Official Journal of Erciyes University Faculty of Medicine

DOI: 10.14744/cpr.2025.73280
J Clin Pract Res 2025;47(2):111–118

CD19 Deficiency Leads to Dysregulation of Phosphoinositide 3-Kinase-Protein Kinase B (*PI3K/AKT*) and Nuclear Factor Kappa B (*NF-κB*) Pathways: Implications for B-Cell Maturation and Immune Function

Serkan Küççüktürk,[1] Mehmet Ali Karaselek,[2] Tuğçe Duran,[3] İsmail Reisli[2]

[1]Department of Medical Biology, Karamanoğlu Mehmetbey University, Faculty of Medicine, Karaman, Türkiye
[2]Department of Pediatric Immunology and Allergy, Necmettin Erbakan University, Faculty of Meram Medicine, Konya, Türkiye
[3]Department of Medical Genetics, KTO Karatay University, Faculty of Medicine, Konya, Türkiye

Some information from the preliminary study of this article was presented as a poster at the 9th National Congress of Clinical Immunology (May 1–4, 2023).

Cite this article as:
Küççüktürk S, Karaselek MA, Duran T, Reisli İ. CD19 Deficiency Leads to Dysregulation of Phosphoinositide 3-Kinase-Protein Kinase B (*PI3K/AKT*) and Nuclear Factor Kappa B (*NF-κB*) Pathways: Implications for B-Cell Maturation and Immune Function. JClinPractRes2025;47(2):111–118.

Address for correspondence:
Serkan Küççüktürk.
Department of Medical Biology, Karamanoğlu Mehmetbey University, Faculty of Medicine, Karaman, Türkiye
Phone: +90 338 226 20 90
E-mail: skuccukturk@kmu.edu.tr

Submitted: 07.11.2024
Revised: 25.12.2024
Accepted: 26.01.2025
Available Online: 24.03.2025

Erciyes University Faculty of Medicine Publications - Available online at www.jcpres.com

ABSTRACT

Objective: CD19 is a cellular receptor belonging to the immunoglobulin (Ig) superfamily and serves as a critical signaling component in B-cells differentiation and activation. This study investigates gene expression changes in the phosphoinositide 3-kinase/protein kinase B (*PI3K/AKT*) and nuclear factor kappa-light-chain-enhancer of activated B cells (*NF-κB*) pathways in patients with CD19 deficiency. The role of CD19 in B-cell function was explored, along with its potential impact on these signaling pathways and the overall immune response.

Materials and Methods: RNA samples were obtained from three patients diagnosed with CD19 deficiency, as well as heterozygous carriers and healthy controls. Gene expression profiles related to the *PI3K/AKT* axis and *NF-κB* pathway were analyzed using quantitative polymerase chain reaction (PCR).

Results: The study revealed significant alterations in the expression of signaling pathway components, including *PI3K*, phosphoinositide-3-kinase regulatory subunit 1 (*p85*), TNF receptor-associated factor 2 (*TRAF2*), forkhead box O1 (*FOXO1*), and *NF-κB*, in CD19-deficient patients. While *PI3K* and *NF-κB* expression were significantly downregulated in these patients, *CD19*, *p85*, *FOXO1*, and *TRAF2* expression were markedly upregulated. These changes suggest impaired B-cell function, leading to weakened immune system responses.

Conclusion: CD19 deficiency disrupts B-cell receptor signaling, resulting in significant alterations in the *PI3K/AKT* axis and *NF-κB* pathways. These disruptions impair B-cell maturation and survival, ultimately leading to compromised immune responses. This study provides the first detailed molecular insights into the effects of CD19 deficiency, enhancing our understanding of how these signaling pathways regulate immune function.

Keywords: B cell maturation, CD19 deficiency, immune responses, nuclear factor kappa B (*NF-κB*), phosphoinositide 3-kinase-protein kinase B (*PI3K/AKT*) axis.

INTRODUCTION

CD19 is a cellular receptor belonging to the immunoglobulin superfamily (IgSF), consisting of a 61 kDa protein with 556 amino acids, localized on chromosome 16. CD19 is a transmembrane protein essential for B-cell development and activation, serving as a critical signaling component.[1–3] CD19 cooperates with CD21, CD81, and CD225 in mature B cells to regulate B-cell receptor (BCR) signaling. The CD19 complex also strengthens adaptive immunity by mediating interactions between the innate and adaptive systems.[4, 5] The cytoplasmic domain of CD19 acts as a specific adapter protein, recruiting multiple kinases upon BCR-mediated signaling.[6] Within the BCR complex, CD19 regulates B-cell function via the phosphatidylinositol 3-kinase-protein kinase B (*PI3K/AKT*) and nuclear factor kappa B (*NF-κB*) signaling pathways.[7,8]

