Casey Hein, RDH, MBA

The IL-1 Polymorphism: The Role of Genetics in Differentiating Susceptibility to Periodontal Disease

CE

Abstract

It is now widely accepted that patients are not equally susceptible to periodontal disease and that not all cases of gingivitis will progress to periodontal disease. For those cases that do progress, the inception of disease and its rate of progression are influenced by many risk factors, such as smoking and diabetes, that predispose patients, and increase their rate of progression to periodontal disease. Given what we now know about this risk stratification, differentiating those patients at greater risk has become a cornerstone of nonsurgical periodontal therapy.

Assessing risk gives clinicians the information they need to customize aggressive treatment plans. Risk assessment also helps to provide more accurate prognoses. Although more clinicians are becoming familiar with how smoking and diabetes may influence the disease trajectory of periodontitis, few have integrated genetic predisposition to periodontal disease into their diagnostic and treatment planning decision making. Understanding how genetics may influence a patient's susceptibility to periodontal diseases is fundamental to customizing periodontal treatment plans. This article will review what it means to be genetically predisposed to periodontal disease, commonly called testing positive for the IL-1 polymorphism.

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Treatment plans that do not distinguish differential levels of susceptibility to periodontal disease may be missing a valuable piece of information—patients' genetic predisposition to periodontal disease. Variations (polymorphisms) in the interleukin-1 (IL-1) cluster of genes (IL-1 genotype) may alter a person's inflammatory response to periodontal pathogens and significantly increase the risk for severe disease.[1] Yet, in many practices across the country, even veteran clinicians are a little spooked about how to incorporate genetics into periodontal disease management strategies. As a result, many treatment plans are still based on the presumption that everyone is universally susceptible to periodontal disease.

Figure 1*—The multifactorial model of increased risk for severe periodontitis as a result of modifying factors.[2]

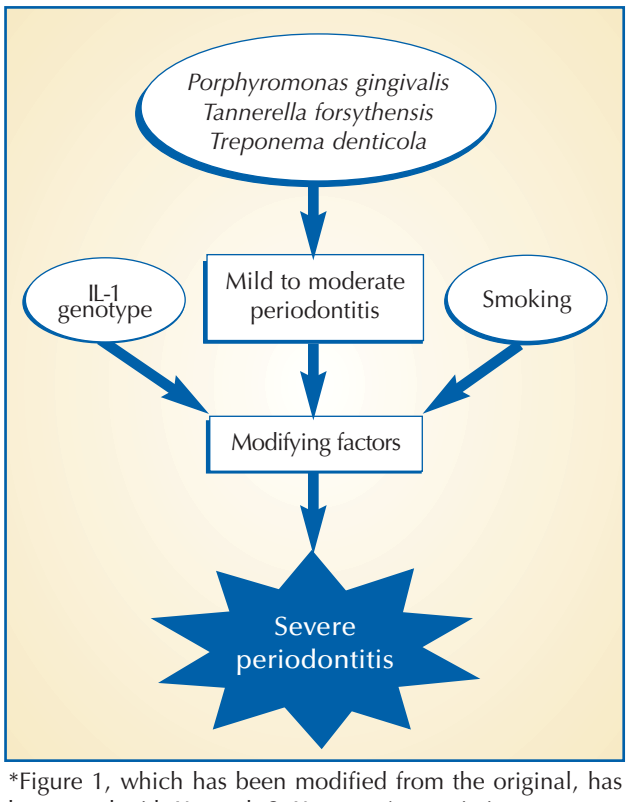


*Figure 1, which has been modified from the original, has been used with Kenneth S. Kornman's permission.

The December 2004 "Perio Pathways" column traced how the theory of periodontal disease etiology has evolved from the Calculus Theory before the 1960s to the Host-bacterial Interaction Theory, the predominate etiological theory currently recognized.[2] In short, the Host-bacterial Interaction Theory hypothesizes that chronic periodontitis is the result of a complex and multifactorial interaction between the host, periodontal pathogens, and genetic and environmental risk factors. The theory of universal susceptibility to periodontal disease has been abandoned for some time now.

