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Impact of ITGA4 (Rs200000911) Polymorphism on Gene Expression and Clinical Behavior in Chronic Lymphocytic Leukemia

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ABSTRACT

Background: Single Nucleotide Polymorphisms (SNPs) are crucial biomarkers in hematological malignancies, influencing disease susceptibility, progression, and treatment response. The Integrin Alpha 4 (ITGA4) gene, encoding the α4 integrin subunit, is critical for lymphocyte homing and adhesion and is a therapeutic target.

Objective: This study aimed to investigate the ITGA4 polymorphism (rs200000911) and its gene expression profile in Chronic Lymphocytic Leukemia (CLL) patients. **Patients and Methods:** A case-control study was conducted with newly diagnosed CLL patients and matched controls. Genomic DNA was extracted from peripheral blood, and the rs200000911 locus was amplified via polymerase chain reaction (PCR) and sequenced using the Sanger method. ITGA4 gene expression was quantified using quantitative real-time polymerase chain reaction (qRT-PCR). Clinical parameters and laboratory findings were correlated with genetic data.

Results: The heterozygous TA genotype of rs200000911 was significantly more frequent among CLL patients than controls (45.9% vs. 13.5%, $p < 0.01$) and was associated with a higher risk of CLL (Odds Ratio; OR = 2.22, 95% CI: 1.26–3.91). CLL patients exhibited markedly elevated *ITGA4* expression levels compared with controls ($p < 0.001$). Among CLL cases, the TA genotype correlated with adverse clinical features, including splenomegaly, lymphadenopathy, elevated lactate dehydrogenase (LDH), and increased β2-microglobulin (β2M) levels. Moreover, upregulated *ITGA4* expression was linked to shorter time to first treatment (TTFT) and features of active disease.

Conclusion: The ITGA4 rs200000911 polymorphism and its associated gene expression pattern may contribute to CLL susceptibility and aggressiveness. The TA genotype appears to confer a higher risk and more active disease profile, supporting its potential as a prognostic biomarker. Further multicenter studies with larger cohorts are warranted to validate these findings and explore their translational implications in CLL management.

Keywords: CLL, ITGA4, Single Nucleotide Polymorphism, rs200000911, Biomarker, Gene Expression.

INTRODUCTION

Chronic Lymphocytic Leukemia (CLL) is a clonal malignancy of mature B lymphocytes characterized by a highly variable clinical course and unpredictable response to therapy. Despite recent advances in targeted therapies, CLL remains incurable, with substantial inter-patient variability in disease progression and treatment response [(1)]. This heterogeneity reflects the combined influence of genetic, epigenetic, and microenvironmental factors that regulate leukemic cell survival, proliferation, and migration [(2-3)].

Accumulating evidence from genome-wide association studies (GWAS) has identified multiple Single Nucleotide Polymorphisms (SNPs) associated with cancer susceptibility and clinical behavior, including in CLL [(4)]. Over 80% of disease-associated SNPs lie within noncoding or regulatory regions of the genome, suggesting that they may alter transcription factor binding, gene expression, or post-transcriptional regulation [(5)]. Such genetic variations can significantly influence disease pathogenesis and patient outcomes by modulating key molecular pathways involved in CLL cell survival and tissue homing [(6-7)].

Among these pathways, integrin-mediated adhesion and signaling have gained particular attention. The integrin α4 subunit**,** encoded by the *ITGA4* gene, forms part of the very late antigen-4 (VLA-4; α4β1 integrin)**,** a critical mediator of lymphocyte adhesion to the vascular cell adhesion molecule-1 (VCAM-1) and fibronectin within the bone marrow and lymphoid tissues [(8)]. Through these interactions, VLA-4 not only regulates the trafficking and retention of CLL cells in protective niches but also promotes anti-apoptotic and proliferative signaling that contributes to treatment resistance [(9)]. Elevated expression of CD49d, the protein product of *ITGA4*, has been consistently associated with a more aggressive clinical phenotype and inferior prognosis in CLL[(10)].

