ORIGINAL RESEARCH

Turkish Journal of Immunology, 13(1):43-53

Fc Receptor-Like 3 Gene Polymorphism and the Risk of Lupus Nephritis in Systemic Lupus Erythematosus Patients

Amany Gamal Thabit[1], Michael Nazmi Agban[1], Rania Mohamed Gamal[2], Ahmed Mahmoud Rayan[3], Mona Sallam Embarek Mohamed[1]

[1]Assiut University Faculty of Medicine, Department of Medical Microbiology and Immunology, Assiut, Egypt; [2]Assiut University Faculty of Medicine, Department of Rheumatology and Rehabilitation, Assiut, Egypt; [3]Pharmacist, Minya University Hospital, 61519 Minya, Egypt

Abstract

Objective: Fc receptor-like 3 (*FCRL3*) is a novel autoimmune activator with an immunoregulatory role in several autoimmune disorders, including systemic lupus erythematosus (SLE). We aimed to assess *FCRL3* gene polymorphism in the risk of nephritis and different clinical and laboratory parameters in Egyptian SLE patients.

Materials and Methods: The study categorized SLE patients into two groups with and without lupus nephritis (LN) and compared them with healthy controls. SLE patients underwent clinical and laboratory assessment. Single nucleotide polymorphism of the *FCRL3* gene was done at positions −169A/G rs7528684 and −110C/T rs11264799.

Results: The study included 47 SLE patients divided into patients with and without lupus nephritis (LN) and 40 healthy controls. SLE patients with LN had higher disease activity, were positive for anti-DNA, and had disturbed kidney and liver functions, disturbed hematological parameters, higher inflammatory markers, and lower immunological markers (complement 3 and 4) levels than patients without nephritis. Statistical analysis showed no deviation of genotype frequencies of rs7528648 and rs11264799 of *FCRL3* gene from Hardy–Weinberg equilibrium, neither in SLE patients compared to controls nor in SLE patients with nephritis compared to patients without nephritis.

Conclusion: For the rs7528648 single nucleotide polymorphism (SNP), the C allele and the CC genotype were non-significantly higher in SLE patients than in patients without nephritis. The rs11264799 SNP showed that the frequency of the G allele and the GG genotype was non-significantly higher in LN patients, while the frequency of the A allele was higher among patients without nephritis.

Keywords: *FCRL3*, lupus nephritis, rs7528684, rs11264799, SLE

Correspondence
Mona Sallam Embarek Mohamed

E-mail
monaembarek@aun.edu.eg

Received
December 28, 2024

Accepted
April 14, 2025

Published
April 29, 2025

Suggested Citation
Thabit AG, Agban MN, Gamal RM, Rayan AM, Mohamed MSE. Fc receptor-like 3 gene polymorphism and the risk of lupus nephritis in systemic lupus erythematosus patients. Turk J Immunol. 2025;13(1):43-53.

DOI
10.36519/tji.2025.569

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs. Its prevalence is higher in women, but its course is more critical in men with bad prognosis expeditious (1). The exact etiology of SLE is unclear. However, an interaction that includes genetic and environmental issues triggers the immune system to produce autoantibodies and cytokine dysregulation, resulting in tissue injury (2). SLE is distinguished by the presence of antinuclear and anticytoplasmic antibodies, and other autoantibodies can be found as well (3).

Lupus nephritis (LN) is a severe complication of SLE. Most SLE patients develop kidney affection during the disease course (4). Fc receptor-like (*FCRL*) proteins are groups of six molecules (*FCRL1-FCRL6*) that belong to the immunoglobulin superfamily (5). *FCRL3* is particularly highly valued because it is a significant marker for B lymphocytes and responsible for the maturation and reaction of these cells (6). Other cells that express *FCRL3* include natural killer (NK) and regulatory T (Treg) cells (7). Single nucleotide polymorphism (SNP) in the *FCRL3* has been identified in previous reports (polymorphisms at rs7528684 and rs11264799), and it is associated with the occurrence of autoimmune diseases like rheumatoid arthritis, Behçet's disease, and multiple sclerosis (MS) (8).

Previous data had found an association between the SNP of rs7528684 of the *FCRL3* gene and the occurrence of SLE in Japan (9). The expression of the *FCRL3* gene on various immune cells could be affected by SNP of the gene, which may lead to modulation of the B and T cell activation and function and alter the signaling pathways in these cells (10). Reports about SNP of rs7528684 and rs11264799 in SLE and LN are globally few and lacking for Egyptian SLE patients. Therefore, in this study, we aimed to assess the potential association of common polymorphism of *FCRL3* gene in SLE Egyptian patients with and without nephritis and to correlate *FCRL3* gene polymorphism with different clinical and laboratory data.

Materials and Methods

Study Design and Participants

This hospital-based case-control study included patients with SLE who met the criteria approved by the European League Against Rheumatism (EULAR) Executive Committee and the Board of the American College of Rheumatology (ACR). They were divided into two groups (based on the results of histopathological examination of renal biopsy): a group of SLE patients without LN and another group included SLE patients with LN. Controls comprised healthy age- and sex-matched individuals. Patients aged <18 years old or >60 years old, coexistence of other autoimmune diseases, viral infections (including viral hepatitis B or C), malignancies, and pregnant or lactating females were excluded.

