

## Original Article

### Association of interleukin-1 $\alpha$ (-889) gene polymorphism in patients with generalized aggressive and chronic periodontitis

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#### ABSTRACT

**Background:** There is a strong evidence that genetic as well as environmental factors affect the age of onset, severity and lifetime risk of developing periodontitis. The objective of the present study was to compare and to evaluate the association between interleukin (IL)-1 $\alpha$ (-889) and gene polymorphisms in patients with generalized aggressive periodontitis, chronic periodontitis and healthy controls.

**Materials and Methods:** A total of 60 Indian patients, with 20 aggressive periodontitis, 20 chronic periodontitis and 20 healthy controls were recruited for this study. From each patient, a volume of 2 ml of blood was collected by venipuncture in the ante-cubital fossa and was stored in sodium EDTA vacutainers and was used for genotyping assays with the polymerase chain reaction restriction fragment length polymorphism technique. Clinical parameters such as oral hygiene index, gingival index and clinical attachment loss (CAL) were evaluated for each patient. Genotype distribution between different groups were analyzed using Chi-square test. A  $P = 0.05$  or less was set for significance.

**Results:** The mean oral hygiene index was  $3.7 \pm 0.86$  and  $3.25 \pm 0.30$  for chronic and aggressive periodontitis cases respectively. The CAL was  $4.29 \pm 0.63$  mm for chronic periodontitis and  $6.44 \pm 0.57$  mm for aggressive periodontitis. Homozygous genotype 2,2 was more predominant in cases of aggressive periodontitis whereas in chronic periodontitis, heterozygous genotype 1,2 was more predominant when compared with others ( $P < 0.001$ ). Odds ratio for aggressive versus chronic periodontitis was calculated as 6.2 (95% confidence interval 6.019-7.892).

**Conclusion:** The results of the present study support a positive association between aggressive periodontitis and the presence of the IL-1 $\alpha$ -889, allele 2 polymorphism in Indian patients.

**Key Words:** Aggressive periodontitis, interleukin-1, single nucleotide polymorphism

Received: July 2013  
Accepted: January 2014

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#### INTRODUCTION

Periodontitis is an infectious disease which is multifactorial, polymicrobial, polygenic in nature and can manifest itself with polymorphic clinical presentations. Along with the presence of various risk

factors associated with development of periodontitis, genetic as well as environmental factors affect the age of onset, severity and development of periodontal diseases. Plaque, being the primary etiologic agent for occurrence of periodontitis, is induced by various microorganisms and also mediated by inflammatory activation of endogenous cytokines; therefore, the candidate gene has been selected from among these pro-inflammatory and regulatory cytokines. Furthermore, increased or upregulated production of inflammatory cytokines in response to bacterial biofilms, occurs in subjects carrying functional polymorphisms in these genes. The pro-inflammatory and bone resorption properties of interleukin-1  $\alpha$  (IL-1  $\alpha$ ) strongly suggest a role for

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this cytokine in the pathogenesis of periodontal disease. [1] IL-1 is also involved in regulating connective tissue remodeling and cellular differentiation of epithelial and ectodermal cells. There are 3 major members of the IL-1 family: IL-1 $\alpha$ , IL-1 $\beta$ , and IL-1 receptor antagonist. IL-1 $\alpha$  is mainly present as the cell-associated precursor pro-IL-1 $\alpha$ , which in contrast to inactive pro-IL-1 $\beta$ , expresses biological activity and acts in an autocrine manner. The gene encoding IL-1 $\alpha$ , located within the IL-1 gene cluster on chromosome 2q13-21, is polymorphic at position -889 from the transcription start site.<sup>[2,3]</sup>

Gene polymorphisms are locations within the genome that vary in sequence between individuals and are very prevalent, affecting at least 1% of the population.<sup>[4]</sup> Polymorphisms of human genes occur at one or more of the following sites: Promoter region, exon, intron or 3'-untranslated region.<sup>[5]</sup>

The most common form of polymorphisms is the single nucleotide polymorphism, which is a deoxyribonucleic acid (DNA) sequence variation occurring when a single nucleotide—A, T, C or G—in the genome differs between members of a biological species or paired chromosomes in an individual.<sup>[2]</sup> IL-1 $\alpha$ -889 is a single-nucleotide polymorphism (SNP) with a cytosine–thymine substitution, which has shown to influence IL-1 protein production.

