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Short communication

Polymorphisms in HLA-C and KIR alleles are not associated with HAM/TSP risk in HTLV-1-infected subjects

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ABSTRACT

Introduction: Several genetic polymorphisms may be related to susceptibility or resistance to viral disease outcomes. Immunological or genetic factors may act as major triggers of the immune pathogenesis of HAM/TSP. This study investigated the association of immune related genetic polymorphisms with viral and immunological markers.

Methods: 247 HTLV-1-infected volunteers, drawn from a larger group of HTLV-infected subjects followed at the Institute of Infectious Diseases "Emilio Ribas" (IIER) for up to 19 years, participated in this study, which ran from June 2011 to July 2016. The subjects were classified according to their neurological status into two groups: Group 1 (160 asymptomatic individuals) and Group 2 (87 HAM/TSP patients). Samples were tested for spontaneous lymphocyte proliferation (LPA) and HTLV-1 proviral load (PVL) and for IFN-λ4, HLA-C and KIR genotypes using qPCR.

Results: We found associations between LPA ($p = 0.0001$) with HAM/TSP and confirmed the IFN-λ4 polymorphism rs8099917, allele GG, as a protective factor using a recessive model (OR = 3.22, CI = 1.10–9.47). Polymorphisms in HLA-C and KIR alleles were not associated with risk of developing HAM/TSP.

Conclusion: We demonstrated that age, LPA and an IFN-λ4 polymorphism were associated with progression to HAM/TSP. Understanding HAM/TSP pathogenesis can provide important markers of prognostic value for clinical management, and contribute to the discovery of new therapeutic interventions in the future.

It has been estimated that between 10 to 20 million people are infected with HTLV-1 worldwide (10 - 20Edlich et al., 2000; Gessain and Cassar, 2012; Mortreux et al., 2003); most of them are asymptomatic. However, a significant proportion will develop a serious neurologic disease, HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HAM/TSP is a chronic disease of insidious onset, affecting one to two percent of infected individuals, leading to a progressive demyelination of the spinal cord. It is associated with a variable degree of sphincter and sensory dysfunction affecting more women than men, usually in their fourth and fifth decades of life (Gessain et al., 1985; Osame et al., 1986). HTLV-1 itself and the interaction with the subject over the last few decades disclosed the role of some immunological or genetic factors as major triggers of the immune pathogenesis of HAM/TSP (Assone et al., 2016).

The importance of the immune response notwithstanding, the host genetic profile may also play an important role in the clinical evolution of HTLV-1 infection. For example, the role of interleukin (IL) 28B (IFN-λ4) on HAM/TSP outcome is incompletely understood (Sanabani et al., 2012; Trevino et al., 2012). However, it has been noted that HAM/TSP patients show an independent association with the polymorphism in

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IL28B SNP rs8099917 (GG), when compared to asymptomatic HTLV-1 carriers (Assone et al., 2014). On the other hand, persons with certain human leukocyte antigen (HLA) class I alleles are more likely to experience disease progression than those with other HLA types (Jeffery et al., 2000). The likelihood of HTLV-1 disease progression likely depends on host genetic background as well as viral and immune factors. Inflammatory cytokines such as IFN-λ, IL-15 and tumor necrosis factor (TNF −α) are involved with HTLV-1 pathogenesis as well (Azimi et al., 1999). In addition to cytokine polymorphisms, other genetic factors may play a role in the pathogenesis of HAM/TSP, such as HLA and natural killer (NK) cell killer-cell immunoglobulin-like receptors (KIRs) (Assone et al., 2014).

These genes have highly polymorphic loci and may interact with each other, but their SNPs and main variants have not been studied yet in the context HTLV-1 infection. The interaction between the immune system and the host genetic background is a relatively under-explored area that may shed light on the pathogenesis of HTLV-1. Therefore, the major aim of this study was to identify potential genetic markers for HAM/TSP development, which could be helpful in clinical practice.We have been following 610 HTLV-1-infected patients since July 1997 at the HTLV outpatient clinic of the Institute of Infectious Diseases “Emilio Ribas” (IIER). For the purpose of this study, we included 247 HTLV-1-infected subjects who were over 18 years old and who remained in active follow-up in the period ranging from June 2011 to May 2012. Of all volunteers, 87 had HAM/TSP and 160 were asymptomatic, a classification performed by neurological assessment, in accordance with previously published data (Croda et al., 2008).

The HTLV-1 proviral load was quantified by real-time PCR, using primers and probes targeting the pol gene, as described previously (Dehee et al., 2002; Montanheiro et al., 2005). T-cell proliferation (LPA) assay using peripheral blood mononuclear cell cultures (PBMC) was performed as described in detail elsewhere (Benard et al., 1996). We analyzed IFN-λ4 (rs12979860 and rs8099917) and HLA-C (rs9264942) polymorphisms using the TaqMan SNP Genotyping Assay system, following the manufacturer's instructions (Applied Biosystems, Foster City, USA) (Scherzer et al., 2011; Vineretsky et al., 2014). For the KIR polymorphisms (KIR2DL2, KIR2DL3, KIR2DS2 and KIR2DS3), we adapted the protocol for use of the PCR technique in real time (qPCR) using SYBR Green and TaqMan system using the primer sequences previously described (Ashouri et al., 2009; Koehler et al., 2009). The Ethical Board of the IIER approved the protocol (Number 13/2011), and we obtained signed informed consent from all participants prior to study inclusion.

