MBL2 gene polymorphisms and its relation to infection in Brazilian systemic lupus erythematosus patients: A 10-years follow-up study

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a multifactorial disease and MBL2 genetic variants, which are associated to differential peripheral MBL levels, potentially affect its etiology and increase infection risk in this population.
Objective: To evaluate the potential association of MBL2 polymorphisms of the coding and promoter gene region and haplotypes on hospitalization, number of admission and days of admission for major infection causes in Brazilian SLE patients. Methods: 325 SLE patients from a southern Brazilian outpatient SLE clinic were genotyped in 2006 for MBL2 gene polymorphisms from coding and promoter region (rs1800450, rs1800451, rs5030737, rs11003125, and rs7096206) and followed until 2016. Clinical and laboratory data from each patient were obtained and information regarding the need for hospitalization, the number of admissions and number of days admitted for infection treatment were compiled and compared with MBL2 gene polymorphisms and haplotypes. A linear regression analysis was constructed considering the variables of bivariate which demonstrated an association (p<0.05) and variables which had a theoretical basement.
Results: No difference was found in polymorphism prevalence when comparing the group that was admitted for infection treatment and the group who did not. Allele C, and haplotypes LY and HY correlated with more infection hospitalizations [wild-type homozygosis for C: 2 (IQR 1–3), heterozygosis for C: 3 (IQR 2–6) p=0.038; LY 2 (IQR 1–3) p=0.049; HY 2 (IQR 1–3) p=0.005] and haplotype HY carriers stayed fewer days in hospital for infection treatment: 18 (IQR 10–38) p=0.041. When linear regression was applied HY associated with shorter admission time for infections (−18.11 days, p=0.021) and HY (−1.52 admission, p 0.001) carriers with older age at diagnosis had less admissions for infection (HY regression model: −0.42, p=0.006; LY regression model −0.04, p=0.010; −0.04, p=0.013).
Conclusion: The presence of the HY promoter haplotype associated to fewer in hospital care for infection treatment probably due to higher MBL plasma levels. Also, HY haplotype and older age at SLE diagnosis is related to less admissions for infection. This factor should be taken into consideration, since infection is a very import cause of mortality in SLE patients being also related to aggressive immunosuppressive treatment.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory multisystem disease characterized by periods of activity and remission. Its etiology is not totally understood but it is known to result from the interaction of hormonal, environmental, and genetic factors.[1,2] Considering the genetic susceptibility factors, gene coding molecules of the complement system were already suggested as important players in the SLE physiopathology. One of these genes, *MBL2*, is responsible for the expression of the mannose-binding lectin (MBL) molecule. It was suggested that the deficiency of complement proteins leads to a prolonged exposition to autoantigens, which takes to higher autoantibody production due to a lack of depuration of such autoantigens.[3]

MBL2 gene is located at the chromosome 10 and is composed by four exons. Polymorphisms at exon 1 and in the promoter region influence MBL plasma levels by the abnormal interaction of transcribed alleles.[4] Translation of polymorphic variants of the *MBL2* gene exon 1 [called as alleles B (rs1800450), C (rs1800451), and D (rs5030737). B, C, and D], results in MBL molecules with a less stable structure, which are more susceptible to degradation. The presence of any of the variants B, C, or D is collectively called allele O, although the simultaneous absence of all variants characterizes the wild-type, or A allele. Promoter region polymorphisms can be assigned as alleles H/L (rs11003125), X/Y (rs7096206), and P/Q (rs7095891), and are associated to differential transcription rates of the *MBL2* gene. The combination of alleles on the promoter region can potentially generate the following haplotypes: LX, LY, HY, and HX, although, due to linkage disequilibrium, HX is rarely seen.[4,5]

As previously mentioned, MBL plasma levels are influenced by the presence of polymorphic alleles from both exon 1 and the promoter region of the *MBL2* gene, as well as by the haplotypes resulting of the combination of such variants. The presence of allele B and C are associated with an important reduction of MBL serum levels, although allele D has a minimum impact on that. The HY promoter region haplotype is related to high levels of MBL in plasma, although the LX haplotype correlates with low concentrations of this protein. Combination of the polymorphic alleles from exon 1 and those from the promoter region results in different haplotypes in which HYA/A and LYA/A are associated to high MBL plasma levels, and haplotypes LYA/0 and LXA/0, respectively, to moderate and very low to deficient plasma levels.[5]

