The association between interleukin-28B gene polymorphisms as a potential biomarker and the risk of chronic Periodontitis in an Iranian population

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Abstract

Background: Chronic Periodontitis (CP) is a common inflammatory disease affects supporting tissues of the teeth and can lead to tooth loss. The objective of this study was to determine the relationship between polymorphisms in the IL-28B gene and chronic periodontitis in an Iranian population.

Methods: Two hundred and ten CP patients and one hundred healthy subjects were enrolled in the present case-control study. The rs12979860 and rs8099917 SNPs were identified using RFLP and T-ARMS-PCR methods respectively.

Results: SNP analysis revealed that the G allele of rs8099917 SNP and T allele of rs12979860 SNP increased susceptibility to CP compared to the A allele and C allele (p < 0.0001, OR = 2.712, CI = 1.783-4.126; p < 0.0001, OR = 2.538, CI = 1.784-3.613 respectively). In addition, the CT/GT, TT/GG and TT/GT haplotypes were predominant in CP patients and significantly associated with the increased risk of CP.

Conclusion: IL-28B polymorphisms may be useful predictive factors for chronic periodontitis and correlated to the susceptibility to CP infection in our population.

Keywords: Chronic Periodontitis (CP), Interleukin-28B (IL-28B), Polymorphism

Background

Chronic Periodontitis (CP) is one of the most common inflammatory diseases affecting the tooth supporting tissues. This Chronic condition is caused by microorganisms that produce dental biofilm on the tooth surfaces. Bacterial plaque triggers the initiation of the inflammation and induces immune responses against infection in the host body. CP destroys soft tissue and the bone that supports the teeth and eventually leads to tooth loss and other serious conditions such as heart attack in progressive modes. CP is an important cause of tooth loss in 10–15% of adults [1]. In regard to the etiology of CP, it seems that bacteria, immune interactions, environmental and genetic factors be responsible [1]. It has been demonstrated that CP related inflammation can affect host immune system by stimulations on the level of cytokines production [2]. On the other hand, twin studies have revealed that genetic factors can modulate the expression of immune mediators and increase the risk of CP [3]. Cytokines and chemokines; as immune mediators, have important roles in pathogenesis of CP [4, 5]. Interleukin-28 (IL-28), also known as IFN-λ, have important role in immune responses against infections. It can modulate the innate and adaptive immune systems against chronic inflammations [6]. This cytokine has two isoforms: IL-28A and IL-28B [7]. In the human genome, interleukin-28A (IL-28A), IL-28B and IL-29, also known as interferon-λ1 (IFN-λ1), IFN-λ2 and IFN-λ3 respectively, have produced a cluster of closely related genes. These genes have biological functions and
antiviral activity and can be induced by various infections [6–10].

Sanders et al. [11], reported the first GWAS of CP among a large community-based sample of Hispanics/Latinos (10,935 adult participants). Genotyping was done with approximately 20 million single-nucleotide polymorphisms. They identified a genome-wide significant association signal in the 1q42.2 locus and four more loci with suggestive evidence of association in 1q22, 5p15.33, 6p22.3 and 11p15.1.

Lopes et al. [12], observed a significantly increased risk of developing chronic periodontitis in individuals with low IL-10 production. They suggested that the polymorphisms A-1082G, C-819 T, and C-592A, are involved in the susceptibility to the development of chronic periodontitis in an admixed northern Brazilian population.

Zhu et al. [13], in an updated meta-analysis of 21 case-control studies, reported that IL-6174 polymorphism is associated with CP susceptibility. Also they revealed that IL-6174 GG genotype plays a role as a risk factor to CP in Brazilian and Caucasian population.

In another meta-analysis, Yang et al. [14], investigated the association between the IL-8 -251A/T polymorphism and the risk of periodontitis. The results suggested that the IL-8 -251A/T polymorphism may increase the risk of periodontitis in Asian and mixed populations.

Lavu et al. [15], in the study of clinical relevance of cytokines gene polymorphisms and protein levels in gingival cervical fluid from chronic periodontitis patients, revealed the presence of higher levels of IL-1β and TNF-α in subjects with periodontitis and genetic control of IL-1β levels in Indians.

Recently, Sheibak [16] et al., studied the quantitative parameters of interdental papilla in chronic periodontitis patients with IFN-γ gene polymorphism. They found that IFN-γ +874 A/T is strongly associated with some quantitative parameters of connective tissue constituents of interdental papilla in CP patients.

