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ORIGINAL ARTICLE

Mannose-binding lectin gene polymorphism in systemic lupus erythematosus nephritis

Osama Sayed Daif Allah[1], Alshimaa Hafez Abdelall[2*], Madeha Mahrous Zakhary[3], Nagwa S. Ahmed[2], Asmaa Mohamed Goda[4]

ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a complex trait characterized by the production of a range of autoantibodies and a diverse set of clinical phenotypes, including skin rash, neuropsychiatric and musculoskeletal symptoms, and lupus nephritis (LN). Mannan-binding lectin (MBL) is a recognition molecule of the lectin pathway of complement activation. We investigated MBL gene polymorphism at exon 1 codon 54 as a potential biomarker for SLE nephritis in the current study.

Methodology: A case–control study screened 70 participants. They were included in the study from the outpatient clinic or the inpatient section of the Rheumatology Department at Sohag University Hospital during July 2017-June 2019 for MBL gene polymorphism at exon 1 codon 54, which was detected by polymerase chain reaction using sequence-specific priming.

Result: There was a predominance of AA (wild) genotype in the control group (40%). Patient groups had a statistically significant equal higher frequency of heterozygous polymorphism (AB) (76%) than the controls. BB genotype showed a statistically significant lowest frequency in the LN group (p-value = 0.04).

Conclusions: MBL AB genotyping was more frequent in SLE patients either with or without nephritis than in the normal Egyptian population. BB genotyping was less frequent in LN patients than in patients without nephritis. The present study supports that the carriage of MBL AB genotype (heterozygous polymorphism at codon 54) was associated with both SLE and LN development in normal Egyptians.

Keywords: Mannose-binding lectin (MBL), systemic lupus erythematosus (SLE), lupus nephritis (LN), gene polymorphism.

Introduction

Systemic lupus erythematosus (SLE) complex is an autoimmune disease characterized by the production of a range of autoantibodies and a diverse set of clinical phenotypes (1). Women of childbearing age are affected about nine times more often than men (2). Life expectancy is lower among people with SLE (3). The rate of SLE varies between countries from 20 to 70 per 100,000 (4), but the rates of disease in the developing world are unclear (5). It is a multifactorial disease, and susceptibility is related to genetic, hormonal, immunological, and environmental factors. A strong genetic link has been identified by using genome-wide association and family studies, and more than 30 SLE-related loci have already been identified (6).

Aberrant complement activation that occurs in SLE leads to inflammation, resulting in tissue injury of multiple organs, including the kidney, causing nephropathy, which is called lupus nephritis (LN). LN typically occurs after at least 3 years since the onset of SLE. LN is a significant risk factor for overall morbidity and mortality in SLE despite potent anti-inflammatory and immunosuppressive therapies still end in chronic kidney disease or end-stage renal disease (ESRD) for too many patients (7). Monitoring for LN development is done with serial creatinine, urine albumin-to-creatine ratio, and urinalysis. This evaluates if there is a rise in creatinine value from baseline creatinine and for the presence of proteinuria seen with LN. Since LN carries a high risk for increased morbidity, treatment plays an essential role in preventing progression to ESRD (8–11). Due to the

Correspondence to: Alshimaa Hafez Abdelall
*Medical Biochemistry Department, Faculty of Medicine, Sohag University, Egypt.
Email: Alshimaaarif1986@gmail.com
Full list of author information is available at the end of the article.
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early recognition and management of SLE, end-stage renal failure occurs in less than 5% of cases, except in the black population, where the risk is many times higher (12). Repeat biopsies have demonstrated considerable discordance between clinically and histologically defined disease activity. After completing 6-8 months of immunosuppressive therapy, 20%-50% of complete clinical renal responders still had histologic evidence of ongoing active inflammation, and 40%-60% of patients with no histologic evidence of disease activity still had persistent, high-grade proteinuria (13,14).

