

Association of HLA DR and DQ with Juvenile Idiopathic Arthritis in Brazilian Piauienses Children

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Abstract

Objectives: Identify and determine HLA-DR and HLA-DQ alleles in Juvenile Idiopathic Arthritis (JIA) and its subgroups as defined by International League of Associations for Rheumatology (ILAR) classification criteria and compares them with the observed in the group control; know the HLA-DR and HLA-DQ alleles are associated with increased susceptibility and conferring greater protection in the population with JIA in its subgroups and identify a relationship between the alleles HLA-DR and HLA-DQ and the most frequent and most aggressive form of the disease.

Methods: PCR using primers specific chains of DR and DQ performed the typing of HLA-DR and HLA-DQ using the technique of amplification was accomplished for 74 JIA children and 101 controls matched according to age, sex, ethnicity.

Results: Among all JIA cases was statistically significant association for susceptibility HLA-DRB1*10 OR 8.8 (CI 1.1 to 74.9) and HLA-DRB1*16 OR 2.8 (CI 1.1 to 7.5). HLA- DRB1*08 allele, OR 4.6 (CI 1.4 to 14.6) was association to susceptibility in Oligoarticular. Systemic was association with HLA-DRB1*10 allele, OR 22.2 (CI 1.8 to 269.5). Polyarticular RF+ was association to susceptibility with HLA-DRB1*09 alleles, OR 12.1 (CI 2.2 to 66.9) and DRB1*10 OR 28.5 (CI 2.3 to 355.0). Polyarticular RF- association to susceptibility was DRB1*16 allele OR 13.4 (CI 1.6 to 111.2). HLA-DRB1*03 OR 0.7 (CI 0.5 to 0.9) demonstrated association for disease protection among all cases of JIA. Systemic form this association also happened DRB1*03 OR with 0.7 (CI 0.6 to 0.8). The study also found, statistically significant difference between the HLA-DQB1*03 OR 6.0 (CI 1.3 to 27.2), and uveitis in patients with oligoarticular form of JIA.

Conclusion: Inherited HLA factors in JIA show similarities overall as well as different patterns of HLA associations evidencing its importance of the aspect of susceptibility as well as protection genetically distinct groups of patients.

Keywords: Juvenile idiopathic arthritis; HLA-DR; Juvenile rheumatoid arthritis; Oligoarticular arthritis; Uveitis and HLA-DRQB1*03

Introduction

Juvenile Idiopathic arthritis (JIA) is characterized by the onset of chronic arthritis of unknown etiology in children younger than 16 years of age [1]. The diagnosis is clinical, made from the observation of edema and / or limitation of movement's joint with presence of heat and pain [2]. Seven distinct subtypes of JIA exist. These subtypes have been well-defined by the International League of Associations for Rheumatology (ILAR): Oligoarthritis (four or less joints involved in the first 6 months of onset), Systemic arthritis (arthritis associated with characteristic fever and rash), Rheumatoid Factor (RF) Positive and Rheumatoid Factor (RF) Negative Polyarthritis (five or more joints involved in the first 6 months), Entesitis-related Arthritis (ERA), Arthritis psoriatic and undifferentiated arthritis. Different classification schemes for the chronic arthritis of childhood encompass various subtypes [3-5].

Although JIA is believed to be influenced by genetic and environmental factors, twin and family studies strongly support a substantial role for genetic factors in JIA support a substantial role for genetic factors in JIA susceptibility [6,7]. JIA has often been described as a complex genetic trait wherein multiple genes interact to result in a specific phenotype [8].

The subtypes of JIA share genetic and phenotypic features with other autoimmune disorders, which are believed to result from the interplay of genetic and environmental factors. Identification of genetic factors associated with susceptibility or protection from autoimmune diseases is important for several reasons. Identification of such variants

has the potential to significantly improve our understanding of disease pathogenesis [9].

Several studies have demonstrated that distinct clinically autoimmune disorders share common genetic susceptibility factors. For instance, polymorphisms of the genes encoding the HLA molecules are associated with diverse autoimmune disorders [10].