Heidari et al. [17] investigated the association of IFN3 gene polymorphisms (rs12979860 and rs8099917) with HBV susceptibility, in chronic HBV-infected patients. Their study showed no significant differences between patients, with at least one rs12979860C and or rs8099917T alleles compared to the healthy controls.

The gene encoding the IL-28B cytokine is located on the long arm of chromosome 19 at position 19q13.13 [18]. Recently, several studies have revealed that genetic variations such as single nucleotide polymorphisms (SNPs) at or near the IL-28B gene can affect the natural history of chronic infections [19–21].

In addition, it has been shown that the expression levels of the IL-28B receptor mRNA increase in antiviral protection in some human organs such as thyroid and pancreas [6, 8]. Recently, Cheng et al. [22] and Osaki et al. [23] have reported that IL-28B gene polymorphisms can affect the development of hepatitis B virus infection. Based on previous studies concerning the effects of this gene SNPs on inflammatory diseases, it seems that interleukin-28B gene variations might have a vital role in the susceptibility to CP. Two SNPs have been found in the IL-28B gene at positions rs8099917 and rs12979860 which associated with the response of individuals to chronic infections [24]. In our knowledge, therefore we assumed that these variations might be possible markers for the detection of CP and the current study was the first investigation that has been conducted on this issue.

Previously, we have studied the relationship between polymorphisms of inflammatory and proinflammatory genes and chronic periodontitis [4, 25–30]. In this study, given the pervasiveness of chronic periodontitis in Iran and the importance of IL-28 in the pathogenesis of inflammation, we decided to examine the impact of these cytokine SNPs in susceptibility to CP. The aim of this paper is to investigate the association between two single nucleotide polymorphisms, rs8099917 and rs12979860, and CP.

Methods

Study subjects

This case-control study was done on 210 CP patients and 100 healthy individuals who were referred from September 2015 until March 2016. All subjects were exclusively Iranian ethnicities from the region of Sistan and Baluchistan. Patients with chronic periodontitis were examined at the Periodontology Department, Dentistry Clinic of Zahedan University of Medical Sciences (ZUMS).

The study was approved by the Institutional Ethics Committee of the Zahedan University of Medical Sciences (No: 6210) and written consent forms were signed by all participants. The study was carried out in Infectious Diseases and Tropical Medicine Research Center, Zahedan, Iran. Chronic periodontitis patients were diagnosed based on the criteria of the International workshop for classification of periodontal diseases and conditions [31]. The disease diagnosis was based on physical examination, medical and dental history, probing depth (measured as the distance from the gingival margin to the bottom of the pocket), and assessment of clinical attachment loss (as the distance from the cement-enamel junction to the bottom of the periodontal pocket). Probing was performed at six sites around each tooth using a WHO periodontal probe and recording the maximum values, tooth mobility, and radiographs. The loss of alveolar bone was determined radiographically [26, 32]. All participants were nonsmokers, had at least 20 teeth and were Iranian ethnicities from the South East of Iran and were of good general health.
Clinical evidence in healthy subjects included: GI < 1 and PPD < 3 mm, and CAL = 0 and they had a healthy periodontium. Signs of clinical inflammation such as GI > 1, PPD > 4 mm, and CAL > 2 mm and bone loss were clinical evidence for chronic periodontitis. Patients were excluded from the study if they had a history of cardiovascular disorders, systemic disorders, immunodeficiency situations and conditions such as use of anti-inflammatory drugs, chemotherapy, individuals with previous orthodontic treatment, pregnant women and smokers.

The control group consisted of 100 unrelated healthy individuals who had no clinical history of periodontal disease. Controls were selected from subjects referred to the Dentistry Clinic for reasons other than periodontal disease and were matched for age, ethnicity, and gender with CP group. There are three main ethnicities in South-East of Iran; Baluch, Sistani and others.

Genotyping of IL-28B polymorphisms (rs8099917 and rs12979860)
Two ml peripheral blood was taken from all participants in Na-EDTA tubes. Genomic DNA was isolated from peripheral venous blood using salting-out method as described previously [33]. Allele specific primers were designed using the Primer BLAST tool from NCBI (https://www.ncbi.nlm.nih.gov/tools/primer-blast/) as shown in Table 1.

