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Exploring Genetic Susceptibility in Peri-Implantitis

Peri-implantitis Gelişiminde Genetik Yatkınlığın İncelenmesi

Rukiye ZİYA[1]
[1] Department of Basic Medical Sciences, Institute of Health Sciences, Marmara University, İstanbul, Türkiye
Tolga POLAT[2]
[2] Department of Basic Medical Sciences, Faculty of Dentistry, Marmara University, İstanbul, Türkiye
Özlem Özge YILMAZ[2]
[2] Department of Basic Medical Sciences, Faculty of Dentistry, Marmara University, İstanbul, Türkiye
Hatice Selin YILDIRIM[3]
[3] Department of Periodontology, Faculty of Dentistry, Marmara University, İstanbul, Türkiye
Beste TACAL ASLAN[2]
[2]Department of Basic Medical Sciences, Faculty of Dentistry, Marmara University, İstanbul, Türkiye

ABSTRACT

The investigation of genetic factors influencing peri-implant diseases, particularly peri-implantitis (PI), offers insights into the complex interplay between host genetics and inflammatory responses within oral tissues. Numerous genes encoding cytokines, receptors, and regulatory proteins have been scrutinized for their roles in modulating immune responses and tissue homeostasis around dental implants. Notably, polymorphisms in genes encoding interleukins (*IL-1, IL-6, IL-17, IL-10*), tumor necrosis factor-alpha (*TNF-α*), and matrix metalloproteinases (*MMPs*) have emerged as potential genetic markers for susceptibility to peri-implant diseases. Additionally, genes involved in bone metabolism, such as osteoprotegerin (*OPG*), receptor activator of nuclear factor kappa-B ligand (*RANK-L*), bone morphogenetic proteins (*BMPs*), and fibroblast growth factors (*FGFs*), contribute to peri-implant diseases. Polymorphisms in these genes affect bone resorption and regeneration processes, influencing the stability of dental implants. Variations in these genes can either enhance or hinder bone regeneration, impacting the healing process and the long-term success of implants. Moreover, investigations into less-studied genes like cluster of differentiation 14 (*CD14)*, Chemokine Receptor 2 (*CXCR2)*, and Fragment crystallizable gamma receptor (*FcγRs)* have revealed additional genetic determinants implicated in the pathogenesis of peri-implant diseases. These genes can influence immune cell function and inflammatory signaling pathways, contributing to the body's response to bacterial biofilms and other factors that compromise implant health. The study of these genetic variations provides a deeper understanding of individual susceptibility to PI and may guide personalized treatment strategies, ultimately improving implant success rate.
Keywords: Peri-implantitis, polymorphism, immunity

ÖZ

Peri-implant hastalıkları, özellikle peri-implantitis (PI) etkileyen genetik faktörlerin araştırılması, konak genetiği ile oral dokulardaki inflamatuar yanıtlar arasındaki karmaşık etkileşime dair içgörüler sunar. Sitokinleri, reseptörleri ve düzenleyici proteinleri kodlayan çok sayıda gen, dental implantlar etrafındaki bağışıklık yanıtlarını ve doku homeostazını düzenlemedeki rolleri açısından incelenmiştir. Özellikle, interlökinleri (IL-1, IL-6, IL-17, IL-10), tümör nekroz faktörü-alfa'yı (TNF-α) ve matris metalloproteinazları (MMP'ler) kodlayan genlerdeki polimorfizmler, peri-implant hastalıklarına yatkınlık için potansiyel genetik belirteçler olarak ortaya çıkmıştır. Ek olarak, osteoprotegerin (OPG), nükleer faktör kappa-B ligandının reseptör aktivatörü (RANK-L), kemik morfogenetik proteinleri (BMP'ler) ve fibroblast büyüme faktörleri (FGF'ler) gibi kemik metabolizmasında yer alan genler peri-implant hastalıklarına katkıda bulunur. Bu genlerdeki polimorfizmler kemik rezorpsiyonunu ve rejenerasyon süreçlerini etkileyerek diş implantlarının stabilitesini etkiler. Bu genlerdeki varyasyonlar kemik rejenerasyonunu artırabilir veya engelleyebilir, iyileşme sürecini ve implantların uzun vadeli başarısını etkileyebilir. Ayrıca, farklılaşma kümesi 14 (CD14), Kemokin Reseptörü 2 (CXCR2) ve Fragment kristalize edilebilir gama reseptörü (FcγR'ler) gibi daha az çalışılmış genler üzerindeki araştırmalar, peri-implant hastalıklarının patogenezinde rol oynayan ek genetik belirleyicileri ortaya çıkarmıştır. Bu genler, bağışıklık hücresi fonksiyonunu ve inflamatuar sinyal yollarını etkileyerek vücudun bakteriyel biyofilmlere ve implant sağlığını tehlikeye atan diğer faktörlere verdiği tepkiye katkıda bulunabilir. Bu genetik varyasyonların incelenmesi, PI'ye karşı bireysel duyarlılığın daha derin bir şekilde anlaşılmasını sağlar ve kişiselleştirilmiş tedavi stratejilerine rehberlik ederek nihayetinde implant başarı oranlarını iyileştirebilir.
Anahtar Kelimeler: Bağışıklık, peri-implantitis, polimorfizm

