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Distribution of Fc Gamma Receptor IIa Genotypes among Malay Patients with Periodontitis

Research Article

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Abstract

Objective: To evaluate the distribution of Fc gamma receptor IIa (FcγRIIa) gene polymorphism and its possible association with periodontitis in Malay patients.
Materials and Methods: Periodontal parameters were recorded in 53 periodontitis and 65 healthy (control) subjects. Samples for genotype analysis were obtained from the buccal cheek mucosa. The FcγRIIa genotypes were determined via nested polymerase chain reaction by using sequence specific primers.
Results: The FcγRIIa R/H131 genotype showed the highest prevalence (56.6% in periodontitis and 50.8% in control) by which the H131 allele was slightly dominant in all subjects (51% in periodontitis and 52% in control). However, no significant association was observed between the periodontal parameters and FcγRIIa genotypes ($p>0.05$).
Conclusion: Within the study limitations, FcγRIIa R/H131 genotype was mostly distributed in Malay subjects. There is no significant association between FcγRIIa gene polymorphisms with periodontitis.

Keywords: Periodontitis; Fc Gamma Receptor IIa; Gene Polymorphism; Genotypes.

Introduction

Periodontitis is a chronic inflammatory disease affecting supporting tissues of teeth such as the gingiva, periodontal ligament, connective tissues, cementum and alveolar bone. Apart from bacterial biofilm as the local etiological factor, impaired host immune response towards bacterial infections also contribute to the disease initiation and progression. Some studies have proposed the idea of genetic risk factor and its subsequent relationship with periodontitis [1-3]. Genetic risk factors have been underlined as the causal chain or expose the host to the causal chain to develop periodontitis. In case of their absence, the possibility of developing the disease may be reduced [4].

Fc is the constant part of antibodies, whereby its receptors provide a crucial link between the cellular and humoral parts of the immune system that confers the potent effector functions to the antibody. In particular, immunoglobulin G (IgG) is the most dominant antibody class in the plasma in which receptors for IgG (FcγR) will trigger various effector functions such as phagocytosis, antibody-dependent cellular cytotoxicity, antigen presentation, cytokine release, degranulation, and regulation of antibody synthesis. FcγR is expressed in a wide variety of cells, including leukocytes from myeloid and lymphoid lineages, endothelial cells, placental tissue, and the synovial and mesangial cells. It is also found on a multitude of immune cells in the periodontal tissues [5].

In leukocytes, FcγR belongs to the immunoglobulin superfamily and may be categorised in three main classes of FcγRI (CD64); FcγRII (CD32); and FcγRIII (CD16). These classes are further subdivided into subclasses: FcγRIa and Ib; FcγRIIa, IIb and IIc; and FcγRIIIa and IIIb. When one or multiple FcγR-mediated leukocyte functions are compromised or exaggerated due to ge-

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netic polymorphism in the FcγR genes, susceptibility to and/or the severity of periodontitis are affected [4]. The structural and functional differences in FcγRIIa, FcγRIIIa and IIIb as a result of polymorphism in the genes have been described by many researchers [4, 6-11].

Normally, the binding of FcγRIIa with IgG2 bound to antigens results in phagocytosis, namely the killing of opsonised cellular target via antibody-directed cell cytotoxicity and respiratory burst [12]. FcγRIIa is the sole receptor on leukocytes that can interact with IgG2 [13]. Meanwhile, IgG2 provides the humoral response against polysaccharide antigens on the cell wall of Gram-negative periodontal pathogens such as *Aggregatibacter actinomycetemcomitans* [14]. In brief, efficient phagocytosis of pathogenic bacteria by phagocytes via IgG2-FcγRIIa interactions is crucial for the purpose of host defenses in periodontal infections.

The gene that codes for FcγRIIa has been known to have a single nucleotide polymorphism (SNP), which is determined by the presence of either histidine or arginine residue at the amino acid position 131. Conversely, different genotypes will affect the binding between the Fc part of the antibody IgG2 and opsonised antigen to the FcγR. Periodontitis patients who are homozygous for the H-allele (H/H 131 genotype) in FcγRIIa gene polymorphism have been linked to more periodontal bone loss compared to those carrying one or two R-alleles [9]. FcγRIIa genotypes have been particularly and significantly associated with a severe case of chronic periodontitis, while the homozygosity for the H-allele has resulted in a significant over-representation in periodontitis smokers [10]. Furthermore, Kobayashi et al. have observed that another genotype of FcγR, namely FcγRIIIa N-allele is over-represented in subjects with severe periodontitis compared to those with a moderate form of the disease [8]. Upon an assessment of a group of Dutch subjects, FcγRIIIa N-allele (V158) has been proposed as a risk factor for periodontitis, especially aggressive periodontitis [9].

