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Genetic Predisposition to Persistent Apical Periodontitis

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Abstract

Introduction—The proinflammatory cytokine interleukin (IL)-1 is a key regulator of host responses to microbial infection and a major modulator of extracellular matrix catabolism and bone resorption. Allele2 of IL-1b is associated with a four-fold increase in IL-1 β production. The aim of this case-control study was to evaluate the gene polymorphism of IL-1 β in the pathogenesis of endodontic failure. We hypothesized that the gene polymorphism (allele2 of IL-1 β) would influence host response and enhance inflammatory reactions predisposing to persistent apical periodontitis (PAP).

Materials and Methods—Subjects with at least 1 year of follow-up after root canal therapy (RCT) were recalled. Inclusion and exclusion criteria were applied, and 34 subjects with signs/symptoms of PAP with otherwise acceptable RCT were included. Sixty-one controls showed healing with acceptable RCT. Genomic DNA from buccal mucosa was amplified by polymerase chain reaction followed by restriction fragment length polymorphism to distinguish the alleles of IL-1 β gene polymorphism.

Results—A significant difference in the distribution of the polymorphic genotype among cases (70.6%) and controls (24.6%) ($P < .001$, Pearson χ^2) was shown.

Conclusions—These findings suggest that specific genetic markers associated with increased IL-1 β production may contribute to increased susceptibility to PAP.

Keywords

Apical periodontitis; cytokines; genetic predisposition; genetic polymorphism; molecular biology

The ultimate goals of root canal treatment (RCT) are the complete healing of the periapical pathosis and the restoration of function. However, failure does occur despite all efforts and strict adherence to the principles of endodontic therapy in 14% to 16% of cases (1). Nair (2) defined apical periodontitis as a sequel to endodontic infection that includes a dynamic encounter between microbial factors and host defenses. Periapical pathology is a multifactorial disease (3) representing an interaction between a microbial challenge and immune response, which results in cytokine production and, ultimately, bone resorption.

Nair (1) reported that the local effects of interleukin (IL)-1 included enhanced leukocyte adhesion to endothelial walls, stimulation of lymphocytes, potentiation of neutrophils, production of prostaglandins and proteolytic enzymes, enhanced bone resorption, and

inhibition of bone formation. IL-1 β is the predominant form of interleukin found in human periapical lesions and their exudates (4–7), whereas IL-1 α is primarily involved in periapical periodontitis in rats (8, 9).

In humans, IL-1 β constitutes most osteoclast activating factor activity, reflecting both a high level of expression and biological potency (10, 11). It has been shown that IL-1 is approximately 500-fold more potent than tumor necrosis factor in stimulating bone resorption (11). This could be because of the amount of expression of suppressors of cytokine signaling proteins (12, 13).

Genetic factors influence inflammatory and immune responses in general, and individuals may respond differently to common environmental challenges. Such a differential response is influenced by the individual's genetic profile. Genetic polymorphisms are types of genetic variants that can contribute to complex diseases (14).

Pociot et al (15) reported that allele 2 of IL-1 β at +3953 was associated with a four-fold increase in IL-1 production. Kornman and di Giovine (16) documented an association between polymorphisms in the genes encoding IL-1 α (–889) and IL-1 β (+3953) and an increased severity of periodontitis. External apical root resorption during orthodontic treatment has a 5.6-fold increased risk in patients homozygous for the IL-1 β allele 1 (17). The resulting products of 85 bp + 97 bp fragments (allele 1) and a single 182-bp fragment (allele 2) are indicative of the gene polymorphism. Apical periodontitis of an endodontic origin shares similarities with periodontal disease such as similar microorganisms (*Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and so on); the periodontal ligament; neighboring spongiosa; and, ultimately, host response to an infectious condition. Can the same genetic profile influence persistent apical periodontitis, periodontal disease, and external apical root resorption? In 1997, Kornman et al (18) showed that specific genetic markers associated with increased IL-1 production are strong indicators of susceptibility to severe periodontitis in adults. They found that the composite genotype (allele 2 of IL-1 α and IL-1 β) was present in 78% of severe cases of periodontitis, 26% of moderate periodontitis, and 16% of mild periodontitis (odds ratio: severe vs mild = 18.9). Based on the strength of evidence from periodontal studies and the mechanisms of action of IL-1 β , the objective of this study was to investigate the relationship of genetic variations in IL-1 β and persistent apical periodontitis.

