

Genetic Predominance in Periodontitis: A Review in Indian Population

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Abstract: The role of Genetics in periodontics has always been a subject of interest for researchers. Is it associated with chronic periodontitis (CP) or aggressive periodontitis? If yes, which genetic codes in Indian population are seen in relation to periodontal diseases? The aim of the publication is to review the studies on the role of genetics in periodontitis in Indian sub-continent. The search duration was 1st January 1997 to 31st December 2016. A total of 24 studies were included out of which 6 studies showed an association between IL-1B gene polymorphism and chronic and/or aggressive periodontitis. 2 studies reported significant co-relation with CP and IL-6 G allele and other 2 studies stated contradictory results for Tumour Necrosis Factor- α (TNFA) and CP. Further studies with larger sample size and high level of evidence are required on other gene polymorphisms (Interleukin-4, Interleukin-6, Interleukin-10 and Interleukin-17, Immunoglobulin G Fc γ Receptors, Cyclooxygenase gene, Toll like receptors, Human Leukocyte Antigen -8 and Human Leukocyte Antigen-9) in periodontitis.

Keywords: Genetics, Gene Polymorphism, Indian Population, Periodontitis

I. Introduction

Periodontal diseases are a heterogeneous group of diseases that affects hundreds of millions around the world. The pathogenesis of the diseases is regulated by a complex interplay between microbes and the immune system. The effectiveness of immune response depends on factors in both internal and external environments. As literature suggests that many cases of periodontal disease are best considered as the outcome of an imbalance in the host-parasites interaction; since they are infectious in origin, the extent and severity of the disease depends upon the interaction between pathogenic challenge and host response. [1]

Identification of genetic factors that control the immune response to various microbial infections in both the human and animal models have been increases and more emphasis on genetically determined host response is focused. Additional support for a genetic contribution for periodontitis emerged recently from identification of certain genetic polymorphisms that correlate with immune response phenotypes found in certain groups of periodontitis patients.[2] The key is to identify the genetic factors that are important enough to impart significant clinical risk. In general, a gene is considered as a candidate for a causative or modifying role in periodontitis if the physiological process is determined by the gene have been associated with the presence or severity of disease.[2]

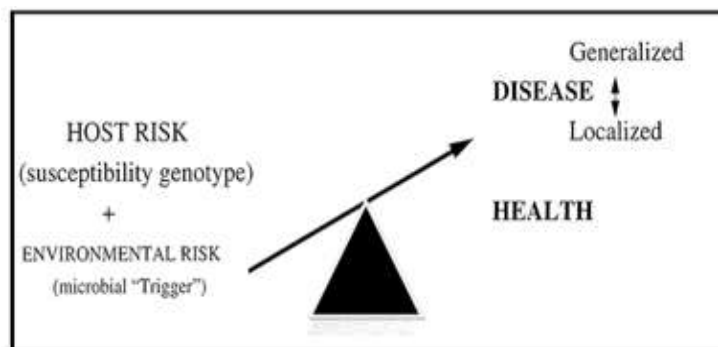


Fig 1: Disease risk = sum of host risk factors + environmental risk factor. In early onset periodontitis (EOP), individuals carry a genotype that greatly increases the propensity for periodontal destruction when exposed to certain microbes (eg:

Actinobacillus actinomycescomitans). Clinical expression of disease depends upon the specific susceptibility genotype present (genes of major effect and modifying genes), as well as quantitative and qualitative aspects of microbial challenge.[3]

II. Search Strategy

Using electronic databases such as the PubMed, Google Scholar, TRIP database with keywords "Indian [All Fields] AND ("population" [Mesh Terms] OR "population" [All Fields] OR "population groups" [Mesh Terms] OR ("population" [All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("periodontitis"[Mesh Terms] OR "periodontitis"[All Fields]) AND ("genetics"[Subheading] OR "genetics"[All Fields] OR "genetics"[Mesh Terms])" were searched. The data was collected from 1st Jan 1997 to 31st Dec 2016. No limit for journal or type of article was set. All the articles, from all types of journals including basic sciences, clinical medical sciences and dental sciences were included. The studies performed on Indian population were only included. All the genetic parameters associated with chronic periodontitis and aggressive periodontitis was taken into consideration.

