Chapter

Genetic Biomarkers in Periodontal Disease Diagnosis

Gurumoorthy Kaarthikeyan and Swarna Meenakshi

Abstract

Periodontitis is a chronic inflammatory disease with multifactorial etiology. The anaerobic bacteria have been implicated as the main etiological factor for periodontal destruction. Not all the individuals having the similar amount of plaque and calculus develop the periodontitis. Thus, the host susceptibility to periodontal pathogens plays a significant role in the etiopathogenesis of periodontitis. The genetic factor is the major determinant of the host susceptibility. There are contradictory results and varied results of the association of various genetic loci of different genes with periodontitis in different ethnic populations. This chapter will briefly discuss the various candidates' gene approach in understanding the etiopathogenesis of periodontitis. This chapter also throws some light on the relationship of the recent advances in genetic analysis like genome wide association studies, epigenetic regulation, and infectogenomics with periodontal destruction.

Keywords: gene polymorphisms, SNPs, periodontitis, genome wide association studies, infectogenomics, epigenetics

1. Introduction

The interplay among the immune system, microbiota, and lifestyle habits like smoking, alcoholism, stress, and diet that leads to constant changes in the host is regulated by genes. These genes encode immune receptors and various molecules involved in the signal transduction pathways that play an essential role in up regulation or down regulation of the immune response essentially the inflammatory reaction in response to a stimuli. Genetic research has focused on understanding how these responses work and also how these responses differ between different individuals. In addition to playing a role in health, the genetic factors also plays a major role in disease susceptibility. This review focuses on the genetic aspects of periodontal diseases wherein researchers are currently focusing on genetic evidences to explain the difference in susceptibility to periodontal disease in different individuals.

Although very prevalent, periodontal diseases are not evenly distributed across populations. Few people, who do not have much contributing local factors such as plaque and calculus, still develop severe destruction of bone whereas some do not develop severe forms of periodontal diseases in spite of having a very poor oral hygiene. This differential expression of periodontitis leads researchers to question if genetics and heritability played a major role. The first evidence that genetics played a role in periodontal diseases emerged in the 1990s. Schafer et al. postulated that a key determinant of whether individuals developed periodontitis or not was

dependent on the way their bodies responded to the microbes [1]. Genetic factors and environmental factors determine the susceptibility to disease.

A biomarker is a substance that could indicate a biologic state and is an objective measure to evaluate the current and future disease activity. The National Institutes of Health Biomarkers Definitions Working Group in 1998 defined a biomarker as "a substance that is measured objectively and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." These biomarkers could be determined in various biological media like saliva, serum, and gingival crevicular fluid in health as well as disease. Generally, a combination of biomarkers is used in order to predict disease activity.

Genetic susceptibility to multifactorial diseases like periodontitis is usually due to several gene polymorphisms instead of a single, or few, gene mutations. Subtle variations in the genetic code may result in altered expression of the encoded proteins, thereby making individuals with genotypes more susceptible to a given disease.

The genetic link with the etiopathogenesis of periodontitis was started with the initial finding of association of composite genotype (Interleukin-1α and IL-1β) with chronic periodontitis in Caucasian population by Kornman et al. [2]. Following him, lot of studies conducted in different ethnic races linking the association of composite genotype with periodontitis. But the results were contradictory in nature. A variety of single nucleotide polymorphisms of various signaling factors, receptors, connective tissue components, enzymes involved in the host defense against the invading microbes have been reported by several researchers. Use of the genetic risk score could be useful in assessing the susceptibility to periodontitis. However, conflicting results have been reported because of the heterogeneticity of the studies. Different variations in frequency of some alleles in different populations have been observed.

2. Candidate gene approach

2.1 Interleukin-1

Interleukin-1 (IL-1) is a pro-inflammatory cytokine, which is encoded by IL-1 gene cluster at the chromosomal position 2q13–21. It is produced by inflammatory cells such as monocytes, macrophages, and dendritic cells, which play an important role in the regulation of immune and inflammatory responses to infections. It is composed of two molecules, IL-1α and IL-1β. The former regulates intracellular events while the latter acts as an extracellular protein. It plays a major role in the regulation of the inflammatory mechanisms. Studies by Lavu et al., Hao et al. have proposed that IL-1 cluster gene single nucleotide polymorphisms were associated with higher risk for periodontitis [3, 4]. Kornman et al. reported a relationship between IL-1α −889 and IL-1β +3954 and the severity of periodontal disease [2].

