

HLA antigens in individuals with down syndrome and alopecia areata

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Abstract

AIM: To describe human leukocyte antigen (HLA) alleles in individuals with Down syndrome and alopecia areata.

METHODS: A cross-sectional study was conducted, which evaluated 109 individuals. Ten with down syndrome (DS) and alopecia areata (AA), ten with DS without AA and ten with AA without DS, and their fami-

lies. The individuals were matched by gender and age. The following data were computed: gender, age, ethnic group, karyotype, clinical presentation and family history of alopecia areata. Descriptive analysis: measures of central tendency and frequency distribution. Inferential analysis: Fisher's exact test to compare categorical data between the three groups and Kruskal-Wallis ANOVA test for numerical data.

RESULTS: Seventy per cent of evaluated individuals in the DS and AA group were male; presented mean age of 18.6 (SD \pm 7.2) years and 70% were Caucasian. We observed involvement of the scalp, with a single lesion in 10% and multiple in 90% of subjects. It was observed that there is no significant difference in the frequency distributions of the alleles HLA loci A, B, C, DRB1 and DQB1 of subjects studied. However, according to Fisher's exact test, there is a trend ($P = 0.089$) of DS group to present higher proportions of HLA-A 36 and HLA-B 15 than the AA group and AA and DS group.

CONCLUSION: There was a tendency for the DS group, to present proportion of HLA-A 36 and HLA-B 15 higher than the AA group and group of individuals with AA and DS. However, there was no significant difference in the frequency distribution of the alleles.

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Key words: Down syndrome; Alopecia areata; Human leukocyte antigen antigens; Immunology; Genetic

Core tip: The prevalence of alopecia areata (AA) in down syndrome (DS) individuals ranges from 1% to 11%, higher than in general population. The frequency distribution of human leukocyte antigen alleles in the groups was heterogeneous; there was a tendency of alleles A-36 and B-15 in DS group. The cause of AA in DS remains unknown.

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INTRODUCTION

Down syndrome (DS) is the most frequent chromosomal anomaly and common cause of mental retardation^[1,2]. The prevalence of DS is approximately 1:770 births, with a slight preponderance in the male gender^[3].

This syndrome presents an increased prevalence of autoimmune disorders^[4]. The prevalence of alopecia areata (AA) in DS ranges from 1% to 11%, more frequent in this group than the general population^[5-11]. Some studies conducted with DS patients with and without AA showed changes related to the immune system. There are few studies involving the histocompatibility antigens (HLA), DS and AA^[12-14].

The purpose of this study was to describe HLA alleles (loci A, B, C, DRB1 and DQB1) in individuals with DS and AA.

MATERIALS AND METHODS

A cross-sectional study was conducted, in which 109 individuals were evaluated; 10 individuals with DS without AA (Group A) and 10 individuals with AA without DS (Group B), 10 individuals with DS and AA (Group C) and their families (Figure 1). The individuals were matched by gender and age. The clinical research protocol was approved by the Ethical Research Committee of the Martagão Gesteira Pediatric Institute (IPPMG) and all participants or their caregivers signed the informed consent.

All DS individuals were diagnosed clinically, most by cytogenetic analysis, and presented a documented medical history of AA or presented alopecia at the time of a consultation at the Medical Genetics Service. AA was considered to be hair loss leading to a “flaw” on any hairy body surface.

All the participants of the study were submitted to anamnesis and clinical exam to confirm DS and/or AA diagnosis by a clinical geneticist and by a dermatologist respectively. Exclusion criteria included: trichotillomania and presence of polycystic ovaries (evaluated by pelvic ultrasound in post-menarche female DS and/or AA patients).

The following data were computed: (1) gender and age; (2) cytogenetic exam; (3) ethnic group; (4) clinical picture of AA; (5) family history of AA; (6) HLA alleles; and (7) evaluation of family.

The HLA typing was performed using commercial kits: LABType® Typing sequence specific oligonucleotide probes (SSO) Tests (One Lambda, Inc. CA, United States), which are based on the use of SSO which are connected on the microbeads encoded by fluorescence identifying alleles encoded by the DNA sample.