The *ITGA4* rs200000911 polymorphism represents a missense variant (A>T) resulting in a lysine-to-arginine substitution at position 256 (Lys256Arg). This amino acid residue lies within a functionally significant extracellular domain involved in ligand and antibody binding [(11)]. Prior studies have suggested that this polymorphism may alter integrin conformation and drug binding affinity, as reported in autoimmune diseases such as multiple sclerosis [(11)]. However, its role in hematologic malignancies, particularly CLL, remains poorly understood. Given the central role of *ITGA4* in CLL cell adhesion, migration, and microenvironmental interactions, genetic variation at this locus could influence disease pathogenesis and progression.

This study aimed to investigate the prevalence and potential clinical relevance of the *ITGA4* rs200000911

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polymorphism and its gene expression pattern in patients with CLL. By exploring its association with disease susceptibility and progression, we sought to elucidate whether this variant could serve as a novel diagnostic or prognostic biomarker, potentially contributing to precision stratification and targeted therapeutic approaches in CLL.

MATERIALS AND METHODS

This case-control study included a total of 37 newly diagnosed, treatment naïve CLL patients, attending at Sohag University Hospital and 37 age and gender matched controls, selected from the outpatient clinic with non-malignant conditions.

The sample size was determined a priori using G*Power software, based on an effect size (Cohen's d = 0.66) derived from prior *ITGA4* protein expression data, requiring a minimum of 37 subjects per group to achieve 80% power at a 5% significance level.

Data collection and procedures:

All patients and controls were subjected to a comprehensive evaluation, which included full history taking (medical, family, and risk factor histories), and a physical examination for both general and specific for signs of CLL. Laboratory investigations comprised a Complete Blood Count (CBC) using a Cell-Dyn 3700 automated cell counter, with morphological assessment of Leishman-stained peripheral blood smears. For CLL patients exclusively, further diagnostic procedures were performed included: bone marrow aspiration to assess marrow involvement and confirm the diagnosis, immunophenotyping via flow cytometry on peripheral blood or bone marrow aspirates to evaluate cell surface markers, and serum testing for LDH and B2-microglobulin levels, biomarkers known to be elevated and correlated with disease activity.

RNA Extraction and Quantitative Real-Time PCR (qRT-PCR):

Total RNA was purified from whole blood using the RNeasy Mini Kit (QIAGEN) on a QiaCube automated extractor according to the manufacturer's protocol. RNA concentration and integrity were assessed using a NanoDrop 2000c spectrophotometer and a Qubit 2.0 fluorometer. Complementary DNA (cDNA) was synthesized from 1 µg of total RNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Gene expression analysis for *ITGA4* (TaqMan Assay ID: Hs00168433_m1) was performed in duplicate on a QuantStudio 3 Real-Time PCR System (Applied Biosystems), with GAPDH (Hs00187842_m1) serving as the endogenous control. The relative expression of the *ITGA4* gene was calculated using the 2^–ΔΔCT method.

DNA Extraction and Genotyping:

Genomic DNA was isolated from peripheral blood samples using the QIAamp DNA Blood Mini Kit (QIAGEN). Primers for the *ITGA4* polymorphism (rs200000911) were designed with Primer Premier 3 software (Macrogen). The optimal annealing temperature for PCR amplification was established at 60°C. Amplification was carried out in a 20 µL reaction volume using a PCR Express thermal cycler (Bio-Rad) with the following profile: initial denaturation at 94°C for 4 minutes; 30 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s; followed by a final extension at 72°C for 7 minutes. The PCR products were purified and sequenced bidirectionally using the Sanger method on an ABI3730XL automated sequencer (Macrogen). Resulting sequences were analyzed for genetic variants using Geneious bioinformatics software, Figure1.

