The Fcγ receptor III genotype as a risk factor for aggressive periodontitis in Korean patients

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I. Introduction

Aggressive periodontitis (AgP) represents an inflammatory disease with pathogenic features, such as onset in the juvenile or early adults years and severe and rapid destruction of periodontal tissue. It is now recognized that microbial factors can not solely be held responsible for AgP, although these are important in the initiation of periodontitis.[1] Genetically determined variance in host immune response bacteria has been identified in individuals with AgP. Many AgP (especially those with localized form) patients display defective neutrophil chemotaxis due to changes in chemotactic receptors or activation pathways.[2,3]

It was after only the Kormann's study4 on the genetic polymorphism of interleukin (IL) that many researchers were really being interested in the genetic factors and trying to find the scientific evidences of genetic factors that affect the pathogenesis of periodontitis. Since then, the wide spectrum of genes that might affect the progression of the peridontal disease, such as IL, tumor necrosis factor-α (TNF-α), Fcγ receptor (FcγR), vitamine D receptor, N- formyl receptor, matrix metalloproteinase (MMP) promoter, Toll-like receptor 2 (TLR2) and TLR4 have been studied for their role in the various types of periodontitis.[5]

Leukocyte receptors for the constant (or Fc-) part of immunoglobulins (FcR) link cellular and humoral branches of the immune systems, which are considered essential for host defense against periodontopathic bacteria. FcR for IgG (FcγR) may play a crucial role in the host defense against periodontopathic bacteria.[6-7] Three receptor

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subclasses (FcγRIIa, FcγRIIIa, FcγRIIIb) have been shown to be functionally polymorphic.[8,9]

FcγRIIa is the most widely distributed of the IgG receptor molecules. It is expressed on all granulocyte, antigen presenting cells (APC), platelets, endothelial cells and a subset of T cells.[9] The G to A transition polymorphism in the FcγRIIa gene at nucleotide position +392 results in the substitution of histidine (FcγRIIa-H131) for arginine (FcγRIIa-R131) at amino acid position 131 of the receptor molecule. This difference affects receptor affinity for IgG2.[9,10] FcγRIIa-H131 is considered the sole leukocyte FcγR capable of interaction with IgG2, a subclass which seems crucial for host defense against encapsulated bacteria.[10]

FcγRIIIa is found on monocytes and macrophages, natural killer (NK) cells and a subset of T cells.[9] The G to T transition polymorphism in the FcγRIIIa gene at the nucleotide position +559, results in the substitution of valine (V) for phenylalanine (F) at amino acid position 158 in the EC2 domain. FcγRIIIa-158V allotype exhibits higher affinity for both monomeric and immune complexed IgG1 and IgG3 than FcγRIIIa-158F does, and is capable of binding IgG4.[11,12]

The PMN-specific FcγRIIIb bears the NA1-NA2 polymorphism caused by 4 amino acid substitutions within EC1 Ig-like domain.[9,13] Both the FcγRIIIb-NA1, NA2 allotypes are capable of binding IgG1 or IgG3 opsonized particles, although the latter allotype interacts less efficiently with ligand than former.[14]

There are some reports that studied the relation between AgP and FcγR polymorphism.[15-17] but most of these researches were done among peoples of Northern European Caucasian[15] and African-American heritages[16]. Recently Kobayashi et al.[17] reported that In Japanese patients, the FcγRIIIb NA2 was associated with early onset periodontitis. Armitage et al.18 suggested that there might be ethical difference of the polymorphism.

It was the aim of this investigation to evaluate the prevalence of the genetic polymorphism of FcγRIII and their association with AgP in Korean patients

II. Material and Methods

1. Study Population

Forty-three Korean patients with AgP (30 males and 13 females; mean age, 31.8 years) referred to the Periodontal Department of Seoul National University Dental Hospital, and 90 race-matched healthy controls (64 males and 26 females; mean age, 27.5 years) was included in this study.

Based on the clinical and radiographic data, the patients were classified as AgP, according to the criteria described by Diehl et al.[19] and the one proposed in the 1999 American Academy of Periodontology (AAP) world workshop. Briefly, we defined AgP on the basis of disease onset up to 35 years of age with at least 8 teeth affected (>5mm in CAL), at least 3 of which were not first molars and incisors. Subjects who showed neither attachment loss nor PD>3mm at more than one site were classified as healthy controls. FcγRIII genotypes of healthy con-

trols have been previously published20 and were used in this study for comparison with those of AgP patients. Informed consent was obtained from all participants. None of the participants had a history or current signs of systemic disease.

