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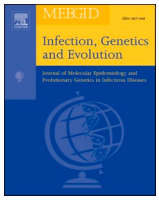

Review

Genetic polymorphisms associated with periodontitis in Japanese populations: A comprehensive review of pathways, interactions, and clinical implications

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ABSTRACT

Periodontitis is a chronic inflammatory disease affecting the supporting structures of teeth, with increasing evidence supporting a significant genetic component in disease susceptibility. This comprehensive review evaluated the associations between genetic polymorphisms and periodontitis in Japanese populations. This narrative review synthesizes available evidence without employing meta-analytical methods. Analysis of relevant studies revealed population-specific genetic architecture, with patterns that suggest possible differences from those observed in Western populations. Significant associations were identified for Japanese populations in immune-related genes (*IL1RN* VNTR: OR 3.40 in G-EOP; *IL1B* -511: OR 1.72 in chronic periodontitis), immunoreceptors (*FCGR3A*-158 V: OR 2.03 in severe chronic periodontitis), tissue remodeling genes (*MMP1* -1607 1G/2G: OR 1.95 in chronic periodontitis), and vitamin D pathway genes (*VDR* +1056 T/C: OR 2.45 in chronic periodontitis). Novel genetic associations with exceptionally strong effect sizes were identified with *ADGRG6* (formerly GPR126) (rs536714306: OR 9.09), *MAEA* (rs6815464: OR 3.73), and *CSF1* genes, expanding our understanding beyond traditional inflammatory pathways. Gene-gene interactions, particularly between *VDR* and *FCGR3B* polymorphisms (composite genotype: OR 5.93), demonstrated substantially stronger associations with periodontitis than individual polymorphisms alone. Protective genetic variants, including *FCGR3B*-NA1 allotype in elderly individuals and *IL1B* rs16944 GA genotype, highlight the concept of genetic resilience. Genetic associations differ markedly between aggressive and chronic forms of periodontitis, with stronger associations typically observed in aggressive/early-onset disease. These findings may contribute to improved risk assessment strategies and personalized approaches to periodontitis prevention and treatment in Japanese individuals, emphasizing the importance of population-specific genetic profiling in periodontal medicine.

1. Introduction

Periodontitis represents a complex inflammatory condition that targets tooth-supporting tissues, characterized by the progressive degradation of both periodontal ligament structures and adjacent alveolar bone. This disease constitutes a substantial public health challenge globally, ranking among the leading causes of dental loss in adult populations and demonstrating significant associations with multiple systemic disorders, including cardiovascular pathologies and glucose metabolism abnormalities (Serón et al., 2023; Ozmeric et al., 2024; Sanz et al., 2020a). The etiology of periodontitis is multifactorial, involving complex interactions between microbial, environmental, and host factors. Over the past two decades, research has accumulated compelling evidence for hereditary influences on both disease initiation and progression patterns (Laine et al., 2012; Nibali et al., 2019). Genetic variations, with particular emphasis on single-nucleotide sequence variations, appear to modulate immune responsiveness, inflammatory signaling pathways, and tissue regenerative capacities—all critical

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components in periodontal pathophysiology (Kinane et al., 2005; Loos et al., 2005; Yoshie et al., 2007). Periodontal disease categorization has undergone significant evolution in recent decades. Earlier classification systems, particularly the framework established at the 1999 International Workshop, separated the condition into distinct entities: aggressive periodontitis (characterized by accelerated tissue destruction typically affecting younger patients with familial clustering) versus chronic periodontitis (a more prevalent form with gradual progression primarily affecting older individuals) (Armitage, 1999; Papapanou et al., 2018). This dichotomous approach was subsequently reconceptualized during the 2017 World Workshop, which introduced an integrated classification that positions all forms under the unified term "periodontitis" but differentiates cases according to a multidimensional matrix of stages (I-IV) reflecting disease severity/extent and grades (A-C) indicating progression rates (Sanz et al., 2020b). Despite this recent modification, most genetic studies discussed in this review were conducted under the previous nomenclature. The genetic architecture underlying periodontal disease susceptibility demonstrates considerable variability across diverse ethnic populations, reflecting differences in genetic foundations and environmental-genetic interplay (Yoshie et al., 2007). Japanese populations, characterized by relative genetic homogeneity and distinctive genomic profiles, provide particularly valuable research contexts for identifying population-specific genetic risk determinants. Numerous investigators have explored genetic variations in relation to periodontitis among Japanese individuals, with particular attention to candidate genes involved in immunological regulation, inflammatory cascade modulation, and tissue homeostasis maintenance. The purpose of this narrative review was to comprehensively evaluate the scientific literature regarding genetic polymorphisms associated with periodontitis specifically in Japanese populations. Through systematic examination of genetic associations across diverse functional pathways, we aimed to identify consistently replicated genetic risk factors and highlight emerging genetic contributors to periodontal disease susceptibility in this population, with potential implications for risk stratification approaches and individualized preventive and therapeutic strategies.

2. Study selection methodology

For this narrative review, we conducted comprehensive literature searches using PubMed, Scopus, Web of Science, and J-STAGE databases through January 2025. Our selection criteria included:

- Minimum sample size of 100 participants (cases and controls combined)
- Clear diagnostic criteria for periodontitis based on clinical parameters (probing depth, clinical attachment loss, and/or radiographic bone loss)
- Appropriate genotyping methods with quality control measures
- Statistical analysis with adjustment for at least age and sex
- Studies conducted specifically in Japanese populations

When multiple studies were available for a single SNP, we prioritized those with:

