Interleukin-1 gene polymorphism in a Well-maintained periodontal patient population

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Abstract

Genetics is considered one of the systemic factors which modulates the host response to bacterial plaque. Individuals showing interleukin-1 gene polymorphism are more prone to develop moderate to severe periodontitis. The prevalence of genotype positive individuals has been estimated around 30% in different populations studied. We have determined a 26% prevalence in a Hispanic population. At the present, minimal information is available related to the response of genotype positive subjects to periodontal therapy. This study assessed restrospectively the response to periodontal treatment in a Hispanic population according to genotype polymorphism. 28 Hispanic subjects regularly maintained in a private practice after receiving comprehensive periodontal therapy, were tested for the interleukin-1 gene polymorphism applying the PST Genetic Test*. Full mouth gingival index, probing pocket depth and clinical attachment levels were recorded, as well as their age and smoking habit. Mean values were compared for genotype positive and negative subjects. Records were reviewed to establish an individual profile of the maintenance needs for each subject. The prevalence of genotype positive subjects was 28%. No differences were found in any of the parameters evaluated between genotype positive and negative subjects. No teeth were lost during maintenance (ranging from 4 to 30 years). However the maintenance demands of the genotype positive subjects were much more stringent, requiring shorter recall intervals, routine scaling and root planing and surgical retreatment almost on an yearly basis. Within the limits of this study it can be concluded that 1) periodontal health can be maintained after treatment in spite of genotype, and 2) genotype positive subjects require closer supervision and more surgical retreatments to achieve periodontal stability.

Key Words:
IL-1 genotype, genetic polymorphism, periodontitis, treatment response, Hispanic population.

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Introduction

Adult periodontitis is considered to be a multi-factorial disease. It is initiated by the accumulation of dental plaque harboring periodontopathic bacteria and conditioned in its manifestation by the host response, which is influenced by systemic, behavioral and environmental factors[11]. One systemic modifying factor is genetics.

Kornman et al reported in 1997 the presence of a genetic marker for the severity of periodontal disease. It relates to the presence of a polymorphism in the interleukin-1 gene. Genotype positive subjects are prone to develop more advanced periodontal breakdown at an earlier age, as a consequence of an over production of interleukin-1 when facing the bacterial challenge. In this article a prevalence of 30% positive individuals was reported in the studied population. Subsequent studies have reported similar values[6,8,10,15], with the exceptions of the Chinese[1] and African-American[14] populations. In the Hispanic population we have reported a prevalence of 26% of genotype positive subjects, which agrees with the prevalence in other ethnic groups reported.

Aside from prevalence reports very few studies have evaluated the response to therapy according to the individual genotype[4,10,12]. We have evaluated the response to mucogingival surgery in a group of 22 Hispanic patients who received a subepithelial connective tissue graft for the treatment of localized gingival recessions, and who otherwise had healthy periodontal conditions[3]. After 3 years post treatment, and routine preventive maintenance those patients presented similar overall periodontal conditions irrespective of their genotype. The amount of root coverage achieved was 3.0 mm in genotype positive subjects and 3.2 mm in genotype negative individuals. Those values corresponded to percentage coverages of 81% and 94% of the original recession. The difference was not statistically significant ($p = 0.71$). Thus we concluded that periodontal health could be maintained with proper maintenance irrespective of the genotype present and that the response to mucogingival surgery to cover localized gingival recessions was similar irrespective of the interleukin-1 periodontal genotype. However, while 100% of root coverage was achieved in 76% of negative genotype subjects, only 40% of genotype positive individuals showed similar results[3].

McGuire and Nunn[10] have reported that genotype positive subjects are 2.7 times more prone to tooth loss than negative subjects. Rotundo et al[12] evaluated 60 subjects with moderate to severe periodontitis for bone and tooth loss over a 10 year maintenance, according to genotype. No differences were found, concluding that, if a strict maintenance protocol was implemented, genotype positive patients could also be successfully treated. De Sanctis and Zucchelli[4] evaluated the impact of genotype on the outcome of guided tissue regeneration. Almost 80% of the genotype positive subjects lost more than 2 mm of clinical attachment over the 4 years of evaluation, as opposed to less than 30% of the genotype negative subjects.