Mannose-binding lectin (MBL) is a calcium-dependent serum protein that plays a role in the innate immune response by binding to carbohydrates on the surface of a wide range of pathogens, where it can activate the complement system or act directly as an opsonin (15). Sugar-binding proteins of MBL result in opsonization and activation of the complement of the lectin pathway and clearance in the pathogen body. During inflammation, MBL levels increase within the 3-4-fold compared to the baseline level (16). Reduced plasma levels of MBL may disrupt the natural immune response and increase the susceptibility to infections (17). There is a hypothesis that infectious diseases, more frequent and severe in individuals with lower serum levels of MBL, may trigger the formation of immunocomplexes in individuals genetically susceptible to LN (18,19). MBL2 gene is present on chromosome 10 in the region 10q21-24. The normal structural MBL allele is named A, whereas the three variant structural alleles, namely “B” (codon 54), “C” (codon 57), and “D” (codon 52), are designated as “O” alleles (20). In general, the MBL rate circulating in human serum is constant and ranges from 3 to 50 µg/mL (21). This difference in the normal and reduced plasma level of MBL is justified by three single nucleotide polymorphisms of Arg52Cys (rs5030737), Gly54Asp (rs1800450), and Gly57Glu (rs1800451) (21–23).

Subjects and Methods

This case-control study was conducted at Sohag University Hospital during the period from July 2017 to June 2019. A total of 75 persons were included in the study)25 patients with SLE nephritis, 25 patients with SLE without nephritis, and 25 healthy adult, age, and sex-matched controls). Patients were recruited from the outpatient clinic or the inpatient section of the Rheumatology Department. Exclusion criteria were as follows: patients with other autoimmune diseases and patients with drug-induced lupus. The ethics committee approved the study protocol of the Sohag Faculty of Medicine. Informed written consents were obtained from all participants, and they were all informed regarding the tests and their clinical meanings before the study. Clinical data were obtained from patients’ files, including age, gender, duration of the disease, history of all possible SLE manifestations and complications, e.g., hair loss, photosensitivity, presence or absence of fever, fatigue, arthralgia, and systematic affection. Furthermore, the data of investigations, e.g., complete blood picture, erythrocyte sedimentation rate (ESR), creatinine blood level, urine analysis, 24 hours’ protein in the urine, antinuclear antibody (ANA), anti-deoxyribonucleic acid (DNA), and the classification of the renal biopsy, were taken from patients files. Venous blood samples were collected from each participant (5 mL) by venipuncture. The samples were then put in vacutainer ethylenediaminetetraacetic acid tubes and kept at 2°C-8°C up to 1 day for DNA extraction.

DNA extraction from blood was done using Blood-Animal-Plant DNA Preparation Kit (Cat. No. PP-213S, Jena Bioscience, Jena, Germany). Polymerase chain reaction (PCR) was carried out using the extracted DNA (from previous step) and the following reagents: ready-to-use master mix (MyTaq Red Mix 2x, Cat. No. BIO-25043: 200 × 25 µl reactions, Bioline, London, UK) [It contains a well-balanced ratio of Taq polymerase, nucleotides (deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxyguanosine triphosphate, and deoxythymidine triphosphate), KCl, $(NH_4)_2SO_4$, $MgCl_2$, red dye, density reagent, and enhancing and stabilizing additives], set of primers (forward and reverse) for target sites (synthesized by Metabion International AG, Munich, Germany) [Codon 52 D forward (F) primer**,** OD: 26.3 nmol, nucleotide sequence: (5′-CTGCACCCAGATTGTAGGACAGAG-3′); Codon 52 D reverse (R) primer, OD: 17.1 nmol, nucleotide sequence: (5′-TCTCCCTTGGTGCCATCACA-3’); Codon 52, non-D (ABC) forward (F) primer**,** OD: 19.1 nmol, nucleotide sequence: (5′ C T G C A C C C A G A T T G T A G G A C A G A G - 3 ′) ; Codon 52 non-D (ABC) reverse (R) primer**,** OD: 22.9 nmol, nucleotide sequence: (5′-TCTCCCTTGGTGCCATCACG-3′); Codon 54 B forward (F) primer**,** OD: 20.4 nmol, Nucleotide sequence: (5′-CTGCACCCAGATTGTAGGACAGAG-3′); Codon 54 B reverse (R) primer, OD: 20.5 nmol, nucleotide sequence: (5′ CCCCCTTTTCTCCCTTGGTGT-3′); Codon 54 non-B (ACD) forward (F) primer**,** OD: 18.8 nmol, nucleotide sequence: (5′-CTGCACCCAGATTGTAGGACAGAG-3′); Codon 54 non B (ACD) reverse (R) primer, OD: 29.5 nmol, nucleotide sequence: (5′-CCCCCTTTTCTCCCTTGGTGC-3′); Codon 57 C forward (F) primer, OD: 22.4 nmol, nucleotide sequence: (5′-CTGCACCCAGATTGTAGGACAGAG-3′); Codon 57 C reverse (R) primer**,** OD: 19.4 nmol, nucleotide sequence: (5′-ACGTACCTGGTTCCCCCTTTTCTT-3′); Codon 57 nonC (ABD) forward (F) primer, OD: 19.8 nmol, nucleotide sequence: (5′-CTGCACCCAGATTGTAGGACAGAG-3′); Codon 57 non C (ABD) reverse (R) primer**,** OD: 22.6 nmol, nucleotide sequence: (5′-ACGTACCTGGTTCCCCCTTTTCTC-3′); Control forward (F) primer**,** OD: 18.6 nmol, nucleotide sequence: (5′-TGCCTTCCCAACCATTCCCTTA-3′); and Control reverse (R) primer, OD: 23.3 nmol, nucleotide sequence: (5′ CCACTCACGGATTTCTGTTGTGTTTC-3′)].