Associations with HLA variants have been validated and confirmed in different populations for autoimmune disorders such as JIA. It has been reported that known variants in the major histocompatibility complex (MHC) explain about HLA-DR of the genetic burden of JIA [10].

The objectives were to identify and determine the HLA-DR and HLA-DQ in a sample of Piauí juvenile population subtypes JIA in oligoarticular, systemic, polyarticular RF +, polyarticular RF -, psoriatic arthritis, entesitis-related arthritis and arthritis indeterminate and compares them with the observed frequencies in the group of healthy

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control; know the HLA-DR and HLA-DQ alleles are associated with increased susceptibility and conferring greater protection in the population with JIA in its various forms and identify a possible relationship between the alleles HLA-DR and HLA-DQ and the most frequent and most aggressive form of the disease in the population studied.

Materials and Methods

Patient population

The type of study was case-control. Between January 2010 and July 2013 were studied 74 patients with JIA classified according ILAR Criterion a regular follow-up the Pediatric Rheumatology Service, Lucídio Portella Children's Hospital (HILP), a tertiary and teaching hospital linked to the UFPI in Teresina-Piauí, northeast of Brazil. All patients were from the state of Piauí.

The control group consisted of 101 healthy children and adolescents did not have any history and/or clinical autoimmune disease and other disease with known genetic or hereditary predisposition, including family. A sample of the 4 ml of peripheral blood with EDTA

was provided for DNA extraction processed in State University of Campinas (UNICAMP) Laboratory of Immunology, obtained after written informed consent.

HLA typing

HLA-DR, HLA-DQ alleles were determined in all patients and controls. DNA extraction was done by the GE Healthcare illustrates blood methodology using the GFX KIT. HLA-DR and DQ genotyping were determined using PCR-SSP amplification sequence specific primers (Micro SSP HLA DNA Typing Trays of ONE LAMBDA Inc. California). The investigated alleles were DRB1 *, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16, DRB3, DRB4, DRB5, DRB4*01 and DQB1*02, *03, *04, *05 e *06. The reading was made through HLA Fusion Software being contacted presence or absence alleles or HLA-DR and DQ alleles groups verified according to their specific model amplification [11].

HLA antigen was considered JIA "Susceptibility" when identified more frequently the cases group when compared to the control group, therefore its presence may increase the risk of developing disease.

Initial forms	Sex				Age onset (Year)		Disease duration (Year)	
	Male		Female		Mean (SD)	Median	Mean (SD)	Median
	n	%	n	%				
Oligo	15	31.9%	32	68.1%	4 (± 3)	3	3 (± 2)	2
Systemic	6	54.5%	5	45.5%	6 (± 2)	7	-	0.5
RF+ Poly	1	11.1%	8	88.9%	7 (± 3)	8	5 (± 3)	1
RF- Poly	4	100%	-	-	7 (± 4)	8	1 (± 0.5)	0.5
Psoriatics	1	33.3%	2	66.7%	11 (± 4)	9	-	2

SD: Std. Deviation

Table 1: Epidemiological characteristics of 74 patients with JIA in the various forms of the disease in Brazilian Piauiense children.

HLA DR	All Form	Oligo Control	Sistemic Control	RF+ Poly Control	RF- Poly Control	Psoriatic Arthritis Control
B1*03	0.7* (0.5 a 0.9)	1.1 (0.5 a 2.2)	0.7* (0.6 a 0.8)	0.3 (0.4 a 2.8)	0.9 (0.1 a 9.1)	0.7 (0.6 a 0.8)
B1*08	1.9 (0.9 a 41)	4.6** (1.4 a 15.6)	1.1 (0.2 a 5.9)	0.6 (0.7 a 5.6)	1.7 (0.1 a 18.1)	0.8 (0.7 a 0.9)
B1*09	1.4 (0.3 a 5.7)	0.5 (0.1 a 4.8)	0.8 (0.8 a 1.0)	12.1** (2.2 a 66.9)	0.9 (0.9 a 1.0)	0.9 (0.9 a 1.0)
B1*10	8.8** (1.1 a 74.9)	4.4 (0.4 a 50.2)	22.2** (1.8 a 269.5)	28.5** (2.3 a 355.0)	0.9 (0.9 a 1.1)	0.9 (0.9 a 1.1)
B1*16	2.8** (1.1 a 7.5)	2.3 (0.7 a 7.1)	2.9 (0.5 a 16.5)	3.8 (0.6 a 22.0)	13.4** (1.6 a 110.2)	0.9 (0.8 a 1.0)

