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Association of matrix metalloproteinase-1-1607 1G/2G single nucleotide polymorphism genotypes with periodontitis in Iraqi population

Associação entre genótipos de polimorfismo de nucleotídeo único de metaloproteinase-1-1607 1G/2G da matriz e periodontite em população iraquiana

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ABSTRACT

Objective and background: Periodontitis is an inflammatory disease which is characterized by a progressive loss in the matrix of soft and hard tissue of periodontium particularly the collagen fibers which are cleaved by matrix Metalloproteinase (MMP). Indeed, increased activity of MMP mediates progression of periodontal diseases but population-based genetic variations could determine the susceptibility to the disease. The aim was to investigate association between MMP-1-1607 polymorphism with periodontitis among Iraqi individuals. **Subjects and methods**: The design of this study was a case-control for Iraqi individuals who were divided into two groups; periodontitis group (cases) and those with healthy periodontium (Control). For each subject, clinical periodontal parameters and demographic characteristics were recorded and venous blood was withdrawn for genetic analysis of MMP-1 by using PCR technique and DNA sequencing. **Results:** Analysis of MMP-1-1607 genotypes, by Hardy-Weinberg equilibrium, showed significant differences in the total sample. The most predominant MMP-1-1607 genotype among Controls was 1G/2G which was significantly different from periodontitis cohorts. Overall, 13 SNP were detected in periodontitis group versus 17 SNP in Control group. In addition, the periodontitis group showed a significant negative association between the probing pocket depth and MMP-1-1607. **Conclusion**: Results suggested that polymorphisms in MMP-1-1607 1G/2G may play a protective role and decreasing the susceptibility to periodontitis.

KEYWORDS

Periodontitis; Polymorphism; Single nucleotide; Genotype; Matrix metalloproteinase 1.

Resumo

Introdução e objetivo: A periodontite é uma doença inflamatória caracterizada pela perda progressiva da matriz dos tecidos moles e duros do periodonto, particularmente as fibras de colágeno clivadas pelas metaloproteinases da matriz (MMPs). De fato, o aumento da atividade de MMPs medeia a progressão das doenças periodontais, mas as variações genéticas baseadas na população podem determinar a suscetibilidade à doença. O objetivo foi investigar a associação entre o polimorfismo MMP-1-1607 e periodontite em indivíduos iraquianos. **População e método:** O desenho deste estudo foi um caso-controle com indivíduos iraquianos, os quais foram divididos em dois grupos: grupo periodontite (casos) e indivíduos com periodonto saudável (controle). Para cada sujeito, os parâmetros clínicos periodontais e as características demográficas foram registrados, e o sangue venoso foi coletado para análise genética de MMP-1 por meio da técnica de PCR e sequenciamento de DNA. **Resultados:** A análise dos genótipos MMP-1-1607, pelo equilíbrio de Hardy-Weinberg, mostrou diferenças significativas na amostra total. O genótipo MMP-1-1607 mais predominante entre os controles foi 1G/2G, o qual foi significativamente diferente das coortes de periodontite. No geral, 13 SNP foram detectados no grupo periodontite versus 17 SNP no grupo

controle. Além disso, o grupo periodontite mostrou uma associação negativa significativa entre a profundidade da bolsa de sondagem e MMP-1-1607. **Conclusão:** Os resultados sugerem que polimorfismos em MMP-1-1607 1G/2G podem desempenhar um papel protetor e diminuir a suscetibilidade à periodontite.

PALAVRAS-CHAVE

Periodontite; Polimorfismo; Nucleotídeo único; Genótipo; Metaloproteinase 1 da matriz.

INTRODUCTION

Periodontitis is an inflammatory disorder characterized by extensive loss of periodontal soft and hard tissue [1] such as Type I collagen [2]. Although interaction between pathogenic periodontal bacteria, anaerobes in particular, and the host immune response is considered as the main trigger for initiation and progression of periodontitis [3]. However, susceptibility of the host to the disease is further determined by other variables including aberrant immune response, environmental, behavioral, and genetic factors [4].

Single-nucleotide polymorphisms (SNP) are the most prevalent form of the human genetic differences and represent an important resource for mapping complex genetic traits [5]. SNP are variations in a single nucleotide that take place at specific positions in the genome and affect gene splicing, protein structure, binding of transcriptional factor, degradation of messenger RNA, or sequencing of noncoding RNA [6]. They also contribute to the variability among individual and their susceptibility to diseases including periodontitis [7].