The rs12979860 polymorphism was identified using polymerase chain reaction (PCR) based restriction fragment length polymorphism (RFLP) assay. A 242 base pair (bp) product was obtained. PCR amplification was carried out in a total volume of 20 μL containing 1 μl of each primer, 100 ng of template DNA and 10 μl of 2X Prime Taq Premix and 10 μl ddH2O. Polymerase chain reactions were run for 30 cycles: initial denaturation; 5 min at 95 °C, denaturation; 30 s at 95 °C, annealing; 30 s at 58 °C, extension; 30 s at 72 °C, final extension; 10 min at 72 °C. Product sizes were 197 bp for G allele, 295 bp for T allele, and 437 bp for the two outer primers (control band). Each reaction was verified on a 2% agarose gel containing ethidium bromide (Fig. 1.).

The rs8099917 polymorphism was determined using tetra-primer amplification refractory mutation system–polymerase chain reaction (T-ARMS-PCR) method as described previously [34]. Amplification was performed in a volume of 25 μL containing 1 μl (10 μM) of each primer, 100 ng of template DNA and 10 μl of 2X Prime Taq Premix and 10 μl ddH2O. Polymerase chain reactions were run for 30 cycles: initial denaturation; 5 min at 95 °C, denaturation; 30 s at 95 °C, annealing; 30 s at 58 °C, extension; 30 s at 72 °C, final extension; 10 min at 72 °C. Product sizes were 197 bp for G allele, 295 bp for T allele, and 437 bp for the two outer primers (control band). Each reaction was verified on a 2% agarose gel containing ethidium bromide (Fig. 2.).

Statistical analysis
All statistical analysis was performed using SPSS version 20.0 software. The Chi-square test was used to assess the descriptive statistics. A P value less than 0.05 was considered statistically significant. The genotypic and allelic frequencies observed in patient and control groups were calculated by direct counting. The associations

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### Table 1

| Polymorphisms | Primer Sequence (5'→3') |
|---------------|-------------------------|
| rs12979860    | Forward: 5'-GCTTATCGCATACGGCTAGG-3' |
|               | Reverse: 5'-AGGCTCAGGGTCAATCACAG-3' |
| rs8099917     | Forward outer: 5'-CATCACCCTACAATCTCATCTCC CTC-3' |
|               | Reverse outer: 5'-GGTATCAACCCCCACCTCAAATATCC TA-3' |
|               | Forward inner [G allele]: 5'-CTTTTTGTGTCTCTGTGAGC AGTGG-3' |
|               | Reverse inner [T allele]: 5'-TATACAGCATGTTCCAATTTG GTAAAA-3' |

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Fig. 1 Electrophoresis pattern of PCR-RFLP for detection of IFNL3 rs12979860 C/T polymorphism. Lane M, DNA marker; lane 1, subjects with homozygote TT genotype; lane 2, subjects with heterozygote CT genotype; lane 3, subjects with homozygote CC genotype.
between the allelic and genotype frequencies and CP, as well as the odds ratio (OR) for the susceptibility to disease were obtained by the $\chi^2$-test and 95% confidence intervals (95% CI) from logistic regression analyses. Quantitative data were presented as mean ± standard deviation.

Results
The study population was composed of 210 chronic periodontitis patients (mean age 28.33 ± 5.765; 95 female and 115 male) and 100 healthy controls (mean age 29.22 ± 3.597; 52 female and 48 male). The clinical data showed that the values of the gingival index (GI), probing pocket depth (PPD), and clinical attachment level (CAL) in CP group were higher than healthy controls ($p < 0.05$). The demographic data showed that the mean age, ethnicity and gender for patients with CP and healthy subjects did not differ between the two groups ($p = 0.159$, $p = 0.186$, $p = 0.265$ respectively) [26].