CD19 gene mutations cause CD19 deficiency, classified as a common variable immunodeficiency (CVID) within the "predominantly antibody deficiencies" subgroup of inborn errors of immunity (IEI).[9,10] Although IEI cases due to variations in the CD19 coreceptor are rare, CD19 deficiency (c.973_973insA; p. Arg325AlafsX4) was first described by our group in 2006, and to date, only 11 cases have been reported in the literature.[11–15] The frequency of CD19 deficiency cases resulting from isolated CD19 gene mutations is relatively low, leading to limited available data on the disease. Current findings indicate that CD19 deficiency clinically presents with recurrent infections, accompanied by laboratory findings such as hypogammaglobulinemia, absent CD19 expression in flow cytometry, low CD21 expression, and altered memory B-cells levels.[11–15]

Although variations in the *CD19* gene affect the BCR complex, no data are available in the literature regarding their impact on downstream signaling pathways. Therefore, this study aimed to evaluate gene expression changes involved in the *PI3K/AKT* (Pathway-1) and *NF-κB* (Pathway-2) signaling pathways, including *CD19*, *PI3K*, AKT, forkhead box O1 (*FOXO1*), *NF-κB*-inducing kinase (*NIK*), tumor necrosis factor receptor-associated factor 2 (*TRAF2*), *TRAF3*, inhibitor of nuclear factor kappa-B kinase subunit alpha (*IKKα*), *NF-κB*, RELB proto-oncogene (*RelB*), nuclear factor kappa B subunit 2 (*p52*), nuclear factor kappa B subunit 3 (*p65*), RELA proto-oncogene (*RelA*), nuclear factor kappa B subunit 1 (*p50*), phosphoinositide-3-kinase regulatory subunit 1 (*p85*), phosphoinositide-3-kinase catalytic subunit alpha (p110), and mitogen-activated protein kinase kinase kinase (*MAP3K*). Gene expression analysis was performed using the quantitative polymerase chain reaction (qPCR) method in patients with CD19 deficiency.

KEY MESSAGES

- CD19 deficiency impairs immune function by disrupting the PI3K/AKT axis and NF-κB signaling pathways, leading to alterations in B-cell function.
- Regarding gene expression changes, decreases in PI3K and NF-κB and increases in CD19, p85, FOXO1, and TRAF2 were prominent among the related mechanisms.
- This study elucidates the molecular mechanisms underlying CD19 deficiency, highlighting the crucial role of these pathways in immune dysregulation.

MATERIALS AND METHODS

Study Design and Patients

This study was conducted in the Department of Pediatric Immunology and Allergy in May 2023. Three previously documented patients with CD19 deficiency (c.973_973insA; p. Arg325AlafsX4; GenBank: AH005421.2) were included (Fig. 2).[11,12,16,17] All patients came from separate families, and consanguinity was present between their parents. The study also included six heterozygous carriers of the identified mutation: four relatives (parents and two siblings) of one patient (P3) and two relatives (child and partner) of another patient (P2). Blood samples (2 mL) were collected from all participants. qPCR analyses were performed in triplicate. Gene expression results were analyzed and compared across three distinct groups: patients, heterozygous carriers, and healthy controls. CD19-mediated signaling pathways are illustrated in Figure 1a. The study received approval from the Institutional Review Board of Necmettin Erbakan University (Approval Number: 2023/4221), and all participants provided written informed consent.

Molecular Analysis

To evaluate gene expression changes involved in the Pathway-1 and Pathway-2 signaling pathways, primers for the target genes were designed (Table 1).

Two-milliliter peripheral blood samples were collected from all participants in K3-EDTA tubes for gene expression analysis. Peripheral blood mononuclear cells (PBMCs) were isolated by gradient centrifugation (400 g, 30 min) using Ficoll-Hypaque. For RNA isolation, peripheral blood mononuclear cells were suspended in 500 µL of QIAzol reagent (Qiagen, India). RNA precipitation was performed following phase separation with chloroform. The RNA was washed with 70% ethanol and stored in nuclease-free