1. Larger sample sizes
2. More comprehensive multivariate analyses
3. Clear phenotype definitions

3. Immune response genes

3.1. Interleukin-1 (*IL1*) gene cluster

The *IL1* gene cluster has attracted significant research interest in periodontal genetics due to its essential role in inflammatory cascade regulation. The IL-1 cytokine family orchestrates multiple aspects of the inflammatory process, functioning to enhance adhesion molecule expression, upregulate inflammatory mediator and metalloproteinase production, activate lymphocyte populations, promote osteoclast-mediated bone resorption, and regulate apoptotic pathways (Dinarello, 2009). In a Japanese population study, Tai et al. (Tai et al., 2002) investigated *IL1* genetic variations in 47 patients with generalized early-onset periodontitis and 97 healthy individuals. Their analysis revealed significantly elevated frequencies of *IL1RN* VNTR polymorphic alleles (2,3,4,5) in G-EOP patients versus controls (OR 3.40, 95 % CI 1.24–9.52, $p = 0.007$), with similarly increased carriage rates (OR 3.81, 95 % CI 1.31–11.31, $p = 0.005$). However, *IL1A* (+4845) and *IL1B* (−511, +3954) variants showed no significant disease associations. Different findings emerged from Kobayashi and colleagues (Kobayashi et al., 2007a), who identified an association between the *IL1B* +3954C/T polymorphism and severe chronic periodontitis in Japanese adults (OR 1.89, 95 % CI 1.54–2.32, $p < 0.001$). Similarly, Shirakata et al. (Shirakata et al., 2001) reported that the *IL1B* -511 variant correlated with chronic periodontitis risk in Japanese non-smokers (OR 1.72, 95 % CI 1.18–2.51, $p = 0.005$). More recently, Tanaka et al. (Tanaka et al., 2014) conducted a larger case-control investigation examining three *IL1* SNPs in 1150 young Japanese women (131 cases, 1019 controls). Their findings revealed a protective effect for the GA genotype of *IL1B* rs16944 (C-511 T), which associated with reduced periodontal disease risk (adjusted OR 0.62, 95 % CI 0.40–0.96, $p < 0.05$). No significant associations emerged for *IL1A* rs1800587 (C-889 T) or *IL1B* rs1143634 (C + 3954 T), and no gene-smoking interactions were detected. Kamei and colleagues (Kamei et al., 2014) expanded the scope of *IL1* genetics research by examining interleukin-1 receptor variants in aggressive periodontitis. Their study revealed potential contributions of specific receptor polymorphisms to disease susceptibility, further highlighting the multifaceted role of IL-1 signaling networks in Japanese periodontal pathogenesis. The inconsistent outcomes observed across these various investigations may reflect methodological differences, variations in sample populations, diagnostic criteria heterogeneity, and specific polymorphic targets examined. Another contributing factor may be the comparatively lower prevalence of certain *IL1* genetic variants in Japanese populations relative to other ethnic groups, potentially affecting statistical power to detect meaningful associations (Kobayashi et al., 2009). These divergent findings concerning *IL1* family polymorphisms in Japanese cohorts illustrate the multifaceted nature of genetic contributions to periodontitis. The established relationship between *IL1RN* VNTR variant alleles and generalized early-onset periodontitis (Tai et al., 2002) indicates that genetic alterations affecting the IL-1 receptor antagonist protein—a critical modulator of IL-1 bioactivity—may have greater relevance to juvenile disease manifestations in Japanese subjects compared to variations within the *IL1A* or *IL1B* genes themselves. Notably, this research observed limited correlation between periodontitis and certain *IL1A*/*IL1B* variants that have been associated with periodontal disease in some Caucasian cohorts, suggesting potential ethnic variations in genetic risk profiles. The later discovery of relationships between *IL1B* polymorphisms and adult-onset chronic periodontitis in Japanese subjects (Shirakata et al., 2001) indicates that specific variants within the interleukin-1 gene family might influence particular periodontal disease classifications differently. This observation supports the concept that periodontal disease genetics demonstrates heterogeneity not just across different ethnic backgrounds but also between clinical subtypes within a single population group. Adding further complexity to this genetic landscape, Tanaka's research (Tanaka et al., 2014) documented a protective association for the GA genotype of rs16944 in *IL1B*, demonstrating how heterozygosity at certain genetic loci may paradoxically enhance resistance to disease rather than increasing susceptibility. This genotypic heterozygote protection pattern appears in several inflammatory disorders beyond periodontitis and constitutes a crucial factor when analyzing results from genetic association research. The comparative rarity of particular *IL1* variants among Japanese

individuals versus Caucasian populations (most notably the *IL1B* + 3954 polymorphism) provides a potential explanation for discordant results between studies. Population-specific allelic distribution significantly affects detection sensitivity, necessitating expanded participant numbers to identify statistically meaningful relationships with uncommon genetic variants. This observation reinforces the requirement for ethnically-targeted genetic investigations rather than generalizing conclusions across diverse ancestral groups. The *IL1* gene family polymorphisms demonstrate variable relationships with periodontal disease in Japanese subjects, with particularly robust associations observed between *IL1RN* VNTR variants and juvenile-onset forms, while *IL1B* polymorphisms show stronger connections to adult chronic manifestations. These potentially ethnicity-dependent genetic patterns may differ from findings reported in studies of European populations, suggesting the importance of considering population-specific factors in genetic risk evaluation approaches.

3.2. Interleukin-6 (*IL6*) and IL-6 receptor

Interleukin-6 functions as a pleiotropic cytokine with critical involvement in periodontal disease mechanisms. This dual-function inflammatory mediator enhances IL-2 receptor expression and promotes inflammatory interleukin secretion while simultaneously inhibiting IL-1 and TNF-α production (Kobayashi et al., 2007a). In bone metabolism, IL-6 exhibits concentration-dependent effects: promoting osteoclastogenesis and bone degradation while suppressing osseous formation (Graves and Cochran, 2003). When present at lower levels, this cytokine facilitates preosteoclast differentiation, whereas at elevated concentrations, it predominantly activates fully-formed osteoclasts. Additionally, IL-6 contributes to periodontal tissue breakdown by modulating matrix metalloproteinase release and activation, enzymes responsible for extracellular matrix degradation during periodontitis. Research by Galicia and colleagues (Galicia et al., 2004) investigated *IL6R* genetic variations in a Japanese cohort comprising 212 periodontitis-affected individuals (169 chronic and 43 aggressive cases) and 210 healthy subjects. Their analysis revealed that the rs8192284 polymorphism (148,892 A/C) demonstrated significant disease associations. Carriers of the A variant showed increased risk for periodontitis generally (OR 1.73, 95 % CI 0.99–3.06, $p = 0.04$) with stronger association specifically for chronic forms (OR 2.25, 95 % CI 1.08–2.25, $p = 0.02$). Genotype distribution analysis also identified relationships with aggressive periodontitis ($p = 0.04$). The biological production of IL-6 appears substantially influenced by hereditary factors, with several functional variants identified within the *IL6* gene promoter region, including -597G/A, -572C/G, and -174G/C. Particularly, the -572G/C and -174G/C regulatory region polymorphisms, which modulate both *IL6* expression levels and circulating IL-6 concentrations, have demonstrated associations with periodontal disease susceptibility (Shao et al., 2009; Brett et al., 2005).

3.3. Interleukin-18 (*IL18*)

Interleukin-18, a member of the IL-1 cytokine superfamily, significantly influences periodontal pathophysiology (Orozco et al., 2007; Dinarello and Fantuzzi, 2003). This inflammatory mediator primarily functions by enhancing interferon-γ production in conjunction with IL-12, thereby modulating both Th1 and Th2 immune responses (Dinarello, 2009; Tai et al., 2002). Through its regulatory actions, IL-18 promotes the release of various inflammatory cytokines including TNF-α, IL-1β, and IL-8, which collectively facilitate neutrophil expansion, directed migration, and functional activation during periodontal infections (Sahoo et al., 2011). Notably, IL-18 demonstrates inhibitory effects on osteoclast-mediated bone degradation, suggesting its potential involvement in skeletal homeostasis regulation during periodontal disease progression (Silva (Silva et al., 2015)). In a case-control investigation, Tanaka and research team (Tanaka et al., 2017) explored relationships between two *IL18* genetic variants (rs1946518 and rs187238) and periodontal disease susceptibility among young female Japanese subjects. Their multivariate analysis, controlling for demographic variables (age and education) and oral hygiene practices (smoking habits and interdental cleaning), revealed that individuals carrying the CC genotype of rs1946518 exhibited substantial protection against periodontitis compared to those with AA or AC genotypes (adjusted OR = 0.54, 95 % CI = 0.29–0.97, $p = 0.04$). The rs187238 polymorphism showed no significant disease associations. Demographic analysis confirmed homogeneity between case and control groups regarding age distribution, educational background, smoking behavior, and interdental hygiene practices. The researchers found no evidence for gene-environment interactions between *IL18* variants and smoking exposure, indicating these genetic factors likely influence disease susceptibility through pathways independent of tobacco effects. These findings establish the rs1946518 polymorphism in the *IL18* promoter region as a biologically relevant genetic marker for periodontitis risk assessment in young Japanese women. The mechanistic basis for this association may stem from the variant's position within a recognized transcription factor-binding domain, potentially altering *IL18* gene expression regulation (Giedraitis et al., 2001; Thompson and Humphries, 2007).

