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FAS −670A/G single nucleotide polymorphism may be associated with human T lymphotropic virus-1 infection and clinical evolution to TSP/HAM

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ABSTRACT

FAS and FASLG genes are closely linked to the apoptosis mechanism of the immune system and several polymorphisms in these genes have been associated with susceptibility to diseases. The present study investigated the polymorphisms at positions −670 in the FAS gene, and −169 and −124 in the FASLG gene, among HTLV-1 infected subjects. Blood samples from HTLV infected subjects and seronegative individuals were collected, and polymorphisms were analyzed using a polymerase chain reaction (PCR) followed by RFLP analysis using restriction endonucleases. The genotype frequencies of the FAS −670 polymorphism was the only one that showed a higher and significant prevalence of genotype −670GG among HTLV-1 infected subjects as compared to the control group ($p = 0.0160$), but the genotype −670AA was more frequent among TSP/HAM patients as compared to the asymptomatic individuals ($p = 0.0005$). $TCD4^+$ and $TCD8^+$ lymphocyte counts from HTLV infected and seronegative subjects, as well as the proviral load values, according to the status of symptomatic and asymptomatic infection carrying different genotypes were compared but showed no statistical significance. The present results suggest that FAS −670 polymorphism seems to be associated with susceptibility to HTLV-1 and may increase the chance to develop TSP/HAM among HTLV-1 infected persons.

1. Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a member of the family Retroviridae, sub-family Oncovirinae, genus Deltaretrovirus. It was isolated for the first time in Japan, from patients with adult T-cell leukemia (ATL) (Uchiyama et al., 1977). Subsequently, the virus was associated with a neurological disease named Tropical Spastic Paraparesis/HTLV-1 associated mielopathy – TSP/HAM (Osame et al., 1987), a chronic and progressive demyelinating disease associated to HTLV-1 infection which affects between 0.2 and 5% of the infected individuals in the fourth decade of life (Kaplan et al., 1990; Vernant et al., 1987).

Initial symptoms of TSP/HAM include weakness and stiffness of the lower limbs, hyper-reflection of the lower limbs and Babinski sign (Osame et al., 1987; Vernant et al., 1987) which progresses to back pain, a variable degree of sensory loss and bladder disorders such as urinary urgency and incontinence (Ferreira Júnior et al., 1997).

FAS (also known as TNFRSF6/CD95/APO-1) is a death domain-containing member of the TNFR (Tumor Necrosis Factor Receptor) superfamily that is involved in apoptotic signaling in several cell types (Itoh et al., 1991; Oehm et al., 1992). It has a central role in the physiological regulation of programmed cell death and has been implicated in the pathogenesis of various malignancies and diseases of the immune system. The FAS receptor induces an apoptotic signal by binding to its ligand, FASL, expressed on the surface of other cells (Baumann et al., 2002; Schmitz et al., 2003). The human FAS gene, located on chromosome 10q24.1, consists of nine exons and eight introns (Inazawa et al., 1992). One important polymorphism which has been identified in the FAS promoter region, includes an A–G substitution at nucleotide position −670 (FAS −670 A>G; rs 1800682) (Huang et al., 1997, 1999).

FASLG (FAS ligand, also known as TNFSF6/CD95LG) is a member of the tumor necrosis factor superfamily and triggers the apoptotic cell-death cascade by linking with its receptor. This ligand is found attached to the cell membrane (40 kDa) or in a soluble form (28 kDa), as a result from the cleavage of the 40 kDa protein. The human FASLG gene is located on chromosome 1q23, and consists of four exons and three introns (Takahashi et al., 1994). Three polymorphisms have been reported within this gene, and two of them

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include a T deletion in position −169 of intron 3 (FASLG IVS3nt −169 T > ΔT; ni) and an A–G substitution at nucleotide position −124 of intron 2 (FASLG INV2nt −124 A>G; rs 5030772) (Bolstad et al., 2000; Pinti et al., 2002; Zhang et al., 2006).

The present study intended to investigate the occurrence of FAS and FASLG polymorphisms and its role in the susceptibility and progression to neurological disease among HTLV-1 infected persons.