INTRODUCTION

Oral and dental health issues stand among the most widespread public health challenges globally, profoundly impacting individuals' overall health and quality of life.[1] A variety of conditions, including

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Sorumlu Yazar/Corresponding author: Rukiye Ziya
E-mail: rukiyeziyaa@gmail.com
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cavities, periodontal diseases, tooth loss, dental fractures, dental fluorosis, and craniofacial disorders, adversely affect life quality.[2] Oral health is a crucial component of overall well-being. In developed countries, efforts to improve oral health aim to minimize social and economic inequalities and facilitate access to effective prevention programs within the community. Conversely, in developing countries, factors such as poverty, and low education levels significantly compromise oral health. [3] The primary source of all diseases in the oral cavity for both adults and children is the biofilm layer.[4] Biofilm is a layer that firmly attaches to the enamel and root surfaces of teeth as well as dental prosthetics, and oral soft tissues. It not only adheres strongly but also multiplies, creating a dense environment rich in pathogenic microorganisms that can influence oral health.[5] Recently, dental implants have become one of the most favored methods for treating or cosmetically resolving toothlessness, thanks to their high success rates.[6] Despite these success rates, dental implants designed to function like tooth roots and made of biocompatible titanium-based materials can encounter complications that lead to loss of osseointegration.[7] The primary treatment goal is to restore the patient's lost function, phonetics, aesthetics, and psychosocial well-being. However, this also introduces new artificial surfaces that can foster bacterial biofilm formation, potentially leading to inflammation of the periodontal tissues that support the teeth.[8] This problem has become more widespread as the number of implant procedures increases daily, leading to a rise in implant-related diseases.[9] The soft tissue around the implant is essential for its long-term success and develops during the healing process post-implantation.[10]

Peri-implant diseases are generally classified into two main categories: peri-implant mucositis (PiM) and peri-implantitis (PI).[11] Peri-implant mucositis is diagnosed when complications around an implant are restricted to inflammation of the mucosa. In contrast, PI is identified when this inflammation is accompanied by alveolar bone loss and the development of pathological pockets.[4] Factors influencing the development of peri-implant diseases include patient-specific factors (the host's inflammatory response, smoking, stress, and genetic diversity in related genes), the presence and condition of keratinized mucosa in the implant area, the quantity and quality of bone and soft tissues, the selected implant system and type, and the forces impacting the implant and surrounding tissues. [12] Inflammation is a critical factor affecting osseointegration and the success of implants. In PI, a significant increase in the levels of inflammatory mediators, particularly interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), interleukin-8 (IL-8), and macrophage inflammatory protein-1A peri-implant fluid has been reported.[13] It is believed that the production of inflammatory cytokines stimulates PI and bone resorption, leading to implant failure.[14] Various studies have reported PiM prevalence rates between 8% and 44%, and PI prevalence rates between 1% and 19%.[15]