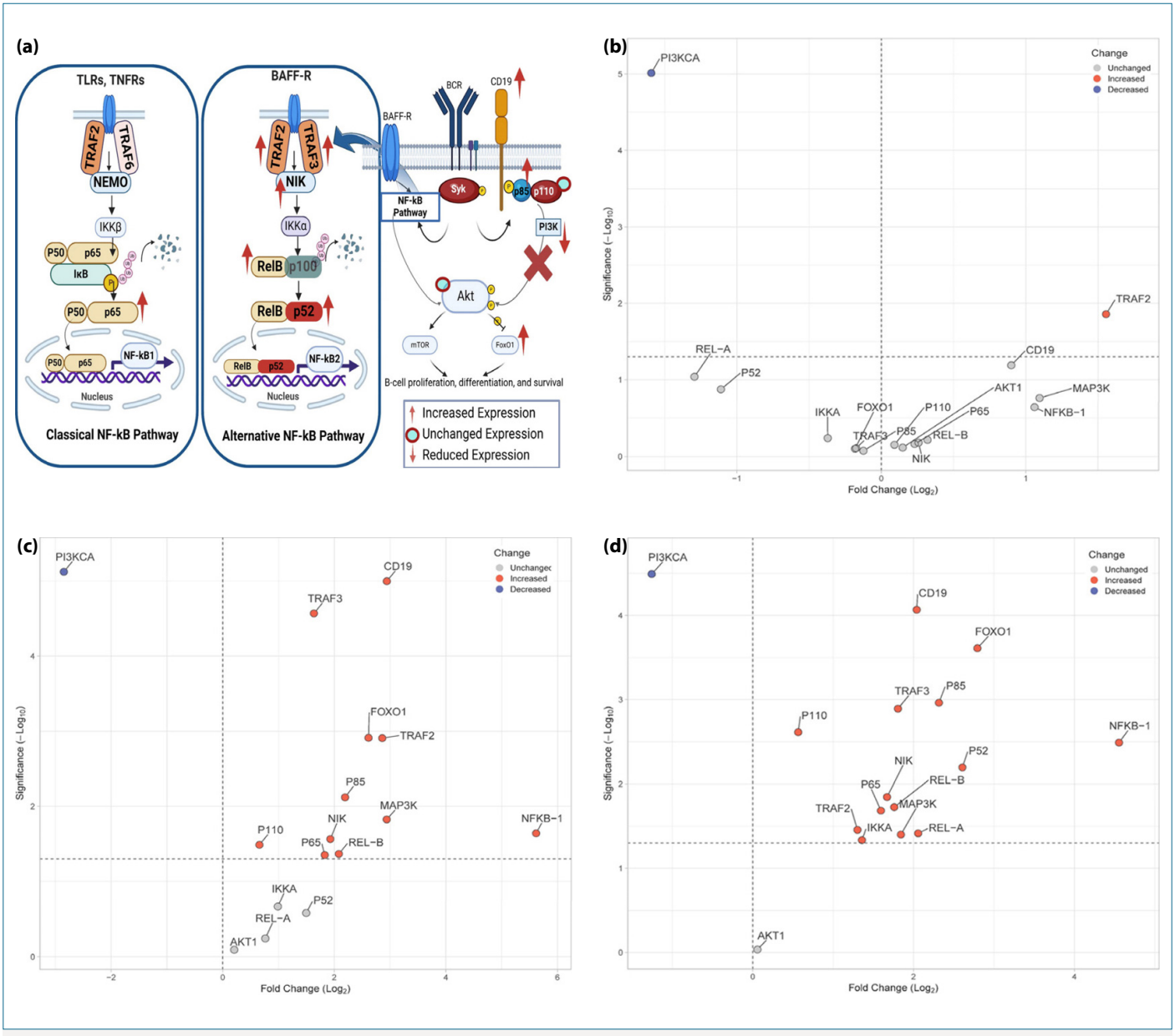

Figure 1. Volcano plot showing gene expression results (log_2): **(a)** CD19-mediated signaling pathways are illustrated, **(b)** Heterozygous vs. control, **(c)** Patient vs. control, **(d)** Patient vs. heterozygous and CD19-mediated signaling pathways. (Red dots indicate increased significant expression, blue dots indicate decreased significant expression, and grey dots represent insignificant changes or unchanged expression. For volcano plots, the right side of the "0" point on the fold-change (Log_2) axis represents increased expression, while the left side represents decreased expression. The value of "1.3"on the significance ($-Log_{10}$) axis indicates $p<0.05$ at the top and $p>0.05$ at the bottom).

water. Complementary DNA (cDNA) synthesis was carried out using a high-capacity kit with an RNase inhibitor (A.B.T™, Türkiye) and the ProFlex 3x32 well polymerase chain reaction (PCR) system (TF Scientific Inc., USA). Subsequently, gene expression levels were evaluated based on qPCR results.