Kobayashi et al. demonstrated that Asians had a low carriage rate of IL-1α −889 R-allele compared to the other populations [5]. A meta-analysis by Mao et al., showed that IL-1β +3954 polymorphism increases the risk of periodontal disease [6]. Other authors like Amirisetty et al., Masamatti et al. suggested a strong association of IL-1β −511 and +3954 with chronic periodontitis in Indians [7, 8]. Whereas the study by Kaarthikeyan et al. did not find any significant association between interleukin-1β (+3954) polymorphism with chronic periodontitis in Indian population [9].

Karimbux et al. in their systematic review and meta-analysis studied 13 studies and found that IL-1α and IL-1β (IL-1α (−889) C > T, IL-1α (+4845) G > T, IL-1β

(+3954) C > T, could be a significant contribution to the risk of developing periodontitis [10]. Similarly, Yin et al. in their meta-analysis has found an association between IL-1α rs17561 and IL-1β rs 1143634 polymorphisms and periodontitis [11]. IL-1 gene cluster single nucleotide polymorphisms cannot be considered a significant risk factor for all populations. They seem to contribute to risk of periodontitis in Asian populations.

2.2 Interleukin-6

Interleukin-6 is produced during inflammation by T cells. It is encoded by the IL-6 gene localized on chromosome 7p21. Interleukin-6 is a potent bone resorbing cytokine. It activates and regulates the osteoclasts. Thus, this plays a major role in the susceptibility and progression of periodontal destruction. Zhang et al. found significant association between IL-6 −1363 G/T and IL-6R +48,892 A/C polymorphisms with periodontitis in Chinese population [12]. In a meta-analysis by Nikolopoulos et al. on cytokine gene polymorphisms such as IL-1α, IL-1β, IL-6, and TNF which included 53 studies, no significant association was detected between IL-6 and chronic periodontitis [13].

2.3 Interleukin-10

It is an anti-inflammatory cytokine expressed by T helper cells. It is encoded on gene at 1q31-q32. The major regions of interleukin-10 single nucleotide polymorphisms studied were −1082, −819, and −592. However, conflicting results have been obtained. Berglundh et al. found positive associations between IL-10 SNP and periodontitis in Swedish and Brazilian population [14]. Scarel-Caminaga et al. did not find any significant association in the Caucasian population [15].

2.4 TNF-α

It is a proinflammatory cytokine produced by macrophages. Gene localized at 6p21.3. A meta-analysis by Nikolopoulos et al., which based on 17 studies showed that there was no association of the TNF-α promoter −308G/A polymorphism with periodontitis while another meta-analysis by Song et al. which also included 17 studies found that TNF-α −308 A allele was associated with periodontitis in Brazilian, Asian, and Turkish populations [13]. Ding et al. in their meta-analysis based on 15 studies found an association between TNF-α SNP and periodontitis in Asian and Caucasian population [16]. Thus, the role of TNF-α SNP in the etiopathogenesis of periodontitis has to be explored with further studies.

2.5 TGF-β

It is a multifunctional cytokine that plays an important role in cellular differentiation, apoptosis and angiogenesis. It exists in three isoforms TGF-β1, β2, and β3. Cui et al. in their meta-analysis found significant association between TGF-β SNP and periodontitis in Asian population. However, few other studies by different authors did not show any association.

2.6 IFN-γ

Produced by natural killer cells. The gene is located on chromosome 12q24. Heidari et al. found an association between IFN-γ SNP in Iranian population, while Holla et al. did not find any significant association [17].

2.7 Vitamin D

Vitamin D and Vitamin D receptor are important mediators of bone metabolism. SNPs or dysfunction could lead to bone resorption. The gene encoding vitamin D is located on 12q12-q14.

