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HLA Types and Immune Reaction

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RESUMEN

Los antígenos leucocitarios (HLA) están vinculados por genes altamente polimórficos, con el complejo mayor de histocompatibilidad localizando en el brazo corto del cromosoma 6. Dos contingentes distintos del gen del HLA se heredan de los padres en forma mendeliana y que se expresan codominantemente para producir dos sets de antígenos de HLA: A, B-C, DR y DQ, así como los fenotipos complementarios. El tipo de HLA y los haplotipos son útiles para la identificación individual y/o grupos genéticos en los seres humanos. Otra importante función de la diversidad del HLA es el reconocimiento inmunológico de los antígenos propios o ajenos. Los autoantígenos originados en células autólogas y los antígenos de origen exógenos son procesados en proteosomas para degradarlos a fragmentos peptídicos los que encajan especialmente de acuerdo a la particular configuración de las moléculas de HLA.

Los complejos HLA peptídicos son reconocidos por un repertorio de linfocitos T o B que expresan una respuesta inmune específica.

Las células T y B que reconocen antígenos autólogos son naturalmente destruidas, mientras que aquellas células expuestas a los antígenos exógenos sobreviven largamente y producen una respuesta amnéstica contra los mismos antígenos. Algunas células T pueden sobrevivir más de 30 años. Así, la memoria inmune a las células T o B es útil para la búsqueda de antiguas epidemias de enfermedades infecciosas sobrepasada por los distintos grupos étnicos. En ese sentido el estudio de HLA entre los andinos, así como los antecedentes que se refieren a su susceptibilidad por las infecciones por HTLV 1 son semejantes a las que expresan los japoneses del sur.

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INTRODUCTION

Primitive life emerged 3 billion years ago on earth with continuous evolution of new species of genes since then. Cells and viruses co-evolved and established host-parasite relationships. The cells can be viewed as autonomous machines which reproduce macromolecules of nucleic acids, proteins and membrane structures incorporating small amino acid and lipid molecules as well as nucleotide precursors which are considered to have been ubiquitously available in the ancient sea waters. Biological interactions between primordial cells and parasites resulted in birth and death of new lives to make the variety of living organisms on the earth.

Horno sapiens evolved around 120,000 years ago developing more than 50,000 genes which are compiled into two strands of DNA, 3.7 meters of length. The DNA strands link the nucleotide sequences of exons and introns of genes to make up the individual haplotype of human chromosomes in the nucleus and mitochondria. The individual haplotype includes many diversified sequences of DNA which identify family or ethnic group and lineages. High polymorphism of human genes is evident in leukocyte antigen (HLA) genes which are composed of more than 500 distinct alleles (genes). Individual HLA haplotypes from maternal and paternal lineages constitute two sets of HLA-A, C, B, DR and DQ alleles which are co-dominantly expressed in the children's cells. Thus, HLA alleles and haplotypes are useful genetic markers to investigate familial and ethnic backgrounds of human populations. HLA molecules encoded by HLA-A, B, C, DR and DQ alleles provide specific protein configurations which recognize the relevant binding motifs of self or non-self peptides to induce the immune response. Thus, HLA alleles define the individual repertoire of the immune system by specific combinations of HLA/peptide complexes which are made of exogenous or endogenous antigen peptides (epitopes). Biological interactions in ethnic groups of human populations result in long-lived T-cells with a memory of immunological impacts of

exogenous antigens of parasites and other disease vectors.
This paper introduces recent advances in molecular genetics of HLA and peptide binding motifs with an ethnoepidemiological comparison of Andeans and Japanese in their immunogenetic background with regard to human T-cell leukemia viruses.