In the PCR reaction (total volume 25 µl): we used 12.5 µl of the master mix, 2 µl of specific codon primer (F) and 2 µl (R),1.5 µl of control primer (F) and 1.5 µl (R), 5 µl of genomic DNA, and 0.5 µl of distilled deionized water. Amplification was done by using Biometra Thermal Cycler-T Gradient software PCR system version 4, such as: one cycle of initial denaturation at 95°C for 10

minutes followed by denaturation at 95°C for 20 seconds, then the annealing step as 30 cycles for 1 minute at the specific temperature, followed by extension step for 1 minute at 72°C, and then, the final extension step as 1 cycle for 5 minutes at 72°C; finally, the reaction was stopped by cooling at 4°C. After the end of PCR, 10 µl of each sample was tested by agarose gel electrophoresis to make sure that the amplification of DNA was done. The DNA samples following PCR were separated by electrophoresis in ethidium bromide-stained 2% agarose gel. The presence of the control band only at 431 bp means negative polymorphism at the specific codon, but the presence of the control band with another specific band means positive polymorphism at the specific codon. The data were analyzed using the Statistical Package for the Social Sciences IBM (SPSS) for Windows, version 25 (IBM Corp., Armonk, NY). The frequencies and proportions of the variables were obtained by applying the Chi-square test. The *p*-value of less than 0.05 was considered to be statistically significant. The SPSS was then used to categorize the sample into those with risk and those without risk for comparison purpose.

Results

A total of 75 persons were included in the study: 25 patients with SLE nephritis (22 females and 3 males) with mean age ± SD of 34.24 ±1 0.05 years (range 22-52 years), 25 patients with SLE without nephritis (23 females and 2 males) with mean age ± SD of 36.84 ± 10.53 years (range 21-65 years), and 25 persons as a control group (23 females and 2 males) with mean age ± SD of 36.12 ± 8.9 years (range 16-50 years) matched for age and sex. The sociodemographic variables of the patients' groups are shown in Table 2. There were no statistically significant differences among the studied groups. The clinical data are shown in Table 3, and there was a significant elevation in the frequency of arthralgia and arthritis in the LN group. Laboratory data of all studied groups are shown in Table 4. The LN group showed significant elevation in ANA, ESR, and platelets (PLTs), whereas SLE group showed a significant elevation in anti-DNA and serum creatinine level. A comparison between all studied groups regarding the presence or absence of MBL gene polymorphism at codons 52, 54, and 57 is shown in Table 5, where the AO genotype is the most frequent genotype among the codons 52, 54, and 57, whereas the OO genotype is the least frequent one, and there was no CC genotype among LN and control groups. In control group for codon 52 polymorphism (D), participants with AA (wild) genotype had a higher frequency than AD genotype (64% *vs.* 36%), whereas for codon 54 polymorphism (B), participants with AB genotype (40%) were more than those with AA genotype (36%) and BB genotype (24%), and for codon 57 polymorphism (C), participants with AC (AO) genotype (72%) had a higher frequency than AA genotype (28%). In patients with SLE without nephritis for codon 52 polymorphism (D), patients with AD (AO) genotype had a higher frequency than AA and DD genotypes (64% *vs.* 28% and 8%), whereas for codon 54 polymorphism (B), patients with AB (AO) genotype had a higher frequency than AA and BB genotype (76% *vs.* 8% and 16%), and for codon 57 polymorphism (C), patients with AC (AO) genotype had a higher frequency than AA and CC genotype (64% *vs.* 12% and 24 %).

