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Juvenile Idiopathic Arthritis and Its HLA Association: A Study from Bangladesh

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Abstract

Background: HLA alleles may have association with overall JIA including specific sub-types. Determation of HLA DRB1, DPB1, DQA1, DQB1 and B27, may be helpful to diagnose JIA cases where diagnostic dilemma is present. The aim of the study was to find out the association of HLA alleles with JIA and its subtypes. **Methods:** This cross sectional study was conducted in the department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from April 2020 to March 2021. A total of 50 cases and 25 controls attending pediatric rheumatology clinic and pediatric OPD were enrolled in the study. Data were collected by a pre-designed questionnaire containing socio-demographic, clinical and laboratory parameters. HLA DR-B1, DQ-A1, DQ-B1 and B27 typing were done for the cases and controls from blood samples by polymerase chain reaction sequence specific primer (PCR-SSP) method. Data were analyzed by SPSS version 26. Frequency, percentage, chi square test and Fisher exact tests were done for statistical analysis. **Results:** HLA DR-B1_10 had significant positive association whereas HLA DR-B1_03 and B1_16 had negative association with overall JIA cases. Poly-articular JIA, oligo-articular JIA and ERA had association with HLA DRB1_01, B1_08 and B1_12 respectively. HLA DQA1-01 and A1_02 had positive association. However, DQ-A1_06 was negatively associated with JIA cases. Oligo JIA was positively associated with HLA DQ-A1_01, whereas poly JIA and ERA had association with A1_02. Though, HLA DQ_B1 had no association with overall JIA cases, analysis showed association of poly JIA with DQ-B1_04. Frequency of HLA DQ-B1_02 and 03 were higher among ERA cases, though not significant, but they had strong association with HLA B27. **Conclusion:** HLA associations were present with overall JIA and each sub-groups had different patterns of HLA associations including some protective roles.

Keywords

JIA, Types, HLA, Allele

1. Introduction

Juvenile Idiopathic arthritis (JIA) is the most common chronic rheumatic disease of children. It is characterized by chronic inflammation of joints in children resulting short and long-term morbidity and disability [1]. JIA represents a heterogeneous group of disorders sharing the clinical manifestation of arthritis. While the precise etiology of JIA remains unknown, immunogenic susceptibility and external trigger are known to play important role in its pathogenesis. T lymphocyte has a central role releasing pro-inflammatory cytokines like TNF-α, IL-1 & IL-6 which induces inflammation in JIA [2] [3]. Genetic factors are likely to be important both in determining the overall susceptibility to JIA and influencing the remarkable clinical heterogeneity of disease presentation including its seven sub-types according to ILAR classification criteria [4]. It has been suggested that certain major histocompatibility complex (MHC)/HLA alleles show strong association with different types of JIA. Reports are available regarding the association between subtypes of JIA and HLA alleles in children from different countries [5] [6] [7] [8] [9].

The aim of this study was to identify the association of different HLA alleles with overall JIA and its subtypes.

2. Materials and Methods

It was a cross sectional study conducted in the pediatric rheumatology clinic and pediatric OPD, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka over a period of one year (April 2020 to March 2021).

A semi-structured questionnaire was developed in Bangla (Bengali). Prior pre-testing was done to test the reliability and validity. Later on the questionnaire was translated in English by competent persons.

Both the Bangla and English version were used according to requirements but data entry and calculation were done in English. Ethical clearance of the study was taken from the institutional review board of BSMMU (BSMMU/2020/4502). IRB board of BSMMU follows declaration of Helsinki. One researcher read the values, while another researcher entered the data in the SPSS software. Frequency, percentage, chi square and Fisher exact tests were done for statistical analysis.

Fifty JIA cases were enrolled in the present study by consecutive sampling. After getting informed consents from the patients/parents/attendants, data of each child was collected by using the questionnaire. Collected data included necessary socio-demographic and clinical information. Patients were classified into seven JIA sub groups by the attending pediatric rheumatologists according to the revised ILAR classification criteria [4]. Two ml blood was taken from each pa-

tient in an EDTA containing test tube for assessing HLA typing.

