A study of CD11b rs1143679 gene polymorphism in Egyptian systemic lupus erythematosus patients

Mona E. Fouda[a], Rasha M. Fawzy[b], Seham G. Ameen[a], Mona M. Shoaib[c], Dalia M. Abd El-Hassib[a]

Departments of [a]Clinical and Chemical Pathology, [b]Rheumatology, Rehabilitation and Physical Medicine, Faculty of Medicine, Benha University, [c]Benha Teaching Hospital, Ministry of Health, Benha, Egypt

Correspondence to Mona M. Shoaib, MSc, Benha Teaching Hospital, Ministry of health, Benha 13511, Egypt. Tel: 01005057044; e-mail: shoaib.mona@yahoo.com

Received: 15 January 2023
Revised: 15 February 2023
Accepted: 20 February 2023
Published: 23 May 2023

Journal of The Arab Society for Medical Research 2023, 18:82–87

Background/aim
The exact cause of systemic lupus erythematosus (SLE), an autoimmune disorder, is still vague. However, it is believed that its pathogenesis could be a result of the interplay between genetics and the environment. One such genetic factor is a single-nucleotide polymorphism in the *CD11b* gene (rs1143679) that has been shown to potentially increase a person's susceptibility to SLE. This study aims to investigate the possible link of *CD11b* rs1143679 gene polymorphism to the risk of developing SLE, as well as the different manifestations and the disease severity in the studied group of Egyptian SLE patients.

Patients and methods
The present study enrolled 50 patients with SLE from Benha University Hospitals, Egypt. In addition to 30 apparently healthy individuals served as control, the *CD11b* gene (rs1143679) genetic variant was investigated by real-time PCR. The individuals with SLE were based on the Systemic Lupus International Collaborating Clinics criteria.

Results
A significant association of GA genotype (odds ratio=1.908, 95% confidence interval=1.021–3.568, $P<0.05$) with the risk to develop SLE and A allele was also linked to an elevated risk for SLE in comparison to the G allele (odds ratio=1.881, 95% confidence interval=1.038–3.408, $P<0.05$).

Conclusion
The *CD11b* rs1143679 gene polymorphism might be a potential risk factor for SLE in Egyptians.

Keywords:
CD11b, Egyptian, gene, lupus nephritis, polymorphism, rs1143679, SLE

J Arab Soc Med Res 18:82–87

1687-4293

Introduction

The complex disorder of systemic lupus erythematosus (SLE) is affected by various factors like genetics, epigenetics, and the environment, and it affects the immune system over an extended period of time [1]. The major pathology of SLE is the expression of autoantibodies by autoreactive B cells that target the nuclear material in cells, and the accumulation of immune complexes in various body tissues [2].

A range of symptoms are often caused by SLE, with the most common being related to the skin, mucous membranes, muscles, joints, and bones. However, any organ in the body can be affected, including blood, kidneys, brain and nervous system, heart and blood vessels, and lungs. These symptoms may not all appear at the same time and may develop over months or years [3].

Due to the heterogeneous and individual nature of the disease, diagnosis can sometimes be difficult. However, the introductions of autoantibody testing and updated classification criteria have improved the identification of the disease. It is believed that earlier diagnosis allows milder cases to be detected, resulting in a better overall prognosis [4].

The *CD11b* gene is located on chromosome 16p11.2. It provides instructions for making a protein called CD11b, which is part of leukocytes. CD11b helps regulate the movement and attachment of leukocytes and plays a role in their ability to engulf and remove the complement-coated particles [5].

The CD11b is a protein found on many types of immune cells like monocytes, macrophages, and neutrophils, which acts as a receptor and binds to various substances like iC3b, fibrinogen, and ICAM-1. It is a key player in some processes such

as adhesion and phagocytosis. *CD11b* is a gene that provides instructions for the expression of CD11b, and variations in *CD11b* have been reported to significantly predispose to SLE [6].

Several genetic variations known as single-nucleotide polymorphisms (SNPs) in the *CD11b* gene have been associated with the risk and severity of some conditions such as melanoma, SLE, and systemic sclerosis, based on the findings from genome-wide association studies [7].