In this study, we noticed that for codon 52, the wild genotype had a statistically significant higher frequency among the controls, whereas AD genotype had a statistically significant higher frequency among the SLE without nephritis group, and DD genotype had a statistically significant higher frequency among the LN group (*p*-value = 0.04). For codon 54, the wild genotype had a statistically significant higher frequency among the controls, whereas AB genotype had statistically significant equal frequencies among the LN and SLE without nephritis groups, and BB genotype had a statistically significant higher frequency among the controls (*p*-value = 0.03). For codon 57 also,

Table 1. *The annealing temperature and the product size for each codon.*

Codon	Annealing temperature	Product size bp
52 D	57.5°C	268
52 non-D (ABC)	55.5°C	268
54 B	56.5°C	278
54 non-B (ACD)	60.5°C	278
57 C	58.5°C	290
57 non-C (ABD)	60.5°C	290

Table 2. *Sociodemographic characteristics among LN, SLE without nephritis patients, and controls.*

Parameter	LN (*n* = 25)	Control (*n* = 25)	SLE without nephritis (*n* = 25)	*p*-value
Age				0.661
Mean ± SD	34.24 ± 10.05	36.12 ± 8.9	36.84 ± 10.53	
Median (range)	34.00 (22-52)	37.00 (16-50)	33.00 (21-65)	
Sex				0.895
Male (M)	3	2	2	
Female (F)	22	23	23	
(M:F ratio)	(1:7.3)	(1:11.5)	(1:11.5)	

p-value < 0.05 is statistically significant.
LN: Lupus nephritis; SLE: Systemic lupus erythematosus.

Table 3. *Comparison between LN versus SLE without nephritis groups regarding some clinical data.*

Parameter	Groups		*p*
	LN (*n* = 25)	SLE without nephritis (*n* = 25)	
Disease duration (mean ± SD)	3.12 ± 3.866	5.32 ± 4.385	0.178
Fever Yes No	 6 19	 6 19	1.00
Fatigue Yes No	 9 16	 7 18	0.544
Weight loss Yes No	 14 11	 10 15	0.267
Malar rash Yes No	 13 12	 17 8	0.257
Discoid rash Yes No	 5 20	 2 23	0.220
Hair loss Yes No	 23 2	 23 2	1.000
Alopecia Yes No	 5 20	 7 18	0.508
Photosenstivity Yes No	 17 8	 19 6	0.538
Oral ulcers Yes No	 20 5	 15 10	0.128
Arthralgia Yes No	 25 0	 21 4	0.03
Arthritis Yes No	 22 3	 11 14	0.001
Systematic affection Yes No	 25 0	 23 2	0.145

p-value < 0.05 is statistically significant.
LN: Lupus nephritis; SLE: Systemic lupus erythematosus.

the wild genotype had a statistically significant higher frequency among the controls, whereas AC genotype had a statistically significant higher frequency among the LN group, and CC genotype was only present at SLE without nephritis group (*p*-value = 0.006).

Univariate binary logistic regression analysis revealed that arthritis [odds ratio (OR): 9.33, 95% confidence interval (CI 95%): 2.2–39.4, $p = 0.002$], ESR (OR: 0.97, CI 95%: 0.95-0.99, $p = 0.02$), PLT count (OR: 0.99, CI 95%: 0.98-1, $p = 0.03$), and anti-DNA (OR: 0.20, CI 95%: 0.05-0.77, $p = 0.02$) were the factors significantly associated with LN development in patients with SLE. Multivariate binary logistic regression analysis confirmed that ESR (OR: 0.96, CI 95%: 0.93-0.99, $p < 0.02$) and PLT count (OR: 0.99, CI 95%: 0.98-0.99, $p = 0.01$) were the predictors significantly associated with LN development in patients with SLE, but the gene polymorphism at codons 52, 54, and 57 at exon 1 cannot be considered as a risk factor for LN in SLE patients in this study as shown in Table 6.

