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SYSTEMATIC REVIEW

Susceptibility Polymorphism in the Promoter Region of IL-4 and IL-13 in Individuals with Periodontitis: A Systematic Review

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ABSTRACT

Objective: To understand the susceptibility to single nucleotide polymorphisms in the promoter region of Interleukin-4 (IL-4) and Interleukin-13 (IL-13) in patients with and without periodontal disease. Thus, a systematic review of available studies on the subject was performed. **Material and Methods:** A protocol was conducted for registration in the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42021246646. For this search, studies were selected from the Scopus, Web of Science, Virtual Health Library, Embase, Cochrane Library, and PubMed databases. The selection criteria consisted of case-control and cohort studies published in English that had data on IL-4 and IL-13 genetic polymorphisms in patients with and without periodontal disease in the same study. The obtained studies were managed by EndNote Program™ X7 version and the Rayyan Platform. Regarding the risk of bias, we used the Newcastle-Ottawa Scale, which classified the studies using high-quality methodology. **Results:** After the selection process, three studies presented the eligibility criteria. No relation between IL-13 and susceptibility to periodontal disease was found. IL-4 gene (IL-4 -590C/T; IL-4-34C/T; rs2243248) was associated with susceptibility to the development of periodontitis. **Conclusion:** An association between IL-4 and the susceptibility of periodontitis was verified. Further case-control studies are needed to create more concrete conclusions on the subject.

Keywords: Polymorphism; Genetic; Periodontitis; Review.

Introduction

Periodontitis is a chronic inflammatory disease characterized by immune cell infiltration into periodontal tissues and associated with dysbiotic microbiota [1,2]. It is considered a primary cause of tooth loss in the population [1,3-5]. The classification proposed by Armitage [6] divided periodontal disease (PD) into two main types: chronic periodontitis, involving slow, progressive destruction of the connective and osseous tissues supporting the tooth, and aggressive periodontitis, causing rapid destruction of tooth-supporting tissues, primarily in young individuals [6,7]. However, in recent decades, new scientific evidence has emerged regarding the pathophysiology and pathogenesis of PD, leading to the inclusion of both diseases in a single category [8,9]. This revised classification considers the rate of progression, staging, and the multidimensional aspect of the disease [8]. Numerous epidemiological studies have provided new evidence regarding the significance of socioeconomic factors, environmental effects, tobacco use, dental care, and genetic factors, such as polymorphisms, in modifying the predisposition to PD [10,11].

Interleukin 4 (IL-4) is an immunoregulatory cytokine known for stimulating the T-helper 2 (TH2) immune response and acting as a crucial regulator of macrophage function [12]. Furthermore, IL-4 has been shown to stimulate the secretion of immunoglobulin G and E in gingival tissues upon stimulation with lipopolysaccharides (LPS) from periodontopathogenic bacteria like *Porphyromonas gingivalis*. Otherwise, reduced IL-4 production in periodontal tissues results in increased expression and production of a cluster of differentiation 14 (CD14), prostaglandin E2 (PG-E2), alpha tumor necrosis factor (TNF-α), and IL-1β [13,14]. Recent discoveries have revealed single nucleotide polymorphism (SNP) variations in IL-4 associated with exacerbating PD. Variations in SNPs, including -590C/T (rs2243250), -33C/T (rs2070874), and -1099T/G (rs2243248), have been linked to heightened IL-4 transcriptional activity (overexpression) and other chronic inflammatory diseases, such as asthma, as well as the progression of PD [10,15,16].

IL-13, with functions similar to IL-4, is a pleiotropic cytokine produced by TH2 cells responsible for stimulating the immune response while suppressing inflammatory activity in the host [10-13]. This anti-inflammatory cytokine triggers the production of transforming growth factor-β (TGF-β) by macrophages, impacting the activity of fibroblasts and regulating the functions of various cell types, including endothelium, smooth muscle, epithelium, and B cells [3,17]. Multiple studies have highlighted the role of IL-13 SNPs (-1502 A/C, -1112 C/T, and +1923 C/T) in the severity and progression of PD [4,18]. Overexpression of IL-13 can negatively affect the regulation of bone metabolism (resorption) [19] and also negatively regulate the activity of other pro-inflammatory cytokines. Additionally, the SNP -1112 C/T has been associated with more advanced stage PD (aggressive behavior) in a Northern European population [4].