Gene polymorphisms are genetic variations found in a population at a frequency greater than 1%, among which single nucleotide polymorphisms (SNPs) are the most prevalent.[16] SNPs occur in both the coding and non-coding regions of genetic sequences. SNPs located within coding sequences have the potential to modify amino acid sequences. Conversely, SNPs that are situated in non-coding regions can influence gene expression or the regulation of RNA sequences.[17] These genetic variations are risk factors for various diseases since they can influence gene expression levels and the synthesis or efficacy of proteins. [18] Studies have identified various genetic variations correlated with PI.[16,18,19] SNPs in inflammatory cytokine and various biomarker genes can create changes in expression levels or amino acid sequences, accelerating the destruction of peri-implant tissues.[19]

GENE POLYMORPHISMS AND PI

Cytokines

Cytokines are small, soluble proteins that regulate inflammation and immunity by mediating intercellular communication.[13] Secreted by various cells, they influence cell growth, mobility, and differentiation, playing a key role in disease pathogenesis.[13] Their detection is crucial for monitoring conditions like periodontal disease and peri-implant infections.[13] Cytokines like interleukins and TNF-α play crucial roles in immune responses and inflammation.

Interleukin-1

Inflammatory cytokines known as interleukins (ILs) play a critical role in regulating the immune response. They initiate the breakdown of the extracellular matrix and bone tissue, and excessive production of these substances plays a significant role in the development and clinical symptoms of inflammatory diseases.[20] There is substantial literature indicating a strong association between various IL-1 gene polymorphisms and PI.[21,22]

The IL-1 family comprises at least 11 cytokines that are crucial for immune function.[22] These cytokines are mapped to the long arm of chromosome 2q and the most extensively researched gene regions within this family include *IL-1α* −889 C/T (rs1800587) and *IL-1β* +3954 C/T (rs1143634). [23] Besides IL-1α and IL-1β, the antagonist IL-1RN also plays a role by binding to the receptor and blocking IL-1 mediated signals, exerting an anti-inflammatory effect. The gene encoding IL-1RA, IL-1RN allele 2, is associated with PI. [24] The effect of IL-1 is derived from the balance between IL-1α, IL-1β, and IL-1RA. IL-1RA binds to the IL-1 receptor, blocking the effects of IL-1α or IL-1β. [25] Genetic variations at -889 in *IL-1α* and +3954 in *IL-1β* lead to higher IL-1 levels, resulting in an increased inflammatory response. Conversely, the presence of *IL-1RN* polymorphisms results in lower levels of this molecule, allowing more molecules to join the IL-1 receptor and thereby enhancing inflammation. Consequently, depending on the alleles an individual possesses, the production of IL-1α, IL-1β, and IL-1RN can increase or decrease. [26] Various studies have found evidence of a combined effect between *IL-1* gene variations, peri-implant bone loss and smoking.[27,28]

Periodontitis, a process similar to peri-implantitis, shares common inflammatory pathways with peri-implantitis, which specifically affects dental implants.[29] A study conducted in the Turkish population investigated *IL-1α* (rs1800587) and *IL-1β* (rs1143634) polymorphisms in periodontitis. [30] While no association was observed between IL-1 *α* and periodontitis, the C allele of *IL-1β* (rs1143634) was found to be more prevalent in healthy individuals, indicating a potential protective role.[30] Another study on PI found that the *IL-1 α* (−889) and *IL-1 β* (+3954) gene polymorphisms had a higher frequency of mutated alleles (T allele) in the PI group compared to the control group. This suggests that these genetic polymorphisms may increase susceptibility to developing PI.[31]

Interleukins-10

As an important anti-inflammatory cytokine, Interleukins-10 (IL-10) plays a vital role in protecting supportive tissues from damage and reducing the production of pro-inflammatory molecules by activating nuclear factor-kappa-B ligand (RANKL) and matrix metalloproteinase (MMP) receptors. [32] Polymorphisms in the 5′ region of the *IL-10* gene are crucial for regulating its production, with the most common variations being −1082 adenine (A) > guanine (G), −819 thymine (T) > cytosine (C), and −592 A > C. Among these, the −1082 A>G variation is most significantly associated with the development of PI, although evidence also suggests a link for the −819 and −592 polymorphisms. [33] However, due to the limited number of studies, their status as definitive risk factors remains unconfirmed.[33] Research by Saremi et

al.[34] emphasized that specific gene polymorphisms like *IL-10* −819 T>C and *IL-10* −592 A>C could play roles in the pathogenesis of PI. Additionally, a study by Taha[35], involving 15 PI patients and 35 individuals with successful implants, identified a correlation between the *IL-10* −1082 A>G polymorphism and PI.