The purpose of the present study was to assess retrospectively the response to periodontal treatment in a Hispanic dental population according to genotype polymorphism.

Material and Methods

Twenty-eight Hispanic subjects who have been maintained regularly in a private practice after receiving comprehensive conventional periodontal therapy were selected for this study. The sample included 12 males and 16 females with the mean age of 45.5 years old and a range from 25 to 66. They have been on maintenance in the same practice, for a mean of 12.5 years (ranging from 4 to 30 years). They had no systemic disease, which may affect the periodontal condition and had not received antibiotics for at least one year. They have been seen for maintenance 2 to 6 times a year, and they were originally treated for advanced periodontitis with periodontal probing depths of 6 mm and more.

The clinical examination included full mouth recordings of 1) gingival inflammation using the Gingival Index of Löe and Silness[19]; 2) probing pocket depth, and 3) clinical attachment levels both measured with a manual probe on six locations around each tooth.

The smoking habit of the subjects was also recorded. They were considered nonsmokers or smokers, irrespective of the number of cigarettes they smoke.

According to the instructions provided the PST Genetic Test was taken: The tip of the middle finger was cleaned with an antiseptic wipe. A finger stick was produced with a lancet and the finger was squeezed to promote bleeding. The blood was collected on each of the three DNA filter paper disks on the collection card, and a band-aid was applied to the finger. The blood sample was allowed to dry for several hours, after which the

collection card was closed, code identified and mailed for processing using PCR-based methodology.

Furthermore, reviewing the periodontal records, a profile of the individual maintenance regime was determined for each subject. Age, current and at the time of treatment, number of years on maintenance, recall interval, and maintenance therapy rendered beyond supportive prophylaxes, were recorded.

Mean values per patient were obtained for Gingival Index, probing pocket depth and clinical attachment levels. Overall mean values for Gingival Index, probing pocket depth, clinical attachment levels and age were determined for the genotype positive and genotype negative groups. The results were analyzed using the Mann-Whitney U test. Data were also evaluated for subjects 30 years and older, and whether they were smokers or nonsmokers.

Results

Out of the twenty-eight subjects examined 8 were genotype positive, given a prevalence of 28%. One genotype positive and 6 genotype negative individuals were smokers.

Table 1 presents the distribution of genotype positive and negative subjects according to the allele polymorphisms.

Table 1 - Distribution of Allele Polymorphisms According to Genotype

Genotype	Allele	Number(%)
Positive	IL-1A 1.2 IL-1B 1.2	6 (75%)
	IL-1A 2.2 IL-1B 1.2	2 (25%)
Negative	IL-1A 1.1 IL-1B 1.1	15 (75%)
	IL-1A 1.2 IL-1B 1.1	5 (25%)

Table 2 presents the mean age, Gingival Index, probing pocket depth and clinical attachment level values according to genotype. No statistical difference was found in any of the parameters evaluated.

Table 2 - Mean Age, Gingival Index, Probing Pocket Depth and Clinical Attachment Level Values According to Genotype

Genotype	N	Age*	G.I.*	P.P.D.*	C.A.L.*
Positive	8	43.8±11.1	1.08±.09	2.57±.28	3.17±.46
Negative	20	45.5±13.6	1.01±.13	2.37±.36	3.35±.84
Sig**		N.S.	N.S.	N.S.	N.S.

***** Mean ± standard deviation
* * Mann Whitney U test p > .05

Table 3 shows the mean values for age, Gingival Index, probing pocket depth and clinical attachment levels according to genotype for nonsmokers, 30 years old and older. No statistical differences were found. Similarly, no differences were found when only subjects 30 years old and older, or nonsmokers, were evaluated independently (data not shown).