The allele frequencies and genotype distributions for the two interleukin-28B gene polymorphisms ($rs8099917$ and $rs12979860$) among CP patients and control group were shown in Table 2. The genotype frequencies were in agreement with the Hardy–Weinberg equilibrium. The frequencies of $IL-28B$ $rs8099917$ and $rs12979860$ genotypes in the chronic periodontitis population were significantly different from the healthy group ($p < 0.0001$). It was revealed that the GG (OR = 5.00; CI = 1.656-15.096) and GT (OR = 3.269; CI = 1.915-5.581) genotypes from $rs8099917$ SNP and TT (OR = 6.457; CI = 3.004-14.025) and CT (OR = 4.478; CI = 2.529-7.927) genotypes from $rs12979860$ SNP were significantly related to the increased risk of CP. In addition, our results indicated significant differences in the distribution of alleles between the two groups at the $rs8099917$ and $rs12979860$ gene polymorphisms (Table 3). SNP analysis for $rs8099917$ and $rs12979860$ SNPs revealed that the G allele and T alleles increased susceptibility to CP compared to the A allele and C allele ($p < 0.0001$, OR = 2.712, CI = 1.783-4.126; $p < 0.0001$, OR = 2.538, CI = 1.784-3.613 respectively). The frequencies of the haplotypes in $IL-28B$ gene in CP patients and controls depicted in Table 3. There was a significant difference in the haplotype frequencies between

Table 2 The frequency of genotypes and alleles of $IL-28B$ ($rs12979860$ and $rs8099917$) polymorphism gene

| $IL-28B$ polymorphisms | CP, N. (%) | Control, N. (%) | OR (95%CI) | P     |
|-------------------------|------------|----------------|------------|-------|
| $rs12979860$C/T         |            |                |            |       |
| CC                      | 32 (15.2)  | 47 (47.0)      | Ref = 1    | -     |
| CT                      | 125 (59.5)| 41 (41.0)      | 4.478(CI = 2.529-7.927) | 0.000 |
| TT                      | 53 (25.2) | 12 (12.0)      | 6.487(CI = 3.001-14.024) | 0.000 |
| CT + TT                 | 178 (48.8)| 53 (53.0)      | 4.933(CI = 2.863-8.498)  | 0.000 |
| Allele                  |            |                |            |       |
| C                       | 189 (45.0)| 135 (67.5)     | Ref = 1    | -     |
| T                       | 231 (55.0)| 65 (32.5)      | 2.538(CI = 1.784-3.613)  | 0.000 |
| $rs8099917$G/T          |            |                |            |       |
| GG                      | 24 (11.4) | 4 (4.0)        | 5.000(CI = 1.656-15.096) | 0.004 |
| GT                      | 102 (48.6)| 26 (26.0)      | 3.269(CI = 1.915-5.581)  | 0.000 |
| TT                      | 84 (40.0) | 70 (70.0)      | Ref = 1    | -     |
| GT + GG                 | 126 (60.0)| 30 (30.0)      | 3.500(CI = 2.104-5.823)  | 0.000 |
| Allele                  |            |                |            |       |
| G                       | 150 (35.7)| 34 (17.0)      | 2.712(CI = 1.783-4.126)  | 0.000 |
| T                       | 270 (64.3)| 166 (83.0)     | Ref = 1    | -     |
chronic periodontitis patients and controls ($p < 0.0001$). The CT/GT, TT/GG and TT/GT haplotypes were predominant in CP patients and significantly associated with the increased risk of CP.

**Discussion**

According to our knowledge, the current investigation is the first study conducted in any population regarding to the association between \(IL-28B\) single nucleotide polymorphisms (\(rs8099917\) and \(rs12979860\)) and chronic periodontitis. This study showed a higher frequency of \(rs12979860\) CT + TT and \(rs8099917\) GT + GG genotypes in CP patients compared to healthy subjects. Our findings revealed that T allele of \(rs12979860\) and G allele of \(rs8099917\) were the predominant alleles among CP patients in comparison to healthy controls. Our study demonstrated the \(rs8099917\) and \(rs12979860\) SNPs are probably genetic risk factors for susceptibility to CP.

IFN-\(\lambda\) family has been divided into three subtypes: interferon \(\lambda1\), \(\lambda2\) and \(\lambda3\). Interleukin-28B or interferon-\(\lambda3\) is an endogenous antiviral cytokine which is required to control the chronic infections. Recently, it was revealed that IFN-\(\lambda\) could inhibit the viral replication in human cells such as hepatocytes [6]. The IL-28B cytokine induces signal transduction through the heterodimer receptor in the cells. Complex of the IL-28B and its receptor can activate the immune mediator transcription and Janus kinase-signal transducer. In addition, IL-28B is related to IFN-\(\alpha\) that controls above mentioned mechanisms which leads to inhibition of cell proliferation, and regulation of immune functions [10, 35]. Therefore, it seems that variation of IL-28B can lead to changes in the regulation of immune activity. On the other hand, IL-28B have important roles in various organs such as heart, thyroid, pancreas and skeletal muscle because high levels of IL-28B receptor mRNA expression has been shown in these organs when an antiviral protection induced [6]. Also, IL-28B transmits information via IL-10 signal cascade. The amount of IL-10 cytokine increases in various inflammations [36]. These facts reveal an association between IL-28B and chronic periodontitis as an inflammatory infectious disease.