2. Methods

2.1. HTLV-1 infected and seronegative controls

The study population included 66 HTLV-1 infected subjects (26 TSP/HAM symptomatic and 40 asymptomatic) registered at the outpatient clinic of the Tropical Medicine Nucleus of the Federal University of Para and 192 seronegative controls. All individuals resided in Belém, were recruited between May 2005 and January 2010 and signed a consent term. Blood samples were collected in Vacuntainer tubes containing K_3-EDTA as anticoagulant in order to obtain plasma and peripheral blood mononuclear cells (PBMC). Samples were directed to the Virus Laboratory of the Biological Sciences Institute of the Federal University of Para and stored at −20 °C before use. Samples were screened for anti-HTLV using an enzyme-linked immunosorbent assay (Orhto Diagnostic Systems Inc., USA) and infection was confirmed by a nested-PCR, as previously described (Vallinoto et al., 2002). The study was conducted within a period of 18 months. The clinical diagnosis of TSP/HAM followed the criteria previously described (Castro-Costa et al., 2006).

2.2. Quantification of HTLV-1 viral load and CD4+/CD8+ T lymphocytes

The quantification of HTLV proviral load was performed by a real-time PCR assay, as previously described (Tamegão-Lopes et al., 2006). Blood samples were processed within 4 h of collection and T-cell subset counts were determined by flow cytometry (FacsCount, Becton & Dickinson, USA) using the FacsCount™ Reagents immunomonitoring kit, according to a standard protocol recommended by the manufacturer (Becton & Dickinson, USA). HTLV-1 infected persons were tested for HTLV-1 proviral load and counting of $CD4^+$ T lymphocytes at the time of entry into the study.

2.3. Polymorphisms analysis

Genomic DNA was extracted from PBMC using the purification kit GFX for genomic DNA (Amersham Pharmacia Biotech, USA). FAS and FASLG polymorphisms were identified using a PCR method. Amplification was performed in a final volume of 30 μL containing 500 ng of total DNA extracted, 0.2 μM of each dNTP, 5 pmol/μL of each primer, $MgCl_2$ 2.0 mM, 50 mM KCl, Tris–HCl pH 8.3 10 mM and 1.0 U of Taq DNA polymerase. The primers used for amplification of FAS and FASLG promoter regions were: 5′-CTA CCT AAG AGC TAT CTA CCG TTC-3′ (forward) and 5′-GGC TGT CCA TGT TGT GGC TGC-3′ (reverse) for FAS −670 A>G polymorphism; 5′-GCA GTT CAG ACC TAC ATG ATT AGG AT-3′ (forward) and 5′-CCA ATT CTC ACC TGT ACC TTC-3′ (reverse) for FASLG IVS2nt −124 A>G; 5′-AGG AAA GGA CTT CAA AGC CTA-3′ (forward) and 5′-TTG ATG CAT CAC AGA ATT TCG TC-3′ (reverse) for FASLG IVS3nt −169 T > ΔT.

The amplification reactions were performed under the following conditions: (i) for the −670 A>G polymorphism followed initial denaturation at 94 °C during 360 s, followed by 35 cycles of 60 s at 94 °C, 60 s at 50 °C and 60 s at 72 °C; (ii) for the −124 A>G polymorphism the reaction mixture was denaturared at 94 °C during 360 s, followed by 35 cycles of 60 s at 94 °C, 60 s at 55 °C and 60 s at 72 °C; (iii) for the −169 T > ΔT polymorphism the reaction was initiated by denaturation at 94 °C, followed by 35 cycles of 60 s at 94 °C, 60 s at 51 °C and 60 s at 72 °C.

PCR products were digested with three restriction endonucleases, MvaI, FokI and HincII, that can distinguish the FAS −670 A>G, FASLG IVS2nt −124 A>G and FASLG IVS3nt −169 T > ΔT polymorphisms, respectively. The products of digestion included three fragments (184, 47 and 101 bp) for the −670 G allele, two fragments (210, 29 bp) for the −124 G allele, and two fragments (162 and 23 bp) for the −169 T allele.

Both PCR and RFLP products were visualized after electrophoresis (100 V/45 min) in a 4% agarose gel in 1× TAE buffer (40× TAE stock – TrisBase 1.6 M, Na acetate 0.8 M and EDTA – Na_2 40 mM/1000 mL deionized water) containing 5 μL of Syber Safe®, using transillumination with a source of ultra-violet light.

2.4. Statistical analysis

The genotypic and allelic frequencies observed were obtained by direct counting. The comparison between allele and genotype frequencies were calculated using the G test. The association analysis between the genotype frequencies and the arithmetic average

Table 1
Genotype and allele frequencies of FAS and FASL polymorphisms among HTLV infected persons (TSP/HAM and asymptomatic) and a control group.