III. Result

Out of all the articles searched 24 (Table 1) were included in this review. The genetic parameters included were from the interleukin family Interleukin-1 α , Interleukin-1 β , Interleukin-4, Interleukin-6, Interleukin-10 and Interleukin-17, Immunoglobulin G Fc γ Receptors, Cyclooxygenase gene, Toll like receptors, Human Leukocyte Antigen -8 and Human Leukocyte Antigen-9 and their associations with aggressive and chronic periodontitis were reviewed.

IV. Discussion

During the past 2 decades, since the Human Genome Project officially began in 1990, the awareness of genetic predisposition in causing the diseases has been widely accepted. The first study relating genetic predisposition to periodontitis was done in 1997 by Kornman. The studies are divided in two categories: Chronic periodontitis and Aggressive periodontitis.

V. Chronic Periodontitis

5.1 Interleukin 1A & 1B

Genetics is the risk determinant for periodontal diseases. It plays a major role in the progression of periodontal diseases. The first study of cytokine gene polymorphism was reported by **Kornman et al** [2] in 1997; who found a significant association between severe adult periodontitis and composite genotype (IL-1A +4845 and IL-1B +3954) located on chromosome 2q13. Genotype positive non-smokers were found to be 6-8 times more likely to have chronic periodontitis than individuals who were genotype negative. Interleukin-1 is a potent pro-inflammatory cytokine, which plays a key role in periodontitis pathogenesis (Birkedal-Hansen, 1993). Single nucleotide polymorphisms (SNP) have been identified at various loci of the interleukin-1 gene (Kinane et al., 2005); they are effective at low concentrations and transiently produced in the tissues. They signal, broadcast and amplify immune responses. In Indian population, studies have reported the association between different interleukins with chronic and aggressive periodontitis. **Agarwal et al (2006)** [3], in his study concluded that IL- 1 genotype is a risk factor for severe chronic periodontitis. He performed Polymerase chain reaction (PCR) to determine the distribution of IL-1 gene polymorphism (IL-1A+4845 and IL-1B+3954) in Maharashtrian ethnicity. He found out 30 % patients with severe periodontitis were positive for composite genotype (allele 2 at IL-1A-889 and IL-1B+3953 loci) and 40 % of severe periodontitis patients were positive for IL-1B allele 2. No healthy subjects had genetic predisposition for composite genotype. However 10% of healthy subjects were positive for IL-1B allele 2. The author reported the reason for this co-relation was that dysregulated production of IL-1 in some individuals overrides the feedback mechanisms that normally master the dose of inflammation to a level sufficient to fight microbial invasion without long-lasting damage to the tissues involved.

In 2010, two studies (**Prakash P et al, Shete AR et al** [4,5]) were performed to identify the association of IL - 1 β gene polymorphism with chronic periodontitis in South Indian population. Both the studies concluded that IL - 1 β +3954 to be an important risk factor for chronic periodontitis. **Gayathri R et al** [6] in 2011, in her case control study determined the role of IL-A + 4845 and IL-1B +3954 polymorphism in predisposition of chronic periodontitis. The distribution of the IL-1 positive composite genotype (periodontitis associated genotype) was in concordance with the frequencies reported in the Caucasians which was 35%. Association was not found for the effect of allele, genotype, composite genotype, and haplotypes of IL-1A+4845 and IL-1B+3954 polymorphisms with periodontitis. In the study by **Lavu et al (2015)** [7], a statistically significant association was established between SNP at + 3954 in the IL 1B gene and chronic periodontitis susceptibility in the dominant and allelic models. The SNP at IL 1B + 3954 position has been identified as a potential risk marker for chronic periodontitis in a similar ethnic population in recent studies (**Shete et al. 2010; Archana et**

al. 2012; Masamatti et al. 2012). In contrast, a previous study by **Kaarthikeyan et al (2009)** [8], reported a lack of association between the SNP at + 3954 in the IL-1B gene and chronic periodontitis susceptibility in a similar population. The observed difference in the results was attributed to the small sample size which used in the study by Kaarthikeyan et al. (2009), which was not adequate to detect the difference in genotypic or allelic variation between the groups. The variant (T) allele frequency observed in the chronic periodontitis subjects of Lavu et al 2015 study population was 25.5% as compared to 38.5% (Masamatti et al., 2012)[9], 46.7% (among severe periodontitis group) (Archana et al.,2012), 14% (Shete et al., 2010) as reported in studies involving subjects of a similar demographic population.