Gross et al. in their study found that Fok1 polymorphism was associated with periodontitis. Brett et al. in their study found TaqI, BsmI, FokI and ApaI SNPs were associated with periodontitis [18]. Kaarthikeyan et al. did not find any significant association of VDR Taq1 polymorphism with periodontitis in south Indian population [19]. Mashhadiabbas et al. in their meta-analysis based on 38 studies found an association of vitamin D receptor BsmI, TaqI, FokI, and ApaI polymorphisms with periodontitis [20].

2.8 Matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase

Matrix metalloproteinases (MMPs) are the key enzymes, which play a major role in the destruction of the collagenous and non-collagenous proteins of the connective tissue component. This is essential for maintaining the normal tissue homeostasis. To date, at least 26 members of MMPs have been identified. In periodontitis, this tissue homeostasis is altered with more destruction of connective tissue components and less inhibition by the TIMPs. Elevated levels of MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9 have been detected in gingival crevicular fluid, peri-implant sulcular fluid, and gingival tissue of periodontitis patients. Thus, the genetic changes of the MMPs and TIMPs might play a role in the etiopathogenesis of periodontitis. According to Li et al., there was no significant association of MMP1, 8, 9, 12, 2, or 13 polymorphism with periodontitis. They did a meta-analysis of 17 studies [21]. Thus, the role of MMPs and TIMPs gene polymorphism with periodontitis has to be explored with further refined studies.

3. Genome wide association analysis

Rhodin et al. in their systematic analysis listed top genes NIN, ABHD12B, WHAMM, AP3B2, CPEB1, HGD, ZNF675, EMK1, TNFRSF10B, HTR4, WDR59, JDP2, OTOF, ANGEL2, etc. that showed evidence of association with severity of periodontitis and colonization of microorganisms [22]. GWAS is a recent development in the field of research. It highlights suggestive loci that could play an important role in periodontitis. However, the method is expensive and technique sensitive. Many GWAS in periodontitis has been carried out and has shown differential expression of varied genes [23–26].

4. Epigenetic modifications

Epigenetic modifications such as DNA methylation, histone modifications and RNA-associated silencing (micro RNA) play a role in susceptibility to disease. These modifications express or repress certain genes.

Loo et al. in their study showed that methylation of E-Cadherin and COX-2 was observed in periodontitis patients. Nahid et al. demonstrated the expression of miR-146a in infections caused by periodontopathic bacteria. Park et al. in their study observed that miRNA-132 played a major role in pathogenesis induced by P. Gingivalis. Several studies have reported the influence of various microRNAs especially miR-146a, let-7a, miR-196a, miR-499a, and miR-125a in susceptibility to

chronic periodontitis [27–29]. Priyanka et al. in their study have found association of microRNA-125a and microRNA-499a polymorphisms with chronic periodontitis in south Indian population [30].

5. Infectogenomics

Infectogenomics refers to the association of the host genetic variants like single nucleotide polymorphisms with the composition of the microbial complexes in the host body. The recent meta-analysis by Nibali et al. has shown an association of 13 host genetic variants with the red/orange complex bacteria in periodontitis. The study by Divaris et al. has shown an association of two genetic loci (KCNK1 and DAB2IP) with high colonization of red complex bacteria. A more detailed knowledge of the human oral microbiome could provide more information on its association with host genetic variants [31, 32].

6. Conclusion

Although there are several studies that associate various candidate gene polymorphisms to periodontitis, till date there is not much clarity in the genetic susceptibility to the disease since there are a multitude of etiological factors and epigenetic factors that contribute to the susceptibility as well as severity of periodontal disease. Future research should focus on the multitude of genes, their multiple interactions and the epigenetic regulation during different stages of periodontal disease pathogenesis is required to fully understand the molecular mechanisms behind the etiopathogenesis of periodontitis.