Ken Kornman, DDS, PhD, internationally respected for his research in genetics and periodontal disease, explains how all these etiological pieces fit together: "The biggest advance in education relative to the knowledge of risk for periodontitis has been the widespread use of the multifactorial model of periodontal disease. This model basically says that although bacteria in the plaque are essential to the initiation and progression of periodontitis, the tissue destruction, and therefore the clinical severity of disease, is really determined by how the body responds to the bacterial challenge. A patient's response to the bacteria is the result of predictable biochemical processes that are shaped by genetic and environmental factors, such as smoking. Therefore, the clinical disease and response to therapy are the result of the bacterial challenge and the factors that influence the body's response. As this model becomes commonly used by practitioners, it will be a natural next step to think more about those risk factors that modify the tissue response" (KS Kornman, written communication, Oct 2004).

When Kornman describes genetic factors that influence the body's response to bacteria, he is referring to the IL-1 genotype, which is a specific genetic marker that identifies patients who have an increased risk of developing severe periodontal disease.[2] Chronic periodontitis, like many other common, chronic diseases, has certain modifying factors that do not directly cause the disease but do influence some aspect of the disease that makes the clinical condition more severe.[2] To that end, it is widely recognized that the IL-1 genotype and other risk factors, such as smoking and poor metabolic control of diabetes, do not directly cause periodontal disease, but do strongly influence the host's response to bacterial challenge, thereby modifying the severity of periodontal disease and its response to treatment (Figure 1).[3]

IL-1 and the Cascade of Destruction of Periodontal Disease

It is broadly accepted by the scientific community that there are 3 chemicals—IL-1, prostaglandin E_2 (PGE_2), and matrix metalloproteinases (MMPs), which are the enzymes that destroy collagen and bone—found in periodontal tissue that are the most consistently associated with severe or actively progressing disease.[4] All 3 of these chemicals are

Learning Objectives

After reading this article, the reader should be able to:

- explain how the IL-1 genotype may influence the response to bacterial challenge.
- describe the usage of the PST Genetic Test.
- describe the variations of the IL-1 among various ethnic populations.
- describe the relationship between the IL-1 genotype and smoking.

important mediators in regulating the inflammatory response and play a fundamental role in stimulating bone loss.[4]

IL-1 is a multifunctional cytokine that also upregulates both PGE_2 and MMPs in a sort of spiraling activity that results in progressive degradation of the periodontium.[4] This explains why studies have shown a direct relationship between advanced bone loss or progressive periodontitis and increased levels of IL-1 within gingival crevicular fluid or periodontal tissues.[4]

> IL-1 genotype-positive patients have more bleeding on probing.

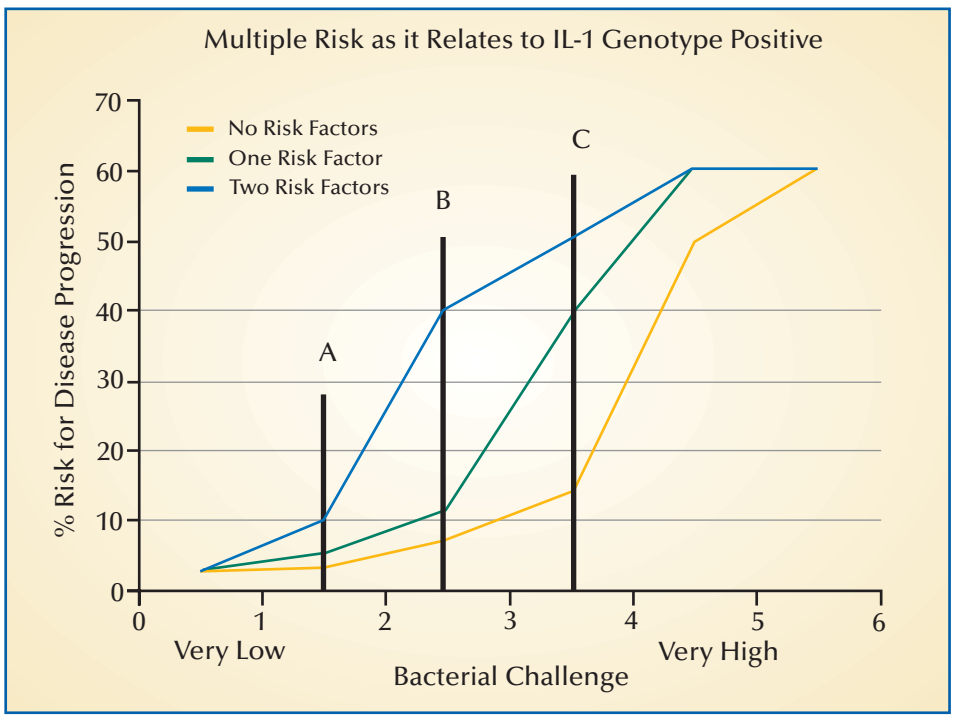
IL-1 and Amplified Inflammatory Response to Bacterial Challenge