5.2 Other Interleukins

Franch-Chillida F et al [10] in **2010** evaluated the association of IL-6 gene polymorphism in Indian population. It was seen that there was an increased prevalence of GG genotype for IL-6 -174 polymorphism in non-smoking subjects with periodontitis. Another study by **Kalburgi N B et al (2010)** [11] reported that G allele was more frequent in chronic periodontitis patients (76.67%), where as C allele was more frequent in the control group (73.33%). **Sharma et al in 2014** reported results which indicated that G allele of IL-6 (-597) could be associated with chronic periodontitis. In their study population, chronic periodontitis and diabetes mellitus group (CPDM) and chronic periodontitis (CP) groups had similar genotype, as well as allele distribution for IL-6 -597 SNP. This may support the hypothesis that a common genetic factor might be involved in the pathogenesis of CP and type 2 DM to some extent.

SNPs in the promoter region of interleukin (IL) 10 gene, which codes for the anti-inflammatory cytokine IL-10 have been analysed in non smoking Indian population by **Crena et al (2015)** [12]. A positive association between the occurrence of AA allele at -1087 locus of IL-10 gene and severe chronic periodontitis was observed.

IL-17 is a pro inflammatory cytokine produced mainly by Th17 cells. There have been 2 studies which have been undertaken to find an association between chronic periodontitis and IL-17. They had different results; the study by **Jain et al (2013)** [13] in Dravidian ethnicity concluded no association with periodontitis at both allelic and genotypic levels whereas in 2016 a study by **Chaudhari et al (2015)** [14] reported that IL-17 gene polymorphism can be a risk factor for chronic periodontitis. Jain et al (2013) in his study also evaluated the association of IL-4 with periodontitis in Malayalam speaking Dravidian population. IL-4+33C/T loci appeared to be an important risk factor for periodontitis. This difference in studies could be explained by different gene polymorphism researched.

Socransky et al 2005 [15] researched IL-1 gene polymorphisms in periodontitis patients and found that the patients who were IL-1 genotype positive tended to have higher levels of damaging microbial species (red and orange complex organisms) associated with periodontal disease.

5.3 Toll like receptors

The primary response to pathogens in the innate immunity system is triggered by pattern recognition receptors (PRRs) that bind pathogen associated molecular patterns (PAMPs). Among the most important families of PRRs are the toll like receptors (TLR), which recognize a large number of varied and complex PAMPs. A total of 13 mammalian TLR paralogs and 11 in humans are identified. **Ashok N et al** [16] in **2014** performed a study to analyze genetic polymorphisms in the toll-like receptor 9 (TLR9) gene at - 1237C/T and its association with chronic in an Indian population. It was seen that there may not be any relationship between chronic periodontitis and TLR9. Another study by **Reddy et al 2011** [17] aimed at analysing the association between TLR-4 Asp299Gly and Thr399Ile gene polymorphisms and chronic periodontitis in South Indian population and did not find any significant association between TLR-4 Thr399Ile polymorphism and chronic periodontitis and TLR-4 Asp299Gly gene polymorphism was not detected in either chronic periodontitis or healthy groups.

5.4 Cyclo-oxygenase gene

Cyclo-oxygenase (COX) enzyme catalyses the production of prostaglandins, which are important mediators in pro-inflammation; Single nucleotide polymorphisms of COX2 enzyme have been associated with increasing susceptibility to inflammatory diseases. In a study by **Daing et al (2012)** [18] it was observed that mutant genotypes (GA and AA) of COX2 -1195 showed more than a two fold risk and COX2 8473 (TC and CC) showed a reduced risk for the disease, but the findings were not statistically significant. Thus, individual genotypes of both the SNPs were not associated; while haplotype AT was found to be associated with chronic periodontitis in North Indians.

5.5 Immunoglobulin G Fc gamma Receptor and Tumour Necrotizing Factor alpha

Polymorphisms in Fc gamma receptor (FCGR) and Tumour necrosis factor alpha (TNFA) genes are known to influence pathogenesis of inflammatory conditions. No association was found between TNFA -1031T/C and -863C/A and CP in a study by **Lavu et al in 2016** [19]. Although in another study by **Sharma N et al (2014)** [20] a significant association between TNFA- 308G/A and susceptibility to chronic periodontitis was seen. This difference can be explained due to the variation of different loci of gene of TNFA being studied.

