

Original Article

Association of interleukin-17A gene promoter polymorphism with the susceptibility to generalized chronic periodontitis in an Iranian population

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ABSTRACT

Background: Chronic periodontitis (CP) is characterized by an immune response, leading to the destruction of periodontal supporting tissue. The effect of inflammatory and genetic factors on periodontitis has been evaluated previously. The interleukin (IL-17) as an inflammation regulator seems to play a critical role in periodontitis pathogenesis. Here, in the current study, we aimed to investigate the association of -197 G > A (rs2275913) IL-17 gene promoter polymorphism with generalized severe CP in an Iranian population.

Materials and Methods: In this case-control study, a total of 54 patients with periodontitis and 118 normals were enrolled. The polymerase chain reaction-restriction fragment length polymorphism technique was applied to detect IL-17 promoter rs2275913 genotypes in association with the susceptibility to severe CP. Chi-square test or Fisher's exact test was employed to compare genotype frequencies between groups. $P < 0.05$ were considered statistically significant.

Results: The distribution of genotypes and alleles was in Hardy-Weinberg equilibrium. Although no significant association was observed between the risk of periodontitis and genotype frequencies under any of the inheritance models, the GG genotype was higher in healthy controls, while the AG genotype was more frequently observed in patients under the codominant model ([odds ratio [OR] = 2.14, 95% confidence interval (CI) (1.01-4.53), $P = 0.13$]). The frequency of AG-AA genotype was higher in patients under dominant inheritance model ([OR = 1.92, 95% CI (0.94-3.93), $P = 0.068$]), while GG-AA and AG genotypes were higher in healthy controls under over dominant model (OR = 0.1.95, 95% CI [0.98-3.86], $P = 0.055$).

Conclusion: The results of this study showed that the presence of allele A and AG genotypes could be considered possible factors in increasing the risk of developing CP, although the differences of allele and genotype frequencies were remarkable but not statistically significant between the two groups.

Key Words: Genetic polymorphism, interleukin 17, periodontitis

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INTRODUCTION

Periodontal disease is defined as a combination of several inflammatory conditions affecting both hard and soft tissues in the oral cavity with a rather high prevalence in developing countries.^[1] Although the colonization of anaerobic pathogenic organisms and lack of normal flora are attributed to plaque-induced inflammatory periodontitis, the progression and clinical features of the disease could be exacerbated by both genetic and acquired factors affecting the susceptibility to infection such as imbalanced immune response.^[2,3]

Chronic periodontitis (CP) as the most common form of periodontitis has been associated with major oral cavity risk factors such as smoking, stress, and impaired immune response in genetically susceptible individuals.^[4,5] The increased occurrence of periodontal disease in identical twins determines the importance of genetic studies on CP.^[6] Although several genes have been proposed to be involved in the onset of periodontitis, alterations of genetic variants in different populations could lead to changes in clinical manifestations of CP.^[7]

As an inflammatory condition which needs effective immune response, numerous studies have considered the association of genetic variants in immunomodulatory molecules with CP.^[8] Single-nucleotide polymorphisms (SNPs) in both coding and regulatory regions of cytokines genes, as the most determinant signaling molecules for immune system function^[9] have been implicated in the susceptibility and progression of CP.^[10,11] Accordingly, several research studies have focused on revealing the association of the SNPs in cytokines genes including transforming growth factor- β ,^[12] tumor necrosis factor-alpha,^[13] interleukin-10 (IL-10),^[8] interferon-gamma,^[14] IL-6,^[15] and IL-17^[16] with CP.

T helper 17 (Th 17) lymphocytes, as a major subset of CD4⁺ T cells, exert their substantial pro-inflammatory effects by producing IL-17 cytokine family.^[17] This group of cytokines is comprised six different molecules including; IL-17A (IL-17; CTLA-8), IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F.^[18] IL-17 plays a pivotal role in the release of several pro-inflammatory precursors in fibroblasts, macrophages, endothelial, and epithelial cells and may be involved in the pathogenesis of periodontal disease by exacerbating the inflammatory response in

periodontal tissue.^[19] Th17 cells and elevated IL-17 cytokine levels have been reported in the inflamed gums, gingival crevicular fluid (GCF), and gingival cell cultures in CP.^[20]

The elevated levels of IL-17 could be associated with the increased susceptibility to CP, which is regulated by its extremely polymorphic promoter region.^[21] IL-17 SNPs have been attributed to the progression and severity of several inflammatory diseases such as autoimmune disorders,^[17] malignancies, and infectious diseases.^[22] Several studies have shown that SNPs in the promoter region of IL-17 could result in altered expression of IL-17 and increasing the risk of CP.^[23]

According to the substantial role of IL-17 in CP pathogenesis and the lack of significant studies in the present population, we investigated the association of -197 G > A (rs2275913) IL-17 gene promoter polymorphism with generalized severe CP in Gorgan, northeast of Iran.