Twenty five relatively healthy children, who attended the out-patient department with acute diarrhea with no dehydration, upper respiratory tract illness and viral fever, were enrolled as controls. Siblings/relatives of JIA children or patients having any connective tissue disorders were not taken as controls.

HLA-DRB1, DQA1, DQB1 and HLA B27 alleles were determined from the serum of all the patients and controls using a commercially available semi-automated PCR sequence specific oligonucleotide probes (PCR-SSOP) in the department of microbiology and immunology. HLA-DP B1 could not be measured because of in availability of kits.

The statistical analysis was done using the SPSS software version 26. Frequency of each HLA allele was calculated for all the JIA cases and controls. Frequency of HLA alleles were compared between JIA cases and controls using chi-square test and Fisher exact test. Associations of different HLA alleles with JIA subtypes were expressed as odds ratios (ORs). A p-value < 0.05 was considered statistically significant with 95% confidence intervals (CI).

3. Results

In this cross-sectional study, a total number of 50 juvenile idiopathic arthritis (JIA) cases with different subtypes and 25 non JIA patients were enrolled with the objective to find out their association with HLA alleles. Among 50 JIA cases, one had psoriatic arthritis (HLA DR B1_03, B1_15, DQ A1 _ 01 and DQ B1_06 positive) and one had unclassified JIA (HLA DR B1_09, B1_10, DQ A1_05 and DQ B1_02 positive).These two cases were excluded while associations of types of JIA were analyzed because of very small number.

In the present study, systemic JIA and ERA were more frequent (28% and 26%) followed by poly and oligo JIA (24% and 18%).

Table 1 shows frequency of HLA DR B1 alleles in JIA patients and controls. HLA DRB1_10 had positive association with JIA patient while DRB1_03 and DRB1_16 were negatively associated with JIA. It is evident from Table 2 that, poly-articular JIA, oligo-articular JIA and ERA had significant association with HLA DRB1_01, DRB1_08 and DRB1_12 respectively.

HLA DQA1-01 and 02 had positive association with overall JIA (Table 3). On the other hand DQA1-06 had negative association with JIA cases.

From Table 4 it is found that, oligo-JIA was positively associated with HLA DQA1_01 and poly JIA and ERA had association with HLA DQA1_02.

While comparing cases and controls, HLA DQ_B1 had no significant positive or negative association with overall JIA (Table 5). But analysis of different HLA DQ_B1 alleles (Table 6), showed a significant positive association with HLA DQB1_04.

Frequency of HLA DQB1_02 and 03 were much higher among ERA cases, but the association was not significant (Table 6). ERA cases had strong positive association with HLA B27 (Table 7).

Table 1. HLA-DR B1 Associations in JIA patients and control (n = 50 + 25).

HLADR B1	Group		P-value	OR	95% CI
	Case (all JIA) N = 50	Control N = 25			
01	7 (14)	2 (8)	0.540	1.87	0.35 - 9.76
03	1 (2)	4(16)	0.021*	0.11	0.01 - 1.01
04	10 (20)	7 (28)	0.435	0.642	0.21 - 1.96
07	10 (20)	4 (16)	0.675	1.31	0.367 - 4.69
08	5 (10)	3 (12)	0.791	0.814	1.17 - 3.72
09	2 (4)	1 (4)	1	1	0.08 - 11.5
10	14 (28)	2 (8)	**0.046***	4.47	0.93 - 21.52
11	4 (8)	1 (4)	0.512	2.08	0.22 - 19.7
12	18 (36)	4 (16)	0.072	2.95	0.87 - 9.9
14	4 (8)	0 (0.0)	0.146	-	-
15	13 (26)	6 (24)	0.851	1.11	0.365 - 3.39
16	0 (0.0)	5 (20)	**0.001***	-	-
Total HLA DRB1 (1 - 16)	88	39	**0.**109	2.06	0.84 - 5.09

Chi-square test was done, $p < 0.05$ is significant (*). (More than one HLA alleles were found positive among few cases and controls).

Table 2. Association between HLA-DRB1 alleles and JIA subtypes and controls (n = 48 + 25).