A descriptive analysis with measures of central tendency and frequency distribution was made and an inferential analysis on exploratory level was made by Fisher's exact test to compare categorical data between the three groups by ANOVA and Kruskal-Wallis test for numerical data. Nonparametric test was used because the variables were not normally distributed (Gaussian), due to the dispersion of the data and rejection of the hypothesis of normality according to the Kolmogorov-Smirnov test. The criterion for determination of significance level was 5%.

RESULTS

Table 1 provides the frequency (*n*) and percentage (%) of categorical variables and disease according to demographic groups (A, B and C) and the corresponding descriptive level (*P* value) of Fisher's exact test. The age in months and the number of family members were expressed as mean, median and standard deviation and compared by Kruskal-Wallis ANOVA.

Table 2 provides the frequency (*n*) and the percentage (%) of the loci of HLA-A, B, C, DQB1 and DRB1 alleles, in the groups (DS, AA and DS + AA) and corresponding descriptive level (*P* value) of Fisher's exact test.

Regarding the relatives evaluation of first and second degrees, it was observed that the majority of alleles showed a low frequency. We emphasize some alleles such as HLA-C 07 (21/55), HLA-DQB1 03 (28/55) and HLA-DQB1 06 (22/55) which had a high frequency (> 50%) in the first-degree relatives of all groups.

DISCUSSION

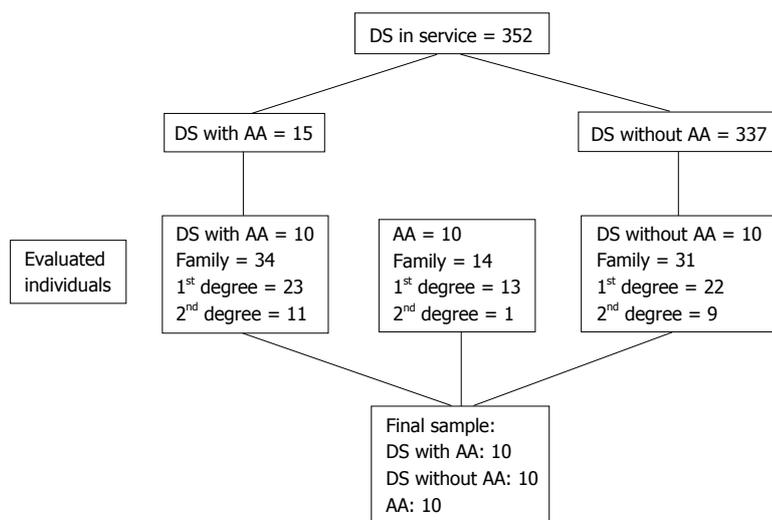
This study reflects an unpublished investigation in patients with DS. However, there was no statistical significance in the distribution of HLA in DS with or without AA. Although the sample size reflected a small number of patients, in general, the groups did not differ (Table 1), reflecting the selection criteria used. Several studies have focused on the association of HLA and AA; some of them correlating prognosis, extent, chance of recurrence and family history with HLA^[15-17]. These studies report that HLADQB1*03 allele was presented in 80% of all patients with AA, independently of the phenotype, and in 92% of individuals with total or universal AA. It was also demonstrated that the frequency of HLA-DRB1*1104 was increased in all sorts of AA^[15,16]. These data were not reported in this study.

Although the literature reports that the AA in individuals with DS is more common in females^[5,18], the sample was predominantly male (70.0%). Schepis *et al*^[19] (2005) studied individuals with DS and AA, and also identified more men with AA (92.3%). Concerning the 352 DS cases recorded in IPPMG, 15 of them presented AA; the most frequently occurrence of AA in males was not significant (*P* > 0.05). AA can occur as a single and self-limited episode, but also can recur in DS patients^[20,21]. In this study, 90% (9/10) individuals with DS and AA had

Table 1 Demographic and disease variables according the group *n* (%)

