DNA AND CELL BIOLOGY
Volume 33, Number 4, 2014
© Mary Ann Liebert, Inc.
Pp. 227–233
DOI: 10.1089/dna.2013.2202

Relationship Between *IL1* Gene Polymorphisms and Periodontal Disease in Japanese Women

Keiko Tanaka,[1] Yoshihiro Miyake,[1] Takashi Hanioka,[2] and Masashi Arakawa[3]

Epidemiological evidence on the relationship between *IL1A* and/or *IL1B* polymorphisms and periodontal disease is inconsistent. We investigated associations between three *IL1* single-nucleotide polymorphisms (SNPs) in genes encoding interleukin (IL) -1α (rs1800587) and IL-1β (rs1143634 and rs16944) and the risk of periodontal disease among young Japanese women. A case–control study was performed with a total of 1150 women, including 131 subjects who had at least one tooth with a probing pocket depth of 4 mm or deeper and 1019 periodontally healthy controls. Compared with a reference group of women with the GG genotype of SNP rs16944, those with the GA genotype had a significantly reduced risk of periodontal disease, while there was no significant relationship between the AA genotype and periodontal disease. No evident relationships were observed between SNP rs1800587 or rs1143634 and periodontal disease. Our study did not reveal any evidence of interaction between the *IL1* polymorphisms and smoking. The results of this study showed that the heterozygous variant genotype of the *IL1* rs16944 was significantly associated with a reduced risk of periodontal disease in young Japanese women. Smoking did not significantly modify the gene–disease associations under study.

Introduction

Periodontal disease is a chronic inflammatory condition initiated by pathogenic microflora in the biofilm or dental plaque, which accumulates in the gingival crevice region (Pihlstrom *et al.*, 2005; Stabholz *et al.*, 2010; Zhang *et al.*, 2011). This inflammatory response of the periodontal tissues to infection is influenced by environmental factors and by genetic factors (Stabholz *et al.*, 2010).

Periodontal disease is characterized by loss of connective tissues within the periodontium and destruction of alveolar bone support. As it is accepted that the immune system plays an important role in the pathogenesis of periodontal disease, most genes that are considered to be responsible for the development of periodontal disease are also linked to the immune response (Stabholz *et al.*, 2010). Interleukin (IL) -1 cytokines are key mediators of immune responses, inflammation, and tissue destruction in periodontal disease (Barksby *et al.*, 2007). Thus, the genetic control of the cytokine function may affect the appearance or the severity of periodontal disease (Nikolopoulos *et al.*, 2008).

Many previous studies have examined the association between *IL1* polymorphisms and periodontal disease. However, the results have been inconsistent. Some studies have found that *IL1A* and/or *IL1B* polymorphisms are associated with periodontal disease (Kornman *et al.*, 1997; McDevitt *et al.*, 2000; Parkhill *et al.*, 2000; Cullinan *et al.*, 2001; Meisel *et al.*, 2002; Meisel *et al.*, 2003; Li *et al.*, 2004; López *et al.*, 2005; Moreira *et al.*, 2005; Agrawal *et al.*, 2006; Moreira *et al.*, 2007; Guzeldemir *et al.*, 2008; Shete *et al.*, 2010; Trevilatto *et al.*, 2011), while others have found no associations between these polymorphisms and periodontal disease (Tai *et al.*, 2002; Soga *et al.*, 2003; Droździk *et al.*, 2006; Sakellari *et al.*, 2006; Maria *et al.*, 2007; Kiani *et al.*, 2009).

To date, two meta-analyses evaluated the association between *IL1* polymorphisms and periodontal disease (Nikolopoulos *et al.*, 2008; Karimbux *et al.*, 2012). A recent meta-analysis of 13 studies limited to Caucasians found significant associations between *IL1A* (rs1800587 or rs17561) and *IL1B* (rs1143634) polymorphisms and chronic periodontal disease (Karimbux *et al.*, 2012). Another meta-analysis of 53 studies performed in 2008 indicated that *IL1A* (rs1800587) polymorphism was associated with periodontal disease in Caucasians, but not in Asians, while *IL1B* (rs1143634) was associated with periodontal disease in Asians, but not in Caucasians (Nikolopoulos *et al.*, 2008). On the other hand, a recent systematic review by Laine *et al.* (2012) concluded that polymorphisms in the *IL1* gene cannot be considered risk factors for periodontitis susceptibility.

[1]Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan.
[2]Department of Preventive and Public Health Dentistry, Fukuoka Dental College, Fukuoka, Japan.
[3]Health Tourism Research Center, Graduate School of Tourism Sciences, University of the Ryukyus, Okinawa, Japan.

It is necessary to accumulate further evidence to clarify the impact of *IL1* polymorphisms on periodontal disease.