On the other hand, it has been shown that IFN-\(\lambda\) polymorphisms were associated to chronic infection outcome and could affect the progression of inflammations [37, 38]. Studies have reported that \(IL28B\) \(rs129798060\) was related to the susceptibility to chronic hepatitis C virus (HCV) infection. HCV infected patients with the CC genotype of \(rs129798060\) were presented convincing response to antiviral therapies [19, 20, 39] and also T allele has been reported as a risk factor for HCV infection [40, 41]. It has been confirmed that the \(rs129798060\) polymorphism could increase the expression of IL-28B [19]. Our findings are in agreement with previous studies [19, 20, 39]. The frequency of \(IL28B\) CT + TT genotypes in chronic periodontitis patients was higher than in controls. It means that T allele is a risk factor for CP. In addition, subjects with CC genotype may be protected against CP inflammation. Moreover, it was revealed that \(rs12979860\) and \(rs8099917\) had vital roles in infection treatment [20, 39]. The IL-28B cytokine can modulate immune responses and change the natural history of other infections but the function of \(IL-28B\) polymorphisms in our recently study presents that \(rs12979860\) CT + TT and \(rs8099917\) GT + GG genotypes are not associated with susceptibility to hepatitis B infection [42]. It seems that IL-28B can regulate HCV related- liver infection [43], so these facts suggested that \(IL-28B\) gene polymorphisms such as SNPs might have important roles in development of CP as an inflammatory disease.

Recently, Xiao et al. [21], Rauch et al. [44], Derbala et al. [45], Lampertico et al. [46], Egli et al. [47], Euirch et al. [48] have reported that \(IL-28B\) polymorphisms associate with the susceptibility to the hepatitis B or C viruses infections, influenza and lower urinary tract symptoms (LUTS). Xiao et al. [21] determined the relationship between \(IL-28B\) \(rs12979860\) and \(rs8099917\) SNPs and LUTS in Chinese patients. In the \(IL-28B\) \(rs12979860\) and \(IL-28Ra\) \(rs10903035\) also \(IL-28B\) \(rs8099917\) and \(IL-28Ra\) \(rs10903035\) interactions analysis,
they found that the CC + AG/GG, CT + AG/GG; and TT + AG/GG, GT + AG/GG genotypes were significantly less frequent in the patients compared to the controls. Rauch et al. [44] reported that the rs8099917 minor allele was associated with progression to chronic infection. The rs8099917 was also associated with failure to respond to therapy in patients with HCV genotype 1 or 4. Derbala et al. [45] indicated that the CC and TT genotypes of rs12979860 and rs8099917 were the more common protective genotypes among infected patients. Egli et al. [47] have identified IL-28B as a key regulator of the Th1/Th2 balance during influenza vaccination. They have demonstrated that the IL-28B TT + GG genotypes of rs8099917 were associated with increased seroconversion following influenza vaccination. Eurich et al. [48] have examined the role of rs12979860 SNP in the development of hepatocellular carcinoma (HCC). They showed that the prevalence of HCC in explanted livers was significantly higher among patients with TT genotype, suggesting a protective role of the C allele in HCC development. In this field, T allele may be regarded as a genetic risk factor for HCV-related severity. Also, as Rizk et al. [49], reported the patients with the C allele of rs12979860 exhibited an approximately eight times higher risk of disease severity compared to patients with the T allele. However, chronic periodontitis is still poor understood and the relationship between rs12979860 and rs8099917 and CP has not been reported till now but our results showed that these SNPs were associated with susceptibility to CP. Our finding revealed that most frequently genotypes in CP patients were CT + TT for rs12979860 and GT + GG for rs8099917 which differs from the study of Barreiro et al. [43] and Rizk et al. [49] but in agreement with many studies by Xiao et al. [21], Derbala et al. [45], Egli et al. [47], Eurich et al. [48].