3.4. Interleukin-12 receptor β2 (*IL12RB2*)

IL-12 is a heterodimeric cytokine that plays a crucial role in cell-mediated immunity by promoting Th1 differentiation and inhibiting Th2 development (Trinchieri, 2003). The IL-12 receptor consists of two subunits, IL-12Rβ1 and IL-12Rβ2, with the latter being particularly important for IL-12 signaling and Th1 differentiation. Takeuchi-Hatanaka et al. (Takeuchi-Hatanaka et al., 2008) conducted a groundbreaking study investigating polymorphisms in the 5′ flanking region of *IL12RB2* in Japanese periodontal patients. This research was motivated by the observation that the expression of IL-12Rβ2 molecule is a crucial regulatory factor in the T-helper type 1 (Th1) differentiation of T cells. Previously, the authors had identified several SNPs in the 5′ flanking region of *IL12RB2*, including -1035A > G, −1023A > G, −650delG, and -464A > G, which affected the expression level of these receptors in lepromatous leprosy patients. In their study of 110 Japanese patients with periodontitis (30 aggressive, 44 severe chronic, and 36 mild chronic) and 43 healthy controls, they found that the frequencies of variant alleles of *IL12RB2* were significantly higher in aggressive periodontitis patients compared to healthy controls or chronic periodontitis patients. For all four SNPs (−1035A > G, −1023A > G, −650delG, and -464A > G), significant differences were detected between aggressive periodontitis patients and both healthy controls (p-values 0.0048, 0.0048, 0.0040, and 0.0021, respectively) and severe chronic periodontitis patients (p-values 0.0048, 0.0048, 0.0010, and 0.0028, respectively). Additionally, the "carrier" subjects (those with at least one variant allele) had significantly deeper mean periodontal pockets than "non-carrier" subjects ($p = 0.0303$). The researchers also measured serum IgG titers against various periodontal bacteria and found that these titers were significantly higher in carrier subjects than in non-carrier subjects for *Actinobacillus actinomycetemcomitans*, *Capnocytophaga ochracea*, *Eikenella corrodens*, and *Fusobacterium nucleatum* ($p < 0.05$ for all). These findings suggest that *IL12RB2* SNPs could be useful genetic markers for determining susceptibility to periodontal disease in the Japanese population. The authors proposed that low cell-mediated immune responses or high humoral responses associated with these polymorphisms may contribute to the pathogenesis of inflammatory periodontal diseases. This study provides important insights into the role of Th1/Th2 balance in periodontitis susceptibility in Japanese individuals, suggesting that subjects prone to periodontal diseases may share a hereditary background characterized by a tendency to have low Th1 responses against pathogens. The identification of these *IL12RB2* polymorphisms represents a significant advancement in understanding

the genetic basis of aggressive periodontitis in the Japanese population and highlights the importance of considering immune response genes beyond the more commonly studied cytokines such as *IL1* and *TNF*. The association between *IL12RB2* SNPs and aggressive periodontitis specifically—but not chronic forms—highlights important distinctions in the genetic architecture of different periodontitis subtypes. This pattern suggests that aggressive periodontitis may involve more profound alterations in T-cell differentiation pathways, potentially explaining its earlier onset and rapid progression. The correlation between *IL12RB2* variant alleles and increased serum IgG titers against periodontal pathogens provides a functional link between genotype and phenotype, supporting the hypothesis that these genetic variations result in a Th1/Th2 imbalance. The shift toward humoral immunity over cell-mediated responses could enable periodontal pathogens to evade host defenses more effectively, despite robust antibody production. This observation aligns with previous findings in lepromatous leprosy, suggesting common immunogenetic mechanisms may underlie susceptibility to diverse infectious diseases. The significantly deeper periodontal pockets observed in carriers of *IL12RB2* variants provides clinical relevance to these genetic associations, linking molecular alterations directly to disease severity.

3.5. Tumor necrosis factor (*TNF*)

TNF-α is a pro-inflammatory cytokine present in periodontal tissues in greater quantity at sites of disease progression. Several studies have examined *TNF* gene polymorphisms in relation to periodontitis in Japanese populations. Soga et al. (Soga et al., 2003) found a significant association between TNF-α promoter polymorphisms (−1031/−863, −857) and severe adult periodontitis in Japanese patients. Japanese patients were more likely to suffer from chronic periodontitis if at least one of the three polymorphisms −1031 (T → C), −863 (C → A), or − 857 (C → T) was present. Kobayashi et al. (Kobayashi et al., 2009) further confirmed the association between the *TNF* -308 G/A polymorphism and chronic periodontitis in a Japanese population (OR 1.65, 95 % CI 1.16–2.35, $p = 0.006$). This study also examined the relationship between cytokine gene polymorphisms and rheumatoid arthritis, finding some shared genetic risk factors between the two inflammatory conditions. These studies suggest that *TNF* gene polymorphisms may influence susceptibility to periodontitis in the Japanese population, particularly in those with severe or chronic forms of the disease. The functional consequences of these polymorphisms may include altered TNF-α production, potentially leading to enhanced inflammatory responses in periodontal tissues.

4. Immunoreceptors

4.1. Fc gamma receptors (*FCGR*)

Fc gamma receptors (FcγR) are cell surface molecules that bind the Fc region of IgG and play a critical role in linking humoral and cellular immune responses (Ravetch and Kinet, 1991). Three main groups of receptors for the Fc fragment of IgG have been identified: FcγRI (CD64) located on mononuclear phagocytes, FcγRII (CD32) located both on mononuclear and multinucleated cells as well as in soluble form, and FcγRIII (CD16) including FcγRIIIa on monocytes and macrophages and FcγRIIIb on neutrophils (Nimmerjahn and Ravetch, 2008). Kobayashi et al. conducted several studies on *FCGR* polymorphisms in Japanese periodontitis patients. They found that the *FCGR3A*-158 V allele was over-represented in severe chronic periodontitis compared to moderate chronic periodontitis (OR 2.03, 95 % CI 1.03–4.01, $p = 0.028$). A composite genotype of *FCGR3A*-158 V plus *FCGR3B*-NA2 was strongly associated with chronic periodontitis severity (OR 4.69, 95 % CI 1.52–15.10, $p = 0.002$ for severe vs. moderate chronic periodontitis; OR 4.10, 95 % CI 1.62–10.59, $p = 0.0009$ for severe chronic periodontitis vs. healthy controls). Patients positive for the composite genotype showed more severe clinical signs, including increased mean probing depth (3.8 mm vs. 3.2 mm, $p = 0.005$), mean clinical attachment level (4.5 mm vs. 3.7 mm, p = 0.005), and mean percentage bone loss (37.6 % vs. 29.9 %, $p = 0.008$) compared to those without the composite genotype (Kobayashi et al., 2007a). Sugita et al. (Sugita et al., 2001) conducted a study on 599 elderly Japanese individuals and reported that the *FCGR3B*-NA1 allotype was overrepresented in periodontitis-resistant subjects (OR 1.87, 95 % CI 1.13–3.10, $p = 0.03$). This finding is particularly interesting as it suggests a potentially protective role for the NA1 allotype against periodontitis development in elderly Japanese individuals. Kobayashi et al. (Kobayashi et al., 2007b) investigated the combined effects of stimulatory and inhibitory *FCGR* genotypes in Japanese adults with systemic lupus erythematosus and periodontitis. They found that the combination of stimulatory *FCGR2A* and inhibitory *FCGR2B* genotypes increased susceptibility to systemic lupus erythematosus and periodontitis in the Japanese population. The *FCGR2B*-232 T/T genotype and 232 T allele were significantly increased in periodontitis patients compared to controls, while the -386G/−120 T haplotype was significantly decreased in periodontitis patients. Wang et al. (Wang et al., 2012) examined *FCGR2B*-nt645 + 25A/G gene polymorphism in Japanese women with preeclampsia and periodontitis. This study included 13 women with preeclampsia and 106 without preeclampsia. They found that the *FCGR2B*-nt645 + 25AA genotype was more frequent in the preeclampsia group ($p = 0.007$), while the GG genotype was associated with periodontitis ($p = 0.048$). This study highlights the potential role of *FCGR2B* polymorphisms in both conditions and suggests a possible genetic link between periodontitis and preeclampsia. These findings collectively suggest that *FCGR* gene polymorphisms play an important role in determining susceptibility to periodontitis in the Japanese population. The functional consequences of these polymorphisms may include altered receptor affinity for IgG, changes in phagocytic activity, and differences in inflammatory responses to bacterial challenge, all of which could influence periodontitis risk and severity.