Previous studies have examined the association between polymorphisms in candidate genes and periodontitis. IL-1 polymorphisms have been associated with severity of periodontitis,<sup>[6,7]</sup> tooth loss<sup>[8]</sup> and increased bleeding on probing.<sup>[9]</sup>

Kornman *et al.* studied the effect of IL-1 single nucleotide gene polymorphisms (SNP) and suggested that the genetic variance is attributed, in part, to allelic variations in the IL-1 gene cluster, which results in increased production of IL-1 $\beta$  and IL-1 $\alpha$ .<sup>[6]</sup>

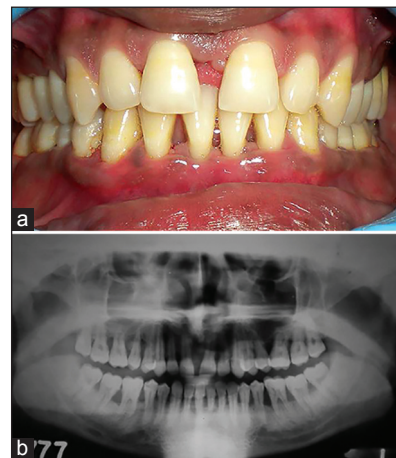
Until date, most of studies have examined the association of a candidate polymorphism with only one form of periodontitis at a time. However, no investigation has attempted to assess if the phenotypic differences seen between aggressive and chronic periodontitis are reflected in a difference in associations with several polymorphisms amongst Uttar Pradesh population of India.

The aim of the present study was to evaluate the association between IL-1 $\alpha$  (-889) gene polymorphisms in patients with generalized aggressive periodontitis, chronic periodontitis and healthy controls.

## MATERIALS AND METHODS

### Subjects

The study protocol was approved by the Institutional Ethics Committee of the ITS Centre for Dental Studies and Research (reference number: ITSCDSR/Director-General/1947). All the subjects included in the study received a detailed description of the study and provided informed written consent to participate in the study. Sixty Indian patients were recruited for the study from the Department of Periodontology, ITS Centre for Dental Studies and Research, Muradnagar, Ghaziabad, UP, India. The patients were diagnosed according to the criteria of the International workshop for classification of periodontal diseases and conditions<sup>[10]</sup> and were classified under either aggressive or chronic periodontal disease category as shown in Figures 1, 2 and Table 1. Cases of uncertain clinical presentation were excluded



**Figure 1:** (a) Clinical photograph and (b) panoramic radiograph of an aggressive periodontitis patient

**Table 1: Classification of periodontitis - International workshop for classification of periodontal diseases and conditions (Armitage, 1999)**

Type of periodontitis	Description/characteristics
Aggressive periodontitis	An otherwise clinically healthy patient Rapid attachment loss and bone destruction Amount of microbial deposits inconsistent with disease severity Familial aggregation of diseased individuals
Chronic periodontitis	Prevalent in adults but can occur in children and adolescents Amount of destruction consistent with local factors Subgingival calculus is a frequent finding; Slow to moderate rate of progression Possibly modified by systemic diseases (diabetes), environmental factors (cigarette smoking)

from the study. A detailed medical, dental and family history were taken, followed by a complete periodontal examination that included gingival status, clinical attachment loss (CAL) at six sites per tooth and appropriate radiographs. A clinical diagnosis of generalized aggressive periodontitis was made for 20 patients while 20 patients were diagnosed as having chronic periodontitis and 20 were control subjects found to exhibit no signs of periodontal disease upon clinical examination. All subjects included in this study were Indians belonging to Ghaziabad district of Uttar Pradesh, with an average age of 34.47 years and with no gender bias. All subjects were in good general health. Smokers and subjects under any medications were excluded from the study.

### Clinical examination

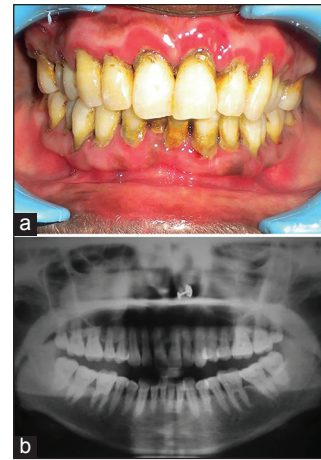
Periodontal examination included assessments of oral hygiene status, gingival inflammation and CAL in all the selected study patients. The oral hygiene status was assessed using the oral hygiene index of Greene and Vermillion<sup>[11]</sup> and gingival inflammation was assessed using the gingival index of Loe and Sillness (modified by Loe in 1967).<sup>[12]</sup> CAL was measured using a Williams graduated periodontal probe at six sites around each tooth: Mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual locations. Measurements were recorded to the nearest millimeter and every observation close to 0.5 mm was rounded to the lower whole number. All measurements were recorded by the same examiner to avoid interexaminer error and patients were classified into chronic and aggressive periodontitis according to AAP classification 1999, with healthy subjects showing no or minimal gingival inflammation.