Interleukins-17

A pro-inflammatory cytokine, Interleukin-17 (IL-17), is produced by CD4+ Th17 cells. It includes six distinct isoforms and interacts with five specific receptors.[36] It plays a crucial role in promoting autoimmune and inflammatory conditions by activating immune responses that increase the production of pro-inflammatory cytokines, neutrophils, and monocytes.[37] The *IL-17* gene, located on chromosome 6p12.1, is particularly important for its ability to stimulate the synthesis of key inflammatory mediators such as RANKL, GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), ICAM1 (Intercellular Adhesion Molecule-1), and prostaglandin E2, which are essential in driving inflammatory processes within the body.[37] A study involving 15 participants in Iraq found that individuals with PI were more likely to possess the *IL-17* (rs2275913) AA or GA genotypes, with the AA genotype significantly more common than the GG genotype and G allele.[37]

Interleukin -6

Interleukin -6 (IL-6) is a key cytokine in the early immune response, produced by various blood cell types to support the body's defense mechanisms.[38] Its levels rise significantly in response to trauma, infections, and chronic inflammation.[38] Alongside IL-1β, IL-6 plays a crucial role in promoting bone resorption by increasing the local secretion and activity of metalloproteinases, leading to the degradation of peri-implant tissues and triggering bone resorption mechanisms.[38] Variations in the promoter region of the *IL-6* gene, especially a substitution from guanine to cytosine, have been associated with elevated plasma levels of this pro-inflammatory cytokine.[38] Although there are only a few studies on the link between this polymorphism and PI risk, some research has shown its impact. [38,39]

A study by Petkovic-Curcin et al.[38] revealed that the *IL-6* (rs1800795) polymorphism showed significant differences in genotype and allele frequency. In patients with PI, only the wild-type GG genotype was present, while the GC and CC genotypes were absent, suggesting that the C allele may have a protective role, though further research is needed to confirm this.[38] These findings were supported by Agrawal et al. [39], who also found that patients with the GG genotype exhibited increased peri-implant bone loss, likely due to an overactive inflammatory response driven by IL-6 after implant placement.

Tumor Necrosis Factor-Alpha

As a key inflammatory cytokine, Tumor Necrosis Factor-Alpha (TNF-α) is important for managing immune response regulation. [40] It not only promotes bone resorption and induces fibroblast apoptosis but also inhibits the limited repair of periodontal tissue by enhancing the local release and activity of metalloproteinases that degrade connective tissue. [41,42] The link between TNF-α and PI is believed to arise from its ability to increase local metalloproteinase release and activity, thereby damaging peri-implant tissues and triggering mechanisms of bone resorption.[43] Specifically, the rs1800629 polymorphism at position +308 in the *TNF-α* gene, which results in a guanine to adenine change, leads to direct alterations in TNF-α secretion.[38] Research indicates that the AA and AG genotypes are more frequently observed in patients with PI compared to the GG genotype and are linked to a higher risk of implant failure.[38]