4.2. Toll-like receptors (*TLR*)

Toll-like receptors (TLRs) are pattern recognition receptors that play a crucial role in the innate immune response by recognizing pathogen-associated molecular patterns (PAMPs) (Akira et al., 2006). TLR4 specifically recognizes lipopolysaccharide (LPS) from gram-negative bacteria, which are prevalent in periodontal infections (Medzhitov, 2001). Fukusaki et al. (Fukusaki et al., 2007) investigated *TLR2* and *TLR4* polymorphisms in 97 chronic periodontitis patients and 100 controls in a Japanese population. They found that the *TLR4* + 3725C/C genotype (rs10759931) was more frequent in moderate/severe periodontitis ($p < 0.05$). This significant association suggests that genetic variations in *TLR4* might alter the host response to periodontal pathogens, potentially influencing susceptibility to periodontitis. Takahashi et al. (Takahashi et al., 2011) specifically examined *TLR2* gene polymorphisms in aggressive periodontitis in Japanese patients. Their findings suggested an association between certain *TLR2* polymorphisms and aggressive periodontitis susceptibility, implicating altered innate immune responses in disease pathogenesis. Imamura et al. (Imamura et al., 2008) conducted a broader investigation of genes encoding TLRs and inflammatory cytokines in periodontal disease in the Japanese population. While they found no significant associations for some of the polymorphisms studied, their research contributed to the growing body of evidence on the role of innate immunity genes in periodontitis susceptibility. These studies suggest that *TLR* gene polymorphisms, particularly in *TLR4*, may influence susceptibility to periodontitis in the Japanese population. Alterations in TLR function due to genetic polymorphisms could affect the host response to periodontal pathogens, potentially influencing periodontitis risk and severity.

4.3. CD14

CD14 is a pattern recognition receptor that functions as a co-receptor for TLR4 in the detection of bacterial LPS (Ulevitch and Tobias, 1995). It is a glycoprotein receptor found on neutrophils, monocytes/macrophages, and fibroblasts, which recognizes bacterial LPS bound to specific LPS-binding proteins circulating in the blood (Medzhitov, 2001). Yamazaki et al. (Yamazaki et al., 2003) examined a single-nucleotide polymorphism in the **CD14* promoter* (-159C/T) and its relationship with periodontal disease expression in a Japanese population. The **CD14** -159 polymorphism may affect the expression level of CD14, potentially altering the host response to bacterial LPS. This could influence inflammatory responses in periodontal tissues and, consequently, susceptibility to periodontitis. The integration of studies on TLRs, CD14, and other pattern recognition receptors provides a comprehensive understanding of how genetic variations in innate immunity pathways may influence periodontitis susceptibility in the Japanese population.

5. Tissue remodeling genes

5.1. Matrix metalloproteinases (*MMP*)

Matrix metalloproteinases constitute a family of zinc-requiring proteolytic enzymes that orchestrate extracellular matrix turnover and remodeling (Birkedal-Hansen, 1993). These enzymes participate in both physiological tissue renovation and pathological degradation during periodontal disease, capable of processing numerous structural components within periodontal tissues—including various collagen types, basement membrane constituents, and additional matrix glycoproteins (Sorsa et al., 2004). Examining regulatory variants in these genes, Itagaki and colleagues (Itagaki et al., 2004) analyzed **MMP1** and **MMP3** promoter region polymorphisms in a Japanese cohort comprising 164 individuals with chronic periodontitis and 100 periodontally healthy controls. Their investigation revealed that the **MMP1** -1607 1G/2G polymorphism (rs1799750) demonstrated significant association with chronic periodontal disease susceptibility (OR 1.95, 95 % CI 1.23–3.09, $p = 0.004$). Notably, the 2G variant—known to enhance **MMP1** transcriptional activity—occurred with greater frequency among affected subjects compared to healthy controls. In a separate study focusing on aggressive periodontitis phenotypes, Kitagaki et al. (Kitagaki et al., 2016) identified an association between the **MMP3** -1171 5A/6A polymorphism (rs3025058) and susceptibility to aggressive periodontal destruction in Japanese individuals (OR 2.17, 95 % CI 1.38–3.42, $p = 0.001$). The 5A variant, which confers increased **MMP3** expression, showed significant enrichment in the aggressive periodontitis group relative to control subjects. These findings suggest **MMP** gene variations contribute substantially to periodontal disease susceptibility profiles within Japanese populations. The functional implications of these regulatory polymorphisms include modified gene expression patterns resulting in altered enzymatic production and activity levels, potentially accelerating connective tissue degradation in periodontitis-susceptible individuals (Rutter et al., 1998; Ye et al., 1996). Both identified polymorphisms (**MMP1** rs1799750 and **MMP3** rs3025058) influence the efficiency of gene transcription, potentially creating an imbalance in the delicate equilibrium between tissue destruction and regeneration that characterizes periodontal homeostasis.

6. Vitamin D pathway genes

6.1. Vitamin D receptor (*VDR*)

The vitamin D endocrine system functions through its nuclear receptor (**VDR**), which orchestrates the cellular responses to 1,25-dihydroxyvitamin D3, the biologically active vitamin D metabolite (van Driel and van Leeuwen, 2023). This transcription factor regulates numerous physiological processes critical to periodontal health, including skeletal homeostasis and immunomodulation. Through VDR signaling, vitamin D enhances the production and mineralization of bone matrix components (Li et al., 2023), while simultaneously modulating immune cell function—particularly monocyte and macrophage activation—thereby strengthening host defenses against microbial challenges (Hayes et al., 2003). Yoshihara et al. (Yoshihara et al., 2001) investigated **VDR** and **FCGR3B** polymorphisms in relation to generalized early-onset periodontitis (G-EOP) in a Japanese population. **VDR** genetic variations are typically characterized through restriction fragment length polymorphisms (RFLPs), with several well-studied variants identified by specific restriction enzymes: *Apa*I, *Bsm*I, TaqI, and *Fok*I (Morrison et al., 1994). This study focused on the BsmI polymorphism of the **VDR** gene and the NA1/NA2 polymorphism of the **FCGR3B** gene. In their study of 42 G-EOP patients, 52 adult periodontitis patients, and 55 healthy controls, they found a lower frequency of **VDR**-B non-carrier and **FCGR3B**-NA2 carrier in G-EOP patients. A strong association was observed between G-EOP and the **VDR**-**FCGR3B** composite genotype (G-EOP vs. adult periodontitis: OR 5.09, $p = 0.009$; G-EOP vs. healthy controls: OR 5.93, $p = 0.004$). Interestingly, there was no direct correlation between the **VDR** genotype alone and G-EOP, highlighting the importance of gene-gene interactions in determining periodontitis susceptibility. Research by Tachi and colleagues (Tachi et al., 2003) established a significant relationship between vitamin D receptor genetic variation and periodontal disease among Japanese females in the postmenopausal period (OR 1.73, 95 % CI 1.08–2.78, $p = 0.02$). Their case-control analysis, comprising 86 women with chronic periodontal destruction and 74 periodontally healthy individuals, demonstrated that the restriction site-positive TaqI variant (t allele) occurred with significantly greater frequency in the disease-affected group. Complementing this female-focused work, Naito's team (Naito et al., 2007) conducted an analysis of VDR haplotype patterns specifically in Japanese males with chronic periodontitis. Their findings further strengthened the evidence linking vitamin D signaling pathway genetic variants to periodontal disease susceptibility within Japanese populations, suggesting these associations transcend gender differences. Tanaka et al. (Tanaka et al., 2013) investigated **VDR** gene polymorphisms, their interaction with smoking, and the risk of periodontal disease in Japanese women. This study highlighted the importance of considering gene-environment interactions in assessing periodontitis risk. The large-scale study conducted by Kobayashi and colleagues (Kobayashi et al., 2009) identified a robust correlation between the **VDR** gene variant at position +1056 (T/C) and increased risk for chronic periodontal disease (OR 2.45, 95 % CI 1.38–4.34, $p = 0.002$) among Japanese subjects. This particular genetic variation, also identifiable through *TaqI* restriction enzyme digestion within exon 9, has previously demonstrated associations with various parameters of skeletal regulation, including circulating osteocalcin concentrations and bone density measurements. These established connections to bone physiology provide credible mechanistic pathways through which this variant might influence periodontal pathogenesis. The accumulated evidence from these diverse studies points toward vitamin D receptor genetic polymorphisms as significant determinants of periodontal disease susceptibility within Japanese populations. At the molecular level, these genetic variations potentially exert their effects through multiple pathways: modifying vitamin D-mediated signaling cascades, altering the delicate balance of bone formation and resorption processes, and reshaping immunological responses—all representing critical factors in both the initiation and progression of periodontal tissue destruction.