It is well established that MBL deficiency predisposes to major infections and that homozygous individuals to *MBL2* gene variants could present a higher risk for such infections.[3,6] This is a quite relevant association, especially considering the frequent need of immunosuppressive drugs in infected patients, and the exacerbation of clinical symptoms in SLE patients associated to infection. Also of note is the fact that infection is still one of the major causes of death in SLE patients.[1] In this scenario, to well establish the relation of the *MBL2* gene polymorphisms and infection could lead to a better management of the SLE patient. Thus, the aim of the present study was to determine if *MBL2* gene polymorphisms from coding and promoter region associated with hospitalization, number of admissions and days of admission for major infection causes in a cohort of SLE patients from the southernmost state of Brazil.

Methods

Study Population

325 consecutive SLE patients, 18 years old or over, were recruited at the lupus clinic from Hospital de Clínicas de Porto Alegre (HCPA), a university hospital located in southernmost state of Brazil, and which is a reference center in rheumatology. Patients were genotyped for *MBL2* gene polymorphisms from both the coding (exon 1) as well as the promoter gene region, as previously published by our group.[5,7] All patients met the American College of Rheumatology revised criteria for SLE classification.[2] Patients were followed from January 2006 to December 2016, and information about admissions and clinical features were collected by chart review of this period. Chart review was performed with a standardized questionnaire to collect demographic, clinical, and laboratory data. Thirty-four patients (10.47%) lost follow-up and were excluded from the analyses.

Infection as a cause of hospitalization

Admission due to major infections was considered for those who stayed more than 48 h in hospital and were treated with antibiotics based on clinical, complementary tests and the clinical response to this treatment. The Brazilian public health system defines hospital admission using this time lag since major infections need more than 48 h of antibiotic regimens in hospital care.

Clinical and laboratory data

Demographic data such as age at the diagnosis, age at the end of the study, ethnic origin, and sex were registered.

Information about SLE clinical manifestation included malar rash, presence of oral or nasal ulcers, arthritis, serositis (pleuritis and/or, pericarditis), nephritis, neurologic disorders (psychosis and seizures), and hematologic disorders (hemolytic anemia, thrombocytopenia, and leukopenia).

Laboratory tests included the evaluation of positivity to antinuclear antibodies (with a titer>1:80), anti-dsDNA,

anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, anticardiolipin, and lupus anticoagulant. SLEDAI and SLICC damage index were applied to each patient at the beginning of the study.[8]

Information about SLE treatment and medical regimens along the disease course was collected, encompassing the use of methylprednisolone pulse therapy, cyclophosphamide, mycophenolate, azathioprine, and antimalarial drugs. Also, data about treatment before admission were compiled, including use of corticoids, cumulative dose of corticosteroids, and the use of immunosuppressants (azathioprine, mycophenolate, or cyclophosphamide) until 3 months before the admission.

Statistical analysis

Categorical data were presented as percentage and continuous variables as mean and standard deviation or median and interquartile range. The association between admissions due to infection, number of admissions, and number of days hospitalized for infection treatment were made using Mann–Whitney or Kruskal–Wallis when appropriate.

Demographic, clinical, and laboratory data comparing patients who were hospitalized for infection treatment and those hospitalized for other causes or not hospitalized, were evaluated by Qui-Square test with Yates correction, t-test for symmetrical variables and Mann–Whitney for asymmetrical variables.

The association between the number of days admitted and the number of hospitalizations for infection treatment with age at diagnosis, time of disease, clinical manifestations, and treatment was accessed by Mann–Whitney for categorical variables and Spearman correlation test for continuous variables. Multiple linear regression was adjusted for those variables in which bivariate analysis demonstrated an association considering a $p<0.05$ and variables which had a theoretical base. As age at the diagnosis and age of patients are related variables ($r=0.82$, $p <0.001$) the multiple linear regression was adjusted only to the first one to avoid multi correlations. The genotypes related to the outcome variables after multivariate analyses were correlated to MBL plasma levels according to haplotypic combinations of exon 1 and promoter region variants of *MBL2* gene.[5] For all analyses, statistical significance was considered if $p<0.05$.