Genotype profile	HTLV patients *n* (%)	Control group *n* (%)	p^*	TSP/HAM*n* (%)	Asymptomatic*n* (%)	p^*
FAS −670 A>G						
AA	15 (22.73)	37 (19.27)	0.0160	11 (42.31)	4 (10.00)	0.0005
AG	20 (30.30)	96 (50.00)		2 (7.69)	18 (45.00)	
GG	31 (46.97)	59 (30.73)		13 (50.00)	18 (45.00)	
A	0.3788	0.4427	0.4385	0.4615	0.3250	0.0671
*G	0.6212	0.5573		0.5385	0.6750	
FASLG IVS2nt −124 A>G						
AA	59 (89.39)	159 (82.81)	0.3743	23 (88.46)	36 (90.00)	0.6232
AG	6 (9.09)	31 (16.15)		3 (11.54)	3 (7.50)	
GG	1 (1.52)	2 (1.04)		0 (0.00)	1 (2.50)	
*A	0.9394	0.9089	0.5840	0.9423	0.9375	0.8771
*G	0.0606	0.0911		0.0577	0.0625	
FASLG IVS3nt −169 T> ΔT						
TT	51 (77.28)	153 (79.69)	0.7665	17 (65.39)	34 (85.00)	0.1259
TΔT	14 (21.21)	38 (19.79)		9 (34.61)	5 (12.50)	
ΔTΔT	1 (1.51)	1 (0.52)		0 (0.00)	1 (2.50)	
T	0.8788	0.8958	0.8756	0.8269	0.9125	0.1123
*ΔT	0.1212	0.1042		0.1731	0.0875	

* Test G.

of the values of proviral load, as well as, the TCD4+ and TCD8+ lymphocyte counts were performed by the Mann–Whitney and Test-*t*, respectively. The analysis and the Hardy–Weinberg equilibrium were calculated using the software BioEstat 5.0 (Ayres et al., 2007). A p value <0.05 was considered to be statistically significant.

3. Results

Allele frequency and genotype distribution of FAS and FASLG genes of both HTLV infected and control groups are shown in Table 1. The allele frequency for FAS −670G was 0.6212 and 0.5573 among HTLV patients and control subjects, respectively. The frequencies for FASLG −124G and FASLG −169ΔT were 0.0606 and 0.1212 among HTLV infected subjects and 0.0911 and 0.1042 among control group, respectively. The differences observed were not statistically significant.

The genotype FAS −670GG was more frequent among HTLV infected subjects (46.97%) than in the control group (30.73%), showing a difference which was statistically significant ($p = 0.0160$, Table 1).

The genotypic frequency observed among HTLV patients was not in Hardy–Weinberg equilibrium for −670 FAS polymorphism ($p = 0.0038$), but it was in equilibrium for FASLG −124 and FASLG −169 polymorphisms ($p = 0.1014$, $p = 0.9721$, respectively), as well as within the control group for the three polymorphisms ($p = 0.8537$, $p = 0.7242$, $p = 0.4021$; data not shown).

The allele and genotype frequencies were also compared according to the presence or absence of overt disease clinically diagnosed as TSP/HAM.

The allele frequencies for FAS −670G were 0.5385 and 0.6750 among TSP/HAM and asymptomatic HTLV infected persons, respectively. For FASLG −124G and FASLG −169ΔT frequencies were 0.0577 and 0.1731 among TSP/HAM patients and 0.0625 and 0.0875 among asymptomatic subjects, respectively. The differences were not statistically significant.

FAS polymorphism showed a higher prevalence of genotype FAS −670AA among TSP/HAM patients (42.3%), as compared to asymptomatic individuals (10%), a difference which was statistically significant ($p = 0.0005$; Table 1).

The average of TCD4+ and TCD8+ lymphocyte counts among HTLV patients and controls are shown in Table 2. No difference was statistically significant. TCD4+ lymphocytes among HTLV infected subjects ranged from 581 to more than 2000 cells/μL with an average of 1164.81 cells/μL, in comparison to a range from 428 to more than 2000 cells/μL, with an average of 1059.59 cells/μL, in the control group. TCD8+ lymphocyte counts ranged from 188 to 1673 cells/μL, with an average of 623.67 cells/μL, and from 162 to 1368 cells/μL with an average of 610.85 cells/μL, respectively.

When the group of infected patients was divided between symptomatic and asymptomatic subjects it was shown that among asymptomatic patients the count of TCD4+ cells ranged from 581 to more than 2000 cells/μL with an average of 1233.96 cells/μL. Among TSP/HAM patients it ranged from 674 to 1883 cells/μL with an average of 1095.65 cells/μL. TCD8+ lymphocytes count in asymptomatic patients ranged from 297 to 1049 cells/μL with an average of 670.77 cells/μL. In TSP/HAM patients TCD8+ lymphocytes count ranged from 188 to 1673 cells/μL with an average of 576.57 cells/μL. There were no statistically significant differences. Furthermore, the differences between LTCD4+/LTCD8+ ratios regarding the genotypes did not show statistical significance.