Variable	Category	DS group (A)		AA group (B)		DS + AA group (C)		P value ¹
Gender	Male	7	(70.0)	7	(70.0)	7	(30.0)	1.000
	Female	3	(30.0)	3	(30.0)	3	(30.0)	
Age, mo	Average ± SD (median)	224.1 ± 86.0 (233.5)		217.3 ± 90.2 (197.0)		224.3 ± 86.9 (223.5)		0.970 ²
Clinical presentation	1 lesion S			1	(10.0)	1	(10.0)	Descriptive
	1 lesion S/cilium			1	(10.0)	0	0.0	
	Lesions S			6	(60.0)	9	(90.0)	
	Lesion S/total			1	(10.0)	0	0.0	
	Lesion S/total/eyebrow			1	(10.0)	0	0.0	
Family history of alopecia	Yes	0	0	2	(20.0)	0	0	0.230
	No	10	(100.0)	8	(80.0)	10	(100.0)	
Karyotype	free trisomy	7	(100.0)			6	(85.7)	0.500
	Translocation	0	0			1	(14.3)	
Ethnic group	Caucasian	6	(60.0)	3	(30.0)	7	(70.0)	0.270
	Non-Caucasian	4	(40.0)	7	(70.0)	3	(30.0)	
Family (<i>n</i>)	0	0	0	2	(20.0)	1	(10.0)	Descriptive
	1	3	(30.0)	5	(50.0)	3	(30.0)	
	2	2	(20.0)	1	(10.0)	0	0.0	
	3	2	(20.0)	1	(10.0)	0	0.0	
	4	0	0.0	1	(10.0)	2	(20.0)	
	5	1	(10.0)	0	0.0	2	(20.0)	
	6	1	(10.0)	0	0.0	1	(10.0)	
	7	1	(10.0)	0	0.0	1	(10.0)	
Family (<i>n</i>)	Average ± SD (median)	3.1 ± 2.2 (2.5)		1.4 ± 1.3 (1)		3.4 ± 2.5 (4)		0.085 ²

¹Fisher exact test; ²Kruskal-Wallis ANOVA. S: Scalp; DS: Down syndrome; AA: Alopecia areata.

**Figure 1** Structure of selected sample. DS: Down syndrome; AA: Alopecia areata.

more than one lesion on the scalp, and 10% (1/10) presented single lesion on the scalp. This finding was similar which is reported in the literature^[19]. AA can affect any hairy area and the most affected is scalp (90%)^[22-25]. All evaluated individuals presented scalp lesion.

Regarding family history, it is present in 10%-25% of cases of AA^[10,26]. In this study we observed two cases (20%) of family history (first degree relative) in AA without DS group.

Genetic studies of AA have focused on HLA antigens due to immunological aspects of the disease^[15,17,27,28]. Some have demonstrated that major complex of histocompatibility genes are the major determinants for dis-

eases mediated by T cells, including AA^[29,30]. In this study, no significant difference was observed at the level of 5% on the proportion of HLA-A between groups. According to Fisher's exact test, there is a trend ($P = 0.089$) of the DS group, present proportion of HLA-A 36 (30%) higher than the AA (0%) and DS with AA (0%) group. Xiao *et al*^[17] (2006) evaluated Chinese individuals, 192 with AA and 252 controls and found higher frequency of HLA-A*02 and A*03 in patients than in controls. Despite not being the same allele, we can see that the distribution is in fact heterogeneous.

In the same study^[17], comparing patients and controls, a higher frequency of HLA-B*18 and HLA-B*27

Table 2 Distribution of the most frequent human leukocyte antigen A, B, C, DQB1 and DRB1 alleles