A SNP, identified as rs1143679 found in exon 3 of *CD11b*, results in a nonsynonymous alteration from arginine to histidine at position 77 of the α1 domain. This change in conformation may reduce the protein's ability to bind to different ligands and considerably decreases the phagocytosis of complement-coated particles. The reduced ability to clear out these immune complexes may trigger the development of SLE [8].

A new approach to treating SLE may involve activating a protein called CD11b, which is produced by the *CD11b* gene. This has been shown to reduce the immune system's overactive response in laboratory and animal studies. Additionally, activating CD11b has been shown to prevent organ damage in mice with lupus. Reducing the immune system's excessive activity is a key goal in treating SLE [9].

The study in our hands aimed at detection of any link between the *CD11b* rs1143679 gene polymorphism and SLE in Egyptian patients and the relationship between this polymorphism and clinical symptoms, laboratory measures, and disease severity.

Patients and methods

Patients

A case–control study was conducted between September 2020 and April 2021 in the Clinical and Chemical Pathology Department at Benha University Hospitals, Egypt.

Study design

This study included 50 individuals with SLE, diagnosed based on the Systemic Lupus International Collaborating Clinics criteria classification system [10], and 30 age-matching and sex-matching controls who were apparently healthy and came from the same ethnic and geographic background as the SLE cases. The SLE cases were diagnosed at the Rheumatology, Rehabilitation and Physical Medicine Department at Benha University Hospitals in Egypt. All participants underwent a thorough clinical examination and had their medical history taken.

Inclusion criteria

SLE patients diagnosed based on the Systemic Lupus International Collaborating Clinics criteria classification system [10].

Exclusion criteria for patients

Individuals with autoimmune diseases other than SLE or those younger than 18 years of age did not participate in the study.

Scoring system of systemic lupus erythematosus

The level of severity of SLE symptoms in cases was assessed using the SLE disease activity index (SLEDAI) score [11].

Ethical consideration

The present study was conducted with the Code of Ethics of the World Medical Association, according to the principles expressed in the Declaration of Helsinki. This study has been approved by the local Ethics Committee of Benha University, Egypt with approval number 0018122017/1017. A written informed consent was provided by each participant prior to their inclusion in the study.

Sample collection

Blood sample

For each patient, a sterile blood collection was performed from the peripheral veins. The collected blood (9 ml) was then separated into three parts. Two tubes containing EDTA were filled with 2 ml per tube of the collected blood, with a concentration of 1.2 mg/ml. One of these tubes was stored at −80°C for later analysis by the real-time PCR to detect the *CD11b* polymorphism (rs1143679). The other tube was used for complete blood counting examination. To perform the erythrocyte sedimentation rate test, a sample of 1.6 ml of blood was mixed with 3.13 mg/ml of sodium citrate in a tube. Natural coagulation was allowed via leaving the sample for 10 min in a plain tube at room temperature to extract the serum from the residual blood, and then the sample spun at a high speed in a centrifuge. On the same day, the sample was also tested for various other markers, including C-reactive protein (CRP), complement protein 3 and 4 (C3 and C4), antinuclear antibodies, antidouble-stranded-DNA antibodies, renal function tests, and liver function tests.

Methods

Lab tests

The complete blood counting was conducted using an automatic cell counter by Sysmex XS-800 I (Kobe, Japan). The erythrocyte sedimentation rate was determined using the Westergren method [12]. The CRP level in the patient's sample was measured using a CRP-Latex Slide Agglutination method by Spinreact kit (Spain) [13]. Tests to assess hepatic and renal functions were conducted using an autoanalyzer by Biosystems (Barcelona, Spain). Indirect immunofluorescence was conducted by Orgentec in Germany to check for the presence of antinuclear antibodies in the patient's blood. This test involved using HEP-2 cells [14]. The patient's blood was tested for the presence of anti-dsDNA antibodies using an enzyme-linked immunosorbent assay) (Catalog Number DSD31-K01, WWW.EagleBio.com; Eagle Biosciences, Medipan, Germany). The C3 and C4 levels were determined using a simple radial immune diffusion method with a kit COMBI-PLATE (FAR, Bologna, Italy) [15].