### Radiographs

Full-mouth radiographs were taken of all patients using panoramic radiographs aided by full-mouth intra-oral periapical radiographs when necessary to assess bone loss.

### Sample collection and DNA extraction

From each patient, a volume of 2 ml of blood sample was collected by venipuncture in the ante-cubital fossa. The blood samples were collected in sodium EDTA vacutainers [Figure 3] and were transported to microbiology lab, Maratha Mandal dental college, Belgaum, Karnataka, India. DNA samples were amplified using 5'AAG CTT GTT CTA CCA CCT GAA CTA GGC 3' (forward) and 5'TTA CAT ATG AGC CTT CCATG 3' (reverse primer) [Figure 4].



**Figure 2:** (a) Clinical photograph and (b) panoramic radiograph of a chronic periodontitis patient



**Figure 3:** Blood sample collected in sodium EDTA vacutainers



**Figure 4:** Primers for deoxyribonucleic acid amplification

### DNA extraction technique

DNA extraction was done using modified proteinase-k method. Blood sample was added into

the test tube containing 200  $\mu$ L of TE buffer (Tris EDTA buffer) and centrifuged at 5,000 rpm for 3-4 min. Supernatant was discarded. The above step was repeated four times by adding fresh TE buffer each time. 500  $\mu$ L of lysis buffer 1 was added and the sample was again centrifuged at 5,000 rpm for 3-4 min and the supernatant was discarded. 50  $\mu$ L of lysis buffer 2 and 5  $\mu$ L of proteinase K was added to the sample and kept in a water bath at 75°C for 2 h. Then, it was kept in boiling water bath for 10 min and stored at -20°C.

Conventional polymerase chain reaction (PCR) thermal cycler of Corbette research was used for DNA amplification [Figure 5], which could heat and cool the tubes with the reaction mixture in a very short time. 35 cycles of incubation at 95°C for 5 min, 95°C for 30 s, 60°C for 30 s and 72°C for 30 s and 72°C for 5 min (final extension) were the steps involved for DNA amplification. The 6  $\mu$ L product was digested with 0.3 unit of Nco-I restriction enzyme at 37°C for 1.20 h. The alleles were separated by 10% agarose gel electrophoresis and stained with 0.1% ethium bromide. Following electrophoresis, PCR products were visualized under ultraviolet light [Figure 6] and the images obtained were stored digitally for later analysis.<sup>[13]</sup>

### Statistical analysis

To determine whether any significant differences in polymorphism frequencies occurred between the cases and control populations and between the different forms of periodontitis, we compared allele and genotype frequencies, using the Chi-square method. A  $P = 0.05$  or less was set for significance. Odds ratio was calculated to assess the risk association of genetic factor with the occurrence of different periodontal diseases.<sup>[14]</sup>



**Figure 5:** Conventional polymerase chain reaction thermal cycler

## RESULTS

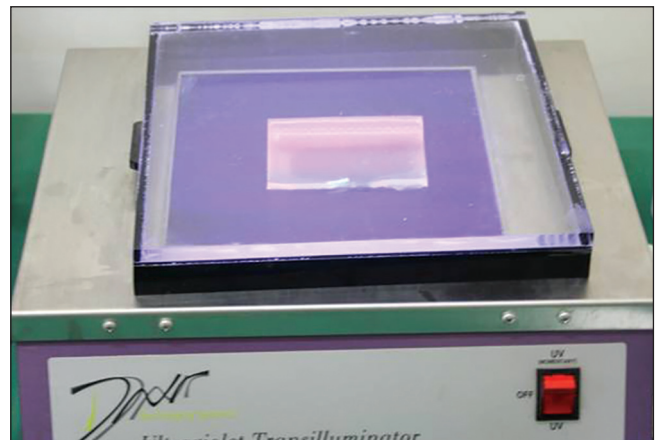
The baseline characteristics were analyzed in all 3 groups that reflect the extent and severity of periodontal destruction in patients. The mean age of the patients was  $44.63 \pm 8.8$  years in chronic periodontitis group and  $23.86 \pm 4.79$  years in aggressive periodontitis group. The mean oral hygiene index was  $3.7 \pm 0.86$  and  $3.25 \pm 0.30$  for chronic and aggressive periodontitis cases respectively. The CAL measured as distance from the cemento-enamel junction to the base of sulcus was  $4.29 \pm 0.63$  mm for chronic periodontitis and  $6.44 \pm 0.57$  mm for aggressive periodontitis [Table 2].