The aim of the present study was to investigate associations between one *IL1A* single-nucleotide polymorphism (SNP), namely, rs1800587 (C-889T), and two *IL1B* SNPs, namely, rs1143634 (C+3954T) and rs16944 (C−511T), and the risk of periodontal disease among young Japanese women, using the data set of the Kyushu Okinawa Maternal and Child Health Study (KOMCHS). In addition, haplotype analyses were performed, and the possibility of interactions between the SNPs and smoking was investigated. It is important to accumulate evidence on risk factors of periodontal disease among young women to prevent future development of the disease.

Materials and Methods

Study population

The KOMCHS is an ongoing prospective prebirth cohort study that investigates risk and preventive factors for maternal and child health problems such as oral health and allergic disorders. The KOMCHS requested that pregnant women complete a baseline survey, which was followed by several postnatal surveys. Eligible subjects were women who became pregnant in one of seven prefectures on Kyushu Island in southern Japan or Okinawa Prefecture between April 2007 and March 2008. At 423 obstetric hospitals, a set of leaflets explaining the KOMCHS, an application form to participate in the study, and a self-addressed and stamped return envelope were distributed to pregnant women, insofar as this was possible. Pregnant women who intended to participate in the KOMCHS returned the application form to the data management center. In the end, a total of 1757 pregnant women between the 5th and 39th week of pregnancy gave their fully informed written consent to participate and completed the baseline survey. Of these 1757 women, 1591 mothers participated in the second survey after birth. Of these 1591 mothers, 1198 women received oral examinations post partum. Around 4 months after delivery, 1492 mothers gave informed consent to genotyping. The present study was restricted to women who both received oral examinations and provided genetic samples, a total of 1157 subjects. The Ethics Committee of the Faculty of Medicine, Fukuoka University approved the KOMCHS.

Selection of cases and control subjects

Oral examinations for periodontal tissue condition were performed by dental hygienists. Probing pocket depth (PPD) was determined with a CPI probe (YDM Corp., Tokyo, Japan) at six sites per tooth for six teeth: the right first molar, right first incisor, and left first molar in the maxilla and the right first molar, left first incisor, and left first molar in the mandible. When the target tooth was missing, the second molar in the same side or the first incisor in the opposite side was examined. The deepest PPD was recorded for each tooth. Periodontal disease was defined as positive if a woman had at least one tooth with a PPD of 4 mm or deeper.

Among the 1157 women, 131 cases of periodontal disease were identified using this definition. The 1026 remaining participants were eligible to serve as control subjects, but seven women were excluded because of missing data on the factors under study; thus 1019 women were classified as control subjects.

Questionnaire

In the baseline survey, each participant filled out a questionnaire and mailed it to the data management center. Research technicians completed missing or illogical data by telephone interview.

The questionnaire in the baseline survey included questions about smoking habits, household income, education, toothbrushing frequency, and use of an interdental brush.

DNA extraction and genotyping

Research technicians or subjects themselves collected buccal specimens with BuccalAmp swabs (Epicenter Bio-Technologies, Madison, WI). Genomic DNA was extracted using a QIAmp DNA mini kit (Qiagen, Inc., Valencia, CA). Genotyping of *IL1* SNPs was performed using TaqMan SNP Genotyping Assays on a StepOnePlus machine (Applied Biosystems, Foster City, CA), according to the manufacturer's instructions.

Statistical analysis

Departures from the Hardy–Weinberg equilibrium were tested among the control subjects using the chi-square test. Linkage disequilibrium was examined using Haploview software version 4.2 (Broad Institute, Cambridge, MA) (Barrett *et al.*, 2005). Estimations of crude odds ratios (ORs) and 95% confidence intervals (CIs) for periodontal disease associated with the SNPs under study were made by means of logistic regression analysis, with the reference category being the homozygote of the major allele. Because the homozygote of the minor allele of rs1800587 and rs1143634 was infrequent (the number of control subjects with the homozygote of the minor allele of rs1800587 and rs1143634 were 9 and 2, respectively. And cases with the homozygote of the minor allele of rs1800587 and rs1143634 were not observed in the present study), the comparison was made between the homozygote of the major allele and the combination of the heterozygote and the homozygote of the minor allele (dominant model). Multiple logistic regression analysis was used to control for age at oral examination, region of residence, education, smoking, toothbrushing frequency, and use of interdental brush. The statistical power calculation was performed using QUANTO version 1.2 (Gauderman, 2002). Haplotypes and their frequencies were inferred according to the expectation maximization algorithm. For differences in haplotype frequency between the cases and control groups, crude ORs and 95% CIs were estimated based on the frequency of each haplotype relative to all other haplotypes combined.