Molecular determination of CD11b (rs1143679) SNP by real-time PCR method

To obtain high-quality DNA from a sample of blood, Gene JET whole-blood genomic DNA purification kit was used to extract the DNA from EDTA-anticoagulated blood (Catalog # K0781; Thermo Scientific, EU). The rs1143679 genotypes were determined using TaqMan SNP genotyping kits (Applied Biosystems, Singapore).

PCR amplification was conducted using StepOne Real-Time PCR [Thermal Cycling Block S/N (271003648); Applied Biosystem]. The experiment used a premade genotyping mix, a genotyping assay, and DNase/RNase-free water. The reaction also included 1.0 µl of DNA that had been adjusted to a concentration of 10 ng/ml. The reaction mixture had a total volume of 10.0 µl.

The sample was subjected to the following protocol: it was heated to 95°C for 10 min to denature the DNA, and then it was subjected to 40 cycles of heating to 92°C for 15 s followed by cooling to 60°C for 1 min to allow the primers to bind to the target DNA sequence and for the polymerase to extend the primers (annealing and extension).

Statistical analysis

The rs1143679 SNP was studied to see how it affected the risk of SLE. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to measure this impact. Statistical significance was set at a *P* value of less than 0.05 at a 95% CI. For variables that were measured on a numerical scale, the average value, how much the values varied (SD), and the range of values are reported. Student's *t*-test was used to assess the statistical significance of the difference between two study group means, while Mann–Whitney test was used to assess the statistical significance of the difference of a nonparametric variable between two study groups. χ^2-test and Fisher's exact test were used to examine the relationship between two qualitative variables. All analyses were performed using the SPSS software version 22 (IBM Corp., Armonk, New York, USA).

Results

The demographic profiles of both study groups are shown in Table 1. Data revealed 50 individuals with SLE, most of them were females (92%). The average age of the patients was 33.3±10.1 years. A family history of SLE was present in 8% of the patients, and the average duration of the disease was 3 years.

The data presented in Table 2 showed genotypic and allelic frequencies of *CD11b* rs1143679 compared between SLE patients and the control group. The genetic makeup and distribution of alleles in the control group were in line with what would be predicted according to the Hardy–Weinberg equilibrium ($P>0.05$). However, the rs1143679 GA genotype (a specific combination of alleles) was significantly more common in patients (42%) than controls (16.7%) ($P=0.043$). The rs1143679 AA genotype, which is the minor allele frequency, was not found in either group.

Additionally, the GA genotype increased the possibility of developing SLE (OR=1.908, 95%

Table 1 The demographic profiles of both study groups

	Control	SLE	
	n=30	*n*=50	*P* value
Age (years)[a]	31.5 ±9.3	33.3±10.1	0.476*
Sex[b]			
Males	3 (10)	4 (8)	0.759**
Females	27 (90)	46 (92)	
Positive family history		4 (8)	
Disease duration (years)			
Median, range		3 (0.25–20)	

SLE, systemic lupus erythematosus. [a]Data presented as mean ±SD. [b]Data presented as numbers (%). *Insignificant difference using Student's *t*-test. **Insignificant difference using χ^2-test.

CI=1.021–3.568), while the homozygous GG genotype offered protection against SLE. Both groups demonstrated a significantly different allelic distribution (P=0.037). A higher SLE risk was common with the A allele than the G allele (OR=1.881, 95% CI=1.038–3.408, P<0.05), as shown in Table 2.

Table 3 shows clinical and laboratory characteristics in SLE patients with GG and GA genotypes. There was no association detected between the rs1143679 SNP and any of the clinical manifestations in the SLE group upon genotype analysis.

The association between activity of SLE patient group and genotypes is shown in Table 4. The *CD11b* genotype did not have an impact on the activity levels of SLE patients.

Table 2 The genotypic and allelic frequencies of *CD11b* rs1143679 compared between SLE patients and the control group

	Control (N=30) [n (%)]	SLE (N=50) [n (%)]	P value	OR (95% CI)
GG	25 (83.3)	29 (58)	0.043*	Reference
GA	5 (16.7)	21 (42)		1.908 (1.021–3.568)
G	55 (91.7)	79 (79)	0.037*	Reference
A	5 (8.3)	21 (21)		1.881 (1.038–3.408)

CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus. *Significant difference using logistic regression test.

