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ORIGINAL ARTICLE

Analysis of the association of TNF-α, IL-1A, and IL-1B polymorphisms with peri-implantitis in a Chinese non-smoking population

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Abstract

Objectives The purpose of this study was to investigate whether the genetic variations which could regulate inflammatory responses were associated with the risk of peri-implantitis.

Materials and methods We evaluated three genetic variants including tumor necrosis factor-alpha (TNF-α) − 308G/A, interleukin-1 alpha (IL-1A) − 889C/T, and IL-1 beta (IL-1B) + 3954C/T, as risk factors for peri-implantitis, in a total of 144 patients with peri-implantitis and 174 healthy controls in a Chinese non-smoking population.

Results Logistic regression analyses revealed that subjects carrying the T allele of IL-1A − 889C/T and IL-1B + 3954C/T had a significant 2.27–2.47-fold (CT, OR [95% CI] = 2.27 [1.12–4.58], $p = 0.021$; TT, OR [95% CI] = 2.47 [1.32–4.69], $p = 0.006$) and 1.9–1.99-fold (CT, OR [95% CI] = 1.99 [1–3.93], $p = 0.041$; TT, OR [95% CI] = 1.9 [1.08–3.43], $p = 0.03$) increased risk of peri-implantitis, respectively, when using the CC genotype as a reference point. And subjects carrying the TT genotype of IL-1A − 889C/T or IL-1B + 3954C/T also had significantly higher periodontal variables including peri-implant pocket depth (PPD), bleeding on probing (BOP), gingival index (GI), plaque index (PI), calculus index (CI), and clinical attachment level (CAL) ($p < 0.05$). However, no associations were found between the TNF-α − 308G/A polymorphism and the risk of peri-implantitis.

Conclusions Our results suggest that the IL-1A − 889C/T or IL-1B + 3954C/T genetic polymorphisms were associated with the risk of peri-implantitis and periodontal status.

Clinical relevance Genetic polymorphisms are constant and can be measured before disease onset, thus it could be of great benefit for treatment planning and prognosis in an early stage.

Keywords Peri-implant disease · Peri-implantitis · Tumor necrosis factor-alpha · Interleukin-1 · Single-nucleotide polymorphism

Introduction

Nowadays, dental implants have become the most chosen option for edentulous patients to repair some or all of their missing teeth and yielded promising results. However, implant failures do occur despite adequate surgical and medical treatments [1]. There have been studies that show the presence of peri-implantitis, which represents a destructive inflammation occurring in the tissues surrounding osseointegrated dental implants and resulting in loss of supporting bone [2], is closely related to the occurrence of implants loss [3, 4]. Many systemic and local factors, such as pathogenic bacteria, lack of oral hygiene, smoking, and alcohol consumption, have been related to the development of peri-implantitis [5, 6]. Also, gene susceptibility has been considered as one of the common etiologies of peri-implantitis, which is revealed by the fact that implant losses tend to cluster in subsets of individuals when exposed to similar risk factors, and patients with one implant failure likely suffer from additional failures [7, 8]. Genetic variations are differences in DNA sequence which may affect the function of genes. Based on the inflammatory nature of peri-implantitis, genetic variations which could influence inflammatory cytokine secretion and regulate inflammatory responses have been extensively investigated.

The variations of tumor necrosis factor-alpha (TNF-α) gene and interleukin-1 (IL-1) gene cluster, including IL-1 alpha (IL-1A) and IL-1 beta (IL-1B) genes, are most commonly studied functional polymorphisms for dental implant loss,

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peri-implantitis, and marginal bone loss [9, 10]. Both the TNF-α and IL-1 are pro-inflammatory cytokines which play significant roles in inflammatory processes [11]. The expression of TNF-α, which is mainly produced by macrophages, has been found to be associated with periodontitis [12, 13], and increases the local secretion and activity of metalloproteinase, resulting in peri-implant tissue destruction and bone resorption by activating osteoclast maturation [14]. Similarly, IL-1 is considered as a major mediator of the osseointegration process [15] and plays an important role in the process of bone destruction and resorption by regulating the production of matrix metalloproteinase (MMP) [16].

