumor Necrosis Factor Receptor) superfamily members upon their activation. TRAFs act as docking platforms, facilitating interactions with diverse receptors, including kinases, ubiquitin ligases, ubiquitin proteases, and other effector proteins (Perez-Chacon et al., 2019). They operate independently or synergistically with other adaptor proteins to serve as signal transducers for a wide array of receptors, especially those involved in innate and adaptive immune responses, as well as cytokine signaling (Lalani et al., 2019).

TRAFs are integral to various physiological processes, including innate and adaptive immunity, inflammation, cellular proliferation and differentiation, embryonic development, cellular homeostasis, apoptosis, cytokine production, autophagy, lymphoid organ development, brain development, osteoclastogenesis, stress responses, and programmed cell death (Park, 2018). Specifically, Tumor Necrosis

Factor Receptor-Associated Factor 1 (TRAF1), a cytoplasmic adaptor protein, is essential in the immune system as a crucial intracellular signaling molecule. TRAF1 expression is minimal in resting lymphocytes and monocytes but significantly increases upon activation via the NF-κB pathway (Edilova et al., 2018). Genetic alterations in TRAF1 occur in less than 4% of human cancers (Zhu et al., 2018). TRAF1 overexpression is well-documented in various lymphoid malignancies, particularly in numerous human B-cell malignancies such as B-cell chronic lymphocytic leukemia (B-CLL), Burkitt's lymphoma, large B-cell lymphoma (Zapata et al., 2012) and non-Hodgkin lymphomas (Dürkop et al., 1999). Polymorphic variations in TRAF1 genes are implicated in the tumorigenesis of non-Hodgkin lymphomas and are associated with various diseases, including rheumatoid arthritis, systemic lupus erythematosus, and atherosclerosis (Cerhan et al., 2007; Xu et al., 2013; Lalani et al., 2019). In conclusion, this case-control study aims to identify potential susceptibility genes, supporting a polygenic model based on genetic variation and gene expression. By examining TRAF1 polymorphisms, we aim to address existing research gaps and offer valuable insights into the genetic factors contributing to leukemia, specifically ALL, within the Saudi population. These findings may have clinical significance, potentially serving as indicators of tumor aggressiveness and as prognostic markers in leukemia and other cancers.

2. Materials and Methods

Criteria for sample selection:

Whole blood samples were collected from 265 individuals for this study. Gender- and age-matched controls and cases were selected. The study cohort consisted of 150 patients diagnosed with Acute Lymphoblastic Leukemia (ALL) who had no other known pathologies, hematological disorders, or prior history of cancer. In addition, 115 unrelated healthy individuals of both genders, without any clinical signs of cancer or other diseases, served as controls.

Blood sample collection

Blood samples were obtained from all subjects via venipuncture, using ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Genomic DNA was then extracted from the whole blood using the DNeasy Blood & Tissue Kit (QIAGEN).

DNA quantification by spectrophotometric method

DNA purity and concentrations were assessed using a Nanodrop ND-2000c spectrophotometer (Thermo Scientific, Wilmington, DE, USA). The samples were taken to room temperature. The spectrophotometer pedestal was wiped with free tissue soaked with Buffer AE and later with a new dry tissue; Buffer AE was

used as blank. After that, the OD260 was evaluated. The purity of DNA was assessed by measuring the absorption ratio at 260 and 280 nm (A260/A280 ratio), with normal levels between 1.7-1.9. DNA samples were diluted with Buffer AE. Hence, the concentration and purity were determined for each sample. Each sample contained 100 μl of working DNA (50 ng/ μl) labeled and stored at – 20° C.

mRNA relative quantification by quantitative PCR

cDNA synthesis and genomic DNA elimination were carried out using the Reverse Transcription System Kit (Promega, Madison, USA). Quantitative PCR (qPCR) was then performed with TaqMan gene expression assays (ThermoFisher), employing specific probes for the TRAF1 gene (Catalog #4331182, Assay ID: Hs01090170_m1). GAPDH served as the reference gene, and its expression was quantified using the TaqMan® gene expression assay (Catalog #4331182, Assay ID: Hs02758991_g1) (ThermoFisher) as an endogenous control for normalization. All reactions were conducted in triplicate, utilizing 25 ng of cDNA per reaction on the QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems, USA). The amplification protocol began with an initial denaturation at 95°C for 5 minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds, annealing at 60°C for 60 seconds, and extension at 72°C for 30 seconds, concluding with a final extension step of 10 minutes at 72°C. Gene expression levels were calculated relative to the control group using the comparative CT method (the $2^{-\Delta\Delta Ct}$).