Genetic polymorphism of the HLA system and the immune response

The ancient environment of the earth was free of living organisms when inorganic and organic substances were first interacting to make chemical complexes. A primordal nucleic acid is thought to have been generated 3 billion years ago and evolved into a primitive RNA, then a catalytic RNA, and a polypeptide of enzymatic activity with reverse transcriptase to make DNA which replicated and enlongated to provide more sophisticated nucleic acids and proteins for making up cell components and concomitantly, RNA and DNA viruses (1). Thus, all species of cellular organisms including prokaryotes, eukaryotes, plants and animals are inherently subjected to viral infections which cause diseases due to cytopathic effects and tissue damage.

Both cellular and viral nucleic acids are changeable by mutations of nucleotide sequences during replication. Neutral mutations (synonymous nucleotide substituions) and functional mutations (non-synonymous nucleotide substitutions to code different amino acids) accumulating in nucleic acid sequences produce genetic diversity to evolve new species of cellular and viral genes.
Human beings have diversified into thousands of

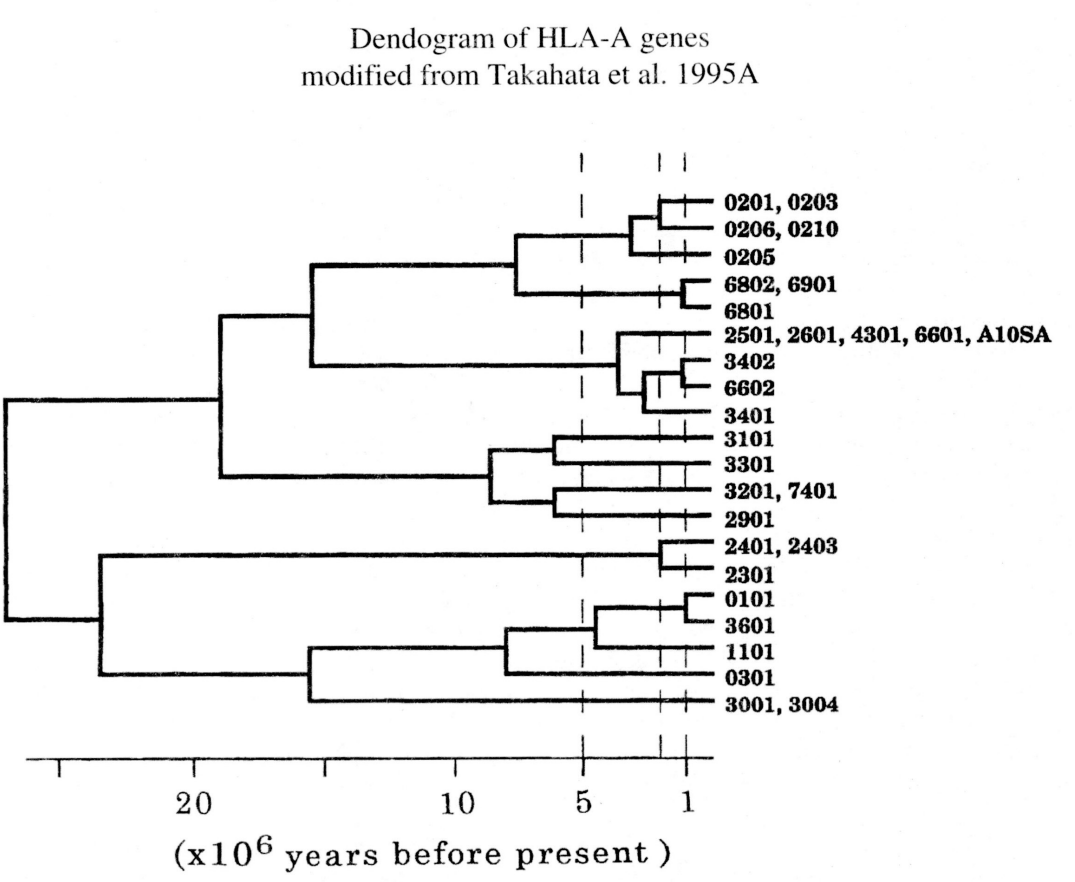

Fig. 1. Dendrogram of HLA-A. Genes HLA-A genes (alleles) have diversified into 30 alleles from two major branches of a genetic tree linked to common ancestral genes from the histocompatiblity complexes of the chimpanzee, gorilla and other primates.