Table 3 - Mean Age, Gingival Index, Probing Pocket Depht and Clinical Attachment Level Values According to Genotype for Non-smokers, 30 Years Old and Older

Genotype	N	Age*	G.I.*	P.P.D.*	C.A.L.*
Positive	7	45.0±11.3	1.09±.1	2.60±.28	3.18±.49
Negative	11	51,4±11.4	1.00±.1	2.28±.30	3.35±.96
Sig**		N.S.	N.S.	N.S.	N.S.

* Mean ± standard deviation
* * Mann Whitney U test p > .05

Tables 4 and 5 present a profile of each subject according to the maintenance demands and genotype.

A summary of those needs is presented in Table 6. Genotype positive subjects were on maintenance from 6 to 20 years. They were recalled every 2 to 4 months. One subject was seen every 2 months for 6 years while another patient was seen every 4 months for 9 years. The remaining were on a strict 3 months recall. All of them received routinely scaling and root planning and many surgical procedures during the maintenance. Genotype negative subjects were on maintenance from 4 to 30 years, and were seen every 4 to 6 months (7 every 4 months and 13 every 6 months). They received routine prophylaxes

with minimal scaling and root planing and no additional surgeries were performed. Irrespective of genotype, no tooth loss occurred during maintenance.

Table 4 - Individual Profiles and Maintenance Demands For Genotype Positive Subjects

N	Sex	Age		Years on Maint.	Smoking	Recall In Months	Treatment Beyond Prophylaxes		
		At Tx.	Now				SRP	# Surg	Distribution
1		30	38	8	N	3	Y	18	3 flaps/1st&2nd yr.
	F	46	66	20	N	3	Y	40	2 flaps/yr. One GTR
2	M	24	30	6	N	2	Y	6	1 flap/yr.
3	F								2 flaps/yr. after.
4	F	33	43	10	N	3	Y	10	1 flap/yr.
5	F	37	51	14	N	3	Y	28	2 flaps/yr.
									1 mth.recall/first 2 yrs.
6	F	26	35	9	Y	4	Y	4	1 flap every 2 yrs.
7	M	39	46	7	N	3	Y	8	2 flaps/yr years 1 to 4
8	M	32	41	9	N	3	Y	1	1 flap the 1st year.

Table 5 - Profiles and Maintenance Demands For Genotype Negative Subjects

N	Sex	Age		Years on Maint.	Smoking	Recall In Months	Treatment Beyond Prophylaxes
		At Tx.	Now				
1	M	30	37	7	N	4	Minimal SRP
2	M	48	70	22	N	6	Minimal SRP
3	F	33	39	6	Y	4	Minimal SRP
4	F	32	40	8	N	4	Minimal SRP
5	M	22	28	6	N	6	Minimal SRP
6	F	48	65	17	N	6	Minimal SRP
7	F	21	25	4	N	4	Minimal SRP
8	M	42	57	15	Y	6	Minimal SRP
9	F	28	48	20	N	6	Minimal SRP
10	F	32	50	18	N	6	Minimal SRP
11	F	30	38	8	N	6	Minimal SRP
12	M	27	57	30	N	6	Minimal SRP
13	F	35	65	30	N	6	Minimal SRP
14	M	22	26	4	N	4	Minimal SRP
15	M	32	52	20	Y	6	Minimal SRP
16	M	35	47	12	N	6	Minimal SRP
17	F	36	54	18	Y	6	Minimal SRP
18	F	36	48	12	N	6	Minimal SRP
19	M	22	26	4	N	4	Minimal SRP
20	F	31	38	7	Y	4	Minimal SRP

Discussion

It is being accepted that one of the multiple factors, which modulate the severity of the periodontal breakdown, is genetics. Subjects with a positive polymorphism affecting the interleukin-1 gene produce more severe periodontal destruction at an earlier age[7], show more bleeding on probing[8] and monocytes produce four times more interleukin-1 to the same bacterial challenge[5]. In most of the different ethnic populations studied the prevalence of genotype positive subjects has been reported around 30%[6,7,8,10]. We have reported a 26% prevalence in a Hispanic Mexican population[2].