Thus, functional polymorphisms in these genes, which could affect the expression levels and protein functions, may influence the development of peri-implantitis. Single-nucleotide polymorphisms (SNPs) are the most common type of genetic variation among people. Many studies have investigated different SNPs in the TNF-α and IL-1 genes as risk factors for dental implant failure and peri-implantitis. Among them, the TNF-α − 308G/A (rs1800629), IL-1A − 889C/T (rs1800587), and IL-1B + 3954C/T (rs1143634) have been mostly investigated [9, 10], because these SNPs have been demonstrated to be associated with directly changed levels of gene expression and secreted cytokines [17, 18]. However, studies have yielded conflicting results on this issue [19–23].

In the present study, we aimed to investigate whether the three functional variants (TNF-α − 308G/A, IL-1A − 889C/T, and IL-1B + 3954C/T) were associated with the risk of peri-implantitis in a Chinese non-smoking population.

Materials and methods

Patients and controls

The present study is a hospital-based case-control study. It was approved by the ethics committee of West China Hospital of Stomatology (81400549). All participants provided written informed consent to approve the use of their oral samples for research purposes. All procedures performed in the study were in accordance with the Helsinki declaration. A total of 144 patients diagnosed with peri-implantitis (TEST group) and 174 individuals with peri-implant health (control group) were recruited between January 2016 and September 2018. All participants were genetically unrelated to ethnic Han Chinese.

The clinical parameters for the subject population were collected, including age, sex, peri-implant pocket depth (PPD), bleeding on probing (BOP), gingival index (GI), plaque index (PI), calculus index (CI), clinical attachment level (CAL), and dental mobility (present or absent). For peri-implantitis patients, inclusion criteria were as follows: (1) PPD ≥4 mm; (2) positive BOP; (3) positive GI; (4) positive PI; (5) recorded radiographic signs of pathologic bone loss involving ≥2 threads compared with the radiograph taken at the time of prosthetic replacement. For peri-implant health individuals, inclusion criteria were as follows: (1) healthy peri-implant tissue and implant-supported restorations after at least 2 years of loading; (2) PPD <3 mm; (3) no BOP; (4) no radiographically evidenced bone loss. Moreover, the exclusion criteria were as follows: (1) smokers; (2) pregnancy and lactation; (3) general health problems including diabetes mellitus, HIV infection, and other chronic diseases; (4) intake of any antibiotics and anti-inflammatory drugs in the past 3 months.

DNA collection, purification, and polymorphism detection

A total of 318 buccal epithelial cell samples from 144 patients and 174 healthy controls were collected and used in the present study. For each subject, a sterile wood spatula was used to scrape oral mucosa, after a mouthwash with 3% glucose solution. The tip of the spatula was immediately shaken into the mouthwash solution. Buccal epithelial cells were pelleted by centrifugation at 2000×*g* for 10 min. The supernatant was discarded. And genomic DNA was isolated from the cell pellet using the QIAamp DNA Mini Kit (QIAGEN, Germany), in accordance with the manufacturer's protocol. After that, the genomic DNA was either stored at − 80 °C or SNP genotyping was conducted on it immediately.

The polymorphisms of three selected genetic variants were determined by the TaqMan SNP Genotyping Assay (Thermo Fisher, USA), Briefly, 30–60 ng of DNA was amplified using TaqMan Genotyping Master Mix (Thermo Fisher, USA) and commercial probes (Thermo Fisher, USA) for TNF-α − 308G/A (rs1800629), IL-1A − 889C/T (rs1800587), and IL-1B + 3954C/T (rs1143634) in a final volume of 25 μL. PCR thermal cycling conditions were as follows: 10 min at 95 °C for AmpliTaq Gold, UP Enzyme activation, and then 40 cycles of denaturation at 95 °C for 15 s, and annealing/extension at 65 °C for 1 min.