The Institutional Review Board of the Faculty of Medicine, Assiut University, approved the study with the number 04-2023-200089. Written consent was obtained from all participants. Each participant was coded by number to ensure confidentiality.

Clinical and Laboratory Assessment

Controls and SLE patients underwent a full medical history and clinical assessment, including chest, cardiovascular, gastrointestinal, eye, genitourinary, neuropsychiatric, and associated comorbidities. Additionally, they underwent an assessment of disease activity (using the SLE disease activity index; SLEDAI) and disease-induced damage (using the SLEDAI-2K index). Laboratory investigations included complete blood count, liver function tests, kidney function tests, complete urine analysis, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), anti-double stranded DNA (anti-ds-DNA), complement 3 (C3), and complement 4 (C4). Renal biopsy for histopathological grading of LN was collected from SLE patients suspected to have LN.

Determination of FCRL3 Gene Polymorphism (SNP Genotyping)

For the SNP genotyping assay of *FCRL3*, 3 mL of peripheral venous blood was collected from SLE patients and controls in labeled EDTA tubes. Genomic DNA (gDNA) extraction from whole blood was done using QIAamp DNA Blood Mini Kit (Qiagen N.V., Germany; Catalog no: 51104) according to the manufacturer's instructions. NanoDrop® Spectrophotometer (*ThermoFisher Scientific, USA*) was used to quantify and assess the purity of DNA in samples. Determination of FCRL3 gene polymorphism of two studied SNPs was performed using TaqMan™ SNP Genotyping Assay (ThermoFisher Scientific, USA) at positions –169A/G rs7528684 (primer sequences were F:5′GAAAATAATACAAATGTACAGATTA3′ and R:5′GGCTTTAAAAACGGTGGTAC3′) and –110C/T rs11264799 (primer sequences were F:5′CTCAATCCCGGTAGTGATACA3′ and R:5′CTCATAAACAACTTATGTGAGA3′) as recommended previously (11). The total reaction

volume of the allele discrimination reaction mix was 20 µL. The reaction mix was composed of 10 µL Applied Biosystems™ TaqMan™ Universal PCR Master Mix (ThermoFisher Scientific, USA), 0.5 µL of 40XSNP genotyping assay, and 9.5 µL of 20 ng purified gDNA diluted in nuclease-free water.

The reaction was conducted on a 7500 Real-Time PCR system (ThermoFisher Scientific, USA). The following protocol was used: denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 seconds and annealing and extension at 60°C for 1 min. The plate's post-PCR fluorescence measurement was evaluated by real-time PCR software (ThermoFisher Scientific, USA).

Statistical Analysis

All statistical calculations were done using SPSS version 22. Data were statistically described as mean ± standard deviation, or median and range as appropriate, frequencies (number of cases), and relative frequencies (percentages) when appropriate. Student-t test, Mann-Whitney U test, and chi-square test were used. Significance was considered when the *p*-value was ≤ 0.05.

Results

Demographic, Clinical Data, And Treatment Regimens of SLE Patients

The study included 47 SLE patients and 40 healthy controls. SLE patients were 46 (98%) females and one (2%) male and aged 33.2 ± 7.9 years (childbearing age). The mean age at onset of SLE disease in patients was 27.6 ± 7.6 (range 18–40.5) years, with a mean disease duration of 5.3 ± 4.5 (range 0.25–21) years. Healthy controls were age- and sex-matched with SLE patients. Histopathological examination of renal biopsies of SLE patients revealed that 22 (47%) patients had no LN; on the other hand, 25 (53%) patients had LN categorized as class 4 in 24 patients and class 5 in one patient. The mean age of LN patients was significantly younger than those without nephritis (30.3 ± 6.9 years vs. 36.4 ± 8 years; p=0.008). The mean disease duration in LN patients was significantly shorter than patients without nephritis (4.4 ± 2.7 years vs 6.3 ± 5.85 years; p=0.034). Body mass index (BMI) was lower for LN patients than patients without nephritis (24.7 ± 2.9 vs. 25.2 ± 4.5), but differences were not significant (p=0.161). Clinical manifestations of LN patients showed that they significantly had frothy urine and suffered nephrotic syndrome and nasal ulcers more than patients without nephritis. Clinical data, including chest, cardiovascular, gastrointestinal, and associated comorbidities, did not show significant differences between the groups. Arthralgia and arthritis affected LN patients more than others, but such differences did not reach significant levels (Table 1). Treatment medication for SLE patients is shown in Table 2. Significantly, a higher number of LN patients were treated with methotrexate, azathioprine, mycophenolate, and methylprednisolone. No significant differences were shown between the two groups regarding other regimens.

