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Research Article

Allelic Frequencies of *HLA-A*, *HLA-B* and *HLA-DRB1* Genes in Children with Adrenocortical Tumor who are Carriers of the Germline Mutation R337H in the *TP53* Gene

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Abstract

Context: Most children and adolescents with Adrenocortical Tumors (ACT) in Paraná (Brazil) carry the germline mutation R337H in the *TP53* gene. However, the mutation alone is not sufficient for the development of the tumor. Close association of the HLA system with certain types of malignancies, such as osteosarcoma, leukemia and Hodgkin´s disease, has been documented and in recent studies, reduced expression of class II HLA complex genes has been shown in adrenocortical carcinomas.

Objectives: To evaluate the allelic frequency of the *HLA-A*, *HLA-B* and *HLA-DRB1* genes in ACT patients with the *TP53* R337H mutation and in Caucasian controls.

Design: Genomic study.

Patients and participants: 39 ACT patients following up regularly at the Pediatric Endocrine Unit of Federal University of Paraná School Hospital and 50,665 controls.

Main Outcome Measure: Frequency of allelic variants of the *HLA-A*, *HLA-B* and *HLA-DRB1* genes.

Results: Compared with controls, the allelic variants *HLA-A*31*, *HLA-B*39* and *HLA-DRB1*08* were significantly more frequent in patients.

Conclusion: These results suggest an association between the HLA system and the development of ACT in children and adolescents with the *TP53* gene germline mutation R337H.

Keywords: Adrenocortical tumor; Children; *TP53*; HLA

Abbreviations

ACT: Adrenocortical Tumors; OR: Odds Ratio; VS: Virilization Syndrome; MS: Mixed Syndrome; CS: Cushing Syndrome

Introduction

Adrenocortical Tumors (ACT) are extremely rare in children, but their prevalence in the South and Southeast regions of Brazil is about fifteen times higher than that worldwide [1-3]. Since both these Brazilian regions have extensive agricultural activity, the possibility of environmental factors, such as exposure to agricultural pesticides, has been considered [1].

The tumor is more frequent in girls below the age of five years and presents most commonly with signs of virilization [4]. The main criterion currently used to establish the prognosis of patients with ACT is clinical staging, which is based on tumor size and presence or absence of metastases on diagnosis [4-6]. In patients without detectable metastases, the diagnosis of ACT may be challenging due to lack of consensus on the reliability of histological analysis in differentiating adenomas from adrenocortical carcinomas [7,8]. The definitive treatment of patients with ACT is surgical resection, and the prognosis correlates negatively with the size of the tumor [4,9]. The increased incidence of childhood ACT in the South and Southeast regions of Brazil has been widely documented. However, the factors associated with this increased incidence remain a matter of research. A recent study by Custodio *et al.* evaluated the presence of the mutation *TP53* R337H in 171,649 neonates born between December 2005 and March 2010 in Paraná, reporting an estimated prevalence of 0.27% [10]. Since this mutation is also found in healthy relatives of children with ACT [11], other factors seem to be also involved in the pathogenesis of ACT.

In a long-term study by Marques-Pereira *et al.* [4], no ACT was identified in a cohort of 65 children (aged 0.25 to 14.6 years) bearing the *TP53* R337H mutation who were followed for three years with clinical, laboratory and imaging tests. The follow-up of this cohort has been extended to four more years and still no evidence of ACT has been found (data not yet published). These data reinforce the concept

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that the mutation *per se* is not enough to explain the emergence of the tumor.

The gene *TP53* codes for a protein that acts as a transcriptional regulator, activating expression of numerous genes involved in cell death, cell cycle arrest, senescence, DNA repair and many others processes. The loss of the wild-type allele and the abnormal nuclear accumulation of the mutant protein in these tumors (a common finding in *p53*-associated cancers) support the premise that this mutation plays an essential role in the development of ACT [12]. In spite of the multiple efforts to characterize the functions of *p53*, the mechanisms of tumor suppression by *p53* remain only partially understood [13].

Population studies have shown an association between the HLA system and development of more than 40 diseases [14]. Evidence also shows a positive association between HLA alleles and susceptibility to Hodgkin's disease [15], leukemia [16] and osteosarcoma [17].

One study has assessed the presence of HLA antigens in ACT. Although a clear relationship between those antigens and the development of the tumor has not been established, a relationship between some alleles of the HLA system and a higher risk of adrenocortical malignancy in adults has been documented [18]. In addition, reduced expression of HLA class II antigens has been shown in adrenal carcinomas, but not in adenomas [19]. In contrast, another study has shown that changes in HLA expression are unable to differentiate adenomas from carcinomas in children [20]. Low expression of HLA class II antigens has been associated with more aggressive disease in several human malignancies including adult ACT, but their clinical relevance in pediatric ACT needs to be investigated.