For qPCR analysis, SYBR mix (Hibrigen, 2x SYBR Green Master Mix, Türkiye) was used, and amplification was performed on the QuantStudio 3 qPCR system (TF Scientific Inc., USA). The final reaction volume was 10 µL, consisting of 5 µL of 2X SYBR mix, 5 pMol primers, and 2 µL of cDNA. The qPCR protocol included an initial denaturation at 95°C for 10 seconds,

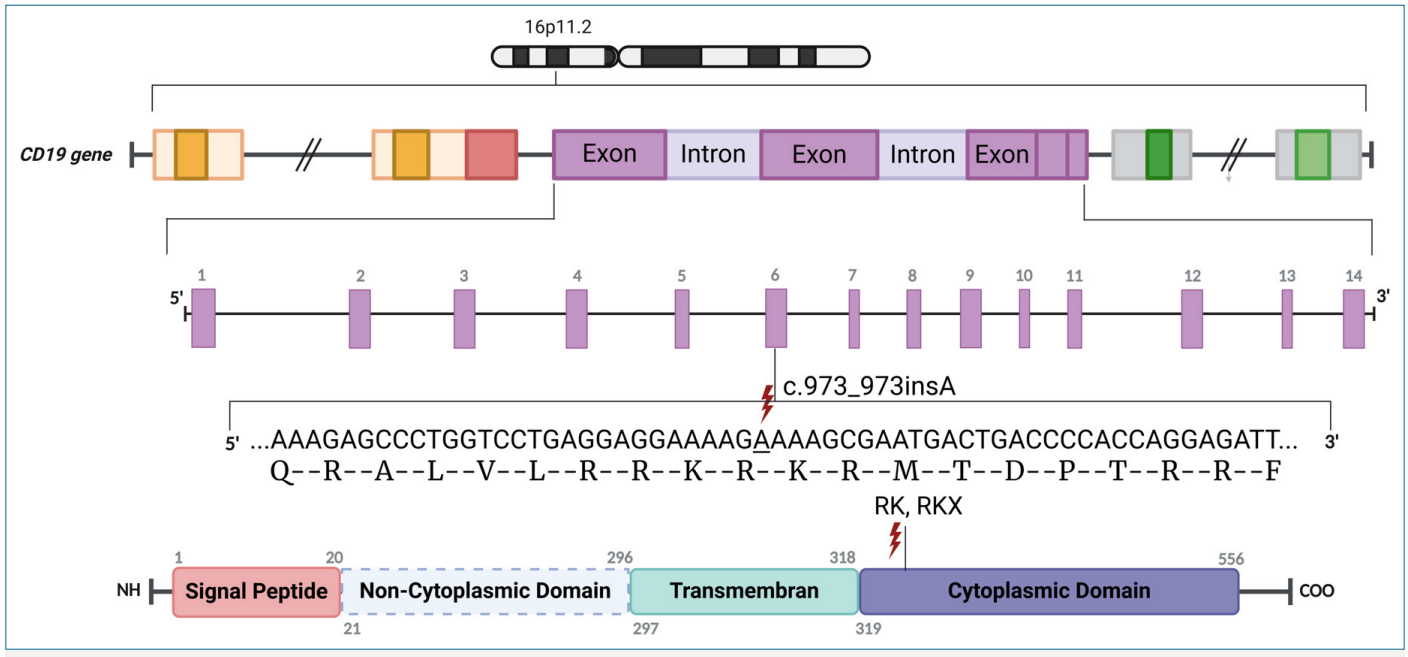

Figure 2. CD19 gene structure, mutation location in the gene, and protein representation (Created in BioRender. Karaselek, M. (2025) https://BioRender.com/z77z651).

followed by 40 cycles of two-step amplification at 95°C for 15 seconds and 57°C for 30 seconds.

Statistical Analysis

Livak's method was used to calculate relative gene expression, normalized (ΔCt) to β-actin.[18] Group comparisons were performed using normalized delta Ct values, analyzed with Jamovi (Version 2.5) (Retrieved from https://www.jamovi.org, Accessed on June 27, 2024), using Student's t-test. An alpha value of 0.05 was set as the threshold for statistical significance. VolcaNoseR was used to generate volcano plots, highlighting distinctive and/or upregulated features.[19]

RESULTS

Demographic Characteristics of Patients

The patients' ages at diagnosis and current age were 8/31 years (P1), 10/21 years (P2), and 6/8 years (P3), respectively. The male-to-female ratio was 1:2. Flow cytometry analysis showed no CD19 expression in patients (Table 2), whereas heterozygous individuals exhibited half the CD19 expression levels observed in controls (Fig. 1b). On admission, all patients presented with recurrent sinopulmonary infections.