In this context, the polymorphisms of IL-4 and IL-13 genes have demonstrated significant functionalities in the pathogenesis of PD. These cytokines are genetically encoded by a cluster of genes on chromosome 5q. They function synergistically with IL-4, regulating T cell differentiation, and IL-13, reducing macrophage activity while diminishing the action of pro-inflammatory mediators [20,21].

Therefore, it becomes essential to understand the biological relationships between these variants and their importance in the immune response to PD. Based on the assumption that these genes act simultaneously to regulate the immune response to periodontitis, this study aimed to comprehend the susceptibility of single nucleotide polymorphisms in the promoter region of IL-4 and IL-13 in patients with and without PD. A systematic review of available literature on the subject was conducted to achieve this.

Material and Methods

The present systematic review was conducted according to the PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses [22]. The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the code (ID Number: CRD42021246646).

The present systematic review attempts to answer the following PECO question (Table 1): "Is there an association between interleukin-4 and interleukin-13 genetic polymorphisms in individuals with PD?"

Table 1. PECO question.

Question	Description
Population	Individuals with Periodontal disease
Exposure to risk factor	Periodontal disease
Comparison	Individuals without Periodontal disease
Outcomes	Susceptibility of Interleukin-4 and Interleukin-13 genetic polymorphism in Periodontal disease

Study inclusion criteria: Case-control and cohort studies, data on IL-4 and IL-13 genetic polymorphisms in patients with and without PD in the same research, and studies published in English were included.

Study exclusion criteria: Letters to the editor, reviews, short communications, clinical trials, case reports, experimental studies (animal and cellular models), and manuscripts that evaluated IL-4 and IL-13 genetic polymorphisms in isolation were excluded.

Detailed search strategies were conducted on PubMed (http://www.ncbi.nlm. nih.gov/pubmed), Scopus (https://www.scopus.com/home.uri), Web of Science (http://www.isiknowledge.com), Virtual Health Library- VHL (https://bvsalud.org/), Embase (https://www.embase.com) and Cochrane Library (https://www.cochranelibrary.com/) databases for publications up to October 2022. No date filters were applied. The Boolean algorithms AND and OR were used between the words, as shown in the diagram below (Table 2).

Table 2. Characterization of the electronic searches in the databases selected by the study.

Database	Number of Articles	Strategic Search
PubMed	07	All fields= ("Periodontal disease" OR "Periodontitis" OR "alveolar bone loss") AND ("Polymorphism, Genetic" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism, Single Nucleotide" OR "Polymorphism" OR "SNP") AND ("IL-13" OR "IL13" OR "interleukin-13" AND "IL-4" OR "IL4" OR "interleukin-4")
Scopus	15	TITLE-ABS-KEY= ("Periodontal disease" OR "Periodontitis" OR "alveolar bone loss") AND ("Polymorphism, Genetic" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism, Single Nucleotide" OR "Polymorphism" OR "SNP") AND ("IL-13" OR "IL13" OR "interleukin-13" AND "IL-4" OR "IL4" OR "interleukin-4")
Web of Science	03	TS= (("Periodontal disease" OR "Periodontitis" OR "alveolar bone loss") AND ("Polymorphism, Genetic" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism, Single Nucleotide" OR "Polymorphism" OR "SNP") AND ("IL-13" OR "IL13" OR "interleukin-13" AND "IL-4" OR "IL4" OR "interleukin-4"))
Virtual Health Library (VHL)	05	TW= ("Periodontal disease" OR "Periodontitis" OR "alveolar bone loss") AND ("Polymorphism, Genetic" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism, Single Nucleotide" OR "Polymorphism" OR "SNP") AND ("IL-13" OR "IL13" OR "interleukin-13") AND ("IL-4" OR "IL4" OR "interleukin-4")

Embase	12	All fields= ("Periodontal disease" OR "Periodontitis" OR "alveolar bone loss") AND ("Polymorphism, Genetic" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism, Single Nucleotide" OR "Polymorphism" OR "SNP") AND ("IL-13" OR "IL13" OR "interleukin-13") AND ("IL-4" OR "IL4" OR "interleukin-4")
Cochrane Library	0	All fields= ("Periodontal disease" OR "Periodontitis" OR "alveolar bone loss") AND ("Polymorphism, Genetic" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism, Single Nucleotide" OR "Polymorphism" OR "SNP") AND ("IL-13" OR "IL13" OR "interleukin-13") AND ("IL-4" OR "IL4" OR "interleukin-4")

