Genetic Polymorphisms in Patients With Systemic Lupus Erythematosus and Jaccoud Arthropathy

A Pilot Study

Anna Paula Mota Duque Sousa, MD,† Giselle Calasans de Souza Costa, PhD,‡§*
Gustavo Nunes de Oliveira Costa, PhD,§ Lúcio Macedo Barbosa, PhD,‡
Maria Fernanda Rios Grassi, MD, PhD,‡ Maria Eduarda Haerdy Monteiro, PhD,§
*Mitermayer Galvão dos Reis, MD, PhD,‡ Maurício Lima Barreto, MD, PhD,‡ Ana Luisa Pedreira, MD,**
Daniel Sá Ribeiro, MD, PhD, Carolina Freitas Lins, MD,* Verena Galvão, PhD,**
Willer Gonçalves Dourado Santos, MD, Viviane Machicado, MD,*† Emanuela Pimenta da Fonseca, MD,**
Carla Baleeiro Rodrigues Silva, MD,† and Mittermayer Barreto Santiago, MD, PhD†‖*

Introduction: Jaccoud arthropathy (JA) is a nonerosive and deforming arthropathy experienced frequently by patients with systemic lupus erythematosus (SLE). Although genetic polymorphisms are associated with SLE development, the association between genetic polymorphisms and JA has not been studied to date. The main objective of this study was to evaluate an association between *HLA*, *STAT4*, *IRF5*, and *BLK* polymorphisms and the presence of JA in Brazilian individuals with SLE.

Methods: Patients were selected from a cohort of individuals with SLE followed at 2 rheumatology reference centers in Salvador, Bahia, Brazil. The JA diagnosis was based on clinical and radiological criteria. The participants were genotyped for rs9271100, rs7574865, rs10488631, and rs13277113 polymorphisms in the *HLA*, *STAT4*, *IRF5*, and *BLK* genes, respectively, using real-time polymerase chain reaction. The presence of JA was correlated with allele frequencies, and clinical and laboratory data.

Results: One hundred forty-four individuals with SLE (38 with JA and 106 with SLE without JA) were studied. The mean age of the patients was 45 ± 12 years; the majority were women and had brown skin. Patients with JA had a longer disease duration than patients without JA. Serositis and neuropsychiatric manifestations were more frequent in the JA population. The A allele of rs13277113 in the *BLK* gene was associated with the presence of JA.

Conclusions: The rs13277113 polymorphism in the *BLK* gene was found to be a possible genetic risk for JA development. However, further studies in larger populations should be performed to confirm this finding.

Key Words: systemic lupus erythematosus, Jaccoud arthropathy, genetic polymorphisms

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Jaccoud arthropathy (JA) is a nonerosive chronic arthropathy, characterized by deformities such as ulnar deviation, "swan neck," "boutonniere," and Z-type, similar to those seen in rheumatoid arthritis (RA) but characteristically "reducible" to passive movement.[1] Jaccoud arthropathy was initially described by François Sigismond Jaccoud in 1869 in patients with rheumatic fever. Later on, it was described in systemic lupus erythematosus (SLE), other diffuse connective tissue diseases, neoplasm, and infectious diseases.[2] There are no definite classification criteria for JA. In 1950, Bywaters[3] described features that might differentiate the chronic post rheumatic arthritis (type Jaccoud) from RA. In 1992, Spronk et al[4] developed a diagnostic "index" to define the presence of JA in SLE patients. A score higher than 5 points suggests JA. We have previously proposed a set of criteria for JA, specifically for SLE, which was recently revised.[5]

