Med Microbiol Immunol (2009) 198:1–3
DOI 10.1007/s00430-008-0096-z

ORIGINAL INVESTIGATION

HLA class I alleles in HTLV-1-associated myelopathy and asymptomatic carriers from the Brazilian cohort GIPH

B. C. Catalan-Soares · Anna Bárbara F. Carneiro-Proietti · F. G. Da Fonseca · R. Correa-Oliveira · D. Peralva-Lima · R. Portela · J. G. Ribas · D. U. Gonçalves · Interdisciplinary HTLV Research Group (GIPH)· F. A. Proietti

Received: 22 December 2007 / Published online: 3 June 2008

Abstract
Introduction and objectives The development of HTLV-1-associated myelopathy (HAM/TSP) in HTLV-1-infected individuals is probably a multi-factor event, in which the immune system plays a crucial role. The efficiency of the host immunity seems to be one of the in vivo determining factors of the proviral load levels and is regulated by genes associated with MHC class I alleles (HLA). Protection or predisposition to HTLV-1-associated diseases according to individual HLA profile was shown in Japanese studies. The present work tested for HLA alleles previously related to protection or susceptibility to HTLV-1-associated myelopathy in a cohort study (GIPH) from Brazil.
Methods A total of 93 HTLV-1-infected individuals participated in the study, as follows: 84 (90.3%) asymptomatic and 9 (9.7%) with HAM/TSP. Alleles related to protection (A*02, Cw*08) and susceptibility (B*07, Cw*08 and B*5401) were tested by the PCR-SSP method.
Results Allele A*02 was more frequent in the asymptomatic group and in its absence, Cw*07 was correlated with HAM/TSP ($P = 0.002$). Allele B*5401 was not present in the Brazilian population. Alleles B*07 and Cw*08 were not different between the groups
Discussion The presence of HLA-A2 elicits a stronger cytotoxic response, which is involved in the HTLV-1 proviral load reduction. This study confirmed a tendency of this allele to protect against HAM-TSP. Therefore, A*02 might be of interest for researches involved with HTLV-1 vacine.

Keywords HTLV-1 · HAM/TSP · HLA

B. C. Catalan-Soares · A. B. F. Carneiro-Proietti (✉) · R. Portela
Fundação Hemominas, Rua Grão Pará,
882, Belo Horizonte, Minas Gerais 30.150-340, Brazil
e-mail: annaproietti@hemominas.mg.gov.br

F. G. Da Fonseca · R. Correa-Oliveira · D. Peralva-Lima
Centro de Pesquisas René Rachou (Fiocruz),
Belo Horizonte, Minas Gerais, Brazil

J. G. Ribas
Rede Sarah de Hospitais do Aparelho Locomotor,
Belo Horizonte, Minas Gerais, Brazil

D. U. Gonçalves · F. A. Proietti
Faculdade de Medicina da Universidade Federal de Minas Gerais,
Belo Horizonte, Minas Gerais, Brazil

Introduction

HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) occurs in about 2–3% of the infected individuals and the great majority of these remain asymptomatic lifelong [1, 2]. The reason why some carriers develop myelopathy, and others do not, has been extensively studied, but not yet completely elucidated [3, 4]. No difference in the virus itself was seen in those who develop HAM/TSP [3]. Therefore, differences in the host response to the virus may be related to the development of axonal damage and demyelination [1, 2]. The influence of HLA class I alleles resulting in protection or susceptibility to HAM/TSP has been studied [3–5]. The presence of HLA-A*02 and Cw*08 was clearly associated with a lower risk of HAM/TSP and a significant reduction in provirus load in asymptomatic carriers [3]. Conversely, it was described that some alleles may predispose to HAM/TSP. Susceptibility was associated with the allele B*5401 in Japan and with the haplotype HLA-B*0702-Cw*0702-DRB1*0101-DQB1*0501 in the absence of A*02 [4].

Of great interest is the possibility of an HLA-based HTLV-1 vaccine, using the A*02 as an epitope in antiretroviral

vaccines to elicit the stronger cytotoxic T lymphocyte (CTL) response against the virus. The aim of this study was to describe the MHC Class 1 genes previously associated with protection or predisposition to HTLV-1 neurological disease in a cohort of Brazilian HTLV-1 asymptomatic carriers (AC) and patients with HAM/TSP, and to compare it with published data.

Methods

Population

All individuals in this study were enrolled in the HTLV Interdisciplinary Research Group (GIPH) cohort study, started in 1997 and coordinated by Fundação Hemominas, Minas Gerais State Blood Center, Brazil. The cohort was composed of former blood donors, their relatives and patients from the Sarah Rehabilitation Hospital. A total of 96 HTLV-1 infected individuals participated in the study, as follows: 84 asymptomatic carriers (ACs) and 9 patients with HAM/TSP, according to World Health Organization diagnostic criteria. Seropositivity was defined by repeated reactive EIA tests (Ortho, USA), confirmed by positive Western blot (Cambridge Biotech, USA) and/or PCR. HLA frequency distribution of age and sex were obtained according to the groups: HAM/TSP or ACs. None of the 96 participants reported Japanese descent.

Ethical issues

Hemominas Foundation Committee on Human Subjects Research (CEP Hemominas) approved the present study, according to Brazilian Committee of Ethics in Research, which is in compliance with the Helsinki Declaration.

HLA class I typing

HLA typing was performed by HLA SSP PCR utilizing the Biotest HLA SSP kit (Biotest, Germany) and protocols indicated by the manufacturer. The reactions were designed to detected 52 alleles of the specificities HLA-A, -B and -C, including those associated with HAM/TSP protection (A*02 and Cw*08) or susceptibility (B*54, Cw*07, B*07) [3, 4].