VI. Aggressive periodontitis

6.1 Interleukin 1

A number of studies in the past have been performed and it has been concluded that aggressive periodontitis does have a familial predilection [21]. A total of three studies have been performed in the past decade to analyse the association between aggressive periodontitis and Interleukin 1 α and 1 β . **Shete et al in 2010** [5] performed a study in which 54 patients with aggressive periodontitis were genotyped for IL-1 β + 3954, -511 and -31 loci in Dravidian population. He concluded that there was no gene polymorphism associated with aggressive periodontitis. Similar results were obtained in another study done by **Masamatti et al in 2012** [9]. In **2014 Puri et al** [22] performed a study to assess the correlation of interleukin 1 α (-889) and aggressive periodontitis and concluded that there is a positive correlation between aggressive periodontitis and the presence of the interleukin 1 α (-889), allele 2 polymorphism. Similar results were seen in a study done by **Kiani et al in 2009** [23]. However **Maria de freitas et al 2007** [24] showed contradictory results saying that that there was no significant positive correlation between them.

6.2 Other Interleukins

Various studies have been done to demonstrate the correlation of interleukin 17 polymorphism and aggressive periodontitis. In study done by **Chaudhari et al in 2016** [14] in 35 patients with localized aggressive periodontitis (LAGP), they found out that IL-17A gene polymorphism at -197A/G was significantly associated with localized aggressive periodontitis in Indian population. Thus it can be considered as a risk factor for LAGP. However, **Jain et al in 2013** [13] concluded that association between IL-17F at 7383A/G and 7488A/G loci could not be ascertained. In the same study they found out a positive correlation between IL-4 + 33 C/T loci and aggressive periodontitis thus proving it to be a risk factor for the same. In contrast to this study, **Gonzales et al 2002** [25] stated that there was no significant IL-4 allele distribution seen in aggressive periodontitis patients.

6.3 Toll like receptors

Toll like receptors polymorphism has been associated with various inflammatory diseases. **Ashok N et al** [16] in **2014** performed a study in which he assessed 30 patients with generalized aggressive periodontitis for genetic polymorphism in the toll like receptor 9 (TLR9) gene at -1237 C/T. They concluded that TLR9 gene polymorphism at -1237 C/T may not be associated with generalized aggressive periodontitis patients in India.

6.4 Human leukocyte antigen

The gene encoding the human leukocyte antigens (HLAs) have been considered as a candidate marker for periodontitis. Various studies have been done to evaluate the same. Two studies have been done in Indian population. In study done by **Thomas et al in 2004** [26], they investigated the HLA-A*9, HLA-A*10 and HLA-A*24 association with aggressive periodontitis in South Indian population. They found that HLA-A*9, HLA-A*24 had a positive correlation with aggressive periodontitis whereas HLA-A*10 did not show any significant variation. Conversely, in other study done by **Roshna et al 2006** [27], they found no association between HLA-A*9 and aggressive periodontitis. However in the study they stated that HLA-A*15 was a significant risk factor for generalized aggressive periodontitis (GAgP) and is positively associated with the severity of the disease.

6.5 Immunoglobulin G Fc gamma receptor IIa

Hans et al in 2011 [28] conducted a study to evaluate whether specific Fc γ Receptor IIa, Fc γ RIIIa and Fc γ RIIIb alleles and genotypes are associated with susceptibility of generalized aggressive periodontitis. They found that Fc γ RIIIa V/V genotype and/or V allele, as well as the Fc γ RIIIb NA2/NA2 genotype and/or NA2 allele appear to be associated with susceptibility to GAgP in a South Indian population. The R131 allele of Fc γ RIIIa occurred more frequently in the GAgP group than in the controls, and was also suggested to be a risk factor for GAgP in this South Indian population.

VII. Conclusion

Genetics holds a considerable importance in the progression of periodontal disease. In the present review, 24 studies describing the correlation between various genetic polymorphisms associated with periodontitis in Indian population were selected. Five studies stated that genetic polymorphism in IL-1B had a

definite positive co-relation, both with chronic and aggressive periodontitis and one study showed similar results with CP and diabetes mellitus patients This was in relation to IL 1B (+3954) which could be a risk factor for chronic periodontitis. It is already established that there is a correlation between IL 1B and Periodontitis. Further studies with more number of patients and high level of evidence are required on other gene polymorphism in periodontitis.