HLA DRB1	JIA				Control (n = 25)
	sJIA (n = 14)	Oligo JIA (n = 9)	Poly JIA (n = 12)	ERA (n = 13)	
01	1 (7.1)	0(0.0)	5 (41.6)	1 (7.6)	2 (8)
p-value	0.923	0.381	**0.014***	0.973	
OR	0.88		8.21	0.95	
04	3 (21.4)	1 (11.1)	3 (25)	3 (23)	7 (28)
p-value	0.652	0.305	0.847	0.743	
OR	0.701	0.321	0.857	0.771	
08	00	4 (44.4)	1 (8.3)	00	3 (12)
p-value	0.177	**0.039**	0.736	0.193	
OR	-	5.86	0.666	-	
09	00	00	2 (16.6)	00	1 (4)
p-value	0.448	0.542	0.186	0.464	
OR	-	-	4.8	-	
10	4 (28.5)	1 (11.1)	3 (25)	4 (30.7)	2 (8)
p-value	0.087	0.777	0.156	0.067	
OR	4.6	1.43	3.83	5.11	

Continued

12	6 (42.8)	3 (33.3)	2 (16.6)	7 (53.8)	4 (16)
p-value	0.065	0.270	0.958	0.014*	
OR	3.93	2.62	1.05	6.12	
15	5 (35.7)	3 (33.3)	5 (41.6)	00	6 (24)
p-value	0.435	0.586	0.271	0.054	
OR	1.75	1.58	2.26	-	

Fisher exact test. P-value < 0.05 is significant (*), OR = Odds ratio. More frequent HLA alleles were shown in the table.

Table 3. Association of HLA-DQ A1 in JIA patients and controls (n = 50 + 25).

HLA DQ A1	Group		P-value	OR	95% CI
	Case (JIA) N = 50	Control N = 25			
01	31 (62)	9 (36)	0.033*	2.90	1.07 - 7.85
02	19 (38)	3 (12)	0.019*	4.49	1.18 - 17.07
03	8 (16)	3 (12)	0.644	1.39	0.33 - 5.8
04	2 (4)	3 (12)	0.190	0.305	0.04 - 1.96
05	3 (6)	3 (12)	0.366	0.46	0.08 - 2.5
06	11 (22)	12 (48)	0.021*	0.305	0.109 - 0.865
Total HLA DQA1 (1 - 6)	74	33	0.307	1.12	0.89 - 1.41

Chi-square test was done, p < 0.05 is significant (*). (More than one HLA alleles were found positive in among few cases and controls).

Table 4. Association between HLA-DQA1 Alleles with JIA subtypes and Controls (n = 48 + 25).

HLA DQA1	JIA				Control (n = 25)
	sJIA (n = 14)	Oligo JIA (n = 9)	Poly JIA (n = 12)	ERA (n = 13)	
01	9 (62.2)	7 (77.7)	8 (66.6)	7 (53.8)	9 (36)
p-value	0.089	0.031*	0.079	0.29	
OR	3.2	6.22	3.5	2.07	
02	5 (35.7)	3 (33.3)	5 (41.6)	6 (46.1)	3 (12)
p-value	0.078	0.149	0.040*	0.018*	
OR	4.07	3.66	5.23	6.28	
03	2 (14.2)	1 (11.1)	3 (25)	2 (15.3)	3 (12)
p-value	0.482	0.943	0.315	0.769	
OR	1.22	0.91	2.44	1.33	
06	3 (21.4)	2 (22.2)	2 (16.6)	4 (30.6)	12 (48)
p-value	0.101	0.177	0.065	0.307	
OR	0.295	0.309	0.21	0.48	

Fisher exact test was done in JIA sub types with Control group, p-value < 0.05 is significant (*), OR = Odds ratio. More frequent HLA alleles were shown in the table.

Table 5. Association of HLA-DQ B1 in JIA patients and controls (n = 50 + 25).