Ethic issues

The study protocol was approved by a local Ethics Committee and informed consent was obtained from all participants at the beginning of the study or at the inclusion of new participants.

Results

Along the 10 years follow-up period of the study (from 2006 to 2016), one hundred and 64 patients were admitted at the hospital at least once, among which 101 were hospitalized due to major infections. In total, there were 194 admissions due to infection, since some patients needed hospitalization more than once. The median and interquartile range (IQR) of total days of under hospital care were 20 (12–42) and the median times of admissions for infection was equal to two.[1–3] Cumulative dose of corticoid 3 months before the first admission had a median of 1.8 g (0.45–3.9), being this same parameter 1.8 g (0.45–4.8) and 1.57 g (0.45–3.6) for the second and the third events of hospitalization.

Baseline clinical, laboratory, and genetic features of patients are shown in Table 1. A tendency of more frequent hospitalization due to infections was seen for patients ethnically classified as European-derived, although this do not reach statistical significance. Patients who were admitted for major infection treatment were younger, had lower disease duration, and more accrual damage at the beginning of the study as compared with the remaining individuals. Besides, nephritis, neurological, and hematological disorders were also conditions more frequently seen amongst the patients admitted due to infections. Indexes of positivity to anti-Ro and anti-La antibodies, as well as the presence of an immunological abnormality (considering the presence of at least one of any of the evaluated features) were also higher amongst the patients who needed hospitalization as compared to the other patients. Of note, such patients also received more frequently methylprednisolone pulses, as well as cyclophosphamide and azathioprine treatments along the disease follow-up. As expected, patients admitted for infection treatment presented a higher mortality rate as compared to patients without infections.

No difference was observed regarding allelic and haplotype frequencies in relation to admission for infection treatment. Nevertheless, when considering the total number of admissions for infection treatment and duration of hospitalization computed by the total number of days in the hospital, allele C, and both haplotypes LY e HY were associated with more infection hospitalizations. Also, individuals with the HY haplotype remained less days under hospitalization for infection treatment as compared with carriers of the other haplotypes (Table 2). These results were used to build a multivariate model including other variables related to the number of admissions and the number of days admitted for infection treatment in the bivariate analyses. Linear regression demonstrated that patients with the HY haplotype remained 18 days less at infection treatment as compared with individuals bearing other haplotypes (Figure 1). Also, the presence of the HY haplotype and older age at diagnosis correlated with fewer infection admissions (Table 3).

As patients with the HY haplotype had shorter and fewer hospitalizations for infection treatment, their haplotypes including exon 1 variants were evaluated taking into consideration their potential inferred MBL levels. This revealed

Table 1. Baseline features of SLE patients admitted for major infection treatment and patients who did not.