The Rayyan selection platform selected studies, and then the references were exported to the EndNote Program™ X7 version (Thomson Reuters, New York, NY, USA). Two calibrated and trained researchers (R.U.O.S and M.T.M.L) read the titles and abstracts of the manuscripts, then those deemed relevant were read and evaluated completely based on the criteria of the studies, and a third evaluator analyzed conflicting information (F.I.D.C). i) author and year of publication; (ii) country; (iii) population; risk factor; (v) objective described in the study; (vi) IL/SNP promoting region; (vii) study groups and diagnostic criteria for PD; (viii) Newcastle-Ottawa Scale (NOS); distribution of IL-4 and IL-13 polymorphism genotypes; (ix) methodologies used in investigations; (x) Hardy-Weinberg equilibrium; (xi) molecular biology technique; (xii) biological sample.

Two researchers (R.U.O.S and M.T.M.L) performed the quality analysis of the manuscripts included in the systematic review. For this, the NOS was used for cross-sectional studies [23]. This scale consists of a score where three points mean "low quality," four and five points mean "moderate quality," six points mean "high quality," and nine points mean "highest quality."

Results

Figure 1 characterizes the process of synthesis of the information obtained in the systematic literature review.

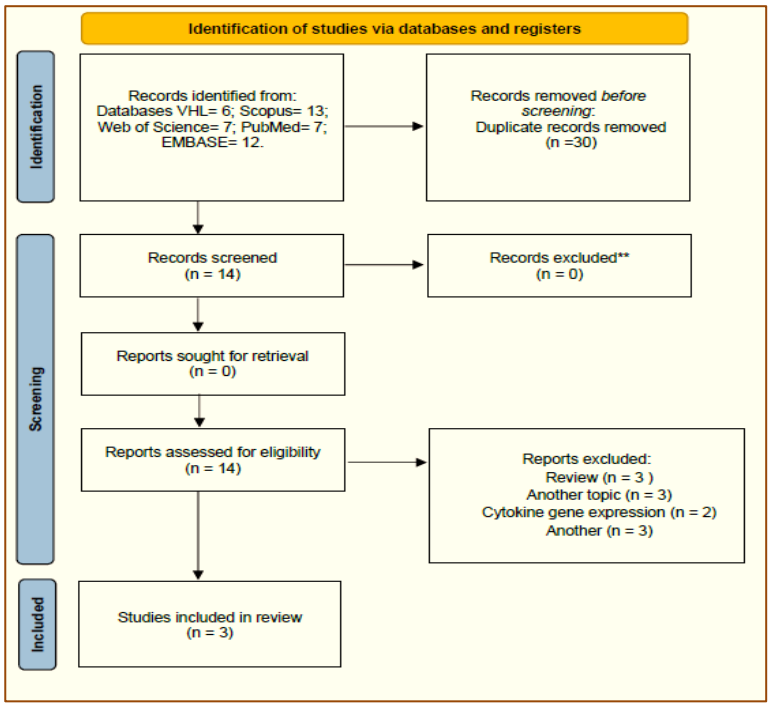

Figure 1. Flow diagram for systematic reviews included searches of databases and registers only.

Initially, 44 studies were identified in the selected databases. Thirty duplicates were removed, totaling 14 unique manuscripts elected for a complete reading of the titles and abstracts. The reasons for excluding each study can be seen in Table 3 [24-34]. After applying the study eligibility criteria, three manuscripts were included for the qualitative synthesis of this review on the susceptibility of IL-4 and IL-13 polymorphism in healthy patients and patients with periodontitis.

Table 3. Excluded studies with exclusion reasons after full-text assessment.

Author/Year	Exclusion Reasons
Zheng et al. [24]	Systematic review and meta-analysis
Dutra et al. [25]	Review
Nakajima et al. [26]	Studies involving gene expression
Liu et al. [27]	Systematic review and meta-analysis
Reichert et al. [28]	Absence of IL-13
Yucesoy et al. [29]	Studies that did not evaluate genetic polymorphisms and PD
Karuppanan et al. [30]	Review
Isacco et al. [31]	Studies that did not evaluate genetic polymorphisms and PD
Gonzales et al. [32]	Studies involving gene expression
Chen et al. [33]	Another language
Mitchison [34]	Studies that did not assess genetic polymorphisms and PD

PD: Periodontal Disease.

Table 2 represents the primary findings in the literature regarding the genetic polymorphism of IL-4 and IL-13 in patients with and without PD. The published studies emphasized the use of the classification predating the 2018 report on the Classification of Periodontal and Peri-Implant Diseases and Conditions.