Results

The studied groups were composed by 9 individuals with HAM/TSP (6 females and 3 males) and 84 ACs (48 females and 36 males). The male/female ratio was 1:2 in the HAM/TSP and 1:1.3 in the AC group. The mean age was 48.9 (SD = 12.74) in the HAM/TSP group and 42.7 (SD = 14.82) in ACs group.

The frequency distribution of the alleles related to HAM/TSP protection or susceptibility is presented in Table 1. Overall, alleles related do "risk" were more frequently detected in the HAM/TSP group and alleles related to "protection" in the ACs group. In order to evaluate the indirect value of HLA-A*02 as a protective allele, the groups were compared, relating the presence of CW*07 with A*02. In the stratified analysis, it was found that in the absence of A*02, the presence of CW*07 was associated with HAM/TSP ($P = 0.002$).

Discussion

HTLV-1 infection is more prevalent in females, and the association of HAM/TSP and feminine gender was found in our cohort, as previously reported [1, 6].

In relation to the allele profile related to HAM/TSP protection or susceptibility, differences were found when Brazilian and Japanese population were compared.

In the Brazilian population, HLA-B*5401 was not observed. This allele was already shown to be found almost exclusively in east Asians [7]. In the Japanese report, the B*5401 was associated with a higher susceptibility to HAM/TSP and this effect was dominant over the A*02-associated protective effect [4].

In our study, a low frequency of HLA-A2 was observed in HAM/TSP patients when compared to ACs (33 vs. 47%). Interestingly, the same difference had also been seen in other geographical Brazilian areas (31 vs. 47%) [8]. Besides, low frequency of HLA-A2 had already been reported for Japanese patients with HAM/TSP [3, 4]. Since HTLV-I contains a dominant A2-restricted epitope, individuals lacking HLA-A2 would present a weaker cytotoxic response against HTLV-I and a higher provirus load [3]. It is noteworthy that, herein, the sample size of HAM/TSP patients was not representative to allow conclusions about

Table 1 Comparison of the specific alleles associated with protection or susceptibility to HAM/TSP in 93 HTLV-1 infected individuals

Alleles related to HAM/TSP		HTLV-1 groups	
		HAM/TSP ($n = 9$)	AC ($n = 84$)
Risk	B*07	2 (22.2)	11 (13.0)
	B*5401	0	0
	Cw*07	6 (66.6)	23 (27.3)
Protection	A*02	3 (33.3)	40 (47.6)
	Cw*08	1 (11.1)	8 (9.5)

GIPH Cohort Study, Belo Horizonte, Brazil

HAM/TSP HTLV-1 associated myelopathy/tropical spastic paraparesis, *AC* asymptomatic carriers

the isolated A*02 effect related to HAM/TSP. However, the present data shows a tendency that confirms the HLA-A2 protective effect.

In relation to Cw*07, a higher frequency was observed in patients with HAM/TSP. In the absence of A*02, a correlation between Cw*07 and HAM-TSP was seen. This association had been seen before, confirming Cw*07 as an allele of risk for HAM/TSP development [4].

The allele Cw*08 was similarly observed in both groups of the present study. There has been controversy about the influence of this allele on the immune system of the HTLV-1 infected population. Whereas protection was found in the Japanese population [3, 4], susceptibility was found in the Iranians [5].

In conclusion, the present investigation showed that although HLA molecules have a polymorphism among populations, perhaps A*02 may be an epitope of interest for researches involved with HLA-based HTLV-1 vaccine.

Acknowledgments Minas Gerais State Centre of Hematology and Blood Transfusion (Fundação Hemominas), Fundação de Amparo à Pesquisa de Minas Gerais (Fapemig) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) supported this work. This work was performed by researchers participating in the HTLV Interdisciplinary Research Group (GIPH), Brazil.

References

1. Osame M, Janssen R, Kubota H et al (1990) Nationwide survey on Human T-cell leukemia/lymphoma virus type I associated myelopathy in Japan. Association with blood transfusion. Ann Neurol 28:50–56
2. Gessain A, Gout O (1992) Chronic myelopathy associated with human T-lymphotropic virus type I (HTLV-I). Ann Int Med 117:933–946
3. Jeffery KJM, Usuku K, Matsumoto W et al (1999) HLA alleles determine human T-lymphotropic virus-I (HTLV-I) proviral load and the risk of HTLV-I associated myelopathy. Proc Natl Acad Sci USA 96:3848–3853
4. Jeffery KJM, Siddiqui AA, Bunce M et al (2000) The influence of HLA class I alleles and heterozygosity on the outcome of human T cell lymphotropic virus type I infection. J. Immunol 165:7278–7284
5. Rafatpanah H, Pravica V, Faridhosseini R et al (2007) Association between HLA-DRB1*01 and HLA-Cw*08 and outcome following HTLV-I infection. Iran J Immunol 4(2):94–100
6. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC et al (2005) Global epidemiology of HTLV-I infections and associated diseases. Oncogene 24:6058–6068
7. Imanishi T, Akaza T, Kimura A, Tokunaga K, Gojobori T (1992) Allele and haplotype frequencies for HLA and complement loci in various ethnic groups. In: Tsuji K, Aizawa M, Sasazuki T (eds) HLA 1991. Oxford University Press, New York, p 1065
8. Borducchi DM, Gerbase DeLima M, Morgum A et al (2003) Human leucocyte antigen and human T-cell lymphotropic virus type 1 associated diseases in Brazil. Br J Haematol 123:954–955