Gene Expression Analyses of Pathway-1 and Pathway-2 Signaling Pathways

Gene expression results for the pathways were compared across three distinct groups: patients, heterozygous carriers, and healthy controls.

Expression levels in patients compared to controls showed significant upregulation of *CD19* (7.67-fold; p<0.001), *p85* (4.57-fold; p=0.007), *FOXO1* (6.11-fold; p=0.001), *TRAF2* (7.25-fold; p=0.001), *TRAF3* (3.10-fold; p<0.001), *NIK* (3.80-fold; p=0.025), *RelB* (4.22-fold; p=0.045), and *MAP3K* (7.66-fold; p=0.015). Conversely, *PI3K* (7.21-fold; p<0.001) and *NF-κB* (1.83-fold; p=0.002) were significantly downregulated in patients (Fig. 1c). No significant alterations were observed in the expression of other genes.

Expression levels in heterozygous carriers compared to controls showed significant downregulation of *PI3K* (3.02-fold; p<0.001) and *NF-κB* (1.48-fold; p=0.038), while *TRAF2* (2.94-fold; p=0.012) and *MAP3K* (2.14-fold; p=0.174) were significantly upregulated. No significant alterations were observed in the expression of other genes (Fig. 1b).

Expression levels in patients compared to heterozygous carriers showed significant upregulation of *CD19* (4.11-fold; p<0.001), *p85* (4.98-fold; p=0.001), *FOXO1* (6.93-fold; p<0.001), *TRAF2* (2.47-fold; p=0.032), *TRAF3* (3.50-fold; p=0.001), *NIK* (3.19-fold; p=0.013), *RelB* (3.38-fold; p=0.017), and *MAP3K* (3.59-fold; p=0.040). Conversely, *PI3K* (2.39-fold; p<0.001) was significantly downregulated in patients (Fig. 1d). No significant alterations were observed in the expression of other genes.

DISCUSSION

CD19 deficiency is a rare disorder characterized by recurrent infections, low antibody levels, and the absence of CD19

Table 1. Genes and primers used in the study

Genes	Forward (5'>3')	Reverse (5'>3')
TRAF2	GCTCATGCTGACCGAATGTC	GCCGTCACAAGTTAAGGGGAA
TRAF3	GCGTGTCAAGAGAGCATCGTT	GCAGATGTCCCAGCATTAACT
NIK	AAAATGGCCCGTGTGTGTTG	GCCGAGTGGAGACTCATCC
IKKA	ATGAAGAAGTTGAACCATGCCA	CCTCCAGAACAGTATTCCATTGC
RELB	CCATTGAGCGGAAGATTCAACT	CTGCTGGTCCCGATATGAGG
NFKB1	GAAGCACGAATGACAGAGGC	GCTTGGCGGATTAGCTCTTTT
RELA	ATGTGGAGATCATTGAGCAGC	CCTGGTCCTGTGTAGCCATT
P65	GTGGGGACTACGACCTGAATG	GGGGCACGATTGTCAAAGATG
P52	GGGCCGAAAGACCTATCCC	CAGCTCCGAGCATTGCTTG
MAP3K	CTACACGCAGTTGCAGTACAT	CAGCAGGATCTGGATCTCCC
PIK3CA	AGTAGGCAACCGTGAAGAAAAG	GAGGTGAATTGAGGTCCCTAAGA
AKT1	TCCTCCTCAAGAATGATGGCA	GTGCGTTCGATGACAGTGGT
P85	TGGACGGCGAAGTAAAGCATT	AGTGTGACATTGAGGGAGTCG
P110	TGAGGTTAAGGCGGCTAGGA	CATGGCGTACTCATCCCCATC
FOXO1	TCGTCATAATCTGTCCCTACACA	CGGCTTCGGCTCTTAGCAAA
CD19	AGAGTCTGACCACCATGCCA	GCGTTATCTCCCTCTTCCACC
β-Actin	CATGTACGTTGCTATCCAGGC	CTCCTTAATGTCACGCACGAT

Table 2. Laboratory features of the patients

Parameters	Patients			Normal range
	P1	P2	P3	
Age at diagnosis (years)	8	10	6	
Lymphocytes (counts/mm^3)	3.700	1.600	1.800	(1.500–5.200)#
CD3+CD4+ (counts/mm^3)	1.369	552	512	(500–2.700)#
CD3+CD8+ (counts/mm^3)	814	637	702	(300–2.100)#
CD19+ (counts/mm^3)	0*	0*	0*	(200–2.200)#
CD20+ (counts/mm^3)	740	820	912	(200–2.000)#
CD3-CD16+CD56+(counts/mm^3)	222	320	252	(200–900)#
IgG (mg/dL)	347*	346*	156*	(842–1.943)#
IgA (mg/dL)	25*	12*	6*	(62–390)#
IgM (mg/dL)	88	56	54	(54–392)#