So far, no studies have shown an association between the profiles of HLA class I genes (*HLA-A, HLA-B*) and the development of ACT in children. As for HLA class II genes, one study has shown a higher prevalence of the variant *DRB1*01* in adrenal carcinomas [21].

Considering the scarcity of data on HLA and ACT reported on literature, we analyzed the HLA-A, HLA-B and HLA-DRB1 profiles in 39 patients and its association with ACT. All patients were HLA genotyped. We also compared the frequencies of these alleles according to clinical presentation.

Patients and Methods

Sample description

The ethnic and racial makeup of the Brazilian population is complex and unique. For administrative purposes, the country encompasses five regions: North, Northeast, Central-West, Southeast and South. The Northeast region, for example, has the greatest proportion of African descendants, whereas the Southern and South regions have a mixture of immigrants from several European countries (Germany, Poland, Italy, Ukraine) during the second half of the 19th and beginning of the 20th century migratory waves [22].

The present study was carried out in the state of Paraná which is located in the Southern region of Brazil. Its population is mainly composed by European descendants as a result of a colonization program of the local government promoted during the 19th and 20th centuries.

Of 153 patients treated for ACT between 1966 and 2011 at the Pediatric Endocrinology Unit of the Federal University of Paraná School Hospital, 45 are currently following up regularly. Most of these patients were born in the state of Paraná (Southern Region of Brazil), whereas a few were born in the state of Santa Catarina (South Region) or in the state of São Paulo (Southeast Region). All patients had been previously tested for the *TP53* R337H mutation according to Ribeiro *et al.* [12]. Five patients who tested negative for the mutation and one whose HLA-B allele genotyping could not be clearly defined despite repeated analysis (including parental haplotype) were excluded from the current study. The remaining analysis of *HLA-A, HLA-B and HLA-DRB1* genotypes was performed in 39 patients ("patients").

Patients HLA genotyping were compared with 50,665 Caucasoid bone marrow donors of the Brazilian Registry of Bone Marrow Donors ("controls"), in the state of Paraná. Tumors were categorized according to the Weiss criteria [5].

The study was approved by the Ethical Committee of the Federal University of Paraná School Hospital.

HLA Typing

Genomic DNA from patients and controls was extracted from peripheral blood with a salting-out procedure [23]. HLA class I (*HLA-A, HLA-B*) and HLA class II (*HLA-DRB1*) typing was performed using available typing systems: Dynal RELI™ SSO complemented when necessary with LABType®SSO, both based on Polymerase Chain Reaction (PCR) essays, according to the manufacturer's instructions.

Allelic and haplotype frequency

Allelic and haplotype frequencies were obtained by direct counting, using the program package ARLEQUIN 3.0 [24].

Statistical analysis

Comparisons between groups (patients *versus* controls) were performed with the G-test of independence using BioEstat version 5.3 [25]. Results were considered statistically significant if $p<0.05$. The Bonferroni method was used to correct the p values. This correction was obtained multiplying the critical p value by the number of comparisons as follows: *HLA-A (*n=21), *HLA-B* (n=35) and *HLA-DRB1* (n=13).

Results

Patient's characteristics

The clinical features of the patients are summarized in Table 1. Of the 39 patients, 26 were females (2:1 ratio).

The median age at diagnosis was 2.1 years (range 0 to 13.4 years). Thirty-one patients (79.5%) were diagnosed during the first four years of life, and in one patient the tumor was diagnosed at birth. The median interval between the onset of symptoms and the diagnosis of the tumor was 6 months (range 0 to 60 months). The median follow-up time was 9.6 years (1.7 to 22.3 years).

On presentation, 19 patients (48.7%) had a Virilization Syndrome (VS), 16 (41%) had virilization plus Cushing syndrome (mixed syndrome, MS), three (7.7%) had a non-functional tumor, and one patient (2.6%) had isolated Cushing Syndrome (CS). Histologically, 32 (82%) tumors were carcinomas, five

Table 1: Clinical presentation of 39 patients with adrenocortical tumors.