7. Novel genetic associations

7.1. G protein-coupled receptor G6 (*ADGRG6*)

ADGRG6 (formerly known as GPR126) encodes a member of the

adhesion G protein-coupled receptor family with established functions in multiple developmental pathways, including peripheral nerve myelination, auditory system formation, and cardiac morphogenesis (Waller-Evans et al., 2010). This gene has recently emerged as a focus of periodontal research due to potential connections with disease mechanisms. In a landmark genetic investigation, Kitagaki and research team (Kitagaki et al., 2016) explored the relationship between *ADGRG6* genetic variations and aggressive forms of periodontitis among Japanese subjects. Their methodological approach combined initial exome-wide sequencing technology with subsequent targeted genotyping in an expanded validation cohort. This systematic strategy led to the identification of a specific nucleotide substitution, rs536714306 (c.3086 G > A), demonstrating significant association with aggressive periodontal disease phenotypes. Quantitative analysis revealed substantially elevated frequency of the minor variant in individuals with aggressive periodontitis (2.44 %) relative to periodontally healthy controls (0.27 %), establishing a particularly robust genetic association (OR 9.09, 95 % CI 1.64–50.36, $p = 0.0022$). The functional significance of this polymorphism was further investigated through in vitro studies. Their experimental work revealed that the A variant at position rs536714306, resulting in an arginine-to-glutamine substitution (R1029Q) in the ADGRG6 protein structure, significantly compromised normal receptor signaling functionality, manifested by reduced intracellular cyclic AMP accumulation. In complementary expression studies, they observed that cells expressing the normal (wild-type) ADGRG6 protein exhibited enhanced transcription of multiple genes involved in tissue mineralization processes (including *BSP*, osteopontin, and *RUNX2*) within periodontal ligament cellular models. Notably, these effects were abolished in cells expressing the variant form of the receptor. Similarly, the native receptor protein promoted expression of several developmental regulators (*BMP2*, *ID2*, and *ID4*), an effect not observed with the variant receptor. These molecular findings suggest ADGRG6 functions as a key regulator of periodontal tissue mineralization and structural integrity, with particular involvement in calcification pathways and skeletal metabolism. The functional impairment caused by the rs536714306 variant likely contributes to aggressive periodontitis pathogenesis through disruption of these essential tissue maintenance mechanisms. This molecular evidence substantially advances our comprehension of the genetic underpinnings of aggressive periodontal disease within Japanese populations, introducing a previously unrecognized pathway in disease development. The identification of ADGRG6 as a candidate gene for aggressive periodontitis introduces a novel pathway beyond the traditional immune and inflammatory mediators that have been the focus of most genetic studies in periodontitis. The functional studies revealing disrupted cyclic AMP signaling pathways and modified expression profiles of mineralization-related genes in cellular models containing the variant ADGRG6 establish a convincing mechanistic link between this genetic alteration and periodontal tissue pathology. These observations suggest that impaired mineral deposition and structural tissue maintenance processes—rather than solely aberrant inflammatory responses—may represent significant contributors to aggressive periodontitis susceptibility. The rs536714306 variant demonstrates population genetics characteristics typical of rare but highly penetrant genetic factors, with limited prevalence in the general Japanese population (0.27 % control frequency) but substantial enrichment among disease-affected individuals (2.44 % in cases). This genetic profile diverges from the more common pattern of frequent variants with modest effects that characterizes many periodontitis-associated polymorphisms. The identification of this low-frequency variant with pronounced biological consequences suggests that rare genetic alterations may contribute more significantly to aggressive periodontal disease phenotypes than previously appreciated in genetic research, potentially explaining some of the distinctive clinical features of these severe disease forms. The discovery of GPR126 as a periodontitis susceptibility gene demonstrates the value of hypothesis-free approaches such as exome sequencing in identifying novel genetic factors. While candidate gene studies focus on established pathways, unbiased approaches can reveal unexpected biological mechanisms that may provide new therapeutic targets. The discovery of the ADGRG6 rs536714306 genetic variant as a contributor to aggressive periodontitis risk establishes a previously unrecognized pathogenic mechanism involving disrupted periodontal tissue mineralization and structural maintenance. With both robust statistical association data and substantive experimental evidence supporting its biological relevance, this polymorphism represents a valuable candidate for inclusion in genetic susceptibility screening panels for Japanese patients with suspected hereditary predisposition to aggressive periodontal disease. From clinical and translational perspectives, the identification of cyclic AMP signaling pathway involvement offers novel therapeutic targeting opportunities distinct from conventional anti-inflammatory treatment modalities. This finding illustrates the significant value of unbiased, comprehensive genetic analysis approaches in revealing unexpected disease-associated biological pathways.

7.2. Macrophage erythroblast attacher (*MAEA*)

The transmembrane protein Macrophage Erythroblast Attacher (MAEA) facilitates proper macrophage maturation through its role in erythroblast-macrophage adhesion complexes (Hanspal et al., 1998). Given that macrophages serve as critical components in periodontal immune surveillance and inflammatory regulation, they represent important cellular mediators in periodontal disease progression (Yin et al., 2022). A significant contribution to this research area came from Che and colleagues (Che et al., 2019), who performed a cross-sectional analysis examining associations between the *MAEA* genetic variant rs6815464 and periodontal conditions specifically in postmenopausal Japanese women. While this polymorphism had previously demonstrated connections with metabolic dysregulation (type II diabetes) among East Asian populations (Cho et al., 2012), its potential influence on periodontal health remained unexplored prior to this investigation. The researchers evaluated 344 postmenopausal Japanese females and discovered that individuals carrying the G allele exhibited more pronounced periodontal destruction, demonstrated by elevated mean clinical attachment levels and a greater proportion of sites showing advanced periodontal measurements (probing depths or attachment loss $\geq$5 mm) compared with non-carriers. Multiple logistic regression analyses demonstrated that carriers of the G variant faced substantially increased risk for developing severe periodontal destruction (OR = 3.73, 95 % CI = 1.36–10.19), an association that remained robust after controlling for potential confounding variables including age, tobacco exposure, and additional clinical factors. Of particular mechanistic interest, the researchers found no significant relationship between this genetic variant and either skeletal mineral density measurements or glycemic control parameters (HbA1c), suggesting the polymorphism's effect on periodontal tissues operates through pathways distinct from these potential intermediate mechanisms. Based on these findings, the investigators established that variation within the *MAEA* gene constitutes an independent risk determinant for advanced periodontal disease specifically among postmenopausal Japanese females. This research expands the candidate gene repertoire for periodontal disease susceptibility beyond conventional inflammatory mediators. The identification of a gene involved in macrophage maturation regulation underscores the fundamental contribution of innate immune cellular populations to periodontal health and creates promising new directions for investigating the genetic architecture underlying periodontal disease susceptibility.

