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SHORT COMMUNICATION

HLA Class I Gene Polymorphism in Iranian Patients with Papillon-Lefevre Syndrome

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ABSTRACT

Background: Papillon-Lefevre Syndrome (PLS) is a rare autosomal recessive disorder characterized by diffused palmoplantar keratoderma and severe periodontitis. Increased susceptibility to infections due to impairment of the immune system is considered to be involved in pathoetiology of this disease. **Objective:** According to the crucial function of HLA molecules in immune responses and association between certain HLA class I alleles and some periodontal or skin diseases, this study was designed to evaluate the relation of HLA class I genes and PLS. **Method:** HLA class I genes were typed by PCR-SSP (Polymerase Chain Reaction with Sequence Specific Primers) method in eight Iranian PLS patients and 89 healthy controls. **Results:** The results showed no significant difference between the patients and controls. Moreover, identical haplotypes or genotypes were also observed among PLS patients and their healthy siblings. **Conclusion:** It seems that further genes are involved in genetic susceptibility to PLS. However the results of this study showed no significant association between HLA class I genes and PLS, molecular analyses of killer immunoglobulin-like receptors (KIRs) and MHC class I chain-related gene A and B (MICA/B) in PLS may clear many obscure points about the genetic factors involved in these diseases.

Keywords: Papillon-Lefevre Syndrome, HLA Class I, Iran

INTRODUCTION

PLS is a rare disorder which is characterized by the development of diffused palmoplantar keratoderma in association with severe periodontitis affecting both the primary and permanent teeth (1). Recurrent skin infections nail dystrophy and hyperhidrosis are also common in the patients (2, 3).

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PLS is transmitted as an autosomal recessive trait. However the etiology of PLS has not exactly been explained, impairment of the immune system and susceptibility to infections are considered as a number of causes involved in pathoetiology of this disease (4).

Despite the presence of accumulating data about PLS, the main cause of the disease which clarifies bout skin and periodontal manifestations has not been explained. Nevertheless, genetic and environmental factors are considered to be involved in the development of this disease (5). Cathepsin C (CTSC) gene was one of the first genes introduced as PLS causal genetic factor (6, 7). CTSC is a lysosomal cysteine proteinase acting as activator of various serine proteases in immune and inflammatory cells (8). It was shown that PLS arises only when CTSC activity is completely deficient and most of the patients are homozygote for CTSC gene mutations (9). However, symptomatic heterozygote patients as well as asymptomatic homozygous subjects with CTSC gene mutations have also been reported (10, 11). According to the existing data, CTSC gene mutations are only responsible for 70-80% of PLS cases (9, 12). Although CTSC deficiency may explain the severe periodontitis in PLS, the relation between the skin and periodontal presentations is still undefined (11).

Table 1. HLA class I allele frequencies in PLS patients and healthy controls

HLA-A	Patients	Controls	HLA-B	Patients	Controls	HLA-C	Patients	Controls
*01	1 (0.0625)	7 (0.0393)	*07	—	4 (0.0225)	*01	—	8 (0.0449)
*02	4 (0.2500)	45 (0.2528)	*08	▪4 (0.2500)	11 (0.0618)	*02	—	2 (0.0112)
*03	3 (0.1875)	12 (0.0674)	*13	—	2 (0.0112)	*03	—	10 (0.0562)
*11	1 (0.0625)	32 (0.1798)	*14	—	4 (0.0225)	*04	3 (0.1875)	51 (0.2865)
*24	2 (0.1250)	13 (0.0730)	*15	—	3 (0.0169)	*05	—	1 (0.0056)
*26	2 (0.1250)	7 (0.0393)	*18	4 (0.2500)	16 (0.0889)	*06	—	8 (0.0449)
*29	—	6 (0.0337)	*27	—	4 (0.0225)	*07	•6 (0.3750)	27 (0.1517)
*30	—	11 (0.0618)	*35	1 (0.0625)	35 (0.1966)	*08	—	7 (0.0393)
*31	—	2 (0.0112)	*38	1 (0.0625)	—	*12	4 (0.2500)	14 (0.0787)
*32	1 (0.0625)	10 (0.0562)	*39	—	1 (0.0056)	*14	—	6 (0.0337)
*33	1 (0.0625)	14 (0.0787)	*40	1 (0.0625)	18 (0.1011)	*15	1 (0.0625)	32 (0.1798)
*51	—	1 (0.0056)	*41	1 (0.0625)	1 (0.0056)	*16	2 (0.1250)	8 (0.0449)
*58	—	1 (0.0056)	*42	—	2 (0.0112)	*17	—	3 (0.0169)
*66	—	1 (0.0056)	*44	—	5 (0.0281)	*18	—	1 (0.0056)
*68	1 (0.0625)	8 (0.0449)	*45	—	3 (0.0169)	Total	16 (1.000)	178 (1.000)
*69	—	1 (0.0056)	*49	—	1 (0.0056)			
*74	—	7 (0.0393)	*50	—	2 (0.0112)			
Total	16 (1.000)	178 (1.000)	*51	4 (0.2500)	21 (0.1180)			
			*52	—	7 (0.0393)			
			*53	—	13 (0.0730)			
			*55	—	7 (0.0393)			
			*56	—	1 (0.0056)			
			*57	—	3 (0.0169)			
			*58	—	9 (0.0506)			
			*73	—	1 (0.0056)			
			*81	—	4 (0.0225)			
			Total	16 (1.000)	178 (1.000)			