Alleles	DS group (A)	AA group (B)	DS + AA group (C)	P value ¹
HLA-A 02	4 (40.0)	3 (30.0)	5 (50.0)	0.890
HLA-A 24	1 (10.0)	0	3 (30.0)	0.290
HLA-A 36	3 (30.0)	0	0	0.089
HLA-B 15	4 (40.0)	0	1 (10.0)	0.094
HLA-B 35	1 (10.0)	2 (20.0)	3 (30.0)	0.850
HLA-B 44	0	2 (20.0)	4 (40.0)	0.120
HLA-B 53	3 (30.0)	1 (10.0)	1 (10.0)	0.570
HLA-C 02	4 (40.0)	0	2 (20.0)	0.120
HLA-C 07	4 (40.0)	3 (30.0)	5 (50.0)	0.890
HLA-C 15	1 (10.0)	3 (30.0)	0	0.290
HLA-DQB1 02	6 (60.0)	3 (30.0)	4 (40.0)	0.530
HLA-DQB1 03	2 (20.0)	6 (60.0)	5 (50.0)	0.270
HLA-DRB1 01	1 (10.0)	2 (20.0)	3 (30.0)	0.850
HLA-DRB1 03	4 (40.0)	3 (30.0)	2 (20.0)	0.880
HLA-DRB1 04	0	1 (10.0)	2 (20.0)	0.750
HLA-DRB1 11	1 (10.0)	3 (30.0)	3 (30.0)	0.640
HLA-DRB1 13	3 (30.0)	2 (20.0)	4 (40.0)	0.880

¹Fisher Exact test. HLA-A 01, -03, -11, -23, -25, -30, -31, -32, -33, -66, -68, -80. HLA-B 07, -08, -13, -14, -27, -37, -40, -42, -48, -49, -50, -51, -52, -57, -58, -81. HLA-C 01, -03, -04, -05, -06, -08, -14, -16, -17. HLA-DQB1 04, -05, -06. HLA-DRB1 01, -07, -08, -10, -12, -15, -16 alleles had a frequency less than 1 and were not included in the Table 2. HLA: Human leukocyte antigen; DS: Down syndrome; AA: Alopecia areata.

was found in patients. In this study there was no significant difference at 5% in the proportion of HLA-B and between groups. According to Fisher's exact test, there is a trend ($P = 0.094$) in DS group presenting a higher proportion of HLA-B 15 (40%) than the others groups. There is few published data on HLA-C and AA. It was described in literature the highest frequency of HLA-Cw*0704 in patients with AA. In this study, it was observed that there is no significant difference at 5%, proportion of HLA-C, HLA-DQB1 and HLA-DRB1 alleles between groups.

This finding was different from some studies reported in the literature, conducted in patients with AA without DS, which showed a predisposition to develop AA in cases with HLA-DRB1*03, HLA-DRB1*04, HLA-DQB1*06, HLADRB1*13, HLADRW52a, DQ7, HLADQB1*03, HLA-DRB1*11^[15-17,27,31,32].

Different HLA types are found in the population and it is rare to find two individuals having the same HLA^[33]. The frequencies of alleles tend to be different among populations racially and ethnically distinct. The Brazilian population is genetically very different and it is justified by the contribution of three groups: Caucasians, Africans and Native Americans^[34]. This fact may explain the heterogeneous distribution in this study and the differences found in earlier studies.

This study was conducted with a small sample. Moreover, it was difficult to collect some relatives of the subjects, especially the second degree, who refused to participate. These two factors were found limitations in this research.

In a conclusion, The frequency distribution of HLA

alleles (loci A, B, C, DRB1 and DQB1) was heterogeneous in the three groups, with no significant difference in the proportion. There was a trend ($P = 0.089$) of the DS group to present higher proportion of HLA-A 36 than the others groups and a trend ($P = 0.094$) of the DS group to present higher proportion of HLA-B 15 than the others groups. HLA-C 07, HLA-DQB1 03 and HLA-DQB1 06 alleles showed high frequency (> 50%) in first-degree relatives of the total sample.

This study was conducted with a small sample. We suggest further studies with larger sample.

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COMMENTS

Background

The prevalence of alopecia areata (AA) in down syndrome (DS) individuals ranges from 1% to 11%, higher than in general population.

Research frontiers

This study was undertaken to describe human leukocyte antigen (HLA) alleles in individuals with DS and AA, and try to explain the higher prevalence of AA in these individuals.

Innovations and breakthroughs

The frequency distribution of HLA alleles in the groups was heterogeneous; there was a tendency of alleles A-36 and B-15 in DS group. The cause of AA in DS remains unknown. The authors suggest further studies with a larger sample.

Peer review

The work presented in the paper provides an indication that individuals with Down syndrome exhibit a higher prevalence of AA than the general population. In spite a small sample size, the manuscript provides some interesting insights into the immune system disturbances in DS individuals.

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