There are 3 extensively studied IL-1 genes in a cluster on human chromosome 2q13. Two of these genes produce proinflammatory proteins—IL-1A produces IL-1α and IL-1B produces IL-1β.[1] The third gene, IL-1RN, produces a chemical that blocks the IL-1 receptor and acts as a naturally occurring regulator of IL-1 biological activity.[1]

When a person tests IL-1 genotype-positive, it means that the person has a variation in the IL-1A and the IL-1B genes.[2] Studies have shown these people produce significantly higher levels of IL-1 than genotype-negative people when exposed to bacterial challenge.[3] Furthermore, the tendency to be a high producer of IL-1 remains constant throughout the lifetime of a genotype-positive person.[3] In addition, high production of IL-1 tends to run in families.[5] The findings of other related research include:

- 67% of patients with severe periodontitis tested positive for the IL-1 genotype.[3]
- IL-1 genotype-positive patients have more bleeding on probing.[3]
- Severe periodontal disease in genotype-negative people may be most pronounced only after the age of 60, but may be present 20 years earlier in those who are genotype-positive.[1]
- Testing IL-1 genotype-positive is an especially strong predictor of severe disease in nonsmokers between the ages of 40 and 60.[1]
- For nonsmokers or former light smokers (<5 packs a year), genotype-positive people are more than 3 times likely to have moderate-to-severe periodontal disease than people who are genotype-negative.[4]
- In patients who were well-maintained but were both genotype positive and smokers, approximately 40% continued to show periodontitis progression, including tooth loss.[6]
- During periodontal maintenance, IL-1 genotype-positive people may be 2.7 times more likely to have tooth loss than genotype-negative people.[7] People who are both genotype-positive and also smoke may be 7.7 times more likely to have tooth loss than nonsmokers who are genotype-negative.[7]
- In considering treatment outcomes of guided tissue regeneration surgery 4 years after the surgery, 73% of the treated sites of genotype-negative patients remained stable compared with 21% of the genotype-positive patients.[8]

Figure 2*—Multiple risk relating to IL-1 genotype-positive.[11]



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- Genotype-positive people have a significantly higher proportion of subgingival periodontal pathogens recognized as being highly virulent (ie, organisms from the red or orange complexes) than genotype-negative patients.[9] The orange and red complexes of microorganisms are composed of a group of specific gram-negative organisms that are highly virulent and are strongly implicated as etiologic agents in chronic periodontitis; the red complex is the most virulent.[10] *Porphyromonas gingivalis, Tannerella forsythensis* (formerly *Bacteroides forsythus*), and *Treponema denticola* are the 3 periodontal pathogens in the red complex.[10] The colonization of the periodontal pocket by these microbial complexes give bacteria within them an ecological advantage over an isolated bacterial species because of the sophistication of the colonization process.[10]

Those who test positive for the IL-1 genotype overexpress the powerful cytokine, IL-1, and, as a result, experience an amplified immunoinflammatory response to periodontal infection, which puts them at greater risk for periodontal destruction.