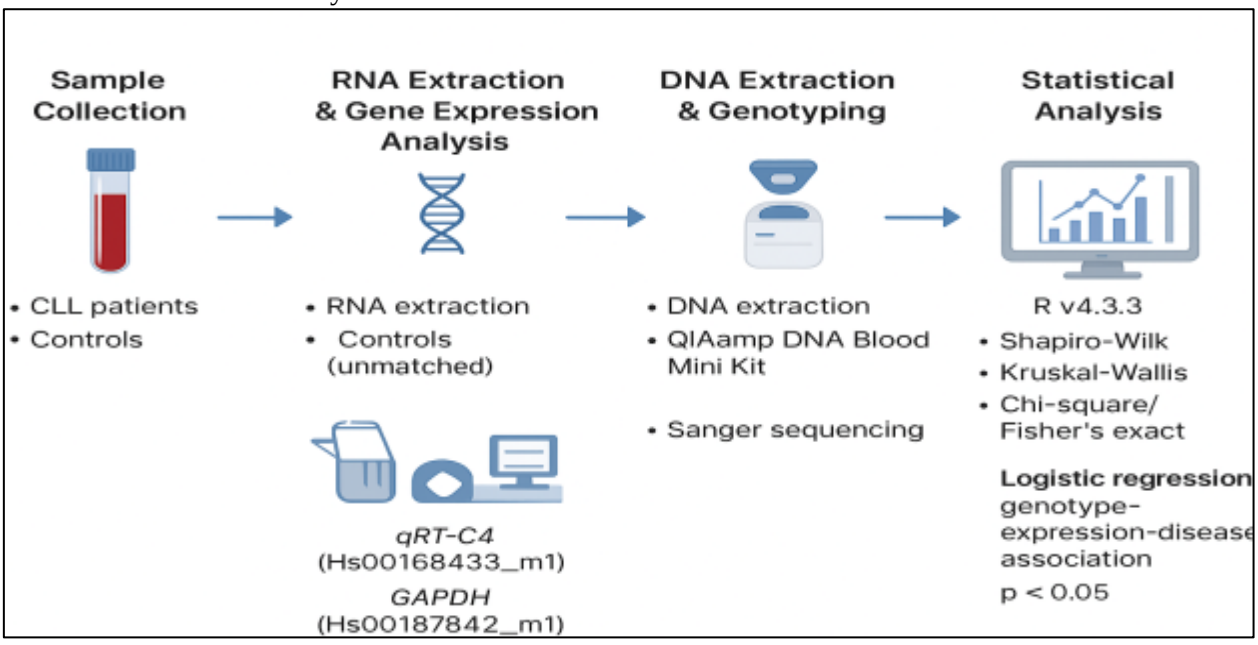

Figure (1): Overview of the experimental workflow for ITGA4 rs200000911 genotyping and expression analysis in CLL patients and controls.

Ethical Considerations:

This study was ethically approved by Sohag Faculty of Medicine's Scientific Ethical Committee. Written informed consent was obtained from all participants. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human subjects.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.3). The Shapiro-Wilk test was used to determine if the data distribution was normal. Continuous variable descriptive statistics were provided as mean ± SD or median and interquartile range, as applicable.

Categorical variables were presented as frequencies and percentages. Group comparisons were conducted using Kruskal Wallis test, X^2-test, or Fisher's exact test. The association between genetic or expression variables and disease status was evaluated using logistic regression. A two-tailed p-value of < 0.05 indicated statistical significance.