MATERIALS AND METHODS

Patients and controls

According to the study of Corrêa *et al.*^[24] considering the alpha error of 0.05 and power of 90%, the sample size was calculated using the G power software (Germany, Düsseldorf, <http://www.gpower.hhu.de/>). A total of 54 patients with generalized severe CP and 118 sex- and age-matched healthy volunteers were engaged in this case-control study from the Periodontal Department of Dentistry School, Golestan University of Medical Sciences, Gorgan, Iran in 2019. Demographic information of the study population is described in Table 1. Written informed consent was obtained from all participants following the Declaration of Helsinki.^[25] The committee of Ethics at the Golestan University of Medical Sciences approved the study design and protocols (Approval Code of Ethics: IR. GOUMS. REC.1398.051).

Table 1: Demographic findings of the study population

Variables	Chronic periodontitis	Healthy controls	P
Gender (%)			
Female	27 (50)	42 (35.6)	0.094 (Chi-square test)
Male	27 (50)	76 (64.4)	
Age (years), mean \pm SD	39.89 \pm 6.1	39.25 \pm 10.7	0.50 (Student's <i>t</i> -test)

SD: Standard deviation

An expert physician examined all patients clinically and radiographically. Probing depth (PD) and clinical attachment loss (CAL) were assessed using a Williams probe at six areas of the teeth: mesio-buccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual.^[8] The O'Leary method was used to record plaque index and consequently match oral hygiene in all patients.^[26] The diagnosis of generalized severe CP was approved according to the amount of CAL (≥ 5 mm) and PD (≥ 4 mm) in more than 30% of the sites. The healthy control group was comprised individuals without attachment and/or bone loss at more than one site on radiography, PD < 3 mm and no history of periodontal disease.^[27]

All participants were nonsmokers, over 18 of age at the time of sampling, and had at least 20 natural teeth except the remaining roots and wisdom teeth. The individuals with a history of systemic diseases affecting periodontal conditions (such as diabetes), alcohol addicts, cigarette smokers, pregnant or lactating women, and those taking antibiotics in the past 3 months were not included.

A volume of 5 mL peripheral whole blood was taken from all participants, labeled proportionally, transferred to the laboratory of Metabolic Disorders Research Center, Gorgan, Iran and stored at -20°C until use.

DNA purification and genotyping

Ron's Blood and cell DNA mini kit (BIORON GmbH, Germany) was used to isolate and purify genomic DNA from 200 μl of previously-stored whole blood, following the manufacturer's protocols. Briefly, the blood cells were lysed using 200 μl of lysis buffer supplemented with proteinase K (20 mg/mL) and incubation at 55°C for 1 h. The lysate was mixed with 200 μl of binding buffer and then was incubated at 70°C for 10 min after. The cell debris was removed by centrifugation at 13,000 rpm for 5 min, and the DNA containing supernatant was mixed with 200 μl ethanol and then was transferred to a mini spin column tube. The column was washed two times with wash buffer and finally, the DNA was eluted using the prewarmed elution buffer and centrifugation.

The quantity and quality of isolated DNA were measured by Pico Drop spectrophotometer (Pico drop Limited, UK) and agarose gel electrophoresis, respectively. The DNA samples were kept at -20°C until use.

For genotyping of the -197 G > A (rs2275913) IL-17 gene promoter SNP, the polymerase

chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used. Briefly, a DNA region containing the rs2275913 SNP was amplified with PCR using specific primers and then it was genotyped using digestion with sequence-specific restriction enzyme XagI (EcoNI). The PCR reaction mixture was prepared in a final volume of 25 μL containing 100 ng of template DNA, 12.5 μL of Taq DNA Polymerase 2X Master Mix RED (Ampliqon, Denmark), 0.4 μM of forward (5'-AACAAAGTAAG AATGAAAAGAGGACATGGT-3') and reverse (5'-CC CCAATGAGGTCATAGAAGAATC-3') primers. PCR amplification was carried out on ABI Veriti™ (Applied Biosystems, USA) thermal cycler, with the following conditions: initial denaturation at 95°C for 5 min, 35 cycles of 95°C for 10 s, annealing at 60°C for 25 s, 72°C for 35 s and final extension at 72°C for 5 min. RFLP digestion was carried out in a final volume of 10 μl containing 5 U of XagI (EcoNI) restriction enzyme (Fermentase, Germany) and incubation at 37°C for 2 h, followed by 1.5% agarose gel electrophoresis.