#: Normal range; *: Below normal value.

expression.[5] Due to the rarity of this condition, studies are limited. In this study, we investigated how CD19 deficiency within the BCR/CD19 complex affects the Pathway-1 and Pathway-2 signaling pathways, focusing on changes in gene expression. This study is the first to report significant alterations in *CD19* expression and downstream signaling pathways at the mRNA level. These findings underscore the critical role of these two signaling pathways in regulating genes related to immune responses and inflammation, potentially influencing disease pathogenesis.

While CD19 aberrations alone can cause inborn errors of immunity, they have also been implicated in lymphomas and autoimmune disorders.[11,20,21] In our cohort, all patients were

diagnosed with IEI, and one patient also had systemic lupus erythematosus (SLE). This observation aligns with previous studies suggesting that CD19 deficiency contributes to both immune dysregulation and autoimmune phenotypes.[5,8]

The CD19 molecule is essential for the functioning of BCR signaling. Upon BCR/CD19 ligation, multiple signaling pathways are activated, notably the *Pathway-1* axis and *NF-κB* cascades, which contribute to B-cell differentiation, proliferation, and survival.[7,22–24] In this study, we found that several genes, including CD19, p85, *FOXO1*, *TRAF2*, *TRAF3*, *NIK*, *RelB*, and *MAP3K*, were more highly expressed in patients than in controls. These findings suggest that highly expressed CD19, a key surface receptor, may indicate hyperactivation or abnormal B-cell responses within the immune system.[25,26]

Despite *CD19* mRNA upregulation, we observed a notable downregulation of *PI3K* and *NF-κB* gene expression, indicating potential suppression of these pathways and their effects on immune responses. Inhibition of the Pathway-1 axis may result in significant impairments in cell growth, survival, and metabolic processes.[23] This suppression may have negative consequences on immune function, contributing to the disease phenotype observed in CD19-deficient patients.

The B-cell activating factor receptor (BAFFR)-*PI3K* axis was also implicated in our findings. BAFFR is responsible for B-cell activation and survival and modulates both the Pathway-1 axis and Pathway-2 signaling.[27,28] The observed suppression of *PI3K* may result from disruptions in BAFFR signaling, affecting B-cell survival and homeostasis.[7,29] As BAFFR-*PI3K* signaling is crucial for B-cell function, its suppression may weaken the immune system and impair B-cell function as the disease progresses.[29,30]

In heterozygous individuals, we observed similar reductions in *PI3K* and *NF-κB* gene expression. This suggests partial disruption of BAFFR signaling, potentially affecting cell survival and homeostasis.[31] CD19, in turn, enhances B-cell activation and strengthens this pathway, which might explain the differing degrees of immune dysregulation observed between heterozygous and homozygous individuals.

Increased expression of TRAF2 and MAP3K highlights their potential roles in disease development. TRAF2, a critical regulator of tumor necrosis factor (TNF) receptor signaling, is crucial for activating the alternative *NF-κB* pathway, which might serve as a compensatory mechanism for BAFFR-*PI3K* disruption. Thus, alternative *NF-κB* activation may help sustain cell survival in this context.[32,33]

Despite increased *CD19* gene expression, the deficiency observed at the protein level could be attributed to post-transcriptional regulation. Increased mRNA synthesis, but reduced mRNA stability or translational efficiency, could explain this discrepancy. Additionally, proteolytic degradation might reduce CD19 protein stability, further contributing to immune dysregulation.[34,35]

When comparing patients and heterozygous individuals, the upregulation of *CD19*, *FOXO1*, *p85*, and *TRAF3* in patients highlights the more severe nature of immune dysfunction. Increased *FOXO1* expression, associated with Pathway-1 inhibition, may trigger apoptosis mechanisms, leading to a reduction in B-cell numbers and a weakened immune response.[26,30]

The upregulation of *TRAF3* is also associated with alternative *NF-κB* pathway activation. *TRAF3* regulates *NIK* degradation, thereby inhibiting the classical *NF-κB* pathway. Consequently, increased *TRAF3* expression shifts signaling towards the alternative pathway, which could exacerbate chronic inflammatory processes and promote disease progression.[22,36,37] We suggest that the increase in *FOXO1* is caused by disruption of the *PI3K/AKT* axis (Pathway-1) and that the CD19 receptor provides an important stimulus within this downstream signaling process.[23,26,28]

In this study, changes in CD19 gene expression levels were thoroughly investigated. However, an important limitation is that the effects of these changes at the protein level and their functional implications were not evaluated. While variations in B-cell subsets can occur in the absence of CD19, our primary focus was on evaluating interactions within signaling pathways rather than B-cell proportions. Therefore, further studies are needed to validate the effects of CD19 deficiency at the protein level, assess B-cell subpopulation differences, and better understand the biological significance of these molecular alterations.