The included studies' methodological quality was good (score 7), and they had adequate sample sizes (Table 4). In addition, the control group and PD were well-defined. The three selected manuscripts were in Hardy-Weinberg equilibrium (Table 5). The included studies evaluated different promoter regions of IL-4 and IL-13 polymorphisms. Two different models were used.

1) Association of IL-4 and IL-13 polymorphisms in healthy individuals and those with chronic periodontitis [15,20]. Adapting the new results to the classification proposed in 2018 [8], one study reported the presence of periodontitis in stages III and IV with grade A [15], while another study reported stages III and IV with grade B [20].

2) Association of IL-4 and IL-13 polymorphism in healthy individuals and those with aggressive periodontitis [35]. Adapting the new results to the classification proposed in 2018 [8], one study reported the presence of periodontitis in stages III and IV with grade B [4].

From these established models, it was possible to observe an association in the IL-4 polymorphism (IL-4-590C/T; IL-4-34C/T) in Caucasian individuals and those with aggressive periodontitis (periodontitis in stages III and IV with grade B) [35]. Furthermore, in the Han Chinese population, a significant association between chronic periodontitis (periodontitis in stages III and IV with grade A) and the IL-4 polymorphism (rs2243248) was found [15] (Table 5). One study found no significant association with the IL-4 polymorphism (rs2070874) [20]. However, none of the studies analyzed by this systematic review showed statistical significance regarding the IL-13 polymorphism [15,20,35].

Regarding the biological sample used by the researchers, it was possible to observe that two studies used venous blood [20,35], and one used Buccal Epithelial Cells [15]. In addition, the molecular biology technique chosen by the studies was Polymerase Chain Reaction (PCR) (Table 5).

Table 4. Chronological characterization of the studies included in the systematic review about the susceptibility of IL-4 and IL-13 polymorphism in patients with periodontitis.

Author/ Year	Country	Male (M)/ Female (F) Age	Risk Factor (Smokers)	Objective described in the study	IL/SNP	Diagnostic Criteria		NOS
						Control	Disease	
Chen et al. [15]	China	Periodontitis: Gender: M= 270/F= 170; Age: 47.8 ± 5.20; Control: Gender: M= 195/F= 129 Age: 50.40 ± 4.60	-	This study aimed to evaluate whether three single nucleotide polymorphisms, rs2070874 and rs2243248 from IL4 and rs1800925 from IL13, are associated with CP in a Han Chinese population consisting of 440 moderate or severe CP patients and 324 healthy controls	rs2070874 rs2243248 rs1800925	The healthy control participants in the present study did not suffer from periodontal disease. Exclusion criteria included any past or current systemic disease, any past or current oral disease other than periodontitis, pregnant or lactating females, and periodontal or antibiotic treatment in the preceding six months. Moreover, the included subjects were nonsmokers who never smoked, whether in a smoking or smokeless form.	Chronic Periodontitis At least ten teeth absent, namely, not more than 18 teeth existing, or at least two interproximal sites (on different tooth) with CAL≥ 6 mm and at least one interproximal site with PD≥ 5 mm or at least two interproximal sites (on different tooth) with CAL≥ 4 mm or at least two interproximal sites (on different tooth) with PD≥ 5 mm	7
Majumder et al. [20]	Indian	Periodontitis: Gender: M= 101/F= 56 Age: 41.59 ± 11.12; Control: Gender: M= 95/F= 105 Age: 38.41 ± 9.48.	Periodontitis: 96 Control: 41	The present study aimed to investigate the possible association between seven interleukin gene polymorphisms and their interaction with the chronic inflammatory oral disease, chronic periodontitis in Indian population.	rs2070874 rs1800925	The healthy control group was selected based on their healthy oral condition. They had no history of teeth loss for the past five years with less than 3 mm PD and CAL. The PI in healthy control was 0 or less than 1, and the GI range was between 0 to 1. They also had local bleeding on probing only (< 30%).	Chronic Periodontitis These clinical assessments were done on six sites per tooth and all remaining teeth of each patient. PD and CAL more than 3 mm. They also showed more than 30% BOP.	7
Gonzales et al. [35]	Germany	Periodontitis: Gender: M= 43.5%/ F= 56.5%. Age: 34 (29-38); Control: Gender: M= 38.3% /F= 61.7% Age: 30 (27-30)	Periodontitis: 7; Control: 9	Investigate possible associations between the IL4-590C-T, IL4-34C-T, IL13-1112C-T and IL13-1512A-C promoter polymorphisms were investigated in subjects with generalized aggressive periodontitis compared with healthy individuals	IL-4:-590C/T IL-4:-34C/T IL-13:-1112C/T IL-13:-1512A/C	The controls must have presented with a minimum of 26 teeth, with 95% of the tooth sites with 4 mm PPD without BOP, no PPD≥5 mm, and no loss of CAL.	Aggressive Periodontitis	7

BOP: Bleeding on Probing; PPD: Probing Pocket Depth; CAL: Clinical Attachment Level; PI: Plaque Index; GI: Gingival Index; PD: Probing Depth; CP: Chronic Periodontitis.