Two hundred forty-seven volunteers with HTLV-1 were included in this study and were divided in two groups based on their clinical condition: 160 asymptomatic volunteers, with a mean age of 53 years, 62% of whom women, and 87 patients with HAM/TSP, with a mean age of 59 years, with approximately the same proportion of women (63.3%). Table 1 shows the demographic and laboratory results. Patients with HAM/TSP were older; indeed, we found a 2.6% risk increment of disease for each additional year of age ($p = 0.001$). Spontaneous lymphocyte proliferation was higher for the HAM/TSP group (Table 1, $p = 0.0001$). On the other hand, the HTLV-1 proviral load was not a significant marker of HAM/TSP ($p = 0.167$) in this cohort. In addition, HLA-C and KIR polymorphisms were not associated with the risk of HAM/TSP. On the other hand, the SNP rs8099917 (TT/GT) of IFN-λ4 was associated with lower risk for HAM/TSP development (Table 1, $p = 0.032$), confirming the association we previously reported (Assone et al., 2014). The Hardy Weinberg equilibrium was calculated in order to evaluate if the frequencies were outside the expected in a pan mixed population. It is important to highlight the polymorphism rs8099917 of IFN-λ4 was not in balance in our study population, which could have played a role on the clinical outcome.A multivariate model including, age, LPA, PVL and SNP rs8099917 showed that LPA (OR = 1.054, IC 95% = 1.025–1.083) and the SNP rs8099917, allele GG (OR = 3.22; IC 95% = 1.10–9.47) were independently associated with HAM/TSP (Table 2). In this model age was also significantly associated with the outcome (OR = 1.025; IC 95% = 1.002–1.049).

HTLV-1 infection can cause a wide spectrum of disease, including inflammatory and neoplastic outcomes (Saito et al., 2012), and it has been shown that immune mechanisms may play an important role in the pathogenesis of HAM/TSP (Fuzii et al., 2014). This study identified that T-cell proliferation capacity was an important marker for clinical outcome, since there was a 0.5% increase in the HAM/TSP risk development for each increment of one thousand counts per minute in the LPA.

One possible explanation for increased lymphocyte proliferation would be higher circulating levels of inflammatory cytokines (Montanheiro et al., 2007, 2009). HTLV-1 can spontaneously promote in vitro proliferation to Tax-induced deregulation, mainly due to IL-2 and IL-2r activation, inducing activation of IL-1α, IL-6 and TNF-α production (Popovic et al., 1984; Usuku et al., 1988). During the initial stages of HTLV-1 infection, infected cells are dependent on IL-2 for proliferation whereas in later stages, this may not be required (Araya et al., 2011).

In addition, a major role for PVL on the promotion of this activation has been postulated, especially during the earlier stage of HAM/TSP, considered the “hot stage” that can lead to the spinal cord damage (Grassi et al., 2011; Mozhgani et al., 2017). Despite this hypothesis not being corroborated by our findings, previous studies with lower sample size have shown a correlation between PVL and HAM/TSP risk (Martins et al., 2017; Montanheiro et al., 2005; Starling et al., 2013; Yamano et al., 2002), thus this observation should be explored in additional studies. The findings of this study and others imply that spontaneous lymphocyte proliferation is a stronger predictor of HAM/TSP than PVL (Norris et al., 2010).

Previous studies reported that most cases of HAM/TSP occur at early adulthood (Casseb, 2008), but in our study the average age with HAM/TSP patients was 59 years. However, is very hard to assess how long the subjects had been infected, it can infer, the association with age could be due bias, where older HTLV-1 infected subjects only return to clinic for follow-up if they are experiencing symptoms. HTLV-1-infected carriers older than forty years of age may have a lower risk for HAM/TSP development, potentially due to immune senescence (Casseb, 2008).

In a previous study the association of the polymorphism of IFN-λ4 in SNP rs8099917 (GG) was reported as an independent factor to HAM/TSP development (Assone et al., 2014); it was confirmed in the present report using a separate group of patients. Given that the implicated polymorphism sits in a cytokine gene, the association may be linked to differential release of cytokines and chemokines, which could result in spinal cord damage (Montanheiro et al., 2007, 2009).