Due to the above mentioned studies and current investigation, it might be presented: that rs12979860 T allele and rs8099917 G allele might be related to the development of chronic infections such as CP, HBV, HCV, LUTS and influenza. Data shows that the C/T alleles and CC/TT genotypes for rs12979860 and rs8099917 respectively occurred frequently in the healthy control group and suggest that the rs12979860 C allele and rs8099917 T allele may useful for inhibition of chronic periodontitis infection and have a protective effect for inflammation. We considered that, a number of differences between current report and Barreiro et al. [43] and Rizk et al. [49] findings might result from different ethnicities of the study populations.

Together with the significant differences of the distributions of the rs12979860 C/T and rs8099917 G/T alleles in the CP and healthy subjects, our findings seemed to propose that the IL-28B SNP might be associated with the risk of CP. In addition, with regards to the stereological analyzes according to the volume of pulp, epithelium, connective tissue, collagenous and non-collagenous matrix, and blood vessels between control and CP groups, it was presented that the transforming growth factor-β1 29C/T [30] and -509C/T [29], tumor necrosis factor-alpha -308G/A [27, 33], interleukine-6-174G/C [4] gene polymorphisms were associated with level of tissue breakdown and periodontal disease progression. These studies supported our conclusion that IL-28B SNPs have an influence on the natural history of chronic periodontitis in which that the subjects who carried the rs12979860 CT/TT or rs8099917 GT/GG genotypes display increased clinical severities of CP than individuals carrying rs12979860 CC or rs8099917 TT variants. It means that rs12979860 C and rs8099917 T alleles may be protective factors in the field of the development of CP. When the haplotype effects of rs12979860 and rs8099917 were analyzed, it was found that CT/GT, TT/GG and TT/GT genotypes have more frequent in CP patients that support our conclusion. One of our hypotheses is that IL-28B SNPs can change the expression and secretion of proinflammatory cytokines in patients with CP and finally affect the development of CP. However, the real functional mechanism of IL-28B SNPs in the development of CP is still unknown. In addition, there are a number of limitations in our study. It seems that chronic infection genotypes have different geographical distributions and susceptibility to infection. In addition, differences among ethnic groups have suggested a genetic contribution in susceptibilities to CP infection. Also, in this study, only the population of the South East of Iran was analyzed which is not representative of the general Iranian CP patients. Therefore, more evidence is required to obtain a conclusion so other SNPs with large enough sample size should be included in the future studies. In summary, our study shows that IL-28B genes polymorphisms have an influence on the natural history of chronic periodontitis in a sample of the Iranian population. Single nucleotide polymorphisms rs12979860 and rs8099917 can influence the natural history of chronic periodontitis in patients.

**Conclusion**

Our findings showed that polymorphisms in IL-28B genes (rs12979860 and rs8099917) correlated to the susceptibility to CP infection in our population.

**Abbreviations**

CP: Chronic Periodontitis; IL-28B: Interleukin 28B; PCR: Polymerase Chain Reaction; RFLP: Restriction Fragment Length Polymorphism; SNP: Single Nucleotide Polymorphism

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Authors’ contribution

BM and MM carried out the molecular genetic studies. BM participated in the sequence alignment and drafted the manuscript. ZH and HM-S participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are available in the Department of Histology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran. [http://www.zaums.ac.ir/].

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of the Zahedan Ethics approval and consent to participate Not applicable. The authors declare that they have no competing interests.