Patients' features[a]	Total (n=290)	Admission for major infection n=101 (100%)	No admission for major infection n=189 (100%)	p-value[b]
Female	268 (92.4)	96 (95)	172 (91)	0.314
European derived	216 (74.5)	68 (67.3)	148 (78.3)	0.570
Age[c]	42 ± 14.1	39 ± 14.3	43 ± 13.8	0.016
Disease duration[c]	31.2 (22.6–42.1)	17 (12–24)	18 (15–26)	0.022
SLE involvement				
SLICC[d]	1 (0–2)	1 (0–3)	0 (0–1)	<0.001
SLEDAI[e]	1 (0–4)	2 (0–4)	0 (0–4)	0.060
Malar rash	158 (54.8)	58 (58)	100 (53.2)	0.512
Arthritis	244 (84.7)	88 (88)	156 (83)	0.339
Neurological disorders[f]	35 (12.2)	17 (17)	18 (9.6)	0.100
Serositis	91 (31.6)	46 (46)	45 (23.9)	<0.001
Nephritis	124 (43.1)	56 (56)	68 (36.2)	0.002
Hematologic disorders[g]	230 (79.9)	87 (87)	143 (76.1)	0.040
Laboratory data at study entry				
ANA	284 (98.6)	99 (99)	185 (98.4)	0.999
anti-dsDNA	139 (48.3)	54 (54)	85 (45.2)	0.195
anti-Sm	57 (19.8)	2 (25)	32 (17)	0.144
anti-Ro/SSA	113 (7.3)	16 (18.2)	16 (9.6)	0.002
anti-La/SSB	32 (12.5)	16 (18.2)	16 (9.6)	0.026
Immunologic alterations	190 (66)	75 (75)	115 (61.2)	0.026
SLE treatment at any time of the disease				
Antimalarial	250 (97.6)	96 (96)	184 (98.4)	0.394
Mycophenolate	16 (5.6)	9 (9)	7 (3.7)	0.112
Methylprednisolone pulse therapy	89 (31)	51 (51)	38 (20.3)	<0.001
Cyclophosphamide	102 (35.4)	48 (48)	54 (28.7)	0.002
Azathioprine	145 (50.3)	66 (66)	79 (42)	<0.001
Coding region *MBL2* gene alleles				
B				
Wild-type homozygous	216 (74.2)	77 (76.2)	138 (73)	0.780
Heterozygous	67 (23.0)	21 (20.8)	46 (24.3)	
Variant homozygous	8 (2.7)	3 (3)	5 (2.6)	
C				
Wild-type homozygous	263 (90.4)	91 (90.1)	171 (90.5)	
Heterogeneous	28 (9.6)	10 (9.9)	18 (9.5)	0.999
D				
Wild-type homozygous	247 (84.9)	90 (89.1)	156 (82.5)	
Heterozygous	41 (14.1)	11 (10.9)	30 (15.9)	
Variant homozygous	3 (1.0)	0 (0)	3 (1.6)	0.213
Promoter *MBL2* gene haplotypes				
LX	187 (64.7)	31 (31.3)	71 (37.6)	0.355
LY	80 (27.7)	70 (70.7)	211 (73.5)	0.709
HY	186 (64.4)	71 (71.7)	114 (60.3)	0.074
Non-survivors, over 10 years	26 (9.0)	16 (16)	10 (5.3)	0.006

[a]Frequencies of all patients and the ones who were admitted or not for major infection treatment.
[b]Chi-Square test with Yates correction between patients admitted and no admitted for major infection treatment, statistical significance was considered with a p-value <0.05.
[c]years ±standard deviation.
[d]SLICC: systemic lupus collaborating clinics, median (25th, 75th percentiles).
[e]SLEDAI: score of disease activity, median (interquartile range).
[f]neurological disorders: psychosis and seizures.
[g]immunologic disorders: presence of at least one (anti-Ro, anti-La, anti-Sm, anti-dsDNA, anti-RNP, anticardiolipin, lupus anticoagulant, VDRL false negative, ANA).
*Some missing data could interfere in total number and percentages.

Table 2. *MBL2* gene polymorphisms and haplotypes associated to admission, number of admissions and days admitted for infection treatment.

MBL2 gene[a]	Admission due to infection		Number of admissions due to infection		Days admitted for infection treatment	
	N=101 (100%)	p-value[b]	Median (IR)	p-value[b]	Median (IR)	p-value[b]
Coding region/exon 1 alleles						
B						
Wild-type homozygous	77 (76.23)		2 (1-3)		21 (11–46)	
Heterozygous	21 (20.79)	0.788	2 (1-3)	0.911	18 (13–35)	0.729
Variant homozygous	3 (2.97)		2 (1-3)		24 (12–36)	
C						
Wild-type homozygous	91 (90)		2 (1-3)		20 (12–39)	
Heterogeneous	10 (9.99)	0.999	3 (2-6)	0.038	40 (14–77)	0.217
D						
Wild-type homozygous	90 (89.10)		2 (1-3)		21 (13–45)	
Heterozygous	11 (10.89)	0.213	2 (1-3)	0.806	16 (8–38)	0.326
Variant homozygous	0		0		0	
Promoter region haplotypes						
LX	31 (30.69)	0.355	2 (1-3)	0.887	18 (9–36)	0.569
LY	70 (69.30)	0.709	2 (1-3)	0.049	20 (14–49)	0.055
HY	71 (70.29)	0.074	2 (1-3)	0.005	18 (10–38)	0.041