Cellular Interaction in Antigen Processing and Presentation

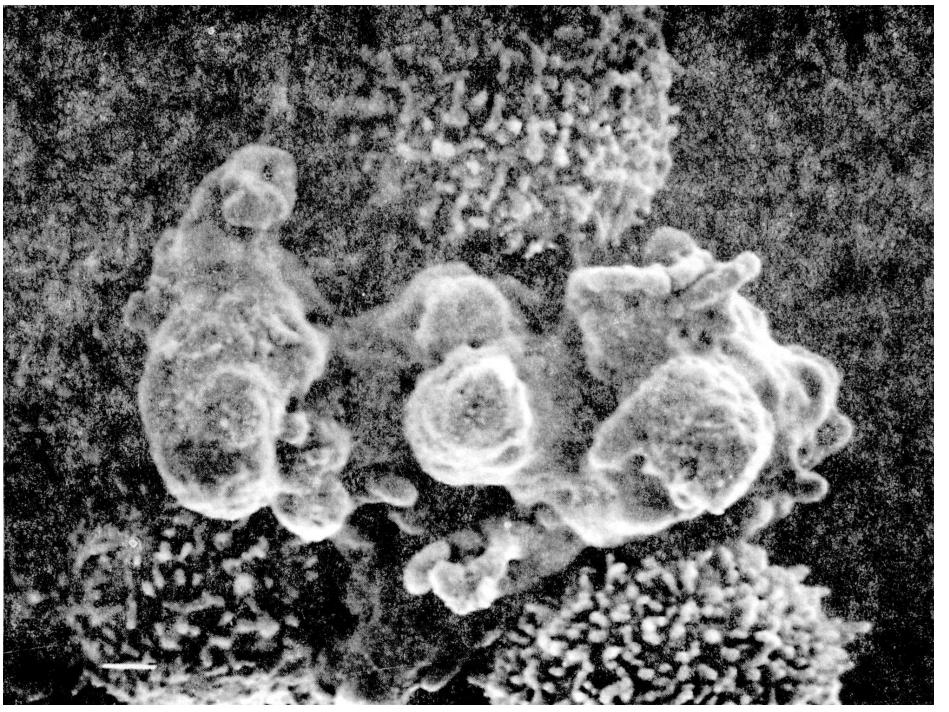

Fig. 2. Cellular Interactions in Antigen Processing and Presentation. Macrophage (ingesting bacteria) and Lymphocytes come in a close contact of their surfaces and cross talk in antigen processing and representation occur.

ethnic groups over the last 3 million years with polymorphic MHC (major histocompatibility complex) genes on chromosome 6 (Table 1), MHC genes do not evolve so rapidly that human leukocyte antigen (HLA) alleles have diverged from ancestral lineage of MHC genes of chimpanzee, gorilla and other primates in the evolution of modern human beings (Fig. 1). The polymorphic genes of HLA were impacted on infectious pathogens in an environment where specific peptide sequences were recognized by one of the HLA antigens composed of glycoproteins encoded from HLA-A, Cw, B, DR, DQ genes (2).

Eighteen families of viruses (6 DNA and 14 RNA viruses) are known to be pathogenic to man (3). Each virus looks for its host to infed and replicate its progeny. Some of the progeny viruses are mutated to evade immune attacks of the human host and to evolve new variants. Natural selection of humans and viruses results in evolution of new genes in tandem.