Table 5. Characterization of the distribution of IL-4 and IL-13 polymorphism genotypes in healthy patients and patients with periodontitis.

Author	SNP	Ethnicity	Disease Type	Control	Case	Case Genotype			Control Genotype			S.S/SNP	HWE	MBT	Biological Sample
						CC	CT	TT	CC	CT	TT				
Chen et al. [15]	IL-4-33C/T (rs2070874)	Caucasian	CP	324	440	21	130	289	18	96	210	No	Tested	PCR	Buccal Epithelial Cells
	IL-4 (rs2243248)					1[a]	38[b]	401	6[a]	57[b]	210	Yes			
	IL-13-1111C/T (rs1800925)					330	96	14	227	93	4	No			
Majumder et al. [20]	IL-4–33C/T (rs2070874)	Hindu/ Muslim	CP	200	157	52	70	35	78	88	34	No	Tested	PCR	Blood
	IL-13-1111C/T (rs1800925)					47	75	35	80	88	32	No			
Gonzales et al. [35]	IL-4–590C/T	Asian	AgP	51	58	23	22	6	29	14	15	Yes	Tested	PCR	Blood
	IL-4-34C/T					32	11	15	24	21	6	Yes			
	IL-13-1112C/T					19	29	10	17	29	5	No			
	IL-13-1512A/C					31	24	3	20	28	3	No			

AgP: Aggressive Periodontitis; CP: Chronic Periodontitis; S.S/SNP: Statistical Significance of SNP; HWE: Hardy-Weinberg equilibrium; MBT: Molecular biology technique; [a]: Genotype GG; [b]: Genotype GT.

Discussion

We examined the available literature to analyze the association of IL-4 and IL-13 polymorphisms in patients with and without periodontal disease. Out of the three studies analyzed, only two case-control studies [4,15] revealed a significant association for IL-4 polymorphism in the evaluated populations. Genetic aspects [36] and the immune system response play crucial roles in this etiopathogenesis [37,38]. Interleukins are essential cytokines synthesized by the immune system and play an active role in different phases of inflammation. Therefore, we conducted this systematic review to elucidate the roles of IL-4 and IL-13 polymorphisms, considering periodontal disease's complex and multidimensional nature. Understanding risk factors becomes crucial for accurate diagnosis and the development of preventive approaches [20].

This systematic review examined information from available literature on genetic polymorphisms of IL-4 and IL-13 and their association with susceptibility to the development of periodontal disease. The analyzed studies encompassed individuals diagnosed with both chronic and aggressive PD, following the classification proposed by Armitage [39]. The criteria used to assess individuals with and without periodontal disease were retained in this systematic review's qualitative synthesis of information, aiming to preserve data originality.

However, the new classification system for Periodontal and Peri-implant Diseases and Conditions grouped these conditions into a single category, considering the complexity and multidimensional nature of the disease [40]. Based on these new criteria [40], the studies addressing susceptibility to IL-4 and IL-13 polymorphisms indicated that most individuals were in stages III and IV of periodontitis. A recent systematic review investigating the relationship between disease/health modulators in periodontitis substantiated these findings [1].

An important point to highlight in this review was the inability to determine the risk of progression of periodontal disease, as none of the three included studies provided information regarding the rate of PD progression in the last five years, determined by the percentage of bone loss relative to age. This limits the implementation of this assessment system. Furthermore, regarding risk factors such as the presence of systemic diseases and smoking, it was observed that two studies [20,35] included smokers (less than ten cigarettes/day), categorizing them as grade B, while one study included patients classified as grade A [15].

This systematic review found significant associations of IL-4 SNPs compared to control patients. The IL-4 gene is located on chromosome 5q31.1 and is considered a pleiotropic interleukin that stimulates the production of helper T cells 2 (Th2) [41-43]. Additionally, it acts as a crucial mediator in the negative feedback of macrophage function and shares biological characteristics with IL-13. Th2 cells and many other immune cells play an essential role in the protective effect on periodontal tissue [44].