Author details

Gurumoorthy Kaarthikeyan* and Swarna Meenakshi
Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, India

*Address all correspondence to: drkarthik79@yahoo.co.in

References

[1] Shlafer S, Riep B, Griffen AL, Petrich A, Hubner J, Berning M, et al. Filifactor alocis—Involvement in periodontal biofilms. BMC Microbiology. 2010;**10**(66):1-13. DOI: 10.1186/1471-2180-10-66

[2] Kornman KS, Crane A, Wang HY, Giovlne FS, Newman MG, Pirk FW, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. Journal of Clinical Periodontology. 1997;**24**(1):72-77

[3] Lavu V, Venkatesan V, Venkata Kameswara Subrahmanya Lakkakula B, Venugopal P, Paul SF, Rao SR. Polymorphic regions in the interleukin-1 gene and susceptibility to chronic periodontitis: A genetic association study. Genetic Testing and Molecular Biomarkers. 2015;**19**(4):175-181

[4] Hao L, Li JL, Yue Y, Tian Y, Wang M, Loo WT, et al. Application of interleukin-1 genes and proteins to monitor the status of chronic periodontitis. The International Journal of Biological Markers. 2013;**28**(1):92-99. DOI: 10.5301/JBM.5000013

[5] Kobayashi T, Ito S, Kuroda T, Yamamoto K, et al. The interleukin-1 and Fcgamma receptor gene polymorphisms in Japanese patients with rheumatoid arthritis and periodontitis. Journal of Periodontology. 2007;**78**:2311-2318

[6] Mao M, Zeng XT, Ma T, He W, Zhang C, Zhou J. Interleukin-1α −899 (+4845) C→ T polymorphism increases the risk of chronic periodontitis: Evidence from a meta-analysis of 23 case–control studies. Gene. 2013;**532**(1):121-126

[7] Masamatti SS, Kumar A, Baron TK, Mehta DS, et al. Evaluation of interleukin-1B (+3954) gene polymorphism in patients with chronic and aggressive periodontitis: A genetic association study. Contemporary Clinical Dentistry. 2012;**3**:144-149

[8] Amirisetty R, Patel RP, Das S, Saraf J, Jyothy A, Munshi A. Interleukin 1ß (+3954, −511 and −31) polymorphism in chronic periodontitis patients from North India. 2015;**73**(5):343-347

[9] Karimbux NY, Jayakumar ND, Padmalatha O, Sheeja V, Sankari M, Anandan B. Analysis of the association between interleukin-1β (+3954) gene polymorphism and chronic periodontitis in a sample of the south Indian population. Indian Journal of Dental Research. 2009;**20**(1):37

[10] Kaarthikeyan G, Saraiya VM, Elangovan S, Allareddy V, Kinnunen T, Kornman KS, et al. Interleukin-1 gene polymorphisms and chronic periodontitis in adult whites: A systematic review and meta-analysis. Journal of Periodontology. 2012;**83**(11):1407-1419

[11] Yin WT, Pan YP, Lin L. Association between IL-1α rs17561 and IL-1β rs1143634 polymorphisms and periodontitis: A meta-analysis. Genetics and Molecular Research. 2016;**15**(1):1-8

[12] Zhang HY, Feng L, Wu H, Xie XD. The association of IL-6 and IL-6R gene polymorphisms with chronic periodontitis in a Chinese population. Oral Diseases. 2014;**20**(1):69-75

[13] Nikolopoulos GK, Dimou NL, Hamodrakas SJ, Bagos PG. Cytokine gene polymorphisms in periodontal disease: A meta-analysis of 53 studies including 4178 cases and 4590 controls. Journal of Clinical Periodontology. 2008;**35**(9):754-767

[14] Berglundh T, Donati M, Hahn-Zoric M, Hanson LÅ, Padyukov L. Association of the −1087 IL-10 gene polymorphism

with severe chronic periodontitis in Swedish Caucasians. Journal of Clinical Periodontology. 2003;**30**(3):249-254

[15] Scarel Caminaga RM, Trevilatto PC, Souza AP, Brito RB, Camargo LE, Line SR. Interleukin 10 gene promoter polymorphisms are associated with chronic periodontitis. Journal of Clinical Periodontology. 2004;**31**(6):443-448

[16] Ding C, Ji X, Chen X, Xu Y, Zhong L. TNF-α gene promoter polymorphisms contribute to periodontitis susceptibility: Evidence from 46 studies. Journal of Clinical Periodontology. 2014;**41**(8):748-759