Immunological interactions between host and exogenous pathogens is complicated by the responses of phagocytic cells and lymphocytes, collaborating in antigen processing and presentation in vivo (Fig. 2). A specific structures of HLA molecules recognize peptide sequences of exogenous pathogens such as shown for the HLA*24 molecule and peptide anchor motifs of human T-cell leukemia virus type 1 (HTLV-I) (Fig. 3). Thus, individual HLA molecules determine the immune response to exogenous peptide antigens depending of such molecular fitness. Some individuals may be good or high immune responders and the others may be poor or low immune responders depending on the HLA/peptide binding compatibility.

Natural history of infectious diseases

Pandemies of infectious diseases are well documented in history. Viral infections resulting in small pox, rabies, polio, mumps, measles and flu are classical examples with repeated worldwide prevalence. Lassa virus, Ebola virus, Hantavirus, ATDS are newly emerging in the human world (Table 2). All the emerging and re-emerging viral diseases are a big challenge to human society so that their control is of major medical interest for health care programs in all countries. Vaccines for small pox, polio and measles can be successfull in preventing infections but vaccines for newly emerging viruses like Lassa, Ebola and AIDS remain to be developed. This is a high priority.

Human T-cell leukemia virus infections and diseases

Human T-cell leukemia virus type I **(HTLV-I)** is causatively associated with adult T-cell leukemia (ATL) and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) as well as other autoimmune diseases depend upon individual disease susceptibility (Fig. 4). ATL patients and their relatives are known to be low immune responders