Statistical analysis

The statistical analyses were performed using the SPSS version 19.0 software. Differences in genotype distribution between groups were evaluated using Pearson's chi-squared test. Risks for developing peri-implantitis were estimated by calculating the odds ratio (OR) and the 95% confidence interval (CI) from logistic regression analyses. Continuous variables were expressed as mean and standard deviation (SD). The Mann-Whitney *U* test was used to determine the differences for continuous variables. A p value of less than 0.05 was considered statistically significant. In addition, the sample size required to achieve statistically significant associations were calculated using the G*Power version 3.1.7 software. The parameters used in sample size calculations were as follows:

power of 80%, α of 0.05, and degrees of freedom of 1. It estimated a sample size of < 100 cases. Thus, our sample size was sufficient to identify significance towards three selected genetic variants in association with peri-implantitis.

Results

Characteristics of the study population

The baseline information of all sampled subjects is summarized in Table 1. A total of 318 unrelated subjects who had at least one dental implant inserted were recruited in this study. The mean age was 44.7 ± 8.6 years (range 30–60 years). No statistical differences were found in age, gender, alcohol consumption, dental implant platform type and position, peri-implant phenotype, and hygiene habits between the two groups ($p > 0.05$). However, positive history of periodontitis was significantly more frequent in the TEST group than in the control group (54.2% . 33.3%, $p = 0.0002$). Evaluating the periodontal status, all variables including GI, PI, CI, PPD, and CAL were significantly higher in peri-implantitis when compared with peri-implant health ($p < 0.05$), except for the presence of dental implant mobility (Table 2).

Allele frequencies

As shown in Table 3, the distribution of allele frequencies did not differ for TNF-α − 308G/A between the TEST and control groups (17.7% vs. 12.6%, $p = 0.0745$). However, statistically significant differences were observed in the distribution of the mutated allele for IL-1A − 889C/T and IL-1B + 3954C/T, in which the frequencies of the T allele (29.9% vs. 15.8%, $p < 0.0001$ and 31.2% vs. 20.1%, $p = 0.0013$, respectively) were higher in the TEST group. These deviations could have been due to genetic associations with the risk of peri-implantitis.

Association of TNF-α and IL-1 polymorphisms with a risk of peri-implantitis

The associations between the risk of peri-implantitis and the genotypes for the TNF-α − 308G/A, IL-1A − 889C/T, and IL-1B + 3954C/T were evaluated (Table 4). Dominant and recessive models are tests for the minor allele with two of the classes pooled. In the single-locus analyses, the genotype frequencies of IL-1A − 889C/T were 62.5% (CC), 15.3% (CT), and 22.2% (TT) in the TEST group and 79.9% (CC), 8.6% (CT), and 11.5% (TT) in the control group; the difference was significant for the CT and TT genotypes ($p = 0.021$ and $p = 0.004$ respectively), when using the CC genotype as a reference point. Logistic regression analyses revealed that subjects carrying the T allele of IL-1A − 889C/T had a significant 2.27–2.47-fold (CT vs. CC, OR 2.27, 95% CI 1.12–4.58; TT vs. CC, OR 2.47, 95% CI 1.32–4.69) increased risk of peri-implantitis. Also, the IL-1A − 889C/T was significant in both dominant (CT + TT vs. CC, OR 2.38, 95% CI 1.43–3.96, $p = 0.0006$) and recessive (CC + CT vs. TT, OR 2.2, 95% CI 1.2–4.11, $p = 0.01$) models. Moreover, subjects carrying the T allele of IL-1B + 3954C/T had a significant 1.9–1.99-fold increased risk of peri-implantitis (CT vs. CC, OR 1.99, 95% CI 1–3.93, $p = 0.041$; TT vs. CC, OR 1.9, 95% CI 1.08–3.43, $p = 0.03$), and it was also significant in the dominant model (CT + TT vs. CC, OR 1.94, 95% CI 1.21–3.15, $p = 0.006$). However, the TNF-α − 308G/A did not exhibit a statistically significant difference in the genotype distributions between the two groups.