Members of matrix metalloproteinases (MMP) family are zinc and calcium-dependent proteases [8]. MMP serve in the degradation and remodelling of both extracellular and bone matrix proteins including several types of collagen [9]. MMP-1 is the important proteolytic enzyme that cleaves Type I and III collagen fibers abundantly found in periodontium [10]. MMP-1 are found in low level in healthy periodontium, which are thought to participate in its physiological turnover [11]. However, the increased expression or activation of MMP mediates numerous pathological processes, including the periodontal diseases [12,13].

Periodontitis may show population-based variations [14], some peoples are significantly more susceptible to periodontitis due to a chromosomal specificity [15]. In addition, available evidence have linked certain SNP to periodontitis [16]. While some studies support the role of matrix metalloproteinase -1–1607 SNP in the susceptibility to periodontitis [17,18], others reported opposite results [2,12,19,20]. Although other three polymorphisms were detected in the promoter region of *MMP*-1 [21,22]; however, polymorphism at −1607 1G/2G location is the most commonly associated with susceptibility to periodontal disease.

Based on the available evidence, we hypothesized that MMP-1–1607 SNP is associated with susceptibility to periodontitis among Iraqi individuals. Therefore, the aim of this study was to investigate the association MMP-1−1607 polymorphism with periodontitis among Iraqi population.

SUBJECTS AND METHODS

Study design and subjects

This study was a case-control observational survey which was conducted in Department of Periodontics, College of Dentistry, University of Baghdad and Iraqi National Blood Bank, Baghdad, Iraq. The study started in January and finished in June 2019. Ethical approval was registered at the Research Ethical Committees of Ministry of Health and Environment and Ethical Committee of College of Dentistry, University of Baghdad. All participants were voluntarily joined after explaining the aims and methods of the study.

All recruited patients were Arab of Iraqi nationality exclusively. Participants were divided in to Periodontitis (cases) group and Control group. All subjects were systemically healthy, non-smoker, able and willing to consent. Furthermore, all subjects were examined by a physician to ensure their general health and exclude anyone with any systemic disease, hormonal changes or post-menopausal women, added to this the patients with oral disease/condition other than

caries or periodontal disease, use of medications e.g., anti-inflammatory, immunosuppressants or chemotherapy, pregnant or lactating mothers, not willing to participate and orthodontic appliance wearers were also excluded from the study.

Case definition of periodontitis followed the criteria of European Federation of Periodontology/ American Academy of Periodontology [23]: in which periodontitis case characterized either by the presence of a detectable interdental clinical attachment loss (CAL) at ≥2 non-adjacent teeth, or 2 Buccal or oral CAL ≥3 mm with pocketing >3mm at ≥2teeth.

Diagnosis statement of periodontitis, for the included cases, followed the following criteria:

1. Extent: generalized in which more than 30% of site included in attachment loss;
2. Staging: Stage III and IV in which the extent of bone loss is in the middle and apical third of the root;
3. Status: Unstable in which bleeding on probing at 4 mm pocket depth or the pocket depth ≥6 mm.

While the control group had a clinically healthy intact periodontium with the following criteria: Probing pocket depth (PPD) (assuming no pseudo pockets) ≤3 mm, Bleeding on probing (BOP) <10% without any CAL [24].

Clinical periodontal parameters and calibrations

Clinical examination, for each subject, included recording periodontal parameters; plaque index (PI), gingival index (GI), BOP, PPD, and CAL.

Prior for enrollment in the current study, calibration sessions between the main examiner and expert periodontist were conducted on four patients until agreement level >75% was reached for all clinical parameters.

