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Distribution of Human Leukocyte Antigens in a Population of Black Patients with Human T-Cell Lymphotrophic Virus Type I-associated Adult T-Cell Leukemia/Lymphoma[1]

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Abstract

Human leukocyte antigens (HLAs) play an important role in regulating the immune response to infectious agents and determinants of malignant transformation. We compared the HLA frequencies of 25 black patients with adult T-cell leukemia/lymphoma (ATL) referred to the National Cancer Institute for therapy with a racially similar, asymptomatic control population of human T-cell lymphotrophic virus, type I (HTLV-I)-seropositive individuals ($n = 45$). Serological typing was performed for MHC class I and II antigens. Antigen frequencies were calculated, and corresponding gene frequencies were estimated using the maximum likelihood method. Comparisons between the ATL and control group were made with χ^2 or Fisher's exact test. Three antigens (A36, B18, and DR53) were found to have a higher frequency in the ATL patients than in the controls (uncorrected two-tailed $P < 0.05$). The gene frequencies for these antigens also were statistically significant in the uncorrected analysis. However, only A36 approached statistical significance after correction of the P value for multiple comparisons ($P = 0.08$). The results of this pilot study indicate that black patients with ATL may have increased frequencies of certain class I HLA when compared with a racially similar HTLV-I-positive reference population. This suggests that either these antigens may represent markers for a population at greater risk of developing ATL once infected with HTLV-I or that they were acquired at some point in the process of malignant transformation or progression from the carrier state to onset of ATL. These antigens should be targeted in larger studies to confirm or refute these findings.

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Introduction

HTLV-I[3] is endemic to specific geographic regions of the world, including the southwestern Japanese provinces of Kyushu and Shikoku, the Caribbean, and parts of sub-Saharan Africa and South America (1, 2). This retrovirus is associated with a variety of illnesses but is most clearly linked etiologically with ATL and HTLV-I-associated myelopathy and tropical spastic paraparesis (3). However, only a small percentage (1–5%) of people infected with HTLV-I will develop either of these diseases. Early life infection with HTLV-I by maternal-to-infant transmission is thought to be critical for later development of ATL (4). Other important determinants among HTLV-I carriers for progression to ATL have not been definitively identified.

HLAs have been suspected to play a role in HTLV-I infection and its oncogenic potential. Mann *et al.* (5) demonstrated *in vitro* that additional HLA antigens were expressed on HTLV-I-positive cultured T cells from ATL patients. Several Japanese investigators have identified certain HLA antigens with an increased frequency among ATL patients compared with population controls and family members (6–8). It has been suggested by Usuku *et al.* (9) that specific HLA haplotypes may be markers of genetic susceptibility to either ATL or HTLV-I-associated myelopathy, also known as tropical spastic paraparesis, by virtue of differences in host immune responsiveness to HTLV-I-specific antigens. However, there is a paucity of data to refute or support these observations from other HTLV-I-endemic areas populated by other racial groups.

Different demographic and clinical features of ATL have been shown for patient populations outside of Japan (10). We had the opportunity to evaluate black ATL patients from the United States and the Caribbean. Our goals in the current study were: (*a*) to determine HLA antigen and gene frequencies in a population of black ATL patients; (*b*) to attempt to identify antigens associated with ATL by comparing this group of black ATL patients with a racially similar HTLV-I-positive control group; (*c*) to compare results with published reports from Japanese ATL patients; and (*d*) to assess the relationship between HLA and clinical characteristics of ATL patients.

Materials and Methods

ATL Patients. Thirty-one patients with ATL were referred to the Metabolism Branch of the National Cancer Institute between April 1987 and May 1994 for protocols using interleukin 2 receptor-directed therapies (11, 12). Diagnostic pathological materials were reviewed by the Hematopathology Section of the Laboratory of Pathology of the National Cancer Institute.

[3] The abbreviations used are: HTLV-I, human T-cell lymphotrophic virus, type I; ATL adult T-cell leukemia/lymphoma; HLA, human leukocyte antigen.

