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Association of single nucleotides polymorphisms of ENTDP1 gene with susceptibility to HTLV and prognosis to HTLV-associated myelopathy (HAM/TSP)

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INTRODUCTION

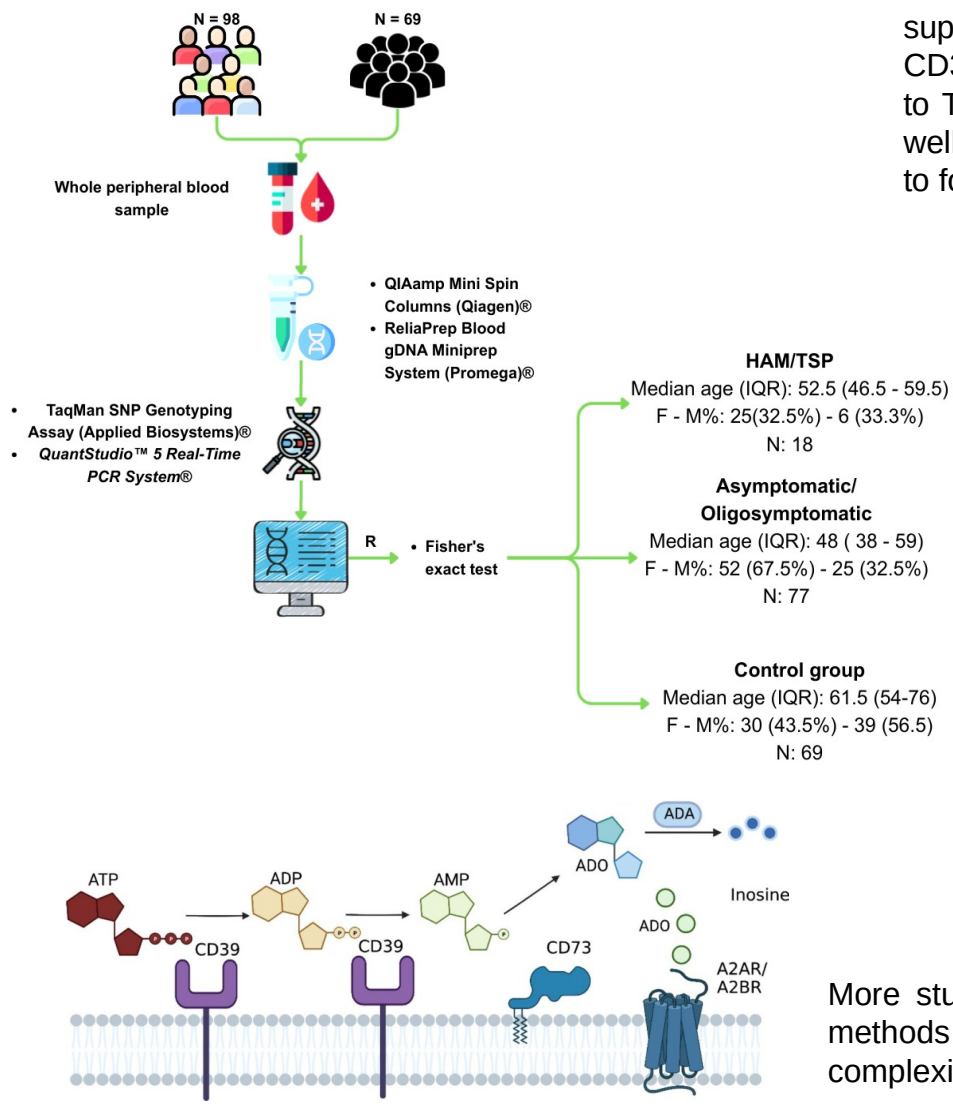
HTLV is a neglected retrovirus that affects around 5-10 million people worldwide, with the highest absolute number of cases in Brazil. Around 0.3-3.8% of people living with HTLV (PLwHTLV) develop HTLV-associated myelopathy, known as HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), a neurological dysfunction mainly resulted from the host's exacerbated immune response to the virus. Currently, there are no established biomarkers to assess the risk of progression to HAM/TSP, among the candidates it is CD39, an ectonucleotidase that mediates the purinergic pathway, who is overexpressed in regulatory T cells (Treg) in patients with HAM/TSP.

OBJECTIVES

In this context, our study aimed to investigate the association of single nucleotide polymorphisms (SNPs) in the gene which encodes CD39 (ENTPD1), with the infection by HTLV and development of the HAM/TSP.