Association of analyzed gene polymorphisms with periodontal status

We investigated the association between the three gene variants and the periodontal index (Table 5). Our results suggest that subjects carrying the TT genotype of IL-1A − 889C/T or IL-1B + 3954C/T had a significantly higher GI, PI, CI, PPD, and CAL ($p < 0.05$), when using the CC genotype as a reference point. There were also significantly higher GI and CAL for subjects carrying the CT genotype of IL-1A − 889C/T (1.78 ± 1.04 vs. 1.25 ± 1.13, $p = 0.007$, and 3.54 ± 1.9 vs. 2.66 ± 1.82 mm, $p = 0.014$, respectively), and PI for subjects carrying the CT genotype of IL-1B + 3954C/T (1.76 ± 1.02 vs. 1.38 ± 1.03, $p = 0.027$). In addition, no associations were found between the TNF-α − 308G/A polymorphism and the periodontal status.

Discussion

Any intense inflammatory response is supposed to stimulate the resorption of supporting bones and damage the process of osseointegration, leading to implant failure [14–16]. TNF-α and IL-1 play critical roles in the immune-inflammatory response. And in vitro study has demonstrated that the A allele of TNF-α − 308G/A, which was located in the promoter region of human TNF-α gene, was a strong transcription activator, resulting in a sevenfold increase of TNF-α levels [18]. Similarly, the polymorphic IL-1A − 889C/T is also located in the promoter region of human IL-1A gene, and the T allele of this polymorphism significantly enhances the transcriptional activity of the gene [17]. The T to C substitution of IL-1B + 3954C/T, which is located in exon five of human IL-1B gene, could lead to a synonymous change, and it has been demonstrated that T allele was associated with a significantly increased production of IL-1B in vitro [24]. Thus, many studies have investigated the association between these genetic variations and the development of dental implant disease including implant failure, peri-implantitis, and marginal bone loss. However, most of the studies focused on Caucasian populations and the results are still

Table 1 Baseline characteristics of the studied population

Variable	Peri-implantitis ($n = 144$)	Healthy implants ($n = 174$)	p value
Age (years), mean ± SD	45.1 ± 8.8	44.3 ± 8.2	0.482
Gender, *N* (%)			
Male	88 (61.1)	92 (52.9)	0.14
Female	56 (38.9)	82 (47.1)	
Alcohol consumption, *N* (%)			
Yes	48 (33.3)	70 (40.2)	0.205
No	96 (66.7)	104 (59.8)	
History of periodontitis, *N* (%)			
Yes	78 (54.2)	58 (33.3)	0.0002*
No	66 (45.8)	116 (66.7)	
Platform type, *N* (%)			
External hex	70 (48.6)	76 (43.7)	0.351
Internal hex	22 (15.3)	39 (22.4)	
Morse cone	42 (29.2)	51 (29.3)	
Others	10 (6.9)	8 (4.6)	
Position, *N* (%)			
Anterior region	67 (46.5)	91 (52.3)	0.306
Posterior region	77 (53.5)	83 (47.7)	
Peri-implant phenotype, *N* (%)			
Thin	79 (54.9)	78 (44.8)	0.075
Thick	65 (45.1)	96 (55.2)	
Brushing daily, *N* (%)			
1–3 times	125 (86.8)	158 (90.8)	0.257
More than 3 times	19 (13.2)	16 (9.2)	
Dental floss daily, *N* (%)			
Yes	55 (38.2)	74 (42.5)	0.413
No	28 (19.4)	20 (11.5)	
Infrequent	61 (42.4)	80 (46)	
Mouth washing daily, *N* (%)			
Yes	41 (28.5)	70 (40.2)	0.088
No	33 (22.9)	35 (20.1)	
Infrequent	70 (48.6)	69 (39.7)	

*p value < 0.05

controversial [9, 10]. These differences in results between studies might be caused by limited sample size, various defined inclusion/exclusion criteria, ethnicity of subjects, potential gene-environment interactions, and confounders such as age, sex, and smoking. To the best of our knowledge, the present study is the first to provide reliable evidence about the association