7.3. Colony stimulating factor 1 (*CSF1*)

The hematopoietic growth factor encoded by *CSF1* serves as a principal regulator governing macrophage lineage development, proliferation, and functional activation (Stanley et al., 1997). Macrophages

are key players in the inflammatory response in periodontitis, and factors that regulate their development and function may influence disease susceptibility. Addressing this hypothesis, Rabello and research collaborators (Rabello et al., 2006) conducted a comprehensive genetic association analysis examining *CSF1* variants in relation to aggressive periodontitis among Japanese individuals. They genotyped 98 Japanese patients with aggressive periodontitis and 88 healthy controls for 43 SNPs in 11 candidate genes. They found significant associations between aggressive periodontitis and three specific *CSF1* gene polymorphisms: *CSF1*-1 demonstrated an association at $p = 0.028$, *CSF1*-2 showed significance at $p = 0.025$, and *CSF1*-5 exhibited a relationship at $p = 0.036$.The researchers further identified a particular CSF1 haplotype pattern (designated as 2212) occurring with significantly higher frequency among individuals with aggressive periodontitis compared to healthy controls ($p = 0.028$). These observations provide genetic evidence supporting the biological plausibility that alterations in macrophage regulatory pathways—specifically involving CSF1-controlled mechanisms—contribute to the pathogenesis of aggressive periodontal destruction in Japanese populations. The researchers further identified a particular *CSF1* haplotype pattern (designated as 2212) occurring with significantly higher frequency among individuals with aggressive periodontitis compared to healthy controls ($p = 0.028$). These observations provide genetic evidence supporting the biological plausibility that alterations in macrophage regulatory pathways—specifically involving *CSF1*-controlled mechanisms—contribute to the pathogenesis of aggressive periodontal destruction in Japanese populations. This adds to the growing body of evidence implicating innate immune cells and their regulatory pathways in the genetic basis of periodontitis. Table 1 summarizes the main genetic polymorphisms associated with periodontitis in Japanese populations discussed in this review. The table highlights the type of periodontitis studied, the strength of association through odds ratios (OR) with 95 % confidence intervals when available, and the relevant references. This synthesis emphasizes both risk and protective factors identified in studies, organized according to genetic functional pathways. As can be observed, the strongest associations were found for the *ADGRG6* rs536714306 polymorphism (OR 9.09) in aggressive periodontitis and for the composite genotype *VDR*-B non-carrier plus *FCGR3B*-NA2 carrier (OR 5.93) in generalized early-onset periodontitis. (See Figs. 1 and 2.)

8. Gene-gene and gene-environment interactions

8.1. Gene-gene interactions

The multifactorial nature of periodontal disease pathogenesis suggests that interactions between multiple genetic factors likely contribute to overall disease susceptibility. Research examining these epistatic relationships has consistently demonstrated that combinations of genetic variants exhibit more robust associations with disease than isolated polymorphisms. In a pivotal investigation, Yoshihara and colleagues (Shimizu et al., 2015) documented that combined *VDR* and *FCGR3B* genetic profiles demonstrated substantially stronger relationships with generalized early-onset periodontitis than either genotype independently. Specifically, individuals carrying both the *VDR*-B non-carrier status and the *FCGR3B*-NA2 allele showed pronounced susceptibility to G-EOP when compared against both adult periodontitis subjects (OR 5.09, $p = 0.009$) and periodontally healthy individuals (OR 5.93, $p = 0.004$). This observation suggests critical interactions between genetic factors regulating skeletal metabolism pathways (*VDR*) and immunological response mechanisms (*FCGR3B*) in determining early-onset periodontal disease risk. Similarly, Kobayashi's research group identified that subjects harboring both *FCGR3A*-158 V and *FCGR3B*-NA2 alleles demonstrated markedly increased susceptibility to severe forms of chronic periodontitis (OR 4.69, 95 % CI 1.52–15.10, $p = 0.002$ when comparing severe versus moderate disease; OR 4.10, 95 % CI 1.62–10.59, $p = 0.0009$ when comparing severe disease versus periodontal health). This combination of genetic variants correlated not only with diagnostic categories but also with quantifiable clinical parameters of disease severity, as carriers exhibited increased probing depths, more extensive attachment level destruction, and heightened alveolar bone resorption compared to non-carriers (Bouillon et al., 2008). These observations underscore the necessity of examining collaborative genetic effects rather than focusing exclusively on isolated polymorphisms when investigating periodontal disease heritability. The considerably higher odds ratios documented for variant combinations versus single polymorphisms provides substantial support for genetic epistasis as a fundamental mechanism underlying periodontitis susceptibility patterns. This pattern aligns with contemporary understanding of complex multifactorial diseases, where phenotypic expression typically results from concurrent alterations across multiple biological pathways rather than from isolated genetic variations. This pattern aligns with our understanding of periodontitis as a complex polygenic disorder where multiple genetic factors likely converge to influence disease risk and severity. The particularly strong association between the *VDR*-*FCGR3B* composite genotype and G-EOP (Chai et al., 2019) highlights how genes operating in distinct biological pathways—bone metabolism and immune function—can interact synergistically to influence disease susceptibility. This observation suggests that periodontitis pathogenesis involves the coordinated dysregulation of multiple homeostatic systems rather than isolated defects in specific pathways. The association of the *FCGR3A*-158 V plus *FCGR3B*-NA2 composite genotype with both disease status and clinical severity parameters provides a direct link between genetic interactions and phenotypic manifestations of periodontitis. These genetic interaction findings establish a robust foundation for implementing multigenic analysis approaches in periodontal risk stratification and therapeutic decision-making frameworks. The documented epistatic effects indicate that simplified single-polymorphism testing strategies likely possess insufficient predictive power for comprehensive periodontal disease susceptibility assessment. Furthermore, the specific combinatorial genetic patterns identified within Japanese cohorts might exhibit substantial heterogeneity when compared across different ethnic populations, reflecting variations in underlying allele distributions and population-specific haplotype structures. This population genetic variability underscores the necessity of conducting genetic investigations across diverse ethnic groups to develop culturally tailored genetic screening protocols with appropriate predictive validity for specific populations. Genetic interaction networks emerge as fundamental determinants shaping periodontal disease susceptibility patterns among Japanese individuals, as evidenced by the observation that variant combinations demonstrate significantly stronger disease associations than isolated polymorphisms. These findings reveal the intricate genomic landscape underlying periodontitis pathogenesis and indicate that effective genetic risk profiling likely requires concurrent evaluation of multiple genetic markers rather than isolated variant analysis. From a mechanistic perspective, the synergistic relationships between genes functioning in separate biological pathways—exemplified by *VDR* and *FCGR3B*—illuminate how simultaneous dysregulation across multiple physiological systems may establish conditions particularly conducive to periodontal tissue breakdown.