The relationship between 3 kinds of genotype of IL-1 $\alpha$ (-889) gene and periodontitis was calculated by determining their frequency distribution as shown in Table 3. In the control group: 40% had homozygous genotype 1,1; 40% had heterozygous genotype 1,2 and 20% had homozygous genotype 2,2. In aggressive periodontitis group: 10% had 1,1 genotype, 20% had 1,2 genotype and 70% had homozygous genotype 2,2 and in chronic

**Table 2: Baseline data and patient characteristics (mean  $\pm$  SD)**

Variables	Healthy	Chronic	Aggressive
Mean age (years)	34.93 $\pm$ 10.04	44.63 $\pm$ 8.8	23.86 $\pm$ 4.79
OHI	2.75 $\pm$ 0.37	3.7 $\pm$ 0.86	3.25 $\pm$ 0.30
GI	1.2 $\pm$ 0.33	2.2 $\pm$ 0.51	1.92 $\pm$ 0.24
CAL (mm)	Not determined	4.29 $\pm$ 0.63	6.44 $\pm$ 0.57

OHI: Oral hygiene index (Greene JC, Vermillion JR 1960); GI: Gingival index (Loe 1967); CAL: Clinical attachment level measured in millimeters; SD: Standard deviation



**Figure 6:** Polymerase chain reaction products visualization under ultraviolet light

periodontitis group 10% had 1,1 genotype, 60% had 1,2 genotype and 30% had 2,2 genotype respectively. Chi-square test was applied and it was observed that in aggressive periodontitis, homozygous genotype 2,2 was more predominant when compared to other groups and in chronic periodontitis, heterozygous genotype 1, 2 was more predominant when compared to others ( $P < 0.001$ ) [Table 4]. Hence, odds ratio for aggressive versus chronic periodontitis, was calculated as 6.2 (95% confidence interval 6.019-7.892) confirming, aggressive periodontitis patients have significantly increased odds of carrying genotype 2,2 than did chronic periodontitis patients. Furthermore, using “The Hardy-Weinberg Equilibrium,”<sup>[15]</sup> allele % was calculated for all 3 groups of patients and we obtained a predominant association of allele 2, with aggressive periodontitis (Allele 1-20% and Allele 2-80%) [Table 5].

## DISCUSSION

Aggressive periodontitis is a group of rare, often severe, rapidly progressive forms of periodontitis often characterized by an early age of clinical manifestation

**Table 3: Genotype distribution between different groups**

Genotypes	Control/healthy group (%)	Aggressive periodontitis (%)	Chronic periodontitis (%)
1,1	8 (40)	2 (10)	2 (10)
2,2	4 (20)	14 (70)	6 (30)
1,2	8 (40)	4 (20)	12 (60)

**Table 4: OR calculated to determine risk of disease development**

Statistical analysis	AGP versus control	CP versus control	AGP versus CP
Chi-squared analysis	$P < 0.001$ (HS)	$P < 0.001$ (HS)	$P < 0.001$ (HS)
OR	0.142	1	6.2
95% CI	0.135-0.1981	0.7-1.3	6.019-7.892

AGP: Aggressive periodontitis; CP: Chronic periodontitis; HS: Highly significant; CI: Confidence interval; OR: Odds ratio

**Table 5: Allele frequency in different groups (according to Hardy-Weinburg Equilibrium)**

Allele frequencies	Control (%)	Aggressive periodontitis (%)	Chronic periodontitis (%)
Allele 1	60	20	40
Allele 2	40	80	60

and a distinctive tendency for cases to aggregate in families. Evidence for the genetic background comes from segregation analyses of families with affected individuals in two or more generations for chronic, as well as, aggressive periodontitis.<sup>[16]</sup>

Results in different sets of families are consistent with autosomal-dominant<sup>[17]</sup> and autosomal-recessive inheritance,<sup>[18]</sup> as well as X-linked dominant inheritance.<sup>[19]</sup> Various polymorphisms have been investigated as possible markers of increased susceptibility for aggressive periodontitis that includes IL-1, IL-4, IL-10, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Fc receptors, human leukocyte antigen, vitamin D receptor and N-formylpeptide receptor.<sup>[20-22]</sup> Cytokines are of special interest in the contest of periodontitis due to their effective bone metabolizing and inflammatory properties.<sup>[13,23]</sup> IL-1 mediates the recruitment of inflammatory cells to the sites of infection, promotes bone resorption, stimulates the production of fibroblasts, induces the synthesis of prostaglandin E2 by macrophages and fibroblasts, stimulates the production of metalloproteinases that degrade extracellular matrix proteins and participates in the host immune response.<sup>[20]</sup>