It was hypothesized that a polymorphism in the gene encoding IL-1 β , which is known to influence host response by enhancing inflammatory reactions, is associated with an increased risk of persistent apical periodontitis.

Materials and Methods

Recruitment of Subjects

This retrospective case-control study was designed to examine the potential association of a genetic polymorphism in the IL-1 β gene and persistent apical periodontitis Genetic Predisposition to Persistent Apical Periodontitis (PAP). The protocol was approved by the Institutional Review Board of Case Western Reserve University, and each subject signed a consent form after being advised of the nature of the study. Participants were recruited during the regular recall (follow-up) visits in the endodontic clinic at the Case School of Dental Medicine and from four private dental practices. Subjects over age 18 and in good general health who met the inclusion/exclusion criteria of this study were asked to voluntarily participate. Inclusion criteria were as follows: no obvious reason for root canal failure, single- or multiple-visit RCT, intracanal medicament used or not, and good general health.

Exclusion criteria encompassed patients younger than 18 years old, the presence of a microleakage (ie, open margin and faulty restoration), missed (unfilled) canals, separated instruments inside the canal, obturation more than 2 mm short from the radiographic apex, an overfilled or overextended canal filling, poorly condensed obturation, vertical root fracture, severe medical conditions (ie, cardiovascular illness, human immunodeficiency virus/AIDS, uncontrolled diabetes, immune or bleeding disorders, and radiotherapy or chemotherapy), and medications that affect inflammatory/immune reactions (ie, corticosteroids and long-term use of nonsteroidal anti-inflammatory drugs). One hundred-fifty patients were examined; 95 (63%) were eligible to take part in this study based on the inclusion/exclusion criteria. Four calibrated examiners applied these inclusion/exclusion criteria to each subject to determine eligibility. Subjects with persistent apical periodontitis or root canal failure with no obvious reason were assigned to the case group. Persistent apical periodontitis was defined as follows: (1) a lack of healing with apparently well-obtured root canal system(s) as determined by a radiographic examination, (2) RCT completed at least a year previously with signs and symptoms of pathosis, (3) the preexisting radiographic lesion remained the same size or increased in size, and (4) the presence of a clinical sign or symptom of periapical disease (ie, sinus tract, pain, and swelling).

Subjects who had RCT accomplished with no signs or symptoms of disease after at least one-year recall were assigned to the control group (healed group). The following criteria were used as practical ways to determine a successful healing outcome: (1) the absence of pain and swelling, (2) disappearance of the sinus tract, (3) no loss of function, (4) no evidence of tissue destruction, and (5) radiographic resolution of the lesion after a posttreatment interval of at least 1 year.

Each subject was evaluated by one or two calibrated examiners for clinical/radiographic signs or symptoms of PAP and classified accordingly (case/control). The periapical status was assessed using the periapical index (19). If the first examiner was not able clearly determine the periapical index, the second examiner was used to verify until consensus was reached.

During the recall visit, two radiographs of the endodontically treated tooth were exposed and intra-/extraoral examinations were performed to evaluate the tooth and or any patient complaints relating to the treatment. Recall radiographs were compared with the immediate postoperative ones. The presence of a periapical lesion after RCT and the persistence of any symptom after RCT were also abstracted as available from the charts or directly from the subject at the recall visit. There were 34 cases with PAP and 61 controls (healed group) in this study.

Analysis of Genetic Polymorphisms

To collect a sample for DNA analysis, the inside of the cheek was scraped with 10 strokes of a sterile nylon bristle brush (Gentra Systems, Minneapolis, MN). Genomic DNA was obtained from these samples using the Puregene DNA Purification Kit (Gentra Systems). The expected yield of DNA was an approximate concentration of 50 ng/ μ L. The DNA was stored at 4°C until genotyping was performed.