2. Clinical Assessments

Clinical parameters including probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), supragingival plaque accumulation (PI, O'leary plaque control record method21) was assessed. Probing depth (PD) and clinical attachment level (CAL) were recorded using the Florida Probe® (Florida Probe Co., Gainesville, Fl. USA) in 6 sites of all existing tooth and they were categorized into 3 groups(<4mm, 4 to 6mm, and >6mm).

Smoking status of patients and controls was classified as either current smoker or not currently smoking, according to a standard questionnaire.

3. Isolation of genomic DNA and Genotyping

Genomic DNA was obtained from peripheral blood of the subjects by using a commercially available DNA extraction kit, (Puregen Gentra System, Minneapolis, MN) according to the manufacture's instructions. The genotyping was performed according to the previously described method by Kobayashi et al.17

(1) Fcγ RIIIa-158V-F.

FcγRIIIa-158V-F genotypes were determined by allele specific PCR previously described by Kobayashi et al.17 In brief, 3 primers were used for the detection of 1 base transition (nt 559-G/T). FcγRIIIa-specific forward primer (5'-TCA CAT ATT TAC AGA ATG GCA ATG G-3'; nt 449-473) was used in both nt 559 G- and T-specific PCR, the nt 559 G-specific reverse primer (5'-TCT CTG AAG ACA CAT TTC TAC TCC CTA C-3'; nt 586-559) was used for finding FcγRIIIa-158V allele, and the T-specific reverse primer (5'-TCT CTG AAG ACA CAT TTC TAC TCC CTA A-3'; nt 586-559) was used for finding FcγRIIIa-158T allele. PCR was performed with PCR premixture (Bioneer, Korea), 100 ng genomic DNA and 200 nM of each primer in a 50㎕ reaction volume starting with 95℃ for 9 minutes, 37 cycles at 95℃ for 30 seconds, 60℃ for 30 seconds, and 72℃ for 20 seconds, with a final extension at 72℃ for 10minutes, yielding a PCR product of 138bp. The PCR products were determined by electrophoresis on a 2% agarose gel stained with ethidium bromide.

(2) Fcγ RIIIb-NA1-NA2.

FcγRIIIb-NA1-NA2 genotypes were determined by allele specific PCR previously described by Kobayashi et al.17 In order to genotype for NA1, 100ng of genomic DNA was added to PCR premixture (Bioneer, Korea) with the sense primer (5'-CAG TGG TTT CAC AAT GTG AA-3'; nt 208-227) or the antisense primer (5'-CAT GGA CTT CTA GCT GCA CCG-3'; nt 329-349). PCR conditions were as follows: 1 cycle at 95℃ for 9 minutes, 35 cycles at 95℃ for 30 sec-

onds, 63℃ for 30seconds, and 72℃ for 30 seconds, ending at 72℃ for 10 minutes.

In order to genotype for NA2, primers were used: NA2 sense primer (5′-CTC AAT GGT ACA GCG TGC TT-3′; nt 128-147) and NA2 antisense primer (5′-CTG TAC TCT CCA CTG TCG TT-3′; nt 277-296). The amplification protocol was as follows: 1 cycle at 95℃ for 9 minutes, 35 cycles at 95℃ for 30 seconds, 64℃ for 15 seconds, and 72℃ for 30 seconds, ending at 72℃ for 10 minutes. After gel electrophoresis the end products of the reactions were 141 bp for NA1 and 169 bp for NA2, respectively.

4. Statistical Analysis

The x2 test was used to compare the FcγRIIIa, FcγRIIIb genotype distributions between patients with AgP and healthy controls (2x2 contingency table: AgP versus healthy control). The same test was performed to assess the role of the FcγRIIIa-158F, FcγRIIIb-NA2 alleles as a risk factor for AgP (2x2 contingency table: AgP versus healthy controls, FcγRIIIa-158F/F and FcγRIIIa-158V/F versus FcγRIIIa-158V/V or FcγRIIIb-NA2/2 and FcγRIIIb-NA1/2 versus FcγRIIIb-NA1/1; 2x2 contingency table: AgP versus healthy controls, FcγRIIIa-158V/158F, FcγRIIIb-NA1/NA2 allelic frequency in the absolute numbers of each allele). Moreover, the occurrence of the FcγR composite genotypes (FcγRIIIa 158F plus FcγRIIIb NA2 allele) was analyzed by the same test as above.