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References

1. Van Dyke TE, Dave S. Risk factors for periodontitis. J Int Acad Periodontol. 2005;7:3–7.
2. Dentino A, Lee S, Mailhot J, Hefti AF. Principles of periodontology. Periodontol. 2013;61:16–53.
3. Michalowicz BS, Diehl SR, Gunsolley JC, Sparks BS, Brooks CN, Koenger TE, et al. Evidence of a substantial genetic basis for risk of adult periodontitis. Periodontol. 2000;7:11(1):1699–707.
4. Heidari Z, Mahmoudzadeh-Sagheb H, Hashemi M, Ansarimoghaddam S. Sheikhb. Estimation of volume density of interdental papilla components in patients with chronic periodontitis and interleukin-6 (−174/G/C) gene polymorphisms. Dent Res J. 2016;13(2):139–44.
5. Kinane DF, Preshaw PM, Loos BG. Host-response: understanding the cellular and molecular mechanisms of host-microbial interactions—consensus of the seventh European workshop of periodontology. J Clin Periodontol. 2011;38(11):44–8.
6. Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlumsrey S, Whittmore TE, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol. 2003;4:633–8.12. Lopes CB, Barroso RFF, Burbano RMR, Garcia PA, Pinto P, Santos N, et al. Effect of ancestry on interleukin-10 haplotypes in chronic periodontitis. Frontiers Biosci (Elite Ed). 2017;9:231–6.
13. Zhu J, Guo B, Fu M, Guo W, Yuan Y, Yuan H, et al. Interleukin-6-174G/C polymorphism contributes to Periodontitis susceptibility: an updated meta-analysis of 21 case-control studies. Dis Markers. 2016;2016:961241.
14. Yang ZJ, Tang XP, Lai QG, CJC, BJ, Yuan KF. Interleukin-8-25A/T polymorphism and periodontitis susceptibility: a meta-analysis. Genet Mol Res. 2016;15(4):621001.
15. Lavu V, Venkatesan V, Venugopalan P, Lakakula BV, Paul SF, Feria K, et al. Clinical relevance of cytokines Gene polymorphisms and protein levels in gingival cervical fluid from chronic Periodontitis patients. Iran J Immunol. 2017;14(1):51–8.
16. Sheikhb, Heidari Z, Mahmoudzadeh-Sagheb H. Quantitative parameters of Interdental Gingiva in chronic Periodontitis patients with IFN-gamma Gene polymorphism. Prag Med Rep. 2017;11(8):37–48.
17. Heidari Z, Moudi B, Mahmoudzadeh-Sagheb H, Hashemi M. The correlation between interferon lambda 3 Gene polymorphisms and susceptibility to hepatitis B virus infection. Hepat Mon. 2016;16(3):e34266.
18. Witte K, Witte E, Sabar R, Wolk K, IL-28A, IL-28B, and IL-29: promising cytokines with type I interferon-like properties. Cytokine Growth Factor Rev. 2010;21(4):237–51.
19. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(399–401.
20. Suppiah V, Moldovan D, Ahnelt R, Berg T, Weltman M, Abate ML. IL-28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet. 2009;41:1100–4.
21. Xiao L, Gao LB, Wei Q. Association of polymorphism within the interferon-28 receptor alpha gene, but not in interleukin-28B, with lower urinary tract symptoms (LUTS) in Chinese. Genet Mol Res. 2015;14(3):10682–91.
22. Cheng M, Si Y, Yang Y, Liu X. Recombinant human interleukin 28B: anti-HCV potency, receptor usage and restricted cell-type responsiveness. J Antimicrob Chemother. 2012;67:1080–7.
23. Orakii, Nishimura T, Shooya I, Takeuchi T. Interleukin-28B genotypes determine response to pegylatedinterferon plus ribavirin therapy in patients with hepatitis C virus infection. Mol Med Rep. 2012;5:525–8.
24. Li WJ, Jiang YJ, Qin Q, Shi X, Jin J, Gao Y, et al. Expression and gene polymorphisms of interleukin-28B and hepatitis B virus infection in a Chinese Han population. Liver Int. 2011;31(8):1118–26.
25. Heidari Z. The association between Proinflammatory Gene polymorphisms and level of gingival tissue degradation in chronic Periodontitis. Gene Cell Tissue. 2014;1:2.
26. Heidari Z, Mahmoudzadeh-Sagheb H, Hashemi M, Ansarimoghaddam S, Moudi B, Sheikhb. Association between IFN-γ, +874 A/T and IFN-γR1 (−611A/G, +189T/G and +95C/T) gene polymorphisms and chronic periodontitis in a sample of Iranian population. Int J Dent. 2015;2015;10:1155/2015/375359.
27. Heidari Z, Mahmoudzadeh-Sagheb H, Hashemi M, Rigi Ladez MA. Stereological analysis of interdental gingiva in chronic periodontitis patients with tumor necrosis factor alpha (−308G/A) gene polymorphisms. Gene Cell Tissue. 2014;1(1):e18315.
28. Heidari Z, Mahmoudzadeh-Sagheb H, Rigi-Ladiz MA, Taheri M, Moazenni-Roodi A, Hashemi M. Association of TGFB-1 (−509) C/T, 29 C/T and 788 C/T gene polymorphisms with chronic periodontitis: a case-control study. Gene. 2013;518(2):330–4.
29. Heidari Z, Mahmoudzadeh-Sagheb H, Sheibak N. Association between TGFBET1 (−509) C/T gene polymorphism and tissue degradation level in chronic periodontitis: a stereological study. Gene Cell Tissue. 2015;2(3):1695–8.
30. Heidari Z, Mahmoudzadeh-Sagheb H, Hashemi M, Rigi Ladez MA. Quantitative analysis of Interdental Gingiva in patients with chronic Periodontitis and transforming growth factor-β1 29C/T Gene polymorphisms. J Periodontol. 2014;85(2):281–9.
31. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol. 1999;4:1–6.
32. Armitage GC. Periodontal diagnoses and classification of periodontal diseases. Periodontol. 2004;34:9–21.
33. Solhjoo S, Mahmoudzadeh-Sagheb H, Heidari Z, Hashemi M, Rigi Ladez MA. Association between TNF-α (−308 G → a) Gene polymorphism and chronic Periodontitis. Zahedan J Res Med Sci. 2014;16(2):10–4.
Hashemi M, Moazeni-roodi A, Bahari A, Taheri M. A tetra-primer amplification refractory mutation system–polymerase chain reaction for the detection of rs 8099917 IL28b genotype. Nucleosides Nucleotides Nucleic Acids. 2012;31(5):55–60.