Disease-Induced Damage Among SLE with and without LN according to SLICC/ACR Damage Index and SLEADI-2K

Out of the 25 SLE patients complicated with nephritis, 10 cases (40%) suffered from disease-induced damage as assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index; on the other hand, this number was 2 (9%) among patients without nephritis (p=0.02). Furthermore, patients with LN suffered significantly higher SLEDAI-2K compared to patients without nephritis (p≤0.001), including 19 (76%) patients who suffered severe disease activity and 6 (24%) who suffered very severe activity. Among non-LN patients, 12 (54.5%) had moderate activity, 6 (27%) had mild activity, and 4 (18.2%) had no flare.

Laboratory Findings

Kidney function tests of SLE patients showed that LN patients had significantly higher blood urea, higher serum creatinine, elevated 24-hour protein in urine, and lower creatinine clearance compared to patients without nephritis. LN patients showed significant proteinuria, increased number of casts, red blood cells (RBCs), and pus cells in urine compared to patients without nephritis. Complete blood count findings showed that LN patients were significantly anemic compared to non-LN patients, and RBC count, white blood cell (WBC) count, and platelet count showed no significant differences between both groups (p>0.05). In addition, patients with LN had significantly higher neutrophils, lower lymphocytes, lower eosinophils, and lower basophils than patients without nephritis. Liver function tests showed that LN patients had significantly lower serum protein levels, albumin levels, total bilirubin levels, and alkaline phosphatase enzyme levels compared to patients without nephritis (p<0.05). Meanwhile, aspartate transaminase (AST) and alanine transaminase (ALT) levels show no significant differences between patients with and without

Table 1. Clinical data of SLE patients with and without lupus nephritis (LN).

Variables	Without LN (n=22)	With LN (n=25)	*p*-value*
	n (%)		
Clinical Presentation			
Fatigue	11 (50)	13 (52)	1.00
Morning stiffness	4 (18)	7 (28)	0.500
Fever	2 (9)	2 (8)	1.00
Raynaud's phenomenon	1 (4.5)	0 (0)	0.468
Delirium	1 (4.5)	0 (0)	0.468
Headache	2 (9)	0 (0)	0.214
Frothy urine	3 (13.6)	22 (88)	**<0.001***
Nephrotic syndrome	0 (0)	5 (20)	**0.050***
Alopecia	19 (86.4)	21 (84)	1.00
Vascular purpura	1 (4.5)	1 (4)	1.00
Urticaria	0 (0)	1 (4)	1.00
Malar rash	12 (54.5)	15 (60)	0.773
Oral ulcers	17 (77)	22 (88)	0.446
Nasal ulcers	1 (4.5)	7 (28)	**0.050***
Genitourinary manifestations	0 (0)	1 (4)	1.00
Photosensitivity	15 (68)	21 (84)	0.300
Chest Manifestations			
Dyspnea on exertion	2 (9)	4 (16)	0.530
Cough	1 (4.5)	0 (0)	
Arthralgia	12 (54.5)	14 (56)	1.00
Arthritis	6 (27)	10 (40)	0.540
Cardiovascular			
Palpitation	0 (0)	1 (3.4)	1.00
History of angina	1 (3.2)	0 (0)	
Gastrointestinal			
Constipation	1 (4.5)	0 (0)	0.214
Epigastric pain	1 (4.5)	0 (0)	
Associated Comorbidities			
Diabetes mellitus	1 (4.5)	2 (8)	1.00
Hypertension	1 (4.5)	1 (4)	
Positive Family History	1 (4.5)	0 (0)	1.00

*Significance defined by $p<0.05$

Table 2. Treatment history of SLE patients with and without nephritis.

Treatment	Without LN (n=22)	With LN (n=25)	*p*-value*
	n (%)		
Methotrexate	11 (50)	21 (84)	**0.026**
Hydroquinone	2 (9)	1 (4)	0.590
Sulfasalazine	0 (0)	4 (16)	0.110
Azathioprine	1 (4.5)	9 (36)	**0.012**
Cyclophosphamide	12 (54.5)	18 (72)	0.240
Steroids	15 (68)	22 (88)	0.150
NSAIDS	2 (9)	5 (20)	0.420
Others			
Mycophenolate	0 (0)	4 (16)	**0.014**
Methylprednisolone	0 (0)	2 (8)	
ACEI	0 (0)	1 (4)	
Calcium channel blocker	0 (0)	1 (4)	
Marivan	0 (0)	1 (4)	

ACEI: Angiotensin converting enzyme inhibitors, **NSAIDS:** Non-steroidal anti-inflammatory drugs, **SLE:** Systemic lupus erythematosus.
*Significance defined by $p<0.05$.

nephritis. SLE patients with LN have significantly higher inflammatory markers (ESR & CRP) and significantly lower immunological markers (C3 & C4) compared to those without nephritis ($p<0.05$). All SLE patients were ANA positive ($p=1.00$), while all LN patients were anti-DNA positive compared to patients without nephritis (were negative for anti-DNA) (chi-square; $p\leq0.001$) (Table 3).