We examined multiplicative interaction between the SNPs under study and smoking with regard to the risk of periodontal disease. The multiplicative interaction was estimated by introducing a multiplicative term into a multiple logistic regression model. Excluding the calculation of linkage disequilibrium and statistical power, all statistical analyses were performed using STATA/SE software version 12.0 (StataCorp, College Station, TX).

Results

The characteristics of cases and controls are shown in Table 1. Compared with control subjects, cases were more likely to live in a prefecture other than Fukuoka in Kyushu. There were no differences between cases and control subjects with regard to age at oral examination, education, smoking, toothbrushing frequency, or use of an interdental brush.

Among our control subjects, the genetic distributions of *IL1* SNPs rs1800587, rs1143634, and rs16944 did not deviate from the Hardy–Weinberg equilibrium ($p = 0.85$, 0.64, and 0.53, respectively). Of the three SNP pairs, two pairs were in strong linkage disequilibrium: D' between rs1800587 and rs1143634, and D' between rs1143634 and rs16944 were 0.95 and 0.83, respectively (Table 2).

No evident relationships were observed between SNP rs1800587 or rs1143634 and periodontal disease under the dominant model (Table 3). With respect to SNP rs1800587, the statistical power calculation revealed that, using our sample size, we could detect the gene–disease association for an OR of 0.449 with an accuracy of more than 80% at a significance level of 0.05 with a two-sided alternative hypothesis under the dominant model. In the multivariate model, compared with a reference group of women with the GG genotype of SNP rs16944, those with the GA genotype had a significantly reduced risk of periodontal disease, while there was no significant relationship between the AA genotype and periodontal disease: the adjusted OR for the GA genotype was 0.62 (95% CI: 0.40–0.96) (Table 3).

According to a general agreement, when subjects who were heterozygous or homozygous with mutated alleles (A) at both SNPs rs1800587 and rs1143634 were designated as ''genotype-positive,'' no evident relationship was observed between the genotype-positive and periodontal disease; the adjusted OR for the genotype-positive was 0.69 (95% CI: 0.30–1.58).

When haplotypes with a frequency of less than 1% in either case or control subjects were deleted, four haplotypes remained; however, none of these were significantly related to the risk of periodontal disease (Table 4).

We did not find that smoking significantly modified the gene–disease associations under study (Table 5).

Table 1. Characteristics of the Study Population

Variable	n *(%)*		
	Cases (N = *131*)	*Controls* (N = *1019*)	p-*Value*[a]
Age, years, mean ± SD	32.9 ± 4.1	32.3 ± 4.2	0.94
Region of residence			< 0.0001
Fukuoka prefecture	52 (39.7)	679 (66.6)	
Other than Fukuoka Prefecture in Kyushu	76 (58.0)	238 (23.4)	
Okinawa prefecture	3 (2.3)	102 (10.0)	
Education, years			0.47
< 13	23 (17.6)	211 (20.7)	
13–14	50 (38.2)	338 (33.2)	
≥ 15	58 (44.3)	470 (46.1)	
Smoking			0.21
Never	86 (65.7)	723 (71.0)	
Ever	45 (34.4)	296 (29.1)	
Toothbrushing frequency, times/day			0.32
< 2	17 (13.0)	131 (12.9)	
2	58 (44.3)	518 (50.8)	
≥ 3	56 (42.8)	370 (36.3)	
Use of an interdental brush			0.30
No	64 (48.9)	547 (53.7)	
Yes	67 (51.2)	472 (46.3)	

[a] χ^2 test or *t*-test.

Table 2. Pairwise Linkage Disequilibrium of *IL1* Polymorphisms (r^2 Below and D' Above the Diagonal)

	rs1800587	*rs1143634*	*rs16944*
rs1800587		0.95	0.03
rs1143634	0.35		0.83
rs16944	0.00	0.02	

Discussion

We observed that the GA genotype of *IL1B* SNP rs16944 was significantly associated with a reduced risk of periodontal disease. A case–control study of Chinese men (100 cases and 92 controls) showed that there was a positive association between the heterozygote of SNP rs16944 and periodontal disease (Li *et al.*, 2004). Three other previous studies regarding the association between SNP rs16944 and periodontal disease observed no significant association among Japanese adults (47 cases and 97 controls, 64 cases and 64 controls) (Tai *et al.*, 2002; Soga *et al.*, 2003) or a Dravidian population (97 cases and 101 controls) (Shete *et al.*, 2010). On the other hand, a study in a Brazilian population showed that the T allele at rs16944 was positively associated with periodontal disease in the group of blacks and mulattos, but not in the group of Caucasians (Trevilatto *et al.*, 2011). These results are at variance with the current findings.