RESULTS

A total of 74 participants, comprising 37 CLL patients and 37 matched healthy controls, were included in this study. The mean age was 64.8 ± 12.3 years in the CLL group compared to 59.1 ± 13.6 years in the control group, a difference that was not statistically significant (p=0.062). The gender distribution was similar between groups (p=0.802). Analysis of the ITGA4 rs200000911 (A>T) polymorphism across the entire cohort revealed the AA genotype as the most prevalent (59.5%), followed by TA (29.7%) and TT (10.8%), with the A allele being the predominant allele at a frequency of 74.3%. A statistically significant difference in genotype distribution was observed between CLL patients and healthy controls (p=0.009). The homozygous AA genotype was more frequent in the control group (73.0%) than in the CLL group (45.9%), while the heterozygous TA genotype was markedly more prevalent in the CLL group (45.9%) compared to the control group (13.5%). The frequency of the homozygous TT genotype was similar between groups (CLL: 8.1%, Control: 13.5%), as shown in Figure 2A and B.

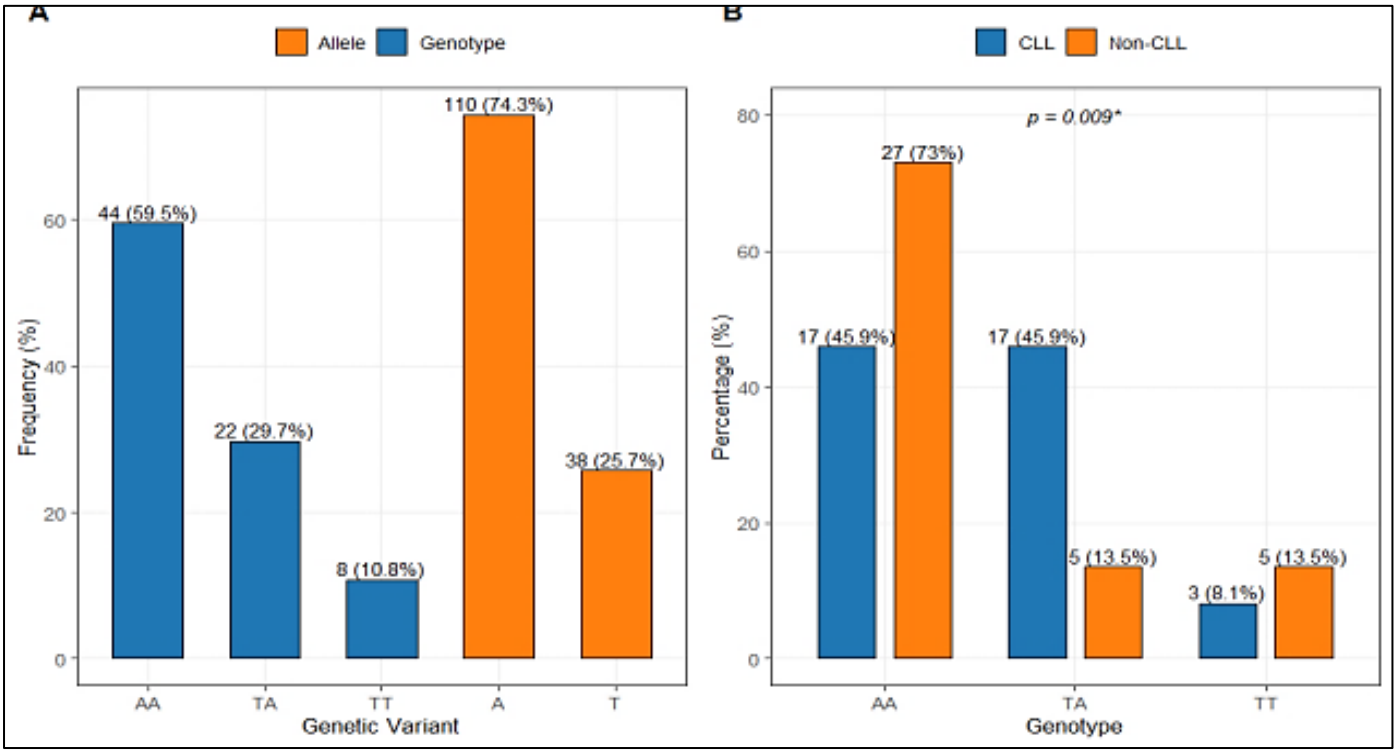

Figure (2): (A) Distribution of genetic variants and Allele frequencies across SNP. **(B)** Genotype distribution by CLL status.