We did not find that HLA-C polymorphisms associated with protection from HAM/TSP. The effectiveness of specific immune response to HTLV-1, especially the CD8+ cytotoxic T-cell lymphocyte response (CTL), is the key to control the HTLV-1 proviral load (Melamed et al., 2015). The CTL response has been associated with protection in a Japanese population, where the presence of either HLA-A*02 or HLA-Cw*08 is associated with a lower proviral load and lower HAM/TSP incidence (Jeffery et al., 2000, 1999). In contrast, the presence of KIR2DL2 may be associated with HAM/TSP protection when associated with HLA-Cw*08 and B*54 in European and Japanese populations (Seich Al Basatena et al., 2011). The influence of the genetic ancestry may explain those conflicting results, given the historical context of the Brazilian mixed population (Ge et al., 2009). In the present report KIR polymorphisms were not associated with HAM/TSP risk, a finding similar to what was seen in a Peruvian population (Talledo et al., 2010), where KIR3DS1 was not associated with proviral load or HAM/TSP (O'Connor et al., 2012).

In summary, this study showed no correlation between KIR and HLA-C polymorphism and HAM/TSP, but did confirm a correlation between LPA and SNP rs8099917 (GG) in IFN-λ4 with HAM/TSP, as

Table 1
Laboratory variables of the 247 HTLV-1-infected subjects.

Variables	Total N(%)	Asymptomatic	HAM/TSP N(%)	OR (95%IC)	P value
Age Mean (± DP)	54 (± 13,91)	53 (± 14,32)	59 (± 12,12)	**1037 (1,0155–1059)**	**0.001**
Lymphocytes proliferation (1000 CPM) mean (± sd)	10302 (± 11446)	**7826 (± 8524)**	**14595 (± 14318)**	**1. 055 (1.027–1.084)**	**0.0001**
Proviral load HTLV-1 (copies/10^4 PBMC)	247 (100)	160 (100)	87 (100)	1.000587 (0.999552–1.00142)	0.167
IFN-λ4					
rs12979860	**247**	**160**	**87**		
CC	97 (39.3)	69 (43.2)	28 (32.2)	1.00	
CT	118 (47.8)	74 (46.2)	44 (50.6)	1.46 (0.82–2.61)	0.194
TT	32 (12.9)	17 (10.6)	15 (17.2)	2.17 (0.96–4.94)	0.064
rs8099917[a]	**245**	**159**	**86**		
TT	160 (65.31)	105 (66.04)	55 (63.95)	1.00	
GT	67 (27.34)	47 (29.56)	20 (23.25)	0.81 (0.43–1.51)	0.509
GG	18 (7.35)	**7 (4.40)**	**11 (12.8)**	**3 (1.1011–8.1729)**	**0.032**
HLA-C					
rs9264942[b]	**241**	**154**	**87**		
TT	99 (41.1)	69 (44.8)	30 (34.5)	1.00	
CT	102 (42.3)	60 (38.9)	42 (48.3)	1.61 (0.89–2.8)	0.109
TT	40 (16.6)	25 (16.3)	15 (17.2)	1.38 (0.63–2.98)	0.82
KIR					
KIR2DL2[c]	**245**	**158**	**87**	1.09 (0.58–2.05)	0.778
Positive	189(77.14)	121 (76.6)	68 (78.2)		
Negative	56 (22.86)	37(23.4)	19 (21.8)		
KIR2DL3[d]	**241**	**157**	**84**	1.65 (0.83–3.25)	0.147
Positive	188 (78)	118 (75.2)	70 (83.3)		
Negative	53 (22)	39 (24.8)	14 (16.7)		
KIR2DS2[e]	**246**	**159**	**87**	1.69 (0.98–2.91)	0.055
Positive	141 (57.32)	84 (52.8)	57 (65.5)		
Negative	105 (42.68)	75 (47.2)	30 (34.5)		
KIR2DS3[f]	**240**	**153**	**87**	0.75 (0.44–1.28)	0.297
Positive	110 (45.83)	74 (48.4)	36 (41.4)		
Negative	130 (54.17)	79 (51.6)	51 (58.6)		

[a] Two volunteres without enough samples for IFN-λ4 rs8099917 assay.
[b] Six volunteers without enough samples for HLA-C rs9264942 assay.
[c] Two volunteers without enough samples for KIR2DL2 assay.
[d] Six volunteers without enough samples for KIR2DL3 assay.
[e] One missing volunteer without enough samples for KIR2DS2 assay.
[f] Seven volunteers without enough samples for KIR2DS3 assay.

Table 2
HAM/TSP-associated *IFN-λ4* polymorphisms using multivariate analysis (recessive model).

Variables	*OR (95% IC)*	*P value*
Age (continuous)	1.025 (1.002–1.049)	**0.029**
LPA (continuous) (1000 CPM)	1.054 (1.025–1.083)	**0.000**
Proviral load HTLV-1 (continuous)	1.000219 (0.9992698–1.00117)	0.628
rs8099917		
TT/GT	1.00	
GG	3.22 (1.10–9.47)	**0.033**

showed in a previous report (Assone et al., 2014). It is known that genetic studies of point mutations are not ideal for assessing the genetic interactions between viruses and host. However, several studies associating genetic polymorphisms with disease prognosis were based on genome-wide association studies (GWAS) (Thio and Thomas, 2010). Although few studies have evaluated in vitro T-cell activation as a disease marker, LPA could be performed as a potential surrogate marker for HAM/TSP progression.

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