Genetic polymorphism analysis was performed by the modified method described by Al-Qawasmī et al (17). The polymerase chain reaction (PCR) for IL-1 β (+3954) gene amplification was performed using AccuPrime High Fidelity *Taq* DNA Polymerase (Invitrogen, Carlsbad, CA) using an Applied Biosystems 2720 Thermal Cycler (Applied Biosystems, Foster City, CA). A total of 1 μ L of DNA from each genomic DNA sample was used as template in a 50- μ L reaction mixture containing 2 μ mol/L forward primer (5'-CTCAGGTGTCCTCGAAGAAATCAA-3') and 2 μ mol/L reverse primer (5'-

GCTTTTTTGCTGTGAGTCCCG-3'). Conditions of PCR were as follows: 1 cycle at 94°C for 2 minutes; 38 cycles for 1 minute each as 94°C, 60°C, and 68°C; and a final cycle at 72°C for 8 minutes.

The PCR product (30 μ L) was digested with 2 μ L *TaqI* (New England Biolabs, Ipswich, MA) at 65°C for 3 hours and examined by polyacrylamide gel electrophoresis using Ready Gel 10% TBE (Bio-Rad Laboratories, Hercules, CA). After electrophoresis, each gel was stained with 0.2 μ g/mL ethidium bromide and visualized under ultraviolet light using KODAK 1D system (Scientific Imaging Systems, New Haven, CA).

Statistical Analysis

Chi-Square analysis and a *t* test were used to analyze the distribution of study factors between the case and control groups. Furthermore, a logistic regression analysis was performed to measure the strength of the association between IL-1 β polymorphism and the presence of persistent apical periodontitis adjusted for the presence of covariates.

Results

There were 34 cases with persistent apical periodontitis and 61 controls (healed group) in this study. The influence of genotype on the case group is evident in the frequency distribution that shows an increased prevalence of persistent apical periodontitis in the genotype comprised of allele 2 of IL-1 β polymorphism. Results showed (Table 1) a significant difference in the distribution of the polymorphic genotype (allele 2 of IL-1 β) among cases (70.6%) and controls (24.6%) ($\chi^2_1 = 17.2$, $P < .001$ [Pearson χ^2]). The polymorphic genotype was defined by the presence of at least one allele 2 in the genotype, which included all heterozygous and/or all subjects homozygous for allele 2. This classification was necessary because of the small number of subjects (7) homozygous for allele 2.

A strong association was observed between PAP (case group) and the presence of genotype comprising at least one allele 2 of IL-1 β polymorphism (crude odds ratio = 7.4; confidence interval, 2.9-18.8; $P < .001$) (ie, the presence of the polymorphism increased the risk of PAP seven-fold compared with those without polymorphism).

The logistic regression analysis was performed to measure the strength of the association between IL-1 β polymorphism and the presence of PAP adjusted for the presence of covariates. Subjects with at least one polymorphic allele (allele 2 of IL-1 β) were seven times more likely to develop persistent apical periodontitis compared with those with no polymorphism or homozygous for allele 1 (odds ratio = 7.6; confidence interval, 2.4-23.7; $P < .001$) even after adjustment for these covariates (Table 2). This implies that, after adjusting for covariates, the odds ratio did not change as compared with the crude odds ratio. Race, sex, age, and medical condition were included as covariates in the logistic regression model mentioned previously, and none of these factors were associated with an increased risk of outcome (PAP).

If genotypes were considered separately as homozygous 1 (wild type, both alleles 1), heterozygous, and homozygous 2 (both alleles 2), the crude (unadjusted) odds ratio would be 11.5 for homozygous 2 but with a wide confidence interval (Table 3). This is provocative preliminary evidence for a possible dose relationship that will need to be confirmed with larger studies and quantification of the gene product.