Statistical Analysis

The control data was evaluated using the Hardy-Weinberg equilibrium test to identify any deviations in the control samples. Chi-square analysis was employed to compare genotype distributions and allele frequency differences between groups. SNP genotypes were categorized into three groups: homozygous for the ancestral allele, heterozygous, and homozygous for the minor allele. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the strength of associations. Statistical significance was determined using a two-tailed p-value threshold of ≤ 0.05. All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

3. *Results:*

Association between TRAF1 (rs2239657 G/A) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

Frequencies of the TRAF1 rs2239657 GG (wild type), GA (heterozygous), and AA (polymorphic homozygous) genotypes were 4%, 36.7%, and 59.30% in ALL patients, and 6.1%, 31.3%, and 62.6% in the healthy control group, respectively. Moreover, frequency of the TRAF1 rs2239657 G allele was 0.22% and 0.22% in the ALL patient and control groups, respectively.

The genotype distribution of the TRAF1 rs2239657 was governed by the Hardy–Weinberg equilibrium ($p > 0.05$). The genotype and allele frequencies did not differ between the patients and the control group for all genetic models except for the over-dominant model, which was found at a higher frequency in cases (36.7%) than in controls (31.3%) as well as a 14.22-fold increased ALL risk **(Table 2).**

Table 2. Association between TRAF1 (rs2239657 G/A) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

Genetic model type	Genotype/ variant	ALL patients N=150		Controls N=115		Control vs Patients			
		Count	%	Count	%	OR (95% CI)	*P*-value	*AIC*	*BIC*
Codominant	A/A	89	59.30	72	62.6	Ref			
	G/A	55	36.60	36	31.3	13.33 (0.85-208.70)	0.33	534	1432.5
	G/G	6	4	7	6.1	0.51 (0.01-42.81)	0.52		
Dominant	A/A	89	59.3	72	62.6	1	0.11	534	1428.9
	G/A-G/G	61	40.7	43	37.4	6.60 (0.57-76.44)			
Recessive	A/A- G/A	144	96	108	93.9	1	0.47	536	1431
	G/G	6	4	7	6.1	0.26 (0.01-11.22)			
Over-dominant	**A/A-G/G**	**95**	**63.3**	**79**	**68.7**	**1**	**0.03**	532	1427
	G/A	**55**	**36.7**	**36**	**31.3**	**14.22 (0.94-214.31)**			
Log-additive	---	---	---	---	---	2.09 (0.38-11.46)	0.38	535.8	1430.7
Allele frequency	A	178	0.78	180	0.78	Ref			
	G	67	0.22	50	0.22	0.96 (0.638-1.462)	0.87	---	---

Association between TRAF1 (rs2416804 G/C) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

Frequencies of the TRAF1 rs2416804 GG (wild type), GC (heterozygous), and CC (polymorphic homozygous) genotypes were 20.7%, 44.7%, and 34.7% in ALL patients, and 10.4%, 55.7%, and 33.9% in the healthy control group, respectively. Moreover, the TRAF1 rs2416804 C allele frequency was 0.57% and 0.62% in the ALL patient and control groups, respectively **(Table 3).**

The results showed that TRAF1 SNP rs2416804 had a statistically significant protective association with Saudi ALL patients. The heterozygous variant "GC" genotype showed significant association against the disease (OR: 0.4; $\chi 2$ =1.21; CI: 0.19-0.85; p= 0.01). Carriage of the C allele was significantly associated with decrease ALL risks (OR: 0.46; 95% CI: 0.32- 0.66; P= 0.0001).

In addition, the genotype distributions did not significantly deviate from Hardy-Weinberg expectations for both groups ($p > 0.05$). For the significant models TRAF1 rs2416804 G/C, the Recessive model was the best fit (AIC= 513 and BIC= 1407.9).

