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HLA and adult T cell leukaemia: HLA-linked genes controlling susceptibility to human T cell leukaemia virus type I

H. UNO, K. KAWANO, H. MATSUOKA & K. TSUDA *Department of Internal Medicine, Miyazaki Medical College, Miyazaki, Japan*

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SUMMARY

HLA antigens of patients with adult T cell leukaemia (ATL), T cell malignant lymphoma (T-ML), and healthy carriers of human T cell leukaemia virus type I (HTLV-I) were investigated in an endemic area of ATL in Japan. Sixty-two patients with ATL were subdivided into three groups based on their clinical features, including two unclassified patients; 36 acute type, 10 chronic type, and 14 smouldering type. The frequency of HLA-Bw62 was significantly increased in acute ATL, compared with control ($Pc < 0{\cdot}0002$). Increased frequency of HLA-DQw3 was observed in patients with ATL, T-ML positive for the antibody to HTLV-I (Ab-positive), and Ab-positive healthy carriers, compared with control ($Pc < 0{\cdot}001$, $Pc < 0{\cdot}01$ and $Pc < 0{\cdot}0001$, respectively). In addition, class I HLA antigens of peripheral lymphocytes of patients with ATL, especially acute ATL, showed altered expression, either extra antigens or decreased antigens. Analysis of 21 families, where more than two members were Ab-positive, showed that there was no linkage between the HLA complex and susceptibility to the virus infection. In 44 couples, in which either or both spouses were Ab-positive, no association with class I HLA antigens was found in either Ab-positive spouses or Ab-negative spouses. These findings might indicate that one class II HLA-linked gene controlled susceptibility to HTLV-I infection, and another class I HLA-linked gene exerted an influence on the clinical course of ATL.

Keywords adult T cell leukaemia (ATL) T cell malignant lymphoma HLA human T cell leukaemia virus type I (HTLV-I)

INTRODUCTION

HTLV-I is the first human virus of type C retrovirus constantly identified in association with specific type of human leukaemia/lymphoma. The virus was isolated from a cell line established from a patient with cutaneous T cell lymphoma (Poiesz *et al.*, 1980; 1981), and subsequently from patients with ATL in Japan (Yoshida, Miyoshi & Hinuma, 1982). Adult T cell leukaemia is a unique malignancy of T cell origin affecting adults, in whom the virus is endemic in certain areas of the world, including the southwestern part of Japan, the Caribbean, the southwestern United States (Uchiyama *et al.*, 1977; Broder *et al.*, 1984).

It is well documented that the major histocompatibility complex (MHC) linked genes control immune responses designed to provide the host with resistance against a broad spectrum of infections. It is also evident that, in mice, host genetic background, H-2 and non-H-2 genes, determine to a large extent the capacity to mount an immune response to tumour antigens, and that genes coding for the H-2 complex play an important role in the regulation of tumour immunity. Ever since the demonstration that the susceptibility of mice to the leukaemia induced by Gross virus or Friend virus was controlled by genes linked to the H-2 complex (Lilly, 1966; 1968), in man a considerable effort has been made to demonstrate a similar strong association between HLA antigens and susceptibility to common forms of haematopoietic malignancies. However, available data have been variable and conflicting (Tiwari & Terasaki, 1985).

We investigated the role of the HLA complex in the pathogenesis of ATL in Kyushu island, Japan, an endemic area of HTLV-I. The association of ATL with HLA was studied not only in the population but also in families. Ab-positive subjects made up three groups, ATL, Ab-positive T-ML, and healthy carriers. Here we report that class I HLA antigens may have influenced the clinical course of the disease, while class II HLA antigens were associated with HTLV-I infection.

Correspondence: Dr Hisamitsu Uno, Department of Internal Medicine, Miyazaki Medical College, Kiyotake, Miyazaki 889-16, Japan.

MATERIALS AND METHODS

Human subjects and patients

All patients and human subjects were residents of Miyazaki district in the southern part of Kyushu island, Japan, where

about 10% of the adult residents are positive for the antibody against HTLV-I (Tajima & Kuroishi, 1985).

Patients with ATL. Sixty-two patients with ATL were subdivided into three groups based on their clinical features and courses according to the criteria reported by Takatsuki and his colleagues (Kawano *et al.*, 1985); 36 patients with acute type of ATL who showed severe clinical symptoms and progressed rapidly, 10 patients with chronic type whose clinical pictures resembled a form of T cell chronic lymphocytic leukaemia, and 14 patients with smouldering type characterized by a long duration of the presence of a few ATL cells in the peripheral blood without any specific symptoms. Two patients were not classified because of their concurrent melanoma and acute myelofibrosis.