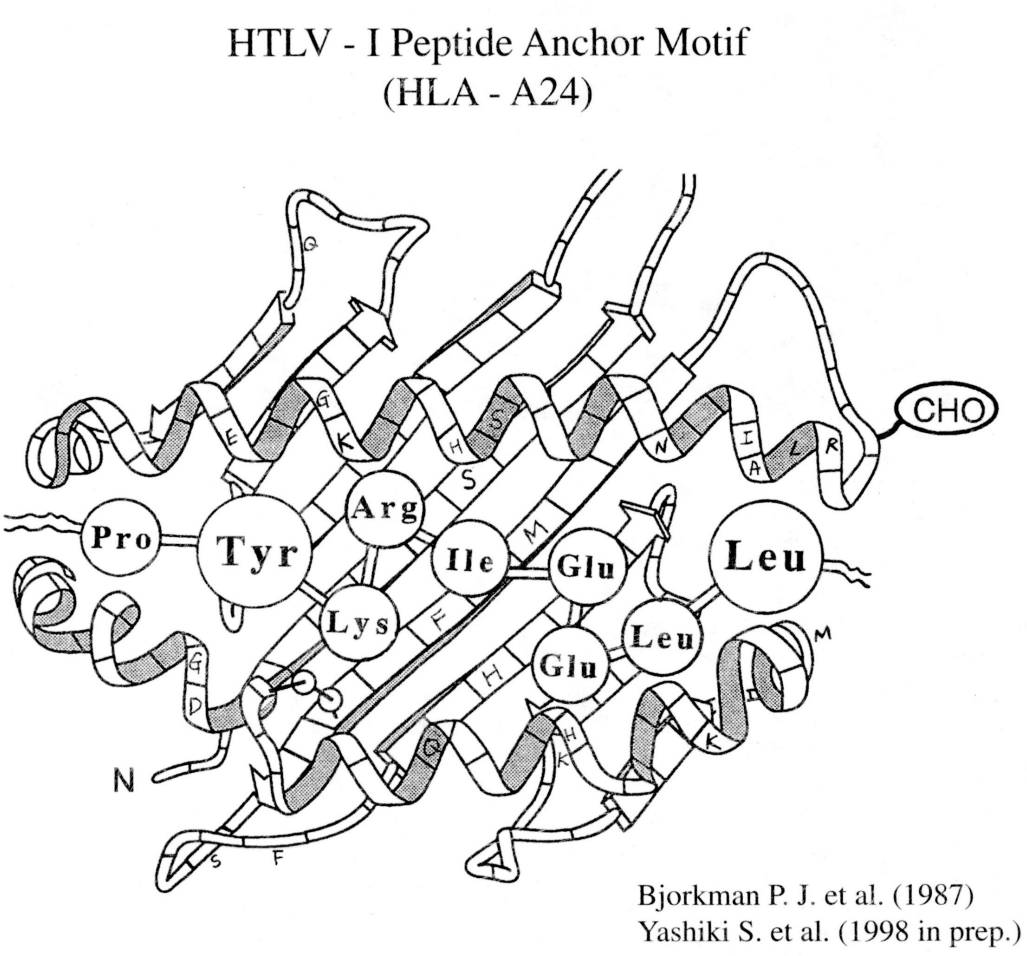

Fig. 3. HTLV-I Peptide Anchor Motif. The HLA-A24 molecule has two basic structures with a helix and b-sheet configurations to recognize a HTLV-I peptide sequence of 9 acids. The principal anchor motifs are Tyrosine at position 2 and Leucine at position 9, respectively binding arginine and methionine of the a-helix polypeptide structure of the HLA-A24 molecule.

Emerging Viruses		
BC 2500 -	Polio	Egypt (Relief in Pyramid)
BC 0400 -	Mumpus	Greek (Hippokrates)
AD 0200 -	Variola	India-China (Vaccination)
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1969	Lassa virus	Lassa fever
1969	Enterovirus 70	AHC (Apolo D)
1973	Rotavirus	
1976	Ebola virus	Ebola HF
1977	Hantavirus	HFRS
1980	HTLV-I	Adult T-cell leukemia
1982	HTLV-II	
1983	HIV-1	AIDS
1986	HIV-2	
1988	HHV6	Examthem subitum
1989	HCV	Hepatitis C
1991	Guanarito virus	Venezuelan HF
1994	Sabia virus	Brazilian HF
Re-emerging Viruses		
Rabie virus		Asia, S. America
Dengue virus		Asia, S. America
Yellow fever virus		Africa, S. America
Hantavirus USA - NM		
(HF with pulmonary syndrome)		

Table 2

to HTLV-I pX peptides while HAM/TSP patients and their relatives are high HTLV-I pX responders. The low and high responsiveness are genetically determined by HLA-A and B alleles and the relevant peptide binding motifs. In fact, HLA-A*26 and B *40 of ATL patients lack any binding motifs to recognize HTLV-I Tax peptides. In contrast, HLA-A*24 and B*07 recognize numerous HTLV-I Tax peptides. HLA-A and B alleles typical of Japanese HAM/TSP cases are also frequently found among Bolivian HAM/TSP patients although no detailed comparison has been made due to the relative lack of ATL patients in the Bolivian population (Table 3). However, a similar HLA background of ATL and HAM/TSP was found among Afro-Caribbean population in Jamaica. This ethnospecificity of HLA alleles and HTLV-I-associated diseases may be explained by a genetic tree of HLA-A lineage among these populations (Fig. 5). Japanese HLA-A*26 is linked in a common branch with HLA A68 and 34 associated with Jamaican ATL, and Japanese HLA-A*24 is close to HLA-A*23 and A*30 but far from the HLA-A*80 of Jamaican HAM/ISP. HLA studies thus provide an insight into immunogenetic back-