Matrix Metalloproteinases

Matrix Metalloproteinases (MMPs) constitute an important subgroup of zinc- and calcium-dependent endopeptidases.[44] The human MMP family includes more than 23 types, mainly responsible for the degradation of various substances, including the extracellular matrix (ECM), which is crucial for cell development and morphogenesis, as well as growth factors, cytokines, chemokines and adhesion proteins.[45] Type I collagen serves as the primary component of the ECM in periodontal diseases, making three collagenases (MMP-1, MMP-8, and MMP-13) and gelatinases (MMP-2 and MMP-9) especially significant. Other MMPs, such as MMP-7, MMP-12, and MMP-14, along with other proteases, are regarded as moderately effective.[46] MMP-8 is capable of breaking down collagen types 1, 2, and 3, but it degrades type 1 collagen more efficiently than other MMPs.[46] It is believed that excessive activation of MMP-8, in conjunction with other MMPs, may induce inflammation linked to tissue degradation in periodontal and other inflammatory diseases.[47] Costa-Junior and his team, [48] examined the connection between the rs11225395 polymorphism in the *MMP-8* gene and early implant failure. Their results indicate that having the T allele and the TT genotype might be risk factors for early-stage failure of implants. [48] Additionally, de Araujo et al. [49] studied the effects of four different SNPs; *MMP-8* (rs11225395), *MMP-1* (rs1144393), *MMP-1* (rs1799750), and *MMP-3* (rs3025058), and found that the SNPs *MMP-1* g.-1607 G > GG (rs1799750) and *MMP-8* g.-799 C > T (rs11225395) each influenced implant loss in their own way. The 2G allele of *MMP-1* g.-1607 G > GG (rs1799750) was a risk factor, while the C allele of *MMP-8* acted as a protective factor. [49]

BONE METABOLISM GENE POLYMORPHISMS AND PI

Bone metabolism-related genes, such as *Bone morphogenetic proteins* (*BMPs)*, *osteoprotegerin* (*OPG*), and *receptor activator of nuclear factor kappa-B ligand* (*RANK-L*), are crucial for bone regeneration and the stability of dental implants.

Osteoprotegerin

OPG, a cytokine receptor, belongs to the TNF receptor superfamily.[50] This secreted glycoprotein, which is crucial in regulating bone resorption, has been linked to PI.[51] The *OPG* gene hosts several polymorphisms, and research often focuses on two functional single nucleotide polymorphisms (SNPs): 950 C/T (rs2073617) and 1181 G/C (rs2073618). [51] A study by Kadkhodazadeh et al. [52] including 77 patients with chronic periodontitis, 40 patients with PI, and 89 periodontally healthy individuals, found that the CC genotype of the 1181 G/C polymorphism was significantly more common in patients with PI than in the other groups. However, when analyzing the 950 C/T genotype, no statistically significant differences were found between the groups.[53] Research conducted by Zhou and Zhao, [51] in the Chinese population indicated that the rs2073618 polymorphism in the *OPG* gene might increase susceptibility to PI, but no link was found with the rs2073617 polymorphism. Additionally, another study in the Chinese population demonstrated a significant association between the allelic distribution of the 1181 G/C polymorphism and PI. [54]

Bone Morphogenetic Proteins

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor beta (TGF-β) superfamily and consist of over 30 osteogenic proteins. They are mainly found in osteoblasts and are encoded on chromosome 14q22-23. [55] These proteins are present in both mineralized and nonmineralized tissues, indicating their versatile roles in the body.

The roles of BMPs extend beyond tissue formation, repair, wound healing, and cellular differentiation; they are also essential for periodontal regeneration and maintaining tooth integrity. [55] In bone regeneration, certain BMPs such as BMP-2, BMP-4, BMP-6, BMP-7, and BMP-14 are particularly crucial as they stimulate new bone formation.[55] They also contribute to periodontal health by promoting cell growth needed for tissue repair and maintenance. [55]

Among them, BMP-2 stands out as a potent inducer of osteogenesis and is the most well-researched. [56] In dental practice, vectors carrying *BMP* genes, *recombinant human BMP-2 (rhBMP-2)* has been successfully used in procedures like maxillary sinus grafting and bone grafting in extraction sockets to enhance bone regeneration.[57] This is typically achieved by delivering *rhBMP-2* to the defect site using synthetic bone graft materials like β-tricalcium phosphate or collagen sponges. [55-58] This tissue engineering approach has also been applied in various PI pre-clinical and clinical treatment studies, where *rhBMP-2* aids in regenerating bone around dental implants, improving the success rate of these treatments.[59]