The undigested PCR product was 102 bp which represented A allele. The presence of the G allele was confirmed by visualizing two fragments of the digested PCR product with 68 bp and 34 bp. Accordingly, homozygous AA genotype represented an undigested 102 bp band, homozygous GG showed two pieces of 68 + 34 digested bands, and heterozygotes AG genotype represented a 102 + 68 + 34 mixed pattern. As mentioned, the number of 172 individuals (118 controls, 54 cases) was enrolled in this study. The PCR-RFLP genotyping method was carried out successfully for 166 individuals (118 control, 48 cases, and 6 cases were nonassigned). To validate the genotyping results by PCR-RFLP method, three distinct samples were randomly selected and analyzed by direct PCR Sanger sequencing [Figure 1].

Statistical analyses

SNP stats software (<https://bioinfo.iconcologia.net/SNPStats>) was used to assess the Hardy-Weinberg equilibrium (HWE), analyzing alleles and genotype frequencies, linkage disequilibrium and reconstruct haplotypes.^[5] SPSS 22.0 (SPSS, Chicago, IL, USA) software was used to analyze data statistically after matching covariates. To evaluate case-control study associations, the odds ratio (OR) and 95% confidence interval (CI) were determined. Chi-square test or Fisher's exact test was employed to compare genotype

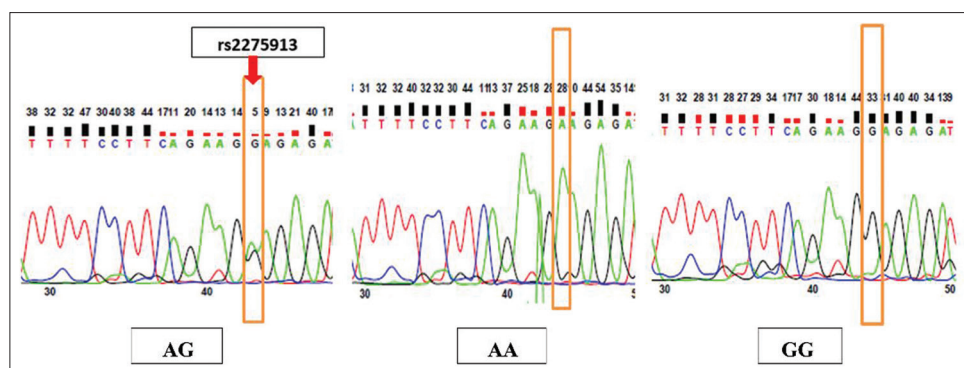


Figure 1: The sequencing results of IL-17 promoter region; the PCR sequencing of three cases showed different genotypes for rs2275913. IL-17: Interleukin-17, PCR: Polymerase chain reaction.

and haplotype frequencies between groups. $P < 0.05$ were considered statistically significant.

RESULTS

A total number of 118 matched healthy individuals (age: 39.25 ± 10.7) and 54 patients (age: 39.89 ± 6.1) with generalized severe CP were enrolled in the study. The PD and CAL were measured in all patients for confirmation of the generalized severe CP. Then, the genomic DNA was extracted from the peripheral blood of all individuals and the -197 G > A (rs2275913) IL-17 gene promoter polymorphism was genotyped using the PCR-RFLP method. The association of -197 G > A (rs2275913) IL-17 gene promoter polymorphism with the susceptibility to severe CP was investigated. The distribution of genotypes and alleles was checked and confirmed to be in HWE under different inheritance models (codominant, dominant, recessive, and overdominant) in both periodontitis patients and healthy controls [Table 2].

Comparison of the rs2275913 (G/A) alleles and genotypes under the codominant model showed that the GG genotype was higher in healthy controls, while the AG genotype was more frequently observed in patients (OR = 2.14, 95% CI [1.01–4.53]). Although the OR was rather remarkable, no significant association was observed between the genotype frequencies under the codominant model and the risk of periodontitis ($P = 0.13$). The frequency of AG-AA genotype was higher in patients under the dominant inheritance model, which was not significantly higher in any of the groups (OR = 1.92, 95% CI [0.35–2.39], $P = 0.068$). Moreover, GG-AA and AG genotypes were higher in healthy controls, which were not significantly different under over

dominant model (OR = 1.95, 95% CI [0.98–3.86], $P = 0.055$).

