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Research paper

Association between -221 X/Y polymorphism of mannose-binding lectin (MBL) gene and susceptibility to HTLV-1 infection among people from an endemic region in the Northeast of Iran

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ABSTRACT

Background: The role of (MBL) gene single nucleotide polymorphisms (SNPs) has been well documented in susceptibility to several infectious diseases. This study aimed to investigate the association between two MBL promoter variants, -550 H/L and -221 X/Y, and susceptibility to HTLV-1 infection.

Methods: A total of 153 subjects infected with HTLV-1 and 169 healthy controls were recruited. SSP-PCR method was applied to genotype -550 H/L and -221 X/Y polymorphisms. Associations between genotypes or alleles and susceptibility to HTLV-1 infection were analyzed by Pearson's Chi-Square. $p \leq .05$ was considered statistically significant.

Results: Statistical analysis revealed significant differences between the two groups in the -221 position ($\chi 2 = 19.709$; $p = .000$). The MBL YX genotype was significantly associated with increased susceptibility to HTLV-1 (OR = 2.73, %95 CI = 1.74–4.30). Combined genotype of the two loci showed that the HYHX genotype (OR = 2.20, 95% CI = 1.95–2.48) and LYLX (OR = 1.97, 95% CI = 1.13–3.45) were associated with an increased risk of HTLV-1 infection.

Conclusion: Our results represent the importance of -221 X > Y variants in acquisition of HTLV-1 as this is the case for several other viral and bacterial infections.

1. Introduction

The human T-lymphotropic virus 1 (HTLV-1) is a member of retroviridae family and deltaretrovirus genus (Tezuka et al., 2018). It was first discovered in the United States in the early of 1980s (Hoshino, 2012). Approximately 10–20 million people worldwide are infected with HTLV-1. Although the virus is spread throughout the world, but it is endemic in some areas including the Southwest of Japan and Okinawa, the Caribbean islands, Central and South of Africa, parts of the Middle East, and the Southeast of the United States (Vallinoto et al., 2018; Willems et al., 2017). Some area in the Northeast of Iran is also considered as an endemic region (Salehi and Mobini, 2015). Most infected people remain asymptomatic and only 1–5% develop an HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) or adult T-cell leukemia (ATL) (Gouhier et al., 2013; Lee et al., 2012). Also, in a small percentage of the carriers, the virus produces various diseases such as dermatitis, polymyositis, autoimmune thyroiditis, uveitis, and chronic respiratory illnesses (Nejmeddine and Bangham, 2010).

Like other infectious diseases, susceptibility to infection and the course of associated disease is determined by virus and host genetic factors and also the environment (Coelho et al., 2013). The influence of host genetic polymorphisms has been reported by several investigations. For example, Carlos et al. reported that a polymorphism in promoter of FAS gene (−670A > G) seems to be associated with susceptibility to HTLV-1 (Vallinoto et al., 2012). Also, other studies showed polymorphisms in CD209, human leukocyte antigen-G (HLA-G) and MASP-2 have roles in the susceptibility to HTLV-1 (Alves et al., 2016; Coelho et al., 2013; Kashima et al., 2009).

Mannose-binding lectin (MBL) is a critical component of innate immune system. MBL, produced by the liver cells, recognizes and binds several carbohydrate structures present on the surfaces of pathogenic micro-organisms and triggers complement activation in an antibody and C1-independent manner (Auriti et al., 2017; de Morais et al., 2019). MBL forms complex with a serine protease, MBL associated serine

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protease 2 (MASP2), and creates a C3 convertase enzyme (Matsushita et al., 2013).

The gene encoding MBL is located on chromosome 10q11.2-q21 and comprises four exons (Garred et al., 2006). Several single nucleotide polymorphisms (SNPs) have been identified in coding and regulatory sequences of MBL gene, some of them may cause quantitative or qualitative changes in the gene expression. Two functional polymorphisms have been found at promoter region in positions -550 H/L (rs11003125) and -221 X/Y (rs7096206) which have been shown to affect expression of the MBL gene (Eisen and Minchinton, 2003; Minchinton et al., 2002). The haplotypes HY, LY, and LX correlate with high, medium, and low levels of plasma MBL respectively (Minchinton et al., 2002). The impact of MBL gene polymorphism on susceptibility to HTLV-1 has been reported in different regions and among different races (Alves et al., 2007; Coelho et al., 2013; Pontes et al., 2005). Victor et al., have shown that the MBL low and MBL defective (low or deficient) combined-genotypes were associated significantly with HTLV-1 infection susceptibility while high producer combined-genotypes were associated with protection against HTLV-1 (Coelho et al., 2013). Pontes et al. reported an increased risk of HTLV-1 infection in Brazilian population bearing BB and OO genotypes (Pontes et al., 2005). Alves et al. revealed a higher prevalence of allele X in position -221 among HTLV-1 infected Brazilian patients (Alves et al., 2007).