Table 1 shows the clinical characteristics of the study population stratified by the rs200000911 genotype. The cohort consisted of 44 patients (59.5%) with the AA genotype, 22 (29.7%) with the TA genotype, and 8 (10.8%) with the TT genotype.

No significant differences were observed across genotypic groups in terms of age (p=0.982), gender (p=0.789), or the presence of hepatomegaly (p=0.343). However, several clinical parameters showed significant associations. The prevalence of splenomegaly was 36.4% in the TA group compared to 20.5% in the AA group (p=0.045). Similarly, the frequency of lymphadenopathy (p=0.020) and hypercellular bone marrow (p=0.042) varied significantly among the genotypes. While the difference in disease stage distribution approached but did not reach statistical significance (p=0.083), the TA genotype group exhibited the highest proportion of early-stage disease (Stage I-II) at 64.7%, whereas the majority of patients in the AA and TT groups appeared to present with later-stage disease (Stage III-IV). A non-significant trend was observed for mortality, with rates of 18.2%, 36.4%, and 50.0% in the AA, TA, and TT groups, respectively (p=0.088).

Table (1): Demographic and clinical characteristics of the study population stratified by the rs200000911 genotype

rs200000911	**AA (N=44)**	**TA (N=22)**	**TT (N=8)**	**p-value**
Age, years, median (IQR)	63.0 (53.8, 71.5)	62.0 (55.2, 70.0)	63.5 (56.0, 69.5)	0.982
Gender, male, n (%)	31 (70.5%)	14 (63.6%)	6 (75.0%)	0.789
Liver, hepatomegaly, n (%)	9 (20.5%)	5 (22.7%)	0 (0.0%)	0.343
Spleen, splenomegaly, n (%)	9 (20.5%)	8 (36.4%)	2 (25.0%)	**0.045***
Regulation, n (%)				0.418
Down regulation	12 (27.3%)	4 (18.2%)	1 (12.5%)	
Normal regulation	17 (38.6%)	6 (27.3%)	2 (25.0%)	
Up regulation	15 (34.1%)	12 (54.5%)	5 (62.5%)	
Stage (I-II), n (%)	7 (41.2%)	11 (64.7%)	0 (0.0%	0.083
Lymph node, lymphadenopathy, n (%)	11 (25.0%)	9 (40.9%)	3 (37.5%)	**0.020***
Bone marrow cellularity, hypercellular, n (%)	14 (31.8%)	15 (68.2%)	3 (37.5%)	**0.042***
Death, yes, n (%)	8 (18.2%)	8 (36.4%)	4 (50.0%)	0.088

*Significant. X^2 or Exact tests were applied for categorical data, which was represented as a number (%). Kruskal Wallis test was applied for numerical data, which was represented as median and IQR (interquartile range).

Table 2 shows the analysis of laboratory parameters by rs200000911 genotype which revealed several significant associations. Statistically significant differences were observed across genotypic groups for Total Leukocyte Count (TLC), platelet count (PLT), and lactate dehydrogenase (LDH) levels. The median TLC was markedly higher in patients with the TA genotype (28.5) compared to the AA (11.8) and TT (12.3) groups (p=0.004). Similarly, LDH levels were significantly elevated in the TA genotype group (median 433.0) versus the AA (67.0) and TT (94.0) groups (p=0.002). Conversely, platelet counts were lowest in the TT genotype group (median 94.0) compared to the AA (225.0) and TA (196.5) groups (p=0.015). No significant differences were found for hemoglobin level, prothrombin time, B2-microglobulin, ITGA4 gene regulation, or peripheral and bone marrow lymphocyte percentages.