At the molecular level, the *BMP-4* gene has been linked to PI, with certain polymorphisms influencing the risk of developing this condition. Specifically, the TT genotype of the *BMP-4* rs2761884 polymorphism was found to be associated with healthier peri-implant conditions, while some *BMP-4* haplotypes have been connected to an increased risk of bone loss around dental implants.[60] This indicates that variations in the *BMP-4* gene can impact bone remodeling and contribute to the body's response to implants, potentially affecting the development of PI. [60]

Receptor Activator of Nuclear Factor Kappa Beta

RANKL, also referred to as TNFSF11, is a part of the TNF ligand superfamily.[61] Its signaling pathway plays a crucial role in the differentiation of monocytes into osteoclasts. This process is initiated when RANKL binds to its receptor, RANK, which is present on the surface of pre-osteoclasts and osteoblasts. Osteoblasts are vital in forming bone stromal cells, while RANKL expression by activated T helper lymphocytes also supports the pathway's function. [62] RANKL has been recognized as a significant genetic factor in the regulation of inflammation within peri-implant tissues.[63] During inflammatory events, the production of RANKL increases, leading to a rise in osteoclast activity and, as a result, an increased rate of bone loss. [64]

Studies have investigated the *RANK* gene polymorphisms rs35211496 (C/T) and rs3018362 (A/G) in individuals with PI, chronic periodontitis, and those with healthy periodontal status within an Iranian population.[64] Results showed that the CC genotype of the rs35211496 polymorphism is significantly associated with PI, indicating it as a potential genetic risk factor for the disease.[64] On the other hand, the distributions of the GG, GA, and AA genotypes of rs3018362, as well as their allele frequencies, did not show any statistically significant differences between the groups.[64] In a separate study involving a Brazilian cohort, researchers examined the *RANK* rs3826620 (G>T) and *RANKL* rs9594738 (C>T) polymorphisms among individuals with healthy and diseased peri-implant tissues.[65] They found no significant association between these polymorphisms and the presence of PI.[65] Furthermore, analysis of *RANKL* gene polymorphisms rs9533156 (T/C) and rs2277438 (A/G) revealed that the CT genotype of rs9533156 has a significant correlation with PI in the Iranian population, indicating its potential as a genetic marker. [62] Conversely, another study concluded that the rs2277438 (A/G) polymorphism did not have a significant association with the failure of dental implants. [66]

Fibroblast Growth Factors

The fibroblast growth factors (FGFs) comprise a family of 22 cell signaling proteins, with 18 functioning as ligands that bind to FGF receptors (FGFRs), a type of tyrosine kinase receptor. This binding triggers the dimerization of FGFRs, leading to the activation of downstream signaling pathways through their intracellular domains.[67] FGFs play important roles in tissue repair and regeneration, with certain members of the FGF family, such as FGF1, FGF3, FGF7 and FGF10, particularly known for and supporting tooth development. [68]

A study of Coelho and his colleagues suggests that the roles of *FGF3* and *FGF10* in supporting tooth structures could potentially contribute to peri-implant failures, as these growth factors are crucial in maintaining the health and integrity of dental tissues.[60] The study showed the relationship between the genes *BMP4*, *FGF3*, *FGF10*, and *FGFR1* and peri-implant bone loss.[60] It identified an association between the *FGF3* rs4631909 (TT+CT genotype) and the control group, while the C allele frequency of *FGF3* rs4631909 showed a potential link to PI. Additionally, *FGF10*-CCTG haplotypes were found to be associated with PI. [60] Notably, this is the only study that has examined the impact of *FGF* gene polymorphisms on PI, emphasizing the need for further research with larger sample sizes from diverse populations and a deeper understanding of the genetic factors contributing to peri-implant bone loss. [60]

OTHER GENES

Cluster of Differentiation 14

PI is a disease influenced by a multitude of genetic factors, encompassing both well-studied genes and others that have been less frequently examined. Among these, cluster of differentiation 14 (CD14) is a glyco-phosphatidylinositol-linked protein found on neutrophils, monocytes/macrophages, and fibroblasts, which can influence the production of pro-inflammatory cytokines.[69] CD14 functions as a versatile high-affinity receptor for binding endotoxins like lipopolysaccharides (LPS). It aids in the transfer of LPS to Toll-like receptors, which in turn triggers LPS-induced bone resorption. [70]

