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Original Article

Association between TNFα-308 G/A and IFN-γ+874A/T Polymorphisms with Oral Lichen Planus

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Abstract

Background: Oral lichen planus (OLP) is a chronic disease that presents with inflammation and has a global prevalence of 0.1-4%. Lesions of the disease occur in the oral mucosa, gums, and rarely in the palate. This study aimed to investigate the relationship between this disease and TNFα-308G/A and IFN-γ+874A/T polymorphisms.

Methods: In this case-control study, oral mucosal samples were collected from 50 healthy subjects, and 50 OLP patients presented to the Kerman Faculty of Dentistry were enrolled using a simple sampling method. Subsequently, we used the amplification refractory mutation system polymerase chain reaction (ARMS-PCR) technique followed by sequencing to determine the presence of TNFα-308G/A and IFN-γ+874A/T polymorphisms in cases and controls.

Results: Compared to the control group, the prevalence of A and GA alleles of the TNF gene was higher than the prevalence of G and GG alleles in OLP patients, while the AA genotype of the gene was not found in OLP patients. Regarding IFN gene polymorphism, the relationship between the T allele and the risk of disease was discovered, but it was not statistically significant (*P* value: 0.068).

Conclusion: Although there is a strong relation between the A allele of TNF-α (-308G/A) polymorphism and the risk of OLP, this association between IFN-γ+874A/T genotype and the disease was not strong enough to predict the possibility of developing OLP.

Keywords: Oral lichen planus, TNF-α gene, IFN-γ gene, Polymorphism

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Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease that affects the oral cavity. The disease was first defined by Wilson in 1869. Lesions are mostly seen in buccal mucus, gingiva, and rarely in the palate (1). OLP is seen in 0.1% to 4% of people. It mostly affects middle-aged and old people, and the ratio of female-to-male involvement is 2:1 (2).

Symptoms include oral ulceration, sensitivity of oral mucosa to hot or spicy foods, mucosal pain, red or white patches on the oral mucosa, and oral ulceration (3). Clinical manifestations of the disease include ulcers, blisters, erythema, and white plaque (4). Clinical evaluation of oral lesions is based on six clinical forms, including reticular, papular, plaque-like, atrophic, erosive, and bullous. Greater malignancy potential is recognized for atrophic, erosive forms of OLP and a plaque-like lesion on the dorsal of the tongue (3).

The most common sites of LP lesions are lower limbs, wrists and shins, the folding surfaces, and the lower central part of the waist, which occur as purple, polygonal papules with flat surfaces and plaques with white reticular and itchy surfaces that are painful during scratching (5,6). Accurate evaluation of papules surfaces indicates fine white Wickham lines (7,8). Lichen planus can also occur in mucus, the most common site is oral and genital mucosa, and uncommon ones are conjunctivitis, nasal mucosa, larynx, esophagus, urethra, and anal mucosa (9). Diagnosis of OLP is based on clinical characteristics, but the pathology may also be needed. The cause of OLP is not known, but it has been found that the immune system plays a major role in the development of this disease (10).

The etiopathogenesis of OLP is the interaction of several factors including genetic factors, environment, and lifestyle (11). Several factors and triggers, such as systemic or local hypersensitivity, mental stress, microorganism

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infection, local trauma (Koebner phenomenon), and immune system response to antigens, play a role in the onset or development of OLP (6,12). The OLP lesions can be caused by drugs or dental materials and are called idiopathic lesions. Some studies have involved hepatitis C virus (HCV) in OLP etiology (11).

Genetic factors affecting the immune function are one of the factors affecting the etiology of this disease (13,14). Cytokines play an important role in the progression and pathogenesis of OLP, the gene polymorphisms of several cytokines such as interferon-gamma (IFN-γ), tumour necrosis factor alpha (TNF alpha), TNF-β, interleukin (IL)-4, and IL-10 have been found to be involved in the susceptibility of OLP (15,16). In addition, IFN-γ, as a proinflammatory cytokine, plays an important role in the defense and regulation of the host immune system in this disease. The gene responsible for the construction of IFN-γ is located on chromosome 12q24 and contains four exons and three introns (17). Polymorphism 874 (rs2430561), located in the first intron of the IFN-γ gene, directly affects INF-γ production (18). The T allele of this polymorphism may be responsible for building a higher level of IFN-γ (19). Codon 10 and 25 TGF-β1 genes regulate protein production in vivo and in vitro (20). T allele of this gene has been associated with increased TGF-β1 levels in plasma and reduced T-cell production. Cytokines regulating inflammation and immune response play a significant role in OLP pathogenesis. Based on race and ethnicity, the genotypes of polymorphisms may have different frequencies (21). In a study conducted in China, 3 (3p13-3q14) was identified as a candidate for OLP gene location (1).