CONCLUSION

The dysregulation observed in the *PI3K/AKT* axis and *NF-κB* pathways suggests that functional immune deficiency and cellular stress may play key roles in disease pathogenesis. The disruptions in the BAFFR-*PI3K* axis could impact immune function and cell survival, while alternative *NF-κB* activation may perpetuate chronic inflammatory processes. Future studies targeting these pathways could provide therapeutic strategies to slow disease progression or enhance immune responses.

Acknowledgements: We would like to thank the individuals who agreed to be contacted for this study.

Ethics Committee Approval: The Necmettin Erbakan University Clinical Research Ethics Committee granted approval for this study (date: 03.03.2023, number: 2023/4221).

Author Contributions: Concept – SK, MAK, İR; Design – SK, MAK, TD; Supervision – MAK, İR; Resource – İR, MAK; Materials – SK, MAK; Data Collection and/or Processing – MAK, TD; Analysis and/or Interpretation – SK, MAK; Literature Search – SK, TD; Writing –SK, MAK; Critical Reviews – SK, MAK, TD, İR.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Carter RH, Fearon DT. CD19: Lowering the threshold for antigen receptor stimulation of B lymphocytes. Science 1992;256(5053):105-7. [CrossRef]
2. Van Noesel CJ, Lankester AC, van Lier RA. Dual antigen recognition by B cells. Immunol Today 1993;14(1):8-11. [CrossRef]
3. Pieper K, Grimbacher B, Eibel H. B-cell biology and development. J Allergy Clin Immunol 2013;131(4):959-71. [CrossRef]
4. Carroll MC, Isenman DE. Regulation of humoral immunity by complement. Immunity 2012;37(2):199-207. [CrossRef]
5. Wentink MWJ, van Zelm MC, van Dongen JJM, Warnatz K, van der Burg M. Deficiencies in the CD19 complex. Clin Immunol 2018;195:82-7. [CrossRef]
6. Okkenhaug K, Vanhaesebroeck B. PI3K-signalling in B- and T-cells: Insights from gene-targeted mice. Biochem Soc Trans 2003;31(1):270-4. [CrossRef]
7. Schweighoffer E, Tybulewicz VL. BAFF signaling in health and disease. Curr Opin Immunol 2021;71:124-31. [CrossRef]
8. Königsberger S, Kiefer F. The BAFFling function of Syk in B-cell homeostasis. EMBO J 2015;34(7):838-40. [CrossRef]
9. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2022;42(7):1473-507. [CrossRef]
10. Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, et al. The 2022 update of IUIS phenotypical classification for human inborn errors of immunity. J Clin Immunol 2022;42(7):1508-20. [CrossRef]
11. Van Zelm MC, Reisli I, van der Burg M, Castaño D, van Noesel CJ, van Tol MJ, et al. An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med 2006;354(18):1901-12. [CrossRef]
12. Artac H, Reisli I, Kara R, Pico-Knijnenburg I, Adin-Çinar S, Pekcan S, et al. B-cell maturation and antibody responses in individuals carrying a mutated CD19 allele. Genes Immun 2010;11(7):523-30. [CrossRef]
13. Kanegane H, Agematsu K, Futatani T, Sira MM, Suga K, Sekiguchi T, et al. Novel mutations in a Japanese patient with CD19 deficiency. Genes Immun 2007;8(8):663-70. [CrossRef]
14. Skendros P, Rondeau S, Chateil JF, Bui S, Bocly V, Moreau JF, et al. Misdiagnosed CD19 deficiency leads to severe lung disease. Pediatr Allergy Immunol 2014;25(6):603-6. [CrossRef]
15. Van Zelm MC, Smet J, van der Burg M, Ferster A, Le PQ, Schandené L, et al. Antibody deficiency due to a missense mutation in CD19 demonstrates the importance of the conserved tryptophan 41 in immunoglobulin superfamily domain formation. Hum Mol Genet 2011;20(9):1854-63. [CrossRef]
16. Efe HI, Karaselek MA, Kapaklı H, Gül Y, Keleş S, Güner ŞN, et al. The use of RFLP method in the diagnosis of CD19 deficiency. Genel Tıp Derg 2021;31(4):420-2. [CrossRef]
17. Karaselek MA, Kapaklı H, Güner ŞN, Kurar E, Küçüktürk S, Keleş S, et al. A family screening of CD19 gene mutation by PCR-RFLP. Eur J Clin Exp Med 2022;20(2):141-5. [CrossRef]
18. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods 2001;25(4):402-8. [CrossRef]
19. Goedhart J, Luijsterburg MS. VolcaNoseR is a web app for creating, exploring, labeling and sharing volcano plots. Sci Rep 2020;10(1):20560. [CrossRef]
20. Küçüktürk S, Karaselek MA, Duran T, Reisli İ. Evaluation of transcription factors and cytokine expressions of T-cell subsets in CD19 deficiency and their possible relationship with autoimmune disease. APMIS 2024;132(2):122-9. [CrossRef]
21. Yang W, Agrawal N, Patel J, Edinger A, Osei E, Thut D, et al. Diminished expression of CD19 in B-cell lymphomas. Cytometry B Clin Cytom 2005;63(1):28-35. [CrossRef]
22. Hobeika E, Levit-Zerdoun E, Anastasopoulou V, Pohlmeyer R, Altmeier S, Alsadeq A, et al. CD19 and BAFF-R can signal to promote B-cell survival in the absence of Syk. EMBO J 2015;34(7):925-39. [CrossRef]
23. Berglund LJ. Modulating the PI3K signalling pathway in activated PI3K delta syndrome: A clinical perspective. J Clin Immunol 2023;44(1):34. [CrossRef]