Blood sampling and genotyping

Vacutainer glass blood collection tubes, 2ml, were used to collect venous blood from the antecubital vein. Then a tube buffered with sodium citrate 3.2% was used for the storage of collected blood and kept at -40C° to avoid DNA degredation until genotyping process of MMP-1 was performed. The processes included DNA extraction, according to the protocol of QIAamp® DNA Mini Kit (QIAGEN, Germany) by isolation of the genomic DNA from blood sample. In details, PCR amplification were done started with primer preparation and optimization. Primers used for MMP-1−1607 were: Forward Primer (5-AATCTAGGCTGGCTGCTTAAC-3), Reverse Primer (5-CTTATGGTGTCTCCCACCTTTC-3). These primers were in lypholized form supplied by Macrogen Company (Macrogen, Korea). Then the amplification of DNA template was done with the same primer pair, Forward and Reverse, at annealing temperatures of 55, 58, 60, 63, and 65°C. After that the PCR amplifications were done. All PCR cycling was completed by using PCR Express (Thermal Cycler, BioRad, USA). At the following temperature program: in which denaturation was done at 94°C for 4 min for 30 cycles followed by annealing which was performed at 55, 58, 60, 63 or 65°C for 30 sec; and extension was completed at 72°C for 30 sec. A final extension incubation of 7 min at 72°C was performed, followed by 10 min incubation at 4°C to stop the reactions. Agarose gel, supplemented with 10mg/ml Ethidium bromide (Promega, USA), electrophoresis (OWL, Thermo, USA) was conducted to confirm the presence of amplification. For PCR product loading, 5μl was directly loaded to each well. Electrical power was turned on at 100 volt/50 mAmp for 90 min. The Ethidium bromide-stained bands in gel were visualized using Gel imaging system (Major Science, Taiwan) (Figure 1). The PCR product was sent for Sanger sequencing using ABI3730XL, automated DNA sequencer Macrogen Company [25]. The results were received by email and analyzed by genious software. Then the sequences of all samples were compared with the orginal source sequence and evaluated by utilizing the Basic Local Alignment Search Tool Program (BLAST) [26].

Statistical analysis

Statistical analysis included both descriptive and inferential statistics. For the latter, normality distribution test was used to determine whether the data are parametric or non-parametric. For categorical variables, Chi square and Fisher's exact test were used. To measure the strength of association between MMP-1−1607 SNP and health/periodontal disease, Odds ratio (OR) was used. Continuous variables were analysed by using Mann-Whitney test. Added to this, to calculate the expected common homozygotes, expected heterozygotes, expected rare homozygotes and