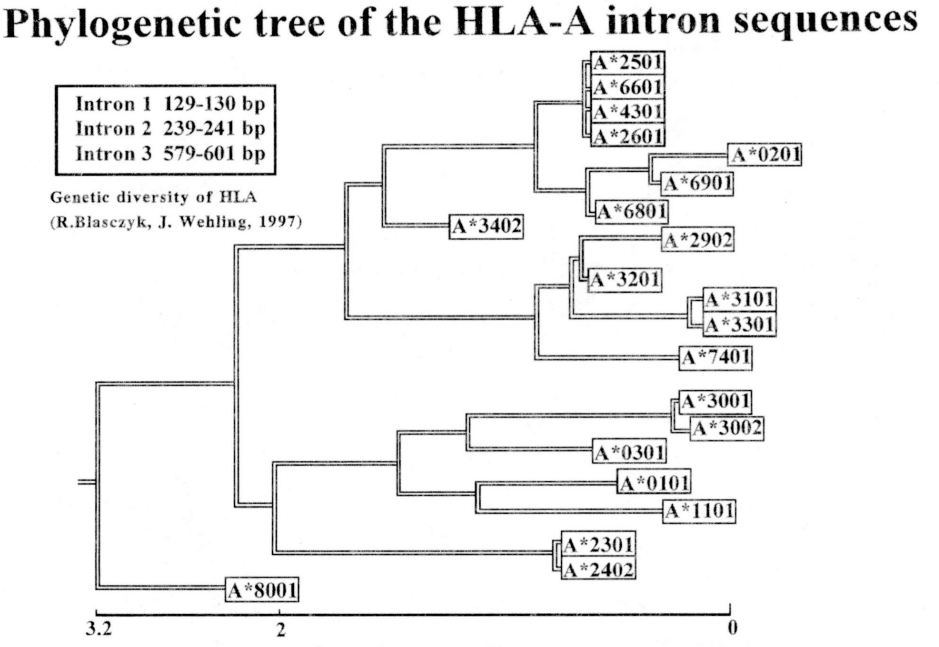

Fig. 4. HTLV-I Infection and Diseases. HTLV-I infected mothers transmit virus via breast milk to infants who become the second generation of HTLV-I carriers and develop diseases depending upon their genetic background. Adult T-cell leukemia (ATL) is segregated from other diseases such as infective dermatitis, HAM/ISP and other autoimmune diseases with HAAP, HAB and uveitis.

Major HLA alleles of ATL and HAM/TSP

Ethnic groups	ATL		HAM/TSP	
Japanese	A*26, A*31 A*33, B*61 B*15, B*44	DRBl*0901, *1301 DRBl*1302, *1401 DRBl*1406, *1501	A*02, A*03 A*11, A*24 A*24, B*07 B*35, B*51	DRB1*0101, *0405 DRB1*0802, *803 DRB1*1402, *1403 DRBl*1502
Bolivian	No cases		A*02, A*24 A*28, A*30 B*08, B*35 B*51	DRB1*0301, *701 DRB1*0802, * 1402
Jamaican	A*01, A*26 A*29, A*30 A*33, A*34 A*36, A*74 A*80, B*40 B*15, B*44 B*53, B*58	DRB1*1101,*1301 DRB1*1401,*1501	A*02, A*03 A*11, A*23 A*28, A*68 B*07, B*08 B*35, B*49 B*57	DRBl*0101,*0301 DRBl*0701,*0802