*Protection
**Susceptibility

Table 2: Odds ratio (Confidence Interval) of relationship between HLA cases and control groups each form of juvenile idiopathic arthritis in Brazilian Piauiense children.

HLA	Oligoarticular with uveitis (n=11)		Oligoarticular without uveitis (n=36)		Total (n=47)	p-value
	n	%	n	%		
DQB1*02	2	14.3%	12	85.7%	14	Ns
DQB1*03	8	42.1%	11	57.9%	19	0.013*
DQB1*04	2	14.3%	12	85.7%	14	Ns
DQB1*05	3	17.6%	14	82.4%	17	Ns
DQB1*06	4	22.2%	14	77.8%	18	Ns

Ns: No significance
*p<0.05

Table 3: Frequency of HLA-DQ in patients with oligoarticular form of JIA uveitis with and without uveitis of JIA and the control group (n=47).

Research (Date)	Population (Country)	Onset form	HLA susceptibility	HLA protection
Prahalad et al. [12]	EUA	RF+ Polyarticular	DRB1*0101 DRB1*0401 DRB1*0404 DRB1*0408 DRB1*1001	-
Farivar et al. [16]	Teerā-Iran	Oligoarticular	DRB1*11 DRB1*08	DRB1*0701
		RF- Polyarticular	DRB1*08	-
Silva Ramirez et al. [23]	México	Oligoarticular	DRB1*11 DRB1*13	-
		Sistemic	DRB1*04 DRB1*01	DRB1*11 DRB1*14
		RF+ Polyarticular	DRB1*04	DRB1*07 DRB1*14
Wu and Zeng. [18]	China	Oligoarticular	DRB1*08	DRB1*15 DRB1*12
		Sistemic	DRB1*08	DRB1*15 DRB1*12
		RF+RF- Polyarticular	DRB1*08	DRB1*12
Hollenback et al. [30]	EUA	Oligoarticular	DRB1*13 DRB1*1103 DRB1*1104	DRB1*0401 DRB1*0701 DRB1*1501
Garavito et al. [13]	Colombia	Oligoarticular	DRB1*1104	DRB1*1501
		Sistemic	DRB1*1602	DRB1*1402
		RF+ Polyarticular	DRB1*04	-
Alsaedi et al. [14]	Kuwait	Oligoarticular	DRB1*0307 DRB1*0308	-
		RF+. RF- Polyarticular	DRB1*0308	-
Thomson et al. [19]	United Kingdom	Oligoarticular	DRB1*13 DRB1*11 DRB1*08	DRB1*07
		Sistemic	DRB1*11	DRB1*04
		RF- Polyarticular	DRB1*08	DRB1*07
		RF+ Polyarticular	DRB1*04	DRB1*07
		Psoriatic Arthritis	DRB1*01	-
Oen et al. [25]	Canada	Polyarticular RF+	DRB1*0404 DRB1*1402 DRB1*0901	DRB1*0802 -
Pires et al.	Piauí-Brazil	Oligoarticular	DRB1*08	-
		Sistemic	DRB1*10	DRB1*03
		RF+ Polyarticular	DRB1*09 DRB1*10	-
		RF- Polyarticular	DRB1*16	-

Table 4: Studies of HLA-DR in JIA in diverse populations.

HLA antigen was considered JIA "Protective" when identified higher frequency in the control when comparing its frequency in cases, so its presence may reduce the risk of developing the disease.

Statistical Analysis

Continuous variables were the mean \pm SD, while categorical data were given as counts and percentages. The differences in frequencies allele between patients and healthy controls were analyzed by 2x test and Fisher's exact test and associations were expressed as Odds Ratios (OR) with their 95% confidence intervals (95% CI) using the SPSS program for Windows. For quantitative variables, the tendency central calculation as mean, median, and dispersion by standard deviation was used. The level significance was ($p < 0.05$).