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Table 1 Demographic characteristics and HLA phenotypes among black ATL patients

Patient	Age (yr)	Sex	Country of birth	ATL subtype	HLA phenotypes[a] A	B	C	DR	DQ	DRW	Survival (mo)[b]
1	39	Female	Jamaica	Acute	2, 28	18, 53	1, 4	nd	nd	nd	3
2	31	Female	Grenada	Chronic/crisis	2, 28	35, 42	4, 7	2, 3	1, 4	52, –	57+
3	31	Female	United States	Acute	2, 30	51, 49	7, –	nd	nd	nd	12
4	53	Female	Trinidad	Acute	2, 33	45, 53	4, –	9, 12	2, 5	52, 53	23
5	32	Female	Jamaica	Acute	32, 36	35, 53	2, 4	11, 14	5, –	52, –	26
6	38	Female	St. Vincent	Lymphoma	2, 28	39, 70	3, –	7, 15	2, 6	53, –	2
7	65	Male	United States	Acute	26, 34	49, 53	4, –	7, 17	2, –	52, 53	59+
8	22	Female	Haiti	Acute	2, 26	35, 70	2, –	9, 17	2, –	52, 53	14
9	44	Male	Jamaica	Chronic	23, 33	7, 52	4, 7	9, 13	2, 6	52, 53	3+
10	48	Female	Guyana	Acute	nd	nd	nd	4, 6	7, –	52, 53	3
11	53	Male	United States	Acute	23, –	45, 63	–, –	5, 6	1, –	52, –	35
12	40	Male	Haiti	Chronic	1, –	53, –	4, –	2, 6	1, –	52, –	21
13	31	Male	Jamaica	Acute	3, 36	13, 53	4, 6	nd	nd	nd	7
14	42	Male	United States	Lymphoma	28, 33	58, 70	3, 4	11, 18	4, 7	52, –	64+
15	62	Female	Jamaica	Chronic	nd	nd	nd	7, –	2, –	53, –	29
16	53	Male	Trinidad	Lymphoma	2, 29	18, 44	7, –	nd	nd	nd	7
17	24	Female	Guyana	Acute	2, –	7, 55	–, –	nd	nd	nd	8
18	40	Male	Jamaica	Acute	2, 36	5, 57	7, –	1, 15	5, 6	–, –	7+
19	65	Female	Jamaica	Acute	23, 30	7, 57	6, 7	8, 15	6, 7	–, –	15
20	34	Male	Jamaica	Lymphoma	28, 34	35, 44	4, 7	1, 2	1, –	–, –	19
21	52	Female	Jamaica	Chronic/crisis	30, 36	13, 42	2, 7	1, 15	5, 6	–, –	5+
22	40	Female	Jamaica	Chronic	1, –	7, 18	–, –	4, 7	2, 3	53, –	129
23	39	Male	Jamaica	Acute	23, 33	7, 73	7, –	9, 15	2, 6	53, –	7
24	37	Female	Jamaica	Chronic	11, 26	14, 57	7, –	8, –	7, –	52, –	44+
25	63	Male	Jamaica	Chronic	2, 23	49, 60	–, –	4, 17	2, 8	52, 53	46+

[a] –, blank HLA loci; nd, not done.
[b] +, patient still alive.

All patients had a diagnosis of ATL determined by: (*a*) the presence of clonal T-cell leukemia or lymphoma, by morphological and immunophenotypic analysis of peripheral blood lymphocytes, lesions of skin and/or lymph nodes; and (*b*) the presence in the serum of antibodies against HTLV-I. Twenty-eight patients were of African descent originating from the United States or the Caribbean. Twenty-five of these patients had evaluable HLA typing performed, and they constitute the case group. Twenty-one patients were African-Caribbean, and four were African-American.

Controls. Because the majority of ATL patients were African-Caribbean in origin, we identified a suitable comparison group of 45 HTLV-I-seropositive African-Caribbean asymptomatic controls from a population-based survey in Jamaica (13). Previous phylogenetic evaluations of HLA for this population confirmed its origin from African black populations with some evidence of variable racial admixture (14). African-Caribbean and African-American black populations were shown to be closely related.

All study participants were enrolled in studies reviewed by human subjects review committees at the National Cancer Institute and/or University of the West Indies.

Laboratory Procedures. Heparinized blood samples were obtained from the 25 patients seen at the National Cancer Institute. Peripheral blood lymphocytes were separated by Ficoll-Hypaque density gradient centrifugation, and serological typing for MHC class I (HLA-A–HLA-C) and II loci (HLA-DR and HLA-DQ) was performed on the fresh cells in the Department of Transfusion Medicine of the Clinical Center (NIH) by either the Amos modified technique or the fluorescent NIH standard technique (15, 16).