Identifier	Sex	Age at diagnosis (months)	Clinical presentation	Staging	Identifier	Sex	Age at diagnosis (months)	Clinical presentation	Staging
1	F	54	MS	IV	21	M	12	MS	I
2	F	15	MS	II	22	F	14	MS	I
3	F	8	MS	II	23	M	39	NF	II
4	F	24	MS	I	24	F	30	VS	I
5	M	13	CS	II	25	F	86	VS	I
6	F	21	MS	I	26	M	17	MS	I
7	F	19	MS	I	27	F	27	VS	I
8	F	10	VS	II	28	F	42	VS	I
9	F	17	VS	I	29	F	0	NF	I
10	F	19	VS	I	30	M	42	NF	II
11	M	95	VS	IV	31	F	19	MS	II
12	M	102	VS	IV	32	M	15	MS	II
13	F	51	VS	II	33	F	26	VS	IV
14	F	11	MS	I	34	F	85	VS	IV
15	F	25	VS	I	35	F	26	MS	I
16	M	36	VS	I	36	M	45	MS	III
17	M	71	VS	I	37	F	39	VS	I
18	F	31	VS	I	38	F	32	VS	I
19	M	20	VS	I	39	F	16	MS	II
20	M	161	MS	III					

VS: Virilization Syndrome; CS: Cushing Syndrome; MS: Mixed Syndrome; NF: Non-Functional

(12.8%) were adenomas and two (5.1%) were classified as indeterminate.

HLA-A, HLA-B and *HLA-DRB1*

Patients *versus* controls: Table 2 shows the significant comparisons of the allelic groups between patients and controls. *HLA-A*31* was more frequent in patients when compared with Caucasian controls (15.4% *versus* 5.3%, p=0.0027, odds ratio [OR] 3.72, 95% confidence interval [95% CI] 2.01–6.90. Similar findings were shown for *HLA-B*39* (12.8% *vs* 3.7%, p=0.0057, OR = 4.40, 95% CI 2.26–8.56) and *HLA-DRB1*08* (14.1% *versus* 6.3%, p=0.041, OR=2.66, 95% CI 1.41-5.05).

When we included clinical manifestations in the comparisons (VS *versus* MS) and tumor histology (carcinoma *versus* adenoma), we found no significant differences regarding the *HLA-A, HLA-B* and *HLA-DRB1* allelic groups.

Table 2: Comparison of *HLA-A, HLA-B* and *HLA-DRB1* allelic groups between patients (n=39) and Caucasian controls (n= 50, 665).

HLA-A	Patients (2n=78)		Caucasian Controls (2n= 101,330) (1)		*Pc*	OR	95% CI
	Abs	Rel (%)	Abs	Rel (%)			
Patients (78)(1) *vs* Controls							
*HLA-A*31*	12	15.4	5,131	5.3	0.0027	3.72	2.01-6.90
*HLA-B*39*	10	12.8	3,565	3.7	0.0057	4.40	2.26-8.56
*HLA-DRB1*08*	11	14.1	6,4	6.3	0.041	2.77	1.36-5.61

Abs: Absolute Frequency; Rel: Relative Frequency; OR: Odds Ratio; (1) allele number. Pc (Bonferroni correct P value)

HLA-A -B** haplotypes

Table 3 shows the most frequent two locus haplotypes observed in patients and controls. The haplotype *HLA-A*31-B*39* was the most frequent in the patients group (5.1%) compared with the controls group (1.12%). Despite the observed higher frequency of this haplotype in patients when compared with controls (p = 0.00756), the association was no longer significant when we applied the Bonferroni correction test (p = 1).

HLA-A-B*- DRB1** haplotype

Table 4 shows the most frequent three locus haplotypes observed in patients and controls.

Discussion

Due to the heterogeneity and scarcity of ACTs, prognostic factors have been difficult to establish. The prognostic value of the tumor based on histology has been controversial [5,6]. In our cohort, no patient diagnosed with adenoma or with a tumor with benign histology has died from the disease. The presence of the mutation does not appear to be sufficient to explain tumorigenesis or prognosis of ACT and the role of factors such as pesticides have not been proved. Class I genes (*HLA-A, HLA-B*) code proteins which are present in all nucleated cells that are essential for presentation of nonself peptides for cytotoxic T CD8+ lymphocytes. In contrast, cells which express class II genes (*HLA-DR, HLA-DQ* and *HLA-DP*) present nonself antigens for T CD4+ lymphocytes, modulating the expression of antibodies and the response of T CD8+ lymphocytes [25]. The presentation of peptides derived from natural proteins transformed during the neoplastic process by class I antigens is crucial for the

Table 3: Most frequents HLA-A*-B* haplotypes in patients and Caucasian controls.