In the present study, there were no significant associations between SNPs rs1800587 or rs1143634 and periodontal disease. These results are in agreement with those of previous studies that found no relationships between SNPs rs1800587 or rs1143634 and periodontal disease (Tai *et al.*, 2002; Soga *et al.*, 2003; Li *et al.*, 2004; López *et al.*, 2005; Droździk *et al.*, 2006; Sakellari *et al.*, 2006; Maria *et al.*, 2007; Kiani *et al.*, 2009; Trevilatto *et al.*, 2011), but they are at variance with those of previous studies showing significant associations between either of the two SNPs and periodontal disease (Parkhill *et al.*, 2000; López *et al.*, 2005; Moreira *et al.*, 2005; Agrawal *et al.*, 2006; Moreira *et al.*, 2007; Guzeldemir *et al.*, 2008; Shete *et al.*, 2010).

Regarding the *IL1* genotype-positive (the presence of the T allele at both SNPs rs1800587 and at rs1143634), we observed no significant association between the *IL-1* genotype-positive and periodontal disease. Kornman *et al.* (1997) reported a positive association between the *IL1* genotype-positive and periodontal disease among nonsmokers, but not in smokers. Since then, the effect of the composite genotype on periodontal disease has been relatively extensively researched (McDevitt *et al.*, 2000; Meisel *et al.*, 2002; Meisel

Table 3. Odds Ratios and 95% Confidence Intervals for Periodontal Disease Associated with *IL1* Polymorphisms in Japanese Women

SNP	*Genotype*	n *(%)*		*Crude OR (95% CI)*	*Adjusted OR (95% CI)*[a]
		Cases (n = *131*) n *(%)*	*Controls,* (n = *1019*) n *(%)*		
rs1800587	GG	114 (87.0)	843 (82.7)	1.00	1.00
	GA + AA	17 (13.0)	176 (17.3)	0.71 (0.42–1.22)	0.68 (0.39–1.18)
rs1143634	GG	123 (93.9)	946 (92.8)	1.00	1.00
	GA + AA	8 (6.1)	73 (7.2)	0.84 (0.40–1.79)	0.76 (0.35–1.65)
rs16944	GG	45 (34.4)	284 (27.9)	1.00	1.00
	GA	54 (41.2)	518 (50.8)	0.66 (0.43–1.00)	0.62 (0.40–0.96)
	AA	32 (24.4)	217 (21.3)	0.93 (0.57–1.51)	0.78 (0.47–1.30)

[a]Adjusted for age at oral examination, region of residence, education, smoking, toothbrushing frequency, and use of an interdental brush. CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

et al., 2003; Li *et al.*, 2004; López *et al.*, 2005; Agrawal *et al.*, 2006; Sakellari *et al.*, 2006). Nevertheless, there are conflicting results. Several studies have observed a positive association between genotype-positive and periodontal disease (McDevitt *et al.*, 2000; Cullinan *et al.*, 2001; Meisel *et al.*, 2002; Meisel *et al.*, 2003; López *et al.*, 2005; Agrawal *et al.*, 2006), while other studies have reported no association (Li *et al.*, 2004; Sakellari *et al.*, 2006).

The inconsistency of our findings compared with those of some previous studies may be at least partly explained by differences in the genetic backgrounds of the populations examined, definitions of periodontal disease, and statistical power.

IL-1 is a potent proinflammatory mediator that is mainly released by monocytes, macrophages, and dendritic cells. Levels of IL-1 have been found to be increased in gingival crevicular fluid of periodontal patients (Preiss and Meyle, 1994; Honda *et al.*, 2006). In an *in vitro* study, SNP rs1143634 was associated with a higher production of IL-1β from monocytes (Pociot *et al.*, 1992). The allelic variations in the *IL1* locus might be expected to have an impact on periodontal disease. Recently, however, no significant association was found between the presence of polymorphisms in the rs1143634 and rs17561 (in linkage disequilibrium with rs1800587) and IL-1β concentration in gingival crevicular fluid (Bascones-Martínez *et al.*, 2012; Yücel *et al.*, 2013).

Table 4. Haplotype Analysis of Three *IL1* Polymorphisms Associated with Periodontal Disease in Japanese Women

Haplotype[a]	*Frequency,* n *(%)*		*Crude OR (95% CI)*[b]
	Cases (2N = 262)	*Controls (2N = 2038)*	
GGG	137 (52.3)	986 (48.4)	1.17 (0.90–1.52)
GGA	107 (40.8)	865 (42.4)	0.94 (0.71–1.23)
AGA	8 (3.1)	82 (4.0)	0.75 (0.31–1.58)
AAG	5 (1.9)	68 (3.3)	0.56 (0.18–1.40)

Rare haplotypes (frequencies less than 1% in either cases or controls) were deleted.