The focus of this study was investigating HLA associations with subtypes of JIA defined by the ILAR classification, comparing each of the HLA phenotypes of interest.

Results

Of the 74 patients with JIA 47 (63.5%) were females and 27 (36.5%) males. The epidemiological characteristics of each form (Table 1). Two HLA-DRB1 alleles were associated with increased risk (DRB1*10 and DRB1*16) and only one with the protective (DRB1*03) considering all forms of the disease together. Some of these phenotypic frequencies differed between the various forms. HLA-DRB1*08 was associated with increased risk in Oligoarticular form. In the Systemic form HLA-DRB1*10 was associated with increased risk and HLA-DRB1*03 association with protection. Two alleles were association with increased risk in Polyarticular RF+ form the HLA-DRB1*09 and HLA-DRB1*10.

In the poly-articular RF-form the association with increased risk was HLA-DRB1*16. In psoriatic arthritis is no type of association was found between HLAs and studied this form of JIA (Table 2).

All cases of uveitis in the study were found in oligoarticular form corresponding to 11 cases (23.4%) in this form, and 14.8% of the cases of all forms JIA together. The HLAs alleles more often found in the complication of JIA were DRB3 (9 cases), DQB1*03 (8 cases), DRB1*08 and DRB1*13 both in 5 cases, of these, only the HLA-DQB1*03 was associated with the risk of uveitis in Oligoarticular JIA, OR 6.06 (CI 1.3 to 27.2) $p = 0.013$ (Table 3).

Discussion

HLA antigens in all forms of Jia presentation

The population of patients included in this study was selected by a well-defined analysis, based both in an epidemiological, as well as ethnic and clinician view, including only patients who fulfilled the ILAR criteria and were in regular monitoring at HILP, which is why we chose to analyze only patients from Piauí State, in northeastern Brazil [12,13].

Although have not shown a high frequency in the study, two HLA-DR alleles showed significant statistical association for disease susceptibility considering all its forms: HLA-DRB1*10 OR 8.8, $p = 0.018$ and HLA-DR*16 OR 2.8, $p = 0.029$. Prahalad et al. in 2012 studied American children with JIA and found similar association to the susceptibility between HLA- DRB1*10 and JIA (most associated with FR+ Poliarticular) [12]. Regarding HLA-DR*16 Garavito et al., found DRB1*1104, the allele strongly associated with disease susceptibility,

followed by HLA-DRB1*1602, in a group of crossbred Colombian children (mixtures of American Indians, European and African).

In our study, HLA DRB1*03 showed a protective effect for the studied population considering all forms of JIA (OR 0.71, $p=0.018$). However, Alsaeid et al. conducted a study in Kuwaitis children with JIA and found a strong association with susceptibility to the HLA-DR3, specifically the DRB1*0307 in oligoarticular and polyarticular forms, and DRB1*0308 in the oligoarticular form [14].

So, studies that demonstrated similarity with our results related to the susceptibility in all forms were: for HLA- DRB1*10, Prahalad et al., in the United States (most associated to RF + polyarticular) and the HLA-DR*16 [12]. Garavito et al., in Colombian children (most associated with the systemic form). In relation to HLA-DRB1*03 alleles, were not found studies to confirm protection for the oligoarticular JIA, but, only susceptibility in Kuwaitis children [14].

Thus, the findings of HLA-DR in children from Piauí suffering from JIA, considering all forms show similarities in terms of susceptibility, and also distinctions, especially regarding the protection, in the associations found in the literature.

HLA antigens and oligo-articular form

The most common HLA-DR antigens in oligoarticular JIA were DRB3, DRB1*08, DRB1*13 and DRB4*01, however, that one showed an association statistically significant for disease susceptibility was HLA-DRB1*08 OR 4.7, $p=0.02$.