Table 2 Periodontal status of the studied population

Variable	Peri-implantitis ($n = 144$)	Healthy implants ($n = 174$)	p value
Gingival index, mean ± SD	2.51 ± 0.5	0.45 ± 0.5	< 0.0001*
Plaque index, mean ± SD	2.37 ± 0.6	0.83 ± 0.78	< 0.0001*
Calculus index, mean ± SD	0.42 ± 0.52	0.25 ± 0.44	0.002*
PPD (mm), mean ± SD	5.61 ± 0.94	1.99 ± 0.6	< 0.0001*
CAL (mm), mean ± SD	4.84 ± 0.67	1.31 ± 0.59	< 0.0001*
Mobility			
Absence	137	171	0.506
Presence	7	6	

PPD peri-implant pocket depth, *CAL* clinical attachment level

*p value < 0.05

Table 3 Allele frequencies of TNF-α − 308G/A, IL-1A − 889C/T, and IL-1B + 3954C/T polymorphisms

Genotyped SNPs	Peri-implantitis ($n = 144$) % (No.)	Healthy implants ($n = 174$) % (No.)	p value
TNF-α − 308G/A			
G	82.3 (237)	87.4 (304)	0.0745
A	17.7 (51)	12.6 (44)	
IL-1A − 889C/T			
C	70.1 (202)	84.2 (293)	< 0.0001*
T	29.9 (86)	15.8 (55)	
IL-1B + 3954C/T			
C	68.8 (198)	79.9 (278)	0.0013*
T	31.2 (90)	20.1 (70)	

*p value < 0.05

between these gene polymorphisms and the risk of peri-implantitis in a Chinese non-smoking population. Genetic polymorphisms are constant and can be measured before disease onset, thus it could be of great benefit for individuals who are at high risk of peri-implantitis, because clinicians could suggest targeted risk reduction strategies in an early stage.

The presence or history of periodontitis is one of the most studied risk factors for peri-implantitis. Previous studies have demonstrated that peri-implantitis-related biofilm was similar to that of periodontitis, comprising high levels of periodontal pathogens [25, 26]. And it has been reported that the microflora present in the oral cavity before implantation determines the composition of the newly establishing microflora on implants [27], suggesting that patients with a history of periodontitis might be at high risk for peri-implantitis. In a recent meta-analysis, Ferreira et al. evaluated 19 eligible studies and found that the presence or history of periodontitis was significantly associated with the occurrence of peri-implantitis [28]. In the present study, our results also demonstrated that there was a significant association between the history of periodontitis and peri-implantitis. For TNF-α − 308G/A polymorphism, two previous studies have investigated the association of this genetic variant with the risk of peri-implantitis [19, 20]. Cury et al. demonstrated that the TNF-α − 308G/A polymorphism was not associated with an increased risk of peri-implantitis in Caucasian non-smoking Brazilian patients (49 cases and 41 controls) [19], while another study by Rakic et al. which includes 369 Southeastern Europe Caucasians (180 cases and 189 controls) demonstrated that AG genotype was associated with peri-implantitis and a fivefold increased risk [20]. Although the number of relevant studies is small, in a recent meta-analysis, the results showed that the pooled ORs did not reveal a significant relationship between the TNF-α − 308G/A polymorphism and risk of peri-implantitis (OR 1.13, 95% CI 0.72–1.78, $p = 0.509$), as well as implant failure [10].

Table 4 Genotype frequencies TNF-α − 308G/A, IL-1A − 889C/T, and IL-1B + 3954C/T polymorphisms

Genotype	Peri-implantitis ($n = 144$)	Healthy implants ($n = 174$)	Additive		Dominant		Recessive	
	No. (%)	No. (%)	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
TNF-α − 308G/A								
GG	113 (78.5)	146 (83.9)	Reference	–	1.52 (0.86–2.63)	0.14	1.59 (0.79–3.12)	0.189
AG	11 (7.6)	12 (6.9)	1.18 (0.53–2.9)	0.698				
AA	20 (13.9)	16 (9.2)	1.62 (0.8–3.18)	0.178				
IL-1A − 889C/T								
CC	90 (62.5)	139 (79.9)	Reference	–	2.38 (1.43–3.96)	0.0006*	2.2 (1.2–4.11)	0.01*
CT	22 (15.3)	15 (8.6)	2.27 (1.12–4.58)	0.021*				
TT	32 (22.2)	20 (11.5)	2.47 (1.32–4.69)	0.004*				
IL-1B + 3954C/T								
CC	87 (60.4)	130 (74.7)	Reference	–	1.94 (1.21–3.15)	0.006*	1.69 (0.94–2.99)	0.07
CT	24 (16.7)	18 (10.3)	1.99 (1–3.93)	0.041*				
TT	33 (22.9)	26 (15)	1.9 (1.08–3.43)	0.03*				