[a]Haplotype order is rs1800587, rs1143634, and rs16944.

[b]Crude OR for each haplotype is relative to all other haplotypes combined.

There is no ready explanation of the underlying mechanisms for the observed significant inverse association between the heterozygosity of rs16944 and periodontal disease. It has been observed, however, that the heterozygosity of rs16944 was associated with a reduced risk of asthma in Finish men, but not in women (Karjalainen *et al.*, 2002). In addition, a study of meningococcal disease in England and Wales showed that the heterozygosity of rs16944 has a protective effect against severe manifestations of meningococcal disease (Read *et al.*, 2000). Thus, the heterozygosity of rs16944 might offer some advantage in several diseases of an inflammatory or infectious nature.

The current study had methodological advantages: study subjects were homogeneous in gender and age group and several confounders were controlled for. In the present study, oral examinations were performed between 1 and 12 months postpartum (66% occurred between 3 and 5 months postpartum). During pregnancy, susceptibility to periodontal infection increases due to immunological and hormonal changes (Mascarenhas *et al.*, 2003). Pregnancy-related changes are most frequent and most marked in gingival tissue. However, these gingival changes usually resolve within a few months of delivery if local irritants are eliminated (Laine, 2002). Thus, our study subjects are unlikely to be unduly affected by pregnancy.

Important weaknesses in the present study should be taken into consideration. First, the participation rate cannot be calculated because the exact number of eligible pregnant women who were provided with the abovementioned KOMCHS documents is not available. In addition, we were not able to assess differences between participants and nonparticipants, because information on personal characteristics such as age, socioeconomic status, and periodontal status among the nonparticipants was not available. Our subjects were probably also not a representative sample of Japanese women in the general population. As an example, educational levels were higher in the current study population than in the general population. According to the 2000 population census of Japan, the proportions of women aged 30 to 34 years in Fukuoka Prefecture with < 13, 13–14, and ≥ 15, and an unknown number of years of education were 52.0%, 31.5%, 11.8%, and 4.8%, respectively (Statistics Bureau, Ministry of Public Management, Home Affairs,

Table 5. Association Between *IL1* Polymorphisms and Periodontal Disease, Stratified by Smoking History in Japanese Women

		Smoking history				
		No (n = 809)		*Yes (n = 341)*		
SNP	*Genotype*	*No. cases/ controls*	*Adjusted OR (95% CI)*[a]	*No. cases/ controls*	*Adjusted OR (95% CI)*[a]	p *for interaction*
rs1800587	GG	74/593	1.00	40/250	1.00	
	GA + AA	12/130	0.68 (0.35–1.32)	5/46	0.68 (0.25–1.89)	0.88
rs1143634	GG	81/671	1.00	42/275	1.00	
	GA + AA	5/52	0.70 (0.26–1.89)	3/21	0.87 (0.24–3.22)	0.92
rs16944	GG	30/202	1.00	15/82	1.00	
	GA + AA	56/521	0.64 (0.39–1.06)	30/214	0.82 (0.41–1.66)	0.92

[a]Adjusted for age at oral examination, region of residence, education, toothbrushing frequency, and use of an interdental brush.

Posts and Telecommunications, 2002). The corresponding figures for the current study in the control group were 20.7%, 33.2%, 46.1%, and 0.0%, respectively. In addition, according to the Survey of Dental Disease conducted in 2011 (Japanese Society for Oral Health, 2013), the prevalence of periodontal disease, defined as one or more periodontal sites with PPD of 4 mm or deeper, was 14.2% of women aged 30–34 years. The corresponding figure for our cohort was 11.4%. The present population might therefore have had a greater awareness about health than would the general population. Nevertheless, the distribution of all three SNPs under study was consistent with the Hardy–Weinberg equilibrium and any selection bias associated with genotype distribution would be negligible.

Second, oral examinations were performed by dental hygienists. The dental hygienists were given detailed criteria for performing the examinations, but they received no specific training aimed at standardizing the procedures. In addition, no reliability assessment of measurements was carried out in the present study. Therefore, it is unknown whether intra- and inter-examiner consistency was established. Further, because partial mouth recording was used in the present study, the prevalence of periodontal disease might have been underestimated. It has been demonstrated, however, that using half-mouth as opposed to full-mouth data collection is unlikely to affect the outcome of analytical studies among young adults (Thomson and Williams, 2002). Moreover, our case definition of periodontal disease was solely based on the measurement of PPD, that is, the distance from the gingival margin to the base of the gingival sulcus or periodontal pocket. Measurements of PPD and clinical attachment level correlate well in many groups, especially younger populations, and both are accepted as measures of periodontal status (Page and Eke, 2007).