Table (2): Hematological and biochemical parameters associated with rs200000911.

rs200000911	**AA (N=44)**	**TA (N=22)**	**TT (N=8)**	**p-value**
TLC (x10^3/ul)	11.8 (8.1, 18.9)	28.5 (15.5, 51.8)	12.3 (7.9, 36.2)	0.004*
Hb (g/dl)	11.2 (9.7, 12.9)	12.2 (10.5, 13.0)	10.8 (10.5, 11.5)	0.428
PLT (x10^3/ul)	225.0 (146.8, 431.2)	196.5 (112.5, 274.2)	94.0 (76.0, 184.8)	0.015*
PT (seconds)	11.9 (11.1, 12.8)	11.9 (10.9, 12.8)	11.9 (11.2, 12.8)	0.806
LDH (U/L)	67.0 (24.5, 288.0)	433.0 (132.0, 660.5)	94.0 (61.2, 244.2)	0.002*
B2 microglobulin	3.6 (2.7, 4.5)	4.1 (3.3, 4.6)	2.8 (2.6, 3.4)	0.120
ITGA4 gene regulation	0.9 (0.5, 2.6)	2.0 (0.9, 3.0)	2.6 (0.9, 3.4)	0.163
Lymph peripheral	3.7 (2.4, 19.0)	21.4 (5.4, 43.8)	3.5 (2.5, 29.2)	0.150
Lymph BM	62.0 (53.0, 75.0)	73.0 (62.0, 84.0)	74.0 (62.0, 76.0)	0.456

*Significant. Kruskal Wallis test was applied for numerical data, which was represented as median and IQR (interquartile range).

The analysis of immunophenotypic profiles revealed a strong association between the *ITGA4* rs200000911 genotype and the characteristic CLL marker pattern (Table 3).

A consistent and statistically significant trend was observed, wherein the heterozygous TA genotype was strongly associated with the classic CLL immunophenotype. Patients with the TA genotype exhibited significantly higher frequencies of positivity for key markers, including CD5 (72.7% vs. 36.4% in AA, p=0.017), CD23 (72.7% vs. 31.8%, p=0.020), CD200 (77.3% vs. 36.4%, p=0.006), and CD19 (72.7% vs. 36.4%, p=0.036), compared to the homozygous AA group. Furthermore, the TA genotype was associated with a higher prevalence of kappa light chain restriction (54.5% vs. 18.2%, p=0.048).

Notably, the homozygous TT genotype did not demonstrate a consistent pattern, with positivity rates for most markers falling between those of the AA and TA groups. No significant genotypic associations were found for other markers, including CD38, CD22, and FMC7.

Table (3): Association of the *ITGA4* rs200000911 genotype with positive immunophenotypic marker expression in CLL patients

rs200000911	**AA (N=44)**	**TA (N=22)**	**TT (N=8)**	**p-value**
CD38, positive	6 (13.6%)	6 (27.3%)	3 (37.5%)	0.390
CD79b, positive	10 (22.7%)	10 (45.5%)	2 (25.0%)	0.029*
CD22, positive	10 (22.7%)	11 (50.0%)	2 (25.0%)	0.082
CD5, positive	16 (36.4%)	16 (72.7%)	3 (37.5%)	0.017*
CD19, positive	16 (36.4%)	16 (72.7%)	2 (25.0%)	0.036*
CD.45, positive	25 (56.8%)	5 (22.7%)	4 (50.0%)	0.031*
sIgM, positive	12 (27.3%)	6 (27.3%)	5 (62.5%)	0.251
Kappa, positive	8 (18.2%)	12 (54.5%)	3 (37.5%)	0.048*
Lambda, positive	5 (11.4%)	5 (22.7%)	1 (12.5%)	0.177
CD20, positive	18 (40.9%)	15 (68.2%)	3 (37.5%)	0.225
FMC7, positive	3 (6.8%)	3 (13.6%)	1 (12.5%)	0.413
CD23, positive	14 (31.8%)	16 (72.7%)	3 (37.5%)	0.020*
CD.200, positive	16 (36.4%)	17 (77.3%)	3 (37.5%)	0.006*

*Significant. X^2 or Exact tests were applied for categorical data, which was represented as a number (%), comparing the distribution of all categories (ND, Negative, Positive) across genotypes.