[a]requencies according to admission for infection treatment and median and interquartile range for number of admissions for infection treatment and number of days in admission for infection.
[b]Mann–Whitney test used when two variables were used for comparing and Kruskal–Wallis test when more than two variables were used for comparing. Statistical significance was considered with a *p*-value <0.05.
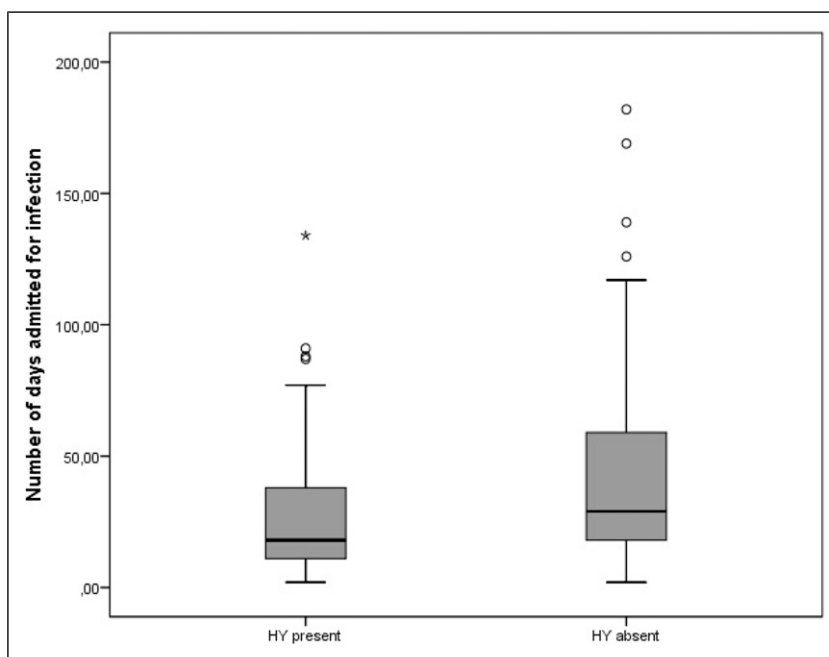

Figure 1. HY promoter haplotype of *MBL2* gene and its relation with median of days admitted for infection treatment.

Table 3. Linear regression model for days admitted for infection and total admissions for infection treatment.

Variables[a]	Days admitted for infection[b]		Total admissions for infection[b]	
	Coef B (IC 95%)[c]	p-value[d]	Coef B (IC 95%)[c]	p-value[d]
Haplotype HY of *MBL2* gene	−18.11 (-33.48−−2.75)	0.021	−1.52 (-2.42−−0.62)	0.001
Haplotype LY of *MBL2* gene		—	0.64 (−0.26–1.55)	0.164
Allele C of *MBL2* gene		—	1.22 (−0.15– 2.60)	0.082
Serositis				
Haplotype HY regression model	14.00 (−0.006–28.02)	0.050	0.44 (−0.37–1.26)	0.280
Haplotype LY regression model			0.53 (−0.32–1.39)	0.221
Allele C regression model			0.55 (−0.28–1.39)	0.195
Nephritis				
Haplotype HY regression model	11.11 (−3.64–25.88)	0.138	−0.21 (−1.07–0.65)	0.629
Haplotype LY regression model			−0.01 (−0.91–0.88)	0.972
Allele C regression model			0.03 (−0.83–0.90)	0.937
Mycophenolate				
Haplotype HY regression model	11.44 (−14.33–37.21)	0.380	0.44 (−1.05–1.95)	0.557
Haplotype LY regression model			0.34 (−1.23–1.93)	0.664
Allele C regression model			−0.02 (−1.62–1.58)	0.979
Corticoid need until 3 months before admission				
Haplotype HY regression model	13.07 (−4.22–30.36)	0.136	0.67 (0.33–1.68)	0.187
Haplotype LY regression model			0.62 (−0.44–1.68)	0.249
Allele C regression model			0.53 (−0.51–1.58)	0.312
Age at diagnose				
Haplotype HY regression model	−0.40 (−0.98–0.17)	0.166	−0.042 (-0.08−−0.01)	0.006
Haplotype LY regression model			−0.04 (-0.08−−0.01)	0.010
Allele C regression model			−0.04 (-0.07−−0.009)	0.013
SLICC				
Haplotype HY regression model	1.70 (−2.5–5.9)	0.422	−0.04 (−0.29–0.19)	0.692
Haplotype LY regression model			−0.02 (−0.27–0.23)	0.869
Allele C regression model			−0.02 (−0.28–0.22)	0.831