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Table 1: Details of genetic studies on periodontitis in Indian sub-continent

Sr. No.	Author, Journal, Year	Sample Size	Participants Included	Outcomes Measured	Results
1.	Thomas R et al 2004	78	Aggressive periodontitis	HLA-A*9, HLA-A*10 and HLA-A*24 using polymerase chain reactions with sequence specific primers (PCR-SSP).	A positive association of HLA-A*24 with aggressive periodontitis was noticed. HLA-A*10 did not vary significantly in both the study groups and is not having an association with disease.
2.	Agrawal AA et al 2006	120	Generalized Chronic Periodontitis	IL-1 gene polymorphism with the help of polymerase chain reaction (PCR) and subsequent allele detection with restriction fragment length polymorphism (RFLP) and separation by gel electrophoresis.	The distribution of the allele1 homozygous genotype was 3%, IL-1B allele 2 was 40% in the severe periodontitis group, and the distribution for the IL-1AB allele2 genotype was 30%. A highly significant difference (p<0.001) was seen between subjects Positive and negative for the composite genotype ((IL-1A allele2 + IL-1B allele2) for severe chronic periodontitis.
3.	Roshna T et al 2006	120	Generalized aggressive Periodontitis	HLA-A*9 and HLA-B*15 typing was carried out using the polymerase chain reaction with sequence specific primers (PCR-SSP)-based molecular method.	HLA-B*15 as a risk factor for Generalized Aggressive Periodontitis HLA-A*9 showed no association
4.	Prakash PS et al 2010	75	Generalized Chronic Periodontitis	IL1B (+3954) gene polymorphism	Polymorphism in the locus +3954 of IL1B gene could be a risk factor for chronic periodontitis in South Indian population.
5.	Shete A R et al 2010	198	chronic periodontitis and aggressive periodontitis	IL-1b +3954, -511, and -31 loci by polymerase chain reaction amplification	IL-1b+3954 appeared to be an important risk factor for chronic periodontitis (odds ratio= 4.35). Association between IL-1β 511 and 31 gene polymorphism and chronic periodontitis or aggressive periodontitis could not be determined.
6.	Kalburgi et al 2010	30	Generalized Chronic Periodontitis	PCR analysis and single nucleotide polymorphism of IL-6	The result showed that the G/G genotype was significantly more frequent in chronic periodontitis and that the C/C genotype was significantly more frequent in healthy patients.
7.	Franch-Chillida F et al 2010	251	chronic periodontitis	Real-time polymerase chain reaction to study IL-6 variants	Increased prevalence of GG genotype was observed for IL-6-174 polymorphism in non-smoking subjects with periodontitis and older subjects (≥45 years old)
8.	Gayathri R et al 2011	103	Chronic periodontitis	Genotyping IL-1A+4845 and IL-1B+3954 polymorphisms by polymerase chain reaction– restriction fragment length polymorphism	Frequency distribution of IL-1 positive periodontitis associated genotype was 35%. Association was not found for the effect of allele, genotype, composite genotype, and haplotypes of IL-1A+4845 and IL-1B+3954 polymorphisms with periodontitis.
9.	Reddy BR et al 2011	120	Chronic periodontitis	TLR4 Asp299Gly and Thr399Ile gene polymorphisms	There is no significant association between TLR4 Thr399Ile polymorphism and chronic periodontitis in a sample of south Indian population.

