RESEARCH PAPER

Genetic association of PPARG gene polymorphism (rs1801282) with susceptibility to Chronic periodontitis

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Abstract:

Introduction: Periodontitis is defined by pathologic loss of the periodontal ligament and alveolar bone. The disease involves complex dynamic interactions among active herpesviruses, specific bacterial pathogens and destructive immune responses. Periodontal diagnostics is currently based on clinical rather than etiologic criteria, and provides limited therapeutic guidance.Apart from its regulatory function in lipid and glucose metabolism, peroxisome proliferator-activated receptor (PPAR)γ has impact on the regulation of inflammation and bone metabolism. The aim of the study was to investigate the association of the polymorph (rs1801282) within the PPARG gene with chronic periodontitis. **Materials and Methods**: This study employed a cross-sectional design involving individuals from Chennai, Tamil Nadu, India. A total of 50 individuals who reported to the Department of Periodontics, Saveetha Dental College, Chennai, were included in this study The subjects were divided into a control group A (N =25) and CP group B (N =25) based on the clinical examination of probing pocket depth, clinical attachment loss and bleeding on probing

Genomic DNA was isolated from the blood of the Control (25) and Case (25) Genotyping was done by RFLP using the Hga1 enzyme. **Results:** The Wild Homozygous frequency in case and control were found to be 16 and 15, respectively. The Heterozygous frequency in case and control were found to be 7 and 9, respectively. The Variant Homozygous frequency in case and control were found to be 2 and 1, respectively. A p-value of 0.3571 suggested that the results were insignificant. **Conclusion:** From the study, it has been concluded that there is no significant assdegree celciusiation of PPARG gene polymorphism (rs1801282) with susceptibility to Periodontitis.Further studies involving other ethnic populations and the functional mechanisms of SNP are needed to confirm the findings in this article

Keywords: Alleles, receptor, Genotype, Chronic periodontitis, PCR, Polymorphism, RFLP,PPARG gene

How To Cite This Article: Panigrahi C, Murthykumar K, Priyadharshini V, Ganapathy D, Marina. Genetic association of pparg gene polymorphism (rs1801282) with susceptibility to chronic periodontitis. Int J Drug Deliv Technol. 2026;16(9s): 362-368; Doi: 10.25258/Ijddt.16.9s.36

Introduction

Periodontitis is a chronic multifactorial inflammatory disease associated with the accumulation of dental plaque, and characterized by destruction of the structures that support the tooth, namely, the periodontal ligament and alveolar bone.(1) This involves dynamic interactions among specific bacterial pathogens, destructive host immune responses, and environmental factors such as smoking. Periodontitis also serves as a constant reservoir of inflammatory mediators and microbial products that can act upon host tissues.(2) The common features of periodontitis include gingival inflammation, clinical

attachment loss, radiographic evidence of alveolar bone loss, sites with deep probing depths, mobility, bleeding upon probing and pathologic migration.(3)

For a susceptible host, microbial infection in subgingival dental biofilm by periodontal pathogens, in particular a group of gram-negative anaerobic species, results in chronic inflammation. These bacteria include Porphyromonas gingivalis and Treponema denticola, which are maximally found in periodontal pockets of patients with periodontitis. Lipopolysaccharide from these periodontal pathogens stimulate the host macrophages, and other inflammatory cells, resulting in the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and prostaglandin E2 (PGE2)(4). The presence of these pro-inflammatory cytokines further stimulates the production of matrix metalloproteinases (MMPs), which in turn then mediate the destruction of collagen fibers in periodontal tissues.

Smoking is the most important environmental risk factor for periodontitis. Compared to non-smokers or past smokers, smokers exhibited a significantly higher prevalence of red-complex periodontal pathogens in their subgingival biofilm. (5)Patients with uncontrolled diabetes are at a greater risk for developing periodontitis as compared to systemically healthy patients or patients with well-controlled diabetes. The association is partly due to alterations in the immune system of patients, which result in impaired neutrophil function or hyper-responsive macrophages producing pro-inflammatory cytokines. (6–10)

According to a common pathogenetic model, the genetic impact on individual susceptibility and severity of periodontitis are mediated by either an inappropriate or exaggerated immune response against a given bacterial stimulus. Hence, polymorphisms of genes that are involved in the stimulation and regulation of inflammatory processes are excellent candidates for the elucidation of the genetic background of the periodontal pathogenesis.