MATERIALS AND METHODS

Between January 2023 to 2024 was collected blood and clinical data of 98 PLwHTLV assisted at Oswaldo Cruz University Hospital (HUOC-UPE), and control group included 69 HTLV-negative individuals, the Ethics Committee Approval was no. 5.543.999. Genotyping was carried out by TaqMan evaluating the rs10748643 and rs11188513, the genotypes were organized into diplotypes according to the levels of expression reported in the literature, followed by statistical analysis in R.



RESULTS AND DISCUSSION

The presence of ENTPD1 diplotypes associated high and moderate expression levels of CD39 was linked with a lower risk of infection by HTLV, either asymptomatic/oligosymptomatic cases (p-value: 0.01; OR: 0.41; IC 95%: 0.20-0.84) as carriers of HAM/SP (p-value: 0.02; OR: 0.26; IC 95%: 0.06-0.90). Just the diplotypes AG/CT was associated with the susceptibility of infection by HTLV, contemplating both cases asymptomatic/oligosymptomatic (p-value: $6.5x10^{3}$; IC 95%: 0-0.64) and HAM/TSP individuals (p-value: 0.04; IC 95%: 0-1.18).

Diplotypes	HAM/TSP vs Asymptomatic/ Oligosymptomatic		Asymptomatic/ oligosymptomatic vs. Control group		HAM/TSP vs Control group	
	P-value[4] (OR)	CI 95%	P-value (OR)	CI 95%	P-value (OR)	CI 95%
High expression genotypes vs. Medium/low expression	0.58 (1.56)	0.46 - 6.19	**0.01 (0.41)**	0.20 - 0.84	**0.02 (0.26)**	0.06 - 0.90
GG/TT [1]	Reference		Reference		Reference	
GG/CT [1] +	-		-		**2.35 x 10^{-5}(-)**	0 - 0.10
AG/TT [1] ++	0.29 (-)	0.33 - inf	**1.68 x 10^{-7}** (-)	0 - 0.11	**1.24 × 10^{-5} (-)**	0 - 0.86
GG/CC [2]	-		-		Reference	
AA/TT [2] ++	0.56 (0.38)	0.03 - 5.84	**1.27 × 10^{-6}** (-)	0 - 0.10	**2.45 x 10^{3} (-)**	0 - 0.41
AG/CT [2] **	0.76 (0.77)	0.18 - 2.96	**6.5 × 10^{-3}** (-)	0 - 0.64	**0.04** (-)	0 - 1.18
AG/CC [3]	1 (-)	0.006 - inf	-		-	
AA/CT [3]	1 (1.72)	0.14 - 94.3	-		-	
AA/CC [3]	0.55 (-)	0.20 - inf	-		-	

The rs10748643 and rs11188513 variants are associated with susceptibility to HTLV infection, but do not have the capacity to support the prognosis of PLwHTLV. Indicating that the alteration in CD39 expression in PLwHTLV with HAM/TSP is possibly specific to Treg cells, requiring the evaluation of other ENTPD1 SNPs as well as the evaluation of serum levels of CD39 as a potential tool to follow-up of PLwHTLV.

Diplotypes	HAM/TSP	Asymptomatic/ oligosymptomatic	Control group
Frequências	Alleles, N (%)	Alleles, N (%)	Alleles, N (%)
High expression	5 (27.8)	29 (37.7)	41 (59.4)
Medium expression	12 (66.7)	34 (44.2)	28 (40.6)
Low expression	1 (5.5)	14 (18.1)	0 (0)
GG/TT [1]	5 (27.8)	20 (26)	0 (0)
GG/CT [1]	0 (0)	0 (0)	19 (24.7)
AG/TT [1]	0 (0)	9 (11.7)	22 (28.6)
GG/CC [2]	0 (0)	0 (0)	5 (6.5)
AA/TT [2]	2 (11.1)	3 (3.9)	11 (14.3)
AG/CT [2]	10 (55.5)	31 (40.3)	12 (15.6)
AG/CC [3]	0 (0)	1 (1.3)	0 (0)
AA/CT [3]	1 (5.6)	7 (9.1)	0 (0)
AA/CC [3]	0 (0)	6 (7.8)	0 (0)

CONCLUSION

More studies on HTLV and ENTPD1 are needed, employing advanced methods like next-generation sequencing to better capture biological complexity and identify relevant genetic markers.

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