HLA DQ B1	Group		P-value	OR	95% CI
	Case (all JIA) N = 50	Control N = 25			
01	0	0	-	-	-
02	13(26)	7 (28)	0.853	0.903	0.30 - 2.6
03	21 (42)	9 (36)	0.617	1.28	0.47 - 3.46
04	7 (14)	1 (4)	0.185	3.9	0.45 - 33.6
05	0	0	-	-	-
06	20 (40)	13 (52)	0.323	0.61	0.23 - 1.6
Total HLADQB1 (1 - 6)	61	30	0.905	1.04	0.52 - 2.08

Chi-square test was done, p <0.05 is significant (More than one HLA alleles were found positive in among few cases and controls).

Table 6. Association between HLA-DQB1 Alleles with JIA subtypes and Controls (n = 48 + 25).

HLA DQB1	JIA				Control (n = 25)
	sJIA (n = 14)	Oligo JIA (n = 9)	Poly JIA (n = 12)	ERA (n = 13)	
02	3 (21.4)	3 (33.3)	3 (25)	4 (30.7)	7 (28)
p-value	0.652	0.763	0.847	0.858	
OR	0.70	1.28	0.857	1.14	
03	5 (35.7)	2 (22.2)	6 (50)	8 (61.5)	9 (36)
p-value	0.985	0.448	0.416	0.133	
OR	0.987	0.507	1.77	2.84	
04	3 (21.4)	1 (11.1)	3 (25)	0(0.0)	1 (4)
p-value	0.085	0.436	**0.049***	0.464	
OR	6.54	3.00	8.00		
06	8 (57.1)	4 (44.4)	4 (33.3)	4 (30.7)	13 (52)
p-value	0.757	0.697	0.286	0.211	
OR	1.23	0.738	0.461	0.410	

Fisher exact test was done in JIA sub types with Control group, p-value < 0.05 is significant (*), OR = Odds ratio. More frequent HLA alleles were shown in the table.

Table 7. Association of HLA B27 with JIA subtypes and controls (n = 48 + 25).

sJIA n = 14	Oligo JIA n = 09	Poly JIA n = 12	ERA n = 13	Control n = 25
00	00	4 (33.3)	11 (85)	
P = 0.499	P = 0.87	P = 0.230	P = 0.05*	4 (16)
OR….	OR….	OR = 2.62	OR = 28.87	

Fisher exact test was done. P-value < 0.05 is significant (*), OR = Odds ratio.

4. Discussion

Human leukocyte antigens (HLA) class I and II genes are closely associated with rheumatic disorders, with an important example of HLA-B27 and spondylo arthropathy [10]. Genetic variation underlying JIA susceptibility is also studied extensively [5] [11]. Associations between HLA polymorphism and JIA subtypes are previously reported [10] [12]. The earliest report was the association of HLA B27 with older children with pauciarticular onset disease [13].

The present study is the first documentation from Bangladesh to show the associations of different HLA alleles with JIA and its subgroups. In the present study, frequency of HLA DRB1_10 allele was significantly high among JIA patients. On the other hand, DRB1_03 and DRB1_16 were significantly higher among controls, which may suggest a negative association with JIA and a protective role.

These associations also varied between subtypes of JIA. Our study used ILAR classification criteria for classifying JIA [4], but because of small sample size, polyarticular RF + ve and RF – ve cases were combined for calculation and cases of psoriatic arthritis and undifferentiated arthritis (1 + 1) were excluded from sub-groups association. Poly-articular JIA, oligo-articular JIA and ERA had significant positive association with HLA DRB1_01, B1_08 and B1_12 respectively.

Prahalad *et al.* [8] found association between HLADRB1_01 and RF + ve poly JIA cases among American children. We also found association with poly articular cases but our cases included both the RF + ve and – ve types. Studies done in Brazil and Iran found [6] [14], significant association of HLA DRB1_08 with oligo JIA. Thomson W *et al.* in their study found in UK, two HLA-DRB1 alleles having association with increased risk (DRB1_08 and 11) and two with decreased risk (DRB1_04 and 07) of JIA [15]. These phenotype frequencies also differed between subgroups. The increased risk associated with HLA-DRB1_08 was largely attributable to persistent oligoarthritis, extended oligoarthritis and RF-negative polyarthritis [15] [16]. Hinks *et al.* in a multicenter study done in USA, UK, Canada, Norway and Germany, showed an association of HLA DRB1_13 with poly JIA [17]. We also found positive association of HLA DRB1_08 with oligoarticular JIA, but no association (positive or negative) was found with DRB1_04 and 07. The present study also did not find any association of DRB1_08 with polyarticular JIA.