OR odds ratio, *CI* confidence interval

*p value < 0.05

Table 5 Association of analyzed gene polymorphisms with periodontal status

Genotype	No. (%)	Gingival index (mean ± SD)	*p* value	Plaque index (mean ± SD)	*p* value	Calculus index (mean ± SD)	*p* value	PPD (mm) (mean ± SD)	*p* value	CAL (mm) (mean ± SD)	*p* value
TNF-α − 308G/A											
GG	259 (81.4)	1.34 ± 1.14	Reference	1.51 ± 1.07	Reference	0.33 ± 0.49	Reference	3.59 ± 1.95	Reference	2.83 ± 1.85	Reference
AG	23 (7.2)	1.48 ± 1.06	0.559	1.52 ± 0.88	0.997	0.3 ± 0.55	0.647	3.79 ± 1.92	0.605	3.01 ± 2.08	0.882
AA	36 (11.3)	1.64 ± 1.13	0.15	1.67 ± 0.94	0.376	0.31 ± 0.46	0.855	3.78 ± 2.08	0.958	3.11 ± 1.83	0.643
IL-1A − 889C/T											
CC	229 (72)	1.25 ± 1.13	Reference	1.44 ± 1.05	Reference	0.28 ± 0.45	Reference	3.44 ± 1.92	Reference	2.66 ± 1.82	Reference
CT	37 (11.6)	1.78 ± 1.04	0.007*	1.57 ± 1.05	0.485	0.38 ± 0.48	0.246	4.14 ± 2.09	0.104	3.54 ± 1.9	0.014*
TT	52 (16.4)	1.71 ± 1.11	0.009*	1.88 ± 0.89	0.006*	0.48 ± 0.6	0.027*	4.11 ± 1.88	0.037*	3.36 ± 1.85	0.046*
IL-1B + 3954C/T											
CC	217 (68.2)	1.29 ± 1.13	Reference	1.38 ± 1.03	Reference	0.28 ± 0.46	Reference	3.38 ± 1.91	Reference	2.63 ± 1.81	Reference
CT	42 (13.2)	1.55 ± 1.07	0.16	1.76 ± 1.02	0.027*	0.38 ± 0.49	0.193	3.99 ± 1.93	0.089	3.26 ± 1.9	0.096
TT	59 (18.6)	1.64 ± 1.16	0.037*	1.9 ± 0.97	0.0007*	0.46 ± 0.56	0.018*	4.29 ± 1.97	0.002*	3.5 ± 1.89	0.002*

OR odds ratio, *CI* confidence interval

*p value < 0.05

Consistently, our results demonstrated that the TNF-α − 308G/A polymorphism was not strongly associated with the risk of peri-implantitis and any variable of individuals' periodontal conditions in a Chinese non-smoking population.

The IL-1A − 889C/T and IL-1B + 3954C/T are two of the most widely studied genetic variants in the issue of implant failure and peri-implant disease [9]. But there were only four studies that have investigated its associations with the risk of peri-implantitis, in which one obtained positive results [22], and the 3 others yielded negative results [21, 23, 29]. Hamdy et al. demonstrated that having T allele at both IL-1A − 889C/T and IL-1B + 3954C/T in patients with inflamed periodontal or peri-implant tissues was a risk factor that leads to greater tissue destruction [22], while Laine et al. reported that no associations were found between the two gene polymorphisms and the risk of peri-implantitis in 120 North Caucasian individuals [21]. Lachmann et al. found that the composite genotype of IL-1A − 889C/T and IL-1B + 3954C/T was not associated with peri-implant crevicular fluid volume and concentrations of crevicular inflammatory mediators [29]. And there was also no significant difference in the concentration of IL-1B detected in the crevicular sulcular fluid between the peri-implantitis patients and controls [23]. However, in a meta-analysis by Liao et al., the results showed that the composite genotype of IL-1A − 889C/T and IL-1B + 3954C/T was significantly associated with an increased risk of peri-implantitis in European descents (OR 2.34, 95% CI 1.03–5.33) [9]. Similar to that, in the present study, we found that subjects carrying the T allele of IL-1A − 889C/T or IL-1B + 3954C/T had a significantly increased risk of peri-implantitis and higher periodontal variables including GI, PI, CI, PPD, and CAL.