In a cohort study in Saudi Arabia, the effect of TH1 and TH2 cytokines, IFNIL-6, and TGF on suspected OLP patients was investigated. This study was conducted on 42 patients with OLP and 195 healthy controls. INF-γ (874A/T), IL-6 (174G/C), and TGF-β1 509 C/T polymorphisms were genotyped. The results of this study showed that the A/T genotype of IFN-γ (874A/T) polymorphism can increase the risk of OLP, while the AA genotype is protective against the disease. They found that IL-6 (174G/C) and TGF-β1 (509C/T) polymorphisms did not show any relationship with the disease in the studied population (21).

The aim of this study was to investigate the relationship between TNFα - 308 G/A and IFN-γ+874A/T polymorphisms with OLP. OLP is a common disease and has many psychological and economic effects. Although the cause and pathogenesis of OLP are not fully understood, we believe that genetic polymorphisms have a major role in its etiology. In addition, there are limited and inconsistent data regarding the impact of these polymorphisms on the risk of OLP in different populations. As far as we know, this is the first study that examines these variants with OLP, and its results can be effective in treating and identifying the cause of the disease.

Methods

In this cross-sectional controlled study, 50 patients from 32 to 62 years old with OLP and 50 healthy individuals were included as case and control groups, respectively. Subjects with oral lesions referred to the clinic of Kerman Dental School were examined by an oral medicine specialist, and diagnosed patients with OLP were enrolled in the study. The control group consisted of patients who had presented to the clinic with complaints other than oral lesions. All subjects were sampled using their buccal mucosa after explaining the plan and obtaining consent. In this technique, the patient's mouth is thoroughly rinsed with water before swabbing. Then, the swab is rubbed vigorously inside each cheek and over the gums of the subject for 30 seconds. Finally, the swab is air-dried for one minute and is placed back into its original pouch. People with autoimmune diseases, viral illnesses such as hepatitis C, diabetes, arthritis, high blood pressure, malaria, and the ones taking heart disease medications were excluded from the study (22).

White blood cells' DNA found in saliva was extracted using the salting out method in a genetic laboratory. Using the amplification refractory mutation system polymerase chain reaction (ARMS-PCR) technique, the presence of TNFα-308 G/A and IFN-γ+874A/T polymorphisms in the case and control groups was determined. Simultaneously, some positive and negative samples were sequenced to confirm the diagnosis. Table 1 lists the primers used to detect these mutations.

After collecting, the data were analyzed using SPSS software version 20. The results were then evaluated using chi-square and independent t-test. A *P* value less than 0.05 is considered statistically significant.

Results

The studied population consisted of 19 (38%) affected men, 31 (62%) affected women, 19 (38%) healthy, men, and 31 (62%) healthy women. The mean age of

Table 1. PCR product lengths and primers used to determine mutations in TNFα-308 G/A and IFN-γ+874A/T

Primer	Sequence 5' to 3'	Size (bp)
TNF-α -308(G)	5'-ATAGGTTTTGAGGGGCATGG-3'	
TNF-α -308(A)	5'-AATAGGTTTTGAGGGGCATGA-3'	184
TNF-α-308 (Common)	5'-TCTCGGTTTCTTCTCCATCG-3'	
IFN-γ+874(T)	5'-TTCTTACAACACAAAATCAAATCT-3'	
IFN-γ+874(A)	5'-TTCTTACAACACAAAATCAAATCA 3'	264
IFN-γ+874 (common)	5'-TCAACAAAGCTGATACTCCA-3'	
F beta	CAA TGT ATC ATG CCT CTT TGC ACC	861
R beta	GAG TCA AGG CTG AGA AGA TGC AGG A	

the subjects was 45.33 ± 9.008 years. The mean age of diagnosis was 43.72 ± 8.23 years. In terms of tobacco use, ten males and three females were smokers. Three of these smokers consumed opium at the same time. Also, two male smokers consumed alcohol at the same time. Overall, 13 patients consumed opium, of whom six were male and seven were female (Table 2).

The most affected area was the buccal mucosa, with 37 out of 50 patients, which was significantly different from other areas. The second most affected area was the tongue with 14 out of 15 cases. The rest of the regions were close to each other in terms of frequency and these regions included a small percentage of the total involved regions. Among those affected by lichen planus, 56% had a family history, of whom 67.8% had a history in their first-degree relatives and 32.1% in second-degree relatives. About 44% of patients did not mention any family history.