Vilcek J. Novel interferons. Nat Immunol. 2003;4:8–9.

Miller LJ, Fischer KA, Goralnick SJ, Lit M. Interleukin-10 levels in seminal plasma: implications for chronic prostatitis-chronic pelvic pain syndrome. J Urol. 2002;167:753–6.

Robek MD, Boyd BS, Chisari FV. Lambda interferon inhibits hepatitis B and C virus replication. J Virol. 2005;79:3851.

Thomas DL, Thio CL, Martinella MP. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798–801.

Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsusaka K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009;41:105–9.

Pár A, Kissfali P, Melegh B, Tomai I, Lengyel G, Nemész Z, et al. Cytokine (IL-10, IL-28B and LTA) gene polymorphisms in chronic hepatitis C virus infection. Clin Exp Med J. 2001;5:9–19.

Par A, Kissfali P, Melegh B, Miseta A, Tomai I, Papp M, et al. Genetic polymorphisms in IL-10R, IL-28B and LTA genes in HCV Infection. Do they have protective role and predict sustained virological response? J Hepatol. 2010;52:457–65.

Moudi B, Heidari Z, Mahmoudzadeh-Sagheb H, Hashemi M. Association between IL-10 gene promoter polymorphisms (−592 A/C, −819 T/C, −1082 A/G) and susceptibility to HBV infection in an Iranian population. Hepat Mon. 2016;16(2):10.5812/hepatmon.32427.

Barreiro P, Pineda JA, Rallón N, Naggio S. Influence of interleukin-28B single-nucleotide polymorphisms on progression to liver cirrhosis in human immunodeficiency virus-hepatitis C virus-coinfected patients receiving antiretroviral therapy. J Infect Dis. 2011;203:1629–36.

Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology. 2010;138:1338–45.

Derbala M, Rizk NM, Al-Kaabi S, John A, Sharma M, El-dweik N, et al. The predictive value of IL28B rs12979860, rs11881222 and rs8099917 polymorphisms and IF-10 in the therapeutic response of Egyptian genotype 4 patients. Virology. 2013;444(1–2):292–300.

Lampertico P, Vigano M, Chenoni C, Facchetti F. IL28B polymorphisms predict interferon-related HBs-Ag seroclearance in genotype D HBsAg-negative patients with chronic hepatitis B. Hepatology. 2012;55:890–6.

Egli A, Santer DM, O’Shea D, Barakat K, Syedbasha M, Vollmer M, et al. IL-28B is a key regulator of B- and T-cell vaccine responses against influenza. PLoS Pathog. 2014;10(12):e1004556.

Eurich D, Boas-Knoop S, Bahra M, Neuhaus R. Role of IL28B polymorphism in the development of hepatitis C virus-induced hepatocellular carcinoma, graft fibrosis, and posttransplant antiviral therapy. Transplantation. 2012;93:644–9.

Rizk NM, Derbala MF. Genetic polymorphisms of ICAM 1 and IL28 as predictors of liver fibrosis severity and viral clearance in hepatitis C genotype 4. Clin Res Hepatol Gastroenterol. 2013;37(3):262–8.