Some studies conducted worldwide, reinforcing our results, between HLA-DR and oligoarticular JIA showed, mostly, a strong association with susceptibility to HLA-DRB1*08, these data were well demonstrated in the study in Iranian children with oligo-articular and RF- poly-articular JIA [15,16]. The HLA -DRB1*08, as our results, and HLA-DRB1*11 were the most strongly associated with susceptibility in oligoarticular JIA in Iranians, in German and Czech children [16,17].

Therefore, some of the populations that were similar to our results regarding the susceptibility in oligoarticular JIA with HLA - DRB1*08 were Iranians, Chinese from province of Guangdong, Norwegians and Polish English, Americans from Cincinnati, Boston and Dallas [16,18-21], German from Munich and patients from Prague [17]. Some of them, as seen, also showed high susceptibility to the HLA-DRB1*11, which was not observed in our study. In association related to protector's antigens, in our study there was no association between the antigens studied and oligoarticular JIA, however, literature reports a strong association that provides protection between HLA- DRB1*04 and HLA - DRB1*07 and oligoarticular JIA [15,16,22,23]. Thus, the findings of HLA-DR in children from Piauí suffering oligo-articular JIA present similarities to susceptibility when compared with literature.

HLA antigens and systemic form

Recent researches about the etiopathogenic mechanism of the systemic JIA has shown that this form of disease is not associated with HLA genes nor with autoantibodies, but with uncontrolled activation of phagocytes, which allows associates it to the group of self-inflammatory diseases [15,24]. However, several studies have found associations of certain HLA with the systemic JIA.

This study found association with susceptibility between HLA DRB1*10 and systemic JIA, (OR 22.2), $p < 0.02$. The study conducted by Prahalad et al. demonstrated a strong association between HLA-DRB1*10 and RF+ polyarticular, noting, in this way, similarity of the results between the two surveys [12].

HLA DRB1*03 showed protective effect to the systemic JIA in the studied population, (OR 0.7). HLA-DRB1*07 was found with low frequency in cases and with higher frequency in controls, but the difference was not statistically significant between the two groups.

The less common HLA- DR antigens in this form were DRB4 and DRB1*14, but the difference was not statistically significant between the two groups. Studies conducted worldwide have shown that HLA most associated with systemic JIA are DRB1*01 and HLA-DRB1*04 in Mexico HLA-DRB1*11 in the United Kingdom, HLA -DRB1*1602 in Colombia, HLA-DRB1*08 in China, it can be seen the great heterogeneity of alleles for this form [13,18,19]. Our study found an association to susceptibility between HLA - DRB1*10 and systemic JIA, this allele is associated to RF + polyarticular in the study by Prahalad et al. [12].

HLA antigens and RF+ polyarticular

The most frequent HLA- DR antigens found in the RF+ polyarticular were DRB4*01, DRB3, DRB5 and DRB1*09. Two antigens were associated with increased risk for RF+ polyarticular JIA HLA DRB1*09 (OR=21.1) and $p=0.011$, and also HLA DRB1*10 (OR=28.6), $p=0.017$.

The research has shown that the presence of HLA - DRB1*09 in females increased by nearly 18 times the risk of developing the RF+ polyarticular JIA, and yet, being female and having the DRB1*10 allele increased about 4 times the risk of developing RF + polyarticular JIA in the studied population. Murray et al. showed in their research that in women predominate features of the association of HLA- DR4 with RF+ polyarticular similar to the adult RA [11,20].

Oen et al. in Canada, found HLA-DRB1*0901, which confers susceptibility to RF+ polyarticular, similar to our results. The Oen et al. research also showed the control population has a high frequency of DRB1*0404 and DRB1*1402 alleles related to the shared epitope, and strongly associated with rheumatoid arthritis in adults and being present in 63% of RF+ poly-articular [25]. In our study, the DRB1*0404 allele was often found very close to cases of the RF+ polyarticular and for control group, though, the HLA - DRB1*1402 allele was found only in controls, nonetheless, there was no significant difference between the two groups. The DRB1*0802 allele was considered protective in Oen et al. research; in our study this allele did not show this effect [25].