A multivariate logistic regression model was constructed to identify independent predictors of CLL (Table 4). After adjusting for covariates, both TLC (OR=1.58, 95% CI: 1.25-2.39, p=0.004) and age (OR=1.08, 95% CI: 1.01-1.23, p=0.013) were significant predictors. Most importantly, the TA genotype of rs200000911 was a strong and independent risk factor for CLL, conferring more than a twofold increase in odds compared to the AA genotype (OR=2.22, 95% CI: 1.20-5.31, p=0.006). The TT genotype did not show a significant association in this model (p=0.454). Hemoglobin, B2 micro globulin, and disease stage were not significant predictors in the final model.

Table (4): Multivariate logistic regression analysis for CLL status.

Predictor	Estimate	p-value	OR	95% CI Lower	95% CI Upper
Age	0.080	0.013*	1.08	1.01	1.23
Stage (I-II)	Ref	Ref	Ref	Ref	Ref
Stage (III-IV)	-0.154	0.99	0.86	0.001	297
Total lymphocytic count	0.456	0.004 *	1.58	1.25	2.39
Hemoglobin	0.042	0.831	1.04	0.70	1.57
B2 micro globulin	-0.148	0.685	0.86	0.30	1.61
rs200000911 (AA)	Ref	Ref	Ref	Ref	Ref
rs200000911 (TA)	0.202	0.006*	2.22	1.20	5.31
rs200000911 (TT)	-4.059	0.454	0.02	0.00	4.97

Null Deviance: 0.0000, Residual Deviance: 2.1466e-10 , AIC: 14, Pseudo R^2: 0.01

DISCUSSION

This study provides novel insights into the potential role of the ITGA4 rs200000911 (A>T) polymorphism and ITGA4 gene expression in the pathogenesis of CLL. Our findings revealed a significant difference in genotype distribution between CLL patients and healthy controls, with the heterozygous TA genotype showing a notably higher frequency among CLL cases. Moreover, the TA genotype was significantly associated with several clinical, hematologic, and immunophenotypic parameters related to disease aggressiveness, suggesting its potential contribution to CLL susceptibility and progression.

The observed enrichment of the TA genotype among CLL patients (45.9%) compared with that in controls (13.5%) and its independent association with CLL risk **(**OR = 2.22, p = 0.006**)** highlighted a possible pathogenic influence of the rs200000911 A>T variant. The A allele was predominant in the overall cohort; however, the T allele, particularly in the heterozygous form, might have exerted **a** dominant or gain-of-function effect influencing leukemogenesis. The lack of a significant association for the TT genotype might have reflected its low prevalence or a possible recessive mechanism that requires larger sample sizes for validation. These findings were consistent with prior reports that implicated integrin gene variants in cancer susceptibility and progression, as such polymorphisms may alter cell adhesion, migration, and signaling pathways critical for tumor survival. Thus, our genetic association findings supported the hypothesis that altered ITGA4 function or regulation contributed **to** CLL pathogenesis [12–13].

No significant associations were found between genotype and age or sex, suggesting that the genotype disease relationships were independent of demographic confounders. Mortality showed a non-significant trend toward higher rates among TA (36.4%) and TT (50.0%) carriers compared with AA (18.2%), consistent with the possibility that ITGA4 variants may influence prognosis [14]. Clinically, the TA genotype was associated with **splenomegaly, lymphadenopathy, and hypercellular bone marrow**, findings indicative of a more proliferative and active disease phenotype. The association pattern is comparable to reports linking polymorphisms in immune-regulatory and adhesion-related genes to enhanced lymphoid proliferation and disease severity[5, 15].