FCRL3 Gene Polymorphism and Risk of LN

Table 4 demonstrates the frequencies of genotypes and alleles of rs7528648 and rs11264799 *FCRL3* in SLE patients and controls. There were no significant genotype differences between patients and controls ($p>0.05$). For rs7528648, we found that SLE patients had a higher predominance of the homozygous CC and TT genotypes vs controls. LN patients had a higher CC genotype than patients without nephritis. The frequencies of C and T alleles were higher in SLE patients than in controls. LN patients had a higher C allele than patients without nephritis. Concerning the rs11264799 SNP, there were no significant differences between patients and controls ($p>0.05$). Nevertheless, SLE patients had a higher predominance of the heterozygous AG genotype and higher G and A alleles than the control group.

LN patients had higher GG and AG genotype frequencies than patients without nephritis. The frequency of the G allele was higher in LN patients than in patients without nephritis, while the frequency of the A allele was higher among patients without nephritis. The genotype and allelic frequencies of rs7528684 and rs11264799 genes in SLE patients regarding different clinical data are shown in Table 5. According to renal biopsy grades of 4 and 5, SLICC/ACR Damage Index, and SLEDAI-2K, the predominance of the TC genotype and C allele for the rs7528684 gene, and the GG genotype and the G allele for the rs11264799 gene was observed. However, this predominance was not significant. The genotype and allelic frequencies of rs7528684 and rs11264799 genes in SLE patients regarding different laboratory data are shown in Table 6. For the rs7528684 gene, predominance of the CC genotype was observed with higher levels of 24h protein, significantly higher levels of C4 in serum, and higher levels of CRP.

On the other hand, the TT genotype was predominant, with higher creatinine clearance and higher C3 levels. The heterozygous TC genotype was predominant in higher ESR levels and among patients with positive anti-DNA.

Table 3. Laboratory and immunologic markers of SLE patients with and without nephritis.

Laboratory Tests	without LN (n=22)	with LN (n=25)	*p*-value*
Kidney Function			
Serum urea (mmol/L)	6.7 ± 6	12.43 ± 12.1	**0.012***
Serum creatinine (µmol/L)	72.6 ± 38.2	104 ± 107.6	**0.033***
Serum uric acid (mg/dL)	3.9 ± 1.4	4 ± 1.6	0.567
24h protein in urine (mg/day)	286 ± 142.5	2880 ± 1956	**<0.001***
Creatinine clearance (mL/min)	104.7 ± 38.2	80.4 ± 42	**0.043***
Liver Function Tests			
Total protein (g/L)	72.5 ± 14.4	58.2 ± 15.8	**0.002***
Serum albumin (g/L)	43.2 ± 3.4	33.3 ± 7.6	**<0.001***
Total bilirubin (µmol/L)	10.4 ± 10.9	5.3 ± 3.8	**0.033***
Aspartate transaminase (U/L)	18.9 ± 10.2	24.6 ± 11.16	0.072
Alanine transaminase (U/L)	25.4 ± 15.9	22.7 ± 16.1	0.566
Alkaline phosphatase (U/L)	60.8 ± 22.3	46 ± 22	**0.029***
Urine Examination, n (%)			
Proteinuria	4 (18)	25 (100)	**<0.001***
Casts in Urine			
None	22 (100)	13 (52)	**<0.001***
Hyaline casts	0 (0)	7 (28)	
Granular casts	0 (0)	5 (20)	
Hematuria (RBCs in urine)	3 (9.7)	12 (41.4)	**0.002***
Pyuria (pus in urine)	2 (90)	20 (80)	**<0.001***
Low (6-10 pus cells/HPF)	2 (9)	2 (8)	
Moderate (11-20 pus cells/HPF)	0 (0)	3 (12)	
High (>20 pus cells/HPF)	0 (0)	15 (60)	
Complete Blood Count			
Hemoglobin level (g/dL)	12.3 ± 1.0	10.8 ± 2.3	**0.008***
RBC (10^6/µL)	4.2 ± 0.54	4.0 ± 0.71	0.216
WBC (10^3/µL)	6.6 ± 2.6	6.9 ± 3.8	0.735
Neutrophils (%)	59 ± 15	74 ± 10	**<0.001***
Lymphocytes (%)	27.5 ± 11	18 ± 12.5	**0.008***
Eosinophils (%)	1.8 ± 1.78	0.96 ± 1.0	**0.007***
Basophils (%)	0.45 ± 0.32	0.28 ± 0.31	**0.050***
Platelets (10^3/µL)	250.4 ± 75.5	272.2 ± 85.5	0.358
Inflammatory and Immunologic Markers			
ESR (mm/h)	29.8 ± 25.7	48.8 ± 30	**0.024***
CRP (mg/L)	9 ± 7.2	13.6 ± 7.6	**0.046***
C3 (g/L)	1.53 ± 0.27	0.12 ± 0.25	**<0.001***
C4 (g/L)	1.1 ± 0.66	0.084 ± 0.14	**<0.001***
ANA: Positive, n (%)	22 (100)	25 (100)	1.00
Anti-DNA: Positive, n (%)	0 (0)	25 (100)	**<0.001***

ANA: Antinuclear antibody, **C3:** Complement 3, **C4:** Complement 4, **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate, **LN:** Lupus nephritis, **RBC:** Red blood cells, **WBC:** White blood cells. *Significance defined by $p<0.05$.