Therefore, our study found a strong association to susceptibility between HLA-DRB1*09 and RF + polyarticular, a result also found in Canadian children The HLA - DRB1*10 also showed an association with risk for this form, which was shown in American populations with RF + polyarticular (12). Most of studies conducted worldwide have shown that most often HLA associated with susceptibility to RF + polyarticular JIA is HLA -DRB1*04, found in populations of English, American, Colombia, Mexican, Canadian children with FR + polyarticular JIA [12,13,19,20,23,25]. Alleles that confer protection to RF+ polyarticular for various populations such as English, Mexican, Canadian are DRB1*07, HLA-DRB1*08, HLA- DRB1*12, HLA-DRB1*14 [23,25]. In our study, the HLA -DRB1*14 allele was found only in controls; however, there was no statistically significant difference between the two groups in relation to RF + polyarticular.

HLA antigens and RF-polyarticular

The DRB4*01 allele was most often found as RF- polyarticular, but without statistically significant difference. Despite the small number of RF-polyarticular cases observed in our study, HLA-DRB1*16 allele was associated with increased risk for this form (OR 13.4, $p=0.036$) [23].

The study conducted with Colombian children showed that HLA-DRB1*16 was strongly associated with susceptibility to systemic JIA, and HLA-DRB1*0404 to RF- polyarticular, the latter allele was also observed in Mexican children these results agree in part with those found in our study [13]. Among English, Chinese and Iranian children with RF- polyarticular JIA was found a strong association to susceptibility of HLA-DRB1*08. In Kuwaitis, association with susceptibility was for HLA-DRB1*03. Plosk et al. found an association among HLAs DRB1*0101, *0102, DQA1*0101 in Norwegian children with RF- polyarticular [12]. The HLA-DRQA1*0501 was the most strongly associated with susceptibility in RF- polyarticular in Greek children [26].

The HLA DRB1*16 associated with susceptibility to RF-polyarticular found in our study, is present in Colombian children with systemic JIA but differ from those found in English, Chinese, Kuwaitis, Iranians and American [13,14,16,18,19,27].

HLA antigens and psoriatic arthritis

The number of psoriatic arthritis cases was very small (3 cases), HLA DR antigen mostly found in this form was the DRB1*01, but due to the low frequency of cases, there was no significant effect of any antigen studied.

The HLA- DRB1*01 antigen was found associated with increased risk for Psoriatic Arthritis in children in the UK in a large study (Table 4) [19].

In mixed populations such as the Brazilian one, polymorphism occurs probably by the aggregation of alleles from several previously separated groups, each one having a distinct set of alleles, rather than by the natural selection of a large number of alleles. If, on the one hand, allelic diversity can make it difficult to identify markers immunogenic of low power association, on the other hand, can bring contributions, identifying new associations, or even reinforcing those already existing. Thus, studies of population characteristics may contribute to understanding of the association between histocompatibility antigens and diseases.

Our study strengthens the existence of numerous associations between HLA polymorphism and the various JIA forms. Progress of the knowledge these associations in diverse populations represents true reflection of the genetic heterogeneity in JIA, being able to contribute to understanding of the diversity clinical, identification of the most severe cases and definition of the most appropriate treatment [28-30].

Conclusion

HLA-DRB1*10 and HLA-DRB1*16 alleles were associated with increasing risk and only HLA-DRB1*03 with protection considering all forms of the disease together. HLA-DRB1*08 showed association with increased risk in oligoarticular form. It was not found any antigen that would provide protection for oligoarticular form. HLA-DRB1*10 was associated with increased risk and DRB1*03 association with protection in Systemic JIA. RF+ polyarticular, association with increased risk occurred for HLA-DRB1*09 and DRB1*10. No HLA type that would provide protection for this form was found. RF-Polyarticular, association with increased risk was HLA - DRB1*16. No types that confer protection to form have been found. Psoriatic Arthritis there was no significant effect any allele on this form of JIA. HLA-DQB1*03 was associated with risk of uveitis in oligoarticular form.

Inherited HLA factors in JIA show similarities overall as well as different patterns of HLA associations evidencing its importance of the aspect of susceptibility as well as protection genetically distinct groups of patients.

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