Patients with T-ML. Among 36 patients with T-ML, 20 patients (55·6%) were Ab-positive. Ab-positive patients were tentatively treated as T-ML, since T-ML could not be distinguished from the lymphoma type of ATL by the presence of the antibody in such an endemic area of the virus.

Healthy carriers. The healthy carriers were 40 unrelated adults who were apparently healthy except for being Ab-positive. Previously, Ab-positive persons had been demonstrated to be carriers of HTLV-I by detection of the virus-positive cells in their peripheral blood lymphocytes (Gotoh, Sugamura & Hinuma, 1982).

Family study. The twenty-one families were composed of 189 members, where 87 (46·0%) were Ab-positive, and 25 (13·2%) were affected with ATL. Twenty-two pairs of siblings positive for the antibody were selected from these families to compare the HLA-haplotypes shared between each sib-pair. Also chosen were 44 couples, of whom 23 had both partners Ab-positive, and 21 had only one Ab-positive.

Control population. One hundred and eighteen healthy residents of Kyushu island were used for the control group of HLA antigen frequencies. They were not examined for the presence of the antibody against HTLV-I.

Detection of anti-HTLV-I antibody

The antibody was detected by an indirect immunofluorescence test (Hinuma *et al.*, 1981). Briefly, a T cell line (MT-2) established by co-cultivation with T cells from a patient with ATL (Miyoshi *et al.*, 1981) was smeared on a glass slide, dried and fixed. Cell smears were treated with appropriately diluted human serum, and washed, then treated with fluorescein-conjugated rabbit anti-human IgG. The smear was washed and examined with a microscope.

HLA typing

Class I HLA antigens were determined with the NIH standard microcytotoxicity method (Manual of tissue typing technique, 1976). Class II HLA typing was performed on B cells separated by the thrombin-nylon wool column technique (Danilovs, Ayoub & Terasaki, 1980) using trays purchased from Dr Terasaki in Los Angeles.

Statistical method

Analysis was made with reference to the HLA phenotype frequency on the patients and compared with that of the control according to the standard chi-square method with Yates' correction. *P* values were corrected (*Pc*) by multiplying them by the total number of HLA antigens tested. Linkage between the HLA complex and genes controlling susceptibility to HTLV-I infection were estimated by the 'affected sib-pairs' method (Cudworth & Woodrow, 1975). Ab-positive sib-pairs were randomly selected from each family and each generation. The number of shared HLA-haplotypes between each sib-pair was counted; HLA-identical, haplo-identical and different (2, 1 and 0 shared parental haplotypes, respectively). The number of sib-pairs of each sharing haplotypes was summed up, then compared with the expected Mendelian segregation of 25%, 50% and 25%.

RESULTS

Expression of HLA antigens on ATL cells

Some patients with ATL, especially acute type, showed altered expression of HLA antigens on peripheral lymphocytes (Table 1). The altered expression appeared to be restricted to class I antigens and related to the proportion of leukaemic cells in the peripheral blood. In Case 1 and Case 2, HLA antigens were ascertained not only by typing their family members but also by comparing antigens in clinically separate phases of the disease in each patient. Case 3 expressed class I antigens only in the B cell rich fraction, while decreased or absent class I antigens were observed in whole lymphocytes or T cells. In Case 4 decreased HLA-B antigen appeared after culturing the cells. The expression of class II antigens was weak, on the whole, when it had been difficult to obtain the B cell rich fraction due to the increased proportion of leukaemic cells in the peripheral lymphocytes.

Including the above cases, equivocal HLA antigens were confirmed by family study or re-examination.

Association of HLA with ATL in unrelated patients

Patients with acute ATL revealed a highly significant increase of HLA-Bw62 ($Pc < 0{\cdot}0002$), while unclassified patients with ATL showed a marginally significant association with the antigen ($Pc < 0{\cdot}05$) (Table 2). The increased frequencies of HLA-A26 and HLA-Cw3 which were in linkage disequilibrium with HLA-Bw62 in the Japanese population were noted. No significant association with class I antigens was found in patients with smouldering or chronic ATL or healthy carriers.

For class II antigens, the frequency of HLA-DQw3 was significantly increased in patients with ATL ($Pc < 0{\cdot}001$). Healthy carriers also showed a significantly increased frequency of the antigen ($Pc < 0{\cdot}0001$) (Table 3).

Association of HLA with T-ML

No association with class I antigens was observed in either Ab-positive T-ML or Ab-negative T-ML. Ab-positive patients with T-ML showed a significantly increased frequency of HLA-DQw3 ($Pc < 0{\cdot}01$) (Table 3). Ab-negative patients with T-ML did not associate with HLA-DQw3, and showed no association with class II antigens.