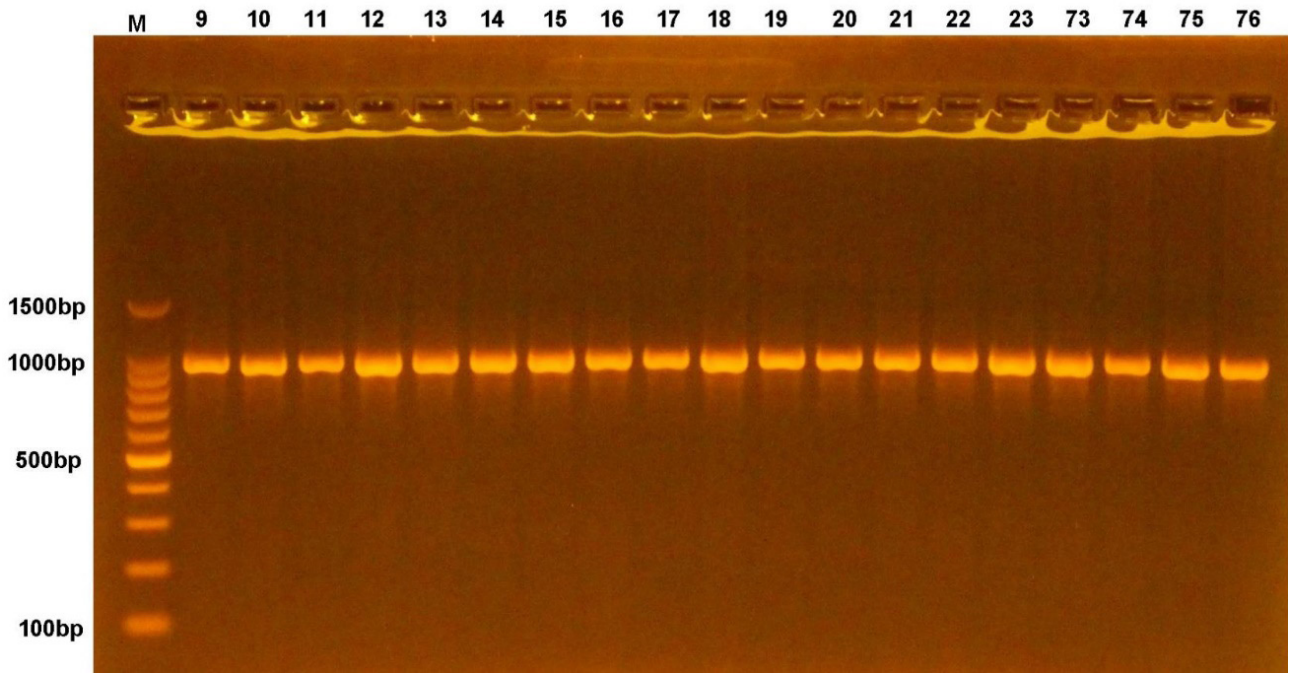

Figure 1 - the amplification of MMP-1–1607 fractionated on 1% agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker. Lanes 1-7 resemble 1500bp PCR products.

the frequency range of the 2 (p and q) alleles from the observed genotypes, Hardy-Weinberg equation was used. Finally statistical analysis was completed by using SPSS (version 21, IBM, USA) software.

RESULTS

Out of 350 subjects who were assessed for eligibility, a total of 38 subjects were enrolled. The age range was 30-60 years, mean ages for Periodontitis and Control groups were 47.40 ± 6.27 and 33.84 ± 4.6 respectively (Table I). Other demographic/clinical variables, sex are illustrated in Table I. Regarding clinical parameters, Periodontitis group exhibited significantly higher PI, GI, and number of missing teeth (Table I).

According to Sanger sequencing, one polymorphism was detected in MMP-1−1607 2G allele indicating a homozygous allele insertion (Figure 2). Analysis by Hardy-Weinberg equilibrium for MMP-1−1607 SNP showed no significant difference in Periodontitis and Control groups whereas significant difference was observed in the total sample (Table II).

No significant difference was shown between Periodontitis and Control groups in the number of SNP of MMP-1−1607 2G allele (Table III).

Table I - Demographic and clinical characteristics of the study population

	Periodontitis	Control	P value
N	20	18	
Age range	37-60	30-50	
Age†	47.40 ± 6.27	33.84 ± 4.6	<0.001*
Sex§			
Male	18, 90%	12, 66.7%	0.035**
Female	2, 10%	6, 33.3%	
Clinical parameters†			
PI	2.56 ± 0.39	0.42 ± 0.06	<0.001*
GI	1.85 ± 0.29	0.39 ± 0.08	<0.001*
BOP	65.33 ± 23.51		
PPD	5.15 ± 0.55		
CAL	6.46 ± 0.72		
Missing teeth	5.38 ± 3.14	0.58 ± 1.07	<0.001*

PI; plaque index, GI; gingival index, BOP; bleeding on probing, PPD; probing pocket depth, CAL; clinical attachment loss. †Mean ± SD; §Frequency, percent; *Significance at p <0.05 by Mann-Whitney test; **Significance at p <0.05 by Chi-square test.

However, a significant difference in the genotype frequency of 1G/2G SNP between the two groups. On the other hand, SNP 2G/2G showed no significant difference between Periodontitis and Control groups (Table III). Further, the 2G/2G genotype showed higher OR (0.17) and population penetrance (22%) than 1G/2G genotype (OR 0.08, population penetrance, 11%) (Table III).