Two studies examining the CD14 gene polymorphisms, 1619A/G (rs2915863) and -159C/T (rs2569190) were conducted in the Serbian population, both indicating that the CC genotype of the -159C/T polymorphism (rs2569190) is linked to a higher risk of developing PI. [71] Later, Li et al. [70] find out these same genetic variations in a Chinese population, finding that the -159C/T polymorphism (rs2569190) of the CD14 gene was significantly associated with an increased susceptibility to PI. [70] In this study, the GG genotype and the G allele were identified as risk factors for PI development, consistent with previous findings. [70]

Chemokine Receptor 2

Chemokine Receptor 2 (CXCR2), which is also referred to as cluster of differentiation 192 (CD192), is situated on chromosome 2q35 and features gene polymorphisms linked to the susceptibility of different conditions. [72] It is found in oral epithelial cells and is associated with the development of chronic periodontitis. Given the similarities between chronic periodontitis and PI, it is hypothesized that *CXCR2* might also be involved in the progression of PI. [72] Additionally, Qi et al. [72] examined two variations in the *CXCR2* gene, responsible for binding IL-8, among the Chinese population. Their results showed a greater frequency of the CT genotype associated with the rs2230054 polymorphism, as well as the AG genotype and G allele for the rs1126580 polymorphism in PI patients. [72]

Fc Gamma Receptor

Fragment crystallizable gamma receptor (*FcγRs*) are receptors found on leukocytes that bind specifically to the Fc region of IgG antibodies.[73] This interaction initiates various immune responses, including phagocytosis, antibody-dependent cytotoxicity, and mast cell degranulation, which are crucial for host defense.[73] In humans, these receptors are encoded by eight genes located on the long arm of chromosome 1 (1q21-24).[74] A polymorphism of two alleles has been

identified in four subclasses of Fcγ receptors: FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb. This variation is considered a potential hereditary risk factor for both autoimmune and infectious diseases.[75] These polymorphisms significantly influence the response of periodontal and peri-implant tissues, thereby playing a vital role in the progression of these conditions. [76]

A study conducted in Iran successfully demonstrated that gene polymorphisms can influence susceptibility to PI.[73] Specifically, the presence of allele R in *FcγRIIa* (rs1801274), allele V in *FcγRIIIa* (rs396991), and allele NA2 in *FcγRIIIb* (rs1050501) were shown to reduce the ability of phagocytes to engulf microbial products, impairing their capacity to contain and control infections.[73] The same polymorphisms and their relationship with PI were studied in 2024 by Peng Li and his colleagues, [77] in the Chinese population. Their results showed that the *FcγRIIIa* rs396991 polymorphism was not associated with PI. Consistent with previous research, the *FcγRIIa* rs1801274 polymorphism has been significantly linked to PI in the Han Chinese population, indicating that the RR genotype might serve as a genetic risk factor for developing PI.[77] It is crucial to recognize that the distribution of *FcγR* genotypes and their allele frequencies can vary among individuals from different ethnic backgrounds.

CONCLUSION

In summary, ongoing genetic research is crucial for understanding the molecular pathogenesis of PI. Currently, the most extensively studied proteins linked to PI in the literature include *IL-10, IL-1, OPG, TNFα*, and the *MMP* family. These proteins play pivotal roles in the development of PI, but the impact of other cytokines could also reveal additional influential factors due to their interactions. Although existing data seem to support the presence of genetic predispositions, there is still a need for further studies with larger sample sizes across various ethnic groups to clarify this issue. Additionally, while genetic factors can serve as diagnostic markers, when combined with general risk factors for PI such as smoking, prior periodontal issues, diabetes, inadequate restorations, and poor maintenance, they can quickly lead to implant loss. Looking ahead, genetic polymorphisms and variations in cytokine expressions may offer promising avenues for new drug interventions, but more research is required in this field.

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