The rs200000911 variant demonstrated strong associations with key hematological markers. Individuals carrying the TA genotype exhibited significantly higher TLC and LDH levels, both indicators of high disease burden, while platelet counts were significantly lower, suggesting more advanced disease in carriers of the T allele. Other parameters, including hemoglobin, prothrombin time, β_2-microglobulin, and ITGA4 regulation status, showed no significant differences across genotypes. These results mirror previous findings linking genetic variants in immune-regulatory and apoptotic genes to hematologic abnormalities in lymphoproliferative disorders [4, 16]. Moreover, similar associations between SNPs and alterations in leukocyte and platelet profiles have been reported in hematological malignancies [17-18]. The elevated LDH and TLC levels among TA carriers further supported the notion that rs200000911 contributed to disease aggressiveness rather than merely disease risk.

Flow cytometry findings reinforced the biological relevance of rs200000911. The TA genotype was significantly associated with higher positivity for CD79b, CD5, CD19, CD45, CD23, CD200, and Kappa light chain ($p < 0.05$ for all). These markers are integral to CLL diagnosis and reflect disease activity. The increased expression of CD5 and CD200 among TA carriers is particularly noteworthy, as both are implicated in immune evasion and sustained B-cell activation, key features of CLL pathophysiology [19-20]. Although markers such as CD38, CD22, and FMC7 did not show statistically significant associations, trends toward higher positivity among TA carriers were observed, suggesting possible genotype-dependent immunophenotypic modulation. These findings correspond with literature highlighting that genetic variations in B-cell regulatory pathways influence immunophenotypic expression in hematologic malignancies [21]. Collectively, these data suggest that rs200000911 may affect surface antigen expression, potentially through alterations in integrin-mediated signaling, thereby modifying the immunophenotypic and biological behavior of leukemic cells.

Logistic regression analysis identified age, TLC, and rs200000911 TA genotype as significant predictors of CLL status. Older age increased risk, while the TA genotype was associated with 2.2-fold higher odds of CLL ($p = 0.006$). These findings reinforce the interplay between host factors and genetic susceptibility in CLL pathogenesis. The TT genotype, although rare, did not reach statistical significance, potentially due to sample size limitations. Other variables, including hemoglobin and β_2-microglobulin, were not significant predictors, consistent with reports of minimal gender or biochemical influence on CLL risk [22].

The strengths of this study included its well-defined, treatment-naïve cohort, the use of standardized molecular assays for both genotyping and expression, and comprehensive clinical and immunophenotypic correlation. However, several limitations should be acknowledged. The sample size, while adequately powered for the primary hypothesis, may limit detection of weaker associations. Functional assays to validate the direct effect of rs200000911 on ITGA4 transcriptional activity were not performed. Finally, the single-center design may affect generalizability, and replication in larger, ethnically diverse populations is recommended.

CONCLUSIONS

The ITGA4 rs200000911 TA genotype is significantly associated with increased susceptibility to CLL and with clinical and immunophenotypic features indicative of a more active disease state. These findings highlight the potential of ITGA4 polymorphisms as novel molecular markers in CLL and underscore the role of integrin-mediated signaling in leukemogenesis. Future studies integrating functional genomics and longitudinal follow-up are essential to confirm these results and explore their translational utility in precision oncology.

Authors' contributions: Amer Ahmed Youssef contributed to study conception, sample collection, data acquisition, and performed molecular analyses. **Abdelrahman A. Elsaied** supervised the study design, provided expert guidance on data interpretation, and critically revised the manuscript. **Ahmed Ahmed Allam** contributed to molecular and statistical analysis, result interpretation, and manuscript drafting. **Heba Abdelhafiz Ahmed** assisted in laboratory validation, data analysis, and manuscript review. The final text was examined and approved for submission by all authors.

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