[a]Were listed variables with p-value <0.05 in bivariate analyses besides age that were used to construct the multivariate model.
[b]Variables with a p-value <0.05.
[c]coef B (IC 95%): coefficient B and confidence interval of 95%.
[d]Statistical significance was considered with a p-value <0.05.

a significant association with high MBL levels haplotypes ($p< 0.003$).

Discussion

In this study the presence of the HY haplotype was an independent factor which correlated to shorter periods of hospitalization for infection treatment. Also, this same haplotype correlated to fewer admissions when considering age at time of diagnosis in our SLE cohort. Besides, the HY haplotype was correlated with coding MBL2 gene variants which confer high MBL plasma levels, suggesting that its presence is an important factor on the regulation of the MBL expression. Of note, this is the first study showing a correlation between the number of days under hospitalization for infection treatment and *MBL2* gene polymorphisms in SLE patients.

Several studies already evaluated genetic factors associating different polymorphic variants and increased risk for infections in SLE patients, including some polymorphisms of the *MBL2* gene.[9–14] Although SLE susceptibility and some clinical features common to this condition are affected by the ethnic background of the patient, it seems that such a feature is not determinant when concerning susceptibility to infection in the SLE patient.[4,15]

Although several studies evaluated *MBL2* polymorphisms and potential association to SLE or MBL plasma levels, the comparison of results is quite difficult since the majority of the studies only evaluated a few variants.[9,10] For instance, the presence of the Y allele was associated to higher MBL plasma levels but in such studies the H allele was not evaluated. According to Ip et al., high MBL serum levels would be driven by the HY haplotype instead of solely by the H allele. In this context, a study with SLE children suggested that high MBL expression genotypes had a protective role against infection, in the same direction of as a previous study from our group, where an association

between HY and coding and promoter region haplotypes of *MBL2* gene related to higher MBL levels and SLE was observed.[5,16] Taking together these data corroborate fewer and shorter admissions due to infections in HY individuals, as seen in the present study.

Mok et al. observed an inverse relation between MBL levels inferred according to *MBL2* genotypes and the number of major bacterial infections in Chinese patients with SLE. In this study, the highest MBL levels were associated to the YA haplotype.[9] Garred et al. showed that homozygosity for polymorphisms of the coding region for *MBL2* gene was associated with and increased risk for complicating infections in SLE patients.[10,14] Similar results were observed by Takahashi et al. concerning to allele B.[12] In our cohort, heterozygous SLE individuals carrying the allele C were admitted more frequently for treatment of major infections as compared to non-carriers of this variant, although after adjusting the analysis for other variables this association lost statistical significance.

As discussed above, high MBL levels or genotypes/ haplotypes associated to high MBL levels are consistently seen as protective factors against infections in the literature, although some controversial data exist. For example, no association between MBL polymorphisms and pneumonia was observed by Kinder et al. (2007) in SLE patients, but it is important to highlight that only the coding region of the gene was analyzed, and the small number, as well as the ethnic diversity, of patients could have influenced these results.[11]

Finally, the group of patients admitted for infection treatment in our study presented a higher SLICC index score, shorter disease duration, more aggressive disease and a high death index as compared to patients who were not hospitalized. Nevertheless, it is important to mention that no differences regarding *MBL2* gene polymorphisms genotypes were observed between these groups.[9–11,14]

In conclusion, the presence of the HY promoter haplotype of the *MBL2* gene in SLE patients was associated to shorter admission periods for infection treatment possibly due to high MBL expression. Although peripheral MBL levels were not directly accessed in this study, our results strongly support the use of *MBL2* genotyping as indicative of the potential of SLE patients to produce high (or low) MBL levels and, therefore, as a potential marker of susceptibility to infections in such patients. Such evaluation could be extremely relevant considering that infection is a very important cause of mortality in SLE patients independently of the use of aggressive immunosuppressive therapy.

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