Table 4. Genotype & allelic frequencies of the studied cohort (SLE patients vs controls) of rs7528684 (T/C) and rs11264799 (A/G) SNPs of FCRL3 gene.

SNPs (genotype/allele)	Controls (n=40)	SLE patients (n=47)	*p*-value*	Patients without nephritis (n=22)	LN patients (n=25)	*p*-value*
rs7528684, n (%)						
CC	8 (20)	12 (25.5)		5 (23)	7 (28)	
TT	3 (7.5)	6 (12.8)		4 (18)	2 (8)	
TC	29 (72.5)	29 (61.7)	0.60	13 (59)	16 (64)	0.643
C	45 (56)	53 (56.4)		23 (52)	30 (60)	
T	35 (44)	41 (43.6)		21 (48)	20 (40)	
rs11264799, n (%)						
GG	26 (65)	26 (55.3)		11 (50)	15 (60)	
AA	6 (15)	4 (8.5)		3 (13.6)	1 (4)	
AG	8 (20)	17 (36.2)	0.241	8 (36.4)	9 (36)	0.567
G	60 (75)	69 (73.4)		30 (68)	39 (78)	
A	20 (25)	25 (26.6)		14 (32)	11 (22)	

*Significance defined by $p<0.05$.

For the rs11264799 gene, predominance of the AA genotype was observed in higher C3, higher C4, higher ESR, and higher CRP serum levels. At the same time, the homozygous GG genotype was predominant in patients with positive anti-DNA.

Discussion

This study aimed to assess the common polymorphism in the *FCRL3* gene in SLE Egyptian patients with and without nephritis, compare them with healthy controls, and evaluate such polymorphisms with clinical and laboratory data in SLE patients. Our SLE patients were mostly females. It is consistent with Narani (12) and Jolly et al. (13), who concluded that SLE is more common in the female sex, especially at childbearing age. The mean age of our patients complicated with nephritis was younger than that of the patients without nephritis. This finding aligned with previous data that declared that the development of LN in SLE patients occurs at an earlier age than in patients with no nephritis. In addition, LN develops early during the disease, within six to 36 months, and may be present at initial diagnosis (14, 15). Clinical evaluation for SLE patients included in the study revealed that frothy urine, nephrotic syndrome, and laboratory evaluation of proteinuria were significantly higher among patients complicated with LN. Parikh et al. (16) concluded that proteinuria must be present to diagnose LN and nephrotic-range proteinuria clinically, which was found in more than half of the cases in their study.

A considerable number of our LN patients suffered from disease-induced damage as assessed by the SLICC/ACR Damage Index vs patients without nephritis. Also, our LN patients suffered significantly higher disease activity compared to patients without nephritis. Previous data revealed that LN is considered a serious organ involvement in SLE that increases the risk of mortality in those patients. Mortality rate ranges from 5% to 25% in LN patients within 5 years of onset.

Moreover, about a third of LN patients may proceed to renal failure that requires renal replacement treatment (17, 18). In the current study, patients with LN had significantly higher serum urea and creatinine levels and

Table 5. Relation between rs7528684 and rs11264799 genes polymorphism and clinical data in SLE patients (n=47).

Variables	rs7528684						rs11264799					
	CC	TT	TC	C	T	*p*-value	GG	AA	AG	G	A	*p*-value
Renal Biopsy, n (%)												
Class 4 (n=24)	7 (29)	2 (8)	15 (63)	29 (60)	19 (40)	0.78	14 (58)	1 (4)	9 (38)	37 (77)	11 (23)	0.721
Class 5 (n=1)	0 (0)	0 (0)	1 (100)	1 (50)	1 (50)		1 (100)	0 (0)	0 (0)	2 (100)	0 (0)	
SLIC/ACR Damage, n (%)												
Yes (n=12)	4 (33)	1 (8)	7 (53)	15 (63)	9 (37)	0.793	7 (58)	1 (8)	4 (33)	18 (75)	6 (25)	0.858
SLEDAI-2K, n (%)												
Mild activity (n=6)	2 (33)	1 (17)	3 (50)	7 (58)	5 (42)	0.956	3 (50)	2(33)	1 (17)	7 (58)	5 (42)	0.429
Moderate activity (n=12)	2 (17)	2 (17)	8 (67)	12 (50)	12 (50)		6 (50)	1 (8)	5 (42)	17 (71)	7 (29)	
Severe activity (n=19)	5 (26)	2 (10.5)	12 (63)	22 (58)	16 (42)		10 (53)	1 (5)	8 (42)	28 (74)	10 (26)	
Very severe activity (n=6)	2 (33)	0 (0)	4 (67)	8 (67)	4 (33)		5 (83)	0 (0)	1 (17)	11 (92)	1 (8)	

Table 6. Relation between rs7528684 and rs11264799 genes polymorphism and some laboratory data in SLE patients (n=47).