Discussion

In this study, the wild type of codons 52,54 and 57 was more frequent in controls than cases, and this is in line with other studies (24,25). On the contrary to this study (26), another study of the role of MBL in SLE reported that there was no difference between frequencies of the wild genotype in SLE patients compared to control. In

Table 4. *Laboratory parameters in the three studied groups.*

Parameter	Groups			*p*-value	
	LN (*n* = 25)	Controls (*n* = 25)	SLE without nephritis (*n* = 25)		
ANA				***p***	***p1***
+ve	25	0	23	0.00	0.14
−ve	0	25	2		
Anti-DNA					
+ve	13	0	21	0.00	0.01
−ve	12	25	4		
Proteinuria					
Yes	19	0	19	0.00	1.000
No	6	25	6		
ESR (mean ± SD)	54.96 ± 21.98	6.9 ± 0.8	38.14 ± 25.31	0.00	0.16
Hemoglobin (Hg) (g/dl) (mean ± SD)	11.07 ± 1.9	12.02 ± 0.77	11.27 ± 1.63	0.07	0.527
White blood cells (WBCs) (10^3/µl) (mean ± SD)	6.94 ± 2.8	6.6 ± 2.4	7.0 ± 3.38	0.85	0.09
PLTs (10^3/µl) (mean ± SD)	298.68 ± 132.4	198.00 ± 27.5	224.6 ± 79.8	0.001	0.13
Creatinine (mg/dL) (mean ± SD)	0.83 ± 0.61	0.66 ± 0.13	1.09 ± 0.60	0.01	0.36

p-value < 0.05 is statistically significant.
p-value compared the three groups
P1 compared LN group with SLE without nephritis group.
LN: Lupus nephritis; SLE: Systemic lupus erythematosus.

Table 5. *The frequencies of codon 52,54, and 57 genotypes of the MBL gene in the three studied groups.*

MBL gene		Groups			*p*-value	*P1*
		LN (*n* = 25)	Control (*n* = 25)	SLE without nephritis (*n* = 25)		
Codon 52	AA (wild) (*n* = 29)	6 (24%)	16 (64%)	7 (28%)	0.04	0.30
	AD (*n* = 38)	13 (52%)	9 (36%)	16 (64%)		
	DD (*n* = 8)	6 (24%)	0	2 (8%)		
Codon 54	AA (wild) (*n* = 15)	4 (16%)	9 (36%)	2 (8%)	0.03	0.513
	AB (*n* = 48)	19 (76%)	10 (40%)	19 (76%)		
	BB (*n* = 12)	2 (8%)	6 (24%)	4 (16%)		
Codon 57	AA (wild) (*n* = 14)	4 (16%)	7 (28%)	3 (12%)	0.006	0.03
	AC (*n* = 55)	21 (84%)	18 (72%)	16 (64%)		
	CC (*n* = 6)	0	0	6 (24%)		

p-value < 0.05 is statistically significant.
p-value compared the three groups.
P1 compared LN group with SLE without nephritis group.
LN: Lupus nephritis; SLE: Systemic lupus erythematosus.

this study, we noticed that for codon 54, the wild genotype had a statistically significant higher frequency among the controls, whereas AO genotype had statistically significant equal frequencies among the LN and SLE without nephritis groups, and it was more frequent than controls. BB genotype had a statistically significant higher frequency among the controls. Furthermore, another study (27) reported that codon 54 substitution is more frequent in SLE patients than in normal Chinese population, and others (28) have reported an increased susceptibility to

Table 6. *Univariate and multivariate binary logistic regression analysis of predictor variables of LN in patients with SLE.*