8.2. Gene-environment interactions

Environmental exposures, with tobacco use representing a particularly significant factor, potentially modulate the phenotypic expression of genetic susceptibility to periodontal disease. Researchers have conducted several investigations examining these gene-environment relationships within Japanese cohorts. A study by Tanaka and colleagues (Tanaka et al., 2013) evaluated whether cigarette smoking altered the relationship between *IL1* genetic variations and periodontal pathology in Japanese female subjects. Their analytical models revealed no statistically significant interaction effects between smoking behavior

Table 1
Summary of genetic polymorphisms associated with periodontitis in Japanese populations.

Gene/pathway	Polymorphism	Type of periodontitis	Association (OR, 95 % CI)	Sample size (cases/ controls)	Genotyping method	Diagnostic criteria	Reference
Immune Response Genes							
IL1RN	VNTR polymorphic alleles (2,3,4,5) (rs2234663)	G-EOP	OR 3.40 (1.24–9.52)	47/97	PCR-VNTR	≥8 teeth with AL	Tai et al., 2002
IL1B	+3954C/T (rs1143634)	Severe chronic	OR 1.89 (1.54–2.32)	219/243	PCR-RFLP	PPD ≥6 mm, CAL ≥5 mm	Kobayashi et al., 2007a
IL1B	-511 (rs16944)	Chronic (non-smokers)	OR 1.72 (1.18–2.51)	67/67	PCR-RFLP	PPD ≥4 mm, CAL ≥3 mm	Shirakata et al., 2001
IL1B	rs16944 (C-511 T) GA genotype	Periodontal disease	OR 0.62 (0.40–0.96), protective	131/1019	TaqMan	CDC/AAP definition	Tanaka et al., 2014
IL6R	rs8192284 (148,892 A/C)	Chronic	OR 2.25 (1.08–2.25)	169 CP, 43 AP/210	PCR-RFLP	Clinical parameters	Galicia et al., 2004
IL18	rs1946518 CC genotype	Periodontal disease	OR 0.54 (0.29–0.97), protective	119/1011	TaqMan	CDC/AAP definition	Tanaka et al., 2017
IL12RB2	-1035A > G, −1023A > G, −650delG, −464A > G	Aggressive	Significant difference in frequencies ($p < 0.01$)	30 AP, 80 CP/ 43	PCR-SSCP	Multiple criteria	Takeuchi-Hatanaka et al., 2008
TNF	−1031 (rs1799964), −863 (rs1800630), −857 (rs1799724)	Severe adult	Significant association	88/80	PCR-SSCP	>30 % sites CAL ≥5 mm	Soga et al., 2003
TNF	−308 G/A (rs1800629)	Chronic	OR 1.65 (1.16–2.35)	157/145	PCR-RFLP	PPD ≥6 mm, CAL ≥5 mm	Kobayashi et al., 2009
Immunoreceptors							
FCGR3A	158 V allele (rs396991)	Severe chronic	OR 2.03 (1.03–4.01)	219/243	PCR-RFLP	PPD ≥6 mm, CAL ≥5 mm	Kobayashi et al., 2007a
FCGR3A-158 V + FCGR3B-NA2	Composite genotype	Severe chronic	OR 4.69 (1.52–15.10)	219/243	PCR-RFLP	PPD ≥6 mm, CAL ≥5 mm	Kobayashi et al., 2007b
FCGR3B	NA1 allotype	Periodontitis resistance	OR 1.87 (1.13–3.10), protective	599 elderly	PCR	Community survey	Sugita et al., 2001
FCGR2B	232 T/T genotype (rs1050501)	Periodontitis	Significant increase	219/243	PCR-RFLP	PPD ≥6 mm, CAL ≥5 mm	Kobayashi et al., 2007a
FCGR2B	nt645 + 25GG genotype	Periodontitis	Significant association (p = 0.048)	13 PE+/106 PE-	PCR-sequencing	Clinical exam	Wang et al., 2012
TLR4	+3725C/C (rs10759931)	Moderate/severe	Significant association (p < 0.05)	97/100	PCR-RFLP	Clinical parameters	Fukusaki et al., 2007
Tissue Remodeling Genes							
MMP1	−1607 1G/2G (rs1799750)	Chronic	OR 1.95 (1.23–3.09)	164/100	PCR-RFLP	Clinical criteria	Itagaki et al., 2004
MMP3	−1171 5A/6A (rs3025058)	Aggressive	OR 2.17 (1.38–3.42)	41/1208	PCR-RFLP	Aggressive Periodontitis criteria	Kitagaki et al., 2016
Vitamin D Pathway Genes							
VDR	TaqI polymorphism (rs731236)	Chronic (postmenopausal women)	OR 1.73 (1.08–2.78)	86/74	PCR-RFLP (TaqI)	Clinical exam	Tachi et al., 2003
VDR	+1056 T/C (rs731236)	Chronic	OR 2.45 (1.38–4.34)	157/145	PCR-RFLP	PPD ≥6 mm, CAL ≥5 mm	Kobayashi et al., 2009
VDR-B non-carrier + FCGR3B-NA2 carrier	Composite genotype	G-EOP	OR 5.93 (vs. healthy controls)	52 G-EOP/52 AP/55 HC	PCR-RFLP	G-EOP criteria	Yoshihara et al., 2001
Novel Genetic Associations							
ADGRG6 (GPR126)	rs536714306 (c.3086 G > A)	Aggressive	OR 9.09 (1.64–50.36)	48 + validation	Exome seq + genotyping	Aggressive Periodontitis criteria	Kitagaki et al., 2016
MAEA	rs6815464 G-allele	Severe (postmenopausal women)	OR 3.73 (1.36–10.19)	344 women	TaqMan	Severe Periodontitis criteria	Che et al., 2019
CSF1	CSF1–1, CSF1–2, CSF1–5	Aggressive	Significant association (p < 0.05)	98/88	PCR-RFLP	Aggressive Periodontitis criteria	Rabello et al., 2006

Abbreviations: *IL* = Interleukin; *TNF* = Tumor Necrosis Factor; *FCGR* = Fc Gamma Receptor; *TLR* = Toll-Like Receptor; *MMP* = Matrix Metalloproteinase; *VDR* = Vitamin D Receptor; *ADGRG6* = Adhesion G Protein-Coupled Receptor G6 (formerly GPR126); *MAEA* = Macrophage Erythroblast Attacher; *CSF1* = Colony Stimulating Factor 1; G-EOP = Generalized Early-Onset Periodontitis; OR = Odds Ratio; CI = Confidence Interval.