Analysis of families affected with HTLV-I

In families affected with HTLV-I (Fig. 1), the proportion of sharing of parental HLA haplotypes between Ab-positive sib-pairs was determined. Out of 22 sib-pairs, 5, 11 and 6 shared 2, 1 and 0 HLA haplotypes, respectively. This proportion did not differ from that of expected Mendelian segregation (5·5, 11 and 5·5, respectively), indicating that there was no strong linkage

Table 1. Altered expression of HLA antigens on peripheral lymphocytes

Patients with ATL	Atypical lymph.* (%)	Cells typed†	HLA antigens A	B	C	DR‡	DQ‡
1	20	whole	2, 26	w61, w62	w1, w3	w8, w52	w3
	96	whole	2, 26	w61, w62	w1, w3		
			w33	7, 12, 17			
2	4	whole	w24	w54, w62	w1, w3	4, w53	w3
	12	whole	w24	(w54, w62)	(w3)		
3	30	whole	(2)	(w44, w62)	ND		
	30	T	ND	ND	ND		
	30	B	2	w44, w62	w1, w3	w8, w52	w3
4	86	whole	2	ND	w3	4, w6, w52	w3
		cell line§	2	w35	w3		

Parenthesis indicates weak reaction on HLA typing.
ND, not detected.
* Percentage of atypical leukaemic cells in the peripheral blood.
† HLA antigens were examined on whole lymphocytes, T cells, or B cells.
‡ Class II antigens were typed on B cell enriched fraction and could not be typed on T cell rich fraction.
§ HTLV-I bearing T cell line derived from the same patient.

Table 2. Association between ATL and class I HLA antigen

Patients		A26	Bw62	Cw3
ATL†	($n=62$)	19 (30·6%)	20 (32·3%)*	42 (67·7%)*
Acute type	($n=36$)	14 (38·9%)	18 (50·0%)**	27 (75·0%)*
Chronic type	($n=10$)	1 (10·0%)	0 (0%)	6 (60·0%)
Smouldering type	($n=14$)	4 (28·6%)	2 (14·3%)	8 (57·1%)
Control	($n=118$)	20 (16·9%)	14 (11·9%)	53 (44·9%)

* $Pc < 0{\cdot}05$, compared with control.
** $Pc < 0{\cdot}0002$, compared with control.
† Two patients with unclassified type of ATL were included.

Table 3. Association between HTLV-I infection and class II HLA antigen

Patients		HLA-DQw3
ATL†	($n=60$)	45 (75·0%)**
T-ML‡		
Ab-positive	($n=17$)	15 (88·2%)*
Ab-negative	($n=15$)	10 (66·7%)
Healthy carriers	($n=40$)	34 (85·0%)***
Control	($n=118$)	52 (44·1%)

* $Pc < 0{\cdot}01$, compared with control.
** $Pc < 0{\cdot}001$, compared with control.
*** $Pc < 0{\cdot}0001$, compared with control.
† Frequencies of HLA-DQw3 in three subdivided groups, acute, smouldering and chronic type, were not significantly different from each other.
‡ Four patients with T-ML were not typed for class II antigens.

between the HLA complex and the genes controlling susceptibility to the virus infection.

In couples, with either or both spouses Ab-positive, the frequency of HLA-Bw62 in Ab-positive spouses was increased but not significantly. This increase was explained by the inclusion of spouses who were relatives of families with acute type of ATL. Ab-negative spouses showed no association with class I antigens.

These family members and couples were not typed for class II HLA antigens.

DISCUSSION

Since ATL is the only human leukaemia whose aetiological agent, HTLV-I, was isolated, the association between the disease and HLA antigens is expected, as demonstrated in murine leukaemias induced by viruses. Previously the lack of association between HLA antigens and ATL in Japan was reported (Tanaka, Sato & Okochi, 1984). However the report examined neither the association in clinically subdivided groups of patients with ATL nor DQ antigens.