Pires *et al.* in a study done in Brazil, reported HLA DR B1_03 as protective for systemic JIA as its frequency was higher in controls, but lower in cases [6]. Our study did not find any such association.

These differences may be explained by ethnic or genetic variation and small sample size. Due to small sample size, and use of different classification systems in different studies it is quite difficult to establish the differences as true reflection of genetic heterogeneity. However, previous studies from our country as well as from neighboring countries show that types of JIA in this region are also different from western countries [18] [19] [20] [21] [22]. In our part of the

world, ERA, systemic JIA and poly-articular cases are common [19] [22], whereas in western part, oligo-articular cases are the commonest [23]. Even ANA positivity is also lower in our part [24] [25]. The present study also found highest number of sJIA cases followed by ERA and poly JIA and lowest number of oligo JIA cases. So, the issue of genetic variation cannot be ignored.

The present study found positive association of HLA DQA1-01 and 02 but DQ A1-06 had negative association with overall JIA cases. When subtypes were analyzed, oligo-JIA was positively associated with HLA DQ A1_01 and poly JIA and ERA had association with DQ A1_02. Thomson W *et al.* showed that, HLA-DQA1_01, 04 and 05 were associated with high risk, while 02 and 03 were associated with low risk of JIA [15].

An interesting finding found in the present study was that, HLA DQ_B1 had no significant positive or negative association with overall JIA cases, but analysis of different HLA DQ_B1 alleles, found that poly JIA was positively associated HLA DQB1_04.

ERA cases had very strongly association with HLA_ B27. HLA_ B27 association with ERA is an established fact and it is reported from different studies conducted in Taiwan, Europe and UK [26] [27] [28]. The European study also found high frequency of HLA B27 in poly JIA (33%). We also found a higher frequency of HLA B 27 in poly JIA cases (33.33), though not significant. Berntson *et al.*, in UK showed that HLA B27 positivity was associated with older age of onset, male population and prolonged disease activity [28]. In the present study, mean age at onset of ERA cases was 9 year and most of the ERA cases were male. Association of duration of disease activity was not assessed in the present study but most of the studies from our country showed a long duration of disease at presentation [18] [19] [29] [30].

In recent years, many important genetic studies reported that, early onset conditions including obesity, inflammatory bowel diseases, type 1 diabetes and frequent relapse nephrotic syndrome cases had association with genetic components [31] [32] [33] [34]. JIA patients are also susceptible to genetic factors evidenced by association of different HLA alleles. Though number of cases and controls were very small, the present study also supports some of the previous findings from different countries. If further multicenter studies with large sample size can be carried out, it may be possible to clearly identify the associations and utilize the HLA alleles as early diagnostic criteria especially in difficult cases.

5. Conclusion

This study, though very small, demonstrates that there are multiple HLA associations with JIA. Along with some common associations with overall JIA, each subgroup had different patterns of HLA association including some protective roles against JIA. HLA DQA1-01 and A1_02 had positive association. However, DQ-A1_06 was negatively associated with JIA cases. Oligo JIA was positively associated with HLA DQ-A1_01, whereas poly JIA and ERA had association with

A1_02. Though, HLA DQ_B1 had no association with overall JIA cases, but poly JIA had association with DQ-B1_04. ERA cases had strong association with HLA B27.

6. Limitation

The present study had very small sample size. Association with all the 7 subtypes of JIA could not be assessed due to small number of cases. Polyarticular RF + ve and RF – ve cases were combined together for calculation and cases of psoriatic arthritis and unclassified cases were excluded from final calculation. Moreover HLA_DPB1 allele could not be assessed due to in availability of logistics.

7. Recommendation

Further study with large sample size should be carried out for drawing more specific conclusion.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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