The purpose of this study was to identify the role of MBL gene promoter polymorphisms (−550 H/L and -221 X/Y) in susceptibility to HTLV-1 infection among blood donors in Khorasan Razavi provine, which is considered as an HTLV-1 endemic region of Iran (Fig. 1).

2. Materials and methods

2.1. Samples

This case-control study was conducted on 153 HTLV-1 infected patients and 169 healthy blood donors as control group. Both patients and controls were from the same geographic area (Khorasan Razavi) and were matched for age and sex. HTLV-1 infection was diagnosed by a commercial ELISA assay (MPD HTLV-I/II ELISA 4.0, Singapore) and confirmed by a Western blot kit (MP Diagnostics HTLV Blot 2.4, Singapore). All participants were also tested negative for HIV-1, HBV and HCV infections. The study was approved by ethic committee of High Institute for Research and Education in Transfusion Medicine. Informed consent was obtained from all subjects.

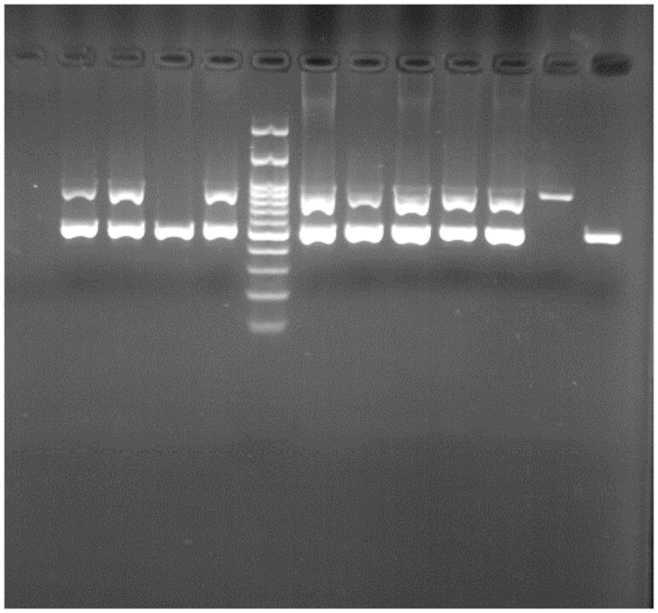

Fig. 1. Gel electrophoresis of SSP-PCR reactions for -550 H/L and -221 Y/X polymorphisms.
PCR reactions for each allele of the two variants were performed separately; PCR products were mixed two by two (each from a variant) and electrophoresed in a single lane. From left to right, lane 1 is negative control, lanes 2–5 and 7–13 are samples and lane 6 is 100 bp DNA size marker. Allele C of -550 H/L and allele G of -221 Y/X are represented by an 815 and 512 bp bands respectively.

Table 1
Primers used in PCR-SSP reactions.

Primer	Sequence (5′ → 3′)	Product length (bp)
Hf	GCTTACCCAGGCAAGCCTGT**G**	815-bp
Lf	GCTTACCCAGGCAAGCCTGT**C**	815-bp
Xf	CCATTTGTTCTCACTGCCAC**C**	512-bp
Yf	CCATTTGTTCTCACTGCCAC**G**	512-bp
Mblr	CAGCCCAACACGTACCTGGT	–

Polymorphic nucleotides have been shown in bold. Mblr is the common reverse primer.

2.2. Molecular analysis

Lymphocytes were separated from EDTA-anticoagulated blood by Ficoll density gradient (Lymphsep, Biosera; UK). Genomic DNA was extracted by a commercial assay (*Prim Prep* Genomic DNA isolation kit from blood, GeNet Bio, Seoul, Korea).

SNPs located within the promoter of MBL (-550 H/L and -221 X/Y variants) were genotyped by sequence-specific primer polymerase chain reaction (SSP-PCR) assay. Primers sequences have been described previously (Boldt and Petzl-Erler, 2002) and have been shown in Table 1.