Third, the current study size was rather small for a valid genetic association study, although a significant association was detected between SNP rs16944 and periodontal disease. The lack of significant relationships between the other SNPs and periodontal disease might be attributable to an insufficient statistical power. In particular, as the minor allele frequency of rs1800587 and rs1143634 is lower in Japanese than in other ethnic populations (Laine *et al.*, 2010), it might be difficult to detect the association between these *IL1* SNPs and periodontal disease.

Fourth, a correction for multiple testing, an appropriate element in initial exploratory analyses, was not performed in this study. As this is a hypothesis testing study, and as part of the current findings is a replication of previously published results, we think that correction for multiple testing would cause us to underestimate our results.

Fifth, although adjustment was made for some confounders, residual confounding effects could not be ruled out. It is possible that our results were confounded by other potentially important factors such as postpartum hormone level and gestational diabetes.

Conclusion

Our present study showed that the GA genotype of *IL1* SNP rs16944 was significantly associated with a reduced risk of periodontal disease. *IL1* haplotypes inferred in the present study were not associated with the risk of periodontal disease. No interaction of any of the *IL1* polymorphisms with smoking was observed. Further studies are needed to confirm these results and to understand the mechanisms behind the observed association between *IL1* SNP rs16944 and periodontal disease.

Acknowledgments

This study was supported by KAKENHI Grants (19590606, 20791654, 21590673, 22592355, 24390158, 25463275, and 25670305), by Health and Labor Sciences Research Grants, Research on Allergic Disease and Immunology from the Ministry of Health, Labor, and Welfare of Japan, by the Central Research Institute of Fukuoka University, and by the Takeda Science Foundation.

The authors would like to acknowledge the Kyushu Branch of the Japan Allergy Foundation, the Fukuoka Association of Obstetricians and Gynecologists, the Okinawa Association of Obstetricians and Gynecologists, the Miyazaki Association of Obstetricians and Gynecologists, the Oita Association of Obstetricians and Gynecologists, the Kumamoto Association of Obstetricians and Gynecologists, the Nagasaki Association of Obstetricians and Gynecologists, the Kagoshima Association of Obstetricians and Gynecologists, the Saga Association of Obstetricians and Gynecologists, the Fukuoka Society of Obstetrics and Gynecology, the Okinawa Society of Obstetrics and Gynecology,

the Fukuoka Dental Hygienists' Association, the Okinawa Dental Hygienists' Association, the Miyazaki Dental Hygienists' Association, the Oita Dental Hygienists' Association, the Kumamoto Dental Hygienists' Association, the Nagasaki Dental Hygienists' Association, the Kagoshima Dental Hygienists' Association, the Saga Dental Hygienists' Association, the Fukuoka City Government, and the Fukuoka City Medical Association for their valuable support, as well as Mrs. Yukari Hayashi for her technical assistance.

Disclosure Statement

No competing financial interests exist.

References

Agrawal, A.A., Kapley, A., Yeltiwar, R.K., and Purohit, H.J. (2006). Assessment of single nucleotide polymorphism at IL-1A + 4845 and IL-1B + 3954 as genetic susceptibility test for chronic periodontitis in Maharashtrian ethnicity. J Periodontol **77,** 1515–1521.

Barksby, H.E., Lea, S.R., Preshaw, P.M., and Taylor, J.J. (2007). The expanding family of interleukin-1 cytokines and their role in destructive inflammatory disorders. Clin Exp Immunol **149,** 217–225.

Barrett, J.C., Fry, B., Maller, J., and Daly, M.J. (2005). Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics **21,** 263–265.

Bascones-Martínez, A., Valderrama, G., Vijande, F., Puyet-Catalina, A., Bascones-Ilundain, J., Arias-Herrera, S., and Garrido-Pertierra, A. (2012). Interleukin-1 gene polymorphisms and periodontal status in a Spanish population. Mol Med Rep **5,** 1335–1339.

Cullinan, M.P., Westerman, B., Hamlet, S.M., Palmer, J.E., Faddy, M.J., Lang, N.P., and Seymour, G.J. (2001). A longitudinal study of interleukin-1 gene polymorphisms and periodontal disease in a general adult population. J Clin Periodontol **28,** 1137–1144.

Droździk, A., Kurzawski, M., Safronow, K., and Banach, J. (2006). Polymorphism in interleukin-1beta gene and the risk of periodontitis in a Polish population. Adv Med Sci **51,** 13–17.

Gauderman, W.J. (2002). Sample size requirements for matched case-control studies of gene-environment interaction. Stat Med **21,** 35–50.

Guzeldemir, E., Gunhan, M., Ozcelik, O., and Tastan, H. (2008). Interleukin-1 and tumor necrosis factor-alpha gene polymorphisms in Turkish patients with localized aggressive periodontitis. J Oral Sci **50,** 151–159.