For the 45 control patients, blood samples were collected using heparinized tubes. Peripheral blood lymphocytes were separated by Ficoll-Hypaque density gradient centrifugation, and the cryopreserved cells were stored in a −70°C freezer until used. HLA-A, -B, -C, -DR, and -DQ were serologically typed using T and B lymphocytes by the standard NIH microcytotoxicity test (16) with local qualified HLA trays in the laboratory of S. Sonoda (Department of Virology, Kagoshima University, Kagoshima, Japan). HLA designations were based on the 1991 nomenclature formulated at the 11th International Histocompatibility Workshop (17).

HTLV-I antibody was detected in sera by ELISA (DuPont, Wilmington, DE) and confirmed by Western blot (Biotech, Rockville, MD).

Statistical Analysis. HLA frequencies were calculated, and comparisons were made with χ^2 or Fisher's exact test (18) using the Statistical Analysis Software program (SAS Institute, Inc., Cary, NC). There were no statistical differences between the HLA antigen frequencies among the African-American and Caribbean patients; therefore, HLA antigen data from all 25 black ATL patients were pooled and compared with the asymptomatic control group. Gene frequencies were estimated from the phenotypic data using the maximum-likelihood method (19), which assumed Hardy-Weinberg equilibrium. Omnibus χ^2 tests (19, 20) were calculated to compare the profile of gene frequencies between ATL patients and controls. In addition, individual χ^2 tests were calculated by comparing cases and controls in each of the specific alleles and blanks at each locus. *P* values of individual χ^2 tests were adjusted for multiple comparisons by the Bonferroni correction method (19). All *P* values reported are two-tailed, with significance defined as $P < 0.05$. Linkage disequilibrium between two alleles in different loci was also evaluated (21). Kaplan-Meier curves were used to estimate the median survival for ATL patients (22). When there were discrepancies between the specificity of the antisera used in the typing of the ATL patients and the controls, the

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Table 2 HLA-A–HLA-D antigen frequencies among ATL patients[a]

Antigen	G[b]	%	Antigen	G[b]	%	Antigen	G[b]	%
A locus			*B* locus			*DR* locus		
A1	2	8.7	B5	1	4.3	DR1	3	15
A2	10	43.5	B7	5	21.7	DR2	2	10
A3	1	4.3	B8	0	0	DR3	0	0
A9	0	0	B12	0	0	DR4	3	15
A10	0	0	B13	2	8.7	DR5	1	5
A11	1	4.3	B14	1	4.3	DR6	3	15
A19	0	0	B15	0	0	DR7	4	20
A23	5	21.7	B16	0	0	DR8[c]	2	10
A24	0	0	B17	0	0	DR9	4	20
A25	0	0	B18[c]	3	13	DR10	0	0
A26	3	13	B21	0	0	DR11	2	10
A28	5	21.7	B22	0	0	DR12	1	5
A29	1	4.3	B27	0	0	DR13	1	5
A30	3	13	B35	4	17.4	DR14	1	5
A31	0	0	B37	0	0	DR15	5	25
A32	1	4.3	B38	0	0	DR16	1	5
A33	4	17.4	B39	1	4.3	DR17	3	15
A34	2	8.7	B40	0	0	DR18	2	10
A36[c]	4	17.4	B41	0	0			
A43	0	0	B42	2	8.7			
A66	0	0	B44	2	8.7	*DQ* locus		
A68	0	0	B45	2	8.7	DQ1	3	15
A69	0	0	B46	0	0	DQ2	9	45
A74	0	0	B47	0	0	DQ3	1	5
			B48	0	0	DQ4	2	10
			B49	3	13	DQ5	5	25
			B50	0	0	DQ6	6	30
C locus			B51	1	4.3	DQ7	4	20
Cw1	1	4.3	B52	1	4.3	DQ8	1	5
Cw2	3	13	B53	6	26.1	DQ9	0	0
Cw3	2	8.7	B54	0	0			
Cw4	10	43.5	B55	1	4.3			
Cw5	0	0	B56	0	0			
Cw6	2	8.7	B57	3	13	*DRW* locus		
Cw7	10	43.5	B58	1	4.3	DRW51	0	0
Cw8	0	0	B59	0	0	DRW52	12	60
Cw9	0	0	B60	1	4.3	DRW53[c]	10	50
Cw10	0	0	B61	0	0			
			B62	0	0			
			B63	1	4.3			
			B64	0	0			
			B65	0	0			
			B67	0	0			
			B70	3	13			

[a] Twenty-three patients had data for A–C antigens, and 20 had data for DR and DQ.
[b] G, antigen frequency.
[c] Antigen frequency in ATL population significantly different from HTLV-I positive controls (*i.e.*, uncorrected $P \leq 0.05$); see text.

splits were combined, and we reported the comparisons of the parent antigens.