Table 1. Clinical Characteristics of subjects with control and AgP

Clinical Parameters	Control (n=90)	AgP (n=43)
Male/Female	64/26	30/13
Age (years)	27.5 ± 6.9	31.79 ± 3.83 *
Number of teeth	28.32 ± 1.63	28.05 ± 2.47
Number of missing teeth	0.40 ± 0.97	1.37 ± 2.14 *
Plaque index	42.84 ± 18.64	66.78 ± 17.31 *
Mean % BOP	11.64 ± 10.59	60.66 ± 15.56 *
Smoking/Non Smoking	21/69	21/22 *
Probing depth (PD) mm	2.06 ± 0.21	3.78 ± 0.74 *
% site of PD<4mm	100	57.14 ± 16.05 *
% site of PD 4-6mm	0	30.76 ± 11.25 *
% site of PD>6mm	0	12.10 ± 10.40 *
Clinical attachment level (CAL) mm	2.10 ± 0.22	4.15 ± 0.88 *
% site of CAL<4mm	100	50.47 ± 18.44 *
% site of CAL 4-6mm	0	32.71 ± 12.45 *
% site of CAL>6mm	0	16.82 ± 12.37 *

* Significantly different from control subject groups (P<0.01)

Differences in clinical parameter values between AgP and healthy controls were compared by Mann-Whitney U test. Significance was set at 95% (P<0.05).

III. Results

1. Clinical parameters

All subjects' clinical characteristic were shown in Table 1.

The control group showed significant difference with AgP in clinical parameters such as plaque index (PI) and mean % of bleeding on probing (BOP) (P<0.01). The mean probing depth, clinical attachment loss and the percentage of sites greater than 4mm in AgP were significantly higher than control (P< 0.01).

2. Distribution of Fcγ RIII Genotypes and Alleles

The distribution of FcγRIII genotype and allele frequency were shown in Table 2.

A significant differences was observed in FcγRIIIa genotype distribution between AgP and healthy control (Table 2; x2=12.737, P=0.002). However, in FcγRIIIb genotyping, both groups showed similar genotypes.

In FcγRIIIa 158V/F allele frequency, the allele frequency of FcγRIIIa-158F was higher in AgP patients as compared to controls, but there was no statistical significance among both groups (Table 2; x2=3.374 P=0.066). Smoking had been previously shown to be associated with serum IgG subclass concentrations.22,23. So, we evaluated FcγRIII genotype distribution in nonsmokers as well. A differences was observed in Fcγ

Table 2. Distribution of Fcγ RIII Genotypes and Alleles in AgP& Controls

		Control (n=90) Number (%)	AgP (n=43) Number (%)
FcγRIIIa			
Genotype*	158V/V	25 (27.78)	2 (4.65)
	158V/F	21 (23.33)	20 (46.51)
	158F/F	44 (48.89)	21 (48.84)
Allelic frequency	158V	71 (39.44)	24 (27.91)
	158F	109 (60.56)	62 (72.09)
FcγRIIIb			
Genotype	NA1/NA1	24 (26.67)	16 (37.21)
	NA1/NA2	53 (58.89)	19 (44.19)
	NA2/NA2	13 (14.44)	8 (18.60)
Allelic frequency	NA1	101 (56.11)	51 (59.30)
	NA2	79 (43.89)	35 (40.70)

* x^2=12.737 , P=0.002

RIIIa genotype distribution between AgP and healthy control, however, there was no statistical significance among both groups (Table3; Fisher's exact test, P=0.060).

We next assessed the carriage rate of FcγRIII alleles in patients with AgP and healthy controls. The percentage of subjects carrying at least 1 copy of FcγRIIIa-158F allele was significantly increased in the AgP as compared to the control groups (Table 2; AgP versus controls: 95.35% versus 72.22% x2=9.619, P=0.002). However, the other alleles carriage rates were not significantly different among the both groups.

The frequency of the composite genotypes comprising FcγRIIIa-158F and FcγRIIIb-NA2 was not significantly different among the both groups. (AgP versus control: 60.47% versus 53.33%, P>0.05)

IV. Discussion

In this study, the FcγRIIIa genotype distribution was significantly different between AgP and healthy controls. Also the carriage rate of FcγRIIIa-158F in AgP was significantly higher than healthy controls.