A recent meta-analysis focused on the role of IL-4, especially the IL-4 gene SNPs of 70 bp, -33 C/T, and -590 C/T, showed inconclusive results regarding susceptibility to PD development. However, another meta-analysis evaluating IL-4 SNPs showed a positive association between IL-4R Q551R polymorphism and chronic periodontitis. When evaluating the IL-4 -33 CT genotype, it was negatively associated with the occurrence of the aggressive phenotype [45].

These findings can be corroborated by a study conducted in the Brazilian population, where significant associations were found between chronic periodontitis and IL-4 gene polymorphisms. Specifically, for alleles -590(T), +33, and the insertion of 70 base pairs, as well as genotypes more prevalent in PD, allele -590, +33, and insertion haplotype (TCI), and the TCI/CCI genotype associated with susceptibility to PD. However, the TTD and TTD/CTI genotypes were associated with protection against chronic periodontitis [13]. These data are reaffirmed by the studies that composed this systematic review, reporting that SNPs -33C/T [20], -590 T/T [35], and -34 T/T [35] were associated with an increased susceptibility to PD.

On the other hand, the IL-13 gene is located on chromosome 5q23.31 and is considered a multipotent cytokine with various biological effects [46]. This gene has a molecular weight of 12,000 Da (in its non-glycosylated form) and a length of 4.6 kb [17]. This interleukin can regulate the inflammatory process in various tissues, making it a therapeutic target for multiple diseases [47]. Additionally, several studies have evidenced the role of this gene in the pathogenesis of PD [7,15,17,20,35]. Recently, the expression of IL-13 gene mRNA was verified in gingival tissues of individuals with and without PD. Analyzing the results, the authors identified higher mRNA expression levels in control patients for PD [35,48].

Analyzing the studies included in this systematic review, it was possible to identify that they did not present a significant association with IL-13 polymorphism [15,20,35]. However, a recent meta-analysis on IL-13 polymorphism, especially the IL-13 -1112 SNP, demonstrated its association with PD development. These findings are corroborated by the studies of Wu et al. [17], who evaluated 359 patients from a Chinese population for the -1112 C/T polymorphism. The results indicated that allele C and genotype CC presented a higher risk of developing aggressive periodontitis in Taiwanese individuals.

The main challenges for future studies involving epidemiological aspects with genetic evaluations (polymorphism studies) consist of finding similar works regarding patient selection criteria and the definition of clinical parameters used for assessment. The recent classification of Periodontal and Peri-implant Diseases and Conditions [8] will be important to assist clinicians in diagnosing and treating their patients appropriately, and researchers investigate the etiology, pathogenesis, natural history, and treatment of these diseases and conditions using standardized methodologies. However, despite this new classification being based on the most substantial

scientific evidence available in the literature, weaker evidence and expert opinions were inevitably used. Therefore, future studies need to be conducted to meticulously assess the effects and impacts of genetic factors on periodontal disease.

This review has several strengths, including the simultaneous analysis of IL-4 and IL-13 polymorphisms since individual meta-analyses were found for each polymorphism. Several major databases were searched to ensure no relevant manuscripts were missed. The main limitation of this review was the need for additional studies on the subject of IL-4 and IL-13 polymorphism susceptibility in patients with and without PD in the same population. The lack of quantitative data in tables and text about allele distribution was considered a limitation for performing a quantitative synthesis (meta-analysis). Additionally, the inclusion criteria for the Healthy and Periodontitis groups, which were distinct in both manuscripts, represented a limitation. The number of subjects (population) varied considerably between studies. The absence of standardization in participant inclusion criteria, such as the lack of uniformity in periodontal disease diagnostic criteria, was also considered a partial limitation of this study. Despite these limitations highlighted by this systematic review, it was possible to identify a significant association of IL-4 polymorphism in individuals with periodontal disease.

Conclusion

Based on current evidence, it was possible to observe that the IL-4 gene (IL-4 -590C/T; IL-4-34C/T; rs2243248) was associated with susceptibility to the development of periodontal disease. Considering the lack of evidence and controversial data in the literature on these genetic polymorphisms and their influence on the etiopathogenesis of periodontal disease, the study performed is relevant to clarify possible mechanisms of immune response and evidence the need for further epidemiological studies involving these markers in health. More concrete conclusions should be based on additional studies on this subject.

Authors' Contributions

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All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.

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None.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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