Table 3 shows the average proviral load among TSP/HAM and asymptomatic subjects according to the genotype and allele frequencies of FAS and FASLG polymorphisms. The statistical analysis showed significant difference regarding the presence or absence of the mutant alleles to each one of the polymorphisms.

Table 2
TCD4+ and TCD8+ lymphocytes among HTLV patients and a control group according to the genotype and allele frequencies of FAS and FASL polymorphisms.

Genotypes profiles	HTLV patients (n)		Control group (n)		p^*		TSP/HAM (n)		Asympt.[a] (n)		p^*	
	Anal.[b]	CD4 CD8 average	Anal.[b]	CD4 CD8 average	TCD4+	TCD8+	Anal.[b]	CD4 CD8 average	Anal.[b]	CD4 CD8 average	TCD4+	TCD8+
FAS −670												
AA	15	1148.557/539.875	37	1020.649/569.405	0.0708	0.9914	11	1275.364/605.000	4	1021.750/474.750	0.2662	0.5162
AG+GG	51	1096.594/629.539	155	1054.235/623.212	0.2318	0.8801	15	1089.327/635.866	36	1103.861/587.874	0.3788	0.1547
FASLG −124												
AA	59	1130.324/640.445	159	1070.132/616.333	0.4593	0.7901	23	1224.870/706.000	36	1035.778/574.889	0.1715	0.1056
AG+AG	7	1293.334/502.417	33	795.395/571.597	0.0550	0.4743	3	1303.667/400.667	4	1283.000/604.167	0.6335	0.2230
FASLG −169												
TT	51	1108.971/595.662	153	1040.843/607.647	0.1796	0.5206	17	1169.824/633.353	34	1048.118/557.971	0.5646	0.3691
TΔT+ΔTΔT	15	1270.456/752.402	39	966.066/623.212	0.1207	0.3300	9	1355.111/741.444	6	1185.800/763.360	0.1092	0.7543

* Student's *t*-test.
[a] Asymptomatic.
[b] Analyzed.

Table 3
Proviral load counts among TSP/HAM and asymptomatic individuals according to the genotype and allele frequencies of FAS and FASL polymorphisms.

Genotypes profiles	TSP/HAM (*n*)		Asymptomatic (*n*)		*p*
	Analyzed	Proviral load	Analyzed	Proviral load	
FAS −670 (A>G)					
AA	11	1575.957	4	84.798	0.0265
AG + GG	15	769.803	36	229.488	<0.0001
FASLG IVS2nt −124 (A>G)					
AA	23	1251.570	36	234.667	<0.0001
AG + GG	3	1167.253	4	50.913	0.0970
FASLG IVS3nt −169 (T > ΔT)					
TT	17	1320.432	34	242.092	<0.0001
TΔT + ΔTΔT	9	1093.392	6	74.064	0.0169

Table 4
Combined genotypes frequencies of the FAS and FASL polymorphisms among HTLV patients and a control group as well as TSP/HAM and asymptomatic patients.

Associated genotypes	HTLV patients *n* (%)	Control group *n* (%)	*p**	TSP/HAM *n* (%)	Asymptomatic *n* (%)	*p**
FAS −670/FASLG IVS2nt −124						
AA/AA	12 (18.18)	33 (17.19)	0.1964	9 (34.61)	3 (7.50)	0.0379
AA/GG + AG	3 (4.55)	4 (2.08)		2 (7.69)	1 (2.05)	
GG + AG/AA	47 (71.21)	126 (65.63)		14 (53.85)	33 (82.50)	
GG + AG/GG + AG	4 (6.06)	29 (15.10)		1 (3.85)	3 (7.50)	
FAS −670/FASLG IVS3nt −169						
TT/AA	14 (21.21)	30 (15.62)	0.3721	10 (38.46)	4 (10.00)	0.0030
TT/GG + AG	37 (56.06)	123 (64.06)		7 (26.92)	30 (75.00)	
ΔTΔT + TΔT/AA	1 (1.52)	7 (3.65)		1 (3.85)	0 (0.00)	
ΔTΔT + TΔT/GG + AG	14 (21.21)	32 (16.67)		8 (30.77)	6 (15.00)	
FASLG IVS2nt −124/FASLG IVS3nt −169						
AA/TT	46 (69.70)	121 (63.02)	0.1502	15 (57.69)	31 (77.50)	0.3686
AA/ΔTΔT + TΔT	13 (19.70)	38 (19.79)		8 (30.77)	5 (12.50)	
GG + AG/TT	5 (7.57)	32 (16.67)		2 (7.69)	3 (7.50)	
GG + AG/ΔTΔT + TΔT	2 (3.03)	1 (0.52)		1 (3.85)	1 (2.50)	

* Test G.