Honda, T., Domon, H., Okui, T., Kajita, K., Amanuma, R., and Yamazaki, K. (2006). Balance of inflammatory response in stable gingivitis and progressive periodontitis lesions. Clin Exp Immunol **144,** 35–40.

Japanese Society for Oral Health. (2013). *Japanese Society for Dental Health: Report on the Survey of Dental Diseases, 2011.* Tokyo: Japanese Society for Oral Health (in Japanese).

Karjalainen, J., Nieminen, M.M., Aromaa, A., Klaukka, T., and Hurme, M. (2002). The IL-1beta genotype carries asthma susceptibility only in men. J Allergy Clin Immunol **109,** 514–516.

Karimbux, N.Y., Saraiya, V.M., Elangovan, S., Allareddy, V., Kinnunen, T., Kornman, K.S., and Duff, G.W. (2012). Interleukin-1 gene polymorphisms and chronic periodontitis in adult whites: a systematic review and meta-analysis. J Periodontol **83,** 1407–1419.

Kiani, Z., Tavakkol-Afshari, J., Hojjat, H., Arab, HR., Radvar, M., Sadeghizadeh, M., and Ebadian, A.R. (2009). Polymorphism of IL-1alpha(-889) Gene and its association with aggressive periodontitis. Iran J Allergy Asthma Immunol **8,** 95–98.

Kornman, K.S., Crane, A., Wang, H.Y., di Giovine, F.S., Newman, M.G., Pirk, F.W., Wilson, T.G., Jr., Higginbottom, F.L., and Duff, G.W. (1997). The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol **24,** 72–77.

Laine, M.A. (2002). Effect of pregnancy on periodontal and dental health. Acta Odontol Scand **60,** 257–264.

Laine, M.L., Crielaard, W., and Loos BG. (2012). Genetic susceptibility to periodontitis. Periodontol 2000 **58,** 37–68.

Laine, M.L., Loos, B.G., and Crielaard, W. (2010). Gene polymorphisms in chronic periodontitis. Int J Dent **2010,** 324719.

Li, Q.Y., Zhao, H.S., Meng, H.X., Zhang, L., Xu, L., Chen, Z.B., Shi, D., Feng, X.H., and Zhu, X.L. (2004). Association analysis between interleukin-1 family polymorphisms and generalized aggressive periodontitis in a Chinese population. J Periodontol **75,** 1627–1635.

López, N.J., Jara, L., and Valenzuela, C.Y. (2005). Association of interleukin-1 polymorphisms with periodontal disease. J Periodontol **76,** 234–243.

Maria, de Freitas, N., Imbronito, A.V., Neves, A.C., Nunes, F.D., Pustiglioni, F.E., and Lotufo, R.F. (2007). Analysis of IL-1A(−889) and TNFA(−308) gene polymorphism in Brazilian patients with generalized aggressive periodontitis. Eur Cytokine Netw **18,** 142–147.

Mascarenhas, P., Gapski, R., Al-Shammari, K., and Wang, H.L. (2003). Influence of sex hormones on the periodontium. J Clin Periodontol **30,** 671–681.

McDevitt, M.J., Wang, H.Y., Knobelman, C., Newman, M.G., di Giovine, F.S., Timms, J., Duff, G.W., and Kornman, K.S. (2000). Interleukin-1 genetic association with periodontitis in clinical practice. J Periodontol **71,** 156–163.

Meisel, P., Siegemund, A., Dombrowa, S., Sawaf, H., Fanghaenel, J., and Kocher, T. (2002). Smoking and polymorphisms of the interleukin-1 gene cluster (IL-1alpha, IL-1beta, and IL-1RN) in patients with periodontal disease. J Periodontol **73,** 27–32.

Meisel, P., Siegemund, A., Grimm, R., Herrmann, F.H., John, U., Schwahn, C., and Kocher, T. (2003). The interleukin-1 polymorphism, smoking, and the risk of periodontal disease in the population-based SHIP study. J Dent Res **82,** 189–193.

Moreira, P.R., Costa, J.E., Gomez, R.S., Gollob, K.J., and Dutra, W.O. (2007). The IL1A (-889) gene polymorphism is associated with chronic periodontal disease in a sample of Brazilian individuals. J Periodontal Res **42,** 23–30.

Moreira, P.R., de Sá, A.R., Xavier, G.M., Costa, J.E., Gomez, R.S., Gollob, K.J., and Dutra, W.O. (2005). A functional interleukin-1 beta gene polymorphism is associated with chronic periodontitis in a sample of Brazilian individuals. J Periodontal Res **40,** 306–311.