In autoimmune diseases such as SLE, environmental factors are presumed to induce modifications to the innate and adaptive immune response, which provokes or accelerates the development of these diseases in genetically susceptible individuals.[6,7] In recent years, genome-wide association studies were critical in identifying susceptibility loci for SLE containing inherited polymorphic mutations denominated as single-nucleotide polymorphisms (SNPs).[8] The strongest genetic associations with SLE are the human leukocyte antigen (HLA) system, mainly the alleles HLA DRB1*1501 (HLA-DR2), HLA DRB1*0301 (HLA-DR3), and non-HLA genes as *STAT4* (signal transducer and activator of transcription 4), *IRF5* (interferon regulatory factor 5), *ITGAM* (integrin alpha M), and *BLK* (B lymphoid kinase).[9–14] Hom et al[9] highlighted the importance of certain non-HLA polymorphisms rs7574865 in *STAT4*, rs10488631 in *IRF5*, and rs13277113 in *BLK* for SLE susceptibility. In HLA class II, there are several SNPs with a strong association with SLE, such as rs2187668, rs9271100, and rs9271366 polymorphisms. They are some of the most relevant polymorphisms in HLA gene in several studied populations (ie, European, Chinese, and African American).[9,15,16]

Several studies investigated whether these SLE risk polymorphisms could also be involved in determining the features of the disease, such as nephritis, discoid rash, arthritis, hematological, neurological manifestations, and specific antibodies.[10,17] To the best of our knowledge, the possible relationship of these risk polymorphisms with JA has not been studied. Only one small study performed in Japan explored the genetic aspect of JA and demonstrated the presence of HLA-A11 and B-61 in 5 of 9 patients with JA.[18] Considering JA as a possible complication/manifestation of SLE, we tested a hypothesis of a possible association of SLE risk polymorphisms with the development of this arthropathy.

Theoretically, the identification of risk polymorphisms for JA could help a better understanding of the pathophysiology of the disease, making possible the choice of more specific therapeutic targets. Moreover, they could be used in the clinical setting of SLE as potential predictors of evolution to JA guiding an earlier therapeutic intervention.

From the *Escola Bahiana de Medicina e Saúde Pública; †Serviço de Reumatologia do Hospital Universitário Professor Edgard Santos–Universidade Federal da Bahia; ‡Instituto Gonçalo Muniz–Fundação Oswaldo Cruz (Fiocruz); §Universidade Federal da Bahia; and ‖Serviços Especializados em Reumatologia da Bahia, Salvador, Brazil.

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Correspondence: Mittermayer Barreto Santiago, MD, PhD, Serviços Especializados em Reumatologia da Bahia, Rua Conde Filho, 117, Graça, Salvador, Bahia CEP 40150150, Brazil. E-mail: mbsantiago2014@gmail.com.

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This pilot study evaluated whether some known SLE risk polymorphisms (rs9271100 in *HLA*, rs7574865 in *STAT4*, rs10488631 in *IRF5*, and rs13277113 in *BLK*) could be associated with JA development. A possible genetic association was tested between these polymorphisms and the presence of JA in patients with SLE.

MATERIALS AND METHODS

Patients

All patients included in this study were followed in 2 rheumatology referral services from Salvador, Bahia, in Northeastern Brazil; that is, the Bahiana School of Medicine and Public Health and the University Hospital Professor Edgar Santos. These public outpatient clinics provide comprehensive care to a total of 812 patients with SLE. Of these patients, 38 individuals also had a diagnosis of JA (with a prevalence of 4.7% among patients with SLE), which is one of the largest cohorts described.[1,19]

We studied a convenience sample of SLE patients that came to our outpatient clinics from November 2015 to July 2016. Patients were sequentially included in the study, following the course of routine medical consultations. The entire population of JA entered into the study. The inclusion criteria comprised individuals from both sexes with a minimum age of 18 years. Patients with SLE were diagnosed based on the American College of Rheumatology criteria[20] and with JA according to the criteria proposed by Santiago.[21] Individuals with other associated autoimmune diseases were excluded.

For better data analysis, we included a comparison group, made up of individuals without SLE, who are part of an epidemiological project, which assesses the genetic background of individuals with obesity, psychiatric disorders, or allergies.[22] The individuals included in this study reside in the same Brazilian state. All of them were born in Brazil.

The demographic and clinical data as well as findings of musculoskeletal examinations of the patients with SLE were obtained by the attending physician and from medical records. Additional laboratory and radiological data were also collected.

The project was approved by the institutional research board of our institution. All participants who agreed to participate in the study signed an informed consent form.