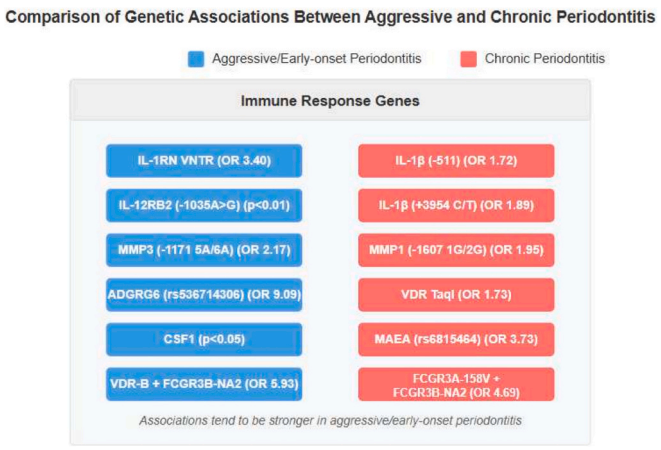

Fig. 1. Comparison of genetic associations between aggressive and chronic periodontitis in Japanese populations. The diagram illustrates the differential genetic associations for immune response genes, with blue boxes representing associations with aggressive/early-onset periodontitis and red boxes representing associations with chronic periodontitis. Odds ratios (OR) are shown for each genetic variant. The comparison demonstrates that associations tend to be stronger in aggressive/early-onset periodontitis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

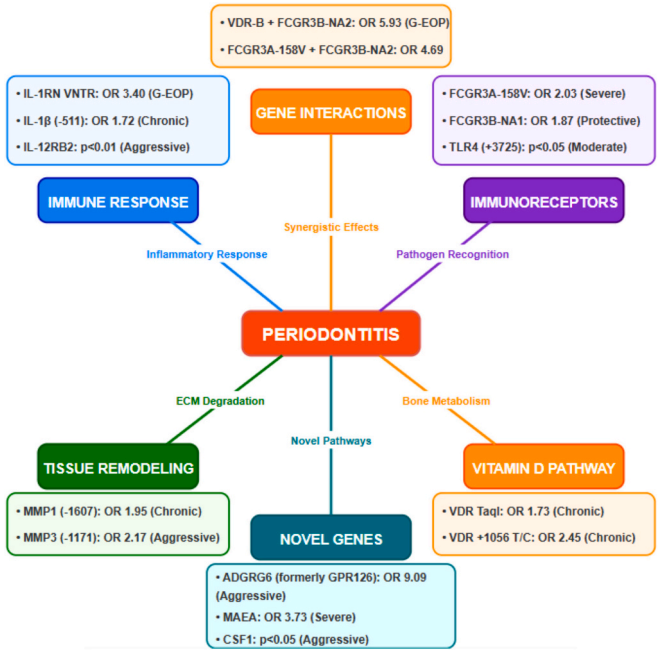

Fig. 2. Fig. 2 Major genetic pathways involved in periodontitis pathogenesis in Japanese populations. G-EOP: Generalized Early-Onset Periodontitis; Chronic: Chronic Periodontitis; Aggressive: Aggressive Periodontitis; Severe: Severe Chronic Periodontitis.

and **IL1** polymorphisms, suggesting these genetic factors likely operate through mechanisms not substantially modified by tobacco exposure. In a separate investigation, this research group reported similar findings regarding **IL18** genetic variations, with no detectable synergistic effects between these polymorphisms and smoking habits on periodontal disease risk. These results warrant cautious interpretation, however, given that the study population comprised predominantly younger women with relatively limited smoking prevalence. Tanaka's team specifically analyzed **VDR** polymorphisms and their potential interaction with tobacco use in relation to periodontal disease susceptibility among Japanese women. While this work emphasized the conceptual importance of considering gene-environment interactions in periodontal risk assessment, their data did not demonstrate robust statistical evidence for specific interaction effects. The relationship between hereditary factors and environmental exposures in periodontal pathogenesis remains incompletely characterized and represents an area requiring further research.

9. Limitations

The studies reviewed in this paper vary considerably in their design and sample size, which may influence the reliability and generalizability of their findings. Most studies employed a case-control design, comparing the frequency of genetic polymorphisms between periodontitis patients and healthy controls. Sample sizes ranged from relatively small (fewer than 100 subjects per group) to quite large (over 1000 subjects). Smaller studies may have limited statistical power to detect modest genetic effects, which could contribute to inconsistent findings across studies. The definition of periodontitis varied across studies, with some focusing on aggressive periodontitis, others on chronic periodontitis, and some including both forms. Additionally, the criteria used to diagnose periodontitis (e.g., probing depth, clinical attachment loss, radiographic bone loss) were not standardized across studies. This heterogeneity in phenotype definition may contribute to inconsistent findings and makes direct comparison between studies challenging. The Japanese population, while relatively homogeneous compared to many other populations, still exhibits genetic heterogeneity. Differences in allele frequencies and linkage disequilibrium patterns may exist between different regions of Japan, which could influence genetic associations with periodontitis. Some studies specifically addressed this issue by recruiting participants from a defined geographic region or by adjusting for regional differences in their analyses. However, not all studies accounted for potential genetic heterogeneity within the Japanese population. Periodontitis is influenced by numerous factors beyond genetics, including age, smoking, oral hygiene practices, and systemic conditions such as diabetes. The extent to which these confounding factors were accounted for varied across studies. Most studies adjusted for basic demographic factors such as age and sex, and many also adjusted for smoking status. However, few studies comprehensively adjusted for all potential confounding factors, which may limit the reliability of their findings. Furthermore, this narrative review has limitations that readers should consider: 1) for some SNPs, we relied on single studies to represent associations in the Japanese population. While we selected studies based on quality criteria, this approach differs from systematic reviews that would include all available evidence; 2) although we used explicit criteria for study selection, our narrative approach may have introduced selection bias compared to systematic methodology, and we acknowledge that even within Japanese populations, results can vary due to regional differences, sample characteristics, and methodological variations.

10. Future directions

Most investigations reviewed in this paper employed a candidate gene approach, focusing on genes with established or hypothesized roles in periodontal pathophysiology. While this methodology has successfully identified several genetic associations, it remains constrained by current limitations in our understanding of disease mechanisms. Genome-wide association studies (GWAS), which examine genetic variations across the entire genome without prior mechanistic hypotheses, offer promising opportunities to identify novel genetic loci associated with periodontitis in Japanese populations. Although numerous genetic associations with periodontitis have been documented, the functional consequences of many identified polymorphisms remain incompletely characterized. Future research should prioritize elucidating the precise biological mechanisms through which these genetic variations influence

periodontal disease initiation and progression.

11. Conclusions

This systematic examination of genetic variations associated with periodontitis among Japanese individuals reveals several significant patterns with implications for both disease understanding and clinical intervention. First, Japanese populations appear to have genetic susceptibility profiles that may differ in some aspects from patterns observed in Western cohorts, particularly regarding certain *IL1* gene family polymorphisms. These population-specific associations emphasize the necessity of developing ethnically-appropriate genetic screening approaches for periodontal risk assessment. Second, combined genetic variations (exemplified by **VDR*-*FCGR3B** composite genotypes) consistently show more robust disease associations than isolated polymorphisms. This pattern suggests periodontal pathogenesis frequently involves simultaneous disruption across multiple biological pathways rather than isolated genetic alterations. Recent identification of novel genetic factors including **ADGRG6** (formerly GPR126), **MAEA**, and **CSF1** has expanded our comprehension beyond traditional inflammation-centered models. These discoveries reveal additional pathogenic mechanisms involving tissue mineralization processes, macrophage development pathways, and structural components of the periodontium. Notably, genetic association patterns differ substantially between aggressive/early-onset and chronic periodontal disease forms, with generally stronger genetic influences observed in aggressive phenotypes. This distinction suggests divergent genetic foundations despite recent modifications to clinical classification systems that combine these previously separate disease categories. Finally, several protective genetic variants have been identified, including **FCGR3B**-NA1 allotype and **IL1*/*IL18** heterozygous configurations. These findings highlight the importance of understanding not only genetic susceptibility but also genetic resilience factors in periodontal disease.

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Elisabetta Ferrara: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Alessandro D'Albenzio:** Investigation, Data curation, Writing – review & editing. **Biagio Rapone:** Supervision, Validation, Writing – review & editing. **Francesco Mastrocola:** Validation, Visualization, Writing – review & editing. **Giovanna Murmura:** Conceptualization, Supervision, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No new data were generated in this study as it is a comprehensive review of published literature. All information analyzed in this review is available in the cited references.

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