Table 3. Association between TRAF1 (rs2416804 G/C) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

Genetic model type	Genotype/ variant	ALL patients N=150		Controls N=115		Control vs Patients			
		Count	%	Count	%	OR (95% CI)	*P*-value	*AIC*	*BIC*
Co-dominant	CC	52	34.7	39	33.9	Ref			
	GC	67	44.7	64	55.7	0.405 (0.192-0.857)	**0.01**	514.7	1413.2
	GG	31	20.7	12	10.4	0.516 (0.235-1.132)	0.09		
Dominant	C/C	52	34.7	39	33.9	1	0.08	533.5	1428.5
	G/C-G/G	98	65.3	76	66.1	16.89 (0.52-545.48)			
Recessive	C/C-G/C	119	79.3	103	89.6	1	0.25	513	1407.9
	G/G	31	20.7	12	10.4	0.447 (0.218-0.916)			
Over-dominant	C/C-G/G	83	55.3	51	44.4	1	0.17	534.7	1429.6
	G/C	67	44.7	64	55.6	0.17 (0.01-2.41)			
Log-additive	---	---	---	---	---	NA (2.44-NA)	0.09	519.7	1414.6
Allele frequency	C	171	0.43	88	0.38	Ref			
	G	129	0.57	142	0.62	0.46 (0.32- 0.66)	**0.0001**	---	---

Association between TRAF1 (rs7021049 G/T) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

The genotype distribution of TRAF1/C5 rs7021049 polymorphism among the control group did not deviate from Hardy-Weinberg equilibrium (p =0.07). As shown **in Table 4,** non-significant evidence was found in neither genotype (p> 0.05) nor allele (T vs. G, p = 0.47) distribution of TRAF1/C5 rs7021049 polymorphism between ALL patients and healthy controls.

Table 4. Association between TRAF1 (rs7021049 G/T) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

Genetic model type	Genotype/ variant	ALL patients N=150		Controls N=115		Control vs Patients			
		Count	%	Count	%	OR (95% CI)	*P*-value	*AIC*	*BIC*

Codominant	TT	48	32	37	32.2	Ref			
	GT	76	50.7	65	56.5	0.58 (0.27-1.23)	0.15	537.1	1435.6
	GG	26	17.3	13	11.3	0.64(0.29-1.43)	0.28		
Dominant	T/T	48	32	37	32.2	1	0.57	536.2	1431.2
	G/T-G/G	102	68	78	67.8	1.96 (0.19-20.13)			
Recessive	T/T-G/T	124	82.7	102	88.7	1	0.44	536	1430.9
	G/G	26	17.3	13	11.3	0.31 (0.02-6.29)			
Over-dominant	T/T-G/G	74	49.3	50	43.5	1	0.25	535.2	1430.2
	G/T	76	50.7	65	56.5	3.84 (0.36-40.87)			
Log-additive	---	---	---	---	---	0.98 (0.21-4.59)	0.98	536.6	1431.5
Allele frequency	T	172	57.3	91	39.5	Ref			
	G	128	42.6	139	60.5	0.88 (0.62-1.24)	0.47	---	---

Association between TRAF1 (rs3761847 G/A) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

Frequencies of the TRAF1 rs3761847 GG (wild type), GA (heterozygous), and AA (polymorphic homozygous) genotypes were 26%, 42%, and 32% in ALL patients, and 8.7%, 59.1%, and 32.2% in the healthy control group, respectively. Moreover, frequency of the TRAF1 rs3761847 G allele was 53% and 62% in the ALL patient and control groups, respectively.

The genotype and allele frequencies of the rs3761847 in TRAF1 gene in ALL patients and the control group are shown in **Table 5.**

There was a highly significant difference in the distribution of TRAF1 rs3761847 genotypes GA vs. AA for the Co-dominant model between the patient and control groups (OR: 0.23; $\chi 2$ =13.22; CI: 0.10-0.51; $p < 0.001$). Moreover, carriers of the minor allele A were at significantly reduced risk of ALL compared with carriers of the G allele (OR: 0.69; $\chi 2$ =4.05; CI: 0.49-0.99; p= 0.044). In addition, the genotype distributions did not deviate from Hardy-Weinberg expectations for both groups (p> 0.05).