In this study, we demonstrated the strong association of the acute type of ATL with HLA-Bw62, or HLA-A26-Bw62-Cw3 haplotype. Class II antigens in linkage disequilibrium with HLA-Bw62 in the Japanese population did not associate with acute type of ATL. The association of HLA-Bw62, therefore, was deemed to be primary. In mice, study of Gross virus-induced incidence of leukaemia revealed that a gene linked to the H-2 complex, designated Rgv-1 (resistence to Gross virus), was involved in the control of leukaemogenesis susceptibility (Lilly & Pincus, 1973). The Rgv-1 was mapped to the K region of the H-2 complex, and appeared to strongly influence leukaemogenesis by several leukaemia viruses. Another class I H-2 gene designated Rfv I (recovery from Friend virus) was shown to be involved in recovery from Friend virus disease (Chesebro, Wehrly & Stimpfling, 1974). The association of HLA-Bw62 with

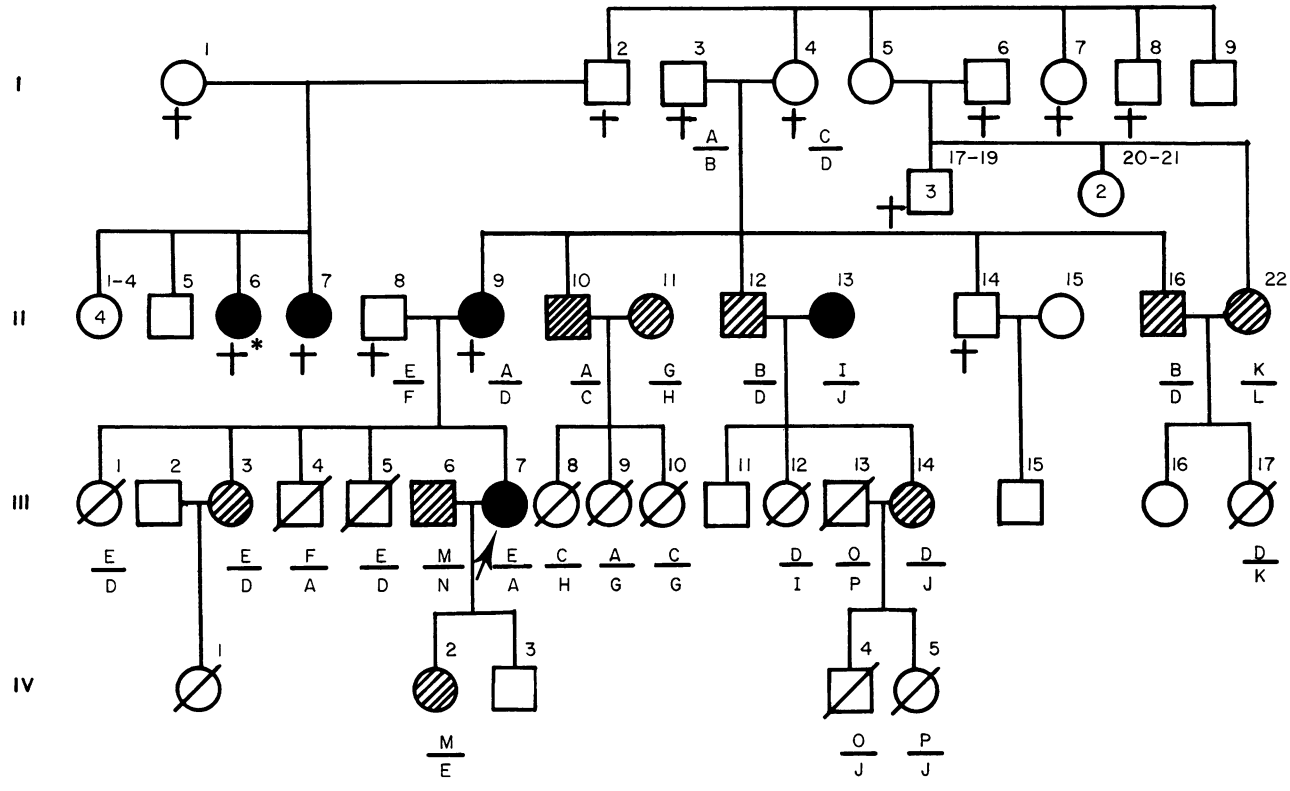

Fig. 1. A family affected with HTLV-I infection. (■, ●) ATL; (▨, ⊘) positive for anti-HTLV-I antibody; (⊠, ∅) negative for anti-HTLV-I antibody; (□, ○) not tested. *, A2, Bw61, Cw−; A, A24, Bw61, Cw3; B, A24, Bw60, Cw3; C, A24, Bw22, Cw1; D, A2, Bw61, Cw−; E, A2, B−, Cw−; F, A26, B−, Cw−; G, A2, Bw61, Cw−; H, A11, Bw62, Cw4; L, A2, Bw22, Cw1; J, A26, Bw60, Cw3; K, A24, Bw52, Cw−; L, A24, Bw54, Cw1; M, A24, Bw52, Cw−; N, A2, Bw62, Cw3; O, A24, Bw52, Cw−; P, A26, Bw61, Cw3.

the acute type of ATL was compatible with the data of mice which implicated the influence of class I MHC genes on the clinical course of virus-induced leukaemias.