For detecting mutations in TNFα-308G/A and IFN-γ + 874A/T, the ARMS-PCR test with the presence of normal primer (wild type), mutant primer (mutant), and common primer on each DNA sample of a patient with lichen planus and healthy control was performed. As can be seen in Figure 1, the amplified fragment length of the IFN-γ gene in mutant and normal state is 264bp.

This fragment in mutant and normal alleles of the TNF-α gene was 184bp (Figure 2). In ARMS, depending on whether a normal or mutant fragment is amplified for each experiment, the genotype can be one of the three states: normal homozygous, mutant homozygous, or heterozygous. The 861bp-long fragment is related to the globin gene amplification used as a control.

In total, 37 heterozygous (GA) for TNF-α and 16 heterozygous (AT) for IFN-γ were detected in patients, while 11 heterozygous for TNF-α, and 13 heterozygous for IFN-γ were found in the control group. There was no homozygous individual (AA) for the A allele in the TNF-α gene in patients with lichen planus and controls. While in the IFN-γ gene, 11 homozygous (TT) individuals were found for the T allele in the patient group and four in the control group. Finally, 13 normal homozygous (GG) individuals related to the TNF-α gene were observed in the case group and 39 in the control group. Also 23 normal homozygous (AA) individuals in the patient group and 33 individuals in the control group were detected in the IFN-γ gene (Tables 3 and 4). Comparison between the A allele (–308) and the normal G allele showed that the difference between healthy and lichen planus patients was statistically significant ($P < 0.05$) (Table 3). There was no statistically significant difference in the T allele (+874) and normal A allele between controls and lichen planus patients ($P > 0.05$) (Table 4).

The prevalence of G allele in the TNF-α gene was 63% in patients and 89% in controls. Allele A related to the same gene was found with a frequency of 37% in the patient group and 11% in the control group. In the IFN-γ gene, the prevalence of the A allele was 62% in patients and 79% in the control group. T allele related to this gene was observed in 38% of patients and 21% of controls (Table 5). Figure 3 shows the sequencing results of TNF-α and IFN-γ genes for some samples.

Discussion

According to studies, various causes, from immune to genetic factors, have been suggested for OLP, but the real reason for its occurrence has not been determined yet. In this study, the association between OLP disease and TNF-α-308G/A and IFN-γ + 874 A/T polymorphisms in

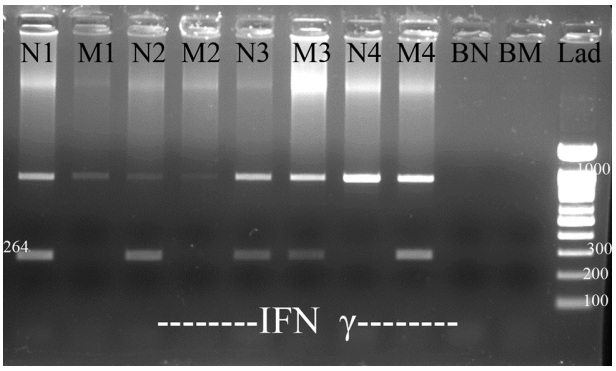

Figure 1. Gel image of ARMS-PCR product of IFN-γ + 874A/T gene polymorphisms. Control band: 861 bp DNA fragment. Normal and mutant bands: 264 bp DNA fragment. Lad: 100 bp ladder. N: Wild type. M: Mutant. B: Blank. Samples 1 and 2 are wild type (A/A). Sample 3 is heterozygote (A/T) and sample 4 is homozygote for T allele (T/T)

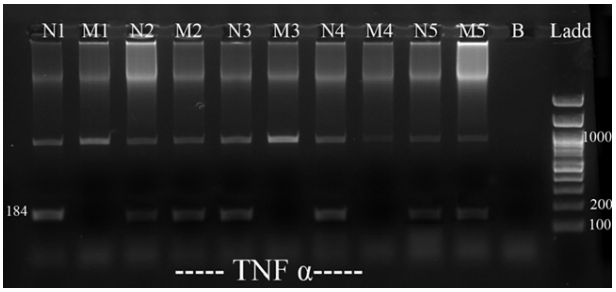

Figure 2. Gel image of ARMS-PCR product of TNF-α-308G/A gene polymorphism. Control band: 861 bp DNA fragment. Normal and mutant bands: 184 bp DNA fragment. Lad: 100 bp ladder. N: Wild type. M: Mutant. B: Blank. Samples 1, 3, and 4 are wild type (G/G). Samples 2 and 5 are heterozygote (G/A)