Results

Demographic and clinical features of the 25 ATL patients are presented in Table 1. All patients were of African descent. Twenty-one were born in the Caribbean, and 4 were born in the United States. They ranged in age from 22 to 65 (median, 40) years. Fifty-six percent of ATL cases were female. The patients were categorized into three of the four subtypes of ATL classified by the Japanese Lymphoma Study Group (23). Thirteen patients (52%) had acute ATL, four (16%) had lymphoma type, and eight (32%) had chronic or crisis ATL. The median survival of these patients from the date of diagnosis was 21 months.

Class I antigen data were available on 23 patients, and class II data were available on 20 ATL patients. Each patient's HLA phenotype is shown in Table 1. Evaluation of the distribution of HLA among the ATL patients revealed no association between any one antigen and any of the following patient or disease parameters: (*a*) age of onset of ATL (*i.e.*, <40 or ≥ 40 years); (*b*) ATL subtype (acute *versus* chronic *versus* lymphoma or acute or lymphoma *versus* chronic); (*c*) response to therapy (complete or partial remission *versus* no response); (*d*) survival (*i.e.*, <12 or ≥ 12 months); (*e*) presence or absence of hypercalcemia; and (*e*) occurrence of opportunistic infections.

The distribution of antigen frequencies among ATL patients is presented in Table 2. Comparing the ATL patients with the HTLV-I-positive control group, three antigen frequencies (A36,

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Table 3 Comparison of estimated individual gene frequencies with significant difference or blank alleles between ATL cases and HTLV-I positive controls

Locus	ATL patients[a]			HTLV-I$^+$ controls[a]			Individual test	Omnibus test
	G	*n*	$f \pm$ SE	G	*n*	$f \pm$ SE	(*P*)	[χ^2 with *df* (*P*)]
A (15 alleles)		(*n* = 23)			(*n* = 45)			23.43 with 15 (0.075)
A36	4	0	8.7 ± 4.2	0	0		0.005[b]	
B (23 alleles)								28.43 with 23 (0.20)
B18	3	0	6.5 ± 3.6	0	0		0.016	
Blank		0	0 ± 2.3		1	11.5 ± 3.9	0.044	
DQ (6 alleles)								13.23 with 6 (0.04)
Blank		0	13.4 ± 7.4		0	0 ± 3.3	0.04	

[a] G, antigen frequency; *n*, number of individuals reacting to a single antigen only; *f*, estimated gene frequency in percent from phenotypic data using maximum-likelihood method.
[b] $P = 0.08$ with Bonferroni adjustment for multiple comparisons.

B18, and DR53) were significantly more frequent in the ATL group (uncorrected two-tailed $P < 0.05$). A36, B18, and DR53 were present in 17, 13, and 50%, respectively, in the ATL patients compared with 0, 0, and 22%, respectively, in the control population. To assure that these differences were not due to racial heterogeneity among our two comparison groups, we did a subset analysis of only ATL patients born in Jamaica. The significant HLA antigen differences remained with increased frequencies for A36 ($P = 0.011$) and B18 ($P = 0.035$). However, when the *P* values were corrected for the number of antigens tested, none was significant. Sixteen (64%) of the ATL patients had one or more of these antigens with increased frequency. The antigen DR8 was found in a higher frequency in the control group (33%) than in the ATL group (10%; uncorrected $P = 0.05$).

Estimation of HLA gene frequencies for ATL patients and comparison with those of HTLV-I-positive controls (Table 3) confirmed our results based on antigen frequencies. Gene frequencies for the antigens A36 and B18 were increased among ATL patients. We did not estimate gene frequency for the supertypic *DR53* allele but determined frequencies for the more specific alleles it represents, *DR4, DR7,* and *DR9*. Among ATL patients, the increased gene frequency for A36 approached significance ($P = 0.08$) after adjusting for multiple comparisons. The Omnibus test approached significance for the *A* locus, reflecting the profile difference in frequencies observed between ATL patients and the controls. This test was significant for the *DQ* locus, for which we identified significant blank alleles, suggesting that there were some unspecified differences we could not determine with available typing methods. We found no survival or clinical differences between the ATL patients with *A36* and the remainder of the ATL patients. There was no evidence from the data that the two class I alleles, *A36* and *B18*, were in linkage disequilibrium.