Class I MHC molecules can function as recognition molecules in T cell-mediated cytotoxicity through non-MHC antigens, for example, virially infected cells (Zingernagel & Doherty, 1974). Subsequent studies revealed that not all H-2K and D antigens were recognized equally by cytotoxic T lymphocytes (CTL) specific for different virus antigens (Doherty, Blander & Zinkernagel, 1976; Zinkernagel & Doherty, 1979). It has been shown in man that HLA antigen structural polymorphism is associated with variability in immune responsiveness to viral antigens, and that CTL play an essential role in immunity to virus infection (McMichael, 1978). Recently, HLA-restricted associative recognition of target antigens expressed on the leukaemic cells was suggested by the fact that the cytotoxic activity by CTL required target tumour cells, not only infected with HTLV-I, but also sharing HLA antigens in common with CTL (Mitsuya *et al.*, 1983; Kannagi *et al.*, 1983; 1984).

An increased frequency of HLA-DQw3 was observed in patients with ATL, Ab-positive T-ML, and healthy carriers. This association might be interpreted that HLA-DQw3 had a relationship with HTLV-I infection. The observations that the genetic loci responsible for the modulation of immune response mapped to the class II region within MHC have led to the conclusion that the I region in mice and the D region in man encode at least some of the immune-response (*Ir*) genes or immune suppression(*Is*) genes. There is now evidence in man that these genes function to regulate immune responsiveness and map to the class II region, in which several subregions have been identified, including HLA-DR and HLA-DQ (Sasazuki *et al.*, 1983; Nishimura & Sasazuki, 1983). The possibility of involvement of *Ir*-genes or *Is*-genes in murine leukaemia induced by viruses has been reported. For example, the ability to generate a cell-mediated response to the tumour antigen of an AKR spontaneous thymoma was linked to the I region of the H-2 complex (Meruelo, Deak & McDevitt, 1977) and the resistance to viremia and leukaemia in Moloney leukaemia virus-induced mice was controlled by two genes mapped in the I region (Debré *et al.*, 1980). In the analogy of murine leukaemias, association between HLA-DQw3 and HTLV-I infection might be attributable to the linkage disequilibrium between HLA-DQw3 and *Ir*- or *Is*-genes controlling susceptibility to HTLV-I infection.

So far, no definite association with HLA-Bw62 or HLA-DQw3 has been reported in any other diseases of haematopoietic malignancies.

Familial aggregation of HTLV-I infection indicated the possibility of vertical and horizontal transmission of the virus (Hino *et al.*, 1985; Nakano *et al.*, 1984). The present analysis of HLA in families affected with HTLV-I failed to demonstrate linkage between the HLA complex and genes controlling susceptibility to HTLV-I infection. In addition, HLA class I antigens exerted no influence on the transmission of the virus between spouses.

Altered expression of class I HLA antigens has been reported in HTLV-I-positive, cultured T cells, on which addi-

tional class I HLA antigens were observed (Mann *et al.*, 1983). We observed an altered expression of class I antigens on peripheral lymphocytes of patients with ATL, without culturing the cells, where either additional antigens or decreased antigen expression was noted. Since the altered expression appeared to be related to the proportion of the ATL cells in peripheral blood and preferentially observed in T cells, lymphocytes showing altered expression were conceivably leukaemic T cells. The individual leukaemic cells should be examined in their HLA expression by a staining method using monoclonal antibodies, which is now under study. The biological significance of altered expression of MHC has been reported in murine haematopoietic malignancies, as concerned T cell cytotoxic activity and natural killer (NK) activity. Studies using AKR leukaemia cell lines revealed that the amount of H-2K antigen expression was related to the resistance to T cell lysis *in vitro* and to the growth in AKR mice (Hui, Grosveld & Festenstein, 1984). These findings and those of others (Eisenbach *et al.*, 1985; Wallich *et al.*, 1985) suggested that the relative absence of H-2K specificity provided tumours with a selective advantage *in vivo*. MHC expression also involved the efficiency of NK cell lysis. Using T lymphoma cell lines, an inverse indirect relation between factors controlling H-2 expression and NK sensitivity was demonstrated (Ljunggren & Kärre, 1985). So far, the biological significance of NK activity in ATL has not been verified. Our preliminary study on NK activity in ATL indicated that peripheral lymphocytes from patients with ATL, healthy carriers, and healthy persons did not show NK activity against HTLV-I bearing T-cell lines which showed increased amount of class I antigens (data not shown). The study should be compared with the NK activity using target cells with impaired expression of class I antigens, which is now under investigation.

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