Table 6 - Summary of Maintenance Needs According to Genotype

	Genotype Positive	Genotype Negative
Recall	2 to 4 months	4 to 6 months
Instrumentation	Routine scaling and root planing	Regular prophylaxes
Additional surgery	Flap for access at least once/year	None
Tooth loss	None	None

Limited evidence exists, however, related to the response of genotype positive subjects to conventional periodontal treatment. McGuire and Nunn[10] evaluated, using the PST Genetic Test, a subgroup of a patient population from a previous study on prognosis. They showed that genotype positive subjects were 2.7 times more prone to loose teeth than genotype negative subjects. However, in their study no mention was made of the degree of maintenance those patients received during supportive periodontal therapy. The results reported by Rotundo et al[12], De Sanctis and Zucchelli[4] and Caffesse et al[3] stressed the concept that stable results could be maintained, even in genotype positive individuals, if a strict maintenance protocol is implemented. It is evident, however, that genotype positive subjects are more prone to loose attachment during maintenance under routine conventional supervision. Sockransky et al[13] have reported that the proportions of "red" and "orange" complex species were significantly higher in deeper pockets of genotype positive than genotype negative subjects. This increase in the proportions of bacteria that are known to be strongly associated with periodontitis may be the reason for the potential relapse after treatment and may justify the need for more stringent maintenance procedures in genotype positive patients.

The present findings fully agree with the results discussed above. We assessed the genotyping of 28 subjects who have been under routine supportive therapy under the same care for periods ranging from 4 to 30 years. In this population 28% of genotype positives was found. The most common polymorphism in

genotype positive subjects was IL-1A=1.2 and IL-1B=1.2. 75% of the positive subjects showed this polymorphism. 75% of the negative subjects showed both genes with alleles 1.1.

When genotype positive and negative subjects were compared according to their mean age, gingival inflammation and periodontal parameters, no differences were found. Kornman et al[7] included in their original publication only subjects 30 years of age and older, nonsmokers. In our population, there were individuals younger than 30 years old and 6 were smokers. To assess whether the results of the analyses would be different the data were analyzed comparing smokers vs. nonsmokers, subjects 30 years and older, and 30 years and older nonsmokers, according to their genotype. No significant differences were found in any one of these assessments. In all these analyses, the mean level of gingival inflammation, the mean probing depth and the mean clinical attachment levels were similar for genotype positive and genotype negative individuals. Furthermore, no teeth were lost during maintenance.

These findings imply that it is possible to maintain a controlled periodontal condition for many years in spite of a genotype positive substrate. However, it needs to be emphasized that these patients have been under the maintenance of the same private periodontist after active therapy, and that the periodontist himself performed the maintenance therapy to his patients.

The question that follows is, of course, how much effort was it necessary to maintain healthy conditions in these patients? Does the genotype affect the maintenance needs? Reviewing Table 4 it is evident that while the maintenance of genotype negative subjects has been routine and uneventful, the maintenance of the genotype positive subjects required much more involved therapy with routine surgical retreatment on an yearly basis. They received from 1 to 40 surgical retreatments, with a mean number of 14 per subject. Since they have been on maintenance from 6 to 20 years, with a mean of 10 years per patient, the average number of surgeries received amounts to 1.4 per patient, per year of maintenance. However, as seen in Table 4 the number of surgical retreatments is not evenly distributed. It is worth mentioning that all the subjects evaluated had originally similar periodontal breakdown, with pockets equal or deeper than 6 mm and requiring resective periodontal surgery. As summarized in Table 6 while lls the genotype negative subjects have been recalled every 4 to 6 months, receiving regular prophylaxes with minimal scaling and root planing and no additional surgeries, the genotype positive subjects have been maintained with routine recalls every 2 to 4 months, with routine scaling and root planning by the periodontist and with 1 to 3 surgical areas for access per year. In essence, these findings indicate that while periodontal health can be maintained in genotype positive subjects, it may require closer supervision, more effort and surgical retreatment by the periodontist.

Conclusions

Within the limits of this study it can be concluded that:

1) Periodontal health can be maintained after treatment in spite of genotype.
2) Genotype positive subjects require closer maintenance recalls, and more surgical retreatments to achieve periodontal stability.

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