The PCR reactions were performed in a final volume of 10 µl using 0.1 µM of each primer and 10–50 ng of genomic DNA. The amplification protocol starts with a 6 min denaturation step at 96 °C, followed by 10 cycles of 30 s at 94 °C, 30 s at 63 °C and 30 s at 72 °C; followed by 23 cycles of 30 s at 94 °C, 30 s at 61 °C and 30 s at 72 °C, and the final extension of 5 min at 72 °C. PCR products were electrophoresed on a 1.5% agarose gel and visualized under ultraviolet light by a DNA intercalating dye (Green viewer, Parstous, Iran).

SSP-PCR results were validated by sequencing of several samples of different genotypes.

2.3. Statistical analysis

Allele, genotype and haplotype frequencies were calculated by direct gene counting. Associations between MBL genotype or alleles and susceptibility to HTLV-1 infection were analyzed by Pearson's Chi-Square ($\chi 2$). Statistical analyses were performed with SPSS v16.0 (SPSS Inc., Chicago, IL, USA). The threshold for statistical significance was set to 5% ($p \leq .05$).

3. Results

This case-control study included 153 subjects infected with HTLV-1 (83.7% male and 16.3% female, mean age = 38.4 years) and 169 healthy blood donors as control group (76.4% male and 23.6% female, mean age = 41.1). Table 2 represents allele and genotype frequencies for −550 H/L and − 221 X/Y variants in two groups. The genotype differences between the two groups were statistically significant in the -221 position. We found a significant difference in the frequencies of the genotypes YY and YX, which were 40.5% and 57.5% among HTLV-infected and 62.1% and 33.1% among controls. The MBL YX genotype was significantly associated with increased susceptibility to HTLV-1 (57.5% in patients vs. 33.1% in controls, OR = 2.73, %95 CI = 1.74–4.30). In addition, X allele showed a significant association with increased risk of HTLV-1 infection (OR = 1.64, 95%

Table 2
Frequency of -550 H/L and -221 X/Y alleles and genotypes among HTLV-1 infected patients and controls.

SNP	HTLV-1 infected No. (%)	Control No. (%)	OR (95% CI)
-550 H/L (rs11003125)			
H	126 (41.1)	141 (41.7)	0.98 (0.71–1.34)
L	180 (58.8)	197 (58.2)	1.02 (0.75–1.40)
Total	306 (100)	338 (100)	
HH	30 (19.6)	25 (14.8)	1.40 (0.78–2.52)
HL	66 (43.1)	91 (53.8)	0.65 (0.42–1.01)
LL	57 (37.3)	53 (31.4)	1.30 (0.82–2.10)
-221 X/Y (rs7096206)			
X	94 (30.7)	72 (21.3)	1.64 (1.15–2.34)
Y	212 (69.2)	266 (78.6)	0.61 (0.42–0.87)
Total	306 (100)	338 (100)	
XX	3 (2.0)	8 (4.7)	0.40 (0.11–1.55)
YX	88 (57.5)	56 (33.1)	2.73 (1.74–4.30)
YY	62 (40.5)	105 (62.1)	0.42 (0.26–0.65)

Table 3
Frequency of -550 H/L and -221 X/Y combined genotypes among HTLV-1 infected patients and controls.

Genotype	HTLV-1 infected No (%)	Control No (%)	OR (95% CI)
HYHY	18 (11.8)	24 (14.2)	0.81 (0.42–1.55)
HYLY	29 (19.0)	59 (34.9)	0.44 (0.26–0.73)
HYLX	37 (24.2)	31 (18.3)	1.42 (0.83–2.43)
HYHX	12 (7.8)	0 (0.0)	2.20 (1.95–2.48)
LYLY	15 (9.8)	22 (13)	0.73 (0.36–1.46)
LYLX	39 (25.5)	25 (14.8)	1.97 (1.13–3.45)
LXLX	3 (2.0)	6 (3.6)	0.54 (0.13–2.21)
LXHX	0 (0)	1 (0.6)	1.91 (1.72–2.12)

CI = 1.15–2.34) while Y allele conferred a protective effect against the HTLV-1 infection (OR = 0.61, 95% CI = 0.42–0.87).

Table 3 has summarized the frequency of combined genotypes of the two polymorphisms. Statistical analysis revealed that genotypes HYHX (OR = 2.20, 95% CI = 1.95–2.48) and LYLX (OR = 1.97, 95% CI = 1.13–3.45) were associated with an increased risk of HTLV-1 infection while genotype HYLY (OR = 0.44, 95% CI = 0.26–0.73) was associated with a decreased risk of the infection.

Table 4 represents frequencies of different haplotypes in both groups. The only significant difference between the case and control groups was for haplotype HX (OR = 4.56, 95% CI = 1.27–16.31) which significantly increased the risk of HTLV-1 infections.