Different ethnic backgrounds carry different prevalence of FcγR genotypes, which is a concept rooted based on previous studies conducted [15]. This is evidenced by the higher carriage rate of R-allele in FcγRIIa gene observed in Caucasians and African-Americans [9, 10]. In contrast, such rates are lower in Japanese population [8]. Meanwhile, to date, no information on the prevalence of FcγRIIa genotypes in periodontitis patients in Malaysia. Therefore, this study was conducted to determine the prevalence of FcγRIIa genotypes and their association with periodontitis among Malay subjects.

Materials and Methods

A cross-sectional study was conducted on 118 Malay patients attending the Dental Clinic, Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia. The criteria included were subjects aged 30 to 65 years old with at least of six teeth are present not including the wisdom teeth. The subjects were included if they were diagnosed with generalised periodontitis and presented with at least 30% (≥30%) of periodontal sites with probing pocket depths (PPD) greater than 3mm, and evidences of alveolar crestal bone loss in the orthopanthomogram radiograph (OPG) of 30% or more sites.

The control group includes subjects who matched the age range and had no evidence of periodontal disease. Those with uncontrolled medical problems, required prophylactic antibiotics prior to any dental procedures, pregnancy, and received antibiotics therapy within six months prior to the study were excluded. Subjects were informed about the study and written informed consent was obtained from each of them upon agreement of participation. Clinical parameters, such as number of missing teeth, plaque index (PI) [16], gingival index (GI) [17], probing pocket depth (PPD), clinical attachment loss (CAL), and alveolar bone loss (ABL) were subsequently recorded. The study protocol was approved by the Human Research and Ethics Committee, USM (USMKK/PPP/JEPeM [232.3.(04)].

DNA sample was collected from the buccal cheek mucosa by using a sterile swab stick. The samples were stored in a -20°C freezer until further use. Genomic DNA was isolated from the buccal cells swab according to the manufacturer's protocols with minor modifications post-optimisation (GeneAll™ Blood SV, GeneAll Biotechnology, Korea). The presence of DNA was ascertained via gel electrophoresis (1%) and viewed under the image analyser (Gel Doc™ XR+ System, Bio Rad, USA).

Determination of FcγRIIa gene polymorphisms was undertaken according to the Nested Sequence-Specific Primer-Polymerase Chain Reaction (SSP-PCR) with minor modifications after optimization [18]. The SSP-PCR method required the product obtained from the first PCR amplification to be re-amplified using a sequence specific primer. The primers for the first step of PCR were designed using a primer pair previously published [19] as follows:

i) sense primer P63 (5'-CAA GCC TCT GGT CAA GGT C) and,
ii) antisense P52 (5'-GAA GAG CTG CCC ATG CTG) primer

Meanwhile the second set of primers utilized, was designed by Carlsson et al. [18] as follows:

i) sense primers of P5G (5'-GAA AAT CCC AGA AAT TTT TCC G) or, P4A (5'-GAA AAT CCC AGA AAT TTT TCC A) – the allele-specific bases are in bold and inserted mismatch bases in the sequence are underlined.

ii) common antisense primer P13 (5'-CTA GCA GCT CAC CAC TCC TC).

The first PCR required approximately 100ng of genomic DNA, which was added to 25µL reaction mixes containing 50mM Tris (pH 8.4); 125mM KCl; 0.02mM $MgCl_2$; 0.05mM of each dNTP; and 0.4µM each of P63 (5'-CAA GCC TCT GGT CAA GGT C) and P52 (5'-GAA GAG CTG CCC ATG CTG) primers. The mixes also contained 0.025µM each of the CRP primers (440bp) (upstream: CCA GCC TCT CTC ATG CTT TTG GCC AGA CAG and downstream: GGG TCG AGG ACA GTT CCG TGT AGA AGT GGA) as the internal control and 0.025U of Taq DNA Polymerase (Invitrogen, Brazil).