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10.	Hans VN et al 2011	120	Generalized Aggressive Periodontitis	FcγRIIa and FcγRIIIa genotyping was performed by polymerase chain reaction (PCR) amplification of DNA with allele-specific primers followed by allele specific restriction digestion of the products, whereas FcγRIIIb genotyping was done by allele-specific PCR.	Fcγ Receptor IIIa V/V genotype and/or V allele, as well as the Fcγ Receptor IIIb NA2/NA2 and/or NA2 allele, along with the Fcγ Receptor IIa- R allele, may be risk factors for GAgP in the population of South India
11.	Archana PM et al 2012	60	Chronic periodontitis	Amplification of IL-1A+4845 and IL-1B+3954 were done by polymerase chain reaction (PCR).	IL-1 gene polymorphism IL-1A+4845, IL-1B+3954 and composite genotype is an indicator of susceptibility to severe periodontitis in adults.
12.	Daing A et al 2012	116	Chronic periodontitis	genotype analysis for mutant genotypes (GA and AA) of Cyclo-oxygenase 2 (COX2)-1195 and COX2 - 8473	Individual genotypes of both the SNPs were not associated while haplotype analysis revealed that the 1195A/8473T haplotype was significantly associated with increased risk (OR: 1.79) for chronic periodontitis, while the -1195G/8473C haplotype showed a reduced risk (OR: 0.501).
13.	Masamatti SS et al 2012	90	Severe chronic periodontitis	PCR with specific primers flanking the locus +3954 of IL-1B	The chronic periodontitis group displayed a higher percentage of T alleles (38%) when compared to the aggressive periodontitis group (20%) and to the control group (19%). +3954 of IL-1β gene could be a risk factor for chronic periodontitis.
14.	Jain N et al 2013	124	Chronic and Aggressive periodontitis	Genotype for IL-4 + 33C/T, IL-17F 7383A/G, 7488A/G by polymerase chain reaction	IL-4 + 33C/T loci appear to be an important risk factor for periodontal disease with a leaning towards aggressive periodontitis. The association between IL-17F at 7383A/G and 7488A/G loci with either chronic or an aggressive periodontitis could not be ascertained.
15.	Kaarthikeyan N D et al 2013	120	Chronic periodontitis	TaqI Vitamin D Receptor gene polymorphism	TaqI Vitamin D Receptor gene polymorphism is associated with Chronic Periodontitis in Dravidian ethnicity.
16.	Sharma N et al 2014	153	Chronic periodontitis with or without diabetes mellitus	Interleukin-1 beta (IL-1 β) +3954, interleukin-6 (IL- 6) -597/-174 and tumor necrosis factor-α (TNF-α) -308 single nucleotide polymorphisms in CP with and without type 2 DM	IL-6 (-597) genotype GA/AA and allele A appears to be protective for Chronic periodontitis with type 2 DM. Allele C of IL-1 β +3954 and allele A of TNF-α -308 appears to be risk factors for chronic periodontitis individuals.
17.	Ashok N et al 2014	90	Chronic and aggressive periodontitis	TLR9 genetic polymorphism at - 1237C/T by using polymerase chain reaction-restriction fragment length polymorphism method.	Toll-like receptor 9 genetic polymorphism at - 1237C/T may not be associated with GAgP and chronic periodontitis patients in Indian population.
18.	Chaudhari HL et al 2015	70	Chronic and localized aggressive periodontitis	IL-17 genetic polymorphism at (-197A/G), by using the polymerase chain reaction-restriction fragment length polymorphism method	IL-17 A gene polymorphism at (-197A/G) is linked to chronic periodontitis and LAgP in Indian population and could be considered as a risk factor for chronic

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					periodontitis and LAgP.
19.	Crena J et al 2015	91	Severe chronic periodontitis	Allele-specific polymerase chain reaction for IL-10	The prevalence of genotype AA alleles at -1087 locus of IL-10 was significantly higher in severe chronic periodontitis patients compared to the healthy controls ($P = 0.05$).
20.	Puri K et al 2015	60	Chronic and aggressive periodontitis	PCR restriction fragment length polymorphism	There is a positive association between aggressive periodontitis and the presence of IL-1 α -889, allele 2 polymorphism in Indian population.
21.	Prakash G et al 2015	200	Chronic Periodontitis	Gene polymorphisms was carried out by PCR	IL-1 β (-511C>T) and IL-1RN (VNTR) are not implied in risk modification of CP
22.	Lavu V et al 2015	400	Chronic Periodontitis	Single nucleotide polymorphisms (SNPs) in IL1B (- 511, +3954), IL1A (-889, +4845)	In the study population examined, the SNP in the IL1B gene (+3954) and VNTR polymorphisms in the IL1RN gene were found to have a significant association with chronic periodontitis susceptibility.
23.	Amirisetty R et al 2015	60	Chronic Periodontitis	PCR-RFLP technique on IL 1B -31, -511, and +3954 variants	A strong association of the TT genotype of -511 and CT genotype of +3954 variant of IL 1B with chronic periodontitis On the other hand, the -31 variant did not show a significant association with the disease.
24.	Lavu V et al 2016	353	Chronic Periodontitis	Immunoglobulin G Fc receptor II (FCGR2A 131His/Arg (rs1801274), FCGR2B 232Ile/Thr (rs1050501), TNFA - 1031T/C (rs1799964) and -863C/A (rs1800630) polymorphisms	FCGR2A 131His/Arg showed significant association with CP (OR: 1.6) A significant redundant interaction between IL1B +3954 C/T and FCGR2A 131His/Arg was observed.