Table 5. Association between TRAF1 (rs3761847 G/A) genotype and allele frequencies for genetic models with the AIC and BIC scores in patients with ALL and control group

Genetic model type	Genotype/ variant	ALL patients N=150		Controls N=115		Control vs Patients			
		Count	%	Count	%	OR (95% CI)	*P*-value	*AIC*	*BIC*
Codominant	A/A	48	32	37	32.2	Ref			
	G/A	63	42	68	59.1	0.23 (0.10- 0.51)	**<0.001**	536.8	1435.3
	G/G	39	26	10	8.7	0.33 (0.14- 0.75)	0.05		
Dominant	A/A	48	32	37	32.2	1	0.68	536.4	1431.3
	G/A -G/G	102	68	78	67.8	0.57 (0.04- 8.41)			
Recessive	A/A- GA	111	74	105	91.3	1	0.2	534.9	1429.9
	G/G	39	26	10	8.7	9.19 (0.25-334.51)			
	A/A-G/G	87	58	47	40.9	1	0.26	535.3	1430.2

Over-dominant	G/A	63	42	68	59.1	0.30 (0.04-2.54)			
Log-additive	---	---	---	---	---	1.64 (0.21-13.12)	0.64	536.3	1431.3
Allele frequency	A	159	47	142	38	Ref			
	G	141	53	88	62	0.69 (0.49-0.99)	**0.04**	---	---

3.2.1. Association of TRAF1 Relative mRNA Expression and ALL.

Analysis of TRAF1 revealed significantly higher mRNA expression in ALL patients in comparison with the control group. Mean Δ Ct of TRAF1; 3.798 ± 0.382 vs 5.057 ± 0.495; p= 0.005 **(Table 6; Figure 1)**. Further analysis of TRAF1 expression using the $2^{\wedge-\Delta\Delta Ct}$ method demonstrated that the expression in ALL patients was also significantly higher than those in healthy donors (fold change: 3.0967 **±** 0.64636, *p*-value: 0.003 **(Figure 2).**

4. Discussion:

TRAF1 (rs2239657G/A, rs2416804 G/C, rs7021049 G/T, and rs3761847 G/A) genotypic analysis: correlation between TRAF1 polymorphism and risk of ALL in Saudi Arabian patients

TRAFs are a family of cytoplasmic adaptor proteins that regulate the signal transduction pathways of many receptors. They play diverse roles in complex signaling pathways in vivo by interacting with various substrates, other adaptors, and transcription factors. These interactions result in distinct outcomes in different signaling complexes. This study is the first to explore whether variants in the TRAF1 gene contribute to the risk of ALL in our population or any other populations. We genotyped four intronic single nucleotide polymorphisms (SNPs) from the TRAF1 adaptor gene.

The frequency of the (G) allele in rs2239657 at the TRAF1 gene in healthy Saudis was 0.22, similar to Africans (0.22) and Punjabis in Lahore (0.23). Furthermore, the highest frequency recorded was in individuals of North and Western European ancestry (0.34). The rs2239657-GA genotype was associated with an increased risk in patients with ALL. These results are in line with the study by Chang et al. (2008), which reported that rs2239657 is a risk factor in American rheumatoid arthritis patients.

Furthermore, the G allele frequency of rs2416804 at the TRAF1 gene in healthy Saudis was 0.62. However, the frequency of the Saudi G allele was higher than that in many populations such as Colombia (0.39), Bengali from Bangladesh (0.29), and Gujarati Indians in Houston (0.27). In contrast, the Mende in Sierra Leone (0.92) and Gambian in Western Division in the Gambia (0.9) have a higher G allele frequency than that of Saudis (1000 Genomes Project Consortium, 2015). In this study, we identified that TRAF1

rs2416804 on chromosome 9 is linked and associated with ALL (G allele; OR: 0.4675; P= 0.0001). Heßler et al. (2016) identified a TRAF1 SNP rs2416804 as associated with carotid intima-media thickness in Germany, which is a marker of the early stage of atherosclerosis. They found that rs2416804 and rs3761847 were in complete linkage disequilibrium, r^2= 0.96. These results contrast with our findings regarding the linkage disequilibrium between rs2416804 and rs3761847 in the Saudi population.