PCR conditions employed were set at 1 cycle at 95°C for 5 min, 55°C for 5 min, and 71°C for 5 min. This was followed by 35 cycles of 95°C for 1 min, 60.4°C for 1 min, and 72°C for 2 min before ending with an extension step at 72°C for 10 min. The conditions for the second PCR were as detailed: 95°C for 5 min and

followed by 30 cycles of 95°C for 15 s 58°C for 30 s, and 72°C for 30 s, with an extension step at 72°C for 10 min. The PCR products were analysed via electrophoresis on 2% agarose gel stained with SYBR Green I Nucleic Acid Gel Stain. The FcγRIIa gene was observed at 278-bp and distinguished as homozygous or heterozygous accordingly by the presence or absence of the band. Meanwhile, the internal control was assessed at 440-bp and viewed under the UV imaging and documentation system (Gel DocTM XR+ System, Bio Rad, USA).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 20 for Windows. The descriptive data was expressed by mean and standard deviation (SD) and, frequency and percentage. The distribution of genotypes between the two groups was further analysed by using the Chi-square test. Furthermore, the association between the genotypes and periodontal parameters (i.e. number of missing teeth, PI, GI, PD, CAL, and bone loss) in the periodontitis group was assessed using the Kruskal-Wallis test as the data were not normally distributed. P values <0.05 at 95% confidence interval (CI) were considered statistically significant.

Results and Discussions

Overall, 118 subjects enrolled, 53 were periodontitis and 65 were control subjects by which females being the majority (71.20%). The mean age of periodontitis and control groups were 44.36 (SD8.19) and 36.06 (SD8.22) years old respectively. A portion of the periodontitis subjects (19%) recorded to have medical problems, such as hypertension, osteoarthritis and hypercholesterolemia, whereas only hypertension was noted in the control group (4.6%). However, the conditions were under-controlled. A small number of the periodontitis subjects (7.5%) and control (1.5%) were smokers. The general characteristics of the study subjects are shown in Table 1. All periodontal parameters were significantly difference ($p<0.05$) between periodontitis and control subjects (Table 2), thus justified the criteria for the control group.

This present study observed that the distribution of FcγRIIa heterozygous R/H131 appeared as the most prevalent genotype in the total subjects (53.4% out of 118 subjects) as seen in Table 3. The allelic frequencies of R131 and H131 alleles were found to be almost equally distributed in periodontitis (51%) and control subjects (52%). Consistently, the result shows periodontitis and control subjects revealed a higher frequency of heterozygous R/H 131 carrier (56.6% and 50.8%, respectively) compared to other

Table 1. General characteristic of chronic periodontitis and control subjects (n=118).

Characteristic	Chronic periodontitis (n=53)	Control (n=65)
Age in years (mean, SD)	44.36 (8.19)	36.06 (8.22)
Gender		
Male	22 (41.5%)	12 (18.5%)
Female	31 (58.5%)	53 (81.5%)
Medical problems		
Yes	10 (18.9%)	3 (4.6%)
No	43 (81.1%)	62 (95.4%)
Smokers		
Yes	4 (7.5%)	1 (1.5%)
No	49 (92.5%)	64 (98.5%)

SD, Standard deviation.

Table 2. Comparison of Clinical Parameters between Periodontitis and Control Group.

Variable	Periodontitis (n= 53) Mean (SD)	Control (n=65) Mean (SD)	Mean differ. (95% CI)	*t* statistic (df)	*P*-value
No. of missing teeth	5.0 (4.43)	2.0 (2.30)	3.57 (2.23- 4.91)	5.3 (74.1)	<0.001
Plaque index	1.27 (0.65)	0.52 (0.60)	0.76 (0.53- 0.99)	6.5 (116)	<0.001
Gingival index	1.40 (0.58)	0.28 (0.36)	1.12 (0.94- 1.30)	12.1 (83.6)	<0.001
Probing pocket depth (mm)	3.02 (0.81)	1.25 (0.29)	1.77 (1.54- 2.00)	15.1 (63)	<0.001
Clinical attachment loss (mm)	3.67 (1.33)	0.07 (0.07)	3.60 (3.23- 3.97)	19.7 (52.7)	<0.001
Bone loss more than 50% of root length	11 (11.50)	0	11 (8- 14)	7 (52)	<0.001

Table 3. FcγRIIa genotypes and alleles distribution in periodontitis and control group.

Variable	n	Periodontitis Frequency (%)	Control Frequency (%)	χ^2statistic† (df)	P value
Genotype					
H/H131	28	12 (22.6)	16 (24.6)	0.424 (2)	0.809
R/H131	63	30 (56.6)	33 (50.8)		
R/R 131	27	11 (20.8)	16 (24.6)		
Allelic frequency					
R131	115	52 (49)	63 (48)	0.404 (2)	0.817
H131	121	54 (51)	67 (52)		

†Chi-square test for independence

Table 4. The association of periodontal parameters with different genotypes in periodontitis subjects (n=53).