Nikolopoulos, G.K., Dimou, N.L., Hamodrakas, S.J., and Bagos, P.G. (2008). Cytokine gene polymorphisms in periodontal disease: a meta-analysis of 53 studies including 4178 cases and 4590 controls. J Clin Periodontol **35,** 754–767.

Page, R.C., and Eke, P.I. (2007). Case definitions for use in population-based surveillance of periodontitis. J Periodontol **78,** 1387–1399.

Parkhill, J.M., Hennig, B.J., Chapple, I.L., Heasman, P.A., and Taylor, J.J. (2000). Association of interleukin-1 gene polymorphisms with early-onset periodontitis. J Clin Periodontol **27,** 682–689.

Pihlstrom, B.L., Michalowicz, B.S., and Johnson, N.W. (2005). Periodontal diseases. Lancet **366,** 1809–1820.

Pociot, F., Mølvig, J., Wogensen, L., Worsaae, H., and Nerup, J. (1992). A TaqI polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion *in vitro*. Eur J Clin Invest **22,** 396–402.

Preiss, D.S., and Meyle, J. (1994). Interleukin-1 beta concentration of gingival crevicular fluid. J Periodontol **65,** 423–428.

Read, R.C., Camp, N.J., di Giovine, F.S., Borrow, R., Kaczmarski, E.B., Chaudhary, A.G., Fox, A.J., and Duff, G.W. (2000). An interleukin-1 genotype is associated with fatal outcome of meningococcal disease. J Infect Dis **182,** 1557–1560.

Sakellari, D., Katsares, V., Georgiadou, M., Kouvatsi, A., Arsenakis, M., and Konstantinidis, A. (2006). No correlation of five gene polymorphisms with periodontal conditions in a Greek population. J Clin Periodontol **33,** 765–770.

Shete, A.R., Joseph, R., Vijayan, N.N., Srinivas, L., and Banerjee, M. (2010). Association of single nucleotide gene polymorphism at interleukin-1beta + 3954, − 511, and − 31 in chronic periodontitis and aggressive periodontitis in Dravidian ethnicity. J Periodontol **81,** 62–69.

Stabholz, A., Soskolne, W.A., and Shapira, L. (2010). Genetic and environmental risk factors for chronic periodontitis and aggressive periodontitis. Periodontol 2000 **53,** 138–153.

Soga, Y., Nishimura, F., Ohyama, H., Maeda, H., Takashiba, S., and Murayama, Y. (2003). Tumor necrosis factor-alpha gene (TNF-alpha) − 1031/ − 863, − 857 single-nucleotide polymorphisms (SNPs) are associated with severe adult periodontitis in Japanese. J Clin Periodontol **30,** 524–531.

Statistics Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications. (2002). *2000 Population Census of Japan, Vol. 3-2-40, Labour Force Status of Population, Industry (Major Groups) of Employed Persons, and Education, Fukuoka-ken*. Tokyo: Statistics Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications (in Japanese), p. 666.

Tai, H., Endo, M., Shimada, Y., Gou, E., Orima, K., Kobayashi, T., Yamazaki, K., and Yoshie, H. (2002). Association of interleukin-1 receptor antagonist gene polymorphisms with early onset periodontitis in Japanese. J Clin Periodontol **29,** 882–888.

Thomson, W.M., and Williams, S.M. (2002). Partial- or full-mouth approaches to assessing the prevalence of and risk factors for periodontal disease in young adults. J Periodontol **73,** 1010–1014.

Trevilatto, P.C., de Souza Pardo, A.P., Scarel-Caminaga, R.M., de Brito, R.B. Jr., Alvim-Pereira, F., Alvim-Pereira, C.C., Probst, C.M., Garlet, G.P., Sallum, A.W., and Line, S.R. (2011). Association of IL1 gene polymorphisms with chronic periodontitis in Brazilians. Arch Oral Biol **56,** 54–62.

Yücel, O.O., Berker, E., Mescil, L., Eratalay, K., Tepe, E., and Tezcan, I. (2013). Association of interleukin-1 beta (+3954) gene polymorphism and gingival crevicular fluid levels in patients with aggressive and chronic periodontitis. Genet Couns **24,** 21–35.

Zhang, J., Sun, X., Xiao, L., Xie, C., Xuan, D., and Luo, G. (2011). Gene polymorphisms and periodontitis. Periodontol 2000 **56,** 102–124.

Address correspondence to:
Keiko Tanaka, DDS, PhD
Department of Preventive Medicine and Public Health
Faculty of Medicine
Fukuoka University
Fukuoka 814-0180
Japan

E-mail: k-tanaka@fukuoka-u.ac.jp

Received for publication September 26, 2013; received in revised form December 11, 2013; accepted December 12, 2013.