Testing for IL-1

The PST (periodontal susceptibility test) Genetic Test (Interleukin Genetics, Inc, Waltham, Mass, www.ilgenetics.com/Kimball Genetics, Denver, Co, www.kimballgenetics.com) identifies patients who have specific variations in the IL-1A and IL-1B genes. Research indicates that patients who have this genetic profile may have a 3- to 7-fold increased risk for periodontal disease and a 3-fold increased risk for tooth loss.[11] The PST Genetic Test analyzes patient DNA from a noninvasive buccal swab collected with a soft brush at chairside by dentists or dental hygienists. The saliva samples, stable at room temperature, can be sent via regular mail. DNA analysis is usually complete within 1 to 2 days, at which time a detailed report that includes an explanation of the results to assist clinicians in customizing a treatment plan is faxed to the dentist.[11]

> The IL-1 genetic test is a risk assessment tool and not a diagnostic test.

Ethnic Variation in IL-1

Genetic susceptibility to severe periodontal disease appears to be different in various ethnic/racial populations. "The original IL-1 genetic test was developed in Caucasians and includes specific genetic variations that were optimized for that ethnic group. Approximately 30% to 35% of Caucasians will be positive for the current IL-1 genetic test. Far fewer people of Asian heritage, including Japanese, Chinese, and Korean, will be positive for the specific IL-1 genetic variations in the current test. Similar to Caucasians, those Asians who are positive for the IL-1 test are at increased risk for periodontitis. [There has been a recent report about] the discovery of new IL-1 gene variations that are found in a substantial number of Asians and appear to increase the risk for periodontitis. These new variations should increase the usage of the IL-1 test for non-Caucasian populations" (KS Kornman, written communication, Oct 2004).

The Influence of IL-1 on the Disease Trajectory

A positive PST result does not mean that a person will necessarily develop periodontal disease, the susceptibility to which is multifactorial and testing genotype-positive for the IL-1 polymorphism (PST-positive) does not exclusively determine whether a person will develop periodontal disease.[12] It is important to emphasize that the IL-1 genetic test is a risk assessment tool and not a diagnostic test.[12] As with any multifactorial disease, periodontal disease involves interactions between environmental factors and variations in multiple genes that yield different degrees of susceptibility.

Risk for disease severity increases with the addition of each modifying factor, yet as Kornman reasons, it will only be when a combination of risk factors reaches a critical threshold that the clinical signs of disease will occur.[12] There is no absolute certainty that a multifactorial disease, such as periodontal disease, will develop until this threshold is reached.[12]

"The multifactorial model of periodontitis explains why we see great variability among our patients. A roulette wheel provides an example of how multifactorial diseases operate. On the roulette wheel, there is a win zone and a lose zone. If you spin the wheel, you will win some percentage of the spins and lose some percentage. The major determinant of that percentage is the relative sizes of the win zone and the lose zone. If you think of risk factors as determining the size of the lose zone, the likelihood of losing each spin increases with the more risk factors one has (ie, the greater the likelihood of getting disease during a specific time period).

"With multifactorial diseases, no single risk factor, and not even all known risk factors combined, guarantees that one will get disease. Currently, it appears that patients with gingivitis or early periodontitis who do not maintain excellent plaque control are substantially more likely to develop moderate-to- severe periodontitis if they are smokers, diabetic, or have the IL-1 genotype" (KS Kornman, written communication, Oct 2004).

> Risk for disease severity increases with the addition of each modifying factor.

The Effect of Bacterial Challenge on IL-1

The degree to which the IL-1 genotype increases the risk of future disease progression depends on other risk factors and also the level of bacterial challenge.[12] This concept is best illustrated in Figure 2—the level of bacterial challenge is represented across the horizontal axis and the risk for periodontal disease progression corresponds to the vertical axis.[12] The curve depicted by the yellow line represents a patient who is a nonsmoker and who has tested genotype-negative for the IL-1 polymorphism. In this patient's scenario, it takes a moderately high level of bacterial challenge to detect change above a 10% increase in risk for disease progression.[12]

The green line represents a patient who is either a smoker or who is IL-1 positive, but not both. For this patient, the percentage increase in risk is very similar to the patient who is a nonsmoker and genotype-negative up to the point that the patient is challenged by a moderate level of bacteria.[12] When this patient has a moderately high level of bacterial challenge, there is a 40% increase in risk for disease progression.