Discussion

ATL is a malignancy of mature T lymphocytes occurring predominantly in patients infected with HTLV-I. The geographic clustering of ATL in southern Japan, the Caribbean islands, and parts of the United States coincides with areas endemic for HTLV-I (2, 23). The great majority of ATL patients have a clonal pattern of HTLV-I provirus integrated in the DNA of their leukemic cells. The clinical manifestations of this disease are quite variable and include lymphadenopathy, leukemia, hepatosplenomegaly, skin rash, lytic bone lesions, fever, opportunistic infections, and hypercalcemia (23, 24). The leukemic cells are variably sized lymphocytes with basophilic cytoplasm and indented or deeply cleft nuclei with clumped chromatin. Four clinicopathological subtypes have been defined that encompass the diverse clinical presentations: smoldering, chronic, lymphoma, and the acute type. Both the smoldering and chronic subtypes can enter a crisis phase in which they behave like the aggressive, rapidly progressive acute subtype (23).

Our data provide evidence that certain HLA alleles may be associated with ATL in a black population. In particular, antigen frequencies of class I HLA-A36 and -B18 and class II HLA-DR53 were elevated. These HLAs were increased in frequency when compared with those in HTLV-I-positive controls, suggesting either that some or all of them represent markers for a population at greater risk of developing ATL once infected with HTLV-I or that these antigens were acquired at some point in the process of malignant transformation or progression from the carrier state to onset of ATL. The estimated gene frequency for A36 was the only one that approached significance ($P = 0.08$) after correction for multiple comparisons. To address the issue of comparability of the control and patient populations, we analyzed our data looking at only the Jamaican ATL patients ($n = 21$) and found that the same significant antigens were identified in the uncorrected test.

The T- and B-Cell Malignancy Study Group in Japan has also identified an association between ATL and certain class I and II HLA antigens (7). When the comparison was made against a control group of subjects from Kyushu and South Shikoku, Japan, ATL-endemic areas from which 91% of their ATL patients originated, higher frequencies were observed for A26 and B39, and lower frequencies were observed for A24, B46, B52, B61, and DR7. These differences were statistically significant (uncorrected $P < 0.05$) but were not significant after correction for the number of antigens tested. There was no concurrence between their findings and those in the current study. Unfortunately, two of the antigens with significantly different frequencies in the present study (A36 and B18) apparently were not available in the antibody or antisera panels used in the Japanese study. Therefore, although, ethnicity could in part account for differences we observed, HLA typing technology was also a factor. However, subsequent analyses of the distribution of HLA in the general Japanese population show a low frequency of A36, and further studies of Japanese ATL patients likewise show no increased frequency of this antigen (25).

Independently, investigators have shown that ATL patients from Japan and those of African descent from the Caribbean have a low lymphocyte-proliferative response when measured spontaneously or in reaction to exogenously administered HTLV-I virions (9, 26). These functionally deficient lymphocytes may in fact result from the altered expression of class I HLA among ATL patients, with resultant immune suppression and heightened susceptibility to opportunistic infections. Uno *et al.* (8) have shown that the enhanced expression

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of class I HLA on peripheral lymphocytes of ATL patients has an inverse relationship to natural killer cell activity. They offer that such a mechanism may contribute to the ability of HTLV-I-infected malignant cells to escape from immune surveillance. Alternatively, others have suggested that the additional antigens resulting from the malignant process and virus infection may result in molecular mimicry of a host protein, also causing evasion of immune surveillance. Certain HLAs have been shown to have structural homology with HTLV-I: the *HLA-B* locus gene, with the envelope gene region of HTLV-I (27), and *HLA-DR53*, with several amino acid sequences similar to HTLV-I (28).

An a priori hypothesis was that host factors such as HLA might also affect the clinical features of a polymorphic disease such as ATL. In this study, no significant relationships between HLA and clinical characteristics of ATL patients were identified. However, real differences could have been missed due to the small sample size.

The generalizability of our findings to other ATL patients of African descent may be limited by the fact that our ATL population consisted of referral patients to a tertiary treatment center and had a greater percentage of the chronic ATL subtype (32 *versus* 3%) and longer survival (21 *versus* 5 months) than ATL patients from incident case series (29). Due to the small numbers of patients in the ATL group, there is insufficient power in this study to suggest that the findings are biologically significant. Nonetheless, these data provide previously unavailable information on associations of HLA with ATL and identify antigens (A36) and gene loci in this population that will be used to narrow the focus for larger studies. Further study with state-of-the-art HLA-typing technology of HTLV-I-infected cohorts and ATL patients and family members in endemic populations will help determine the significance of these findings.

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