▪p = 0.024, pc = 0.624, • p = 0.035, pc = 0.49

Numerous diseases have been found to be associated with HLA genes (13). Accumulating evidence support a direct role for HLA molecules in this process. However due to strong linkage disequilibria between the genes in highly dense HLA region, identification of the actual responsible gene is difficult (14). Since highly polymorphic HLA gene products are critically involved in the immune responses and these molecules have a critical role in many immune-related diseases, this study was designed to find a possible relation between HLA class I alleles and PLS in Iranian patients.

There are several controversial reports about the association of various HLA class I alleles and different types of periodontal diseases. Roshna et al. showed a positive association between HLA-B*15 and generalized aggressive periodontitis (15) while Shapira et al. found no significant association between HLA-A, B, C antigens and the localized form of early-onset periodontitis (16). Correlation between various HLA alleles has also been reported in psoriasis, a skin disease with hyperkeratosis (17, 18). The association between HLA-B*13, B*17, Cw*06 and DR7 antigens and a significant risk of psoriasis has been shown in Croatians (19). Such association with HLA-A*03, DR*07, Cw*01, and DR*08 in Kuwaiti children (20) as well as HLA-B*57 and DRB1*07 in Northeast of Turkey has also been reported (21). In this study; HLA-A, B, and C alleles were determined in eight PLS patients and 89 unrelated healthy controls using PCR-SSP (Biotest AG, Dreieich, Germany). The results of this study showed that HLA-B*08 allele was more frequent in PLS patients in comparison to normal controls (Table 1). However, this difference was not statistically significant when p-value was corrected by Bonferroni's correction ($p = 0.024$, $pc = 0.624$). This inconsistency might be explained by extensive variation of HLA allele frequencies among the races.

Moreover, identical haplotypes or genotypes were also observed among PLS patients and their healthy siblings (Table2). It seems that further genes in addition to HLA are involved in genetic susceptibility to PLS.

Machulla et al. reported a significantly increased occurrence of HLA-Cw*08 in rapidly progressive periodontitis and adult periodontitis (18). Recently, Gudjonsson et al. showed a strong association between HLA-Cw*0602 allele and psoriasis (22). The results of the current study also revealed that HLA-Cw*07 allele was more frequent in PLS patients than normal subjects. However, this association was not statistically significant ($p = 0.035$, $pc = 0.49$) which may be due to the small number of the PLS cases in this study.

Table 2. Distribution of HLA class I alleles in four PLS patients and their family members (P: patient, B: brother, S: sister, F: father, M: mother)

	HLA-A	HLA-A	HLA-B	HLA-B	HLA-C	HLA-C
Family 1						
P1	02	03	08	51	07	16
P2	26	03	08	38	07	12
B	02	03	08	51	07	16
F	02	03	08	38	07	12
M	02	26	38	51	16	12
Family 2						
P3	02	68	18	35	04	04
S	02	68	18	35	04	04
F	02	68	18	35	04	12
M	26	68	35	40	03	04
Family 3						
P4	01	24	18	52	12	12
F	01	02	35	52	04	12
M	11	24	18	44	12	14

MICA and MICB are also polymorphic genes located in the HLA class I region and encode for MHC class I like molecules which are mainly induced on epithelial cells in certain conditions like infections or malignant transformations.
These molecules are recognized by NKG2D which are mainly expressed on γδ T lymphocytes and NK cells (23). Thus the polymorphic MICA and MICB genes can also considered as excellent candidate genes for providing the genetic background of PLS.
KIRs are the major NK cell receptors which recognize HLA class I molecules on target cells. KIRs are divided into activating and inhibitory receptors and the balance between these signals regulates the NK cell function. Deregulation in this process might be involved in the pathogenesis of some diseases (24, 25).
However the results of this study showed no significant association between HLA class I genes and PLS. Future studies on KIR, MICA, and MICB genes in PLS and other periodontal and skin disorders with the same manifestations can clear many obscure points about the genetic factors involved in these diseases.

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