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HLA-DR Frequency in Individuals with Rheumatoid Arthritis and Lung Affection

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Abstract

Objective: Establishing the frequency of HLA-DR antigens in a group of individuals with rheumatoid arthritis (RA) and investigate the correlation of such antigens with pulmonary involvement.

Participants and methods: The sample comprised 97 individuals. HLA-DR was genotyped by means of polymerase chain reaction amplification.

Results: A total of 54 participants (56.0%) exhibited extra-articular manifestations, most frequently subcutaneous nodules (19.0%). Lung assessment detected affection in 54 (55.7%) participants. HLA-DRB4*0101 was the most frequently found allele, followed by HLA-DRB1*0401, HLA-DRB3 and HLA-DRB1*0101, whereas the most frequent alleles were HLA-DRB1*0901, HLA-DRB4 and HLA-DRB1*1201 in the participants with lung affection.

Conclusion: HLA-DRB4*0101 was the allele most frequently found overall, and HLA-DRB1*0901 was the most frequent allele among the participants with lung affection; however, the association was not statistically significant.

Keywords

Rheumatoid arthritis, HLA, Lung involvement

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease whose etiology is unknown, while its immunopathogenesis involves the participation of both genetic and environmental factors. Human leukocyte antigen DR4 (HLA-DR4) exhibits a strong association with RA in various populations and ethnic groups; in addition, a heightened frequency of HLA-DR1 among individuals with RA has been found in some populations [1-4]. According to several studies, the presence of HLA-DR4 is more strongly associated with aggressive RA, characterized by the progression of radiological erosion, positive rheumatoid factor (RF) and extra-articular manifestations, than with susceptibility to the disease [5-7].

Homozygosity for the HLA-DR1 allele with shared epitope, particularly alleles *0401 and *0404, seems to correlate strongly with severe manifestations of the disease, including the presence of subcutaneous nodules, positive RF and radiological erosion [8]. With regard to such findings, it has been suggested that genotyping individuals with RA might afford information relevant to their prognosis [9].

Although RA can affect any joint, the participation of the metacarpal, metatarsophalangeal, proximal interphalangeal, wrist and knee joints is most frequent and is characterized by swelling, sensitivity on palpation, morning stiffness and severe motion impairment [10].

Some patients also exhibit signs and symptoms of severe extra-articular affection involving distant organs [11]. The frequency of such manifestations is difficult to estimate, but they are known to occur more frequently among individuals with severe active disease [12].

The lung is a frequent site of extra-articular RA, reported to be either the second most common cause of death (18%) following infection (27%) [13,14] or the third (9.9%) following infection (23.5%) and cardiovascular disease (17.3%) [12].

Pulmonary involvement in RA is highly variable; its earliest stage is usually asymptomatic, and the clinical manifestations are unspecific [15], usually including progressive dyspnea on exertion and dry cough [16].

The pathogenesis of RA as a systemic and lung disease has not yet been elucidated [17]. The reported prevalence of lung affection among individuals with RA is variable. Such variability might be partially accounted for by the genetic basis of the investigated population as a function of the influence of genes, such as HLA-DR1 and HLA-DR4, on the phenotype of disease. Polymorphisms of the alleles HLA-B40 and B54 are particularly associated with lung abnormalities, fibrosis and bronchiolitis [18,19].

High-resolution computed tomography (HRCT) of the chest affords the best means for early diagnosis of lung disease in RA. Its diagnostic power was documented in a study in which it was able

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to detect interstitial lung disease in 50% of the participants with RA, whereas only 10% of them exhibited relevant clinical symptoms [20].

The possibility of establishing the risk of severe and destructive joint and extra-articular manifestations of RA early in the course of disease might contribute to the prevention of irreversible joint and systemic damage [21].

As the Brazilian population exhibits genetic diversity, with variable patterns of DR alleles and haplotypes, the assessment of DR alleles in a population of individuals from Piaui with rheumatoid lung disease might contribute to assessing the prognosis of patients with that condition.

Participants and Methods

Participants

Ninety-seven patients diagnosed with RA according to the American College of Rheumatology (ACR(revised criteria [22], were selected during the years of 2011 and 2012. The volunteers were followed-up by the same physician at a university hospital and at the physician's private office and were requested to respond to a questionnaire including data on the age at onset, length of disease and the presence or absence of extra-articular manifestations. They agreed to participate in the study after reading and signing the Consent Form approved by the Medical Ethics Committee.

A total of 85 participants (88.0%) were female; 77.0% were non-white; and the average age of the sample was 47.3 years old. A total of 54 participants (56.0%) exhibited extra-articular manifestations, most frequently subcutaneous nodules (19.0%).

Detection of rheumatoid factor

RF was detected by the quantitative method of nephelometry and the values were considered positive when > 30 IU/mL.

High-resolution computed tomography of the lungs

The volunteers were subjected to HRCT, which was performed in a supine position, using a Siemens Somatom Spirit scanner with two channels and GE Healthcare LightSpeed Pro 16; all the scans were encoded.