FcγRIIIa is expressed on NK cells, macrophages, and subsets of monocytes and γδT cells and is an important imunomodulatory molecule.24,25 Individuals who are homozygous for the FcγRIIIa-158V allele have a higher affinity for IgG1 and IgG3 than subjects homozygous for the FcγRIIIa-158F allele. Moreover, subjects carrying the FcγRIIIa-158V allele can bind IgG4 while those with FcγRIIIa-158F allele are unable to do so.8,9 FcγRIIIa-158V allele is proposed as a putative susceptibility factor for periodontitis, in particular for aggressive perio-

Table 3. Distribution of Fcγ RIII Genotypes and Alleles in AgP& Controls in Non-smokers

		Control (n=69) Number (%)	AgP (n=22) Number (%)
FcγRIIIa			
Genotype ‡	158V/V	21 (30.43)	2 (9.09)
	158V/F	19 (27.54)	11 (50.00)
	158F/F	29 (42.03)	9 (40.91)
Allelic frequency	158V	61(44.20)	15 (34.09)
	158F	77 (55.80)	29 (65.91)
FcγRIIIb			
Genotype	NA1/NA1	20 (28.99)	9 (40.91)
	NA1/NA2	39 (56.52)	8 (36.36)
	NA2/NA2	10 (14.49)	5 (22.73)
Allelic frequency	NA1	79 (57.25)	26 (59.09)
	NA2	59 (42.75)	18 (40.91)

‡ Fisher's exact test, P=0.060

dontitis in a group of Dutch patients.[15] Also, Meisel et al,[26] in a German population, studied FcγRIIIa polymorphism in relation to periodontitis severity; they observed more severe periodontal bone destruction in homozygous FcγRIIIa-158V allele patients (FcγRIIIa-158V/V). In a Japanese patients, It was found that FcγRIIIa-158F allele was over represented in patients with periodontal disease recurrence.[27] In contrast, another Japanese researchers reported that the FcγRIIIa-158V allele was over-represented in patients with severe periodontitis versus subjects with moderate disease.[28] In this study, a significant association was observed between the FcγRIIIa-158V/F polymorphism and AgP patients. Moreover, the FcγRIIIa-158F allele was more frequently detected in AgP over healthy controls.

FcγRIIIb is a neutrophil specific receptor and bears the functional NA1-NA2 polymorphism which determines IgG1- and IgG3-mediated neutrophil effector function.8,9 FcγRIIIb NA2 type receptor binds less efficiently with IgG1 and IgG3 immune complexes.[8,9] In Japanese patients, FcγRIIIb NA2 allele was associated with Generalized (G)-EOP[17] and was found more often in adult periodontitis with disease recurrence.[29] The combined carriage rate of both FcγRIIIb NA2 and FcγRIIIa-158F gene was more frequently detected in G-EOP over healthy controls.[17] In African Americans, an association between the FcγRIIIb and localized AgP has been found.16 However, In this study, no significant association was observed between the FcγRIIIb polymorphism and AgP.

Comparing with other ethnic groups, it is assumed that there was ethnical difference in the prevalence of genetic polymorphism in AgP (Table 4).

Smoking has been shown to be associated with increased disease severity of G-EOP.[30,31] So, we further analyzed the as-

Table 4. Carriage rate of the Fcγ RIIIa 158F allele

Reference	Ethnicity of subjects	Patients			Controls		Association
		Diagnosis	n	Carriage %	n	Carriage%	
Loos et al.(2003)	Caucasian	AgP/CP	68	**48**	61	**80**	+‡
Kobayashi et al. (2000)	Japanese	G-EOP	38	**90**	104	**90**	-
Fu et al. (2002)	African-American	L-AgP	48	**58**	67	**54**	-
This study	Korean	AgP	43	**95**	90	**72**	+
Carriage rate of FcγRIIIb NA2 allele							
Loos et al.(2003)	Caucasian	AgP/CP	68	**88**	61	**92**	-
Kobayashi et al. (2000)	Japanese	G-EOP	38	**83**	104	**64**	+
Fu et al. (2002)	African-American	L-AgP	48	**77**	67	**64**	+
This study	Korean	AgP	43	**63**	90	**73**	-

‡ FcγRIIIa 158V allele is associated with AgP

sociation of FcγRIII polymorphism and AgP risk in non-smoker subjects to exclude a possible confounding effect of smoking. A considerable differences was observed in FcγRIIIa genotype distribution between AgP and healthy control, however, there was no statistical significance among both groups (Fisher's exact test, P=0.060). Individuals carrying the FcγRIIIa 158F allele exhibited increased risk for AgP (AgP: 90.91%, Control: 69.54%, Fisher's exact test, P=0.032). These results further support the FcγRIIIa polymorphism as risk marker of AgP.