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor super- family and are ligand activated transcription factors. Three subtypes have been identified so far: PPARa, PPARb/d, and PPARg.(11) The PPARs are mainly involved in lipid and lipoprotein metabolism, glucose homeostasis, along with cell proliferation and differentiation.(12)

A growing level of evidence suggests that at least PPARg plays a significant role in regulation and mediation of inflammatory reactions. To be specific , PPARg influences the differentiation of monocytes and attenuates the expression of various pro-inflammatory mediators such as TNF-a, IL-1b and IL-6 along with matrix metalloproteinase, which is involved in periodontal inflammatory process. (13)

Various polymorphisms at the human PPARG locus have yet been described. It has been suggested that some of these variants (rs10865710, rs2067819, rs3892175, rs1801282, rs3856806) might be functionally effective, particularly leading to impaired anti-inflammatory effects of PPARg. For instance, the variants rs1801282 and rs10865710 were shown to be associated with the risk of myocardial infarction and with systemic levels of inflammatory markers in patients with end-stage renal disease. The aim of this study is to determine the genetic association of PPARG gene polymorphism (rs1801282) with susceptibility to periodontitis.

Materials and Methods

This study employed a cross-sectional design involving individuals from Chennai, Tamil Nadu, India. A total of 50 individuals who reported to the Department of Periodontics, Saveetha Dental College, Chennai, were included in this study. The subjects were divided into a control group A (N =25) and CP group B (N =25) based on the clinical examination of probing pocket depth, clinical attachment loss and bleeding on probing. The periodontitis group contained 25 patients with a mean age of 39.02 ± 8.22 years. The patients were recruited based on the 1999 criteria of the American Academy of Periodontology and were chosen based on the 2018 classification of stage II and above . The control group contained 25 periodontally healthy subjects with mean age of 41.34 ± 7.49 years.

A detailed history of dental treatment, family history of periodontal diseases, smoking habits as well as general health concerns were obtained from the subjects. Except for the presence of periodontitis, the patients included in this study were systemically healthy. Smokers, pregnant or lactating mothers, immunocompromised individuals and subjects who had undergone periodontal therapy

within the past 6 months were excluded from this study. The study was approved by the institutional ethics committee (SRB/ MDS/PERIO/18-19/0046).

Statistical Analysis

All statistical analysis was performed using the Statistical Package for the Science version 23.0 for Windows (SPSS Inc., Chicago, IL). The distribution of genotypes and allele frequencies in the periodontitis and control groups was compared using the Chi- square test. The risk as degree celciusiated with individual alleles or genotypes was calculated as the odds ratio (OR) with 95% confidence intervals. Statistical significance in all tests was determined at $P < 0.05$.

PCR Amplification was done using the following primer:
PPARG F: 5'- GCCAATTCAAGCCCAGTC - 3'
PPARG R: 5'- GATATGTTTGCAGACAGTGTATC - 3'
Genotyping was done by RFLP using the Hga1 enzyme.

Results

The present study evaluated the association between **PPARG gene polymorphism (rs1801282)** and susceptibility to **chronic periodontitis** among individuals from Chennai, Tamil Nadu, India. A total of **50 participants** were included in the study and divided equally into **two groups: 25 chronic periodontitis patients (cases) and 25 periodontally healthy individuals (controls).**

Genomic DNA was successfully isolated from peripheral blood samples of all participants. The **PPARG gene fragment containing the rs1801282 polymorphic site** was amplified using polymerase chain reaction (PCR). The amplified products were visualized through **agarose gel electrophoresis**, confirming successful amplification of the target gene segment. Subsequent **restriction fragment length polymorphism (RFLP) analysis** using the **Hga1 restriction enzyme** allowed differentiation of the genotypes based on fragment sizes.