Very few studies have been conducted in Indian population evaluating the role of such markers that plays such an important role in the pathogenesis of periodontal disease. In the present study, the patients with aggressive periodontitis and chronic periodontitis were compared with a group of systemically healthy samples. In previous studies, conflicting results have been presented regarding the relationship between the genotype of these genes and susceptibility to aggressive periodontitis in different populations. A study done by Kiani *et al.*<sup>[13]</sup> revealed significant linkage between allele 2 of IL-1 $\alpha$ -889 polymorphism and IL-1 $\beta$ -3953 polymorphism in patients of aggressive periodontitis. Similarly, Kornman *et al.*<sup>[6]</sup> in their study have reported that the presence of the allele 2 of the IL-1 $\alpha$  gene C-T nucleotide exchange at position -889 was associated with severity of periodontitis. Maria de Freitas *et al.*<sup>[20]</sup> did not obtain significant difference in allele distribution of IL-1 $\alpha$  (-889) and TNF $\alpha$  (-308) gene polymorphism in Brazilian aggressive periodontitis patients. Similarly, Li *et al.*<sup>[24]</sup> did not obtain any significant results for specific IL-1 genotypes and/or alleles to predict susceptibility to generalized aggressive periodontitis in Chinese population. Hamdy and Ebrahim<sup>[25]</sup> reported that the combination of IL-1 allele 2 (IL-1 $\alpha$  -889 and

IL-1 $\beta$ (+3954) in patients with inflamed periodontal or peri-implant tissues acts as a risk factor that leads to greater tissue destruction and may affect outcomes of treatment for peri-implantitis in genotype-positive individuals. Loo *et al.*<sup>[26]</sup> reported that cytokine gene polymorphisms may be used as a marker for periodontitis susceptibility, clinical behavior and severity and offers early diagnosis and induction of prophylaxis to other family members against disease progression. Karimbux *et al.*<sup>[27]</sup> concluded that IL-1 gene polymorphisms, most prominently IL-1 $\alpha$ (-889), IL-1 $\alpha$ (+4845) and IL-1 $\beta$ (+3954), have been associated with periodontitis in whites.

The results of the present study show that there is a significant increase in frequency of the IL-1 $\alpha$ (-889) genotypes containing the allele 2 (IL-1 $\alpha$ -889) with homozygous genotype 2,2 in aggressive periodontitis and allele 1 (IL-1 $\alpha$ (-889)1,1 and 1,2) in patients with chronic periodontitis, with a predominance of heterogeneity as compared to control group. IL-1 $\alpha$ -889 gene polymorphism has a predominant role in the pathogenesis of aggressive forms of periodontitis.

The differences in result of various researches attributed to risk for developing periodontal disease is not same for all individuals. Epidemiological surveys have shown that the prevalence of aggressive periodontitis varies widely among races, regions and countries. Mc Guire and Nunn<sup>[8]</sup> conducted a study and reported that IL-1 genotype-positive people are 2.7 times more likely to have tooth loss than genotype-negative people. Smokers are 2.9 times more likely to develop periodontitis and patients who are both IL-1 genotype positive and smokers are 7.7 times more likely to have tooth loss than non-smokers who are genotype-negative.<sup>[8]</sup> The study has proven that the variation in development of periodontitis in genotype positive individuals can be as a result of environmental factors. The present study is of particular importance as it attempts to study the genotype of IL-1 $\alpha$  alleles of aggressive periodontitis with chronic periodontitis and healthy subjects in Uttar Pradesh, India. Future implications for this study suggest the role of host genes in the etiology and pathogenesis of the periodontal diseases, which is just beginning to be understood. Genetic tests may prove useful for identifying patients who are most likely to develop disease, suffer from recurrent disease, or tooth loss as a result of disease.

## CONCLUSION

The results of the present study support a positive association between aggressive periodontitis and the presence of the IL-1 $\alpha$ -889, allele 2 polymorphism. Further researches are required to establish the role of host genes in the etiology and pathogenesis of the periodontal diseases.

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**How to cite this article:** Puri K, Chhokra M, Dodwad V, Puri N. Association of interleukin-1  $\alpha$  (-889) gene polymorphism in patients with generalized aggressive and chronic periodontitis. *Dent Res J* 2015;12:76-82.

**Source of Support:** Nil. **Conflict of Interest:** None declared.