Variables	H/H131 (n=12) Median (IQR)	R/H131 (n=30) Median (IQR)	R/R131 (n=11) Median (IQR)	X^2 statistic (df)‡	P value
No. of missing teeth	5 (7)	3 (7)	5 (8)	0.85 (2)	0.654
Plaque index	1.48 (1.23)	1.02 (0.43)	1.38 (1.21)	1.41 (2)	0.494
Gingival index	1.55 (0.93)	1.33 (0.67)	1.33 (0.96)	0.94 (2)	0.624
Probing pocket depth (mm)	2.38 (1.24)	3.00 (1.3)	3.44 (0.47)	3.92 (2)	0.141
Clinical attachment loss (mm)	3.19 (1.76)	3.31 (1.38)	3.58 (1.68)	3.04 (2)	0.219
Sites with alveolar bone > 1/2 of root length	9 (22)	6.5 (13)	9 (19)	0.54 (2)	0.762

‡Kruskal-Wallis Test; IQR, Interquartile range

FcγRIIa genotypes. Such genotypic prevalence is in agreement with the local findings by Yap and co-workers among healthy and systemic lupus erythematous patients [11]. We also showed that there was no significant difference of genotype distribution between the periodontitis and control subjects (p=0.809).

This current study shows that FcγRIIa gene polymorphisms were not found to be significantly associated with the periodontal parameters i.e. number of missing teeth, PI, GI, PPD, CAL, and ABL (Table 4). PPD and CAL were slightly higher in the R/R 131 genotypes, although not by a significant value. In terms of bone loss evaluation, the amount of sites having severe bone loss of more than half of root length was found to be almost equally presented among the three genotypes. In contrast with previous study in Chinese Han population, the frequency of genotype R/R131 was suggested as one of the contributors for the increased susceptibility of severe periodontitis as it was found to be significantly higher ($P < 0.0125$) compared to their healthy patients [20]. The prevalent of R/R genotype also have been demonstrated by the study on Iranian population with periodontitis and peri-implantitis [21].

A study done among the Taiwanese population showed that the genotypes with at least one R-allele in the FcγRIIa gene polymorphism were over-presented in the generalised aggressive periodontitis subjects [22]. The study on South Indian population resulting in similar findings, with the R-allele being more prevalent in the population and was also significantly over-presented in aggressive periodontitis subjects [6]. A subsequent study on the same population but incorporating generalised periodontitis subjects had further found over-representation of R/R genotype [7]. Nevertheless, an insignificant difference in the distribution of genotypes in periodontitis and healthy control subjects was seen, which was consistent with the current study.

It was suggested that the measurement of in-vitro activity of FcγRIIa genotypes may not be related to the severity of the diseases as speculated, such as the hyper-responsive PMNs with FcγRIIa H/H131 genotype [12]. Both H131 and R131 alleles were almost equally present in periodontitis and control subjects, although H131 was slightly over-represented in this study. Furthermore, it was reported that the H131 allele was associated with poor receptor binding with IgG2 immune complex *in-vitro* [23]. Such feature could possibly explain the less severe pattern of periodontal destruction observed. However, another previous study assessing Caucasian smokers showed that the carriage rate of FcγRIIa H/H131 genotype was enriched and associated with more severe periodontal breakdown [10]. The work also concluded that the H/H 131 genotype and smoking had a synergistic effect. With respect to the population in this current study, a very small number of the periodontitis patients and controls were current smokers, thus rendering the association unjustifiable.

Genetic polymorphism studies aimed to evaluate the association with periodontal disease have been reported with having inconsistent findings. This is predictable due to the variations in ethnic

groups, limited sample sizes, variable definitions used to define the disease, and covariates and risk factors that needed adjustments. Genotyping of FcγRIIa gene in periodontitis subjects have been conducted in some Asian countries. The distribution of FcγRIIa genotypes in a Malay population with periodontitis has never been reported despite existed in other populations. In Malaysia, the prevalence of these gene polymorphisms were demonstrated in a study of Malay patients in relation to systemic lupus erythematosus [11].

The results of the current study revealed a low carriage rate of the genotype expressing the hyper-responsive receptor-IgG2 binding. This is suggestive of the population being studied requiring more and further research into other modifiable risk factors, such as the plaque control process and efficiency. By controlling the modifiable risk factors, it will be possible to strongly suggest the non-modifiable risk factors (e.g. genes) to be the main contributing aspect of severe or advanced periodontal destruction, provided the finding is found to be significant.

Conclusion

Within the study constraints, FcγRIIa R/H 131 genotype was shown to be prevalent in Malay subjects. Nonetheless, the genotypes distribution across both groups and FcγRIIa gene polymorphisms were not significantly associated with periodontitis. However, the findings on this genotype may serve as a baseline data for Malay population. It is recommended an extensive future study with a larger sample size that will justify the current findings.

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