Characteristics	Univariate analysis		Multivariate analysis	
	OR (CI 95%)	*p*-value	OR (CI 95%)	*p*-value
Age	1.026 (0.970-1.085)	0.370	0.923 (0.83-1.01)	0.095
Gender	1.568 (0.239-10.3)	0.639		
Disease duration	1.148 (0.985-1.338)	0.078	1.005	0.958
Fever	1.00 (0.273-3.662)	1.00		
Fatigue	1.44 (0.438-4.781)	0.54		
Weight loss	1.90 (0.6-5.8)	0.26		
Malar rash	0.51 (0.1-1.610)	0.25		
Discoid rash	2.87 (0.5-16.477)	0.23		
Alopecia	0.64 (0.173-2.388)	0.50		
Hair loss	1.00 (0.13-7.717)	1.00		
Photosenstivity	0.67 (0.19-2.3)	0.53		
Oral ulcers	2.66 (0.7-9.5)	0.13		
Arthritis	9.33 (2.2-39.4)	0.002		
Arthralgia	1.92	0.99		
Systematic affection	1.75	0.99		
Hg	1.06 (0.7-1.4)	0.69		
WBCs	1.01 (0.84-1.2)	0.86		
PLTs	0.99 (0.98-1)	0.03	0.99 (0.98-0.99)	0.01
ESR	0.97 (0.95-0.99)	0.02	0.96 (0.93-0.99)	0.02
ANA	1.83	0.99		
Anti-DNA	0.20 (0.05-0.77)	0.02		
Serum creatinine	2.19 (0.74-6.4)	0.15		
Proteinuria	1.00 (0.27-3.6)	1.00		
Codon 54				
AA				
AB	2.00 (0.32-12.25)	0.45	2.3 (0.04-126.6)	0.68
BB	4.00 (0.36-44.11)	0.25	1.6 (0.06-44.09)	0.76

p-value < 0.05 is statistically significant.
OR: odds ratio; CI 95%: 95% confidence interval.
LN: Lupus nephritis; SLE: Systemic lupus erythematosus.

nephritis in lupus patients with a mutation in codon 54 of exon 1, whereas a study (29) reported that the frequency of individuals with homozygous codon 54 mutation (allele B) of the MBL gene was significantly increased in the Japanese patients with autoimmune disorders, in particular, SLE compared to Japanese healthy volunteers without known autoimmune disorders. We also noticed in this study that alleles B and C were more frequent in patient groups than allele D. This is in line with the other studies (30). AD genotype had a statistically significant higher frequency among the SLE without nephritis group, and DD genotype had a statistically significant higher frequency among the LN group (*p*-value = 0.01); also, there was a study, reporting that those with the O/O genotype were more likely to report renal events (30). We also noticed that the wild genotype of codon 57 had a statistically significant higher frequency among the controls, whereas AC genotype had a statistically significant higher frequency among the LN group, and there was no CC genotype at the control and LN groups; this is in line with a study of MBL gene polymorphism in North American patients with SLE, it was reported that the prevalence of the A/C genotype was higher in patients with SLE (especially, African-American patients) than healthy controls, and CC genotype was only present at SLE without nephritis group (*p*-value = 0.009) (30).

Conclusions

MBL codon 52, 54, and 57 substitutions were more frequent in SLE patients either with or without nephritis than the normal Egyptian population, and the wild genotype of the studied codons was more frequent at the normal Egyptians than at the patients. Codon 54 and 57

substitutions were more frequent than codon 52. Codon 52 substitution was more frequent at LN than SLE without nephritis patients, whereas codon 54 and 57 substitutions were more frequent in SLE without nephritis than LN patients. The AO genotype was found the most frequent genotype among the codon 52, 54, and 57, whereas the OO genotype was the least frequent one.

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Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
The study was approved by the Ethics Committee of Sohag Faculty of Medicine.

Consent for publication
Informed consent was obtained from the participants

Author details
Osama Sayed Daif Allah[1], Alshimaa Hafez Abdelall[2], Madeha Mahrous Zakhary[3], Nagwa S. Ahmed[2], Asmaa Mohamed Goda[4]

1. Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Sohag University, Egypt
2. Medical Biochemistry Department, Faculty of Medicine, Sohag University, Egypt
3. Medical Biochemistry Department. Faculty of Medicine, Assuit University, Egypt
4. Medical Microbiology and Immunology Department, Faculty of Medicine, Sohag University, Egypt

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