Table 3 Clinical and laboratory characteristics in SLE patients with GG and GA genotypes

	GG (n=29) [n (%)]	GA [(n=21) n (%)]	P value*
Oral ulcer	14 (48.3)	8 (38.1)	0.474
Hair loss	13 (44.8)	10 (47.6)	0.845
Malar rash	14 (48.3)	9 (42.9)	0.704
Hand and feet joint arthritis	2 (6.9)	4 (19.0)	0.223
Elbow joint arthritis	3 (10.3)	1 (4.8)	0.630
Knee joint arthritis	9 (31.0)	4 (19.0)	0.340
Wrist joint arthritis	6 (20.7)	3 (14.3)	0.716
Hip joint arthritis	1 (3.4)	0	0.390
Dyspnea	6 (20.7)	3 (14.3)	0.716
Interstitial lung disease	0	1 (4.8)	0.420
Palpitation	1 (3.4)	0	0.390
Chest pain	1 (3.4)	1 (4.8)	0.998
Mitral regurge	2 (6.9)	1 (4.8)	0.754
Pulmonary hypertension	1 (3.4)	0	0.390
Pericardial effusion	3 (10.3)	1 (4.8)	0.630
Deep venous thrombosis	0	2 (9.5)	0.171
Stroke	0	1 (4.8)	0.420
Nephritis	24 (82.8)	15 (71.4)	0.491
Bilateral cotton wool spots	0	1 (4.8)	0.420
Maculopathy	0	1 (4.8)	0.420
Retinal vasculopathy	1 (3.4)	0	0.390
Anemia	18 (62.1)	11 (52.4)	0.493
Leukopenia	0	2 (9.5)	0.171
Lymphopenia	2 (6.9)	4 (19.0)	0.223
Thrombocytopenia	3 (10.3)	2 (9.5)	0.924

All data are presented as numbers and percentage. SLE, systemic lupus erythematosus. *Insignificant difference using χ^2 and Fisher's exact tests.

Discussion

SLE has been linked to some specific genetics [16]. Research using genome-wide association study has identified SNPs in the *CD11b* gene that may increase the susceptibility to develop autoimmune disorders such as SLE with more severity [7].

The SNP variant rs1143679 leads to a change in the amino acid arginine to histidine at position 77 in the integrin protein. This change disrupts the protein's ability to bind to ligands and may cause macrophages with this variant to have difficulty clearing apoptotic cells and produce excessive levels of the proinflammatory molecule interleukin-6, potentially contributing to the development of SLE [17].

Our research on a group of Egyptian patients showed a higher risk to develop SLE among people having the GA genotype (OR=1.908) compared with those with the GG genotype. Both groups did not present the AA genotype, possibly due to its low prevalence in the population. Additionally, we found that the A allele was more common in SLE patients than the healthy controls.

According to Kim-Howard and colleagues and Gupta and colleagues, SLE demonstrated a significantly higher prevalence of the *CD11b* rs1143679 GA genotype than the controls (P<0.0001). Additionally, an allelic association test showed that

Table 4 Association between activity of SLE patient group and genotypes

	GG (n=29)	GA (n=21)	P value
SLEDAI score[a]	16 (4–22)	23 (0–26)	0.270*
Activity (severity)[b]			
No	0	1 (4.8)	
Mild (0–10)	2 (6.9)	0	0.190**
Moderate (11–20)	9 (31)	11 (52.4)	
High (21–45)	15 (51.7)	6 (28.6)	
Very high (>45)	3 (10.3)	3 (14.3)	

SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index. [a]Data are presented as median (range). [b]Data are presented as numbers and percentage. *Insignificant difference using Mann–Whitney test. **Insignificant difference using Fisher exact test.

the risk allele A occurred more frequently in cases than in controls in lupus patients with European ancestry and North Indian population ($P<0.001$) [8,18].