Table 2. Demographic data of case and control groups

Sex	Number (%)	Mean Age	Smoking (%)	Opium (%)	Alcohol (%)	Smoking & Opium	Smoking & Alcohol
Man	38 (38)	45.33 ± 9.008	10 (76.93)	6 (46.15)	4 (66.67)	3 (100)	2 (100)
Woman	62 (68)	45.33 ± 9.008	3 (23.07)	7 (53.85)	2 (33.33)	0 (0)	0 (0)

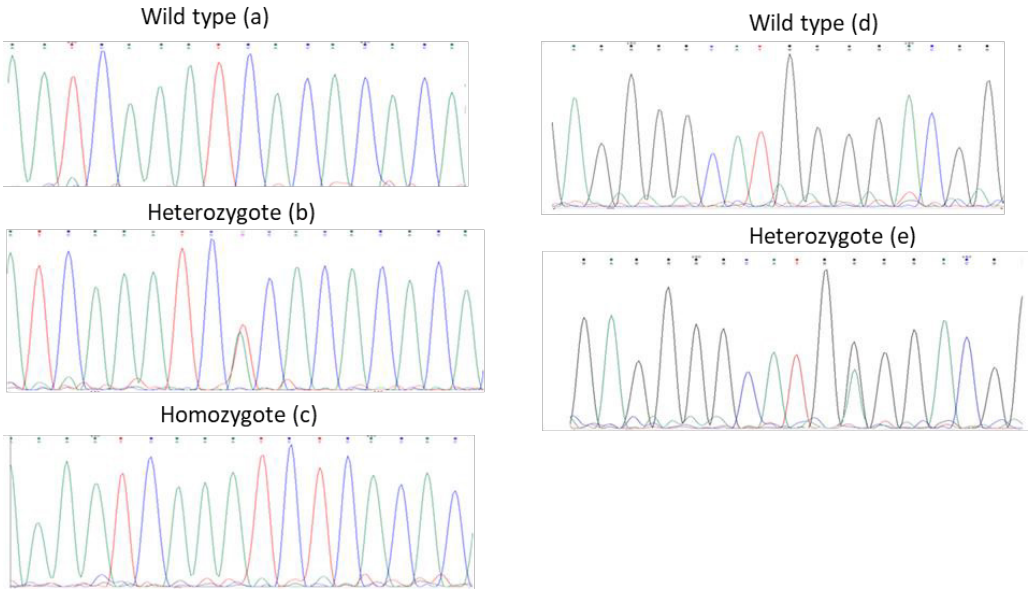

Figure 3. Results of TNF-α and IFN-γ gene sequencing in patients with lichen planus and healthy control group. IFN-γ+874A/T. a). Normal homozygote (AA). b): Heterozygous (TA). c): Homozygous mutant. (TT)TNF-α-308G/A (d: Normal homozygote (GG). e): Heterozygous (GA). This gene lacks homozygous polymorphism (AA)

Table 3. Prevalence of the TNF-α-308G/A polymorphism genotypes

	Cases, No. (%)			Controls, No. (%)			*P* value
	GG	AG	AA	GG	AG	AA	
TNF-α -308 G/A	13 (26)	37 (74)	0 (0)	39 (78)	11 (22)	0 (0)	<0.0001
Total	50 (100)			50 (100)			

Table 4. Prevalence of 874A/T+polymorphism genotypes in the IFN-γ gene

	Cases, No. (%)			Controls, No. (%)			*P* value
	AA	AT	TT	AA	AT	TT	
IFN-γ + 874A/T	23 (46)	16 (32)	11 (22)	33 (66)	13 (26)	4 (8)	0.068
Total	50 (100)			50 (100)			

Table 5. Prevalence of IFN-γ and TNF-α genes alleles

	IFN-γ		TNFα	
	T	A	A	G
Allele frequency (N) % in control	21 (21%)	79 (79%)	11 (11%)	89 (89%)
Allele frequency (N) % in cases	38 (38%)	62 (62%)	37 (37%)	63 (63%)

50 patients and 50 healthy controls was investigated.

The number of heterozygotes (AG) of TNFα-308 G/A polymorphism was higher in the patient group compared to the control group (74% in the patient group and 22% in the control group). However, the number of normal homozygous (GG) in this gene was higher in the control group than in patients (26% in the patient group and 78% in the control group). Although no allele A homozygous related to this gene was found in studied groups, increasing the number of heterozygotes in the patient group may indicate the association of this disease with polymorphism -308 G/A.