A patient who is both genotype-positive and a smoker is depicted by the blue line.[12] Even with low and moderately low levels of bacterial challenge, this patient will experience amplified risk for periodontal disease progression; with moderate bacterial challenge, this person's risk for disease progression will be increased by 40%; with a moderate-

ly high level of bacterial challenge, that same person's risk will be increased by 50%.[12]

Another way to look at these relationships is to consider the area between points A and B where bacterial challenge is low.[12] In this situation, a single risk factor may lead to increased risk, but it often cannot be detected clinically.[12] When bacterial challenge is moderate (between points B and C), a single risk factor is likely to lead to increased risk for disease progression; a combination of smoking and being IL-1 genotype-positive will spike to an even greater increased risk. When bacterial challenge is high (to the right of point C), a single risk factor (smoking or being IL-1 genotype-positive) places a patient at extreme risk for disease progression.[12] At levels of bacterial challenge this high, it is unlikely that the addition of a second risk factor will result in any other amplification of risk.[12]

> "Perhaps the greatest value of knowing someone's risk factors is to help them prevent disease and its complications."

Administering the PST Genetic Test

The PST Genetic Test is a way to identify patients who are at higher risk for more severe periodontal destruction.[13] This kind of prognostic information is valuable because it may help dental hygienists determine which patients need to be referred to a periodontist. Kornman believes that the greatest use of the PST Genetic Test is in the hands of highly competent, scientifically grounded dental hygienists in general practice settings.[13]

"Perhaps the greatest value of knowing someone's risk factors is to help them prevent disease and its complications. The practitioners who are seeing most of the healthy and early disease patients are the obvious group to effectively use genetic risk factors to benefit their patients" (KS Kornman, written communication, Oct 2004). This seems to describe the dental hygienists who are aware of the new knowledge about who gets severe periodontitis (KS Kornman, written communication, Oct 2004).

Regarding dental hygienists who are dedicated to perfecting the outcomes of the nonsurgical periodontal care they render, Kornman advises that "For patients with gingivitis or early periodontitis who are smokers, diabetic, or IL-1 genotype-positive, the therapist should focus on bacterial control and management of the risk factors. If the patient's tissues do not respond predictably to good bacterial control, it may be appropriate to consider a test to better understand which specific bacteria may be involved" (KS Kornman, written communication, Oct 2004).

"The key elements of periodontal care are very clear today:

- Identify each patient's risk for the moderate-to-severe forms of chronic periodontitis.
- If a patient has none of the risk fac-

tors for more severe disease, reduce bacterial deposits on a regular basis and monitor the tissue response. We should expect great success with these cases.

- For those at high risk, the therapist should consider more intensive bacterial control and closer monitoring. If the high-risk patient does not show a predictable response to therapy, aggressive therapies should be considered, including local antimicrobials and host modulating drugs" (KS Kornman, written communication, Oct 2004).

Genetic Variations in IL-1

A tremendous amount of recent research has been published about chronic inflammation and its systemic effects. Even some consumer publications have picked up this information.[14] Many research studies have investigated a common set of genetic variations in the IL-1 gene and its association to increasing risk for such things as rheumatoid arthritis, polyarthritis, coronary artery disease, and inflammatory bowel disease.[15-18] Some of the research points to a direct link between the tendency to exhibit hyperinflammatory response as a result of a variety of host responses that go haywire, including a key genetic factor in this equation.[19]

Kornman explains the role that the IL-1 polymorphism may play in human disease relating to generating excessive inflammatory response or the hyperinflammatory response associated with C-reactive protein and other systemic conditions by saying, "The IL-1 gene variations are major determinants of an individual's lifelong inflammatory response. In studies published from the Mayo Clinic, individuals with certain IL-1 genetic variations were shown to have significantly higher levels of C-reactive protein and other inflammatory mediators. It does appear that IL-1 gene variations influence the risk for other diseases that have an inflammatory component, but it may not be the same IL-1 gene variations that increase the risk for periodontitis" (KS Kornman, written communication, Oct 2004).