There was no significant association between alleles and genotypes of -550 H/L polymorphism and the risk of the infection (Table 2).

4. Discussion

MBL is a key component of innate immunity (Matsushita et al., 2013). It has been realized that several polymorphisms in the MBL gene could alter the function of the protein and could result in susceptibility to infectious diseases (Eisen and Minchinton, 2003; Garcia-Laorden et al., 2008; Minchinton et al., 2002). Two of these variants, -551 H/L (rs11003125) and -221 X/L (rs7096206), have been extensively investigated in different diseases. Both are located in promoter region of the gene and cause a G > C substitution (Endeman et al., 2008; Halla et al., 2010). Here we report the association of one of these polymorphisms with the susceptibility to infection in a cohort of HTLV-1 infected population in Mashhad, an HTLV-1 endemic region in the Northeast of Iran.

Table 4
Frequency of −550 H/L and − 221 X/Y haplotypes among HTLV-1 infected patients and controls.

Haplotypes	HTLV-1 infected No (%)	Control No (%)	OR (95% CI)
HY	114 (37.3)	138 (40.8)	0.86 (0.63–1.18)
LY	98 (32.0)	128 (37.9)	0.77 (0.56–1.07)
LX	82 (26.8)	69 (20.4)	1.43 (0.99–2.06)
HX	12 (3.9)	3 (0.9)	4.56 (1.27–16.31)
Total	306 (100)	338 (100)	–

Our findings revealed that -221Y/X variant is associated with susceptibility to HTLV-1 infection. Allele Y confers protection against HTLV-1 while allele X increases the risk of infection (OR = 0.61 and 1.64, respectively, Table 2). The heterozygous XY also increases the risk of HTLV-1 (OR = 2.73). This is consistent with finding of several studies in HTLV-1(Alves et al., 2007) and other infectious diseases like tuberculosis (Chen et al., 2015; Da Cruz et al., 2013) and may be explained by lower MBL protein production when compared with wild-type YY genotype (Madsen et al., 1998; Vasconcelos et al., 2011).

The variant -550 H/L did not show any significant difference between the two groups. This was also reported by Alves et al. in HTLV-1 and Cristina in HCV (Alves et al., 2007; Halla et al., 2010). However, Wu et al. reported of association between this variant and susceptibility to tuberculosis infection (Wu et al., 2015).

Analysing combined genotypes of the two variants (-550 H/L and -221 Y/X) is indicative of association between specific genotypes and acquisition of the infection both as protective and as a risk factor. The HYHX and LYLX genotypes were associated with susceptibility to HTLV-1 and the HYLY genotype had a protective role. Our findings is partly consistent with those reported by Alves et al. although in that study the HYHX genotype was not associated with susceptibility to HTLV-1 infection (Alves et al., 2007). The differences observed in the allele and haplotype frequencies described in our study with those reported for Brazilian, Danish and Japanese can be attributed to the variety of the genetic background among different ethnic groups (Alves et al., 2007; Madsen et al., 1998; Matsushita et al., 1998).

In this research we did not determine proviral load of patient group. Previous studies by Nishimura et al. (Nishimura et al., 2003), Pontes et al. (Pontes et al., 2005), and Alves et al. (Alves et al., 2007) have analysed MBL mutations in HTLV-1 patients in order to determine a possible association with proviral loads, however they have produced different and even contradictory results (Alves et al., 2007; Nishimura et al., 2003; Pontes et al., 2005) so there is no strong evidence in support of MBL polymorphisms and HTLV-1 proviral load. Also, although determination of plasma MBL concentration is a direct marker of gene expression, but different studies showed the genotype and haplotype determination as a better choice especially because MBL is a component of acute phase reactant and its plasma concentration may be influenced by factors other than HTLV-1 infection (Madsen et al., 1998; Soltani et al., 2014; Steffensen et al., 2000).

5. Conclusions

In conclusion several studies have been documented the role of MBL polymorphisms in susceptibility to several viral and bacterial infections including HTLV-1. Our findings also support this role especially the -221 Y/X variant. It will be of great interest to investigate the possible role of MBL in the long-term complications of HTLV-1 infection like HAM/TSP and ATL.

Authors' contribution

AA performed laboratory tests. FM recruited the patients and controls and collected samples. MM designed the study and performed the statistical analysis. MS designed the study and prepared the manuscript.

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the High

Institute for Research and Education in Transfusion Medicine and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants.

Declaration of Competing Interest

The authors declared they have no conflict of interest.

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