[17] Holla LI, Hrdlickova B, Linhartova P, Fassmann A. Interferon-γ + 874A/T polymorphism in relation to generalized chronic periodontitis and the presence of periodontopathic bacteria. Archives of Oral Biology. 2011;**56**(2):153-158

[18] Gross C, Krishnan AV, Malloy PJ, Eccleshall TR, Zhao XY, Feldman D. The vitamin D receptor gene start codon polymorphism: A functional analysis of FokI variants. Journal of Bone and Mineral Research. 1998;**13**(11):1691-1699

[19] Kaarthikeyan G, Jayakumar ND, Padmalatha O, Varghese S, Anand B. Analysis of association of TaqI VDR gene polymorphism with the chronic periodontitis in Dravidian ethnicity. Indian Journal of Human Genetics. 2013;**19**(4):465

[20] Mashhadiabbas F, Neamatzadeh H, Nasiri R, Foroughi E, Farahnak S, Piroozmand P, et al. Association of vitamin D receptor BsmI, TaqI, FokI, and ApaI polymorphisms with susceptibility of chronic periodontitis: A systematic review and meta-analysis based on 38 case–control studies. Dental Research Journal. 2018;**15**(3):155

[21] Li W, Zhu Y, Singh P, Ajmera DH, Song J, Ji P. Association of common variants in MMPs with periodontitis risk. Disease Markers. 2016;**2016**:1-20

[22] Rhodin K, Divaris K, North KE, Barros SP, Moss K, Beck JD, et al. Chronic periodontitis genome-wide association studies: Gene-centric and gene set enrichment analyses. Journal of Dental Research. 2014;**93**(9):882-890

[23] Hong KW, Shin MS, Ahn YB, Lee HJ, Kim HD. Genomewide association study on chronic periodontitis in Korean population: Results from the Yangpyeong health cohort. Journal of Clinical Periodontology. 2015;**42**(8):703-710

[24] Divaris K, Monda KL, North KE, et al. Exploring the genetic basis of chronic periodontitis: A genome-wide association study. Human Molecular Genetics. 2013;**22**(11):2312-2324

[25] Sanders AE, Sofer T, Wong Q, Kerr KF, Agler C, Shaffer JR, et al. Chronic periodontitis genome-wide association study in the Hispanic community health study/study of Latinos. Journal of Dental Research. 2017;**96**(1):64-72

[26] Offenbacher S, Divaris K, Barros SP, Moss KL, Marchesan JT, Morelli T, et al. Genome-wide association study of biologically informed periodontal complex traits offers novel insights into the genetic basis of periodontal disease. Human Molecular Genetics. 2016;**25**(10):2113-2129

[27] Nahid MA, Rivera M, Lucas A, Chan EK, Kesavalu L. Polymicrobial infection with periodontal pathogens specifically enhances microRNA miR-146a in ApoE−/− mice during experimental periodontal disease. Infection and Immunity. 2011;**79**(4):1597-1605

[28] Perri R, Nares S, Zhang S, Barros SP, Offenbacher S. MicroRNA modulation in obesity and periodontitis. Journal of Dental Research. 2012;**91**(1):33-38

[29] Kebschull M, Papapanou PN. Mini but mighty: Micro RNA s in the pathobiology of periodontal disease. Periodontology 2000. 2015 Oct;**69**(1):201-220

[30] Venugopal P, Lavu V, Rao SR, Venkatesan V. Association of microRNA-125a and microRNA-499a polymorphisms in chronic periodontitis in a sample south Indian population: A hospital-based genetic association study. Gene. 2017;**631**:10-15

[31] Nibali L, Di Iorio A, Onabolu O, Lin GH. Periodontal infectogenomics: Systematic review of associations between host genetic variants and subgingival microbial detection. Journal of Clinical Periodontology. 2016;**43**(11):889-900

[32] Divaris K, Monda KL, North KE, Olshan AF, Lange EM, Moss K, et al. Genome-wide association study of periodontal pathogen colonization. Journal of Dental Research. 2012;**91**(7_suppl):S21-S28