Variables	rs7528684				rs11264799			
	CC	TT	TC	p-value	GG	AA	AG	*p*-value
24 h protein (mg/day)	2381 ± 2778	897±1186	1529 ± 1568	0.257	1714 ± 1885	1414 ± 2036	1652 ± 2083	0.960
Urea (mg/dL)	7.2 ± 5.8	12.3±15.2	10.3 ± 10.4	0.55	11 ± 12	10.7 ± 12	7 ± 5	0.269
Creatinine (mg/dL)	74.8 ± 52	99 ± 45	93 ± 99.4	0.78	100 ± 106	104 ± 85	70 ± 23	0.495
Creatinine clearance (mL/min)	94 ± 36	104 ± 39	88.2 ± 45	0.68	89.3 ± 47	93 ± 54	95 ± 32	0.899
C3 (g/L)	0.75 ± 0.76	1 ± 0.84	0.73 ± 0.76	0.643	0.7 ± 0.76	1.43 ± 0.23	0.74 ± 0.78	0.198
C4 (g/L)	0.65 ± 0.8	0.5 ± 0.56	0.53 ± 0.67	0.852	0.43 ± 0.55	1.4 ± 0.8	0.54 ± 0.44	**0.026**
ESR (mm/h)	36 ± 24	37 ± 27	42 ± 32	0.81	42.3 ± 32	48 ± 33	34 ± 24	0.573
CRP (mg/L)	15.7 ± 7.8	9.3 ± 8.9	10.2 ± 6.7	0.086	11.1 ± 8.6	15.8 ± 4.3	11 ± 6.7	0.517
Anti-DNA: positive (n=25), n (%)	7 (28)	2 (8)	16 (64)	0.643	15 (60)	1 (4)	9 (36)	0.567

significantly lower creatinine clearance compared to SLE patients without nephritis. Also, patients with LN have significantly higher 24-hour protein in the urine, higher hematuria, pyuria, and increased urinary casts compared to patients without nephritis. Previous reports revealed that abnormal laboratory findings of kidney function tests raise the possibility of LN and necessitate renal biopsy for proper diagnosis and grading (16). Also, Pons-Estel et al. (17) declared that LN is a type of glomerulonephritis and represents an important organ manifestation of SLE associated with disturbed renal functions and may lead to end-stage renal failure.

In our study, analysis of liver function tests showed that patients complicated with LN had significantly lower total protein, lower serum albumin levels, and lower total bilirubin levels compared to patients without nephritis. González-Regueiro et al. (19) correlated the degree of hypoalbuminemia and lower total protein level in patients with LN to the degree of proteinuria. Also, intensive

drug therapy for high-class LN can explain the disturbed liver function tests (14). Previous data determined the antioxidant and immunomodulator role of bilirubin, thus acting as a protector against autoimmune diseases (20). In a meta-analysis conducted in 2023, the authors found that levels of bilirubin were significantly elevated in SLE patients without nephritis than in patients with nephritis, as revealed in our study (21).

Our LN patients were significantly anemic compared to those without nephritis. Previous studies clarified that decreased erythropoietin production and erythropoietin resistance in LN contribute to anemia in SLE (22). Additionally, in this study, patients with LN suffered significantly higher neutrophils, lower lymphocytes, lower eosinophils, and lower basophils when compared to patients without nephritis. Abdalhadi et al. (23) explained that high neutrophil counts in SLE patients with nephritis are due to the inability of the complement pathway to get rid of the lupus neutrophils, thus leading to their accumulation. Wanitpongpun et al. (24) declared that the low lymphocytes, eosinophils, and basophils counts in patients with LN were explained based on intensive myelosuppressive drugs used for these patients.

Patients with LN included in this study had significantly higher inflammatory markers (ESR & CRP) and significantly lower immunological markers (C3 & C4) compared to those without nephritis. Our findings are consistent with previous data that declared LN to be a form of glomerulonephritis (inflammation of renal parenchyma) that is markedly associated with elevated inflammatory markers (i.e., ESR & CRP) (17). Complement proteins are engaged in the pathogenesis of LN; any decline in complement levels in serum or the complement deposition/activation in kidney tissues are related to LN and can be used as a diagnostic label for LN (25).

All patients with LN in our study had positive anti-DNA in contrast to patients without nephritis, who were all negative for anti-DNA. Rekvig (26) assumed that the pathogenic potential of anti-DNA interactions is to stir up LN, which could be related to a common pathogenic sequela. Previous reports on genetic polymorphism in the *FCRL3* gene and its relation to SLE are scarce. We evaluated the genotype frequency for rs7528648 and rs11264799 genes of *FCRL3*. Statistical analysis showed no deviation of genotype frequencies of rs7528648 and rs11264799 of *FCRL3* neither in SLE patients in comparison to controls nor LN patients in comparison to non-LN patients. However, certain genotypes and certain alleles were associated with some clinical or laboratory data in SLE patients, such as the predominance of the TC, GG genotypes, and C and G alleles in patients with severe kidney affection, SLICC/ACR damage, and degree of disease activity. Meanwhile, the TT genotype was associated with improved creatinine clearance and elevated C3 levels. The AA genotype was associated with elevated C3 and C4 levels but also with elevated levels of inflammatory markers. Although such associations did not reach significant values, they are still promising. With larger-scale studies, results could reveal significant values.