Pulmonary function test

All participants were subjected to spirometry using a Beatrice Pulmonary Assessment System (Sistema de Avaliação Pulmonar Beatrice - PC). The device was coupled to a computer, and the results were compared to the predicted values for healthy individuals of the same age, gender and height (Brazilian Society of Pneumology and Phthisiology/Sociedade Brasileira de Pneumologia e Tisiologia – SBPT) using the reference values used described by PEREIRA et al. [23].

HLA genotyping

Typification of class II HLA alleles was carried out through the DNA/PCR/SSP molecular method at medium and high resolution. DNA was extracted through a salting-out procedure of peripheral blood of each individual participating in the research. The alleles were quantified at a medium or generic resolution using the PCR/SSP technique for primers of "One Lambda"(One Lambda Inc., CA, UK).

Statistical analysis

The frequency of each HLA-DR subtype was established together with the corresponding confidence interval. The correlation between HLA and lung affection was assessed using the chi-square test, and the risk was estimated by calculating the odds ratios, the corresponding confidence interval and bivariate analysis.

Results

Clinical characteristics

Most participants were female (88.0%) and non-white (77%).

Table 1: RA - Disease characteristics of the 97 participants with rheumatoid arthritis.

F:M		**85:12**
White: non-white		23:74
Average age (years)		47.3 ± 11.18
Average length of disease (years)		7.72 ± 7.79
Positive rheumatoid factor		84 (87%)
Extra-articular manifestations	Total	54 (56%)
	Nodules	18 (19%)
	Anemia	32 (33%)
	Ulcers	05 (5%)
	Raynaud	04 (4%)
	Weight loss	20 (21%)
Pulmonary symptoms	Total	35 (36%)
	Dyspnea	19 (20%)
	Chest pain	13 (13%)
	Cough	21 (21%)

Table 2: Results of pulmonary function tests in 97 individuals with rheumatoid arthritis.

Pattern	**n (%)**	**%**
Normal	65 (67%)	67
Restrictive	12 (12%)	12
Obstructive	18 (19%)	19
Mixed	02 (2%)	2

Table 3: Findings on HRCT of the chest corresponding to 97 individuals with rheumatoid arthritis.

Pattern	**N**	**%**
Normal	57	59
Nodules	12	12
Fibrosis	31	32
Bronchiectasis	05	5
Pleura affection	05	5

Table 4: The allele frequency of HLA-DRB in rheumatoid arthritis patients.

HLA-DR	**Participants**	
	n = 97	**%**
HLA-DRB4*0101	51	52.6%
HLA-DRB1*0401	42	43.3%
HLA-DRB3*0101	22	22.7%
HLA-DRB1*0101	20	20.6%
HLA-DRB1*1301	20	20.6%
HLA-DRB5*0101	19	19.6%
HLA-DRB1*1101	18	18.6%
HLA-DRB1*0701	15	15.5%

The average age of the sample was 47.3 years old; the average length of disease was 7.72 years; and 84 (87%) participants tested positive for RF. Extra-articular manifestations (subcutaneous nodules, anemia, skin ulcers, Raynaud's phenomenon) were identified in 54 participants (56%), most frequently subcutaneous nodules (19%); 32 volunteers (33.0%) exhibited more than one type of extra-articular manifestation. Pulmonary symptoms were found in 35 participants (36.0%), most frequently dyspnea (20.0%), chest pain (13.0%), dry cough (11.0%) and productive cough (10.0%) (Table 1).

Lung involvement

The pulmonary function test (PFT) results were normal in 65 participants (67.0%), while 12 (12.0%) exhibited restrictive ventilatory defect, 18 (19.0%) obstructive ventilatory defect and 2 (2.0%) a mixed pattern (Table 2).

On HRCT, the results were normal in 57 (59.0%) participants, while nodules were found in 12 (12.0%) and fibrosis in 31 (32.0%) (Table 3). Joint analysis of the HRCT and PFT results indicated lung affection in 54 (55.7%) participants.

Table 5: HLA-DR allele frequency in the RA patients with and without lung affection.

HLA-DR	Group 1	Group 2	Total of patients	Chi-square	p-valor
DR-B1*0101	7	13	20	0.889	0.346
DR-B1*0301	6	2	8	3.323	0.068
DR-B1*0401	15	27	42	2.28	0.136
DR-B1*0701	10	5	15	3.587	0.058
DR-B1*0801	4	5	9	0.000	0.994
DR-B1*0901	2	2	4	0.054	0.816
DR-B1*1001	2	3	5	0.040	0.841
DR-B1*1101	10	8	18	1.129	0.288
DR-B1*1201	3	2	5	0.525	0.469
DR-B1*1301	6	14	20	2.096	0.148
DR-B1*1401	4	4	8	0.114	0.736
DR-B1*1501	5	6	11	0.006	0.936
DR-B1*1601	5	5	10	0.145	0.703
DR-B3	10	12	22	0.015	0.904
DR-B3*0101	2	-	2	2.565	0.109
DR-B3*0107	3	2	5	0.525	0.469
DR-B3*0201	3	7	10	0.928	0.335
DR-B*0218	4	2	6	1.293	0.255
DR-B4	1	3	4	0.632	0.427
DR-B4*0101	22	29	51	0.062	0.803
DR-B5	10	9	19	0.660	0.417
DR-B5*0101	-	1	1	0.805	0.370
DR-B5*0113	1	-	1	1.269	0.260

(Group 1) - Number total de patients without lung affection and with allele

(Group 2) - Number of patients with lung affection and with allele

HLA genotyping

HLA-DRB4*0101 was the most frequently found HLA subtype (52.6% of the participants), followed by HLA-DRB1*0401 (43.3%), HLA-DRB3 (22.7%) and HLA-DRB1*0101 and HLA-BRB1*1301 (both in 20.6% of patients) (Table 4).