Table 3

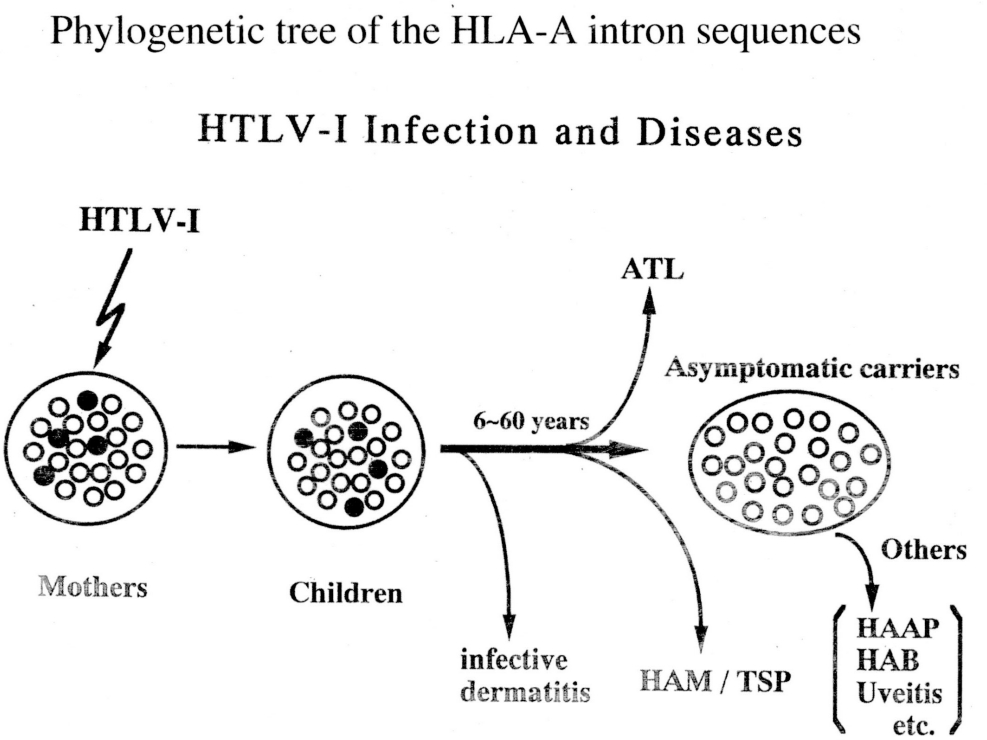

Fig.5. Phylogenetic tree of HLA-A intron sequences. HLA-A alleles are related in a tree of HLA-A intron sequences. HLA-A*26 is one of the major HLA alleles associated with Japanese ATL, while HLA-A*24 is associated with Japanese HAM/ISP. The HLA-A*26 and A*24 alleles are remote in their relationship and segregated in the phylogenetic tree. Jamaican ATL is linked with HLA-A *66, 68 while HAM/TSP is associated with HLA-A*023 and A*03 alleles. Bolivian HAM/TSP is found among carriers of HIA-A*24 and A* 11 alleles.