Discussion

Bacteria cause periodontal disease as well as apical periodontitis (20–23), but other factors may determine the severity of the disease and how a specific patient responds to therapy or pathogenic bacteria (24). Bacteria are still required to initiate the patient's inflammatory response, but other factors can modulate or amplify that inflammatory response to change the clinical presentation and the progression of disease (25–28). Smoking, diabetes, and genetic influences put certain individuals at a high risk for infection (26, 29). Numerous recent studies have begun to define and evaluate potential genetic contributions to the risk of developing adult periodontitis and other chronic inflammatory diseases. For example, the study by Kornman and di Giovine (16) examined IL-1 polymorphism in chronic periodontitis. The results indicated that, excluding smokers, a particular IL-1 allele was significantly associated with severe adult periodontitis. The results suggest that IL-1 genotyping and smoking history can be independent risk factors for periodontal disease.

By bringing this genetic perspective to endodontics, we investigated whether specific variants in this proinflammatory gene (allele 2 of IL-1 β) contribute to an individual's response to microbial challenge predisposing to complex multifactorial diseases as PAP. The findings of this study suggest that a specific genotype in the IL-1 β gene cluster is associated with an increased frequency of signs and symptoms after RCT. Thus, a genetic mechanism by which some individuals, if challenged by bacterial accumulations, may have a more vigorous immunoinflammatory response might contribute to the pathogenesis of PAP. This is the first report to describe a genetic marker that might identify people with an increased risk to PAP before the beginning of endodontic treatment.

The association of the IL-1 β genotype with PAP appears to connect multiple lines of research. It is notable that the IL-1 β polymorphism associated with PAP is also known to correlate with IL-1 β production rates *in vitro*. Monocytes from people homozygous for the IL-1 β +3954 allele 2 produce four-fold more IL-1 β and heterozygous cells produce approximately two-fold more IL-1 β than cells from those homozygous for allele 1 (wild type) (15). This increase in IL-1 production could contribute to perpetuating the inflammatory response found at the periapical area of a tooth even after RCT. Such quantitative *in vitro* evidence also aligns with the preliminary observation of an increased risk of PAP associated with both the homozygous allele 2 over the heterozygous condition compared with the wild type.

The results of this study are also in agreement with the findings of Kornman et al (18). In their study, Kornman et al showed that specific genetic markers associated with increased IL-1 production are a strong indicator of susceptibility to severe periodontitis in adults. They found that the composite genotype (allele 2 of IL-1 α and IL-1 β) was present in 78% in severe cases of periodontitis, 26% of moderate periodontitis, and 16% of mild periodontitis (odds ratio: severe vs mild = 18.9). Socransky et al (30) also suggested that in IL-1 genotype-positive patients (allele 2), the pieces will be in place for a more chronic persistent infection and resultant inflammation. Pociot et al (15) reported that a biallelic polymorphism of the IL-1 β gene at position +3954 resulted in the production of a greater amount of this cytokine by monocytes. De Sa et al (24) evaluated the influence of genetic polymorphisms on the development of symptomatic dental abscesses by investigating five functional gene polymorphisms: CD14, IL-1 β , IL-6, IL-10, and tumor necrosis factor- α . Their study suggested that genetic factors are associated with a susceptibility to develop symptomatic dental abscesses.

The clinical implication is that potential endodontic patients can be screened for the IL- β genotype by analyzing the DNA from a simple cheek swab to identify those who carry

copies of the high-risk allele (allele 2 of IL-1 β). It would then be possible to counsel patients about their predispositions before starting treatment.

Treatment modifications for those at a higher risk may include interappointment intracanal medications, closer monitoring and follow-up, or extraction. A more aggressive approach during and after RCT in those patients at risk may include preoperative antimicrobial rinses, increased apical preparation size (31) to mechanically reduce the number of microbians (32), and the inclusion of 2% chlorhexidine in combination with sodium hypochlorite to clean and shape the root canal system (33). Multivisits with the use of 7 to 10 days of calcium hydroxide as an intracanal medication (32, 34) may be considered for certain individuals. According to Ng et al (1), failure does occur despite all effort and strict adherence to the principles of endodontic therapy in 14% to 16% of cases. Patients should also be advised of the possible need for future apical surgery if healing is not achieved.