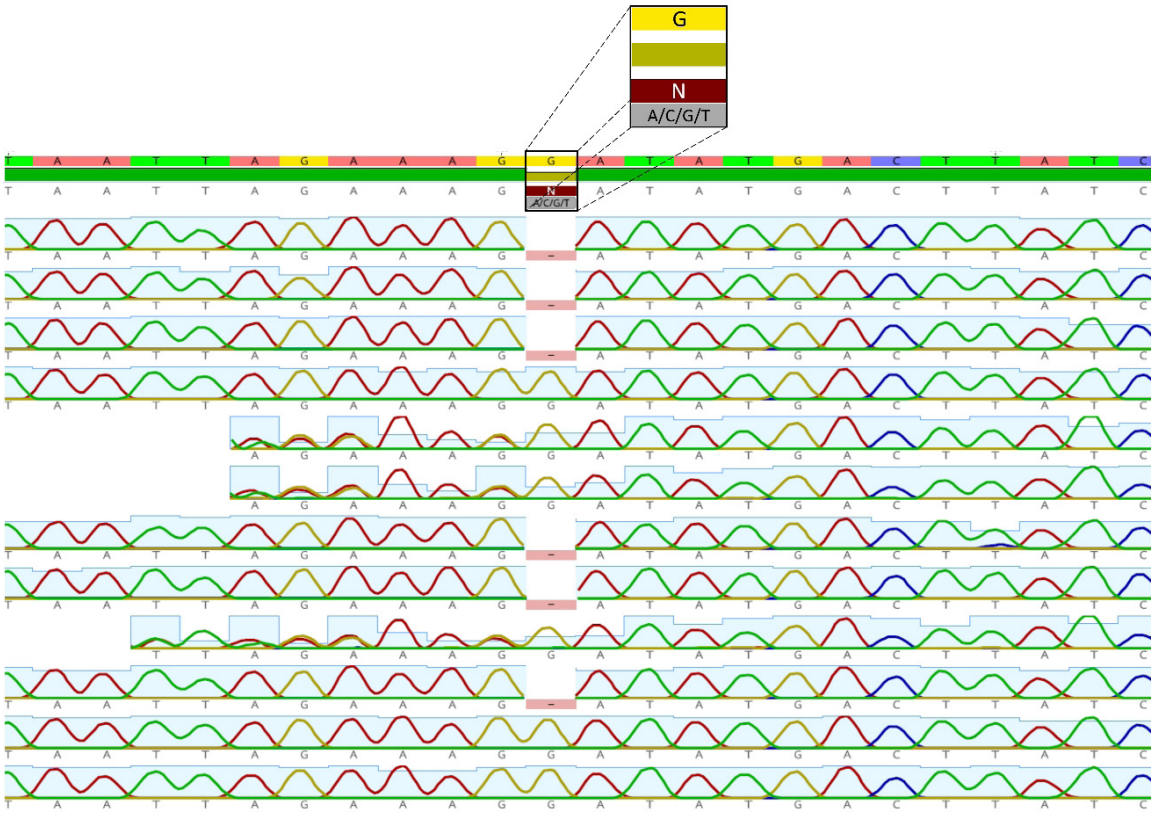

Figure 2 - Analysis of MMP-1–1607 SNP of using Sanger sequencing. "G" peaks indicative of insertion homozygous allele, While no peaks indicative of deletion allele. Present of mix of peaks at the variation point indicative of ins/del heterozygous allele.

Table II - Distribution of genotypes for MMP-1–1607

MMP-1-1607 genotype	Periodontitis N=20		Control N=18		Total N=38	
	Observed	Expected	Observed	Expected	Observed	Expected
1G/1G	7	5	1	0.7	8	4.8
2G/2G	6	10	5	5.6	11	17.4
1G/2G	7	5	12	11.7	19	15.8
Hardy-Weinberg equilibrium	3.2		0.23		5.14	
P value*	0.07		0.63		0.023	

*Significance at p <0.05.

Table III - Frequency of MMP-1–1607 SNP genotype in Periodontitis and Control group

MMP-1–1607 Genotype	Periodontitis†	Control†	P value*	OR‡	CI§	Population penetrance
1G/2G	7, 35%	12, 66.66%	0.02	0.08	0.01 to 0.83	0.11
2G/2G	6, 30%	5, 27.78%	0.15	0.17	0.02 to 1.90	0.22
Total	13, 65%	17, 94.44%	0.05	0.109	0.0119 to 1.0021	

†Frequency, percent; *Significance at p <0.05 by Fisher's exact test. ‡OR: odds ratio; §CI: Confidence interval at 95%.

Correlation between MMP-1–1607 SNP and periodontal parameters showed a significant negative correlation with PPD in Periodontitis group. Other clinical parameters, in both groups, did not show any significant difference with MMP-1–1607 (Table IV).

DISCUSSION

Current study specified that polymorphism of MMP-1–1607 1G/2G allele potentially exhibits a protective effect against susceptibility to periodontitis. This was supported by observing a

Table IV - Correlation of MMP-1–1607 SNP with clinical periodontal parameters

rs1799750 SNP		PI	GI	BOP	PPD	CAL
Periodontitis	r	-0.25	-0.25	0.03	-0.55	-0.22
	P value*	0.27	0.29	0.87	0.012	0.35
Control	r	0.26	-0.31			
	P value*	0.29	0.216			

PI; plaque index, GI; gingival index, BOP; bleeding on probing, PPD; probing pocket depth, CAL; clinical attachment loss; r: correlation coefficient. *Significance at p <0.05 by Spearman's correlation test.

negative correlation between MMP-1–1607 SNP and increasing depth of periodontal pockets. To the best of authors' knowledge, the present study was the first study that investigate the association of the MMP-1–1607 SNP with pathogenesis of periodontitis among Iraqi populations.