In 22% of patients, the+874A / T polymorphism in the IFN-γ gene was homozygous (TT), while it was homozygous in 8% of the control group. In addition, the number of heterozygotes in the patient group for this polymorphism was higher than in the control (32% in the patient group and 26% in the control group). The number of normal homozygotes related to the IFN-γ gene was higher in the control group than in the patients (66% in the control group and 46% in the patients). Therefore, the findings related to the IFN-γ gene suggest a link between+874A/T polymorphism and 308G/A polymorphism with lichen planus.

In a 2018 study, Zhou et al concluded that the TNF-α-308G/A polymorphism is a potential genetic marker for OLP (11), which is consistent with our study. Another study conducted in 2016 on the control and patient groups in Saudi Arabia found that the A/T genotype of the IFN-γ 874A/T polymorphism was associated with a risk of OLP and the AA genotype was immune to OLP, (21) which confirms the results of our survey.

In a study conducted by Kimkong et al on a Thai population, they revealed that the T allele was significantly associated with an increased risk of OLP compared to the A allele (23). Although there was an association between the IFN-γ+874A/T and OLP susceptibility in our study, this relationship was not statistically significant. The reason for this discrepancy is that the study was conducted on different races, and naturally, their gene pool is not the same.

Genetics has a significant role in the development of OLP disease, and many genes have been studied

in this regard. An association between the A-allele of Interleukin 8 rs4073 and OLP pathogenesis was found by Azab and colleagues (24). However, they detected little association between IFN-γ rs2430561 and OLP severity. The association between OLP and IL-18 gene polymorphisms was investigated in an Indian population in 2019 (22). This study showed -137GG and G allele genotypes in IL-18 were genetically linked to OLP, while 137GC and C alleles may play a protective role against the disease. Interleukins are involved in the immune system; it confirms the association between OLP disease and immune factors.

In a Chinese cohort study, the human IFN-γ and IL-4 human genes were compared with OLP (25). They found highly significant increases in the IFN-γ + 874A/T genotype and T allele frequencies in both the OLP patient group (p = 0.033, 0.003) and the erosive OLP (p = 0.013, 0.001) in comparison with controls. However, no difference was found between the OLP patient and the healthy control group in the IL-4 allele. They suggested that IFN-gamma gene polymorphism may predispose these ethnic Chinese people to OLP. In a systematic review, Motahari et al. reported a positive relationship between the IFN-γ (+ 874 A/T) gene polymorphism and the risk of affection with OLP (26). These two papers confirm what we found in this study.

The role of TNF-α and IL-6 polymorphism genes in OLP has been studied in 101 individuals of Malayalam-speaking ethnicity from South India (Kerala). The results demonstrate that IL-6-597 does not have any disease association with OLP, while A allele in the TNF-α-308 polymorphism could play an important role in the susceptibility to OLP (27). This result supports our results, in which a significant relation between TNF-α-308 polymorphism and lichen planus was found (P value < 0.05).

The relationship between several other gene variants and lichen planus has been investigated. The relation between Interleukin-18 variants and OLP has been studied in another Chinese survey (28). They showed a significant difference in IL18-607 frequency between the subjects and controls (P < 0.001), and it seems that the -137G/C polymorphism is also related to the erosive OLP subgroup (P = 0.023). In a Japanese study, 32 patients with OLP and 99 healthy controls were compared by genotyping of 14 single nucleotide polymorphisms (SNPs) for immune response genes (29). An increased frequency of TNFR2 + 587 G allele was observed in patients compared to controls (allele frequency: P = 0.049). Another 13 SNPs were not associated with OLP. Such studies are very important and show the role of genetics in this disease.

Conclusion

Comparison of individuals in the two groups with lichen planus and the healthy group as controls with each other in terms of the genotype in TNF-α-308G/A mononucleotide polymorphism in our study showed a close relationship between them. The association between IFN-γ + 874A/T polymorphism and the risk of OLP was also confirmed, but this association was not statistically significant. In conclusion, since increased associational tendency between polymorphism and lichen planus has been reported in different studies, TNFα-308 G/A polymorphism may be considered a risk factor for predicting OLP. Due to the limitation in the number of participants as well as the geographical area under study, it seems that more studies are required with larger populations in wider geographical areas.

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Authors' Contribution

Conceptualization: Nasrollah Saleh Gohari.
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Competing Interests

None declared.

Ethical Approval

The Ethics Committee of the Kerman University of Medical Sciences approved this work (IR.KMU.REC.1398.693).

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