The genotypic distribution revealed that the **wild homozygous genotype (CC)** was the most frequently observed genotype in both groups. In the chronic periodontitis group, **16 individuals exhibited the CC genotype**, whereas **15 individuals in the control group** showed the same genotype. The **heterozygous genotype (CG)** was detected in **7 individuals among the cases** and **9 individuals among the controls**. The **variant homozygous genotype (GG)** was the least common genotype, observed in **2 individuals in the periodontitis group** and **1 individual in the control group**.

Statistical analysis was performed using the **Chi-square test** to evaluate differences in genotype distribution between the two groups. The analysis revealed that the distribution of genotypes did not significantly differ between individuals with chronic periodontitis and the healthy control group. The calculated **p-value of 0.3571** was greater than the threshold value of **0.05**, indicating that the observed differences in genotype frequencies were **not statistically significant**.

Similarly, the allele frequency analysis showed **no significant difference in the distribution of the C and G alleles** between the case and control groups. The odds ratio and confidence interval calculations further supported the absence of a statistically significant association between the **PPARG rs1801282 polymorphism** and susceptibility to chronic periodontitis in the studied population.

The graphical representation of allele frequencies also demonstrated that the polymorphic variation in the **PPARG gene** did not exhibit a marked difference between individuals with periodontitis and healthy controls. These findings suggest that the **rs1801282 polymorphism may not play a major role in determining genetic susceptibility to chronic periodontitis within this population group.**

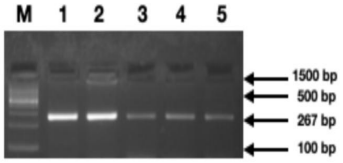


Figure 1: Agarose gel electrophoretogram showing partial amplification of gene PPARG spanning polymorphic site (rs1801282) run along with standard DNA ladder [Lane M = 100 bp DNA marker]

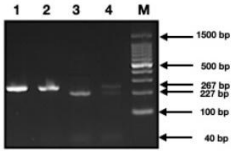


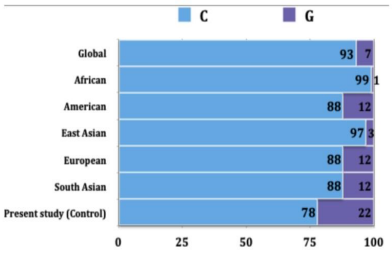
Figure 2: Agarose gel electrophoreto gram showing gal digested amplicon of spanning rs1801282 site of PPARG gene (Homozygous CC - 267 bp; Heterozygous CG - 267+227+40 bp; Homozygous GG -227+40 bp) [Lane M = 100 bp DNA marker]

Groups	CC	CG	GG	C	G	HWE (p value)*
Case (N=25)	16	7	2	0.78	0.22	0.3571
Control (N=25)	15	9	1	0.78	0.22	0.8066

Table 1: Genotype frequencies of PPARG gene polymorphism (rs1801282) among the cases and controls

Dominant				
Genotypes	Case	Control	Unadjusted OR [95% CI]	P value
CC	16	15	1.1852 [0.3778 - 3.7182]	0.7709
CG+GG	9	10		
Recessive				
CG+CC	23	24	0.4792 [0.0406 - 5.6519]	0.5590
GG	2	1		
Allele				
C	39	39	1.0000 [0.3882 - 2.5762]	1.0000
G	11	11		

Table 2: Overall genotype distribution of the PPARG gene polymorphism (rs1801282) in cases and controls



Graph 1: The graph depicts the allele frequency of PPARG gene polymorphism (rs1801282) in different population [Data acquired from Ensembl database]

Discussion

Genetic polymorphisms, like SNPs, may influence disease in multiple complex ways acting with other genetic variants and environmental factors to influence disease susceptibility and progression. Many studies have revealed that SNPs may be assdegree celciusiated with susceptibility to periodontitis. (Zhou et al. 2022)