There are several limitations that should be acknowledged. The sample size was not large enough to achieve nominal significance, which is often in the 1000 to 10,000 range [30]. And the recruited subjects may not be representative of the general population, because it was a hospital-based case-control study. Further studies are required to confirm the present findings. In conclusion, our results demonstrated that the IL-1A − 889C/T or IL-1B + 3954C/T genetic polymorphisms were associated with the risk of peri-implantitis and periodontal status in a Chinese non-smoking population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Alsaadi G, Quirynen M, Komárek A, van Steenberghe D (2008) Impact of local and systemic factors on the incidence of late oral implant loss. Clin Oral Implants Res 19(7):670–676
2. Smeets R, Henningsen A, Jung O, Heiland M, Hammächer C, Stein JM (2014) Definition, etiology, prevention and treatment of peri-implantitis–a review. Head Face Med 10:34
3. Esposito M, Hirsch JM, Lekholm U, Thomsen P (1998) Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. Eur J Oral Sci 106(1):527–551
4. Roos-Jansåker AM, Renvert H, Lindahl C, Renvert S (2006) Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. J Clin Periodontol 33(4): 296–301
5. Lindhe J, Meyle J, Group D of European Workshop on Periodontology (2008) Peri-implant diseases: consensus report of the Sixth European Workshop on Periodontology. J Clin Periodontol 35(8 Suppl):282–285
6. Galindo-Moreno P, Fauri M, Avila-Ortiz G, Fernández-Barbero JE, Cabrera-León A, Sánchez-Fernández E (2005) Influence of alcohol and tobacco habits on peri-implant marginal bone loss: a prospective study. Clin Oral Implants Res 16(5):579–586
7. Montes CC, Pereira FA, Thomé G, Alves ED, Acedo RV, de Souza JR, elo AC, Trevilatto PC (2007) Failing factors associated with osseointegrated dental implant loss. Implant Dent 16(4):404–412
8. Alvim-Pereira F, Montes CC, Mira MT, Trevilatto PC (2008) Genetic susceptibility to dental implant failure: a critical review. Int J Oral Maxillofac Implants 23(3):409–416
9. Liao J, Li C, Wang Y, Ten M, Sun X, Tian A, Zhang Q, Liang X (2014) Meta-analysis of the association between common interleukin-1 polymorphisms and dental implant failure. Mol Biol Rep 41(5):2789–2798
10. Mo YY, Zeng XT, Weng H, Cen Y, Zhao Q, Wen X (2016) Association between tumor necrosis factor-alpha G-308A polymorphism and dental peri-implant disease risk: a meta-analysis. Medicine (Baltimore) 95(35):e4425
11. Petkovic-Curcin A, Zeljic K, Cikota-Aleksic B, Dakovic D, Tatic Z, Magic Z (2017) Association of cytokine gene polymorphism with peri-implantitis risk. Int J Oral Maxillofac Implants 32(5):e241–e248
12. Ding C, Ji X, Chen X, Xu Y, Zhong L (2014) TNF-α gene promoter polymorphisms contribute to periodontitis susceptibility: evidence from 46 studies. J Clin Periodontol 41(8):748–759
13. Song GG, Choi SJ, Ji JD, Lee YH (2013) Association between tumor necrosis factor-α promoter −308 A/G, −238 A/G, interleukin-6 -174 G/C and −572 G/C polymorphisms and periodontal disease: a meta-analysis. Mol Biol Rep 40(8):5191–5203
14. Boyce BF, Li P, Yao Z, Zhang Q, Badell IR, Schwarz EM, O'Keefe RJ, Xing L (2005) TNF-alpha and pathologic bone resorption. Keio J Med 54(3):127–131