Genotype polymorphisms of FAS and FASLG were grouped according to HTLV infected patients and control group as well as TSP/HAM and asymptomatic patients (Table 4). Statistically significant associations were observed when combining FAS −670 and FASL −124 ($p = 0.0379$), as well as, FASLG −169 and FAS −670 ($p = 0.0030$), when comparing TSP/HAM and asymptomatic individuals.

4. Discussion

The study examined the occurrence of single nucleotide polymorphism (SNP) in *FAS* and *FASLG* genes, and their association with the susceptibility to HTLV-1 infection as well as to the risk of progression to TSP/HAM. The association of the genotypes for both FAS and FASLG polymorphisms may contribute to the prediction of some effector immune response to eliminate the virus or to render the host susceptible to the development of TSP/HAM.

Previous studies have suggested that *FAS* promoter polymorphism are associated with the risk of diseases including cervical carcinogenesis, esophageal squamous-cell carcinoma, prostate cancer and squamous cell carcinoma of the head and neck (Zhang et al., 2006; Ueda et al., 2005; Sun et al., 2004; Lima et al., 2008), although some studies have reported no association between *FAS* −670 polymorphism and diseases like rheumatoid arthritis, systemic lupus erythematosus, breast cancer and multiple sclerosis (Huang et al., 1999; Zhang et al., 2006; Sibley et al., 2003; Crew et al., 2007; Niino et al., 2002). In the present study, we observed that the *FAS* −670GG genotype showed a higher prevalence among HTLV-1 infected persons than in controls, but the genotype *FAS* −670AA was more frequent among TSP/HAM patients as compared to the asymptomatic individuals, suggesting that the *FAS* −670A/G polymorphism may be associated, not only with the susceptibility to HTLV infection, but also with the progression to TSP/HAM. The process seems to be controlled by a two-step mechanism in which the already HTLV-1 infected individuals carrying the FAS −670AA genotype carry a great chance and a higher susceptibility to progress to overt clinical disease such as TSP/HAM.

It is possible that the physical location of a SNP of *FAS* (−670A/G) may favour its binding to the site of the signal traducer and activator of transcription (STAT1), and it would be sufficient for the up and down regulation of the expression of the *FAS* gene. The results presented herein describe a strong association between this SNP and HTLV infection and suggest that HTLV-1 infected subjects carrying by the *FAS* −670GG genotype may have a lower affinity to STAT1 binding as compared to subjects carrying the *FAS* −670AA genotype. This could lead to a decrease or increase of the apoptotic potential of the FAS receptor among patients carrying *FAS* −670GG and AA genotypes, respectively, which corroborates a recent result showing that this functional *FAS* promoter polymorphism is significantly associated to the susceptibility to HTLV-1 and to the clinical manifestation and survival of HTLV-1 patients presenting adult T-cell leukemia – ATL (Farre et al., 2008), although it remains unclear how the presence of this polymorphism could influence the susceptibility to infection.

The analysis of 66 HTLV-1 infected patients and 192 control subjects showed that the *FASLG* −124 and −169 polymorphisms (both located within intronic regions of the *FASLG* gene) are not associated with the susceptibility to the infection. The analysis of the same groups for the *FAS* −670A/G polymorphism showed association with an increased risk for HTLV infection but not for the *FASLG* gene polymorphisms. This polymorphism was initially described among Sjögren's syndrome patients (Bolstad et al., 2000) and few studies have been reported about *FASLG* IVS2nt −124 and *FASLG* IVS3nt −169 (Pinti et al., 2002; Zhang et al., 2006; Vasilescu et al., 2004).

FAS receptor is expressed in the TCD4$^+$ cell surface which is the main target of HTLV-1 infection, thus the activation of this receptor by interacting with its natural ligand FASLG may be induced

by the viral infection (Debatin et al., 1994; Richardson et al., 1990; Shirono et al., 1989; Worner et al., 1990). The current results suggest that the average levels of the $TCD4^+$ and $TCD8^+$ lymphocytes between patients and control groups with the presence of the alleles *FAS* −670G, *FASLG* −124G or *FASLG* −169ΔT, show no difference that implies in association of these polymorphisms, but the proviral load count showed statistically significant difference according to the genotype profile. Considering that there was no significant difference regarding viral load counts when assessing intra-group values, it is possible that the differences were attributed to the clinical status and not to the genetic background.

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