Genotyping

The genomic DNA of mononucleated cells in peripheral blood was extracted using a DNA Blood Mini Kit (Qiagen, Valencia, CA). The SNPs rs9271100 in *HLA*, rs7574865 in *STAT4*, rs10488631 in *IRF5*, and rs13277113 in *BLK* were genotyped by real-time polymerase chain reaction using a Taq-Man SNP genotyping assay kit (Applied Biosystems, Foster City, CA) containing specific probes for high- and low-frequency alleles. The manufacturer's instructions were strictly followed.

Statistical Analysis

The Statistical Package for the Social Sciences software (version 21; IBM SPSS, Armonk, NY) was used for the descriptive and comparative evaluation of the demographic, clinical, and laboratory data of the patients with SLE with or without JA. The frequencies were expressed in proportions or mean ± standard deviation. The χ^2 test, exact Fisher test, or Student *t* test was used to compare different parameters.

The patients' allelic frequencies were calculated using the PLINK program (version 1.9; Shaun Purcell, New York, NY). The associations between allelic frequencies and JA, SLE, and control group were tested by odds ratio (OR) calculations, exact Fisher or Armitage tests using Stata software (version 14; STATA Corp, College Station, TX), or the PLINK program. A model of allelic inheritance was used. *p* values of 0.05 or less were considered statistically significant.

RESULTS

A total of 144 patients with SLE were evaluated: 38 patients also had JA, whereas 106 patients did not have JA.

The main clinical and laboratory findings of the studied population are described in Table 1. The patients' mean age was 45 ± 12 years, and the majority were women with brown skin. The most common lupus features were arthritis, photosensitivity, malar rash, and leukopenia. Patients with JA had swan neck deformity (100% of patients), cubital deviation (52%), Z-thumb deformity (26%), and hallux valgus (7%). It was observed that all

TABLE 1. Demographic, Clinical, and Laboratory Characteristics of Patients With SLE With or Without JA

	SLE With JA	SLE Without JA	*p*
	n/n Total (%)[a]	n/n Total (%)[a]	value
Sample (n total)	38	106	—
Age, y	46 ± 12	44 ± 12	0.40
Female	37/38 (97)	104/106 (98)	0.80
Skin color			0.79
Brown	19/33 (58)	44/80 (55)	
Black	6/33 (18)	19/80 (24)	
White	8/33 (24)	17/80 (21)	
Duration of disease, y	13 ± 5	10 ± 5	**0.004**
Malar rash[b]	22/36 (61)	48/93 (52)	0.33
Lupus discoid[b]	4/35 (11)	26/94 (28)	0.06
Photosensitivity[b]	28/36 (78)	72/96 (75)	0.74
Oral ulcers[b]	12/34 (35)	35/94 (37)	0.84
Arthritis[b]	36/36 (100)	93/97 (96)	0.21
Serositis[b]	14/36 (39)	18/93 (19)	**0.02**
Nephritis[b]	18/35 (51)	38/94 (40)	0.26
Hemolytic anemia[b]	5/34 (15)	15/92 (16)	1.00
Leukopenia <4000[b]	20/34 (59)	50/93 (54)	0.61
Lymphopenia <1500[b]	15/34 (44)	42/90 (47)	0.79
Thrombocytopenia <100,000[b]	2/34 (6)	6/90 (7)	1.00
Neuropsychiatric disorders[b]	9/35 (26)	10/94 (11)	**0.04**
ANA[b]	36/36 (100)	97/97 (100)	0.18
Anti-Sm[b]	10/34 (29)	15/60 (25)	0.64
Anti-DNA[b]	21/36 (58)	36/81 (44)	0.16
Anti-SSA	17/33 (51)	23/64 (36)	0.14
Medication			
Hydroxychloroquine	13 (52)	33 (46)	0.63
Prednisone	16 (64)	34 (48)	0.16
Methotrexate	3 (12)	7 (10)	0.78
Azathioprine	2 (8)	14 (20)	0.16
Other immunosuppressants	6 (24)	8 (11)	0.12
Without medication	0 (0)	13 (18)	**0.02**

Statistically significant associations are in bold.