Our study results showed that the genotype frequency of PPARG(rs1801282) polymorphism did not differ significantly. The prevalence of homozygous and heterozygous mutant genotype had no significant difference between periodontitis and the healthy control group. The detected frequency of AG and AA genotypes had no significant difference between periodontitis group and healthy controls. There was no significant difference in A allele and G allele between periodontitis and the healthy control group. PPARG is a promising biomarker candidate for periodontitis. PPARG signaling is best known for its role in regulating macrophage recruitment and polarization during inflammation. PPARG regulates cellular adhesion and chemotaxis of macrophages, and inflammation. Thus, synthesis and activation of PPARG are important steps in the pathological extracellular matrix destruction assdegree celciusiated with the periodontal Disease. (PPARG Measurement in HIV-1 Infected MDM, CEM-CCR5 Culture Media and HeLaCells," n.d.) (14)The PPARG has potent mononuclear cell chemo-attractant properties, modulates fibroblast and endothelial cell phenotype which plays roles in inflammation.

These concepts gave the insight to design the current study to analyze the association of PPARG gene polymorphism and Periodontitis.(15)

Researchers reported that the single nucleotide polymorphism of PPARG substitution by A may play a role in periodontitis.. There was a significant assoctaion between type of periodontitis and having allele A or G in the PPARG polymorphism. GAgP patients were 3.7 times more likely than CP patients and 2.0 times more likely than CG patients to have allele A, instead of allele G, in PPARG. GAgP patients were 3.1 times more likely than CG patients to have AG versus GG genotype. GAgP patients were also 5.0 and 19.8 times more likely than CP patients to have AG and AA genotypes, respectively, compared to GG.These differences maybe due to the different ethnicity and larger sample size.(15,16)

Schaefer et al reported that The PPARG gene rs2230054 and rs1126580 polymorphisms were assdegree celciusiated with the peri-implantitis susceptibility in the Chinese Han population. (17) The CT genotype of rs2230054 and the AG genotype and G allele of rs1126580 serve as risk factors for the degree celciuscurrence of peri-implantitis. The difference in the results from the present study could be because of different ethnicity and due to larger sample size than what is in the present study.

Since the present study was subjected to one particular ethnicity, the future studies need to evolve such that multicenter studies are conducted to have better understanding of PPARG gene polymorphism among various populations. The strength of the present study is

that all the confounding factors such as smoking and systemic disorders were excluded during the recruitment of the sample. Further studies are required to explore the interaction of gene with microbial and environmental factors in the etiopathogenesis of periodontitis.

Conclusion

Within the limitations of the present study, the results indicate that **PPARG gene polymorphism (rs1801282) does not show a statistically significant association with susceptibility to chronic periodontitis** among the studied South Indian population. The genotype distribution of **CC, CG, and GG variants** did not differ significantly between patients with chronic periodontitis and periodontally healthy individuals. Furthermore, the allele frequency comparison also demonstrated no significant variation between the two groups.

Although **PPARG is known to play an important regulatory role in inflammatory responses, macrophage activation, and bone metabolism**, the present findings suggest that the **rs1801282 single nucleotide polymorphism may not independently contribute to the genetic predisposition of chronic periodontitis** in this population. Periodontitis is a multifactorial disease influenced by complex interactions between **genetic, microbial, environmental, and host immune factors**, and therefore a single genetic polymorphism may not be sufficient to determine disease susceptibility.

The findings of this study should be interpreted with caution due to certain limitations, including the **relatively small sample size and the restriction to a single ethnic population**. Future investigations involving **larger sample populations, multicenter studies, and diverse ethnic groups** are required to validate these results. Additionally, studies focusing on **gene–gene interactions, gene–environment interactions, and functional analyses of PPARG polymorphisms** may provide deeper insights into the genetic mechanisms underlying periodontal disease.

Further research exploring the role of **other inflammatory gene polymorphisms, molecular signaling pathways, and host immune responses** could enhance our understanding of the genetic basis of chronic periodontitis and potentially contribute to the development of **personalized diagnostic and therapeutic strategies in periodontal disease management.**

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