DISCUSSION

CP is the most common type of periodontitis caused by an imbalance between periodontal pathogens and the host immune system.^[16] The IL-17 family is a collection of pro-inflammatory cytokines produced by T-helper 17 cells that participate in both acute and chronic inflammatory immune responses.^[17] IL-17 appears to play a key role in stimulating bone resorption of osteoclasts and thus, increasing the risk of periodontal disease.^[28] According to the decisive role of genetic variations in the promoter region of cytokines in determining their expression level, we investigated the association of -197 G > A (rs2275913) IL-17 gene promoter polymorphism and generalized severe CP in Gorgan, northeast of Iran. Our findings indicated that, although it was nonsignificant, the presence of the A allele and AG genotype in rs2275913 could be considered a possible factor in increasing the risk of disease, which was in consistent with a previous study by Hatami and Hosseinpour.^[16] Furthermore, Vahabi *et al.*^[29] showed that IL-17 gene promoter SNPs were not significantly associated with CP. The alleles and genotype frequencies were in HWE indicating that the result obtained from the studied population could be generalized and also the internal validity of the PCR-RFLP was confirmed using Sanger sequencing for some samples.

A meta-analysis by da Silva *et al.* showed no association between rs2275913 in the promoter region of IL-17 and CP.^[30] Similarly, an original study in a Japanese population showed no association of rs2275913 with the altered risk of CP.^[31] However, other studies reported a significant association of

Table 2: The genotype and allele frequencies of -197 G>A (rs2275913) interleukin-17 gene promoter polymorphism in severe chronic periodontitis patients and healthy controls under different inheritance models

Genotypes and alleles	Cases (n=48)†, n (%)	Controls (n=118), n (%)	OR (95% CI)	P
rs2275913				
G	56 (58)	156 (66)		
A	40 (42)	80 (34)		
Co-dominant model				
GG	15 (31.2)	56 (47.5)	Reference	
AG	26 (54.2)	44 (37.3)	2.14 (1.01-4.53)	0.13
AA	7 (14.6)	18 (15.2)	1.39 (0.48-3.99)	
Dominant model				
GG	15 (31.2)	56 (47.5)	Reference	
AG + AA	33 (68.8)	62 (52.5)	1.92 (0.94-3.93)	0.068
Recessive model				
GG + AG	41 (85.4)	100 (84.8)	Reference	
AA	7 (14.6)	18 (15.2)	0.92 (0.35-2.39)	0.86
Over-dominant model				
GG + AA	22 (45.8)	74 (62.7)	Reference	
AG	26 (54.2)	44 (37.3)	1.95 (0.98-3.86)	0.055
χ^2 HWE (P)*	0.56	0.67		

*P-values lower than 0.05 are considered to be statistically significant. Significant associations are also shown in Bold. Exact test for HWE was also conducted, †Total cases was=54 (48 were genotyped, 6 samples were nonassigned). HWE: Hardy-Weinberg equilibrium, OR: Odds ratio, CI: Confidence interval

it with CD in various populations. For example, Chaudhari *et al.* revealed that the presence of allele A in the -197 G > A (rs2275913) IL-17 gene promoter SNP, could be a risk factor for CP in an Indian population.^[32] In a similar study on a Brazilian population, Zacarias *et al.* showed that the presence of allele A and AA genotype in -197 G > A (rs2275913) IL-17 SNP was significantly associated with CP.^[33] Corrêa *et al.* also reported a significant association between -197 G > A (rs2275913) IL-17 SNP and CP in Brazil.^[24] A closer look at the results of previous studies reveals that the genetic variation of rs2275913 shows a population-based effect, while similar results have been obtained in similar populations/ethnicities. Accordingly, geographical differences and ethnic diversities could be considered the most determining factors of IL-17 genetic variation in the promoter region and consequently its expression level.

Our study, similar to most of the conducted research studies in the literature, was associated with limitations including heterogeneous levels of social and oral health in the participants. Accordingly, we adjusted the samples by matching the plaque index to overcome that limitation. Although the small sample size could be another limitation affecting the conclusions of our study, these findings could be generalized to a healthy and nonsmoking Iranian population. Repeating the present study in different ethnicities and geographical areas, and also in a

population with a larger sample size in addition to simultaneous examination of serum IL-17 level or its expression in GCF and assessing its relationship with the severity of periodontal disease are recommended for future studies.

CONCLUSION

The results of this study showed that the presence of allele A and AG genotype could be considered as a possible factor in increasing the risk of developing CP, although the differences of allele and genotype frequencies were high and the ORs were considerable, but not statistically significant between the two groups. Therefore, based on the results of this study, a remarkable but not statistically significant association was found between 197 G > A (rs2275913) IL-17 gene promoter polymorphism and severe generalized CP which could be due to the small sample size among the cases and further investigations are highly suggested.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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