[a]Percentage of valid data.

[b]American College of Rheumatology classificatory clinical and laboratory criteria, 1997.

ANA, antinuclear antibody.

TABLE 2. Allele Distribution of 4 SNPs in Patients With SLE With or Without JA

SNP	Alleles	SLE With JA, n (%), n = 38	SLE Without JA, n (%), n = 106	OR	95% CI	*p* value
rs9271100 (*HLA*)	C	52 (68.5)	153 (74.3)	1	0.68–2.37	0.32
	T	24 (31.5)	53 (25.7)	1.28		
rs7574865 (*STAT4*)	G	52 (68.5)	148 (69.8)	1	0.57–1.94	0.82
	T	24 (31.5)	64 (30.2)	1.06		
rs10488631 (*IRF5*)	T	45 (90)	183 (89.8)	1	0.27–2.83	0.59
	C	5 (10)	21 (10.2)	0.96		
rs13277113 (*BLK*)	G	47 (65.3)	166 (76.1)	1	1.06–3.74	**0.02**
	A	25 (34.7)	44 (20.9)	2.0		

Association by allelic model of inheritance. Statistically significant association is in bold.

CI, confidence interval.

patients with JA used some medication for underlying disease. In at least 84% of situations, this treatment was maintained to control the articular symptoms. They had serositis and neuropsychiatric disorders more frequently than the sample of patients with SLE without JA. The duration of the disease was higher in the JA group.

The comparative analysis of allelic frequencies among subgroups with or without JA showed a more significant frequency (34.7%) for the A allele instead of G allele in rs13277113 polymorphism of *BLK* gene in the population with JA (OR, 2.00; 95% confidence interval, 1.05–3.74; $p = 0.02$) (Table 2). The other alleles had the same distribution in both populations. Patients with JA had minor allele frequencies of 31% of T allele of rs9271100 in *HLA*, 31% of T alleles of rs7574865 in *STAT4*, and 10% of C allele of rs10488631 in *IRF5*.

The comparisons of the frequencies of polymorphisms between the groups of patients with SLE, with or without JA, and with the comparison group, without SLE, are shown in Table 3. The risk allele of rs7574865 polymorphism in *STAT4* gene was more prevalent in the group of patients with SLE, regardless of the presence of JA. However, the risk allele of rs13277113 polymorphism of *BLK* gene was more prevalent in the population with JA when compared with the group without SLE and also to the group with SLE but without JA. Thus, *STAT4* was more associated with the SLE outcome and *BLK* with the JA outcome.

DISCUSSION

The physiopathogenic mechanisms for the development of JA are unknown. However, an association of the presence of JA with biomarkers, such as anti-DNA, anti-Ro, and antiphospholipid antibodies, has already been demonstrated in the literature, but these results are still controversial.[23,24]

Wallace et al[25] suggested that interleukin 6 (IL-6) is involved in the hyperactivity of B cells and autoantibodies production in patients with SLE, influencing the differentiation of Th17 cells and the acute phase proteins, which increases the inflammatory response. Previous studies also suggested that IL-6 could play a role in the development of JA.[26,27]

In agreement with the observations of most researchers, patients with JA in our study had a longer duration of SLE compared with patients with SLE alone (13 and 10 years, respectively, $p = 0.02$). In a prospective study, Piga et al[28] observed that prolonged joint and tendon inflammation and longer SLE duration were associated with an increased risk for JA development. These authors suggested that JA may not be a distinct subtype of SLE arthritis, but only a complication consequent to therapeutic failure.[28] This hypothesis was corroborated by a recent study conducted by our group, which demonstrated that half of the patients with JA had subclinically active joint and periarticular inflammation as detected by ultrasound and without association with other systemic signs.[29] However, the variable "duration of disease" alone does not seem to justify the development of JA because it would significate the presence of JA in all patients with SLE of longer duration, which is not true.[2] It is likely that this variable alongside other variables, such as a possible genetic predisposition for JA, manifested in a multifactorial way, would determine the development of this complication.