Periodontitis is a multifactorial disease which is modulated by several factors such as genetics [27]. In the last decades, interest in investigating SNP of cytokines and inflammatory mediators as a possible pathogenic mechanism of periodontal disease has been increased [28,29]. These studies could help to elucidate the pathogenesis of periodontitis more accurately and aid in developing new therapeutic and preventive strategies [30]. Members of MMP family including MMP-1 have a crucial role in the soft tissue destruction of the periodontium. Meta analyses about the role of *MMP-1* polymorphism and increased susceptibility to periodontitis showed inconsistency and highlighted a gap of knowledge in this area [31,32].

Polymorphism of MMP-1−1607 1G/2G, located on 11q22-q23 chromosome, is one of the most investigated SNP of this enzyme in relation to periodontitis [31,32]. In the current study, significant differences were detected between the two investigated groups concerning the SNP of MMP-1−1607 1G/2G. In addition, 13 SNP were found in the periodontitis group while 17 SNP were found in the control group. The 1G/2G allele was significantly 2-fold higher in the control group with a frequency of 66.6% as compared to 35% in periodontitis group. These findings were in harmony with a result of study conducted on Chinese population which showed the same result with a higher frequency of the 1G/2G allele in the control group [18]. Consistently, similar findings were reported in Brazilian population [2]. However, the Indian population showed opposite pattern in which the periodontitis group had higher frequency of the 1G/2G [33]. Further, no significant association was observed between MMP-1−1607 1G/2G and periodontitis among Turkish population [34]. The conflicting results of literatures could be explained by ethnic variations, sample size, case definitions of health and periodontal disease, and various environmental factors that affect the host response. Therefore, one population or racial group could be totally different in another population in respect to polymorphism of the same gene.

Evidence reported from previous literatures revealed that peoples expressing 2G/2G genotype appeared to be at a greater risk for periodontitis development than individuals expressing 1G/1G and 1G/2G genotypes [17,35]. In contrast, our study indicated that the 2G allele was slightly higher in the periodontitis group than the control group with no significant differences between the two groups. The result of current study are in agreement with previous studies [2,33] but disagree with the study conducted in India [36]. Some researchers demonstrated that MMP-1–1607 2G allele was associated with increased MMP-1 mRNA expression *in vivo* [11]. The 2G allele at MMP-1−1607 created a new 5′-GGA-3′ core recognition sequence for members of the erythroblast transformation specific family as the binding site. This in turn results in an increased in the transcriptional activity, and protein over-expression, which expounding the molecular basis of an anabatic matrix degradation [36]. This is supported by the significant correlation between increasing pocket depth and MMP-1–1607 polymorphism. Therefore, it is biologically acceptable that people carrying MMP-1–1607 2G allele were associated with over-expression of MMP-1; hence, more susceptibility to periodontitis [37]. However, the presence of different alleles responsible for genetic predisposition for the same disease may explain the variations in results among different races or certain population [20].

Influence of genetics on multifactorial disease requires studying other environmental and pathologic factors that may trigger or amplify a particular genetic variation. In our study, other risk factors of periodontal disease such as diabetes and smoking were not included for standardization purposes; however, they may contribute to increase susceptibility to periodontal disease in the presence of SNP. In addition, small sample size and genetic heterogenicity of periodontal disease are other limitations that restrict generalizing the results. Nevertheless, this study was among few studies that investigated the role of genetic aspect of periodontal disease in Iraqi population.

CONCLUSIONS

Despite limitations, it can be concluded that polymorphisms in MMP-1-1607 1G/2G may play a protective role and decreasing the susceptibility to periodontitis. Furthermore, the negative association between PPD and MMP-1-1607 SNP suggested a potential role in decreasing the severity of the disease.

Authors' Contributions

RF: providing the idea, writing the protocol, collecting the sample. HMA: writing of the article, doing the statistics, editing.

AN: providing the idea. SSG: editing, writing and reviewing.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects

The approval code for this study is: 59 in 5/8/2019.

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