The G allele frequency in rs7021049 at the TRAF1 gene in the healthy participants was 60.5%. A comparison of this studied SNP between the healthy Saudi population and different populations revealed that many populations have a much higher G allele frequency than that of Saudi Arabia, for instance, Gambian in Western Division in the Gambia (0.91) and Mende in Sierra Leone (0.92). However, many populations have a lower G allele frequency than our population, such as Gujarati Indians in Houston (0.27) and Bengalis from Bangladesh (0.3). The association pattern of the TRAF1 gene variant (rs7021049) with ALL resembles the patterns observed in American rheumatoid arthritis patients (Chang et al., 2008).

Additionally, the G allele frequency of rs3761847 (G/A) at the TRAF1-C5 locus in healthy subjects was 62.0%. This is similar but not identical to the data from multiple populations, such as Mende in Sierra Leone (0.62) and Gambian in Western Division in the Gambia (0.6). However, the highest frequency recorded was in the Luhya in Kenya (0.76). Many populations have a lower G allele frequency than that of Saudi Arabia, for instance, Bengalis from Bangladesh (0.29) and Punjabis in Lahore, Pakistan (0.34). The TRAF1/C5 region located on 9q33-34 contains the TRAF1 gene as well as the C5 gene, both of which might be implicated in the development and susceptibility to different diseases. Similarly, Marino (2014) found that the G allele is associated with an increased risk of Alzheimer's disease. Conversely, Huang et al. (2019) did not find any significant association between the rs3761847 polymorphism and genetic susceptibility to rheumatoid arthritis under any genetic models in Chinese. Thus, ethnic disparities account for the differences in frequency among groups.

In this study, we examined the expression levels of TRAF1 in patients with ALL. Our results revealed a markedly elevated expression of the TRAF1 gene in Saudi patients diagnosed with ALL, in contrast to the minimal expression observed in healthy controls. This upregulation is presumably linked to the absence of pharmacological intervention, as the patients were newly diagnosed, potentially influencing the onset and progression of this acute malignancy. Our findings suggest that TRAF1 expression could function as an independent prognostic marker in ALL patients. Furthermore, we hypothesize that SNPs affecting TRAF1 may lead to allele-specific variations in mRNA expression in ALL patients compared to healthy individuals. These polymorphic variations may contribute to the differential regulation of gene expression and are frequently associated with disease susceptibility.

Compared to the control group, TRAF1 mRNA expression was significantly higher in ALL patients. This increased expression might reflect an impaired response toward the malignant clonal populations. Among the TNFR family, TRAF1 is predominantly expressed in the lymphoid system, with its expression restricted to lymphoid tissue (Dürkop et al., 1999). TRAF1 is present at minimal levels in resting lymphocytes and monocytes, similar to our findings in the healthy group, and its expression increases upon activation through the NF-κB pathway (Edilova et al., 2018). Extensive evidence supports the alteration of TRAF1 expression in hematological malignancies (Munzert et al., 2002). Many human B-cell malignancies, including B-cell chronic lymphocytic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and Burkitt's lymphomas, exhibit constitutive activation of the signal transduction system mediated by TRAF1 with CD30, and CD40L, potentially activating NF-κB. Such mutations in TRAF1 have been detected in some blood cancers (Edilova et al., 2018), contributing to apoptosis resistance. Remarkably, TRAF1 is a potential candidate for transducing NF-κB/Rel activity, which mediates the inhibition of apoptosis (Schwenzer et al., 1999).

In this study, the association of the TRAF1 gene with ALL resembles patterns observed in various leukemias and cancers. Munzert et al. (2002) reported TRAF1 and TRAF2 overexpression in B-CLL compared to normal CD19+ B cells, alongside constitutive NF-κB/Rel activation, consistent with findings by Furman et al. (2000). Similarly, Zapata et al. (2000) found TRAF1 overexpressed in 48% of non-Hodgkin lymphoma cases, with the highest levels in B-CLL compared to normal peripheral blood B cells. Overexpression of TRAF1 has been detected in lung cancer (Wang et al., 2018), while low to moderate expression levels have been detected in anaplastic large cell lymphoma and diffuse large B-cell lymphoma (Dürkop et al., 2003). These findings are consistent with our data. Edilova et al. (2018) demonstrated that TRAF1 polymorphism may increase the expression and production of pro-inflammatory cytokines, including TNF and IL-6, suggesting the potential impact of SNPs in TRAF1.

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