In contrast to our findings, SNP at rs7528684 was found to be related to SLE in Japanese patients but not in African Americans or European Americans (9). Ikari et al. (27) studies, including rheumatoid arthritis patients in Japanese, Dutch Caucasian, and several autoimmune thyroiditis cohorts in the United Kingdom (UK) and Caucasian populations, reported an association between *FCRL3* variants and these autoimmune diseases. Also, they reported its association with autoimmune pancreatitis in Japan. So, findings reveal that *FCRL3* SNP relations with disease susceptibility are common in variable autoimmune diseases and ethnic populations. The polymorphism in the promoter region of *FCRL3* increases its expression in the disease-risk allele. The preferred expression of *FCRL3* in B-cell's germinal center can influence B cell maturation and reactivity, which may enhance autoimmune responses by B cells. Furthermore, previous clinical data stated that the production of autoantibodies that are elevated in patients with the disease-susceptibility genotype reveals the important role of *FCRL3* in B cell-driven autoimmunity (28).

Study Limitations

The study was limited by the small number of participants, and only a limited number of SNPs were tested.

Conclusion

SLE patients with nephritis suffered higher grades of disease activity than patients without nephritis. For the rs7528648 SNP, the C allele and the CC genotype were non-significantly higher in LN patients than in patients without nephritis. The rs11264799 SNP showed that the frequency of the G allele and the GG genotype was non-significantly higher in LN patients, while the frequency of the A allele was higher among patients with-

out nephritis. Although these differences did not reach significant levels, larger-scale studies, different ethnic groups, and different SNPs have to be performed to decide whether *FCRL3* gene polymorphism is related to the occurrence of SLE or a risk factor for LN, relation to the disease activity index and patient outcome.

Ethics Committee Approval: The study was approved by the Institutional Review Board of the Faculty of Medicine, Assiut University in April 2023 with the decision number 04-2023-200089.

Informed Consent: Written informed consent was obtained from all participants, including information about the aim of the study and their right to withdraw at any time. Each participant was assigned a numerical code to ensure confidentiality.

Peer-review: : Externally peer-reviewed

Author Contributions: Concept – A.G.T., M.S.E.M.; Design – A.G.T., M.N.A.; Supervision – A.G.T., M.N.A.; Fundings – A.M.R.; Materials – R.M.G., A.M.R.; Data Collection and/or Processing – A.M.R., M.S.E.M.; Analysis and/or Interpretation – R.M.G., M.N.A., M.S.E.M.; Literature Review – A.G.T., M.S.E.M; Writer – M.S.E.M., A.M.R.; Critical Reviews – A.G.T., M.N.A., R.M.G., M.S.E.M.

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

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

References

1 Ameer MA, Chaudhry H, Mushtaq J, Khan OS, Babar M, Hashim T, et al. An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus. 2022;14(10):e30330. [CrossRef]

2 Karrar S, Cunninghame Graham DS. Abnormal B Cell Development in Systemic Lupus Erythematosus: What the Genetics Tell Us. Arthritis Rheumatol. 2018;70(4):496-507. [CrossRef]

3 Didier K, Bolko L, Giusti D, Toquet S, Robbins A, Antonicelli F, et al. Autoantibodies associated with connective tissue diseases: What meaning for clinicians? Front Immunol. 2018;9:541. [CrossRef]

4 Yo JH, Barbour TD, Nicholls K. Management of refractory lupus nephritis: challenges and solutions. Open Access Rheumatol. 2019;11:179-88. [CrossRef]

5 Rostamzadeh D, Kazemi T, Amirghofran Z, Shabani M. Update on Fc receptor-like (FCRL) family: new immunoregulatory players in health and diseases. Expert Opin Ther Targets. 2018;22(6):487-502. [CrossRef]

6 Ehrhardt GR, Leu CM, Zhang S, Aksu G, Jackson T, Haga C, et al. Fc receptor-like proteins (FCRL): immunomodulators of B cell function. Adv Exp Med Biol. 2007;596:155-62. [CrossRef]

7 Bajpai UD, Swainson LA, Mold JE, Graf JD, Imboden JB, McCune JM. A functional variant in FCRL3 is associated with higher Fc receptor-like 3 expression on T cell subsets and rheumatoid arthritis disease activity. Arthritis Rheum. 2012;64(8):2451-9. [CrossRef]

8 Martínez A, Mas A, de Las Heras V, Bartolomé M, Arroyo R, Fernández-Arquero M, et al. FcRL3 and multiple sclerosis pathogenesis: role in autoimmunity? J Neuroimmunol. 2007;189(1-2):132-6. [CrossRef]