Li and colleagues found that the rs1143679 AA genotype was not present in either SLE patients or controls in the Han Chinese population, which supports our findings. The GA genotype was more frequently observed in the SLE group (0.48%, $P=0.02$) compared with the control group. Individuals with the GA genotype had a higher risk of developing SLE (OR=4.00, 95% CI: 1.11–14.41) and those with the GG genotype had a lower risk. The distribution of alleles between SLE patients and controls was significantly different ($P=0.02$). The minor allele (A) was associated with an increased risk of SLE compared with the major allele (G) (OR=3.97) [19].

In a study conducted by Ramırez-Bello and colleagues in 2019, the allelic association between controls and adult SLE patients in Central Mexico was examined. The SNP rs1143679 was found to be significantly associated with SLE, with the allele A showing an OR of 1.65 and a *P* value of 0.005. Additionally, the group also analyzed a group of SLE patients from Yucatan and found a strong association with the allele, with an OR of 24.6 and a *P* value of 9.3×10^{-6} [20].

Research has demonstrated that having the A variant of the *CD11b* gene reduces the ability of human monocytes and monocyte-derived macrophages to adhere to surfaces and engulf particles, but does not alter the level of CD11b expression on the surface of the cells [19].

The arginine-to-histidine substitution has been found to decrease its ability to stick to iC3b and to effectively eat up (phagocytosis) particles. It also increases the production of substances that cause inflammation (cytokines). It is possible that the inability to effectively take up dying cells (apoptotic cells) through phagocytosis may lead to the cells becoming necrotic and releasing proteins from their nucleus into the surrounding tissue. These proteins can then be picked up by dendritic cells and presented to T cells, causing them to become activated and activating B cells to produce antibodies to the nuclear proteins, a common occurrence in SLE [21].

The rs1143679 genetic variant is present at a frequency of 9–11% in populations such as Europeans, Hispanics, Brazilians, and African Americans, and has been linked to an increased risk of developing SLE. However, this variant is less common in Asian populations from Thailand and Hong Kong, with a frequency of only around 2%.

In our study, the GA genotype does not have a significant impact on lupus nephritis (LN), skin symptoms, or other clinical features of the disease. Additionally, it does not significantly affect the age at which the disease begins or the severity of the disease.

A meta-analysis, including three studies, was conducted to examine the connection between the rs1143679 genetic variation and LN. The findings indicated that the presence of the A allele was linked to LN in Europeans with a strong statistical significance that is not in line with our results. However, a study in Latin America found no significant association between the A allele and LN in this population in line with our results [5].

According to research conducted by Li and colleagues in 2018, people with renal nephritis were more likely to have the *CD11b* rs1143679 GA genotype than those without the condition ($P=0.005$). This particular genotype has been associated with nephritis and that was not in line with our results [19]. Genetic variations may affect the functioning of complement receptors in the kidneys, causing a buildup of deposits and an inflammatory environment that can lead to LN [22].

Our study found that there is no significant connection between *CD11b* genotypes and alleles with cutaneous symptoms, similar to the findings of Skonieczna *et al.* [23]. *CD11b* rs1143679 has been linked to discoid lupus erythematosus [18,24]. The *CD11b* risk allele has been found to increase the risk of renal failure and discoid rash in individuals with lupus [25].

There are several potential reasons why our results may differ from those of other studies, including the small sample size, variations in the clinical presentation of patients, the use of different types of therapy, different gene polymorphism kits, and different statistical methods of analysis.

Conclusion

The genetic variation of *CD11b* rs1143679 may increase the possibility of developing SLE in Egyptians.

Acknowledgments

The authors express their gratitude to all individuals in the Clinical and Chemical Pathology Department at

Benha University Hospitals, Egypt, who participated in this study.

Authors' contributions

M.E.F. was responsible for methodology, project administration, supervision, and review editing. S.G. A. helped in data curation, reviewing, and editing. D. M.A.E.-H. was taking part in data investigation, in addition to the paper revision and laboratory investigations. R.M.F. was in charge of interpretations and clinical history-taking. M.M.S. was responsible for the submission of the paper to the journal. All authors read and approved the final paper.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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