24. Li X, Ding Y, Zi M, Sun L, Zhang W, Chen S, et al. CD19, from bench to bedside. Immunol Lett 2017;183:86-95. [CrossRef]
25. Deaglio S, Vaisitti T, Billington R, Bergui L, Omede' P, Genazzani AA, et al. CD38/CD19: A lipid raft-dependent signaling complex in human B cells. Blood 2007;109(12):5390-8. [CrossRef]
26. McCaleb MR, Miranda AM, Khammash HA, Torres RM, Pelanda R. Regulation of Foxo1 expression is critical for central B cell tolerance and allelic exclusion. Cell Rep 2024;43(6):114283. [CrossRef]
27. Jellusova J, Miletic AV, Cato MH, Lin WW, Hu Y, Bishop GA, et al. Context-specific BAFF-R signaling by the NF-κB and PI3K pathways. Cell Rep 2013;5(4):1022-35. [CrossRef]
28. Srinivasan L, Sasaki Y, Calado DP, Zhang B, Paik JH, DePinho RA, et al. PI3 kinase signals BCR-dependent mature B cell survival. Cell 2009;139(3):573-86. [CrossRef]
29. Gardam S, Brink R. Non-canonical NF-κB signaling initiated by BAFF influences B cell biology at multiple junctures. Front Immunol 2014;4:509. [CrossRef]
30. Baracho GV, Miletic AV, Omori SA, Cato MH, Rickert RC. Emergence of the PI3-kinase pathway as a central modulator of normal and aberrant B cell differentiation. Curr Opin Immunol 2011;23(2):178-83. [CrossRef]
31. Smulski CR, Eibel H. BAFF and BAFF-receptor in B Cell selection and survival. Front Immunol 2018;9:2285. [CrossRef]
32. Khan WN. B cell receptor and BAFF receptor signaling regulation of B cell homeostasis. J Immunol 2009;183(6):3561-7. [CrossRef]
33. Sun SC. The non-canonical NF-κB pathway in immunity and inflammation. Nat Rev Immunol 2017;17(9):545-58. [CrossRef]
34. Del Nagro CJ, Otero DC, Anzelon AN, Omori SA, Kolla RV, Rickert RC. CD19 function in central and peripheral B-cell development. Immunol Res 2005;31(2):119-31. [CrossRef]
35. Watanabe R, Ishiura N, Nakashima H, Kuwano Y, Okochi H, Tamaki K, et al. Regulatory B cells (B10 cells) have a suppressive role in murine lupus: CD19 and B10 cell deficiency exacerbates systemic autoimmunity. J Immunol 2010;184(9):4801-9. [CrossRef]
36. Tang X, Zhang L, Wei W. Roles of TRAFs in NF-κB signaling pathways mediated by BAFF. Immunol Lett 2018;196:113-8. [CrossRef]
37. Grech AP, Amesbury M, Chan T, Gardam S, Basten A, Brink R. TRAF2 differentially regulates the canonical and noncanonical pathways of NF-kappaB activation in mature B cells. Immunity 2004;21(5):629-42. [CrossRef]