The contribution of genetic factors in the development of SLE has been addressed frequently in the literature.[8] Several genes were associated with the development of SLE and with certain clinical and laboratory characteristics of the disease.

This study shows that *BLK* seems to have a possible relationship with JA, in this sample of Brazilian SLE patients. The A allele of rs13277113 polymorphism is the least frequent one; therefore, it is the risk allele. Systemic lupus erythematosus patients who have A allele instead of G allele in rs13277113 polymorphism of *BLK* gene could have a greater risk for the development of JA.

BLK codes for a nonreceptor Tyrosine-Kinase from the Scr family, which is involved in the signaling, development, and differentiation of B lymphocytes.[30] The SNP rs13277113 is found in an area located between the *BLK* and *C8orf1* genes. This SNP and its variants significantly reduce the expression of *BLK*, which increases the risk of developing SLE.[9] The altered levels

TABLE 3. Comparisons of Allele Frequencies Between Patients With SLE, With or Without JA, and Population Without SLE

SNP	Alleles	SLE + JA$^+$, n (%), n = 38	SLE-JA$^-$, n (%), n = 614	*p* value	SLE + JA$^-$, n (%), n = 106	SLE-JA$^-$, n (%), n = 614	*p* value
rs9271100 (*HLA*)	C	52 (68.5)	954 (77.5)	0.07	153 (74.3)	954 (77.5)	0.221
	T	24 (31.5)	277 (22.5)		53 (25.7)	277 (22.5)	
rs7574865 (*STAT4*)	G	52 (68.5)	1010 (79.2)	**0.02**	148 (69.80)	1010 (79.2)	**5.96^{-5}**
	T	24 (31.5)	255 (20.8)		64 (30.2)	255 (20.8)	
rs10488631 (*IRF5*)	T	45 (90)	1170 (93.9)	0.26	183 (89.8)	1170 (93.9)	0.062
	C	5 (10)	76 (6.1)		21 (10.2)	76 (6.1)	
rs13277113 (*BLK*)	G	47 (65.3)	969.9 (79.9)	**4×10^{-3}**	166 (79.1)	969.9 (79.9)	0.989
	A	25 (34.7)	247 (20.1)		44 (20.9)	247 (20.1)	

Statistically significant association is in bold.

of *BLK* protein are postulated to influence the tolerance mechanisms of B lymphocytes and possibly of T cells, Th-17 cells, and plasmacytoid dendritic cells. The relationship between *BLK* and IL-6 is not known. However, both can modulate B cell expression and differentiation. No other study has tested the frequency of *BLK* polymorphisms in patients with JA. Thus, this finding can raise questions on the role of B cells and their performance in the pathogenesis of JA.

De Carvalho et al[31] evaluated 2 families (5 patients) with an autosomal-dominant phenotype that includes musculoskeletal disease, mimics JA, and is associated with other characteristics (eg, psoriasis, dental abnormalities, cardiac valve involvement, glaucoma, and basal ganglia calcification). They identified an increased expression of interferon-stimulated genes in all patients. They also identified a mutation in the *IFIH1* gene that results in the activation of MDA-5 (melanoma differentiation-associated protein 5), which constitutes part of the type I interferonopathy disease spectrum. *IFIH1* has a relationship with SLE, and probably, its polymorphisms can increase proinflammatory mediators such as IL-6.[32] It can provide a possible new way for the understanding of the JA pathogenesis.[31]

A limiting factor of our work was the sample size and the small number of polymorphisms analyzed. Another point of concern is the difference in disease duration between the SLE groups, raising questions if those patients in the no-JA group will develop JA in the future. Although we are not able to exclude this possibility, it is unlikely, because we have been following these patients for a long time, some of them for more than 10 to 20 years.

Although the results did not allow a definitive conclusion about the genetic susceptibility of JA, they suggest a possible association between the rs13277113 polymorphism in *BLK* and JA. Others, perhaps multicentric studies including a larger sample of JA and evaluating other polymorphisms, such as from *HLA* and *IF1HI* genes, should reexamine the relationship between genetic polymorphisms and this complication.

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