Class II													Class I						
DPB1		DPA1	DQB1	DQA1	DRB1				DRB3	DRB4	DRB5	B				Cw	E	A	
01011	3401	0103	0501	0101	0101	0410	1128	1406	01011	01	01011	0702	1532	3702	4702	0102	0101	0101	2411N
01012	3501	0104	0502	01021	01021	0411	1129	1407	01012	0101101	01012	0703	1533	3801	4801	0103	0102	0102	2413
3601	0105	05031	01022	01022	0412	1130	1408	01013	0102	0102	0102	0704	1534	3802	4802	02021	01031	0201	2414
02012	3701	02011	05032	0103	0103	0413	1201	1409	0102	0103101	0103	0705	1535	39011	4803	02022	01032	0202	2501
02013	3801	02012	0504	0104	0104	0414	12021	1410	0201	0103102N	014	0706	1536	39013	4901	02023	0104	0203	2502
0202	3901	02021	06011	0105	15011	0415	12022	1411	0202	0104	0105	0707	1537	39021	5001	0302		0204	2601
0301	4001	02022	06012	0201	15012	0416	12031	1412	0203	0105	0106	0708	1801	39022	5002	0303	**5**	0205	2602
0401	4101	0203	0602	03011	15021	0417	12032	1413	0204	0201N	0107	0801	1802	3903	51011	0304		0206	2603
0402	4401	0301	0603	0302	15022	0418	1204	1414	0205	0301N	0201	0802	1803	3904	51012	0401		0207	2604
0501	4501	0401	0604	0303	1503	0419	1205	1415	0206		0202	0803	1804	3905	51021	0402		0208	2605
0601	4601		06051	0401	1504	0420	1301	1416	0301	**9**	0203	0804	1805	39061	51022	0403		0209	2606
0801	4701	**10**	06052	0501	1505	0421	1302	1417			0204	1301	2701	39062	5103	0501		0210	2607
0901	4801		0606	05011	1506	0422	13031	1418	**11**			1302	2702	3907	5104	0602		0211	2608
1001	4901		0607	05012	16011	0423	13032	1419			**12**	1303	2703	3908	5105	0701		0212	2901
11011	5001		0608	05013	16012	0424	1304	1420				1304	2704	3909	5106	0702		0213	2902
11012	5101		0609	0502	16021	11011	1305	1421				1401	27052	3910	5107	0703		0214	2903
1301	5201		0610	0503	16022	11012	1306	1422				1402	27053	3911	5108	0704		0215N	3001
1401	5301		0611	0601	1603	11013	1307	1423				1501	2706	3912	5109	0705		0216	3002
1501	5401		0612		1604	1102	1308	1424				1502	2707	40011	52011	0706		0217	3003
1601	5501		0201	**18**	1605	1103	1309	1425				1503	2708	40012	52012	0707		0218	3004
1701	5601		0202		1606	11041	1310	1426				1504	2709	4002	5301	0801		0219	31012
1801	5701		0203		1607	11042	1311	1427				1505	2710	4003	5302	0802		0220	3201
1901	5801		0301		1608	1105	1312	1428				1506	2711	4004	5401	0803		0221	3202
20011	5901		0302		03011	1106	1313	1429				1507	3501	4005	5501	12021		0222	3301
20012	6001		03032		03012	1107	1314	0701				1508	3502	4006	5502	12022		0301	3303
2101	6101N		0304		03021	11081	1315	0801				1509	3503	4007	5503	1203		0302	3401
2201	6201		0305		03022	11082	1316	08021				1510	3504	4008	5504	1204		0303N	3402
2301	6301		0306		0303	1109	1317	08022				1511	3505	4009	5505	1301		1101	3601
2401	6401N		0307		0304	1110	1318	08031				1512	3506	4010	5601	1402		1102	4301
2501	6501		0401		0305	1111	1319	08032				1513	3507	4101	5602	1403		1103	6601
26011	6601		0402		0306	1112	1320	08041				1514	3508	4102	5603	1502		1104	6602
26012	6701				0307	1113	1321	08042				1515	35091	4201	5701	1503		2301	6603
2701	6801		**31**		0308	1114	1322	0805				1516	35092	4202	5702	1504		2402101	68011
2801	6901				0309	1115	1323	0806				1517	3510	4402	5703	15051		2402102	68012
2901	7001				0310	1116	1324	0807				1518	3511	44031	5704	15052		2403	6802
3001	7101				0311	1117	1325	0808				1519	3512	44032	5801	1601		2404	6803
3101	7201				04011	1118	1326	0809				1520	3513	4404	5802	1602		2405	6901
3201	7301				04012	1119	1327	0810				1521	3514	4405	5901	1604		2406	7401
3301					0402	1120	1328	0811				1522	3515	4406	67011	1701		2407	7402
					0403	1121	1329	0812				1523	3516	4407	67012	1702		2408	7403
77					0404	1122	1330	0813				1524	3517	4408	7301	1801		2409N	8001
					04051	1123	1401	0814				1525	3518	4409	7801	1802		2410	
					04052	1124	1402	0815				1526N	3519	4410	78021				
					0406	1125	1403	0816				1527	3520	4501	78022	**42**		**83**	
					0407	1126	1404	09012				1528	3521	4601	8101				
					0408	1127	1405	1001				1529	3701	4701	8201				
					0409							1530							
							185					1531		**186**					

Table 1

ground of diseases with respect to low and high immune responses against HTLV-I peptide antigens. It is conceivable that ATL and HAM/TSP offer the best model to investigate the HLA and immunogenetic background of diseases caused by one pathogenic species of virus, HTLV-I. This HTLV-I model might be useful to understand the immunogenetic background of other infections like hepatitis virus, papovavirus and herpes virus, naturally occurring among contemporany human populations.

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