9 Gibson AW, Li FJ, Wu J, Edberg JC, Su K, Cafardi J, et al. The FCRL3-169CT promoter single-nucleotide polymorphism, which is associated with systemic lupus erythematosus in a Japanese population, predicts expression of receptor protein on CD19+ B cells. Arthritis Rheum. 2009;60(11):3510-2. [CrossRef]

10 Salles JI, Lopes LR, Duarte MEL, Morrissey D, Martins MB, Machado DE, et al. Fc receptor-like 3 (-169T>C) polymorphism increases the risk of tendinopathy in volleyball athletes: a case control study. BMC Med Genet. 2018;19(1):119. [CrossRef]

11 Shahram F, Kazemi J, Mahmoudi M, Jadali Z. Single nucleotide polymorphisms of FCRL3 in Iranian patients with Behcet's disease. Iran J Public Health. 2019;48(6):1133-9.

12 Narani A. Systemic lupus erythematosus (SLE)-a review of clinical approach for diagnosis and current treatment strategies. Jaffna Medical Journal. 2019;31(2):9-13. [CrossRef]

13 Jolly M, Sequeira W, Block JA, Toloza S, Bertoli A, Blazevic I, et al. Sex differences in quality of life in patients with systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2019;71(12):1647-52. [CrossRef]

14 Al-Gahtani SN. A review of systemic lupus erythematosus (SLE): symptoms, risk factors, treatment, and health related quality of life issues. Open J Rheumatol Autoimmune Dis. 2021;11(4):115-43. [CrossRef]

15 Kosałka-Węgiel J, Dziedzic R, Siwiec-Koźlik A, Spałkowska M, Milewski M, Żuk-Kuwik J, et al. Clinical and laboratory characteristics of early-onset and delayed-onset lupus nephritis patients: A single-center retrospective study. Rheumatol Int. 2024;44(7):1283-94. [CrossRef]

16 Parikh SV, Almaani S, Brodsky S, Rovin BH. Update on lupus nephritis: Core curriculum 2020. Am J Kidney Dis. 2020;76(2):265-81. [CrossRef]

17 Pons-Estel GJ, Serrano R, Plasín MA, Espinosa G, Cervera R. Epidemiology and management of refractory lupus nephritis. Autoimmun Rev. 2011;10(11):655-63. [CrossRef]

18 Borchers AT, Leibushor N, Naguwa SM, Cheema GS, Shoenfeld Y, Gershwin ME. Lupus nephritis: a critical review. Autoimmun Rev. 2012;12(2):174-94. [CrossRef]

19 González-Regueiro JA, Cruz-Contreras M, Merayo-Chalico J, Barrera-Vargas A, Ruiz-Margáin A, Campos-Murguía A, et al. Hepatic manifestations in systemic lupus erythematosus. Lupus. 2020;29(8):813-24. [CrossRef]

20 Filipyuk AL, Bek NS, Sklyarova VO, Filipyuk IT, Huk-Leshnevska ZO, Zhakun IB. Low serum bilirubin levels in women with the antiphospholipid syndrome. Wiad Lek. 2022;75(1 pt 2):203-8.

21 Yu Y, Wang Q, Zhang D, Wu W, Jiang Z. Relationship between bilirubin and systemic lupus erythematosus: A systematic review and meta-analysis. Immun Inflamm Dis. 2023;11(12):e1115. [CrossRef]

22 Ardalan MR. Anemia in lupus nephritis; etiological profile. J Renal Inj Prev. 2013;2(3):103-4. [CrossRef]

23 Abdalhadi S, Khalayli N, Al-Ghotani B, Kudsi M. Systemic lupus erythematosus disease activity and neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: a cross-sectional case-control study. Ann Med Surg (Lond). 2023;85(5):1448-53. [CrossRef]

24 Wanitpongpun C, Teawtrakul N, Mahakkanukrauh A, Siritunyaporn S, Sirijerachai C, Chansung K. Bone marrow abnormalities in systemic lupus erythematosus with peripheral cytopenia. Clin Exp Rheumatol. 2012;30(6):825-9.

25 Gandino IJ, Scolnik M, Bertiller E, Scaglioni V, Catoggio LJ, Soriano ER. Complement levels and risk of organ involvement in patients with systemic lupus erythematosus. Lupus Sci Med. 2017;4(1):e000209. [CrossRef]

26 Rekvig OP. The dsDNA, Anti-dsDNA antibody, and lupus nephritis: What we agree on, what must be done, and what the best strategy forward could be. Front Immunol. 2019;10:1104. [CrossRef]

27 Ikari K, Momohara S, Nakamura T, Hara M, Yamanaka H, Tomatsu T, et al. Supportive evidence for a genetic association of the FCRL3 promoter polymorphism with rheumatoid arthritis. Ann Rheum Dis. 2006;65(5):671-3. [CrossRef]

28 Kochi Y, Myouzen K, Yamada R, Suzuki A, Kurosaki T, Nakamura Y, Yamamoto K. FCRL3, an autoimmune susceptibility gene, has inhibitory potential on B-cell receptor-mediated signaling. J Immunol. 2009;183(9):5502-10. [CrossRef]