However, the limitations of the current study including the small sample size and the ethnic diversity in the pool of subjects need to be taken into consideration. The effects of those limitations are unknown and could have resulted in ambiguous results or maybe an even stronger association. Another limitation of this study is that only the IL-1 β polymorphism was analyzed. In the study performed by Kornman and Giovine (16), a composite genotype was evaluated. This composite genotype comprised polymorphism in both IL-1 α and IL-1 β to account for the severity of periodontitis.

The results of this study are not in agreement with other studies (35, 36). Siqueira et al (35) reported little to no association with polymorphism and posttreatment apical periodontitis. The differences could be explained by their smaller sample size with polymorphism in the gene encoding IL-1 β ($n = 16$) for the posttreatment disease, whereas ours was more than twice larger ($n = 34$). However, the authors did report that allele 1 (for IL-1 α and IL-1 β) was always detected higher in diseased than in healthy/healing individuals, but significance was not observed. Also, the authors reported that only individuals carrying both allele H131 and allele NA2 were highly associated with disease (87.5% of patients and 49% of controls, $P < .01$). A recent study by Burgener et al (36) did not report a significantly higher level of IL-1 β or dentin sialoprotein in the gingival crevicular fluid of teeth with apical periodontitis; the observed presence of a significantly higher level of total protein in the gingival crevicular fluid of diseased teeth suggested the possible role of the total protein level as a marker for periapical disease.

If we can understand the genetic basis of diseases, genetic tests to assess disease risk and to develop modifying factors for the treatments will soon be a reality. We may still be a long way from determining the genetic basis for PAP, but we may gain some insight into the understanding of how genetic polymorphism may influence host response.

In order to fully understand genetic factors in PAP, more formal genetic studies including a more rigorous association study design with an increased sample size, twin studies, segregation studies, and, ultimately, linkage analysis are required. Further studies might include transmission disequilibrium testing with parental DNA to detect excess transmission of the disease-associated genotypes to affected offspring.

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TABLE 1

Distribution of Study Factors among Cases/Controls

	Case n = 34 (35.8%)	Control n = 61 (64.2%)	Total n = 95 (100%)	P value
Age/Years				
Mean (+/-SD)	51.3 (17)	54.5 (12.8)		.36 T test
Sex				
Male (%)	14 (41.7)	17 (27.9)	31 (32.6)	
Female (%)	18 (52.9)	42 (68.9)	60 (63.2)	.17
NA (%)	2 (5.9)	2 (3.2)	4 (4.2)	Π^2
Race				
White	27 (79.4)	53 (86.9)	80 (84.2)	
Black	4 (11.8)	4 (6.6)	8 (8.4)	.4
Native American	3 (8.8)	4 (6.6)	7 (7.4)	Π^2
Medical condition (%)				
Any	13 (38.2)	29 (47.5)	42 (44.2)	.4
None	21 (61.8)	32 (52.5)	53 (55.8)	Π^2
Genotype (%)				
Wild type	10 (29.4)	46 (75.4)	56 (58.9)	<.001
Any polyallele	24 (70.6)	15 (24.6)	39 (41.1)	Π^2

TABLE 2Multivariate Logistic Regression Model for IL-1 β Polymorphism

	Odds ratio (adjusted)	95% Confidence interval	P value
Age/Years	1.0	0.95-1.0	.99
Sex			
Male	1.0		
Female	0.62	0.2-1.9	.42
Medical condition			
None	1.0		
Any	0.93	0.28-3.1	.90
Genotype			
Wild type	1.0		
Any polyallele	7.6	2.4-23.7	<.001

TABLE 3

Association of Homozygous Two Polymorphism with Cases

	Odds ratio	CI
n = 56, homozygous 1	1.0	
n = 32, heterozygous	6.7	(2.5-18)
n = 7, homozygous 2	11.5	(2.0-68)