In our previous study, Shin et al.[20] reported that comparing the FcγRIII genotype distribution between severe chronic periodontitis (severe CP) and healthy control, there was statistically significant different in FcγRIIIa polymorphism. It is considered that FcγRIIIa polymorphism could have the possibility of risk factor of AgP susceptibility as well as disease severity in Korean patients. Most of study on the relation between AgP and FcγR polymorphism compared three groups: healthy control, AgP, adult periodontitis (AP).[15,17]. However, these study compared AgP with only health control. Further study of FcγRIII polymorphism in AP are needed to confirm our results.

Within the limit of our study, our results have shown that FcγRIIIa 158V/F polymorphism are associated with AgP risk in Korean subjects. It is also considered that the frequency of FcγR polymorphism in Korean patients is different from the other ethnic groups. Identification of this specific genetic risk factor in AgP susceptibility will aid diagnosis, treatment of AgP. Further studies of the other candidate genes, especially FcγRIIa, in Korean AgP are needed to extend to our results. These types of studies need to be large scale in consortium based approach.

V. References

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-Abstract-

한국인 급진성 치주염 환자의 위험요소로서 FcγIII 수용기의 유전형

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연구배경

IgG에 대한 Fcγ 수용기는 치주병인균에 대한 숙주 반응에 있어서 중요한 역할을 하는데, 이 중 FcγRIIIa는 NK 세포, 대식세포, 단핵구, γδT세포에서 발현되며, EC2 도메인에서 158 아미노산 부위의 valine (V)-phenylalanine (F)의 유전자다형성을 보인다. FcγRIIIb는 특이적으로 중성구에 발현되는데, extracellular (EC1) Ig-like 도메인 내 4개의 아미노산 치환(substitutions)에 의한 NA1-NA2 유전자다형성을 보인다.

이 연구의 목적은 한국인에서 급진성 치주염 환자와 FcγIII 수용기의 유전자다형성과의 관련성을 알아보는 것이다.

연구방법 및 재료

치주적으로 건강한 90명 (대조군, 남자 64명, 여자 26명)과 서울대학교 치과병원 치주과에 내원하여 급진성 치주염으로 진단된 환자 43명 (aggressive periodontitis patients: AgP, 남자 30명, 여자 13명)을 대상으로 하였다.

모든 실험 대상자는 임상 실험에 대해 동의 하였고, 초진 시 전자 탐침(Florida Probe® Co. Gainesville, FL)을 이용하여 탐침 시 치주낭 깊이 (PPD), 임상부착수준 (CAL), 치태지수(PI), 탐침 후 출혈지수(BOP)를 측정하였다. 또한 이들의 정맥혈에서 추출한 DNA를 PCR법, 전기영동법 등을 이용하여 FcγRIIIa, FcγRIIIb의 대립 유전자의 존재여부를 확인하였다. 이를 바탕으로 FcγRIII 복합 유전형을 확인하여 각 군 간을 비교하였다.

연구 결과

1. FcγRIIIa에 대한 유전자다형성 연구 결과 대조군과 급진성 치주염 환자 군(AgP)사이에서는 대립 유전자 분포가 서로 유의성 있는 차이를 나타내었고 ($P<0.05$), FcγRIIIb에서는 유의성 있는 차이를 발견할 수 없었다. ($P>0.05$)
2. FcγRIIIa 158F 대립형질이 급진성 치주염 환자에서 유의성 있게 많이 발견되어졌다. ($P<0.05$)

결론

이 연구를 통하여 FcγRIIIa 유전자의 분석이 한국인의 급진성 치주염에 대한 감수성의 위험요소의 표지자로 활용할 수 있을 것으로 사료되며, 향 후 더 많은 환자를 대상으로 하는 추가 연구가 필요하다고 생각된다.

주요어 : 한국인, 급진성 치주염, 유전자 다형성, FcγRIII