HLA-A* -B* haplotypes	Patients (2n= 78)(1)		HLA-A* -B haplotypes	Controls (2 n=101330)(1)	
	Abs	Rel(%)		Abs	Rel(%)
HLA-A*31 -B*39	4	5,1	HLA-A*01 -B*08	3755	3.7
HLA-A*68 -B*40	4	5,1	HLA-A*02-B*44	3637	3.6
HLA-A*02 -B*14	3	3,8	HLA-A*02 -B*51	3508	3.4
HLA-A*03 -B*35	3	3,8	HLA-A*02-B*15	2827	2.8
HLA-A*31 -B*15	3	3,8	HLA-A*03 -B* 07	2825	2.8

Abs: Absolute Frequency; rel: relative frequency; (1) allele number.

Table 4: Most frequent HLA-A* -B* -DRB1* haplotypes in patients and controls.

HLA-A* -B* -DRB1* haplotypes	Patients (2n= 78)(1)		HLA-A* -B* -DRB1* haplotypes	Controls (2n=101330)(1)	
	Abs	Rel(%)		Abs	Rel(%)
HLA-A*01 -B*08 -DRB1*03	2	2,6	HLA-A*01 -B*08 -DRB1* 03	2855	2,8
HLA-A*02 -B*07 -DRB1*15	2	2,6	HLA-A*03 -B*07 -DRB1*15	1491	1,5
HLA-A*02 -B*15 -DRB1*08	2	2,6	HLA-A*29 -B*44 -DRB1*07	1478	1,5
HLA-A*24 -B*14 -DRB1*01	2	2,6	HLA-A*02 -B* 07 -DRB1*15	942	0,9
HLA-A*68 -B*40 -DRB1*04	2	2,6	HLA-A*11 -B*35 -DRB1*01	833	0,8
HLA-A*68 -B*40 -DRB1*13	2	2,6	HLA-A*33 -B*14 -DRB1*01	831	0,8
			HLA-A*03 -B*35 -DRB1*01	800	0,8
			HLA-A*23 -B*44 -DRB1*07	773	0,8
			HLA-A*02 -B*44 -DRB1* 04	770	0,8
			HLA-A*02 -B*44 -DRB1*07	725	0,7

Abs: Absolute Frequency; rel: relative frequency; (1) allele number.

initiation of immune reactions directed towards elimination of the tumor. Subjects with certain allelic variants may have lower efficacy regarding presentation of oncogenic peptides, and consequently, activation of T CD8+ lymphocytes, which favors the escape of the neoplastic cells from the immune surveillance [26].

Class II HLA antigens are expressed in cells of the adrenal cortex (zona reticularis). Their expression coincides with an increase in androgen production during childhood [18]. Reduced expression of class II HLA antigens seems to be linked to a low rate of apoptosis in ACTs when compared with normal adrenals. It has been hypothesized that a possible mechanism of immune escape in adrenocortical carcinomas could be the loss of class II HLA antigens expression and a compromised expression of Fas/Fas-L [21].

As for the *HLA-DRB1* gene, there was a greater frequency of *HLA-DRB1*08* in patients compared with controls, as well as a higher prevalence in stages I and II tumors and adenomas (data not shown). This result should also be interpreted with caution and further analysis including a greater number of patients is required to confirm this finding. Although only a few studies have addressed the association between class II alleles and adrenocortical tumorigenesis, a reduced expression of the *HLA-DRB1* antigens in ACT, especially in carcinomas, has been documented [18,20]. Wolkersdörfer *et al.* identified a greater prevalence of the *HLA-DRB1*01* allelic group in six of eleven carcinomas (54.5%) [21]. In the present study, the frequency of this allelic variant was 12.8% in patients with carcinoma, which is not different from that in the control population (10.4%). However, the *HLA-DRB1*08* allelic group was more frequent among patients than in controls, a finding that extends to patients with tumors stage I and II, but not III and IV. These data suggest that *HLA-DRB1*08* is a marker to be considered in the outcome of patients with ACT, since patients with stages I and II disease have longer survival.

This study sought to investigate the contribution of HLA genes with adrenocortical cancer (susceptibility). Statistically significant associations with variants of *HLA-A*31, HLA-B*39* and *HLA-DRB*08* were observed, which proved to be individually more frequent in patients than with controls. We also observed that the haplotype *HLA-A*31 - HLA-B*39* was more frequent in patients. Ethnic diversity, population stratification and sample size may result in spurious associations. Therefore, these results should be interpreted with caution and confirmed in future studies including a larger number of patients.

Although our data show a higher frequency of certain alleles of the HLA system in children and adolescents with ACT positive for the *TP53* gene germline mutation R337H, further studies, especially those involving tumor tissue are necessary to confirm these findings.

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