HLA-DRB alleles and lung affection

The alleles most frequently found among the participants with lung affection were HLA-DRB1*0901 (50%), HLA-DRB4 (25%), HLA-DRB1*1201 (20%) and HLA-DRB3 (9%). No statistically significant association was found between any HLA-DR subtype and lung affection at alpha = 5% (chi-square and Fisher's exact tests) nor by bivariate analysis (Table 5).

HLA-DRB1*0901 was the allele most frequently found among the participants with lung affection, identified in 50% of them.

Discussion

The clinical progression of RA is variable, including mild, moderate or destructive alterations, significant joint deformities, functional disability and extra-articular manifestations. The possibility of predicting the occurrence of extra-articular manifestations at the onset of disease might allow the establishment of more aggressive treatment at the early stages of affection [24]. HLA genotyping might contribute to defining the prognosis, especially when it is performed at an early stage of the disease, i.e., before the establishment of irreversible joint damage and appearance of extra-articular manifestations [25]. As ethnic differences in gene determinants might influence the expression of the disease [9], we investigated the HLA system in individuals with RA and compared the results for individuals with and without lung affection.

The results of this study show that most participants (54.6%) exhibited some modality of lung affection. This high prevalence agrees with reports by previous authors, such as Skare et al. [26], who found lung alteration in 55% of 71 individuals; Zrour et al. [27], who found lung alteration in 49.3% of 75 individuals in Tunisia; and Bilgici et al. [28], who found lung alteration in 67.3% of 52 individuals in Turkey. In addition, Teraski et al. [29] assessed a sample of individuals with RA and respiratory symptoms and found CT changes in 90% of them.

In our sample, HLA-DRB4*0101 was found in 51 participants (52.6%) and HLA-DRB1*0401 in 42 (43.3%). Several studies have found an association between RA and five alleles in various ethnic groups, i.e., DRB1*0401, DRB1*0404 and DRB1*0101 in whites, DRB1*0405 in Asians and DRB1*1402 in Native Americans [30,31]. The DR4 alleles have been associated with the most severe forms of the disease and allele DRB1*0101 with milder progression. DRB1*0401/DRB1*0404 heterozygous individuals exhibit a fivefold to tenfold higher risk compared to the carriers of either allele alone. That allele combination has also been associated with susceptibility to early manifestation of the disease [3]. The data on Latin America are heterogeneous. In Brazil, Bertolo et al. [9] found that the alleles HLA-DRB1*0101 and *0102 were associated with susceptibility to RA and the alleles HLA-DRB1*0401 and *0404 with the aggressive form of the disease. In a study with 67 Puerto Rican descendants, Teller et al. [32] found that the DR frequency was higher among individuals with RA compared to controls; however, the subtypes corresponding to the shared epitope (SE) were infrequent, especially subtype *0411. In Chileans with RA, Gonzalez et al. [33] did not find any difference in the DR4 or DR1 frequency between individuals with RA and the controls, possibly due to the high prevalence of subtype *0403 in that population.

In the study conducted by Do Monte et al. [34] to investigate HLA polymorphism in a racially mixed sample from Teresina, Piaui State, the four most frequent specificities in each locus were as follows: HLA-A: A*02, A*03, A*24 and A*68; HLA-B: B*07, B*44, B*15 and B*35; HLA-DRB1: DRB1*11, DRB1*04, DRB1*13 and DRB1*03; and HLA-DQB1: DQB1*0301, DQB1*06, DQB1*02 and DQB1*05. Those results agree in part with ours, as we found that HLA-DRB4*01 and HLA-DRB1*04 were the most frequent alleles in our sample. Perhaps those alleles were the most frequently found because they are the most common in the overall population of Piaui.

HLA-DRB1*0901 was the allele most frequently found among the participants with lung affection, at a rate of 50%.

Although no statistically significant association was found between any HLA-DR subtype and lung affection through bivariate analysis, the pattern exhibited by HLA-DRB1*0301 and DRB1*0701 was different from the remainder of the subtypes, as the p-value was remarkably higher (p > 10%). Therefore, one might infer that those HLA subtypes may be associated with a lower risk of lung affection. As a function of the high variability in the distribution of the variables among the population, the sample size of this study yields insufficient statistical power to test such a possible protective effect (type II error - failure to find an actually existing association). The elucidation of that issue will require further studies with larger samples, although it is worth noting that the number of participants in this study was considerable compared to other studies [9,32,33].

Conclusion

In this study, HLA-DRB1*0901 was the allele most frequently found among the participants with lung affection, identified in 50% of them.

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