> Research studies have investigated a common set of genetic variations in the IL-1 gene and its association to increasing risk.

The PST Genetic Test Controversy

Some researchers consider the PST Genetic Test controversial.[20] "It is to be expected that a concept as new as the role of genetic risk factors for chronic periodontitis will be uncomfortable to some. Many of us remember that the role of diabetes in periodontal disease was hotly debated from 1982 to the early 1990s. One factor that led to the controversy was that the techniques for studying disease modifying factors, such as diabetes, were not well understood. A similar situation exists today with the genetics of complex diseases. Today, there are more than 15 published studies that show a significant IL-1 genetic influence on the severity of chronic periodontitis, yet these studies are still very complicated for many readers to analyze and interpret" (KS Kornman, written communication, Oct 2004).

Conclusion

The best clinicians in nonsurgical periodontal care are abandoning cookie-cutter approaches to treatment of periodontal disease in favor of customized treatment plans that are more patient-specific. The most skilled clinicians also recognize when it's time to refer a patient to a periodontist. Recognizing that patients are not equally susceptible to periodontal disease is one of the hallmarks of a periodontal therapist because identification of patients in different risk categories with varying levels of periodontal disease severity is essential in formulating effective case management strategies and appropriate triage of care. The patient who presents with a risk profile of a smoker and who is also IL-1 genotype-positive will likely have a less favorable response to conventional treatment. The PST Genetic Test is a valuable tool for determining which patients may have this genetic trait associated with a hyperinflammatory response. COH

Disclosure

Kenneth S. Kornman, DDS, PhD, is a cofounder, chief scientific officer, and director of Interleukin Genetics Inc, which developed the PST Genetic Test.

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1. Variations in the IL-1 cluster of genes are called:
a. bimorphism.
b. monomorphism.
c. polymorphism.
d. trimorphism.

2. What is the predominate etiological theory currently recognized?
a. Calculus Theory
b. Gram-negative Spirochete Theory
c. Host-bacterial Interaction Theory
d. Universal Susceptibility Theory

3. IL-1, prostaglandin E_2, and matrix metalloproteinases are enzymes that destroy:
a. cementum.
b. collagen and bone.
c. enamel.
d. fibroblasts.

4. Which gene produces a chemical that blocks the IL-1 receptor?
a. IL-1A
b. IL-1B
c. IL-1AB
d. IL-1RN

5. In considering treatment outcomes of guided tissue regeneration surgery 4 years after the surgery, what percentage of the treated sites of genotype-negative patients remained stable?
a. 63%
b. 73%
c. 83%
d. 93%

6. The PST Genetic Test analyzes patient DNA from a:
a. noninvasive buccal swab.
b. large gauge needle stick.
c. small gauge needle stick.
d. minor biopsy.

7. As with any multifactorial disease, periodontal disease involves interactions between environmental factors and what that yield different degrees of susceptibility?
a. consistencies in individual genes
b. variations in individual genes
c. consistencies in multiple genes
d. variations in multiple genes

8. The degree to which the IL-1 genotype increases the risk of future disease progression depends on:
a. other risk factors only.
b. the level of bacterial challenge only.
c. other risk factors and also the level of bacterial challenge.
d. neither risk factors nor bacterial challenge.

9. Many research studies have investigated a common set of genetic variations in the IL-1 gene and its association to increasing risk for such things as:
a. coronary artery disease.
b. inflammatory bowel disease.
c. rheumatoid arthritis.
d. all of the above.

10. How many published studies show a significant IL-1 genetic influence on the severity of chronic periodontitis?
a. more than 15
b. more than 30
c. more than 45
d. more than 60

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