15. Panagakos FS, Aboyoussef H, Dondero R, Jandinski JJ (1996) Detection and measurement of inflammatory cytokines in implant crevicular fluid: a pilot study. Int J Oral Maxillofac Implants 11(6): 794–799
16. Birkedal-Hansen H (1993) Role of cytokines and inflammatory mediators in tissue destruction. J Periodontal Res 28(6 Pt 2):500–510
17. Dominici R, Cattaneo M, Malferrari G, Archi D, Mariani C, Grimaldi LM, Biunno I (2002) Cloning and functional analysis of the allelic polymorphism in the transcription regulatory region of interleukin-1 alpha. Immunogenetics 54(2):82–86
18. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW (1997) Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A 94(7):3195–3199
19. Cury PR, Horewicz VV, Ferrari DS, Brito R Jr, Sendyk WR, Duarte PM, Shibli JA (2009) Evaluation of the effect of tumor necrosis factor-alpha gene polymorphism on the risk of peri-implantitis: a case-control study. Int J Oral Maxillofac Implants 24(6):1101–1105
20. Rakic M, Petkovic-Curcin A, Struillou X, Matic S, Stamatovic N, Vojvodic D (2015) CD14 and TNFα single nucleotide polymorphisms are candidates for genetic biomarkers of peri-implantitis. Clin Oral Investig 19(4):791–801
21. Laine ML, Leonhardt A, Roos-Jansåker AM, Peña AS, van Winkelhoff AJ, Winkel EG, Renvert S (2006) IL-1RN gene polymorphism is associated with peri-implantitis. Clin Oral Implants Res 17(4):380–385
22. Hamdy AA, Ebrahem MA (2011) The effect of interleukin-1 allele 2 genotype (IL-1a(−889) and IL-1b(+3954)) on the individual's susceptibility to peri-implantitis: case-control study. J Oral Implantol 37(3):325–334
23. Melo RF, Lopes BM, Shibli JA, Marcantonio E Jr, Marcantonio RA, Galli GM (2012) Interleukin-1β and interleukin-6 expression and gene polymorphisms in subjects with peri-implant disease. Clin Implant Dent Relat Res 14(6):905–914
24. Pociot F, Mølvig J, Wogensen L, Worsaae H, Nerup J (1992) A TaqI polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion in vitro. Eur J Clin Investig 22(6):396–402
25. Shibli JA, Melo L, Ferrari DS, Figueiredo LC, Faveri M, Feres M (2008) Composition of supra- and subgingival biofilm of subjects with healthy and diseased implants. Clin Oral Implants Res 19(10): 975–982
26. Hultin M, Gustafsson A, Hallström H, Johansson LA, Ekfeldt A, Klinge B (2002) Microbiological findings and host response in patients with peri-implantitis. Clin Oral Implants Res 13(4):349–358
27. Mombelli A, Marxer M, Gaberthüel T, Grunder U, Lang NP (1995) The microbiota of osseointegrated implants in patients with a history of periodontal disease. J Clin Periodontol 22(2):124–130
28. Ferreira SD, Martins CC, Amaral SA, Vieira TR, Albuquerque BN, Cota LOM, Esteves Lima RP, Costa FO (2018) Periodontitis as a risk factor for peri-implantitis: systematic review and meta-analysis of observational studies. J Dent 79:1–10
29. Lachmann S, Kimmerle-Müller E, Axmann D, Scheideler L, Weber H, Haas R (2007) Associations between peri-implant crevicular fluid volume, concentrations of crevicular inflammatory mediators, and composite IL-1A −889 and IL-1B +3954 genotype. A cross-sectional study on implant recall patients with and without clinical signs of peri-implantitis. Clin Oral Implants Res 18(2):212–223
30. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN (2003) Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet 33(2):177–182